

## Contents

**Preface** *XXIII*

**List of Contributors** *XXV*

### **Part One Biochemistry and Molecular Genetics of Drug Metabolism 1**

- 1 Drug-Metabolizing Enzymes—An Overview 3**  
*Pavel Anzenbacher and Eva Anzenbacherová*
- 1.1 Introduction: Fate of a Drug in the Human Body 3
- 1.2 Classification Systems of Drug-Metabolizing Enzymes According to  
Different Criteria 4
- 1.3 Overview of the Most Important Drug-Metabolizing Enzymes 6
- 1.3.1 CYPs 6
- 1.3.2 Peroxidases 8
- 1.3.3 Flavin Monooxygenases 10
- 1.3.4 Other Oxidases: Amine Oxidases, and Molybdenum-Containing XO  
and AO 11
- 1.3.5 NADPH Oxidase, NAD(P)H Oxidoreductase, and Dihydropyridine  
Dehydrogenase 13
- 1.3.6 Reductases 14
- 1.3.7 Conjugating Enzymes 15
- Acknowledgments 20
- References 20
- 2 Cytochromes P450 27**  
*F. Peter Guengerich*
- 2.1 Introduction and Historical Perspective 27
- 2.2 Nomenclature and Gene Organization 29
- 2.3 Regulation 32
- 2.3.1 Transcriptional Regulation 32
- 2.3.2 Post-Translational and Epigenetic Regulation 34
- 2.3.3 Post-Translational Regulation 34

|          |   |           |
|----------|---|-----------|
| 2.4      | Polymorphisms   | 35        |
| 2.5      | Protein Structure   | 37        |
| 2.6      | Catalytic Mechanisms  | 40        |
| 2.7      | What Determines P450 Catalytic Selectivity?   | 45        |
| 2.8      | Oxidative Stress and P450s  | 47        |
| 2.9      | Relevance in Drug Metabolism and Clinical Medicine  | 48        |
|          | References  | 53        |
| <b>3</b> | <b>UDP-Glucuronosyltransferases</b>   | <b>67</b> |
|          | <i>Christian P. Strassburg and Sandra Kalthoff</i>  |           |
| 3.1      | Introduction  | 67        |
| 3.2      | A Simple Phenotype: Unconjugated Nonhemolytic Hyperbilirubinemia and Glucuronidation                      | 67        |
| 3.3      | Organization of UGTs and the <i>UGT1A</i> Gene Locus  | 68        |
| 3.4      | <i>UGT1A</i> Gene Nomenclature  | 70        |
| 3.5      | Human <i>UGT1A</i> Gene Locus and Sequence Variability  | 71        |
| 3.6      | Glucuronidation of Bilirubin  | 78        |
| 3.7      | <i>UGT1A1</i> Gene  | 79        |
| 3.8      | Is There an Advantage or Risk Associated with <i>UGT1A1</i> Variability?                                  | 80        |
| 3.9      | <i>UGT1A1</i> Gene and Pharmacogenetic Protection   | 82        |
| 3.9.1    | Cardiovascular Disease  | 82        |
| 3.9.2    | Cancer  | 82        |
| 3.10     | <i>UGT1A1</i> Gene and Pharmacogenetic Risks  | 83        |
| 3.10.1   | Disposition to Drug Toxicity  | 83        |
| 3.10.1.1 | Irinotecan Toxicity   | 83        |
| 3.10.1.2 | Jaundice in Protease Inhibitor Therapy (Atazanavir and Indinavir)   | 86        |
| 3.11     | <i>UGT1A1</i> Variability and Cancer Risk   | 86        |
| 3.11.1   | CRC   | 87        |
| 3.11.2   | Breast Cancer   | 87        |
| 3.12     | <i>UGT1A3</i> Gene  | 87        |
| 3.13     | <i>UGT1A7</i> Gene  | 88        |
| 3.13.1   | CRC   | 93        |
| 3.13.2   | HCC   | 93        |
| 3.13.3   | Pancreatic Cancer   | 94        |
| 3.14     | Transcriptional Regulation of <i>UGT1A</i> Genes  | 95        |
| 3.15     | Aryl Hydrocarbon Receptor/Aryl Hydrocarbon Receptor Nuclear Translocator Regulation of <i>UGT1A</i> Genes | 95        |
| 3.16     | Regulation by Hepatic Nuclear Factors   | 97        |
| 3.17     | Regulation by the Farnesoid X Receptor  | 97        |
| 3.18     | Regulation by Nuclear Factor Erythroid 2-Related Factor 2   | 98        |
| 3.19     | Regulation by Splice Variants   | 98        |
| 3.20     | Animal Models to Study <i>UGT1A</i> Genes   | 99        |
| 3.21     | Outlook   | 100       |

Acknowledgments 101

References 101

#### **4 Sulfotransferases 117**

*Michael W. H. Coughtrie*

4.1 Introduction 117

4.2 Background 118

4.3 PAPS Synthesis 119

4.4 SULT Enzyme Family 121

4.4.1 SULT1 Family 121

4.4.2 SULT2 Family 126

4.4.3 SULT3, 4, 5 and 6 Families 127

4.5 Assays for SULT Activity 128

4.6 Structure and Function of SULT 128

4.7 SULT Pharmacogenetics 132

4.8 Bioactivation and the Role of SULTs in Toxicology 133

4.9 Conclusions and Future Perspectives 135

References 135

#### **5 Glutathione S-Transferases 147**

*Miroslav Dostalek and Anna-Katarina Stark*

5.1 Introduction and History 147

5.2 Nomenclature, Structure, and Function 148

5.2.1 Cytosolic GSTs 148

5.2.1.1 GSTA, GSTM, and GSTP Classes 149

5.2.1.2 GSTS Class 149

5.2.1.3 GSTT Class 149

5.2.1.4 GSTO Class 150

5.2.1.5 GSTZ Class 150

5.2.2 Mitochondrial GSTs 150

5.2.3 Microsomal GSTs 150

5.3 Substrates 151

5.4 Regulation, Induction, and Inhibition 151

5.5 Gene Polymorphism of GSTs 155

5.5.1 GSTA Polymorphism 156

5.5.2 GSTM Polymorphism 156

5.5.3 GSTT Polymorphism 156

5.5.4 GSTP1 Polymorphism 157

5.5.5 GSTO Polymorphism 157

References 157

#### **6 Hydrolytic Enzymes 165**

*Bingfang Yan*

6.1 Carboxylesterases 165

6.1.1 Overview 165

|          |   |            |
|----------|---|------------|
| 6.1.2    | Classification and Structural Features                                    | 166        |
| 6.1.2.1  | Human Carboxylesterases   | 166        |
| 6.1.2.2  | Salient Features of Carboxylesterases                                     | 167        |
| 6.1.2.3  | Secondary and Crystal Structure   | 167        |
| 6.1.3    | Catalytic Mechanism, Substrate Specificity, and Activators and Inhibitors | 168        |
| 6.1.3.1  | Catalytic Mechanism   | 168        |
| 6.1.3.2  | Substrate Specificity   | 169        |
| 6.1.3.3  | Activators and Inhibitors   | 170        |
| 6.1.4    | Pharmacogenomics of Carboxylesterases                                     | 172        |
| 6.1.4.1  | Polymorphisms   | 173        |
| 6.1.4.2  | Interaction with the Cytochrome P450 Enzyme System                        | 173        |
| 6.1.4.3  | Interaction with UDP-Glucuronosyltransferases                             | 174        |
| 6.1.4.4  | Interactions with Drug Transporters                                       | 175        |
| 6.1.4.5  | Drug–Insecticide Interactions   | 175        |
| 6.1.5    | Comparison between Human and Animal Carboxylesterases                     | 175        |
| 6.1.5.1  | Tissue Distribution   | 176        |
| 6.1.5.2  | Species-Specific Hydrolysis   | 176        |
| 6.1.5.3  | Ontogenic Expression  | 177        |
| 6.1.5.4  | Regulated Expression  | 177        |
| 6.2      | Epoxide Hydrolases  | 178        |
| 6.2.1    | Overview  | 178        |
| 6.2.2    | Classification and Structural Features                                    | 179        |
| 6.2.3    | Catalytic Mechanisms  | 180        |
| 6.2.4    | Comparison among Various EHs  | 181        |
| 6.3      | Paraoxonases  | 183        |
| 6.3.1    | Overview  | 183        |
| 6.3.2    | Classification and Structural Features                                    | 184        |
| 6.3.3    | Catalytic Mechanism   | 185        |
| 6.4      | Other Hydrolases  | 188        |
| 6.4.1    | Carbonic Anhydrases   | 188        |
| 6.4.2    | Cholinesterases   | 188        |
| 6.4.3    | $\beta$ -Glucuronidase  | 189        |
| 6.4.4    | Lipases   | 190        |
| 6.4.5    | Peptidases/Proteases  | 190        |
| 6.4.6    | Valacylovirase  | 190        |
|          | References  | 191        |
| <b>7</b> | <b>Transporting Systems</b>   | <b>199</b> |
|          | <i>Anne T. Nies, Claudia Resch, and Tadashi Namisaki</i>                  |            |
| 7.1      | Introduction  | 199        |
| 7.2      | Classification of Drug Transporters and Transport Mechanisms              | 199        |
| 7.3      | Drug Transporters of the SLC Superfamily                                  | 200        |
| 7.4      | ABC Drug Transporters   | 208        |

|       |  |     |
|-------|--|-----|
| 7.5   | Drug Transporters and Disease  | 208 |
| 7.6   | Drug Transporters and Pharmacokinetics   | 212 |
| 7.6.1 | Intestinal Transporters  | 212 |
| 7.6.2 | Hepatic Transporters   | 213 |
| 7.6.3 | Renal Transporters   | 213 |
| 7.6.4 | Transporters at the Blood–Brain Barrier  | 214 |
| 7.7   | Role of Drug Transporters in Chemotherapy Resistance                           | 214 |
| 7.8   | Pharmacogenomics of Drug Transporters: Implications for Clinical Drug Response | 215 |
|       | Acknowledgments  | 215 |
|       | References   | 216 |

## **8 Transcriptional Regulation of Human Drug-Metabolizing Cytochrome P450 Enzymes** 223

*Zdenek Dvorak*

|         |  |     |
|---------|--|-----|
| 8.1     | Factors Affecting Drug-Metabolizing Cytochromes P450 | 223 |
| 8.1.1   | Genetic Polymorphism                                 | 223 |
| 8.1.2   | Physiological and Pathophysiological Factors         | 224 |
| 8.1.3   | Environmental Factors                                | 224 |
| 8.2     | Transcriptional Regulation of CYP                    | 224 |
| 8.2.1   | Xenoreceptors, and Steroid and Nuclear Receptors     | 225 |
| 8.2.1.1 | Aryl Hydrocarbon Receptor                            | 225 |
| 8.2.1.2 | Pregnane X Receptor                                  | 226 |
| 8.2.1.3 | Constitutive Androstane Receptor                     | 226 |
| 8.2.1.4 | Steroid and Nuclear Receptors                        | 227 |
| 8.2.2   | Transcriptional Mechanisms                           | 227 |
| 8.2.2.1 | Direct Binding to the Gene Promoter                  | 227 |
| 8.2.2.2 | Indirect Binding to the Gene Promoter                | 227 |
| 8.2.2.3 | Regulating the Regulator                             | 228 |
| 8.2.3   | Receptor Cross-Talk                                  | 228 |
| 8.2.3.1 | Ligand Sharing                                       | 228 |
| 8.2.3.2 | Response Element Sharing                             | 228 |
| 8.2.3.3 | Receptor Cascade                                     | 228 |
| 8.2.3.4 | Coactivator Sharing                                  | 229 |
| 8.2.3.5 | Metabolic Cross-Talk                                 | 229 |
| 8.2.4   | Ligands–Agonists and Antagonists                     | 229 |
| 8.3     | Regulation of Drug-Metabolizing CYPs                 | 230 |
| 8.3.1   | CYP1A Subfamily                                      | 230 |
| 8.3.2   | CYP1B1   | 232 |
| 8.3.3   | CYP2A6   | 233 |
| 8.3.4   | CYP2B6   | 234 |
| 8.3.5   | CYP2C Subfamily                                      | 235 |
| 8.3.6   | CYP3A Subfamily                                      | 236 |
|         | Acknowledgments                                      | 238 |
|         | References   | 238 |

|          |   |     |
|----------|---|-----|
| <b>9</b> | <b>Importance of Pharmacogenomics</b>                             | 259 |
|          | <i>Ulrich M. Zanger, Kathrin Klein, and Jessica Rieger</i>        |     |
| 9.1      | Introduction  | 259 |
| 9.2      | Pharmacogenetic Polymorphisms                                     | 260 |
| 9.2.1    | Lessons from Early Examples                                       | 260 |
| 9.2.2    | Cytochrome P450 Polymorphisms                                     | 263 |
| 9.2.3    | Polymorphisms in Further Drug-Metabolizing Enzymes                | 268 |
| 9.2.4    | Polymorphic Drug Transporters                                     | 269 |
| 9.3      | Polygenic and Multifactorial Aspects of Drug Metabolism Phenotype | 270 |
| 9.3.1    | Polygenic Inheritance: CYP1A2 and CYP3A4 Conundrums               | 270 |
| 9.3.2    | Epigenetic Influences on Drug Metabolism                          | 272 |
| 9.4      | Genomics Technologies and Approaches                              | 273 |
| 9.4.1    | GWAS—A Matured Tool in Pharmacogenomics                           | 274 |
| 9.4.2    | Genetical Genomics: Identifying Novel Polymorphic ADME Genes      | 275 |
| 9.5      | Conclusions   | 276 |
|          | References  | 276 |

## **Part Two Metabolism of Drugs** 285

|           |  |     |
|-----------|--|-----|
| <b>10</b> | <b>Introduction to Drug Metabolism</b>                       | 287 |
|           | <i>Ulrich M. Zanger</i>                                      |     |
| 10.1      | Introduction   | 287 |
| 10.2      | Historical Aspects   | 287 |
| 10.3      | Diversity of Drug Metabolic Pathways                         | 288 |
| 10.4      | Influence of Drug Metabolism on Pharmacological Activity     | 289 |
| 10.5      | Biotoxification  | 290 |
| 10.6      | Extrahepatic Drug Metabolism                                 | 290 |
| 10.7      | Factors Affecting Drug Metabolism Activity                   | 291 |
| 10.7.1    | Genetic Polymorphism   | 291 |
| 10.7.2    | Sex  | 292 |
| 10.7.3    | Age  | 293 |
| 10.7.4    | Influence of Diseases and Pathophysiological Factors         | 294 |
| 10.7.5    | Environmental Influences                                     | 294 |
| 10.8      | Conclusions  | 296 |
|           | References   | 296 |
| <b>11</b> | <b>Central Nervous System Drugs</b>                          | 301 |
|           | <i>Pierre Baumann and Christoph Hiemke</i>                   |     |
| 11.1      | Introduction   | 301 |
| 11.2      | Antidepressants  | 301 |
| 11.2.1    | Tricyclic Antidepressants and Structurally Related Compounds | 302 |
| 11.2.2    | SSRIs  | 303 |
| 11.2.3    | Other Recent Antidepressants                                 | 305 |

- 11.2.4 MAO Inhibitors 306
- 11.3 Antipsychotics 306
  - 11.3.1 Phenthiazines and Thioxanthenes 306
  - 11.3.2 Butyrophenones and Related Compounds 307
  - 11.3.3 Atypical Antipsychotics 307
- 11.4 Tranquillizers and Hypnotic Agents 309
- 11.5 Psychostimulants 311
- 11.6 Anticonvulsants and Mood Stabilizers 311
- 11.7 Agents for Dementia and Cognitive Enhancers 313
- 11.8 Antimigraine Drugs 313
- 11.9 Other Drugs 314
- 11.10 Conclusions 314
- References 315
  
- 12 Cardiovascular Drugs 331**  
*Stephan Riedmaier and Ulrich M. Zanger*
- 12.1 Introduction 331
- 12.2 RAAS as a Target for Angiotensin-Converting Enzyme Inhibitors and AT<sub>1</sub> Receptor Blockers 331
  - 12.2.1 ACE Inhibitors 332
  - 12.2.2 ARBs 334
- 12.3 Adrenergic Receptor Agonists 337
  - 12.3.1  $\alpha_1$ -Selective Adrenergic Receptor Agonists 337
  - 12.3.2  $\alpha_2$ -Selective Adrenergic Receptor Agonists 338
  - 12.3.3  $\beta$ -Selective Adrenergic Receptor Agonists 339
- 12.4 Adrenergic Receptor Antagonists 339
  - 12.4.1  $\alpha_1$ -Selective Adrenergic Receptor Antagonists 339
  - 12.4.2  $\alpha_2$ -Selective Adrenergic Receptor Antagonists 340
  - 12.4.3  $\beta$ -Selective Adrenergic Receptor Antagonists 342
- 12.5 Diuretics 342
  - 12.5.1 Carbonic Anhydrase Inhibitors 344
  - 12.5.2 Osmotic Diuretics 344
  - 12.5.3 Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> Symport Inhibitors 345
  - 12.5.4 Thiazide or Thiazide-Like Diuretics 345
  - 12.5.5 Nonspecific Cation Channel Inhibitors 347
  - 12.5.6 Inhibitors of Renal Epithelial Na<sup>+</sup> Channels 347
  - 12.5.7 Mineralcorticoid Receptor Antagonists 348
- 12.6 Antiarrhythmics 349
  - 12.6.1 Calcium Channel Blockers 349
- 12.7 Anticoagulants 351
  - 12.7.1 Heparin 352
  - 12.7.2 Vitamin K Antagonists 352
  - 12.7.3 Antiplatelet Drugs 352
- 12.8 Cholesterol-Lowering Drugs 353
  - 12.8.1 Bile Acid Sequestrants 354
  - 12.8.2 Cholesterol Uptake Inhibitors 354

- 12.8.3 Fibrates 354
- 12.8.4 Statins 355
- References 357

**13 Anticancer Drugs 365**

*Matthias Schwab, Elke Schaeffeler, and Hiltrud Brauch*

- 13.1 Introduction 365
- 13.2 Alkylating Drugs 365
  - 13.2.1 Oxazaphosphorine (Cyclophosphamide, Ifosphamide) 365
  - 13.2.2 Melphalan 366
  - 13.2.3 Ethyleneimines (Thiotepa) 366
  - 13.2.4 Busulfan 366
  - 13.2.5 Methylhydrazines (Procarbazine) 367
- 13.3 Platinum-Containing Agents 367
- 13.4 Antimetabolites 367
  - 13.4.1 Folic Acid Antagonist (Methotrexate) 367
  - 13.4.2 Pyrimidine Analogs (5-Fluorouracil/Capecitabine/Tegafur) 368
  - 13.4.3 Cytidine Analogs 368
    - 13.4.3.1 Cytarabine and Gemcitabine 368
    - 13.4.3.2 Azacitidine and Decitabine 369
  - 13.4.4 Purine Analogs 369
    - 13.4.4.1 6-Thiopurine Analogs 369
    - 13.4.4.2 Fludarabine Phosphate 370
- 13.5 Natural Products 370
  - 13.5.1 Vinca Alkaloids (Vincristine) 370
  - 13.5.2 Taxanes (Paclitaxel, Docetaxel) 370
  - 13.5.3 Camptothecin Analogs 371
    - 13.5.3.1 Topotecan 371
    - 13.5.3.2 Irinotecan 371
- 13.5.4 Antibiotics 371
  - 13.5.4.1 Dactinomycin 371
  - 13.5.4.2 Anthracyclines 372
    - 13.5.4.3 Epipodophyllotoxins 372
- 13.6 Endocrine Therapy 372
  - 13.6.1 Selective Estrogen Receptor Modulator (Tamoxifen) 372
  - 13.6.2 Aromatase Inhibitors 373
- 13.7 Histone Deacetylase Inhibitor (Vorinostat) 373
- 13.8 Tyrosine Kinase Inhibitors 373
- 13.9 Proteasome Inhibitor (Bortezomib) 374
- References 374

**14 Antimicrobial Agents 379**

*Chantal Csajka, Oscar Marchetti, Oriol Manuel, Laurent Decosterd, and Amalio Telenti*

- 14.1 Introduction 379



|           |  |            |
|-----------|--|------------|
| 14.2      | Pharmacokinetics/Pharmacodynamics of the Main Families of Antimicrobial Agents | 380        |
| 14.2.1    | Aminoglycosides  | 380        |
| 14.2.2    | Vancomycin   | 382        |
| 14.2.3    | $\beta$ -Lactams   | 383        |
| 14.2.4    | Antifungal Agents  | 386        |
| 14.2.5    | Antiviral Agents (Non-HIV)   | 389        |
| 14.2.5.1  | Drugs for Herpes Virus Infection   | 390        |
| 14.2.5.2  | Drugs for Viral Hepatitis  | 390        |
| 14.2.5.3  | Drugs against Respiratory Viruses  | 391        |
| 14.2.6    | Anti-HIV Agents  | 391        |
| 14.3      | Pharmacogenetics   | 393        |
| 14.4      | Conclusions  | 397        |
|           | Acknowledgments  | 398        |
|           | References   | 398        |
| <b>15</b> | <b>Drugs against Acute and Chronic Pain</b>                                    | <b>403</b> |
|           | <i>Andrew A. Somogyi and Janet K. Collier</i>                                  |            |
| 15.1      | Introduction   | 403        |
| 15.2      | Acute Pain   | 403        |
| 15.2.1    | Dexmedetomidine  | 403        |
| 15.2.2    | Paracetamol/Acetaminophen  | 407        |
| 15.2.3    | Nonsteroidal Anti-Inflammatory Drugs   | 408        |
| 15.2.3.1  | Diclofenac   | 408        |
| 15.2.3.2  | Flurbiprofen   | 408        |
| 15.2.3.3  | Ibuprofen  | 408        |
| 15.2.3.4  | Ketoprofen   | 409        |
| 15.2.3.5  | Ketorolac  | 409        |
| 15.2.3.6  | Meloxicam  | 409        |
| 15.2.3.7  | Naproxen   | 409        |
| 15.2.4    | Cyclooxygenase-2 Selective Inhibitors  | 410        |
| 15.2.4.1  | Celecoxib  | 410        |
| 15.2.4.2  | Etoricoxib   | 410        |
| 15.2.4.3  | Parecoxib  | 410        |
| 15.3      | Chronic Pain   | 410        |
| 15.3.1    | Tricyclic Antidepressants  | 410        |
| 15.3.1.1  | Amitriptyline  | 410        |
| 15.3.1.2  | Nortriptyline  | 411        |
| 15.3.1.3  | Imipramine   | 411        |
| 15.3.1.4  | Desipramine  | 412        |
| 15.3.2    | SNRIs  | 412        |
| 15.3.2.1  | Duloxetine   | 412        |
| 15.3.2.2  | Venlafaxine  | 412        |
| 15.3.3    | SSRIs  | 413        |
| 15.3.3.1  | Citalopram   | 413        |

|           |  |     |
|-----------|--|-----|
| 15.3.3.2  | Fluoxetine   | 413 |
| 15.3.3.3  | Paroxetine   | 414 |
| 15.3.4    | Ketamine   | 414 |
| 15.3.5    | Antiepileptics                                     | 415 |
| 15.3.5.1  | Carbamazepine                                      | 415 |
| 15.3.5.2  | Valproate  | 415 |
| 15.3.6    | Miscellaneous                                      | 415 |
| 15.3.6.1  | Gabapentin   | 415 |
| 15.3.6.2  | Pregabalin   | 415 |
| 15.3.6.3  | Tapentadol   | 415 |
| 15.3.7    | Opioids  | 416 |
| 15.3.7.1  | Buprenorphine                                      | 416 |
| 15.3.7.2  | Butorphanol  | 416 |
| 15.3.7.3  | Codeine  | 416 |
| 15.3.7.4  | Dextromoramide                                     | 417 |
| 15.3.7.5  | Dextropropoxyphene                                 | 417 |
| 15.3.7.6  | Dihydrocodeine                                     | 417 |
| 15.3.7.7  | Alfentanil, Fentanyl, Sufentanil, and Remifentanil | 417 |
| 15.3.7.8  | Heroin (Diamorphine (3,6-Diacetylmorphine))        | 417 |
| 15.3.7.9  | Hydrocodone  | 418 |
| 15.3.7.10 | Hydromorphone                                      | 418 |
| 15.3.7.11 | Ketobemidone                                       | 418 |
| 15.3.7.12 | L- $\alpha$ -Acetylmethadol                        | 418 |
| 15.3.7.13 | Levorphanol  | 418 |
| 15.3.7.14 | Loperamide   | 418 |
| 15.3.7.15 | Methadone  | 419 |
| 15.3.7.16 | Morphine   | 419 |
| 15.3.7.17 | Nalbuphine   | 419 |
| 15.3.7.18 | Nicomorphine (3,6-Dinicotionylmorphine)            | 419 |
| 15.3.7.19 | Oxycodone  | 420 |
| 15.3.7.20 | Oxymorphone  | 420 |
| 15.3.7.21 | Pentazocine  | 420 |
| 15.3.7.22 | Pethidine  | 420 |
| 15.3.7.23 | Piritramide  | 420 |
| 15.3.7.24 | Tilidine   | 420 |
| 15.3.7.25 | Tramadol   | 421 |
|           | References   | 421 |

## **16      Drugs of Abuse (Including Designer Drugs)    429**

*Markus R. Meyer and Hans H. Maurer*

|        |                        |     |
|--------|------------------------|-----|
| 16.1   | Introduction           | 429 |
| 16.2   | Classic Drugs of Abuse | 432 |
| 16.2.1 | Morphine and Heroin    | 432 |
| 16.2.2 | Cocaine                | 432 |
| 16.2.3 | THC                    | 433 |

- 16.2.4 Amphetamine/Methamphetamine 434
- 16.2.5 LSD 434
- 16.2.6 PCP 434
- 16.3 Designer Drugs of Abuse 435
  - 16.3.1 Amphetamine Derivatives 435
    - 16.3.1.1 Methylenedioxyamphetamines 435
    - 16.3.1.2 *p*-Substituted Amphetamines 437
    - 16.3.1.3 2,5-Dimethoxyamphetamines 438
  - 16.3.2 Phenethylamines (2Cs) 439
    - 16.3.2.1 2C-B 439
    - 16.3.2.2 2C-I 440
    - 16.3.2.3 2C-D 440
    - 16.3.2.4 2C-E 440
    - 16.3.2.5 2C-T-2 440
    - 16.3.2.6 2C-T-7 441
    - 16.3.2.7 Enzymes Involved in the Metabolism of 2,5-Dimethoxyamphetamines 441
  - 16.3.3 Cathinones 441
    - 16.3.3.1 Methylone 441
    - 16.3.3.2 Butylone 442
    - 16.3.3.3 Ethylone 442
    - 16.3.3.4 Mephedrone 442
  - 16.3.4 Phencyclidine Derivatives 443
    - 16.3.4.1 *N*-(1-Phenylcyclohexyl)-3-ethoxypropylamine (PCEPA) and *N*-(1-Phenylcyclohexyl)-3-methoxypropanamine (PCMPA) 443
    - 16.3.4.2 *N*-(1-Phenylcyclohexyl)propanamine (PCPr) 443
    - 16.3.4.3 *N*-(1-Phenylcyclohexyl)-2-ethoxyethanamine (PCEEA) and *N*-(1-Phenylcyclohexyl)-2-methoxyethanamine (PCMEA) 444
    - 16.3.4.4 Enzymes Involved in the Metabolism of Phencyclidine Derivatives 444
  - 16.3.5 Piperazines 444
    - 16.3.5.1 *N*-BZP 445
    - 16.3.5.2 1-(3,4-Methylenedioxybenzyl)piperazine (MDBP) 445
    - 16.3.5.3 1-(3-Trifluoromethylphenyl)piperazine (TFMPP) 445
    - 16.3.5.4 1-(3-Chlorophenyl)piperazine (mCPP) 446
    - 16.3.5.5 1-(4-Methoxyphenyl)piperazine (MeOPP) 446
  - 16.3.6 Pyrrolidinophenones 446
    - 16.3.6.1  $\alpha$ -Pyrrolidinopropiophenone (PPP) 447
    - 16.3.6.2 4'-Methoxy- $\alpha$ -pyrrolidinopropiophenone (MOPPP) 447
    - 16.3.6.3 Methylenedioxy- $\alpha$ -pyrrolidinopropiophenone (MDPPP) 447
    - 16.3.6.4 4'-Methyl- $\alpha$ -pyrrolidinopropiophenone (MPPP) 448
    - 16.3.6.5 4'-Methyl- $\alpha$ -pyrrolidinohexanophenone (MPHP) 448
    - 16.3.6.6 4'-Methyl- $\alpha$ -pyrrolidinobutyrophenone (MPBP) 449
    - 16.3.6.7 4'-Methyl- $\alpha$ -pyrrolidinovalerophenone (PVP) 449

|           |   |            |
|-----------|---|------------|
| 16.3.6.8  | 3',4'-Methylenedioxypropylvalerone (MDPV)   | 449        |
| 16.3.7    | Tryptamines   | 450        |
| 16.3.7.1  | 5-Methoxy-diisopropyl-tryptamine (5-MeO-DIPT)   | 450        |
|           | References  | 450        |
| <b>17</b> | <b>Nicotine Metabolism and its Implications</b>   | <b>465</b> |
|           | <i>Andy Z.X. Zhu and Rachel F. Tyndale</i>  |            |
| 17.1      | Introduction  | 465        |
| 17.2      | Absorption and Distribution of Nicotine   | 465        |
| 17.2.1    | Absorption  | 465        |
| 17.2.2    | Distribution  | 466        |
| 17.3      | Excretion of Nicotine   | 466        |
| 17.4      | Metabolism of Nicotine  | 468        |
| 17.4.1    | Primary Metabolites of Nicotine   | 468        |
| 17.4.2    | Secondary Metabolites of Nicotine   | 470        |
| 17.4.3    | Tertiary Metabolite of Nicotine   | 470        |
| 17.5      | Sources of Variation in Nicotine Metabolism   | 471        |
| 17.5.1    | Genetic   | 471        |
| 17.5.1.1  | CYP2A6 and Nicotine C-Oxidation   | 471        |
| 17.5.1.2  | Using the 3'-Hydroxycotinine: Cotinine Ratio as an <i>In Vivo</i> Probe for CYP2A6 Activity | 471        |
| 17.5.1.3  | Interethnic Variability in Nicotine C-Oxidation   | 476        |
| 17.5.1.4  | Genetic Influences on Other Nicotine-Metabolizing Enzymes                                   | 476        |
| 17.5.2    | Gender and Pregnancy  | 477        |
| 17.5.3    | Age   | 478        |
| 17.5.4    | Meals and the Chronopharmacokinetics of Nicotine  | 479        |
| 17.5.5    | Xenobiotics   | 479        |
| 17.5.6    | Smoking   | 480        |
| 17.5.7    | Menthol   | 480        |
| 17.5.8    | Other Factors   | 480        |
| 17.6      | Implications of Variation in Nicotine Metabolism and CYP2A6 Activity                        | 481        |
| 17.6.1    | Variation in Nicotine Metabolism is Associated with Altered Smoking Behaviors               | 481        |
| 17.6.2    | Variation in Nicotine Metabolism May Alter the Health Consequences of Smoking               | 481        |
| 17.6.3    | Variation in Nicotine Metabolism Alters Smoking Cessation Outcomes                          | 482        |
| 17.7      | Conclusions   | 483        |
|           | Acknowledgments   | 483        |
|           | References  | 484        |
| <b>18</b> | <b>Metabolism of Alcohol and its Consequences</b>   | <b>493</b> |
|           | <i>Helmut K. Seitz and Sebastian Mueller</i>  |            |
| 18.1      | Introduction  | 493        |

|        |   |     |
|--------|---|-----|
| 18.2   | Properties and Sources of Ethanol                             | 494 |
| 18.2.1 | Chemical Properties of Ethanol                                | 494 |
| 18.2.2 | Ethanol Content of Alcoholic Beverages                        | 494 |
| 18.2.3 | Ethanol Generation in the Human Body                          | 494 |
| 18.3   | Ethanol Absorption and Elimination                            | 495 |
| 18.3.1 | Ethanol Absorption and Ethanol Blood Levels                   | 495 |
| 18.3.2 | Calculation of Ethanol Elimination Using the Widmark Equation | 496 |
| 18.4   | Ethanol Metabolism  | 497 |
| 18.4.1 | Ethanol Metabolism via ADH                                    | 497 |
| 18.4.2 | Gastric FPM of Ethanol  | 502 |
| 18.4.3 | Ethanol Metabolism via the MEOS                               | 504 |
| 18.4.4 | Ethanol Metabolism via Catalase                               | 510 |
| 18.4.5 | Nonoxidative Metabolism of Ethanol                            | 510 |
| 18.4.6 | Acetaldehyde Metabolism via ALDH                              | 510 |
|        | Acknowledgments   | 511 |
|        | References  | 511 |

### **Part Three Metabolism of Natural Compounds 517**

|           |  |            |
|-----------|--|------------|
| <b>19</b> | <b>Introduction and Overview</b>   | <b>519</b> |
|           | <i>Michael Murray</i>  |            |
| 19.1      | Introduction   | 519        |
| 19.1.1    | Sources and Functional Importance of Natural Products                        | 519        |
| 19.1.2    | Plant Products as Drugs: A Historical Perspective                            | 520        |
| 19.1.3    | Considerations with the Use of Natural Products as Drugs                     | 520        |
| 19.1.4    | Biotransformation of Natural Products  | 521        |
| 19.1.5    | Classes of Natural Products  | 521        |
| 19.2      | Terpenoids: A Structurally Complex Group of Natural Products                 | 522        |
| 19.2.1    | Terpenoid Biosynthesis   | 522        |
| 19.2.2    | Biotransformation of Terpenoids  | 524        |
| 19.2.2.1  | Monoterpenoids   | 524        |
| 19.2.2.2  | Sesquiterpenoids   | 527        |
| 19.2.2.3  | Diterpenoids   | 528        |
| 19.2.2.4  | Triterpenoids  | 528        |
| 19.2.2.5  | Triterpenoids  | 530        |
| 19.3      | Other Classes of Natural Products  | 531        |
| 19.3.1    | Biosynthesis of Polyketides, Shikimates, and Alkaloids                       | 531        |
| 19.3.2    | Biotransformation of Important Polyketides, Shikimates, and Alkaloids in Man | 532        |
| 19.4      | Summary and Conclusions  | 536        |
|           | Acknowledgments  | 536        |
|           | References   | 536        |

|           |   |
|-----------|---|
| <b>20</b> | <b>Flavonoids</b> 543   |
|           | <i>Petr Hodek</i>   |
| 20.1      | Flavonoids–Plant Phytochemicals 543   |
| 20.1.1    | Classification of Flavonoids and Their Physicochemical Properties 543                                 |
| 20.1.2    | Biosynthesis of Flavonoids and Their Biological Function in Plants 545                                |
| 20.2      | Absorption and Metabolism of Flavonoids 545   |
| 20.2.1    | Flavonoid Bioavailability 545   |
| 20.2.2    | Metabolism of Flavonoids 547  |
| 20.2.2.1  | Intestinal Metabolism 548   |
| 20.2.2.2  | Decisive Role of Colonic Microflora 549   |
| 20.2.2.3  | Metabolism in Liver 549   |
| 20.2.2.4  | Flavonoid Excretion 550   |
| 20.2.3    | Overall Flavonoid Fate in Organisms 551   |
| 20.2.3.1  | Plasma Levels and Pharmacokinetics of Flavonoids 553  |
| 20.3      | Interactions of Flavonoids with Mammalian Proteins with Possible Implications for Drug Metabolism 554 |
| 20.3.1    | Plasma Proteins 554   |
| 20.3.2    | ATP-Binding Proteins 555  |
| 20.3.2.1  | MRPs 555  |
| 20.3.2.2  | Kinases 556   |
| 20.3.3    | Flavonoid-Binding Receptors 557   |
| 20.3.3.1  | Estrogen Receptor 557   |
| 20.3.3.2  | GABA-A Receptor 558   |
| 20.3.3.3  | Aryl Hydrocarbon Receptor 558   |
| 20.3.4    | Redox Enzyme Activity Modulation 559  |
| 20.3.4.1  | Xenobiotic-Metabolizing Enzymes 560   |
| 20.3.4.2  | LOXs, COXs, and XO <sub>s</sub> 561   |
| 20.4      | Dietary Flavonoids–Health Issues 562  |
| 20.4.1    | Antioxidant and Pro-Oxidant Properties 562  |
| 20.4.2    | Antiviral, Antibacterial, and Antifungal Agents 563   |
| 20.4.3    | Other Biological Activities of Flavonoids 564   |
| 20.4.4    | Flavonoids as Nutraceuticals 565  |
| 20.4.4.1  | Cytotoxic and Cytoprotective Effects 566  |
| 20.4.5    | Flavonoid Interference with the Metabolism of Endo- and Xenobiotics 567                               |
| 20.4.5.1  | Flavonoid Impact on the Metabolism of Endogenous Compounds 568  |
| 20.4.5.2  | Effect of Flavonoids on Carcinogen Activation 568   |
| 20.5      | Flavonoid–Drug Interactions 570   |
| 20.6      | Conclusion–Double-Edged Sword Properties of Flavonoids 573  |
|           | References 574  |
| <b>21</b> | <b>St John's Wort (<i>Hypericum perforatum</i> L.)</b> 583  |
|           | <i>Miroslav Dostalek and Anna-Katarina Stark</i>  |
| 21.1      | The Name Hypericum 583  |

|           |  |            |
|-----------|--|------------|
| 21.2      | Chemical Constituents of <i>Hypericum perforatum</i>   | 583        |
| 21.3      | Clinical Pharmacology of <i>H. perforatum</i>  | 587        |
| 21.3.1    | Antidepressive Activity  | 587        |
| 21.3.2    | Photodynamic Therapy and Cancer  | 587        |
| 21.3.3    | Antiviral Activity   | 587        |
| 21.3.4    | Other Pharmacological Activities   | 587        |
| 21.4      | Pharmacokinetics and Pharmacokinetic Interactions of <i>H. perforatum</i>                      | 588        |
| 21.4.1    | Phloroglucinols: Hyperforin  | 588        |
| 21.4.2    | Naphthodianthrones: Hypericin and Pseudohypericin  | 588        |
| 21.4.3    | Flavonoids: Rutin and Quercetin  | 589        |
| 21.5      | <i>In Vitro</i> Studies  | 591        |
| 21.6      | <i>In Vivo</i> Studies   | 592        |
|           | Acknowledgments  | 592        |
|           | References   | 603        |
| <b>22</b> | <b>Food Components and Supplements</b>   | <b>611</b> |
|           | <i>Alexandr Parlesak</i>   |            |
| 22.1      | Introduction   | 611        |
| 22.2      | Food Contaminants  | 612        |
| 22.2.1    | Polycyclic Aromatic Hydrocarbons and Polycyclic Aromatic Amines                                | 612        |
| 22.2.2    | Acrylamide   | 613        |
| 22.2.3    | Nitrosamines   | 614        |
| 22.2.4    | Fungal Toxins  | 614        |
| 22.3      | Vitamins   | 616        |
| 22.3.1    | Vitamin A, Retinoic Acid, and Carotenoids  | 616        |
| 22.3.2    | Vitamin D (Cholecalciferol and Ergocalciferol)   | 618        |
| 22.3.3    | Vitamin E (Tocopherol)   | 619        |
| 22.3.4    | Water-Soluble Vitamins (Thiamine and Riboflavin)   | 620        |
| 22.4      | Macronutrients   | 620        |
| 22.4.1    | Protein  | 620        |
| 22.4.2    | Fatty Acids  | 621        |
| 22.4.3    | Carbohydrates  | 622        |
| 22.5      | Secondary Plant Metabolites  | 622        |
| 22.5.1    | Grapefruit Juice, Naringenin, and Presystemic Drug Clearance by CYP3A4                         | 622        |
| 22.5.2    | Inhibition of Metabolic Activation of Drugs by CYP3A4  | 623        |
| 22.5.3    | Secondary Plant Metabolites, CYP Modulation, and Intestinal Inflammation                       | 623        |
| 22.5.4    | Parallel Consumption of Drugs and Inhibitors of Intestinal Drug Metabolism—Threats and Chances | 624        |
| 22.5.5    | Glucosinolates and Allylsulfides   | 625        |
| 22.5.6    | Caffeine   | 626        |
| 22.5.7    | Cholesterol  | 626        |

- 22.6 Probiotics and Prebiotics in the Modulation of Drug Metabolism 628  
References 629

#### **Part Four Metabolism of Unnatural Xenobiotics 637**

- 23 Environmental Pollutants 639**  
*Marie Stiborova*
- 23.1 Introduction—An Overview 639
- 23.1.1 Types of Environmental Pollutants 640
- 23.2 Overview of Environmental Pollutants 641
- 23.2.1 Air Pollutants 641
- 23.2.2 Water Pollutants 642
- 23.2.3 Soil Pollutants 642
- 23.3 Toxic and Hazardous Environmental Pollutants Interacting with Drug Metabolism 642
- 23.3.1 Acetaldehyde 642
- 23.3.2 Acetonitrile 643
- 23.3.3 2-Acetylaminofluorene 643
- 23.3.4 Acrolein 643
- 23.3.5 Acrylamide 643
- 23.3.6 4-Aminobiphenyl 644
- 23.3.7 *o*-Anisidine 644
- 23.3.8 Acrylonitrile (2-Propenenitrile) 644
- 23.3.9 Arsenic and Arsenic Compounds 645
- 23.3.10 Asbestos 645
- 23.3.11 Antimony Compounds 646
- 23.3.12 Benzene 646
- 23.3.13 Benzidine 647
- 23.3.14 1,3-Butadiene (Vinyl Ethylene) 647
- 23.3.15 Cadmium Compounds 647
- 23.3.16 Carbon Tetrachloride 648
- 23.3.17 Carbon Monoxide 648
- 23.3.18 Chloroform 649
- 23.3.19 Chloroprene 649
- 23.3.20 Cr (VI) Compounds 650
- 23.3.21 Cobalt and Cobalt Compounds 650
- 23.3.22 1,4-Dichlorobenzene 651
- 23.3.23 1,3-Dichloropropene 651
- 23.3.24 Dichloromethane 651
- 23.3.25 1,1-Dimethylhydrazine 652
- 23.3.26 Ethylene Oxide 652
- 23.3.27 Formaldehyde 652
- 23.3.28 Heptachlor 653
- 23.3.29 Hexachlorobenzene 653



|           |   |            |
|-----------|---|------------|
| 23.3.30   | Hydrazine   | 654        |
| 23.3.31   | Lead and Lead Compounds   | 654        |
| 23.3.32   | Lindane (All Isomers)   | 655        |
| 23.3.33   | Mercury Compounds   | 655        |
| 23.3.34   | NO <sub>x</sub>   | 656        |
| 23.3.35   | Ozone   | 656        |
| 23.3.36   | Parathion   | 656        |
| 23.3.37   | Phthalates  | 657        |
| 23.3.38   | Polycyclic Aromatic Hydrocarbons                                      | 657        |
| 23.3.39   | Polychlorinated Biphenyls   | 658        |
| 23.3.40   | Polychlorinated Dioxins and Furans                                    | 658        |
| 23.3.41   | Styrene and Styrene Oxide   | 659        |
| 23.3.42   | Sulfur Dioxide  | 659        |
| 23.3.43   | Tetrachloroethylene (Tetrachloroethene, Perchloroethylene)            | 660        |
| 23.3.44   | Vinyl Chloride  | 660        |
| 23.4      | Summary   | 660        |
|           | References  | 661        |
| <b>24</b> | <b>Environmental Estrogens</b>  | <b>671</b> |
|           | <i>Miroslav Machala and Jan Vondráček</i>                             |            |
| 24.1      | Introduction  | 671        |
| 24.2      | Estrogen Receptor Signaling Pathways                                  | 672        |
| 24.3      | Agonistic/Antagonistic Effects of Xenobiotics on ERs                  | 673        |
| 24.4      | Effects of EDCs on Biosynthesis and Metabolism of Estrogens           | 676        |
| 24.5      | Case of Polychlorinated Biphenyls                                     | 677        |
| 24.6      | Conclusions   | 678        |
|           | References  | 679        |
| <b>25</b> | <b>Biotransformation of Insecticides</b>                              | <b>685</b> |
|           | <i>Corie A. Ellison, Alice L. Crane, and James R. Olson</i>           |            |
| 25.1      | Introduction to Insecticides  | 685        |
| 25.1.1    | Organophosphate Insecticides  | 685        |
| 25.1.2    | Carbamate Insecticides  | 687        |
| 25.1.3    | Pyrethroid Insecticides   | 687        |
| 25.1.4    | Organochlorine Insecticides   | 688        |
| 25.2      | Metabolism of Insecticides  | 688        |
| 25.2.1    | Hepatic Phase I Enzymes Involved in Biotransformation of Insecticides | 688        |
| 25.2.1.1  | Cytochrome P450s  | 688        |
| 25.2.1.2  | Flavin-Containing Monooxygenases                                      | 691        |
| 25.2.1.3  | Others  | 692        |
| 25.2.2    | Phase II Metabolism of Insecticides                                   | 692        |
| 25.3      | Extrahepatic Metabolism of Insecticides                               | 693        |
| 25.4      | Factors Affecting Metabolism  | 694        |
| 25.4.1    | Route of Exposure   | 694        |

|        |   |     |
|--------|---|-----|
| 25.4.2 | Interaction of Xenobiotics                    | 695 |
| 25.4.3 | Impact of Age, Gender, Species, and Pathology | 695 |
| 25.4.4 | Interindividual Genetic Variability           | 696 |
| 25.5   | Conclusions                                   | 697 |
|        | Note  | 697 |
|        | References                                    | 697 |

|              |     |
|--------------|-----|
| <b>Index</b> | 703 |
|--------------|-----|