THE USE OF ANTIBIOTICS

A Comprehensive Review with Clinical Emphasis

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and

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THIRD EDITION

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THIRD EDITION

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Preface to First Edition

This book aims to provide a concise, systematized description of antibiotics in current use in antibacterial chemotherapy. Commonly used synthetic antibacterial chemotherapeutic agents are included, but compounds used solely for tuberculosis and leprosy have been omitted. Although primarily designed for clinicians, the book may well be useful for bacteriologists, pharmacists, pharmacologists and undergraduates.

The presentation of a personal viewpoint has been consciously avoided, if this is possible, in favour of a balanced account of data and informed opinion from the medical literature. I have accordingly attempted to acknowledge all of my sources of information in the text.

Where conclusions are in doubt or controversial, the known facts and opinions are recorded for the reader to assess and apply in relevant circumstances.

Each chapter is devoted to one or several related drugs and divided into ten standard sections for ease of reference. A brief introductory description is followed by sections relating to the antibacterial spectrum, *in vitro* sensitivities, administration and dosage, serum levels, excretion, body distribution, mode of action, toxicity and clinical application.

Many colleagues, in particular the senior medical staff of Fairfield Hospital, have assisted with the preparation of this book. Dr. John A. Forbes, the Medical Superintendent and Dean of the Hospital Clinical School, encouraged me some six years ago to write, for use in our hospital, systematized notes on antibiotics which form the basis of this book. He has also read all of the manuscript, and has made many valuable suggestions. I would especially like to thank my colleague, Dr. Noel McK. Bennett, Specialist Physician and Deputy Medical Superintendent, who has been of immense assistance to me. He aided in the detailed editing of the text, and has contributed to much of the content of the book. Dr. Joan D. Schiavone, formerly Assistant Pathologist at Fairfield Hospital, now Senior Lecturer in the Department of Microbiology, University of Melbourne, has helped with many bacteriological aspects.

I would also like to thank my secretary, Mrs. Ann Cullen, for typing the manuscript and Miss Jean Foreman, the hospital medical librarian, for collecting much of the medical literature. I am also indebted to my publishers, particularly Mr. Owen R. Evans, Managing Director, for advice on matters pertinent to medical publication, and for undertaking on my behalf the task of obtaining permission from other authors and publishers to reproduce tables and figures in the text.

A. Kucers

Melbourne, Australia
April 1972

Preface to Second Edition

A considerable amount of new information on chemotherapeutic agents has accumulated in the three years since the first edition of this book was published. We have aimed to make this edition an 'up-to-date' reference text, incorporating the significant advances which have occurred. This has entailed a full revision in which many sections and some chapters have been completely re written. The modest success and generally favourable reviews of the first edition have encouraged us in this task. The responsibility for this publication is now shared by two authors, but this is only an extension of the close working relationship which we enjoyed when the previous edition was written.

The contents of the book have been enlarged by the addition of chapters on drugs used for the treatment of tuberculosis and fungal diseases. There is also a section on those antiviral drugs which on present evidence appear to be of value in human therapeutics. We have tried to retain the 'concise, systematized description' which was the format of the first edition. The main purpose of this book is still to provide clinicians with comprehensive information on the use of individual chemotherapeutic agents. The text does not deal primarily with the treatment of diseases, although this information is available through the Index. Many of the compounds described are synthetic drugs, and not true antibiotics, but nowadays this distinction is of only academic interest to the clinician. Again we have endeavoured to present the comparative value of various drugs in an unbiased fashion according to published experience, though on controversial subjects we have also expressed our opinion.

We are grateful to Dr. Ray S. A. Marshman, The Director of Tuberculosis in Victoria, for his valuable criticism and comments on the chapters concerning drugs used for the treatment of tuberculosis. Our colleagues, the Senior Medical Staff at Fairfield Hospital, have once again been most tolerant and helpful during the period in which this book was written.

We would like to thank our secretaries, Mesdames Ann Cullen, Ann Fumi, Biddy Gibson and Janet Johnson, the medical librarian Miss Jean Foreman and proof reader Mrs. Anda Kucers for their respective contributions to this edition.

Melbourne, Australia
February 1975

A. Kucers
N. McK. Bennett

Preface to Third Edition

Similar to our second edition, this one follows its predecessor within a period of about four years. In this short time there have been considerable changes in the sensitivities of various organisms to chemotherapeutic agents. The appearance of gonococci and pneumococci resistant to penicillin G are two obvious examples. Where possible we have tried to indicate the best possible alternative drug(s) for the treatment of infections due to drug-resistant strains. The spread of multiple-antibiotic resistant strains of Gram-negative organisms, such as Serratia marcescens in hospitals, has also posed therapeutic problems. Treatment of infections due to these bacteria is difficult and often involves the concomitant use of two or more drugs, so that we have frequently included details of synergistic drug combinations which may prove of value.

Further chemical modifications of the penicillin and cephalosporin molecules have led to a bewildering number of new derivatives. In this edition there are descriptions of the newer penicillins and cephalosporins which are already available commercially; included are also some of these drugs which may be marketed in the future. Based on published data we have endeavoured to put these compounds in their proper clinical perspective. The newer aminoglycosidic aminocyclitols such as tobramycin, amikacin, sisomicin and netilmicin have been similarly assessed. New chapters cover the nitroimidazole drugs, in particular metronidazole, which is proving to have an important place for the treatment of bacterial as well as parasitic infections. Other innovations are descriptions of newer macrolides such as josamycin and rosamicin and the antifungal drugs, miconazole and econazole. Nearly every chapter has been extensively revamped so that this edition is virtually a new text-book. For the benefit of clinicians in countries like Australia who now use SI units, biochemical values are expressed additionally in these units. We have collaborated closely on every chapter to ensure accuracy, relevant cross-referencing and to avoid contradictions. This has been a considerable task for two practising clinicians but we feel that our unified approach to each drug would be difficult to retain with further dilution of authorship.

Once again we express our thanks to Dr. Ray S. A. Marshman who until recently was The Director of Tuberculosis in Victoria, for his wise counsel on the use of drugs for the treatment of tuberculosis. We are also extremely grateful to our secretaries, Mesdames Ann Fumi and Kay Munro. They had the mammoth task of typing the manuscript which they accomplished with accuracy and in record time. The hospital's librarian, Miss Jean Foreman, was ever available to obtain the most obscure reference and she with Mrs. Anda Kucers again helped with the tedious task of proof-reading. Our publishers have been most cooperative in expediting the production of this book. Finally we would like to thank the many medical practitioners throughout the world who have expressed their appreciation of our book in various ways. It was solely this response which encouraged us to write this third edition.

Melbourne, Australia
February 1979

Alvis Kucers
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Part I
Antibiotics

Penicillin G

Description

Penicillin was isolated from Penicillium notatum by Fleming in 1929 and introduced into clinical medicine in 1941 by Florey, Chain and associates (Fleming, 1929; Chain *et al.*, 1940). The history of penicillin, including its early use in treatment of human infections, is recorded in a number of informative monographs such as those by Stewart (1965), Hare (1970) and Bickel (1972).

The pencillin used by early investigators was an amorphous compound containing impurities, which were introduced during the fermentative processes used in its manufacture, and its activity and dosage were expressed in units. The early penicillin was also a mixture of several penicillin compounds, designated as F, G, X and K. Penicillin G (benzylpenicillin) was found to be the most satisfactory, and this is now used in a highly purified and crystalline form for clinical purposes. Penicillin G as such is a rather unstable acid, and currently the following relatively stable salts are used clinically:

1. *Sodium penicillin G or sodium benzylpenicillin.* This is a highly soluble salt, and a dose can be dissolved completely in a few ml of water prior to administration. The dosage of this and other penicillin G preparations is still commonly expressed in units. One unit of activity is equal to 0·6 μg of pure sodium penicillin G.

2. *Potassium penicillin G* similarly is a very soluble salt. One unit of activity is equal to 0·625 μg of pure potassium penicillin G.

The term 'crystalline penicillin G' or simply 'crystalline penicillin' is often used as a synonym for either of the above highly soluble benzylpenicillin salts, but all other penicillins in use are also crystalline in form, unlike the early impure amorphous compound.

3. *Procaine penicillin G* (*Procaine benzylpenicillin or procaine penicillin*). This is a much less soluble salt, and it is administered intramuscularly as a suspension of crystal particles. These particles dissolve slowly after administration, so that absorption from the injection site takes place over a prolonged period. One unit of activity is equal to 1·0 μg of pure procaine penicillin.

4. *Benzathine penicillin G* (*Di-benzyl-ethylene-diamine penicillin or DBED penicillin*). This salt is even less soluble than procaine penicillin, so it is even more slowly absorbed from an intramuscular injection site. One unit of activity is equivalent to 0·75 μg of the pure substance.

The procaine and benzathine salts of penicillin G are known as the 'long acting', 'depot' or 'repository' forms of penicillin G.

Sensitive Organisms

1. *Gram-positive cocci.* Penicillin G is highly active against many of these bacteria. Strep. pyogenes (Group A) has remained very sensitive (Finland *et al.*, 1976a) and routine sensitivity testing is not required. The same was generally true for Strep. pneumoniae, but since about 1970 relatively resistant strains, and more recently also pneumococcal strains with complete penicillin resistance, have been isolated from patients or pneumococcal carriers.

Relatively resistant pneumococcal strains require from five to a hundred times higher penicillin concentrations for inhibition, than sensitive strains (Table 1). These strains were first detected in Papua New Guinea and Australia (Hansman *et al.*, 1971; Hansman, 1972; Hansman *et al.*, 1973; 1974; Hansman, 1974). More recently they have appeared in other countries such as New Mexico (Tempest *et al.*, 1974), North America (Naraqi *et al.*, 1974; Paredes *et al.*, 1976a; Finland *et al.*, 1976b; Cooksey *et al.*, 1978) and Britain (Howes and Mitchell, 1976). Such pneumococcal strains are also relatively resistant to penicillin V (page 55), methicillin (page 64), cloxacillin (page 79) and to cephalothin and cephaloridine (page 199). By contrast they remain either fully ampicillin-sensitive (page 99), or only show a slight decrease in sensitivity (Hansman, 1975). Most human infections caused by these pneumococci probably would respond to penicillin G, provided that sufficiently large doses are used (Hansman, 1976), but this may not be invariable. Already there are several case reports describing serious infections caused by relatively resistant pneumococci, which responded poorly to standard penicillin G regimens. These include meningitis (Naraqi *et al.*, 1974; Paredes *et al.*, 1976a; Howes and Mitchell, 1976; Mace *et al.*, 1977), and severe pneumococcal pneumonia (Devitt *et al.*, 1977) (*see also* pages 32, 33).

More recently pneumococci, completely resistant to penicillin and also to other antibiotics have been detected in South Africa (Appelbaum *et al.*, 1977; Center for Disease Control, 1977c). Type 19a pneumococci, resistant to penicillin G (MIC 4–8 μg per ml), cephalothin (MIC 4–15), chloramphenicol (MIC 9–37) and partially resistant to ampicillin (MIC 1–4) were isolated from five children in a hospital in Durban, South Africa. Three of these patients died from pneumococcal meningitis; the other two who had pneumonia and septicaemia respectively, recovered after prolonged treatment with antibiotics such as ampicillin, erythromycin and rifampicin. Since then carriers of the same resistant pneumococcal strains have been found in several Durban hospitals.

Multiply-resistant pneumococci were also soon found in Johannesburg in South Africa, a city approximately 300 miles inland from Durban. The first patient was a three-year-old boy who developed measles and pneumococcal pneumonia following cardiac surgery. He recovered with cephalothin and ampicillin treatment, although the type 19 pneumococcus isolated from his sputum was relatively resistant to both these drugs. In addition this strain was resistant to penicillin G (MIC 4–8 μg per ml), methicillin, erythromycin, clindamycin, tetracycline, chloramphenicol, co-trimoxazole and the aminoglycosides. This strain was therefore resistant to more antibiotics than the strain detected in Durban; it was fully sensitive only to rifampicin, vancomycin and bacitracin and moderately sensitive to sodium fusidate (MIC 2 μg per ml). Many carriers of this multiply resistant pneumococcus were detected

among both patients and staff in the same hospital, and a few serious infections such as septicaemia also occurred, which were difficult to treat. Attempts to eliminate pneumococci from the carriers by using a rifampicin/sodium fusidate combination were complicated by the emergence of rifampicin-resistant pneumococcal strains (page 552). In Johannesburg some patients were also found to harbour penicillin and tetracycline-resistant type 6 pneumococci.

Subsequent surveys in several communities in South Africa showed that antibiotic-resistant pneumococci have at least five resistance patterns: (1) penicillin resistance only; (2) penicillin and tetracycline resistance; (3) penicillin, tetracycline and chloramphenicol resistance; (4) penicillin and chloramphenicol resistance; (5) penicillin, tetracycline, chloramphenicol, erythromycin and clindamycin resistance. Strains from the last group are now referred to as 'multiply-resistant', and some of these have also developed resistance to other antibiotics such as rifampicin (*vide supra*). The multiply-resistant pneumococci and also those with other resistance patterns were either type 6 or type 19a (Center for Disease Control, 1978a).

A pneumococcus resistant to chloramphenicol and tetracycline and relatively resistant to penicillin G (MIC 0·25 μg per ml, compared with 0·03 μg per ml for sensitive strains) has been isolated in England from a patient who had recently returned from Spain (Meers and Matthews, 1978). A type 14 pneumococcus, resistant to penicillin (MIC 4 μg per ml) has also been isolated from the blood of a five-year-old girl in Minnesota in the United States (Center for Disease Control, 1977d). This patient had pneumonia and because of immunodeficiency she had been frequently treated by penicillin in the past. This pneumococcal strain was sensitive to other antibiotics such as chloramphenicol and erythromycin, so that it differed both in serotype and antibiotic-resistance pattern from the multiply-resistant strains detected in South Africa (*vide supra*).

The occurrence of penicillin-resistant and multiply-resistant pneumococcal strains, raises fears that they may emerge in other parts of the world. The mechanisms of pneumococcal resistance is unknown, but the isolation in South Africa of serologically identical pneumococci with similar resistance patterns to several unrelated antibiotics, suggests the possibility of transferable drug resistance by R plasmids (page 422). However beta-lactamase production was not demonstrated in any of the resistant pneumococci isolated in Durban (Applebaum *et al.*, 1977).

In view of these reports it is now advisable for all clinical laboratories to routinely test the sensitivities of all pneumococcal isolates (Leading article, 1977d).

Group B beta-haemolytic streptococci, often normally present in the vagina of both pregnant and non-pregnant women (Baker *et al.*, 1977; Baker, 1977), have increasingly been recognized as an important cause of neonatal infections since about 1960 (McCracken, 1973; Berg *et al.*, 1977; Annotation, 1977). More recently they have also been implicated in certain adult infections (Anthony and Concepcion, 1975; Bayer *et al.*, 1976). These streptococci are consistently sensitive to penicillin G, but their degree of sensitivity is about ten-fold less than that of Group A streptococci (Table 1). Most studies show that the penicillin G sensitivity of Group B streptococci has remained unchanged in recent years (Anthony and Concepcion, 1975; Baker *et al.*, 1976). In a survey