ANTIBIOTICS

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Preface to Second Edition

It was stated in the preface to the first edition of Antibiotics that the purpose of the authors was to "present in a succinct, integrated plan the facts and principles of fundamental and permament value relating to antibiotics." Their purpose in the present edition remains the same.

Important discoveries based on principles developed earlier in the study of antibiotics have emerged from the more than 7,000 research papers that have appeared in the 4 years since the first edition was published. For a clear perspective of the field of antibiotics these discoveries must be considered in relation to the previously established facts and principles, some of which in turn must be re-evaluated in relation to the newer developments.

To that end, 5 new chapters have been written, and the earlier material has been revised. To show each new phase of the subject of antibiotics in its proper perspective, this edition has been organized into 4 parts: Fundamental Aspects, Industrial Aspects, Applied Aspects, and Modification of Biologic and Social Systems. At the end of each chapter a few guides to the pertinent literature are listed.

The "Suggested Reading" lists have been reduced to the minimum compatible with giving the reader a key to the literature. In areas covered by textbooks or by comprehensive reviews, only these readily available publications are cited. Following chapters dealing with newly opened fields, bibliographic citations aim at indicating the scope of interest among various professions in different parts of the world.

We wish to acknowledge the co-operation of those who have contributed in different ways to the present revision. Thanks are due the Research Directors of the several pharmaceutical and chemical manufacturers for their help in providing some technical data not available in the literature. Among the organizations that have been especially helpful are Eli Lilly and Co., Lederle Laboratories, the Merck Insti-

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Finally, we desire to express our special gratitude to Jean Pratt, who has been a constant and unfailing teammate. No task has been too trivial or monotonous to command her earnest attention or so large or difficult as to discourage her. To her, as to Janet Pratt, who cheerfully gave valuable help in proofreading, we give our most heartfelt thanks.

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Preface to First Edition

The purpose of this book is to present in a succinct, integrated plan the facts and principles of fundamental and permanent value relating to antibiotics. Much of this information is now widely scattered in thousands of publications embracing the vast scientific literature of the subject. Some of it is derived from the authors' own researches in this field published over a period of years.

The object has been, first, to give an understanding of the fact that, in developing chemical therapy by means of antibiotics, man has merely adapted to his own ends the capacity that certain microorganisms possess to wage a war of extermination against other microorganisms, and, second, to present a general survey of the principles involved in the industrial, commercial, pharmaceutical, and medical aspects of the field of antibiotics.

The advent, about 1942, of the modern era of antibiotic chemotherapy for the treatment of systemic infections unquestionably marks one of the greatest advances in man's continuing battle against infectious diseases.

In terms of human suffering that has been alleviated, the discovery of practical means of applying microbial antagonisms for curative purposes easily ranks with the great contribution of the nineteenth century, i.e., the introduction of anesthesia in surgery one hundred years earlier.

In terms of volume, the industrial production of antibiotics outranks all other medicinals. It has been estimated that in 1948 penicillin and streptomycin alone accounted for more than one half of manufacturers' income from the sale of synthetic drugs. This figure is especially impressive when it is realized that penicillin first became available commercially in 1943 and that streptomycin was not available commercially until two or three years later. Within the last year three additional antibiotics, bacitracin, aureomycin, and chloromycetin have become available. More will undoubtedly follow.

Penicillin proved to be of immense value in World War II, not only in humanitarian terms, but also in military terms, because its use returned to active service many men who otherwise would have succumbed to infection or would have been permanently disabled. In the same way, on a larger scale, many other antibiotics are proving of immense economic as well as humanitarian value in the postwar era, by reducing periods of hospitalization or of quarantine, and by rehabilitating many chronic cases. Thus, proper use of antibiotics lightens the financial burden of public health and welfare agencies.

For this reason, countries not self-sufficient with respect to production of antibiotics, find it economically advantageous to spend their limited supplies of dollars for importation of these agents in preference to a number of other "essential" commodities. Drug exports from the United States for 1948 totaled 191 million dollars: approximately 40 per cent of this sum was spent for antibiotics (mostly penicillin and streptomycin).

Antibiotics have been used largely for treatment of human patients, but with increasing production, the cost of penicillin has dropped so markedly that its wide application in veterinary medicine has become practicable, resulting in large savings for cattle, dairy, poultry, and other livestock industries. With time, similar developments may be expected for other antibiotics.

There is a genuine need for a treatment of the broad principles of antibiotics and antibiotic chemotherapy sufficiently comprehensive to satisfy those whose business is concerned with the health sciences but not so technical as to discourage the interested individual whose major activities lie in other fields.

The authors modestly hope that the present volume will help to satisfy this need by filling the gap between the necessarily brief popular accounts on the one hand and the technical accounts intended for specialists on the other hand.

Since the aim of this book has been to achieve an integration of pertinent facts and principles in a coherent picture, no attempt has been made to cite exhaustively all of the extensive literature pertaining to the several aspects of the subject, but all important critical

review papers are listed, as are the principal scientific articles of historical interest.

ROBERTSON PRATT
JEAN DUFRENOY

It is with deep appreciation that we acknowledge the services of Louise Noack Gray, who designed the cover of this book, and the ceaseless secretarial and proofreading labors of my wife, Jean, and my mother. R. P.

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Contents

PART I. FUNDAMENTAL ASPECTS

1. Antibiosis and Antibiotic Spectra 3
   - The Concept of Antibiosis 3
   - Natural Sources of Antibiotics 8
   - Criteria for Identification of Antibiotics 12
   - The Concept of Antibiotic Spectra 24

2. Biologic Significance of Fields of Diffusion 31
   - Mutual Relations Among Organisms 31
   - Significance of Fields of Diffusion 31
   - Modification of the Sigmoid Curve 38
   - The Concept of Threshold and Optimal Concentrations 39

3. Antibiotics and Chemotherapy 45
   - The Concept of Chemotherapy 45
   - Requisites for an Ideal Antibiotic 47

PART II. INDUSTRIAL ASPECTS

4. Industrial Production of Antibiotics 53
   - Production by Fermentation 53
     - Preparation of Inoculum or "Seed" 54
     - Biosynthesis 58
     - Extraction and Purification 64
     - Testing 64

5. Screening and Assaying Antibiotics 69
   - Screening Tests 69
   - Assaying Antibiotics 72
     - Biologic Assays 74
     - Chemical and Physical Assays 83

PART III. APPLIED ASPECTS

6. Penicillin 87
   - Penicillin as a Chemical Compound 87
     - The Family of Penicillins 87
     - Biosynthesis 90
     - Extraction and Purification 103
     - Stability 105

6. PENICILLIN (*Continued*)
Penicillin as a Chemotherapeutic Agent 109
Factors Influencing Antibacterial Action 111
Sensitivity of the Pathogen 111
Number of Organisms Initially Present 112
pH of the Medium 113
Presence of Inhibitors or Interfering Substances 114
Presence of Enhancing Factors, Activators or Synergists 115
The Type of Penicillin 117
Chemotherapeutic Use 122
Infections in Which Penicillin Is Useful 123
Absorption, Blood Levels and Excretion 123
Prolonging Duration of Therapeutic Blood Levels 136
Physiologic Effects of Penicillin on the Patient 138

7. BACITRACIN, SUBTILIN AND TYROTHRICIN 142
Bacitracin 143
Biosynthesis 143
Extraction 143
Bacitracin as a Chemical Compound 144
Bacitracin as a Chemotherapeutic Agent 144
Physiologic Effects of Bacitracin on the Patient 147
Subtilin 147
Tyrothricin 150
Microbiology 150
Tyrothricin as a Chemical Compound 152
Tyrothricin as a Chemotherapeutic Agent 153

8. STREPTOMYCIN 156
Streptomycin as a Chemical Compound 157
Different Forms of Streptomycin 158
Biosynthesis 160
Extraction and Purification 162
Expressing the Potency of Streptomycin (Unitage) 162
Stability 163
Streptomycin and Dihydrostreptomycin as Chemotherapeutic Agents 165
Factors Influencing Antibacterial Action 166
Sensitivity of the Pathogen 166

8. STREPTOMYCIN (*Continued*)
The Number of Organisms Initially Present..... 168
The pH of the Medium..... 169
"Hyperactive Forms" 170
Presence of Inorganic Salts and Various Organic Substances 171
Chemotherapeutic Use 173
Absorption, Blood Levels and Excretion..... 173
Infections in Which Streptomycin Is Indicated..... 175
Development of Resistance Among Pathogens..... 175
Physiologic Effects of Streptomycins..... 182

9. VIOMYCIN, NEOMYCIN AND POLYMYXIN..... 186
Viomycin 186
Neomycin 188
Neomycin as a Chemical Compound..... 188
Neomycin as a Chemotherapeutic Agent..... 188
Polymyxin 190
Microbiology 191
Polymyxins as Chemical Compounds..... 192
Polymyxins as Chemotherapeutic Agents..... 193

10. CHLOROMYCETIN, AUREOMYCIN AND TERRAMYCIN..... 195
Chloromycetin (Chloramphenicol) 195
Industrial Sources 196
Chloromycetin as a Chemical Compound..... 196
Chloromycetin as a Chemotherapeutic Agent..... 197
Physiologic Effects of Chloromycetin on the Patient.. 202
Aureomycin and Terramycin..... 204
Microbiology of Aureomycin and Terramycin..... 204
Aureomycin and Terramycin as Chemical Compounds 206
Aureomycin and Terramycin as Chemotherapeutic Agents 208
Effects of Aureomycin and Terramycin on the Patient. 213

11. ERYTHROMYCIN AND CARBOMYCIN..... 217

12. MIXED ANTIBIOTIC THERAPY..... 222
Principles of Mixed Antibiotic Therapy..... 222
Some Indications and Contraindications..... 227
Joint Use of Pairs of Antibiotics..... 227
Joint Use of Antibiotics with Other Chemicals..... 234
Conclusions 238

13. Antibiotics in Dental Practice and Oral Surgery 240
Penicillin 242
When to Use Penicillin 242
How to Use Penicillin 243
Which Penicillin to Use 245
Bacitracin 246
Aureomycin and Terramycin 247
Streptomycin 248
Chloramphenicol 248
Mixed Antibiotic Therapy 249

14. Antibiotics in Agriculture 251
Veterinary Uses 252
Serum and Plasma Levels of Antibiotics 254
Penicillin 256
Streptomycin 259
Bacitracin 261
Tyrothricin 262
Chloramphenicol 262
Aureomycin 263
Terramycin 263
Mixed Therapy 266
Antibiotics as Growth Stimulants for Animals 269
Poultry 269
Swine 272
Ruminants 273
The Mode of Action of Antibiotics as Growth Stimulants 274
Antibiotics in Plant Pathology 277
Antibiotics in Food Processing 286

PART IV. MODIFICATION OF BIOLOGIC AND SOCIAL SYSTEMS

15. Emergence of Resistant Strains of Micro-organisms 293
Significance of Resistant Strains in Antibiotic Therapy 293
How Resistant Strains Arise 297
Mutation and Natural Selection 297
Adaptation 300
Antibiotic-Dependent Strains 301
The Problem of Cross Resistance 302
Curtailing Development of Resistant Strains in vivo 307

16. Mechanisms of Antibiotic Action 310
Distinguishing Characteristics of Antibiotics 310
Penicillin 313
Streptomycin 329
Chloromycetin 336
Aureomycin and Terramycin 339
Tyrothricin (Gramicidin and Tyrocidin) 341
Mechanisms of Action, Sensitivity and Resistance 342
Changes in Antigenicity 345
17. Some Social and Economic Aspects of Antibiotics 348
Appendix I. Antimicrobial Substances from Chlorophyllous Plants and from Animals 357
Appendix II. Schematized Structures of Selected Antibiotics Derived from Micro-organisms 365
Index 371

PART I

FUNDAMENTAL ASPECTS

Chapters 1 to 3

1

Antibiosis and Antibiotic Spectra

THE CONCEPT OF ANTIBIOSIS

The component members of any society, whether it be an aggregation of human beings or of other living organisms, are continuously influenced by their environment. Furthermore, the neighboring beings or organisms or cells constitute an important part of that environment. Several organisms or cells, whether of the same or of different kinds, cannot long exist in a limited space without affecting and (or) being affected by their neighbors. This fact is fundamental in all studies of growth and development, whether one is concerned with an individual organism or with the growth, the development and the decline of mixed populations of plants or of animals. The same principle applies even in the waxing and the waning of human civilizations.* This book treats of various ways in which some of these relationships among micro-organisms can be applied for practical clinical control or cure of pathogenic disorders of man and his domestic animals and plants, of industrial developments that have made antibiotics available for ever-increasing applications, and of socio-economic consequences of widespread use of antibiotics.

The term "antibiotic," according to its derivation, has a very broad meaning and might be used to indicate any agent or condition detrimental to life. The word "antibiosis" appears to have been coined in 1889 by Vuillemin who wrote, "The lion that springs on its prey and the serpent that poisons the wound before devouring its victim are not considered to be parasites. There is nothing unequivocal about it—

* For a more comprehensive treatment of this idea, developing some of the points of similarity between microbial societies and societies of higher animals, including man himself, see Pratt, R., 1949, Texas Rep. Biol. & Med. 7:12-21.

one creature destroys the life of another in order to sustain its own, the first being entirely active, and the second entirely passive; one is in unrestricted opposition to the other. The relation is so simple that it has never been named, but instead of being examined in isolation it can be viewed as a factor in more complex phenomena. For simplicity we shall refer to it as *antibiosis;* the active participant will be the antibiote." As currently used in pharmaceutical and medical practice, however, the term antibiotic has a very definite and limited connotation. It is used to designate a metabolic product of one micro-organism that is detrimental or inimical to the life activities of other micro-organisms, usually even when present in extremely low concentrations. According to this commonly employed definition, antimicrobial substances derived from higher plants or from animals (other than protozoa) would be excluded from the subject matter of antibiotics.*

Until the last decade, antibiotic principles were known only from crude extracts of liquids fermented by biosynthesizing micro-organisms or, more rarely, from extracts of the micro-organisms themselves. Despite the industrial development of purified antibiotics, the crude extracts still retain interest because frequently they contain enhancing substances that increase the antibacterial action of the antibiotic and antidotic substances that tend to counteract the action of bacterial toxins.

Antibiotics have been known, if not in the pure form, at least by their effects for centuries; but have only recently assumed the dominating position in clinical medicine and in the pharmaceutical industry that they now occupy. Although the Chinese were aware at least 2,500 years ago of the ameliorating properties of molded curd of soy bean when applied to carbuncles, boils and like infections and used this treatment as standard procedure in such conditions, the potential significance and value of micro-organisms as curative agents or as sources of useful drugs for the treatment of systemic infections seems to have been neglected until the latter part of the nineteenth century. This is not surprising, however, when one realizes that the subject of bacteriology, as

* The major portion of this book is concerned with the antimicrobial properties of substances produced by micro-organisms, but some of the antimicrobial substances from higher plants and animals are discussed briefly in Appendix I.