CONTENTS

Preface xiii

1 ANTIBIOTICS: THE GREATEST TRIUMPH
OF SCIENTIFIC MEDICINE 1

Selectivity 3
Development of Resistance 4
Sulfonamide: The First Antibacterial Agent Acting
Selectively 5
Chemotherapeutics and Antibiotics 9
Penicillin: The First Antibiotic 9
The First Therapeutic Trial 12
Rediscovery of Penicillin by a Basic Scientific
Approach 13
Betalactams 14
Streptomycin: The Second Antibiotic in the History
of Antibacterial Agents 16
The First Remedy for Tuberculosis 18
Conclusion 19
## CONTENTS

### 2 DISTRIBUTION OF ANTIBIOTICS  

Quantitative Evaluation of Antibiotics Consumption  
  Defined Daily Doses  
  International Distribution of Antibiotics:  
    A Scandinavian Example  
Control of Antibiotics Overuse

### 3 SULFONAMIDES AND TRIMETHOPRIM  

General Aspects Regarding the Development of Resistance  
Sulfonamides  
  Sulfonamides as Remedies  
  Resistance to Sulfonamide  
  Resistance to Sulfonamides in *Neisseria meningitidis*  
    Characterization of the Sulfonamide-Resistant Dihydropteroate Synthase in N. meningitidis  
    Characterization of the Other Sulfonamide-Resistant Dihydropteroate Synthase in N. meningitidis  
  Resistance to Sulfonamides in *Streptococcus pyogenes*  
  Resistance to Sulfonamides in *Campylobacter jejuni*  
  Resistance to Sulfonamides in *Streptococcus pneumoniae*  
  Resistance to Sulfonamides in *Pneumocystis jiroveci* (carinii)  
  Resistance to Sulfonamides in *Staphylococcus aureus* and *S. haemolyticus*  
  Resistance to Sulfonamides in *Mycobacterium leprae*  
  Plasmid-Borne Resistance to Sulfonamides  
  Trimethoprim
CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate Resistance to Trimethoprim</td>
<td>55</td>
</tr>
<tr>
<td>Chromosomal Resistance to Trimethoprim</td>
<td>56</td>
</tr>
<tr>
<td>Plasmid-Borne Resistance to Trimethoprim</td>
<td>59</td>
</tr>
<tr>
<td>Possible Pathogenicity Change in <em>C. jejuni</em> by Acquiring Trimethoprim Resistance Genes</td>
<td>65</td>
</tr>
<tr>
<td>Experimental Test of the Reversibility of Trimethoprim Resistance</td>
<td>66</td>
</tr>
<tr>
<td>Conclusion</td>
<td>67</td>
</tr>
</tbody>
</table>

4 PENICILLINS AND OTHER BETALACTAMS                                      69

- The Betalactam Ring: The Characteristic of all Betalactams             70
- The Antibacterial Mechanism of Betalactams                             73
- Penicillins                                                           74
  - Penicillins with an Enlarged Spectrum                                75
  - Penicillins Stable to Penicillinases                                77
  - Counteracting Resistance by the Inhibition of Betalactamases        80
- Other Antibacterial Betalactams                                       81
  - Cephalosporins                                                     81
  - Monobactams                                                        84
  - Thienamycins                                                       85
- Betalactamases                                                       87
  - Horizontal Spread of Betalactamases                                87
  - Penicillin-Binding Proteins                                        90
  - Resistance to Betalactams by Changes in the PBPs                   91
- A Very Old Prophecy Came True                                         94

5 GLYCOPEPTIDES                                                          95

- Mechanism of Antibacterial Action                                     96
6 AMINOGLYCOSIDES
The Antibacterial Mechanism of Streptomycin 104
Bactericidal Effect 106
Clinical Side Effects 106
Bacterial Resistance to Aminoglycosides 109
Horizontal Spread of Aminoglycoside Resistance 110
Conclusion 113

7 OTHER ANTIBIOTICS INTERFERING WITH BACTERIAL PROTEIN SYNTHESIS
Chloramphenicol 115
   Clinical Side Effects 117
   Bacterial Resistance to Chloramphenicol 117
Tetracyclines 119
   Mechanism of Action 120
   Clinical Side Effects 121
   Bacterial Resistance to Tetracyclines 121
Erythromycin and Related Antibiotics 123
   Macrolides 123
      Resistance to Erythromycin 124
      Clinical Use of Macrolides 125
   Lincosamides 125
   Streptogramins 126
Fusidic Acid 128
CONTENTS

Linezolid 129
Conclusion 131

8 QUINOLONES 133

The Effect of Quinolones on Bacteria 134
Clinical Use of Quinolones 136
Bacterial Resistance to Quinolones 139
   Mutational Resistance 139
   Resistance by Quinolone Efflux 140
   Transferable Plasmid-Borne Resistance 140
Conclusion 145

9 ANTIBACTERIAL AGENTS NOT RELATED TO THE LARGE ANTIBIOTIC FAMILIES 147

Remedies for Tuberculosis 147
   Rifampicin 149
      Mechanism of Action 150
      Resistance 151
      Plasmid-Borne Resistance 151
Other Agents Against Tuberculosis 152
   Isoniazid or Isonicotinic Acid Hydrazide 153
   Pyrazinamide 154
   Ethambutol 155
   Cycloserine 156
   para-Aminosalicylic Acid 157
Tuberculostatic Drugs Recruited from Earlier Known Groups of Antibiotics Found Originally with Other Antibacterial Spectra 158
# CONTENTS

## Diarylquinolines

159

The Battle Against Tuberculosis

159

Nitrofurantoin

161

Nitroimidazoles

161

Phosphomycin

163

Conclusion

165

## 10 MECHANISMS FOR THE HORIZONTAL SPREAD OF ANTIBIOTIC RESISTANCE AMONG BACTERIA

167

Transferable Resistance: Conjugation

167

Mutational Resistance

170

Plasmid-Borne Resistance Against Antibacterial Agents

171

Plasmids

173

The Origin of R Plasmids

176

Transposons

178

Integrons

182

## 11 HOW TO MANAGE ANTIBIOTIC RESISTANCE

187

Cross Resistance Between Related Antibiotics

188

The Evolution of Antibacterial Resistance

188

How to Counteract Resistance Development

190

Curtailing the Use of Antibiotics

191

Introduction of Truly New Antibacterial Agents

193

Antibacterial Peptides

193

Inhibition of Pathogenicity

197

Inhibition of Bacterial Fatty Acid Synthesis

198

Resistance Development Accelerates

200

Index

203