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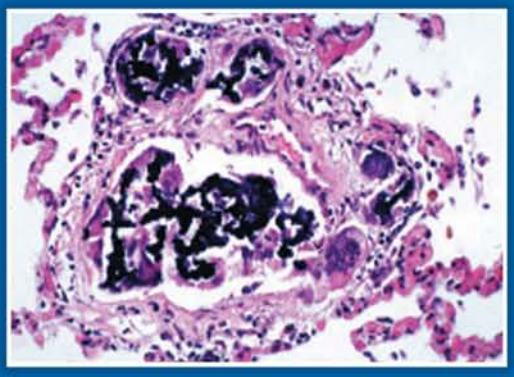

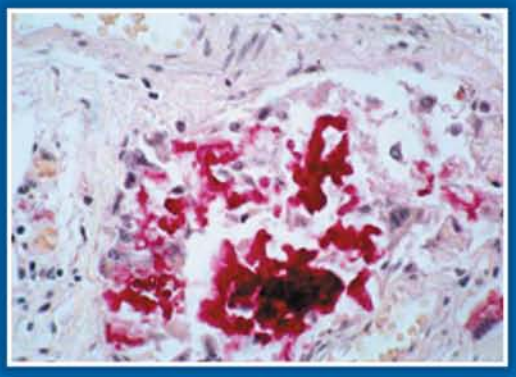

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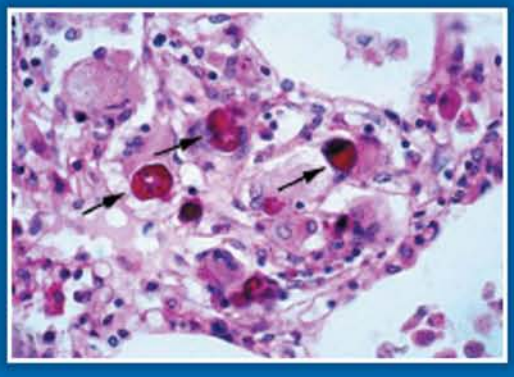

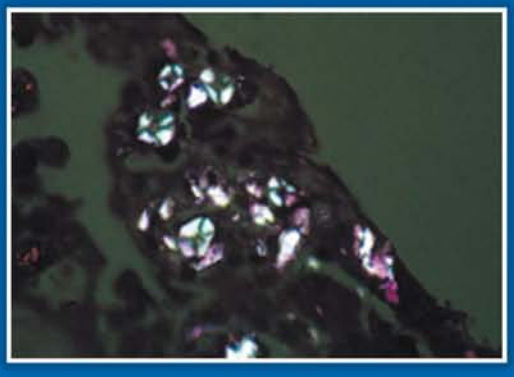

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Dedication

For my wife Donna and her support, which was often needed, and for Dr. Sheldon Kabaker, who introduced the two of us and became my closest friend. For Hardwin and Roger, who try very hard. And for Henry Urich, whose brilliance inspired me, and Margaret Billingham, whose brilliance, tenacity, and hard work were more than just inspirational. For Miriam and Sam, who never got to see any of the books, and especially Richard and Gail Ullman of Princeton, New Jersey—good people and good friends.

Contents

1 Cocaine 1

References 2
1.1 Incidence of Abuse 3
References 6
1.2 Epidemiology 6
References 8
1.3 History 9
References 18
1.4 Current Affairs 19
1.4.1 Cocaine Availability 21
1.4.2 Cultivation and Crop Yields 22
1.4.3 Paste Production 24
1.4.4 Quality 28
References 29
1.5 Routes of Ingestion 30
1.5.1 Overview 30
1.5.2 Coca Leaf Chewing 30
1.5.3 Snorting (Insufflation) 31
1.5.4 Surgical Application 32
1.5.5 Intravenous Use 33
1.5.6 Genital Application 34
1.5.7 Dermal Absorption 34
1.5.8 Inhalation 35
1.5.9 Gastrointestinal Absorption 37
1.5.10 Special Maternal/Fetal Considerations 41
References 43
1.6 Metabolism of Cocaine and Its Metabolites 47
1.6.1 Cocaine 47
1.6.2 Benzoylecgonine (BZE) and Ecgonine Methyl Ester 49
1.6.3 Cocaethylene 52
1.6.4 Anhydroecgonine Methyl Ester (Methylecgonidine) 54
1.6.5 Norcocaine 54
References 55
1.7 Fetal Metabolism 58
References 59
1.8 Problems of Cocaine Test Interpretation 60
1.8.1 Introduction 60
1.8.2 Tolerance 61

1.8.3 Postmortem Redistribution 62
1.8.4 Cocaine-Related Deaths 62
1.8.5 Estimating Time of Ingestion 63
1.8.6 Low Cocaine Concentrations 64
1.8.7 Cocaine and Prescription Drug Interactions 65
1.8.8 Adulterants 66
References 67
1.9 Cocaine Tissue Disposition 69
1.9.1 Human Postmortem Measurement 70
1.9.2 Brain 70
1.9.3 Hair 71
1.9.4 Heart 72
1.9.5 Kidneys 72
1.9.6 Liver 73
1.9.7 Skin and Nails 73
1.9.8 Biofluids 76
1.9.8.1 Amniotic Fluid 76
1.9.8.2 Breast Milk 76
1.9.8.3 Fetal Gastric Aspirates 77
1.9.8.4 Oral Fluid (Saliva) 77
1.9.8.5 Spinal Fluid 78
1.9.8.6 Urine 78
1.9.8.7 Vitreous Humor 80
1.9.8.8 Sweat 82
1.9.8.9 Semen 82
References 82
1.10 Electrophysiology of Sudden Death in Cocaine Abusers 87
1.10.1 Myocardial Remodeling 87
1.10.2 Hypertrophy 89
1.10.3 QT Dispersion 93
1.10.4 Ion Channel Remodeling and Interactions 93
1.10.5 The Theory of "Multiple Hits" 94
1.10.6 The Role of Catecholamines 96
1.10.7 Mechanisms of Catecholamine Toxicity 98
1.10.8 Histopathology of Catecholamine Toxicity 99
1.10.9 Contraction Band Necrosis and Sudden Death 104
1.10.10 Hereditary Channelopathies 104
References 105
1.11 External Markers of Cocaine Abuse 109
1.11.1 Perforated Nasal Septum 109
1.11.2 "Parrot Beak" Nails 110
1.11.3 "Crack Thumb" 111
1.11.4 "Crack Lips" 111
1.11.5 "Track" Marks 111
1.11.6 "Crack" Keratitis 113
1.11.7 Dental Erosions and Oral Lesions 114
1.11.8 "Crack Hands" 114

1.11.9 Evidence of Terminal Seizures 115
1.11.10 Marks and Mutilation 115
References 115
1.12 Skin Toxicity 117
References 118
1.13 Cardiovascular System, General Overview 119
1.13.1 Myocardial Infarction 119
1.13.2 Microvascular Disease 122
1.13.3 Atheromatous Coronary Artery Disease 123
1.13.4 Coronary Artery Spasm 124
1.13.5 Decreased Flow Reserve 125
1.13.6 Centrally Mediated Vascular Disease 126
1.13.7 HIV-Related Myocardial Disease 127
1.13.8 Valvular Heart Disease 128
1.13.9 Aorta and Peripheral Vessels 129
1.13.10 Eosinophilic Myocarditis 130
1.13.11 Coronary Artery Dissection 132
1.13.12 Nonatheromatous Coronary Artery Disease 132
References 132
1.14 Excited Delirium and the Neuroleptic Malignant Syndrome 137
1.14.1 History and Overview of Excited Delirium 137
1.14.2 Excited Delirium and the Redefinition of "Positional Asphyxia" 139
1.14.3 The Exercise Physiology of "Positional Restraint" and "Restraint Asphyxia" 140
1.14.4 The Neurochemistry of Excited Delirium 142
1.14.5 Autopsy Findings 145
1.14.6 The Toxicology of Excited Delirium 145
1.14.7 Cause of Death Determination 146
References 148
1.15 Cocaine-Associated Pulmonary Disease 150
1.15.1 Barotrauma 151
1.15.2 Parenchymal Disease 153
1.15.3 Vascular Adaptations 156
References 157
1.16 Neurological Disorders, Introduction 162
1.16.1 Cocaine Neurotoxicity 163
1.16.2 Psychiatric Syndromes 164
1.16.3 Ischemic Stroke 165
1.16.4 Cerebral Vasculitis 167
1.16.5 Subarachnoid and Intraventricular Hemorrhage 169
1.16.6 Seizures 171
1.16.7 Movement Disorders 173
1.16.8 Blood–Brain Barrier Alterations 173
References 174
1.17 Renal Disease 179
References 183

1.18 Hematologic Abnormalities 185
1.18.1 Thrombocytopenic Purpura 185
1.18.2 Thrombosis 185
1.18.3 Erythrocytosis 186
1.18.4 Methemoglobinemia 186
References 187
1.19 Hormonal Alterations 188
1.19.1 Overview 188
1.19.2 Prolactin 188
1.19.3 Sex Hormones 189
References 190
1.20 Immune System Abnormalities 191
1.20.1 Overview 191
1.20.2 Immune Responses 192
References 192
1.21 Gastrointestinal Disorders 193
1.21.1 Introduction 193
1.21.2 "Body Packing" 193
1.21.3 Ischemic Bowel and Stomach Injuries 193
1.21.4 Hepatic Disease 195
References 198
1.22 Pregnancy Interactions 200
References 202
1.23 When Is Cocaine the Cause of Death? 204
References 207

2 Natural Stimulants 209

2.1 Absinthe 210
2.1.1 Incidence and Epidemiology 210
2.1.2 History 211
2.1.3 Manufacture 214
2.1.4 Routes of Administration 214
2.1.5 General Pharmacology 215
2.1.6 Tissue Concentrations 216
2.1.7 Toxicity by Organ System 216
References 217
2.2 Caffeine 218
2.2.1 Incidence 218
2.2.2 Epidemiology 219
2.2.3 History 221
2.2.4 Chemical Constants 222
2.2.5 Sources 223
2.2.6 Routes of Administration 224
2.2.7 Metabolism 224
2.2.8 Mechanisms of Action 225
2.2.9 Pharmacokinetics 226

2.2.10 Tissue Concentrations 227
2.2.11 Toxicity by Organ System 229
2.2.11.1 Neurologic 229
2.2.11.2 Cardiovascular 230
2.2.11.3 Hematologic 232
2.2.11.4 Ergogenic Effects 232
2.2.11.5 Maternal/Fetal Effects 233
2.2.12 Autopsy Studies 233
References 234
2.3 Ephedrine 239
2.3.1 General 240
2.3.2 Epidemiology 241
2.3.3 History 241
2.3.4 Sources 242
2.3.5 Routes of Administration 242
2.3.6 Metabolism and Pharmacology 243
2.3.7 Toxicity by Organ System 245
2.3.7.1 Neurological 246
2.3.7.2 Renal 246
2.3.7.3 Cardiovascular 246
2.3.7.4 Gastrointestinal 248
2.3.7.5 Dermatological 248
2.3.8 Drug Testing 248
2.3.9 Postmortem Tissue Measurements and Autopsy Findings 248
References 249
2.4 Khat 253
2.4.1 Incidence and Epidemiology 254
2.4.2 Cultivation and Manufacture 254
2.4.3 History 255
2.4.4 General 256
2.4.5 Clinical Studies 257
2.4.6 Detection 259
References 259

3 Synthetic Stimulants 261

3.1 Amphetamines 261
3.1.1 Incidence and Availability 264
3.1.2 Epidemiology 265
3.1.3 History 267
3.1.4 Illicit Manufacture 271
3.1.5 Routes of Administration 273
3.1.6 Metabolism 274
3.1.7 Tissue Disposition 276
3.1.7.1 Interpretation of Infant Postmortem Blood Concentrations 277
3.1.8 Interpretation of Adult Postmortem Blood Concentrations 279
3.1.8.1 Autopsy Series 279

3.1.9 Measurements in the Living 281
3.1.10 Impairment 281
3.1.11 Toxicity by Organ System 282
3.1.11.1 Cardiovascular 282
3.1.11.2 Pulmonary 286
3.1.11.3 Central Nervous System 288
3.1.11.4 Genitourinary Tract 290
3.1.11.5 Oral 291
3.1.11.6 Gastrointestinal Tract 292
3.1.12 Attention Deficit/Hyperactivity Disorder 292
References 294
3.2 Methylphenidate (Ritalin®) 302
3.2.1 Incidence and Epidemiology 303
3.2.2 Names and Drug Constants 304
3.2.3 Routes of Administration 304
3.2.4 Mode of Action 304
3.2.5 Pharmacokinetics 305
3.2.6 Methylphenidate Blood Concentrations 305
3.2.7 Breast Milk Concentrations 305
3.2.8 Methylphenidate Tissue Disposition 306
3.2.9 Urine Concentrations 306
3.2.10 Postmortem Measurements 306
3.2.11 Toxicity by Organ System 306
3.2.11.1 Overview 306
3.2.11.2 Integument 306
3.2.11.3 Cardiovascular 307
3.2.11.4 Pulmonary 307
3.2.11.5 Gastrointestinal Tract 307
3.2.11.6 Nervous System 308
References 308

4 Hallucinogens 313

4.1 Introduction 313
4.2 Incidence 313
References 314
4.3 Tryptamine Derivatives 315
4.3.1 Mescaline 315
4.3.1.1 History 315
4.3.1.2 Production 316
4.3.1.3 Mechanism of Action 317
4.3.1.4 Metabolism and Tissue Levels 317
4.3.1.5 Clinical Syndromes 318
4.3.1.6 Pathologic Findings 318
4.3.2 Substituted Amphetamines 318
4.3.2.1 TMA 318
4.3.2.2 DOM 319

4.3.2.3 PMA ... 320
4.3.2.4 DOB ... 321
4.3.2.5 4-Bromo-2,5-Dimethoxyphenethylamine ... 323
4.3.2.6 Nutmeg ... 323
4.3.2.7 4-Chloro-2-5-Dimethoxyamphetamine (DOC) ... 325
4.3.2.8 2,5-Dimethoxy-4-Iodophenethylamine ... 325
4.3.3 Piperazines ... 325
References ... 327
4.4 Hallucinogenic Amphetamines ... 329
4.4.1 MDMA ... 329
4.4.1.1 History ... 330
4.4.1.2 Incidence and Epidemiology ... 331
4.4.1.3 Illicit Production ... 332
4.4.1.4 Metabolism ... 333
4.4.1.5 Clinical Syndromes ... 334
4.4.1.6 Blood and Tissue Concentrations ... 336
4.4.1.7 Neurotoxicity ... 337
4.4.1.8 Cardiovascular Toxicity ... 338
4.4.1.9 Hepatotoxicity ... 340
4.4.2 MDA (3,4-Methylenedioxyamphetamine) ... 340
4.4.2.1 History ... 341
4.4.2.2 Clinical ... 341
4.4.3 MDEA (Eve) ... 343
4.4.3.1 Introduction ... 343
4.4.3.2 Physiologic Effects in Humans ... 343
4.4.3.3 Illicit Synthesis ... 344
4.4.4 4-MAX (U4Euh, EU4EA, U4EA), Aminorex ... 344
4.4.5 Other MDMA Homologs ... 345
4.4.6 ***N***-Methylcathinone ... 345
References ... 346
4.5 Phenylalkylamines ... 351
4.5.1 Simple Tryptamines ... 351
4.5.2 DMT ... 352
4.5.3 Bufotenine ... 354
4.5.4 5-MeO-DMT (5-Methoxy-*N*,*N*-Dimethyltryptamine) ... 355
References ... 356
4.6 Psilocybin ... 357
4.6.1 History ... 357
4.6.2 Physiologic and Psychological Effects ... 358
4.6.3 Pharmaco- and Toxicokinetics ... 359
References ... 359
4.7 α-Ethyltryptamine ... 360
References ... 360
4.8 Ergolines ... 361
4.8.1 Lysergic Acid Diethylamide ... 361
4.8.1.1 Introduction ... 361
4.8.1.2 History ... 362

4.8.1.3 Incidence and Epidemiology 363
4.8.1.4 Illicit Production 363
4.8.1.5 Metabolism 364
4.8.1.6 Blood and Tissue Concentrations 364
4.8.1.7 Testing 365
4.8.1.8 Clinical Syndromes 365
References 365

5 Opiates and Opioids 367

5.1 Incidence 367
5.2 Epidemiology 368
5.3 Classifying Narcotic and Non-Narcotic Agents 368
5.3.1 Opiate Receptors 368
5.3.2 Opiates and G Coupled Proteins 370
References 371
5.4 History of Opiate Abuse 372
5.4.1 Origins in Antiquity 372
5.4.2 Introduction to Europe and Asia 372
5.4.3 Invention of the Hypodermic Syringe 374
5.4.4 Synthesis of Heroin 376
5.4.5 The First Pathology Studies 378
References 378
5.5 Cultivation and Manufacture 380
5.5.1 Botany 380
5.5.2 Opium Production 382
5.5.3 Heroin Manufacture 383
5.5.4 Sample Analysis 384
References 386
5.6 Morphine and Heroin 387
5.6.1 General Considerations 389
5.6.2 Morphine Metabolism 392
5.6.3 Morphine Metabolites 395
5.6.3.1 Morphine-3-Glucuronide 395
5.6.3.2 Morphine-6-Glucuronide 396
5.6.3.3 Normorphine 397
References 398
5.6.4 Absorption and Routes of Administration 400
5.6.4.1 Intravenous Injection 400
5.6.4.2 Subcutaneous Injection 401
5.6.4.3 Oral 401
5.6.4.4 Rectal 403
5.6.4.5 Intranasal 403
5.6.4.6 Inhalation 404
5.6.4.7 Skin 406
5.6.4.8 Maternal/Fetal Considerations 406
References 407

5.7 Tissue Disposition 409
5.7.1 Blood 410
5.7.2 Brain 412
5.7.3 Liver 414
5.7.4 Lymph Nodes 415
5.7.5 Other Biofluids 415
5.7.6 Urine 416
5.7.7 Postmortem Tissue Measurements 416
5.7.8 Excretion and Detectability 418
References 419
5.8 Interpretation of Opiate Blood and Tissue Concentrations 422
5.8.1 Introduction 422
5.8.2 Urine Testing 422
5.8.3 Blood Testing 423
5.8.4 Determining the Cause of Death 424
5.8.4.1 Value of Scene Investigation 424
5.8.4.2 Toxicology 426
5.8.5 Provenance 426
5.8.6 Postmortem Chemistry 427
5.8.6.1 Redistribution and Diffusion 427
5.8.6.2 Apparent Steady State Volume of Distribution (V_{ss}) 427
5.8.6.3 Other Confounding Variables 428
5.8.6.4 What Is a Complete Autopsy? 430
References 430
5.9 Individual Opiates 433
5.9.1 Buprenorphine 433
5.9.1.1 General Considerations 435
5.9.1.2 Pharmacology 436
5.9.1.3 Detection 437
5.9.1.4 Drug Concentrations 437
5.9.1.5 Maternal/Fetal Considerations 438
5.9.1.6 Postmortem Considerations 438
References 438
5.9.2 Codeine 439
5.9.2.1 General Considerations 441
5.9.2.2 Routes of Administration 442
5.9.2.3 Codeine Tissue Disposition 443
References 443
5.9.3 Fentanyl 444
5.9.3.1 General 446
5.9.3.2 Pharmacology and Pharmacokinetics 448
5.9.3.3 Routes of Administration 449
5.9.3.4 Metabolism and Excretion 450
5.9.3.5 Tissue Concentrations 451
5.9.3.6 Maternal/Fetal Considerations 452
5.9.3.7 Autopsy Findings 452
References 453

5.9.4 Hydrocodone 456
5.9.4.1 Clinical Considerations 456
5.9.4.2 Postmortem Data 456
5.9.4.3 Maternal/Fetal Considerations 457
References 457
5.9.5 Hydromorphone 457
5.9.5.1 General Considerations 458
5.9.5.2 Clinical Considerations 458
5.9.5.3 Postmortem Data 458
References 459
5.9.6 Kratom 459
5.9.6.1 General Considerations 459
5.9.6.2 Active Agents 459
5.9.6.3 Clinical Information 459
References 460
5.9.7 Methadone 460
5.9.7.1 General 462
5.9.7.2 Pharmacology 463
5.9.7.3 Clinical Considerations 464
5.9.7.4 Metabolism and Pharmacokinetics 465
5.9.7.5 Maternal/Fetal Considerations 466
5.9.7.6 Hospice and Pain Patients 466
5.9.7.7 Routes of Administration 467
5.9.7.8 Compliance Monitoring 467
5.9.7.9 Autopsy Findings 467
5.9.7.10 Postmortem Blood Concentrations 468
References 469
5.9.8 Meperidine 472
5.9.8.1 General Considerations 474
5.9.8.2 Metabolism 474
5.9.8.3 Toxicity 476
5.9.8.4 Drug Interactions 477
5.9.8.5 Patient-Controlled Anesthesia Devices 477
5.9.8.6 Postmortem Issues 478
References 479
5.9.9 Oxycodone 481
5.9.9.1 History and Extent of Use 482
5.9.9.2 Pharmacology 483
5.9.9.3 Drug Interactions 483
5.9.9.4 Maternal/Fetal Considerations 484
5.9.9.5 Postmortem Issues 485
References 486
5.9.10 Oxymorphone 487
5.9.10.1 Pharmacology 488
5.9.10.2 Pharmacokinetics 488
References 488

5.9.11 Propoxyphene 489
5.9.11.1 General Considerations 489
5.9.11.2 Metabolism and Pharmacokinetics 490
5.9.11.3 Tissue Distribution 491
5.9.11.4 Excretion and Detectability 492
5.9.11.5 Maternal/Fetal Considerations 492
5.9.11.6 Histologic Abnormalities and Autopsy Findings 493
References 493
5.9.12 Tramadol 495
5.9.12.1 General Considerations 495
5.9.12.2 Metabolism 496
5.9.12.3 Clinical Issues 496
5.9.12.4 Postmortem Considerations 496
References 497
5.10 Medical Consequences of Opiate Abuse 497
5.10.1 Dermatologic Sequelae 498
5.10.1.1 Fresh Needle Punctures 498
5.10.1.2 Atrophic Scarring 499
5.10.1.3 Abscesses and Ulceration 500
5.10.1.4 "Track" Marks 501
5.10.1.5 Tattoos 502
5.10.1.6 "Puffy Hands" Syndrome 502
5.10.1.7 Necrotizing Fasciitis 502
5.10.1.8 Histamine-Related Urticaria 503
5.10.1.9 Acute Generalized Exanthematous Pustulosis 504
5.10.1.10 Fungal Lesions 504
5.10.1.11 Miscellaneous Cutaneous Abnormalities 506
References 506
5.10.2 Cardiovascular Disorders 509
5.10.2.1 Introduction 509
5.10.2.2 HIV-Associated Cardiovascular Pathology 511
5.10.2.3 Endocarditis 513
5.10.2.4 Myocardial Fibrosis 516
5.10.2.5 Myocardial Hypertrophy 516
5.10.2.6 Coronary Artery Disease 517
References 518
5.10.3 Pulmonary Complications 521
5.10.3.1 Pulmonary Edema 521
5.10.3.2 Needle and Mercury Emboli 523
5.10.3.3 Foreign Body Granulomas 523
5.10.3.4 Injuries of the Great Vessels 526
5.10.3.5 Aspiration Pneumonia 527
5.10.3.6 Community-Acquired Pneumonia 527
5.10.3.7 Fungal Pneumonia 528
5.10.3.8 Tuberculosis and Melioidosis 528
5.10.3.9 Septic Pulmonary Emboli 529

5.10.3.10 Emphysema 529
5.10.3.11 Cotton Fever 529
References 530
5.10.4 Gastrointestinal Disorders 533
5.10.4.1 Introduction 533
5.10.4.2 Bowel Disorders 533
5.10.4.3 Liver Disease 534
5.10.4.4 Porta Hepatis Adenopathy 535
5.10.4.5 Inflammatory Disease 535
5.10.4.6 Hepatitis 537
5.10.4.7 Hepatitis A Virus 537
5.10.4.8 Hepatitis B Virus 537
5.10.4.9 Hepatitis C Virus 538
5.10.4.10 Steatosis 539
5.10.4.11 HIV Infection 540
5.10.4.12 Amyloidosis 541
References 541
5.10.5 Renal Disease 544
5.10.5.1 Introduction 544
5.10.5.2 Focal Segmental Glomerulosclerosis 544
5.10.5.3 Necrotizing Angiitis 546
5.10.5.4 Acute Renal Failure and Nontraumatic Rhabdomyolysis 546
5.10.5.5 Secondary Amyloidosis 548
References 548
5.10.6 Neuropathology 549
5.10.6.1 Introduction 549
5.10.6.2 Hypoxic Encephalopathy 551
5.10.6.3 Neurologic Complications of Endocarditis 552
5.10.6.4 Complications of HIV Infection 553
5.10.6.5 Primary Phycomycosis 554
5.10.6.6 Spongiform Leukoencephalopathy 554
5.10.6.7 Transverse Myelitis 557
5.10.6.8 Peripheral Neuropathy 557
5.10.6.9 Rhabdomyolysis 558
5.10.6.10 Stroke 559
5.10.6.11 Parkinsonism 560
5.10.6.12 Seizures 561
References 562
5.10.7 Hormonal and Immune Alterations 566
References 569
5.10.8 Bone and Soft Tissue Disorders 570
5.10.8.1 Introduction 570
5.10.8.2 Bone and Joint Infections 571
5.10.8.3 Soft Tissue Infections 572
5.10.8.4 Fibrous Myopathy 572
References 572

6 Dissociative Anesthetics 575

6.1 Introduction 575
References 576
6.2 Phencyclidine (PCP) 576
6.2.1 Incidence 577
6.2.2 History 577
6.2.3 Clandestine Laboratories 578
6.2.4 Routes of Administration 578
6.2.5 Metabolism 579
6.2.6 Tissue Concentrations 580
6.2.7 Interpreting Blood and Tissue Concentrations 581
6.2.8 Toxicity by Organ System 582
6.2.8.1 Neurologic Disorders 582
6.2.8.2 Cardiovascular Disease 583
6.2.8.3 Renal Disorders 583
References 583
6.3 Ketamine 585
6.3.1 Incidence 586
6.3.2 Epidemiology 586
6.3.3 History 586
6.3.4 Clandestine Laboratories 587
6.3.5 Routes of Administration 587
6.3.6 Metabolism 587
6.3.7 Pharmacokinetics 588
6.3.8 Tissue Concentrations 588
6.3.9 Interpreting Blood Concentrations 588
6.3.10 Toxicity by Organ System 589
6.3.10.1 Neurological Disorders 589
6.3.10.2 Cardiovascular Disease 590
6.3.10.3 Hematologic Disorders 590
References 590
6.4 γ-Hydroxybutyrate (GHB) 591
6.4.1 Incidence 592
6.4.2 Epidemiology 592
6.4.3 History 593
6.4.4 Clandestine Synthesis 593
6.4.5 Routes of Administration 594
6.4.6 Metabolism 594
6.4.7 Pharmacokinetics 595
6.4.8 Tissue Concentrations 595
6.4.9 Interpreting Tissue Concentrations 596
6.4.10 Clinical Considerations 597
6.4.11 Organ Toxicity 597
References 597

6.5 Salvia Divinorum 599
6.5.1 History 599
6.5.2 Epidemiology 601
6.5.3 Pharmacology 601
6.5.4 Pharmacokinetics 601
References 602
6.6 Dextromethorphan (DXM) 602
6.6.1 General Considerations 603
6.6.2 Incidence, Epidemiology, and History 604
6.6.3 Synthesis 604
6.6.4 Routes of Administration 605
6.6.5 Pharmacology 605
6.6.6 Pharmacokinetics 605
6.6.7 Tissue Levels 605
6.6.8 Toxicology by Organ System 606
References 606

7 Anabolic Steroids 609

7.1 Testosterone 609
7.1.1 Prevalence and Epidemiology 610
7.1.2 History 611
7.1.3 Steroid Abuse 613
7.1.4 Pharmacology 614
7.1.4.1 Synthesis and Metabolism 614
7.1.4.2 The Andropause 615
7.1.4.3 Legitimate Clinical Indications 616
7.1.5 Steroid-Related Disorders 617
7.1.5.1 Liver Disease 617
7.1.5.2 Cardiovascular Disease 619
7.1.5.3 Neurological Disorders 621
7.1.5.4 Musculoskeletal Disease 622
7.1.6 Detecting Steroid Abuse 623
7.1.7 Postmortem Considerations 626
References 627

8 Solvents 635

8.1 Introduction 635
8.2 Incidence 636
8.3 Epidemiology 636
8.4 General Considerations 636
8.5 Absorption and Tissue Disposition 638
8.6 Clinical Syndromes 639
8.6.1 Neurologic Disorders 639
8.6.2 Renal Disease 642
8.6.3 Gastrointestinal Disease 642
8.6.4 Cardiovascular Disease 642

8.6.5 Maternal/Fetal Considerations 643
8.6.6 Clinical Toxicology 643
8.6.7 Postmortem Considerations 644
8.6.7.1 Storage and Sample Handling 644
References 645

9 Marijuana 649

9.1 Botany 650
9.2 Epidemiology 650
9.3 Origins 650
9.4 Pharmacology 653
9.4.1 Alternative Testing Matrices 653
9.4.2 Hair and Saliva Testing for Marijuana 654
9.5 Absorption 654
9.6 Detection Times 655
9.7 Distribution 656
9.8 Blood Levels 656
9.9 Metabolism and Excretion 657
9.10 Cardiovascular Effects 658
9.11 Pulmonary Complications 659
9.12 Postmortem Measurements 659
References 661

Appendix 1: Conversion Formulas 665

Appendix 2: Blood Alcohol Concentrations 667

Appendix 3: Volume of Distribution Calculations 669

Appendix 4: Normal Heart Weights 671

Index 675

Preface to the Fourth Edition

The last edition of this book is now more than six years old. Much has been discovered. Sadly, most of the advances that have occurred have come from the laboratories of molecular bilogists and geneticists, not forensic pathologists. Forensic toxicologists have fared somewhat better, but they, at least, have the support of the reagent makers. Forensic pathology remains grossly under supported with most research self-funded, done by pathologists on their own time. Which is to say that things have not changed all that much since the first edition of this book, written 15 years ago. Yet we continue to make progress, largely by serendipity. Two examples come immediately to mind.

Twenty years ago it was clear that stimulant abuse caused myocardial remodeling and that most deaths were a consequence of persistent neurochemical and anatomic alterations within the heart and brain. At the time, we were all sure that these changes were a consequence of chronic catecholamine toxicity, but we were mistaken. The real explanation is activation of the Calmodulin Kinase II gene; increased levels of this enzyme produce myocardial hypertrophy. Similarly, we presumed that sudden death in methadone users was a consequence of respiratory depression. But the real explanation is vastly more complicated, having to do with genetic polymorphism, the inability of some individuals to properly metabolize the I-form of methadone, and the I-form's ability to bind the hERG channel.

None of these insights would have occurred were it not for explosive advances in our ability to detect genomic DNA variation. The advent of the diagnostic DNA microarray has done more to advance the field of drug abuse research than any single event in the last quarter century. Yet, all these advances seem to be occurring in a vacuum with no one paying any attention. Many forensic pathologists still believe that postmortem drug measurements bear some sort of predictable relationship to drug concentrations in the immediate antemortem period. Toxicologists and pathologists still rely upon "therapeutic drug ranges," as if drug concentrations measured in the dead bear any relationship to concentrations measured in the living. A void continues to separate hard science from forensic science. Until this void is breached, forensic pathology will continue to be the least evidence-based branch of medicine, with guilt or innocence determined by the luck of the draw.

I do not know if there will ever be a fifth edition of this book, but I do know this much: anyone who chooses to read the 5th edition it is going to need to know much more about DNA technology and molecular biology than they do now.

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Berkeley, California
August 1, 2008

About the Author

Dr. Steven B. Karch received his undergraduate degree from Brown University in Providence, Rhode Island, and attended graduate school in anatomy and cell biology at Stanford University. He received his MD degree from Tulane University School of Medicine in New Orleans, and did postgraduate training in neuropathology at the Royal London Hospital and in cardiac pathology at Stanford University, Palo Alto. Dr. Karch is a fellow of the Faculty of Forensic and Legal Medicine of the Royal College of Physicians (London). He is a retired Assistant Medical Examiner in San Francisco.

Dr. Karch is the author of nearly 100 papers and book chapters, most having to do with the effects of drug abuse on the heart. He has published ten books (*Karch's Pathology of Drug Abuse*, 1st, 2nd, 3rd, and 4th editions, *Drug Abuse Handbook,* 1st and 2nd editions, *A Brief History of Cocaine,* 1st and 2nd editions, *The Consumer's Guide to Herbal Medicine,* and *A History of Cocaine: The Mystery of Coca Java and the Kew Plant*, an account of the Southeast Asian cocaine industry in the early 1900s. He is currently at work on a novel about Napoleon and his doctors. He was Forensic Science Editor for Humana Press, and continues as associate editor for the *Journal of Clinical Forensic Medicine (London)*, editor of *Forensic Drug Abuse Advisor*, and serves on the editorial boards of *Clarke's Analysis of Drugs and Poisons* and the *Journal of Forensic Science*.

Dr. Karch is a fellow of the American Academy of Forensic Sciences, the Society of Forensic Toxicologists (SOFT), the National Association of Medical Examiners (NAME), the Royal Society of Medicine in London, The Forensic Science Society in the UK, and is a member of The International Association of Forensic Toxicologists (TIAFT).

Cocaine

1

Cocaine

Synonyms: badrock, bazooka, benzoylethylecgonine, benzoylmethylecgonine, bernice, bernies, beta-cocain, blast, blizzard, blow, bouncing powder, bump, burese, "C", carrie, coc, cabello, candy, carrie, caviar, cecil, charlie, chicken scratch, cholly, coca, cocain, cocaina, cocaine free base, cocaine, *l*-cocaine-M, cocktail, coke, cola, corine, d-pseudococaine, dama blanca, delcaine, depsococaine, dextrocaine, dust, ecgonine, methyl ester, benzoate, eritroxilina, erytroxylin, flake, flex, florida snow, foo foo, freeze, g-rock, girl, gold dust, goofball, green gold, happy dust, happy powder, happy trails, heaven, hell, isocaine, isococain, isococaine, jam, kibbles 'n' bits, kokain, kokan, kokayeen, *l*-cocain, *l*-cocaine, lady, leaf, line, methyl benzoylecgonine, moonrocks, neurocaine, none, pimp's drug, prime time, rock, sleighride, snort, star dust, star-spangled powder sugar, sweet stuff, toke, toot, trails, white girl or lady, yeyo, zip

Systematic name: methyl-3-benzoyloxy-8-methyl-8 azabicyclo[3.2.1]octane-4-carboxylate

Formula: $C_{17}H_{21}NO_4$

Molecular weight: 303.353 daltons

C_{max}: (20 mg IV, $n = 7$) 124 ± 11.7, (40 mg IV, $n = 7$) 382.79 ± 84 ng/mL (Winhusen et al., 2006); (15 mg, $n = 5$) 191 ± 67.6, (40 mg, $n = 5$) 470.4 ± 70.8 (Cone et al., 1988)

Elimination rate constant: (40 mg IV, $n = 7$) 0.13, (40 mg IV, $n = 7$) 0.12 (Winhusen et al., 2006)

Elimination half-life (min): (40 mg IV, $n = 7$) 58.5 ± 8.4, (40 mg IV, $n = 7$) 60.6 ± 5.9 (Winhusen et al., 2006), (15 mg, $n = 5$) = 32.5 ± 5, (40 mg, $n = 5$) = 37.3 ± 1.8

AUC (ng/mL/min): (20 mg IV, $n = 7$) 11,461 ± 1326, (40 mg IV, $n = 7$) 28,510 ± 2304 (Winhusen et al., 2006), (40 mg, $n = 5$) = 21,838 ± 2970 (Cone et al., 1988)

Volume of distribution$_{ss}$ (L/kg): (20 mg IV, $n = 7$), (40 mg IV, $n = 7$) 2.22 ± 0.121 ± 0.13, 0.020 ± 0.003 (Winhusen et al., 2006); (15 mg, $n = 5$) = 1.63 ± 0.324; (40 mg, $n = 5$) = 1.5 ± 0.27

Clearance (L/min/kg): 0.026 ± 0.003 (Winhusen et al., 2006), ($n = 5$, 15 mg), = 2359 ± 200 L/min/kg), = 2042 mg/L ± 312 ($n = 5$, 40 mg) (Winhusen et al., 2006)

Cocaine hydrochloride, stored in a tightly closed container at room temperature, will not decompose for at least five years. Solutions are stable for at least 21 days, provided the temperature is below 24°C and the pH is below 4.0. At pH levels above 4.0 hydrolysis rapidly occurs (Muthadi and Al-Bader, 1986).

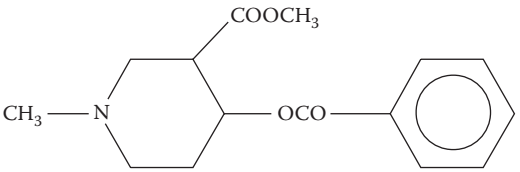

Figure 1.1 Cocaine, molecular weight = 300.4 daltons.

Cocaethylene (adapted from Hart et al., 2000)

Synonyms: none

Systematic name: ethyl (2R,3S)-3-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate

Formula: $C_{23}H_{18}NO_4$

Molecular weight: 317.38 daltons

Bioavailability: 100%

Metabolism: carboxylesterase breakdown followed by glucuronidation

C_{max}: ($n = 6$, 0.25 mg/kg IV) 195 ± 57.11; ($n = 6$, 0.50 mg/Kg) 444 (93.54); 68–60 minutes

T_{max}: 68–60 minutes (Baker et al., 2007)

$T_{½}$: ($n = 6$, 0.25 mg/kg IV) 91 minutes ($n = 6$, 0.50 mg/kg) 1.94 ± 0.21

V_{ss}: ($n = 6$, 0.25 mg/kg IV) 2.40 ± 0.33 ($n = 6$, 0.50 mg/kg) 1.94 ± 0.21; (Hart et al., 2000) 2.2 L/kg; 68–60 minutes (Baker et al., 2007)

Drug interactions: In humans and experimental animals, simultaneous administration of cocaine and ethanol results in higher plasma cocaine concentrations than does the same amount of cocaine given alone, but the effect seems to be not very great and may be accounted for by the longer half-life of cocaethylene, which is several times that of cocaine. When the clinical outcomes of 190 emergency room patients with urine tests positive for just benzoylecgonine were compared with the clinical course and outcome of 125 other patients where both benzoylecgonine and ethanol were detected, little morbidity was observed in either group. In fact, the only substantial difference between these two groups was that alcohol-positive patients had, as might be expected, more marked decreases in level of consciousness (Signs et al., 1996).

Clearance (mg/min/kg): ($n = 6$, dose 0.25 mg/kg), = 160 (40.53); ($n = 6$, dose = 0.50 mg/kg), = 329 (71.32)

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1.1 Incidence of Abuse

Cocaine is still very widely abused within the United States, and the use of this drug is also growing at an accelerating rate in the United Kingdom and Europe. Detailed figures on drug consumption are hard to obtain. Most of what is known about the prevalence of drug abuse comes from annually conducted surveys, such as the National Household Survey of Drug Abuse (NHSDA). Other sources, such as treatment program demand data, criminal justice databases, records of drug-related emergency room visits and medical examiner data, are provided by the Drug Abuse Warning Network (DAWN), a product of a federal agency known as the Substance Abuse and Mental Health Services Administration or SAMHSA. Another method of assessing prevalence of cocaine usage has recently introduced by the Europeans, and is now being used in the U.S.; monitoring sewerage effluent for drugs and projecting consumption based on metabolite concentrations found in the effluent.

If American government statistics are correct, 2.5% of the residents of Fairfax County, or 25,000 people have used cocaine in the past year, while data from the National Survey on Drug Use and Health suggest that about 9000 have used cocaine within the past 30 days (Anon., 2007). The reliability of these estimates is difficult to assess. The conclusions are partly based on the process of confidential self-reporting, and partly on regular sampling of sewage effluent from the Potomac River Basin for the urinary by-products of cocaine.

To make these estimates, technicians collect five days' worth of water samples from an inlet at a pollution control facility. The plants chosen each process millions of gallons of water a day, containing both commercial and residential sewage water. Five hundred milliliter samples are analyzed for traces of benzoylecgonine (BZE), cocaine's principal metabolite. In 2005, scientists of the Mario Negri Institute for Pharmacological Research in Milan tested waters from the Po River, the main river running through Florence and Northern Italy. They estimated that the Po carried the equivalent of about four kilograms of cocaine every day, which translates to 40,000 doses a day. That result was more than twice the amount that the government had predicted (Hawkes, 2006). Very similar findings have been reported from elsewhere in Italy and even in London (Orr and Goswami, 2005). The problem with these calculations is that the numerator is not known. Do 10,000 people use 4 doses per day or do 20,000 people take 2 doses? There is no way to know.

In a similar fashion, Irish researchers devised a method to measure cocaine and BZE in wastewater treatment plants around Dublin but, in addition to sampling fluids entering the facilty, they also collected random samples immediately downstream of the treatment plants in an attempt to investigate the effect of dilution.

The load of cocaine within the treatment plant on any given day was calculated by measuring drug concentrations found in the influent, and then multiplying that sum by 90% (since only 10% of cocaine is excreted in the urine, yielding an approximation of the amount of cocaine consumed and excreted each day, assuming an average dose of 100 mg). Once that value had been determined it was used to calculate the number of daily doses per thousand population equivalents, thereby providing an indicator of cocaine use in the area being serviced by the plant.

It was found that significant quantities of cocaine were being consumed within Dublin, and that nearly as much drug was being used in neighboring bedroom communities. The numbers are quite stunning. Ten years ago, cocaine use was unheard of in Dublin.

Table 1.1.1 The Six Most Common Types of Drug Deaths Reported to DAWN

	Cocaine	Heroin	Methamphetamine	Methadone	Oxycodone	Hydrocodone
1994	3020	2333	163	430	35	46
2001	3865	3189	499	647	452	413
2002	4707	3719	1089	1036	—	—
2003	3027	4831	419	418	474	522

* Totals include Los Angeles data from years 2001, 2002, and 2003.

Now over 2 kg per day of cocaine (2.245 g) is passing through the wastewater plant. That translates to the use of 819 kg of cocaine per year in Dublin and its environs—roughly a ton per year. It may be that in the future this sort of monitoring becomes much more widespread.

Table 1.1.1 contains a tabulation of the totals for the six most frequently mentioned drugs in 2001, 2002, and 2003 DAWN reports (the most recent year for which SAMHSA provides figures). For purpose of comparison, totals from 1994 are also included. Los Angeles and six other cities have been dropped (with no explanation or comment) from the 2002 and 2003 reports.

The more traditional method of assessing drug usage is by repeated survey, and there are a number of such test instruments. The best known of these instruments, among physicians at least, is the DAWN report. DAWN is part of a public health surveillance system intended to monitor drug-related emergency department visits and deaths. DAWN data may be accessed directly at http://dawninfo.samhsa.gov. Regrettably DAWN is a monitoring system in name only. SAMHSA's Office of Applied Studies (OAS) produces DAWN reports. In theory, the basis for the reports is data supplied to the government by (1) medical examiners across the country who submit information about drug-related deaths, and (2) hospitals that supply information about emergency room visits. The OAS then tabulates and publishes the information. The value of the information is substantially diminished by the two- to three-year time lag required to collect, publish, and disseminate it.

In the early 1990s, DAWN received and processed data from more than 134 medical examiner's offices, located in 27 different metropolitan areas of the U.S. During 1994, for example, the 138 medical examiners reporting to DAWN had performed approximately 70% of all forensic autopsies in the U.S., which strongly suggests that the sample analyzed was representative. In that year, 8246 drug-related deaths were reported. Three quarters occurred in men, and 70% involved the use of more than one drug. The current iteration of DAWN (last printed in 2006 but containing data from 2004) provides information from only six metropolitan areas, and these areas do not include major centers like Los Angeles and the City of San Francisco, which were initially key components of the original DAWN project.

From the beginning, DAWN reports were always published with a disclaimer, explaining that the data provided were "not representative of all such deaths that occurred in the United States." Still, it was possible to read the reports and get some feel for national trends. In 1990, for example, there were fewer than 5500 cocaine- and heroin-related deaths, with three cocaine deaths for every two heroin. More than half the deaths were reported from

Rank	Drug name	Number of mentions	Percent of total episodes	Rank	Drug name	Number of mentions	Percent of total episodes
1	Cocaine	3,465	46.00	39	Dextromethorphan	55	0.73
2	Alcohol-in-combination	2,944	39.09	40	Doxylamine Succinate	46	0.61
3	Heroin/Morphine [1]	2,912	38.66	41	Meperidine HCl	42	0.56
4	Codeine	880	11.68	42	Trazodone	42	0.56
5	Diazepam	640	8.50	43	Oxycodone	41	0.54
6	Methadone	431	5.72	44	Chlorpromazine	38	0.50
7	Amitriptyline	414	5.50	45	Mesoridazine	38	0.50
8	D-Propoxyphene	398	5.28	46	Pentobarbital	37	0.49
9	Marijuana/Hashish	359	4.77	47	Ephedrine	30	0.40
10	Nortriptyline	335	4.45	48	Promethazine	29	0.39
11	Diphenhydramine	318	4.22	49	Pseudoephedrine	27	0.36
12	Acetaminophen	298	3.96	50	Oxazepam	26	0.35
13	Methamphetamine/Speed	234	3.11	51	Brompheniramine Maleate	26	0.35
14	Quinine	203	2.70	52	Hydromorphone	25	0.33
15	Doxepin	195	2.59	53	Theophylline	25	0.33
16	Phenobarbital	182	2.42	54	Phenylpropanolamine	24	0.32
17	Amphetamine	155	2.06	55	Quinidine Sulfate	24	0.32
18	Lidocaine	155	2.06	56	Ibuprofen	24	0.32
19	Desipramine	151	2.00	57	Lithium Carbonate	23	0.31
20	PCP/PCP Combinations	146	1.94	58	Caffeine	22	0.29
21	Unspec. Benzodiazepine	130	1.73	59	Glutethimide	21	0.28
22	Fluoxetine	122	1.62	60	Clonazepam	21	0.28
23	Hydantoin	115	1.53	61	Propanolol HCl	20	0.27
24	Aspirin	113	1.50	62	Amoxapine	19	0.25
25	Alprazolam	109	1.45	63	Hydroxyzine	18	0.24
26	Chlordiazepoxide	99	1.31	64	Benztropine	18	0.24
27	Fentanyl	96	1.27	65	Haloperidol	17	0.23
28	Hydrocodone	92	1.22	66	Lorazepam	17	0.23
29	Imipramine	87	1.16	67	Ethchlorvynol	16	0.21
30	Butalbital	85	1.13	68	Trifluoperazine	14	0.19
31	Chlorpheniramine	70	0.93	69	Triazolam	14	0.19
32	Thioridazine	69	0.92	70	Household/Commercial Subs	13	0.17
33	Meprobamate	68	0.90	71	Amobarbital	13	0.17
34	Temazepam	67	0.89	72	Loxapine	12	0.16
35	Secobarbital	62	0.82	73	Metoprolol	12	0.16
36	Carisoprodol	61	0.81	74	Phentermine	11	0.15
37	Carbamazepine	60	0.80	75	Cyclobenzaprine	11	0.15
38	Flurazepam	56	0.74	76	Metoclopramide	11	0.15

NOTE: Percentages are based on a total raw medical examiner drug abuse case count of 7,532.

[1] Includes opiates not specified as to type.

See general footnotes at end of table.

Figure 1.1.1 Drug-related deaths mentioned in the DAWN report, Medical Examiner's component, 1992 report. Then and now, cocaine, alcohol in combination, and heroin were the most frequently encountered. The government no longer publishes similar data, but it is safe to assume that the number of cocaine, heroin, and alcohol deaths has, at minimum, tripled since 1990. ([1]Includes opiates not specified as to type. Percentages are based on a total raw medical examiner drug abuse count of 7532.)

New York and Los Angeles. When Los Angeles was dropped from the rolls, it became very hard to draw meaningful conclusions about trends.

Another useful feature contained in the DAWN reports of the 1990s was a listing of "Drugs Mentioned More Frequently by Medical Examiners." In 1994 cocaine and heroin accounted for roughly equal numbers of reported deaths (3981 and 3552, respectively), but the report for that year also showed how many deaths occurred as a consequence of abusing ephedrine, oxycodone, and amitriptyline. Obviously, the numbers could not be generalized to all jurisdictions in America, but trends were visible. That is no longer the case,

and there is, for example, no way to estimate the size of the methamphetamine problem in the U.S., except by resorting to some surrogate measure—perhaps by gathering information on expenditures for toxic waste cleanup, or counting the number of prisoners testing positive for methamphetamine at the time of arrest.

Individual researchers are now forced to review the DAWN report page by page, city by city, and tabulate the cases listed. The number of cities reporting is now quite small, and the significance of the numbers reported is, therefore, quite doubtful. As mentioned earlier, deaths from Los Angeles are no longer included, nor are deaths from the city of San Francisco, where more cocaine and heroin deaths occur in one week than in the surrounding area in one or two months. SAMHSA has also changed its mission statement. No longer content to point out that the data might not be representative of patterns throughout the entire country, new DAWN reports carry the disclaimer "DAWN cases reflect the number of drug abuse deaths reviewed, identified, and reported by participating medical examiners and coroners in selected metropolitan areas. These findings can be used to monitor changes over time." Perhaps, but they certainly cannot be used to monitor national trends.

In 2002, 127 jurisdictions in 38 metropolitan areas submitted data to DAWN. In 2003 that number had dropped to 33, and in all but three of the metropolitan areas reporting, the most frequently reported drugs were heroin/morphine, cocaine, and alcohol-in-combination.

Drug abuse-related emergency room visits, collected by DAWN from a representative sample of hospitals across the U.S., as well as data on drug abuse-related deaths investigated by a handful of medical examiners and coroners are flawed: they co-aggregate all non-cocaine, but stimulant-related deaths, making it impossible to accurately estimate the number of methamphetamine-related deaths, or deaths due to methylenedioxymethamphetamine (MDMA) or piperazines. The same problem exists for opiates, where oxycodone and hydrocodone are simply classified as opiates.

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1.2 Epidemiology

Men die of drug abuse much more often than women. In the past, men have comprised 68% of the drug misuse deaths reported to DAWN, with values ranging from 52% in Louisville to 77% in Phoenix. After adjusting for population size, the death rates attributable to drug misuse per 1,000,000 men are 2.4 times those for females. Drug deaths among children and adolescents (age 6 to 20) are relatively infrequent, accounting for less than 4% of DAWN cases. Decedents aged 35 to 54 accounted for more than half of the drug misuse deaths reported.

According to the 2003 DAWN report, cocaine continues to be the most frequent cause of drug deaths. On average, cocaine alone, or in combination with other drugs, was responsible for 39% of drug misuse deaths reported in metropolitan areas (range 8% to 70%) in 2003. About three quarters of the deaths involved cocaine and at least one other drug.

Information obtained from the U.S. National Household Surveys on Drug Abuse (NHSDA) indicates that most current cocaine abusers began the practice no more than 24 months prior to identification (median time was only 12–13 months). Of these, some 5–6% exhibit an explosive onset of DSM-IIIR syndrome of cocaine dependence occurring within the first two years of use (Wagner and Anthony, 2002). Further analysis suggests that there are three types of cocaine users. Only about 4% meet DSM-IV criteria for cocaine dependence syndrome, another 16% meet DSM criteria for cocaine dependence prodrome, but 80% of recent onset cocaine users exhibit few or no clinical features of dependence (Reboussin and Anthony, 2006). In other words, they do not exhibit demonstrable harm (unless, of course, they are arrested).

The evidence suggests that the likelihood of rapidly becoming cocaine dependent is small and contingent on two variables: the age of the new user and how much education they have had. In 1998, among adults 18 years and older, those who had not completed high school had a current use rate of 1.4%. That rate was only 0.8% for those with a high school education. Among college graduates, the rate was even lower—0.4%.

The available data suggest that a shift in the pattern of usage occurred in the U.S. during the early 1990s, with more and more users coming from the ranks of the economically disadvantaged. The same pattern appears to be repeating itself now in Europe and

Figure 1.2.1 Freighter captured in the Caribbean carrying 21 tons of cocaine to the U.S. in April 2007. There was no effort at concealment; the cocaine was simply stacked in bales on deck. The following month a shipment of 14 tons was intercepted in the same manner. (From the website of the Drug Enforcement Administration [DEA].)

the U.K. Where cocaine use was once confined to rock stars and supermodels, it is becoming more and more an indulgence of the poor, rather than the rich. This would not be the first time such a shift has occurred. In the 19th century, opiate addiction was predominantly a middle-class concern, but by the early 1940s most heroin users were young working-class men and women. The same pattern is also apparent now with cigarette smoking—the higher a person's socioeconomic status, the less likely they are to smoke (Miech et al., 2005).

Substantial evidence points to the role of poverty. Clustering of cocaine users occurs within neighborhoods, suggesting a contagious spread of the habit. The probability that a person will develop a particular disease, and its outcome, are dependent upon the degree to which others in the community already have the disease; the more people addicted in a particular neighborhood, the more likely it is that non-users will become users. Professor David Musto was the first to use this model to account for the recent cocaine pandemics, and his assumptions appear to have been proven correct, not so much in the sense that use of the drug causes a DSM classifiable disease, but in the sense that current drug users must be present in sufficient numbers to encourage use among non-users (Behrens et al., 1999). Epidemiologic evidence suggests that disease (i.e., the beliefs and behaviors indicating that cocaine use is harmless) is transmitted from neighbor to neighbor, and neighborhood to neighborhood. The evidence strongly suggests that these ideas do not penetrate into wealthy neighborhoods (Petronis and Anthony, 2003).

Employment is another significant predictor of cocaine use. According to DAWN, the rate of current cocaine use is highest among the unemployed (3.4% of the unemployed over 18 years old). Cocaine use among individuals with full- or even part-time employment was 0.9%. In terms of absolute numbers, most cocaine users were employed. Of the 1.8 million adult current cocaine users in 1998, 1.1 million (70%) were employed either full or part time. According to the Medical Examiner component of the DAWN report for 1999, cocaine was the most common cause of drug-related death among blacks (64% of episodes), second among Hispanic decedents (45%), and third among white decedents (32%) (Kissin et al., 2000).

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1.3 History

The word "coca" comes from the Aymara *khoka*, meaning the tree. Coca has nothing to do with the chocolate-producing nut called cocoa, and its only relation to the kola nut is phonetic. Although it is claimed that measurable quantities of cocaine and nicotine have been detected in 3000-year-old Egyptian mummies (Balbanova et al., 1992), these claims remain unconfirmed and unlikely. Cocaine and nicotine are derived from New World plants, and how they would have come to be used in Africa before the discovery of the New World remains a mystery. Even if the ancient Egyptians knew of such plants, Europeans did not hear about them until the Spanish colonized South America. When Spain took Peru in the 1500s, Spanish soldiers and explorers encountered Indians who had been chewing coca leaf for thousands of years.

The experience of the Indians with coca was recounted in Nicolas B. Monardes' monograph, *Joyfulle News Out of the Newe Founde Worlde, wherein is declared the Virtues of Herbs, Treez, Oyales, Plantes, and Stones*. Monardes' book was reprinted many times after first being published in Barcelona some time in the early 1550s. In 1559, a translation by an English merchant was published in London (Monardes, 1559). Monardes' book contained accurate descriptions of many New World plants, including tobacco and coca. He was fascinated by the fact that coca appeared to allow users to go without food, but he also was aware that coca had undesirable side effects. He observed, "Surely it is a thyng of greate consideration, to see how the Indians are so desirous to bee deprived of their wittes, and be without understanding" (Geuerra, 1971).

For a very long time the medical community remained unimpressed with coca. Hermann Boerhave favorably mentioned coca in his textbook on medicinal plants, published in 1708 (Mortimer, 1901), but in spite of Boerhave's initial enthusiasm, more than 100 years elapsed before the first illustration of coca appeared in an English magazine. An article on coca by Sir William Hooker, then curator of the Royal Botanical Gardens at Kew, appeared in 1835. In addition to illustrations of the coca plant, the article also contained Hooker's translation of a book by German explorer and naturalist Edward Poeppig. Poeppig thought that coca chewers were very much like opium addicts, and warned against the immoderate use of coca (Poeppig, 1832). Other travelers and explorers had more positive impressions, but the potential toxicity of coca was known even before it became widely available in Europe.

Johan von Tschudi was one of the early explorers of the Amazon. He was a prolific writer, and his travel books were popular in Europe and the U.S. He, too, was impressed with the apparent ability of coca to increase endurance, but he was concerned that Europeans might develop a "habit." His book *Travels in Peru*, published in 1847, contains the first accurate description of cocaine "binging" (von Tschudi, 1847). The term describes the tendency of cocaine users to consume, in one session, all the drug in their possession. According to von Tschudi, "They give themselves up for days together to the passionate enjoyment of the leaves. Then their excited imaginations conjure up the most wonderful visions. I have never yet been able to ascertain correctly the conditions the Coquero passes through on returning to his ordinary state; it, however, appears that it is not so much a want of sleep, or the absence of food, as the want of coca that puts an end to the lengthened debauch."

In 1857, von Tschudi persuaded a professor of chemistry at the University of La Paz, Enrique Pizzi, to try to isolate the active principle of coca. Pizzi thought he had succeeded and gave von Tschudi a sample to take home to Europe. Returning to Göttingen, von Tschudi

gave the sample to his friend, Carl Wöhler, the chemist who had first synthesized urea. Wöhler gave the sample to Albert Niemann, his graduate student. Niemann found that the sample contained only gypsum. Wöhler remained curious and, when he heard that Archduke Ferdinand was sending a frigate on an around-the-world training cruise, approached Carl von Scherzer, chief scientist of the expedition, and asked him if he could bring back enough coca leaves to analyze (von Tschudi, 1847). von Scherzer returned three years later with 60 pounds of leaves and gave them to Wohler, who again gave them to Niemann.

Given an adequate supply of leaf, purification of cocaine proved relatively simple. Niemann published his Ph.D. thesis, "On a New Organic Base in the Coca Leaves", in 1860 (Niemann, 1860). Even after the purification of cocaine, interest in its therapeutic applications remained slight, and reports in journals were still almost all anecdotal. Other than the fact that he was the first to isolate cocaine, very little is known about Niemann, and he died shortly after his thesis was published.

A *Lancet* editorial published in 1872, 12 years after cocaine had been purified, stated that "there is considerable difference of opinion as to its effects upon the human subject, and the published accounts are somewhat conflicting; but we think that there is strong evidence in favor of its being a stimulant and narcotic of a peculiar kind, and of some power." Coca-containing wines became popular in France and Italy during the late 1860s (Figure 1.3.1). Angelo Mariani manufactured the most famous of these. It contained 6 mg of cocaine per ounce and was advertised as a restorative and tonic; that seems to be how it was used. Satisfied customers endorsing *Vin Mariani* (Figure 1.3.2) included Thomas Edison, Robert Louis Stevenson, Jules Verne, Alexander Dumas, and even Pope Leo III. Within 10 years of their introduction in Paris, Mariani's wines were in much demand throughout the U.S. (Figure 1.3.2). The amount of cocaine contained in these products was modest. It is now known that when alcohol and cocaine are combined, a new metabolite called *cocaethylene* is formed (Hearn et al., 1991). It has the same affinity for the dopamine

Figure 1.3.1 Coca-containing wines. These wines became popular during the 1860s. Among the many competitors, the most famous was *Vin Mariani*. The average product contained 5 to 10 mg of cocaine per ounce. (SB Karch, MD—private collection.)

Figure 1.3.2 Newspaper advertisement for *Vin Mariani*. Angelo Mariani was a master at self-promotion, and it is difficult to decide for which of his two great inventions he should be remembered: the popularization of coca wine or the invention of the modern publicity campaign. *Vin Mariani* was immensely popular. Mariani sent cases of free wine to celebrities, who would then write thank-you notes or even endorsements that Mariani collected and published. Thomas Edison and Sarah Bernhardt wrote endorsements, as did Pope Leo III. President William McKinley's secretary, John Addison Porter, wrote to Mariani to thank him and assured Mariani that the wine would be used whenever the occasion required. This advertisement, featuring a picture of the Pope, appeared in a London newspaper in 1899.

receptor as cocaine itself, which means that it should be just as psychoactive. Because cocaethylene has a half-life that is many times longer than that of cocaine, combinations of alcohol and cocaine may be quite intoxicating.

In the early 1880s, Parke Davis and Company began to sell a fluid extract containing 0.5 mg/mL of semi-purified cocaine. At about the same time, physicians began prescribing elixirs containing cocaine for treatment of a variety of ailments, including alcohol and morphine addiction. In spite of the inappropriate use of these mixtures, reports of toxicity and cocaine-related disease were rare. Concurrent with the increased dispensing by physicians, patent medicine manufacturers began adding cocaine extract to nearly all of their products. One such promoter was John Styth Pemberton. He went into competition with Mariani and began selling "French Wine Cola." His initial marketing efforts were not very successful. In what proved to be a wise marketing move, Pemberton dropped the wine from the product and added a combination of cocaine and caffeine. The product, reformulated in 1886, was named "Coca-Cola" (Pentegrast, 2000).

Two events occurred in 1884 that significantly changed the pattern of cocaine use in the U.S. and Europe. The first was the publication of Freud's paper, *Über Coca* (Freud, 1884). The second was Köller's discovery that cocaine was a local anesthetic (Figure 1.3.3)

THE OPHTHALMOLOGICAL CONGRESS IN HEIDELBERG.

(From our Special Correspondent.)

MURIATE OF COCAINE AS A LOCAL ANÆSTHETIC TO THE CORNEA—NO RADIATING MUSCULAR FIBRES IN THE IRIS—ACTUAL CAUTERY IN SUPERFICIAL CORNEAL ULCERATIONS—OPTICO-CILIARY NEURECTOMY—IS CATARACT THE RESULT OF CHRONIC BRIGHT'S DISEASE?—PROFESSOR ARLT AND HIS RECENT WORK IN GLAUCOMA.

KREUZNACH, GERMANY, September 19, 1884.

SIR: The usual Ophthalmological Congress in Heidelberg has just closed its session, and a few cursory notes at this early date may interest some readers. At this meeting elaborate papers are not read, but condensed statements are presented of the subjects introduced. The notable feature of this Society is that only new things or new phases of old topics are presented. This is not from any expressed rule, but is from the tacit understanding which controls men who are so diligently investigating the unknown in science as are these eager workers. These men have no patience with mere reiterations. Perhaps the most notable thing which was presented was the exhibition to the Congress upon one of the patients of the Heidelberg Eye Clinic, of the extraordinary anæsthetic power which a two per cent. solution of muriate of cocaine has upon the cornea and conjunctiva when it is dropped into the eye. Two drops of the solution were dropped into the eye of the patient at the first experiment, and after an interval of ten minutes it was evident that the sensitiveness of the surface was below the normal, then two drops more were instilled and after waiting ten minutes longer there was entire absence of sensibility, a probe was pressed upon the cornea until its surface was indented, it was rubbed lightly over the surface of the cornea, it was rubbed over the surface of the conjunctiva bulbi, and of the conjunctiva palpebrarum; a speculum was introduced to separate the lids and they were stretched apart to the uttermost; the conjunctiva bulbi was seized by fixation forceps and the globe moved in various directions. In all this handling the patient declared that he felt no unpleasant sensation, except that the speculum stretched the lids so widely asunder as to give a little discomfort at the outer canthus. Before the experiment his eye was shown to possess the normal sensitiveness, and the other eye, which was not experimented on, was in this respect perfectly normal. The solution caused no irritation of any kind, nor did it at all influence the pupil. The anæsthetic influence seemed to be complete on the surface of the eye, and it lasted for about fifteen minutes and the parts then resumed their usual condition. This first experiment was done in the presence of Professor Arlt, of Professor Becker, of the clinical staff, of Dr. Ferrer of San Francisco, of some other physicians, and of the writer. The next day the same experiment was performed on the same patient in the presence of the Congress and with the same results. This application of the muriate of cocaine is a discovery by a very young physician, or he is perhaps not yet a physician, but is pursuing his studies in Vienna, where he also lives. His name is Dr. Koller, and he gave to Dr. Brettauer, of Trieste, a vial of the solution, to be used in the presence of the Congress by Dr. Brettauer. Dr. Koller had but very recently become aware of this notable effect of cocaine, and had made but very few trials with it. These he had been led to make from his knowl edge of the entirely similar effect which it has for some year or more been shown to have over the sensibility of the vocal cords, and because of which laryngologists pencil it upon their surface to facilitate examinations.

The future which this discovery opens up in ophthalmic surgery and in ophthalmic medication is obvious. The momentous value of the discovery seems likely to prove to be in eye practice of more significance than has been the discovery of anæsthesia by chloroform and ether in general surgery and medicine, because it will have therapeutic uses as well as surgical uses. It remains, however, to investigate all the characteristics of this substance, and we may yet find that there is a shadow side as well as a brilliant side in the discovery. Professor Kühne, who in the Heidelberg Physiological Laboratory worked out the details of Boll's discovery of the visual purple of the retina, received the news of this new discovery with the liveliest interest. We may, perhaps, get from him a further investigation into its properties. The substance makes a clear solution, and is found in Merck's catalogue.

Another notable statement came from Dr. Eversburch, of Munich, as the result of very exact and elaborate studies, to the effect that there are no radiating muscular fibres in the iris; in other words, that the dilator iridis has no existence in man. It is found, he says, in some animals, and especially in those which have oblong pupils, whether vertical or horizontal, and in the form of fasciculi at the extremities of the slit. He absolutely denies the existence of such fibres in the human eye, and asserts that the fibres hitherto described under this name are nerve-fibres. These revolutionary assertions were received with respect and attention, because the investigator was known to be a careful and competent anatomist. If his declarations should be confirmed, and they will not be lightly accepted, we must find out a new theory for the active dilatation of the pupil. A good deal of physiology will have to be cast into a new form. It is true that the anatomical discussion has not been closed on this point, but in favor of the existence of the dilator stand the names of Merkel, Henle, and Iwanoff among recent investigators. Eversburch has in his possession the preparations of Iwanoff, who died a few years ago, and he knows the nature of the contest into which he enters.

The uses of the actual cautery in superficial forms of corneal ulceration and in some other superficial processes, especially in those of micrococcic origin, were discussed both here and in Copenhagen. There seems to be a general consensus as to the usefulness of this treatment in selected cases of superficial corneal disease, viz., in ulcus rodens, in superficial suppurative processes, in atonic ulcers, and by Nieden in xerophthalmus. Nieden will shortly announce his views in full in an article in the *Archives for Ophthalmology*. He presented a most delicate and elegant form of galvano-cautery which he had devised, and to which he had applied a very delicate and promptly acting key invented by Professor Sattler. Another form of cautery is in use in the Heidelberg Eye Clinic, which has been devised by Professor Becker, and is a very small and utilizable Paquelin cautery. Both these instruments can be handled with nicety and delicacy, and without frightening the patient, and also in most cases without giving him any pain. This treatment, as well as the scraping of such ulcers by a sharp spoon, as does Meyer, of Paris, is founded on the micrococcic theory of the pathology of these processes, and marks another forward step in ophthalmic therapeutics.

Optico-ciliary neurectomy as a preventive of sympathetic ophthalmia has not passed out of practice, as to a considerable degree has become the case among us. So able an observer and logical a reasoner as Professor Schweigger, of Berlin, recommends its performance and holds it in higher esteem than enucleation. He divides the internal rectus muscle to gain easy approach to the nerve, and he lifts it from its bed by a sharp double hook and excises 10 mm. of it. He is said to be extremely skilful in this proceeding, and the very small disturbance which he causes in the structures of the orbit may perhaps explain the success which he has had and the confidence which he expresses in its prophylactic virtue. Among over a hundred cases which furnished the material for his conclusions, in two cases he saw occur in the opposite eye an acute neuro-retinitis, with opalescent infiltration, etc. There was no reduction of vision either central or peripheral. In two weeks the appearance

Figure 1.3.3 Cocaine as a local anesthetic. The discovery that cocaine was a potent local anesthetic revolutionized surgery. It was first reported at an ophthalmology congress in Heidelberg. Shortly thereafter an account appeared in the Medical Record of October 11, 1884. (From the Medical Library at the University of California, San Francisco.)

Figure 1.3.4 Advertisement for Burnetts Dandruff Shampoo containing cocaine. The manufacturers never explained why cocaine should be good for the scalp. (SB Karch, MD—private collection.)

(Noyes, 1884). By the time Freud sat down to write his paper, American physicians had already published more than a dozen papers recommending cocaine in the treatment of morphine addiction (Bentley, 1880). Freud enthusiastically accepted this American notion and even elaborated on it, recommending cocaine as a remedy for a host of conditions that are not even recognized as diseases today. Köller's discovery was far more important. The availability of an effective local anesthetic had tremendous impact on the way medicine was practiced.

Physicians around the world were soon experimenting with the use of cocaine in a wide range of conditions. Some of the applications, such as eye and hemorrhoid surgery (Anon., 1886a), were quite appropriate. Other applications, such as the treatment of hay fever, were more questionable (Anon., 1886a). Still other uses were bizarre and potentially dangerous (Anon., 1885a, b). With so many physicians experimenting with the drug, not much time elapsed before the first reports of cocaine toxicity began to appear. Less than one year after Köller's and Freud's papers were published, an article in the *British Medical Journal* described the toxic reactions associated with cocaine use in ophthalmologic surgery (Anon., 1885a). At about the same time, the popular press began carrying accounts of cocaine-related deaths (Anon., 1886b). The first cocaine-related cardiac arrest was reported in 1886 (Thompson, 1886), as was the first cocaine-related stroke (Catlett, 1886). In 1887, Mattison reviewed 50 cases of cocaine toxicity, four of which were fatal. Each of the fatalities

Figure 1.3.5 Advertisement for *Maltine*, a coca-based wine that competed with *Vin Mariani*. (Courtesy of Michael A. Bozarth, Ph.D., University of Buffalo, Dept of Psychology.)

had the characteristics associated with cardiac arrhythmias (Mattison, 1887a). The following year Mattison published data on an additional 40 cases, including two more fatalities.

None of these negative reports appeared to have had much impact. Patent-medicine manufacturers continued to cash in on the popularity of coca by replacing low-concentration cocaine extracts with high concentrations of refined cocaine hydrochloride. Thousands of cocaine-containing patent medicines flooded the market, some with truly enormous amounts of cocaine. Dr. Tucker's Asthma Specific, for instance, contained 420 mg of cocaine per ounce and was applied directly to the nasal mucosa. Absorption was nearly total. As the cocaine content of the products increased, so did the number of reported medical complications. The situation rapidly deteriorated when users learned they could "snort" cocaine. Until the early 1900s, cocaine had been taken mainly by mouth or by injection. The fact that the first cases of septal perforation and collapse (saddle nose deformity) were not reported until 1904 suggests that "snorting" had only become popular a year or so earlier (Maier, 1926).

As demand for cocaine grew, alternate sources came on line, and a South East Asia cocaine industry came into existence. Coca was also grown in Nigeria, Sri Lanka, Malaysia, Indonesia, Taiwan, and Iwo Jima (Figure 1.3.6). But the Javanese plantations were the main suppliers, and Japanese pharmaceutical companies were the main buyers. European drug manufacturers, such as Merck, even bought their own Javanese plantations, shipping dried coca leaves back to Germany for refining. In order to remain competitive, Dutch coca growers, along with The Dutch Colonial Development Board, formed a joint venture and built their own refinery in Amsterdam. The Nederlandsche Cocaine Fabriek (NCF) opened on March 12, 1900, in Amsterdam (Figure 1.3.7). The Amsterdam plant was so successful that a second floor was added to the factory in 1902. By 1910, coca exports from Java exceeded those from South America (Karch, 2003; 2005).

The first histological studies of cocaine toxicity were published in 1888. Vasili Zanchevski of St. Petersburg, Russia, studied the acute and chronic effects of cocaine in dogs. After a single lethal dose (24 mg/kg), the animals had changes said to be typical of acute asphyxia, though given the design of the experiment, it is unlikely that such changes could have been exhibited. Smaller daily doses given for several weeks caused a marked hyperemic condition of the central nervous system, in contrast to the rest of the organs,

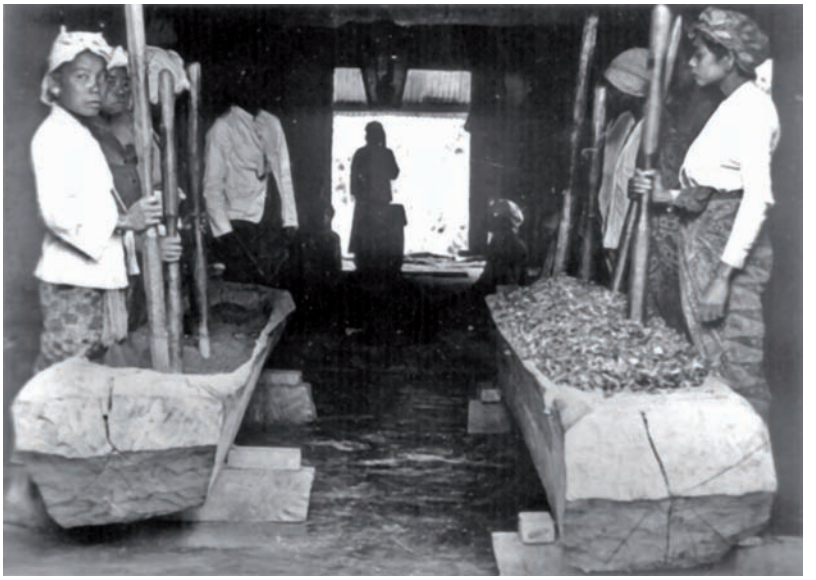

Figure 1.3.6 Indonesian coca production. During the 1920s, Indonesian plantations exported more coca leaf than producers in South America. This photograph, taken in 1927, shows workers sorting coca leaf. (Photograph courtesy of the Tropen Museum Photo Bureau, Amsterdam.)

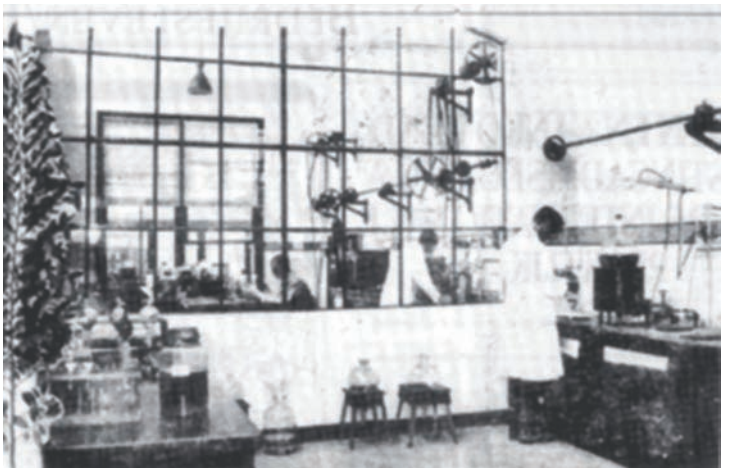

Figure 1.3.7 The Nederlandsche Cocaine Fabriek: The Dutch Colonial Development Board and coca growers in Java formed a joint venture and built a refinery to better compete with Merck and the other German cocaine manufacturers. The Nederlandsche Cocaine Fabriek (NCF) opened in Amsterdam on March 12, 1900. The Dutch plant was so successful that a second floor was added to the factory in 1902. By 1910, NCF claimed to be the largest cocaine manufacturer in the world, producing more than 1500 kg of refined cocaine per year. This photograph is from a trade publication, *Het Pharmaceutisch Weekblad*, published in 1925. (Courtesy of Marcel de Kort, Netherlands Ministry of Health.)

which were anemic. There were focal degenerative changes in the spinal ganglia, heart, and liver. In some cases, the myocytes had "lost their striae and [were] intensely granular" (Zanchevski, 1888). Although illustrations are lacking, Zanchevski's descriptions suggest that he was the first to observe a lesion called contraction band necrosis (CBN) occurring as a result of cocaine toxicity.

French researchers were the first to systematically study cocaine's psychological effects, largely because cocaine and morphine addiction were such a major problem in Paris. In 1889, at a meeting of the Biological Society of Paris, Valentine Magnan presented three cases illustrating that cocaine users were subject to tactile hallucinations. The symptom complex became known as "Magnan's symptom" and is still frequently diagnosed today, though the name of the discoverer has long since been forgotten. In 1914, Georges Guillain contrasted the differences between cocaine- and alcohol-induced hallucinations, commenting on how variable the effects of a given dose of cocaine could be (Maier, 1926).

One psychiatric disorder that has become quite common today is cocaine-associated excited delirium (some use the term *agitated* instead of *excited*, but the words are used interchangeably). This disorder first came to widespread public attention in 1914 when the *New York Times* carried a front-page article written by an American physician, Edward Williams. The article describes "crazed Negroes" who were threatening the women of the New South (Williams, 1914). Because Williams' writings were patently racist, and because he only described the syndrome in blacks (at the turn of the last century, black farm laborers were often paid in cocaine) (Karch, 2005), later historians were prone to write off his observations as mere racist hysteria (Kennedy, 1985).

New reports of the syndrome (hyperthermia, followed by agitated psychosis, respiratory arrest, and death) reappeared at the start of the current pandemic. Although the disorder has nothing to do with race, it is quite real (Wetli, 2006) and the underlying neurochemical changes have now been extensively characterized (see Section 1.14). Excited, or agitated, delirium was a known clinical entity long before the *New York Times* ever headlined its dire warnings. In 1849, 25 years prior to commercial availability, a physician named Lester Bell published a paper describing exactly the same sort of symptoms in hospitalized psychiatric patients. Journal editors today would probably not have allowed Bell quite as much latitude in the title of his paper, but it was descriptive: "On a form of disease resembling some advanced stages of mania and fever, but so contra distinguished from any ordinarily observed or described combination of symptoms as to render it probable that it may be an overlooked and hitherto unrecorded malady" (Bell, 1849).

The first human autopsy study of a cocaine-related death was published in 1922. Bravetta and Invernizzi described a 28-year-old man who had been sniffing cocaine regularly for some months prior to his death. He neither drank nor used other drugs (Bravetta and Invernizzi, 1922). Hyperemia of the brain, lungs, and adrenals was noted, and the heart was described as "flaccid" (cardiomyopathy?). The accompanying hand-drawn illustrations of the autopsy showed lesions similar to those described by Zanchevski. Animal studies by the same authors confirmed the autopsy findings and also demonstrated widespread endothelial injuries. These studies were reprinted in Maier's classic text on cocaine abuse, published in 1926.

The tissue disposition of cocaine was studied at an even earlier date. In 1887, a German chemist, Helmsing, published his technique for the detection of cocaine in urine and tissues. The technique was fairly sensitive, and Helmsing was able to detect cocaine in urine

from a cat that had been given 8 mg of cocaine (Anon., 1887). In 1951, Woods and his colleagues developed a calorimetric technique capable of detecting levels of cocaine as low as 500 ng/mL (Woods et al., 1951). A quarter century later, in 1975, Jatlow and Bailey used gas chromatography to lower the limits of detection to 5 ng/mL (Jatlow and Bailey, 1975).

Shortly after Maier's text was published, case reports simply stopped appearing. Between 1924 and 1973 there was only one cocaine-related fatality reported, and it involved a surgical misadventure. In 1977, Suarez first described the "body packer" syndrome, where death results from the rupture of cocaine-filled condoms in the smuggler's intestines (Suarez et al., 1977). The absence of case reports no doubt reflected a decline in cocaine use, but the decline itself is difficult to explain. Certainly the passage of laws restricting the sale of cocaine (the Pure Food and Drug Act of 1906 and the Harrison Narcotic Act of 1914) had a great deal to do with it, but other factors were involved (McLaughlin, 1973).

Professor David Musto, of Yale University, has suggested that cycles of drug abuse begin when a generation of young people no longer remembers the adverse consequences experienced by the preceding generation. Cycles end when drug users realize that other drug users they know are becoming ill. As their awareness increases, experimentation falls off, and the cycle eventually ends (Musto, 1987; Behrens et al., 1999).

Current drug users tend to recruit new ones, so in this respect Musto's theory treats cocaine addiction in the same way as any contagious disease: victims can be affected mildly or severely, or even die. Those experimenting with drugs, the "light users," will suffer few adverse consequences from their "disease" but are the ones most likely to recruit new users and spread the disease to others. "Heavy users" will suffer extreme ill effects, even death, and so are unlikely to recruit any new users. Someone who dies of an acute overdose the first time they use a drug is unlikely to infect many others or create new recruits. If this model is correct, then the memories of those who have had bad experiences with a drug will be balanced against the memories of those who have not. When there are more light users who have not had bad experiences, then the use of drugs will increase, always supposing, of course, that the drug supply is elastic—as demand increases, so does supply, although this is not always the case.

Musto's model seems to fit the current situation very well. By the 1920s, initial enthusiasm for cocaine had waned, partly because of efforts by the U.S. to prohibit drug use but, and it is really impossible to apportion credit, also because nearly everyone knew someone who had been damaged by cocaine. Even though there was a great deal of cocaine available, and at very reasonable prices, no one wanted to use it because the downside appeared too great. Cocaine had gone from a wonder drug to a scourge. Apart from a few show business celebrities, those who took cocaine were thought of as deviant losers. During the interwar years, another anti-drug element was added—availability decreased and prices increased. Not only had many people become ill taking the drug, it was now also expensive. Taken together, the high prices and known deleterious effects were a powerful disincentive to users. Cocaine remained available, but only as an expensive indulgence, not a drug for the masses. In 1934, Cole Porter wrote about sniffing cocaine in his play *Anything Goes*; the song was sung by an aristocrat wearing top hat and tails. Working people and college students were not experimenting with cocaine.

Another factor that contributed to the end of the first pandemic may have been the introduction of amphetamines. Like cocaine, amphetamine is a potent stimulant but its use seemed, at least at the time, to carry less opprobrium. It was more readily available, and it also was much cheaper than cocaine.

Significant toxicity from the use of coca leaf and coca extract was never a problem in Europe or the U.S. Toxicity only emerged when purified cocaine became readily available and individuals could increase their dosage by orders of magnitude. The small amounts of cocaine in *Vin Mariani* were apparently harmless, but the huge amounts in Dr. Tucker's formula were occasionally lethal. With the appearance of "crack" cocaine in 1986, another order of magnitude in dosage was achieved (Jekel et al., 1986). That cocaine-related illness is now a significant cause of morbidity and mortality should not be surprising. More people are using the drug; they are using more of it, and using it more effectively.

The number of reported cocaine-related deaths rose rapidly during the late 1980s and continued to rise during the early 1990s. From 1990 to 1992, the number of cocaine-related deaths increased by nearly 25% (from 2408 to 3220), but the process now appears to have leveled off. In 1999, the most recent year for which complete statistics are available, medical examiners reported 4864 deaths, amounting to 41.8% of all reported drug-related deaths. That number is essentially unchanged from the previous two years. Because the medical examiners participating in the DAWN survey perform only 70% of all autopsies done in the U.S., the total of all cocaine-related deaths reported must have been substantially higher. Worse, the methodology used by the DAWN survey was such that the total number of cocaine-related deaths was consistently underestimated, even by districts that filed reports with the survey (Brookoff et al., 1993). Still, the old DAWN report supplied at least some of the problem's dimension. With the dismantling of DAWN, the number of deaths is anyone's guess, but it certainly still amounts to more than 5000 cases every year, and the true total may be much higher.

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1.4 Current Affairs

On August 5, 2004, John Walters, the head of the U.S. Office of National Drug Control Policy (ONDCP), gave a speech to narcotics officers attending a conference in Bogota, Colombia. He stated that in 2003, 440 tons of cocaine had been seized in Latin America, the U.S., the U.K., and Europe. He stated that this number represented 40% of the estimated

flow of cocaine to those countries. He added, "In the next 12 months, we will see changes in availability of the drug—probably first lower purity, followed by higher prices." For a time the prices were higher, but they now have returned to levels seen in the early 2000s.

If Mr. Walter's numbers were correct, and 440 tons only amounted to 40% of the world's total cocaine production, then total world production must have been on the order of 1100 tons, roughly twice the number that has repeatedly been suggested by officials of both the U.S. government and by the United Nations. This discrepancy may explain why the National Drug Threat Assessment for 2008 puts the figure at 970 tons (Department of Justice, 2008).

Even though 2005 was a record year for cocaine interdiction, there have been no sustained cocaine shortages, nor is there any indication that such shortages exist anywhere in the U.S. market. The only possible explanation is that previous estimates have been inadequate and need to be revised upward. In fact, the supply and purity of cocaine have increased and the price is beginning to decline. According to figures released in the Spring of 2007 by the White House "Drug Czar," retail cocaine prices in 2006 had fallen by more than 12% from January to October, while average purity of cocaine seized by authorities rose from about 68% to 73%. The figures were never publicized or released to the general public; the "Czar" simply included them in a letter to U.S. Senator Charles E. Grassley (R-Iowa) (Enriques, 2007).

The movement of cocaine shipments from South America toward the U.S. has notably shifted. In the past, the primary point of cocaine entry into the U.S. was via Mexico. According to a former U.S. ambassador, that pattern has now shifted and cocaine shipments flow with little resistance from Colombia producers to Venezuelan exporters. From there cocaine is shipped by the ton on ships to both U.S. and European markets. Since Hugo Chavez became president of Venezuela in 2002, transshipment of cocaine has increased by 30 tons a year, reaching an estimated 300 tons in 2006, according to U.S. Ambassador William Brownfield. There is also evidence that Haiti has become an important transshipment staging area (Williams, 2007). In fact, cocaine trafficking organizations have thus far succeeded in maintaining sufficient cocaine production and delivery capacity with very little problem. Eradication and spraying have only succeeded in forcing farmers into nontraditional coca-growing areas, even though production in some other areas has diminished (Department of Justice, 2006).

According to U.S. government reports, the acreage devoted to coca cultivation in Colombia was 250,000 hectares in 2004, slightly less than the same acreage that had been devoted to Colombian coca during the previous 3 years. In 2004, herbicide fumigation destroyed 136,555 hectares of coca compared to a paltry 43,246 hectares in 1999. If you subtract the amount fumigated from the amount grown in 1999, 122,500 hectares of coca remained. If you subtract the amount fumigated today, 136,555 hectares, from the 250,555 hectares planted, 114,000 hectares of viable coca are still growing. In other words, Plan Colombia has succeeded, but only to a very limited degree. In spite of all the expenditures, and in spite of the huge area defoliated, output has dropped by only 8500 hectares since 1999, from 122,500 to 114,000 (these numbers are based on a March 25, 2005, press release from the Office of the Drug Czar). By any standard, the program has failed, and seems destined for further failure.

The former chairman of the House International Relations Committee, Henry Hyde, criticized the Bush administration for claiming a "premature victory" in the war against Colombian drug traffickers. Hyde was concerned that the U.S. government is shifting its

focus to the Middle East. Money that was originally intended for growth suppression in South America is now being shifted to the "war on terror." To some extent, Hyde's suggestions are true. In 2003, homeland security needs in the U.S. resulted in a 70% reduction in the aircraft available to the Colombian and U.S. navies for interdiction efforts. Surveillance planes have been grounded because of wing-structure problems, and many other aircraft were shot down by smugglers or farmers, or crashed. As a result interdiction flight hours declined from 6860 in 2000 to 2940 in 2005 (Seper, 2006). The problem is not likely to improve any time soon.

The President's proposed budget for 2007 includes cuts in anti-narcotics aid to most countries that make up the Andean Counterdrug Initiative, including Brazil, Ecuador, Panama, Peru, and Venezuela. Colombia is the only nation for which Bush has proposed a funding boost, and most of that money will go to replace aircraft that have already been destroyed. U.S. funding for Bolivian anti-drug efforts has been declining since 2001 (UNO-DCCP, 2006), even though cocaine output, according to the U.N., is rising.

The problem with defoliation is not just that it is dangerous and expensive; it may not be very effective either. In late August of 2004, newspapers began reporting that Colombian authorities suspect hybridized, if not genetically engineered, coca is now being planted. The plants are said to be taller (coca shrubs are usually 5 feet high), herbicide resistant, and have higher cocaine content. A toxicologist who advises Colombia's anti-narcotics police, told reporters that the new "super plants," some 7–12 feet tall, have been seen in the Sierra Nevada in northern Colombia, and in La Macarena, a savannah and jungle-covered region in central Colombia. Similar sightings are alleged in other areas, including Putumayo state in southern Colombia, where locals call the new varieties White Bolivian and Black Bolivian (Molinski, 2004).

These reports have yet to be independently confirmed. But whether or not any "super plants" are really being grown, there is ample evidence from U.S. government laboratories that Andean growers are hybridizing their plants to improve yield. According to a report by U.S. government researchers, DNA profiling showed that nearly a third of the samples collected from illicit coca fields in Colombia from 1997 to 2001 had been genetically altered—whether in the laboratory or by more traditional cross breeding, it is impossible to say (Johnson et al., 2003). But if Monsanto can manufacture Roundup Ready™ soybeans, can Roundup Ready Coca be far behind? One thing is for sure though: in 2005, more coca was grown in Colombia than in 2000, the year that Plan Colombia started.

1.4.1 Cocaine Availability

Cocaine supplies have been relatively stable and, perhaps, increasing for the past few years, but once the effects of interdiction and eradication have been factored in, production and demand seem well matched. Wholesale purity has increased since 2000 and has remained stable ever since. There is some recent evidence, much publicized by the government, that retail cocaine prices have begun rising and purity declining but, over the longer term, prices and purity today look not much different than they did when the last edition of this book was published (see figure from ONDCP webpage, www.whitehousedrugpolicy.gov). If there have been changes in either price or purity, these changes are not reflected in reports from law enforcement agencies. According to the 2006 National Drug Threat Assessment, currently available national-level data and law enforcement reporting tend to indicate stable domestic cocaine availability, even in smaller drug markets, though there is some evidence that the purity of cocaine is starting to decline. The reason is not apparent.

1.4.2 Cultivation and Crop Yields

Coca leaf has been grown in the Andean sub-region for thousands of years. Early explorers found it all along the eastern curve of the Andes, from the Straits of Magellan to the borders of the Caribbean. Coca grows best on the moist, warm slopes of mountains ranging in elevations from 1500 to 5000 feet. If they have not been genetically manipulated, coca shrubs grow to heights of 6–8 feet (Figure 1.4.2.1). The trunk of the plant is covered by rough, somewhat glossy bark that has a reddish tint. Its flowers are small and usually white or greenish yellow. Leaves are elliptical, pointed at the apex, and dark green in color. All cultivated coca is derived from two closely related species that grow naturally only in South America, *Erythroxylum coca* Lam and *Erythroxylum novogranatense* Hieron. Each species has one distinct variety designated as *E. coca* var. *ipadu* (Plowman) and *E. coca novogranatense* var. *truxillense* (Rusby) Plowman (Plowman, 1985). All four types are cultivated, although the alkaloid content of the different plants varies considerably (Plowman and River, 1983). *E. coca ipadu* is cultivated only in the Amazon valley of Brazil, Colombia, and Peru. Of all the cultivated varieties, *E. coca ipadu* contains the least alkaloid, less than

Figure 1.4.2.1 The first illustration of cocaine. The first illustration of coca to appear in an English publication (*Companion to the Botanical Magazine*) was published in 1836. It was drawn by Sir William Hooker, then director of the Royal Botanical Gardens at Kew. (Illustration courtesy of the library at the Royal Botanical Gardens at Kew, England.)

0.5%, and very little of that is cocaine. *E. novogranatense* is cultivated more widely and is better adapted to growth in hotter, drier climates.

Although there is some controversy, it seems likely that *E. novogranatense* was the variety cultivated in Java, Ceylon, India, and Taiwan. This variety may contain anywhere from 1 to 3% total alkaloid, with cocaine constituting as much as one half of the total alkaloid present (Lee, 1981; Bohm et al., 1982; Plowman and River, 1983; Plowman, 1985; Schlesinger, 1985). A strain of *E. novogranatense* cultivated in the desert coast region of Peru, near Trujillo, is the plant used to flavor Coca-Cola and other cola beverages.

Colombia remains the world's leading producer of cocaine, accounting for at least 75% of all cocaine production. There are a number of factors that could change the situation quite quickly. According to reports from the Drug Enforcement Agency (DEA), production in Bolivia and Peru is increasing, perhaps because of increased enforcement efforts in Colombia. And, of course, the possibility of resumed production in South East Asia always remains viable. But the real concern is genetic manipulation. Irrefutable evidence exists that Bolivian coca producers have been hybridizing *E. coca* var. *ipadu* in order to increase its cocaine yield. Several years ago, U.S. government scientists collected and analyzed a total of 132 coca samples from the highest producing areas of Bolivia. These samples were then compared for cocaine content with other specimens in their library. The age of the plants, and the original planting date, were estimated when the samples were collected and confirmed with DNA fingerprinting.

When overlapping DNA patterns were correlated with the samples, several clustered linkages were apparent. For example, one cluster of five samples with very closely related DNA all came from an area in the northern state of Guaviare and the adjacent state of Meta. Based on their findings the researchers concluded that regionalized populations of *E. coca* var. *ipadu* are being developed rapidly in Colombia in a number of areas. The main center for these new populations is the Putumayo/Caqueta region of Colombia; at least 5–8 new populations of *E. coca* var. *ipadu* have been or are being developed and several of those strains have gained regional widespread use. It is also clear that in several regions of Colombia new strains are being field-tested and developed. The process is probably relatively informal and occurs independently of any cartel interference.

Whether as a result of traditional techniques of plant hybridization, or modern genetic manipulation, the coca now being grown in the Andes has been modified in such a way that it contains more cocaine than in the past. The most obvious consequence is that more cocaine comes to market. Just how much is anyone's guess; without knowing the yield of the plants being grown, it is impossible to estimate output. Figure 1.4.2.2 shows the U.S. and European wholesale and retail prices per gram from 1990 through 2005. Note that U.S. wholesale prices have dropped hardly at all while prices in Europe continue to gradually increase.

Major coca growing areas in the Andes share many characteristics. Yungas, which is close to La Paz, has an average annual rainfall of 45.7 inches. Chaparé, which is close to Cochabamba, has an annual rainfall of 102 inches. The plantations in Yungas can be harvested three times per year. Each harvest yields from 2 to 2.7 tons per hectare per year. Chaparé leaf contains, on average, 0.72% cocaine. It is estimated that present refining techniques are only 45% effective (less than half the cocaine is actually recovered from the leaf). As a result, at least 390 kg of Chaparé leaf are required to produce 1 kg of cocaine base. The requirements would be higher in Yungas, where coca is said to have an alkaloid content of 0.85% (Abruzzese, 1989).

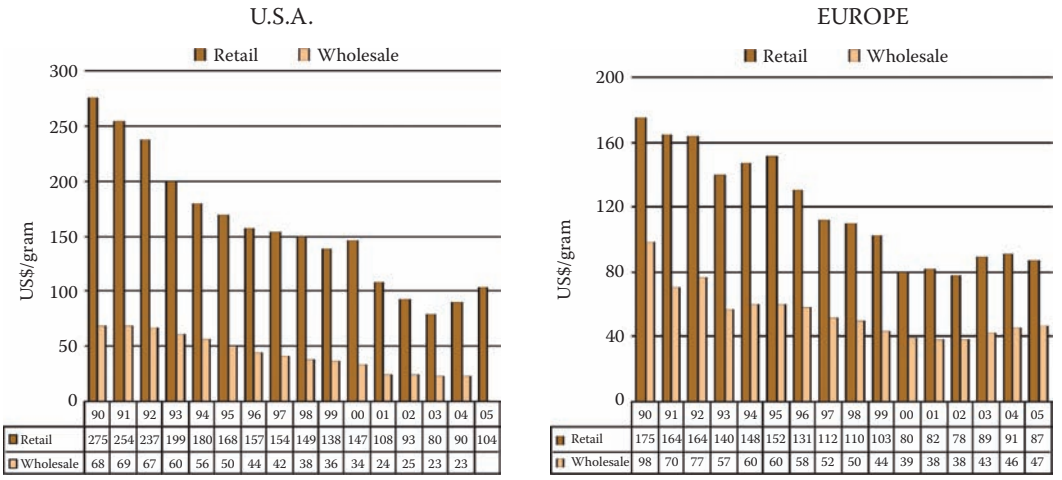

Figure 1.4.2.2 Graphs showing European and U.S. retail and wholesale price per gram for cocaine from 1990 through 2005. U.S. wholesale prices have dropped hardly at all while those in Europe have crept up slightly. (Source: UNODCCP, 2006, Volume #1 Analysis.)

1.4.3 Paste Production

Criminal organizations often use the Amazon to smuggle drug-processing chemicals from Brazil to cocaine laboratories in Bolivia, Colombia, Peru, and to laboratories believed to be operating in the western part of Brazil near the Paraguayan and Bolivian borders.

Controlling precursor chemicals in Brazil is an enormous task. The country has a huge chemical industry and much uncharted territory, providing ample opportunity for criminal labs to turn coca into cocaine. Brazil's role as South America's leading manufacturer of acetone and ether, the top two solvents used in the processing of cocaine, has become a key factor in the complex cocaine economy of the region. An estimated 25,000 registered chemical factories, trade, and transport companies, and an unknown number of unregistered plants and companies handle large quantities of processing chemicals as well as precursors for making Ecstasy and methamphetamine (Anon., 2007).

Cocaine extraction is a two- or three-step process carried out in a series of laboratories. The first steps occur on site. Immediately after harvesting, coca leaves are placed in a shallow pit lined with heavy plastic. The leaves are then soaked in a dilute solution of water and strong alkali, such as lime, for three or four days. An organic solvent is added. Methyl isobutyl ketone (MIBK) is the solvent of choice for this purpose, but nearly a dozen other solvents have been identified in samples that have been confiscated by the DEA and other agencies (International Narcotics Control Board, 1999). In recent years, the use of ethyl acetate and *n*-propyl acetate has become increasingly popular, but kerosene, gasoline, or even acetone can be used if no other solvents are available.

Extracted coca leaf is discarded and sulfuric acid is then added to the extract, dissolving a complex mixture of alkaloids in the aqueous layer. If the alkaloid content of the leaves is very high (as in Bolivia), hydrochloric acid may be used instead of sulfuric. The organic solvent is then removed, and the remaining aqueous solution is made alkaline by the addition of lime, ammonia, or the equivalent, causing the more basic alkaloids to precipitate out. This crude form of cocaine, called coca paste, is allowed to dry in the sun. The site where the initial steps occur is referred to as a "paste lab" (Figure 1.4.3.1). Laborers, called

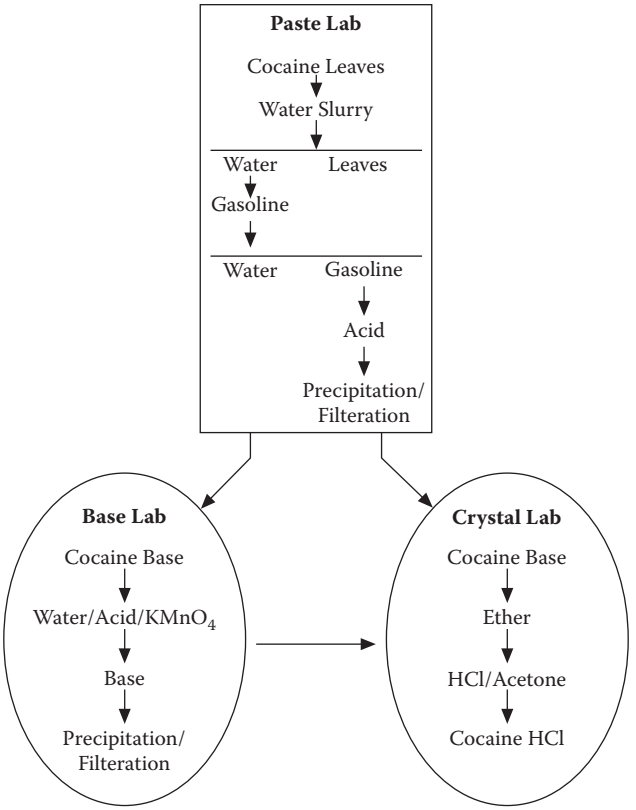

Figure 1.4.3.1 Flow chart of illicit cocaine processing. The preparation of purified cocaine from leaf. (Reproduced from the Drug Enforcement Agency's website.)

pisacocas, keep the alkali–coca leaf mulched by stirring it with their hands and walking through it with their bare feet. The fluid is quite corrosive, and the workers quickly develop large extremity ulcers. The pisacocas tolerate the ulcers only because they are given a constant supply of coca paste to smoke (Weatherford, 1988).

The dried product is a mixture of cocaine, *cis*- and *trans*-cinnamoylcocaine, tropine, tropacocaine, hygrine, cuscohygrine, ecgonine, BZE, methylecgonine, and isomers of truxillines. The mixture also contains a host of soluble organic plant waxes and benzoic acid. Depending on the alkaloid content of the coca leaves and on how the leaves were processed, it takes between 100 and 150 kg of dry leaf to produce 1 kg of coca paste (Montesinos, 1965; Brewer and Allen, 1991). Once the paste is prepared, the clandestine manufacturer has two options. The paste may be further purified at a base lab, or the producer may go directly to a "crystal lab." At base labs, paste is dissolved in dilute sulfuric acid. Potassium permanganate (potassium dichromate or sodium hypochlorite can be used just as effectively) (Figure 1.4.3.2; International Narcotics Control Board, 1999) is added until the solution turns pink, thereby destroying the cinnamoylcocaine isomers present as impurities in the paste. The isomers of cinnamoylcocaine are converted to ecgonine and, because ecgonine is very water soluble, it is easy to separate it from the cocaine. The job of the clandestine chemist is to stop the oxidation process (usually by adding ammonia or some other alkali)

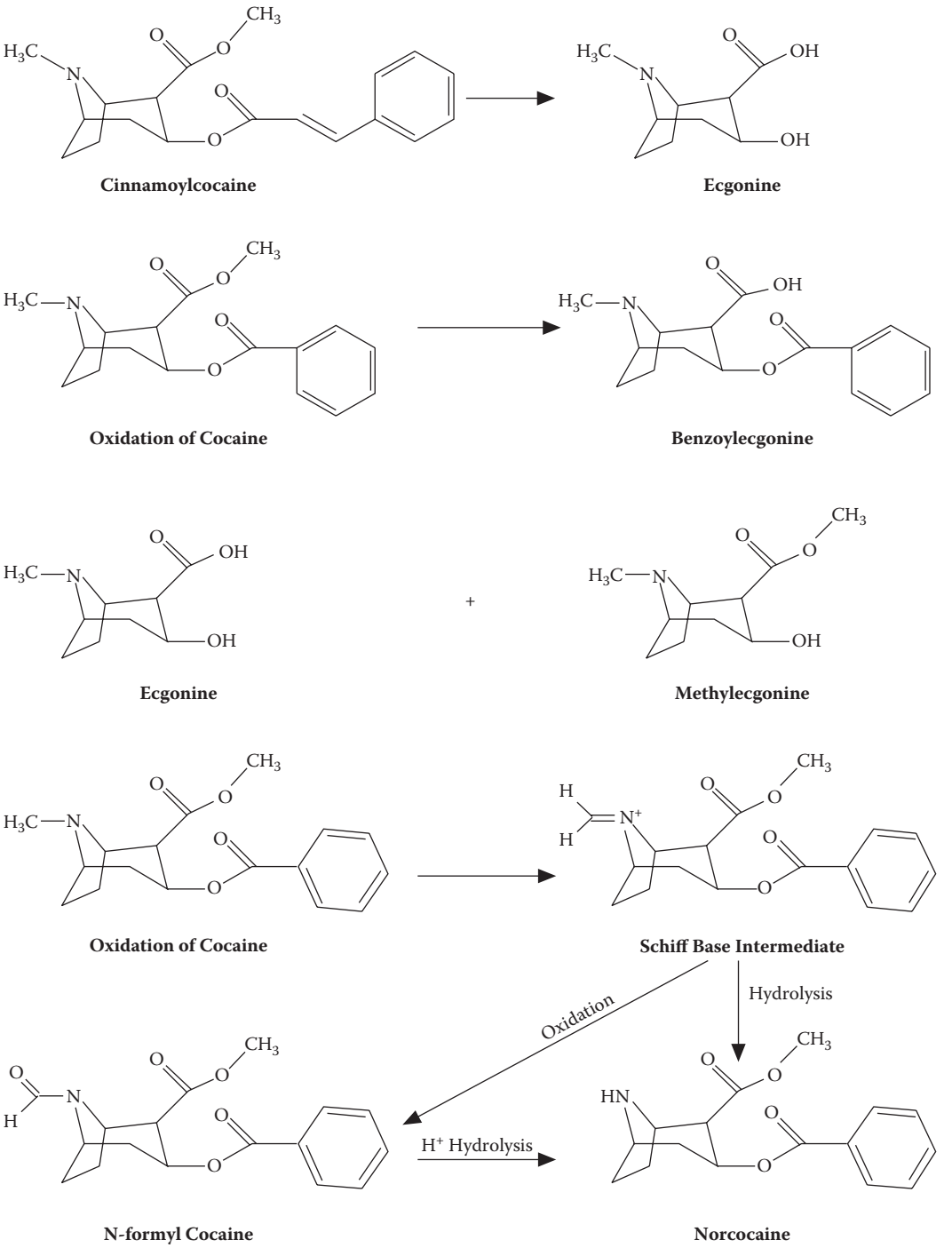

Figure 1.4.3.2 Cocaine refining. Cocaine refiners often add potassium permanganate to remove impurities. Cinnamoylcocaine is converted to ecgonine, which is water soluble and easy to separate from cocaine. If the process is allowed to continue for too long, the cocaine itself is degraded and the yield drops. Norcocaine, which may be hepatotoxic, is formed at the same time.

	2001	2002	2003	2004	2005
Net Cultivation (hectares)	221,800	200,750	166,300	166,200	208,500
Bolivia	19,900	21,600	23,200	24,600	26,500
Colombia	169,800	144,450	113,850	114,100	144,000
Peru	32,100	34,700	29,250	27,500	38,000
Potential Pure Cocaine Production (metric tons)	920	820	675	640	780
Bolivia	60	60	60	65	70
Colombia	700	585	460	430	545
Peru	160	175	155	145	165

Source: Crime and Narcotics Center.

Figure 1.4.3.3 Estimated Andean region coca cultivation and potential cocaine production, 2001–2005. (From the U.S. National Intelligence Drug Report for 2006.) Given the massive drug seizures now occurring offshore in the U.S. and Europe, the figures are almost certainly a gross underestimate.

before the cocaine starts to oxidize and the yield drops. Analysis of impounded samples suggests that permanganate oxidation is used only about 60% of the time.

The reddish-pink solution is allowed to stand, then it is filtered and the filtrate is made basic with ammonia. The cocaine base precipitates out. The precipitate is filtered, washed with water, and then dried. Finally, it is dissolved in diethyl ether or acetone. After filtering, concentrated hydrochloric acid and acetone are added, causing purified cocaine hydrochloride to precipitate out. This final step may be done on site or the semi-purified cocaine may be transported to a "crystal lab" usually located in one of the larger Colombian cities, although some drug producers have begun to set up labs in the U.S. As much as 50 kg may be processed at one time (Lee, 1981). The semi-purified cocaine is dissolved in a solvent, often ether. Hydrochloric acid is then added, along with a bridging solvent such as acetone, and white crystals precipitate out. The crystals are collected by filtration. Traces of the solvent remain, and their presence can sometimes be used to identify the origin of cocaine samples. In coca-producing countries, there is a significant market for the semi-purified paste itself. Paste is smoked, rolled up in pieces of newspaper, or packed into cigarettes. Many of the ingredients introduced during the manufacturing process are still present in the coca paste and are inhaled as pyrolysis products. Coca paste smoking is a major cause of morbidity in coca-producing countries, but there is a paucity of scientific data about it (Paly et al., 1982).

When permanganate is added during the refining process, the *N*-methyl group of cocaine is oxidized, leading to the formation of *N*-formyl cocaine. Hydrolysis of *N*-formyl cocaine leads to the formation of norcocaine. The presence of these last two compounds can have forensic and clinical significance. Because *N*-formyl cocaine is a product of permanganate oxidation, it is not present in coca paste. Accordingly, the presence of this compound may yield valuable information about how, and possibly where, the cocaine sample was produced (Brewer and Allen, 1991).

Norcocaine is potentially hepatotoxic but, as a rule, only small amounts are formed by human metabolism, and then usually only when ethanol is also present. The norcocaine content of raw cocaine is low as well. Analysis has shown norcocaine concentrations in illicit samples

ranging from 0.01 to 3.70% (Moore et al., 1993; Stein and Kraatz, 1996). As expected, chemical analysis of coca paste will disclose the presence of all the elements used during its manufacture, including benzoic acid, methanol, kerosene, sulfuric acid, cocaine sulfate, and other coca alkaloids (Jeri, 1984; Moore and Casale, 1994). Impurities may constitute from 1 to 40% of a given sample of paste. Paste can be broken down into neutral, acidic, and basic fractions. Gasoline residues are particularly common in the neutral fraction (elSohly et al., 1991), and their presence is generally an indicatior that the preferred solvents are not readily available.

Unlike amphetamines, which may occasionally be contaminated with lead during the course of manufacture, coca paste samples have always been found to be lead free. However, paste can contain large amounts of manganese, and the amount of manganese present is a marker for where the paste was produced. Colombian paste is manganese-rich while Peruvian is not (elSohly et al., 1991). Limited studies of blood levels in chronic users suggest that the results of coca paste smoking are not much different than those for "crack" smoking (Paly et al., 1982).

The total synthesis of cocaine is possible, and clandestine cocaine laboratories have been confiscated. The process is, however, a great deal more demanding than the synthesis of amphetamine and has never been attempted on a large scale. The synthetic origin of the cocaine will be evident from the contaminants found along with the cocaine. Diastomers of cocaine, such as pseudococaine, allococaine, and the *d,l-* form (which does not occur in nature) of cocaine, are not found in cocaine refined from coca leaf (Soine, 1989).

1.4.4 Quality

According to data from the Drug Enforcement Agency's STRIDE report, cocaine price and purity trends reported today mirror those reported in the past: very sharp (roughly 70%) price declines during the 1980s through 1989 at all quantity levels, a pronounced (22–35%) one-year increase from 1989 to 1990, and gradual declines during the 1990s, interrupted briefly in 1995. Hence, prices at the end of the 1990s were 30–40% below those in 1989. There was an apparent price jump between 1999 and 2000 that was sustained until 2001, at least at the lowest quantity level. Prices then declined uniformly from 2001 to 2003, reaching all-time lows that are roughly 12–21% below prices in 1999.

Cumulatively, powder cocaine prices have declined by roughly 80% since 1981. The average purity of powder cocaine in 2003 was high and was similar across quantity levels (60–80%) but was still well below the peak levels of the late 1980s. Through the late 1980s, there were pronounced differences in average purity between the two lower quantity levels and the two higher quantity levels. Now those differences are quite small, suggesting that "cutting" or diluting powder cocaine as it moves from the higher (~100 gram) to the lower (~1 gram) quantity levels is not as common as it used to be.

Prices for crack cocaine display many of the same features as the powder cocaine series: sharp price declines through 1989, an even more pronounced (30–45%) one-year increase from 1989 to 1990, and gradual, modest declines at higher quantity levels during the 1990s. There are some differences, however. "Crack" prices rose from 1998 to 1999 and from 1999 to 2000, whereas powder cocaine prices did not begin to increase until 2000, and, notably, "crack" prices at the lowest quantity level did not decrease during the 1990s. As a result, while "crack" prices at higher quantity levels reached all-time lows in 2003, "crack prices" at the lowest quantity level did not. In addition, there are some unique city-specific price and purity trends for "crack" cocaine that diverge widely from the national pattern.

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Figure 1.5.1.1 Crack cocaine. Unlike cocaine hydrochloride, "crack" sublimates at a lower temperature, enabling it to be smoked. (From the website of the Drug Enforcement Agency.)

1.5 Routes of Ingestion

1.5.1 Overview

Ethical considerations prevent the administration of cocaine in anywhere near the amounts consumed by real addicts during a binge. As a consequence, cocaine pharmacokinetics in real cocaine abusers remains largely unstudied and poorly understood. In 2005 and 2006, large, population-based studies of heroin addicts taking realistic doses were finally performed, but it is not clear that similar studies will ever be undertaken in cocaine abusers. Still, a handful of important pharmacokinetic studies have been published. In one of these, an uncontrolled clinical study, plasma cocaine concentrations in 111 symptomatic cocaine users were measured and an attempt made at correlation of plasma with clinical symptoms (Blaho et al., 2000). In another study, the half-life of cocaine was estimated in a group of addicts admitted to a closed ward (Moolchan et al., 2000). Studies using realistic doses of the principal metabolite, BZE, have also been performed. The results of these studies suggest that: (1) chronic users may consume multi-gram quantities of cocaine with relative impunity; (2) a variety of cocaine metabolites, previously thought to be insignificant (ecgonine methyl ester, norcocaine), are actually formed in fairly substantial amounts; and (3) in chronic users, the half-life of cocaine may be much longer than had previously been thought. All of these variables are partly a function of the route of administration (Figure 1.5.1.2).

1.5.2 Coca Leaf Chewing

Coca has been chewed for over 3000 years, but the pharmacokinetics of this process has only recently been characterized. Habitual users chew an average of 12–15 g of leaf three or four times a day. Depending on the quality of the leaf, the alkaloid content is usually less than 0.5%. Thus, the total amount of coca consumed at any one time is unlikely to amount to more than 75 mg. In one experiment, novice chewers who spit out their saliva had average peak plasma concentrations of 38 ng/mL at 1 hour. Experienced users, who

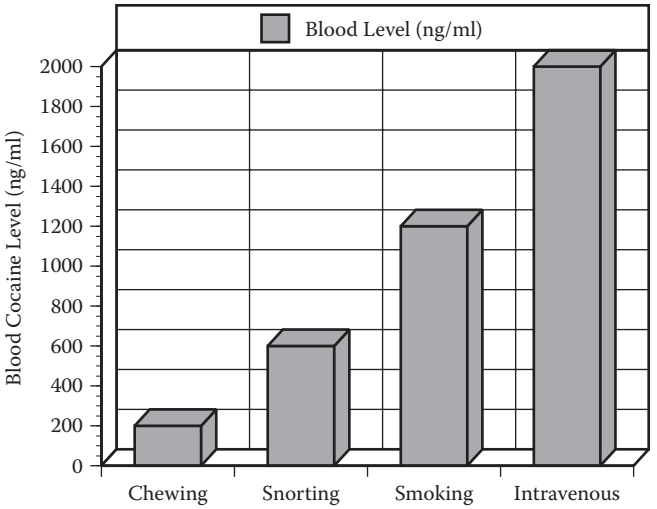

Figure 1.5.1.2 Blood levels and routes of administration. The route of ingestion determines cocaine blood levels. "Crack" smokers may have blood levels three or four times as high as leaf-chewing Indians. Levels after snorting are intermediate.

swallow their saliva, had mean values of 249 ng/mL; however, the range was extremely variable—from 130 to 859 ng/mL (Homstedt et al., 1979; Paly 1979). These concentrations are toward the lower end of the spectrum of levels attained when the drug is snorted.

1.5.3 Snorting (Insufflation)

When cocaine is snorted, peak plasma concentrations are proportional to the amount of cocaine ingested (Wilkinson et al., 1980). Absorption is rapid and bioavailability is good, with half absorbed in less than two minutes (Jeffcoat et al., 1989). However, because cocaine is also a vasoconstrictor, it inhibits its own absorption, and the time required to reach peak concentration becomes longer as the dose increases. One hundred milligrams, which is approximately the equivalent of two to three "lines," will produce a plasma concentration of 50–100 ng/mL, sufficient to cause transient increases in pulse and blood pressure (Fischman et al., 1983; Javaid et al., 1983; Foltin et al., 1988).

In a 2001 study, intranasal application of 1.5 mg/kg (equivalent to 90 mg in a 60-kg man) produced peak plasma concentrations of 120–474 ng/mL within 30–60 minutes of administration (Van Dyke et al., 1976). When somewhat larger doses were given (2 mg/kg), peak plasma concentrations ranged from 131 ng/mL up to 1012 ng/mL, with an average of 370 ng/mL observed at 30 minutes, then falling to 295 ng/mL at 60 minutes, and 223 ng/mL at 90 minutes (Brogan et al., 1992).

Laboratory studies have shown that nasal insufflation is at least as efficient a method for administering cocaine as intravenous injection or smoking. Evidence of behavioral and vascular tolerance begins to emerge almost as soon as the second dose is taken. In a 1994 study (Foltin et al., 1998), two doses of intranasal cocaine, separated by 40 minutes, were administered (0.06, 0.34, 0.69, and 1.37 mg/kg) to four volunteers and dose–response curves measured. Intranasal cocaine produced dose-related increases in ratings of "positive" drug effects, heart rate, and blood pressure. Plasma cocaine levels peaked following the

second cocaine insufflation of each session, while metabolite levels continued to increase. Although the plasma cocaine level approximately doubled following the second cocaine administration, the ratings of positive drug effects, heart rate, and blood pressure did not increase after the second cocaine administration. Clearly, acute within-session tolerance develops during repeated administration of intranasal cocaine (Foltin and Haney, 2004).

In practice, the amount of cocaine taken by users is considerably greater than the test doses given in the laboratory. Blaho et al. (2000) reported that plasma concentrations in four symptomatic cocaine "insufflators" were 0.21 ± 0.20 mg/L. That value is not significantly different than a mean cocaine concentration of 0.18 ± 0.06 mg/L measured in 46 symptomatic "crack" smokers who presented at hospital emergency departments for treatment (Blaho et al., 2000). The plasma concentrations observed in the symptomatic patients are surprisingly close to results observed in volunteers taking cocaine in a controlled setting. Perhaps the most striking aspect of the Blaho study was the enormous amount of drug being ingested. Given that cocaine has a half-life of roughly one hour, along with the reality that many of those included in the study had had symptoms for several hours, it is obvious that, at one point, some of the patients would have had plasma concentrations of more than 5 mg/L!

1.5.4 Surgical Application

Cocaine is still used by otorhinolaryngologists as well as cosmetic and plastic surgeons, but this practice has decreased greatly in the past 25 years. The explanation has partly to do with physicians having found alternative anesthetics that are equally effective, and partly because of the decreasing number of physicians with experience using cocaine. Alternatively, the decline might just reflect doctors' reluctance to take on the extra accounting and paper work required to use cocaine. In 2004, Long et al. mailed 7815 surveys to practicing otorhinolaryngologists and nearly half responded. Only half of the respondents said they had used cocaine in their practice during the previous year (Long et al., 2004). Nonetheless, the combination of cocaine and epinephrine is still used, especially in the management of children with lacerations (Kennedy et al., 2004), and complications with this approach seem quite rare.

When cocaine-soaked pledgets are used to control epistaxis, considerable cocaine is absorbed, and plasma concentrations may exceed 600 ng/mL within the first half hour (Liao et al., 1999). High plasma levels may explain why the occasional myocardial infarct has been reported in conjunction with the practice (Laffey et al., 1999).

At the turn of the century, cardiac arrest was a relatively frequent complication of cocaine and cocaine/epinephrine anesthesia (Mayer, 1924). The practice has now largely been abandoned, but cocaine is still occasionally mixed with an epinephrine solution to produce something known as cocaine paste or mud. Occasionally bicarbonate is added to the mix, but even then the resultant plasma levels can be very high. Concentrations of over 2000 ng/mL have been observed (Lips et al., 1987; Bromley and Hayward, 1988). Injected epinephrine is, of course, absorbed along with the cocaine, and this may lead to toxicity. Potential for the occurrence of an untoward event such as myocardial infarction is very real (Meyers, 1980; Chiu et al., 1986; Littlewood and Tabb, 1987; Ross and Bell, 1992; Ashchi et al., 1995; Noorily and Noorily, 1996; Laffey et al., 1999; Osula et al., 2003).

The surgical application of even small amounts of cocaine will cause the patient to test positive for cocaine for up to three days. When patients undergoing lacrimal duct surgery

were anesthetized with less than 3 mL of topical 4% cocaine hydrochloride, urine specimens obtained 24 hours later were almost all found to have cocaine concentrations that exceeded 300 ng/mL, which is the National Institute on Drug Abuse (NIDA) cutoff for a positive test. Urine from some of the patients still exceeded the cutoff at 48 hours, and in a few, cocaine was still detectable 72 hours later, though at levels less than 300 ng/mL (Cruz et al., 1991). In a separate study, patients were given either 160 or 400 mg of cocaine when they were undergoing septoplasty; 90% of the drug was absorbed within the first 15 minutes. Plasma from the group receiving 400 mg, drawn 20 minutes after application, had a mean concentration of 0.608 ± 0.09 mg/L (Liao et al., 1999).

Surgeons may accidentally contaminate themselves and test positive for cocaine. One study considered several possible exposure scenarios (Bruns et al., 1994). The study involved 22 patients who had routine nasal surgery and the surgeons who operated on them. The surgeons participating in the study used their fingers to mix 4 mL of 4% cocaine into cotton pledgets that were then inserted into the patient's nostrils. The surgeons wore masks at all times. In six cases they also wore gloves, and in six cases they did not. In order to test for cumulative effects, a separate experiment was done; a single physician handled cocaine on Day 1 once every 2 hours for 6 hours, and on Day 2, once every hour for 6 hours. Cotton-soaked pledgets were prepared as if surgery was to be performed. The cotton was handled for 2 minutes, and the surgeon then washed his hands 15 minutes later.

When surgeons wore gloves, no cocaine metabolite was detected. When the surgeons did not wear gloves, BZE appeared in their urine, although at levels well below NIDA or Department of Defense (DOD) cutoffs, either for screen assays or gas chromatography/mass spectrometry (GC/MS) confirmation. The mean BZE concentration was 30.1 ng/mL at 8 hours and 18.8 ng/mL at 24 hours. The highest BZE level recorded was 53 ng/mL. However, much higher levels were observed when one surgeon handled the cocaine-soaked cotton for the 2-day study, and a cumulative effect was definitely observed. Twelve hours after the first exposure (once every 2 hours for 6 hours), BZE levels were approximately 90 ng/mL. Eighteen hours after the second exposure, levels measured by GC/MS had risen to 245 ng/mL, a positive result by either military or civilian standards.

1.5.5 Intravenous Use

Intravenous cocaine produces much higher plasma concentrations of cocaine than coca leaf chewing, which is almost certainly why intravenous users are more likely to experience illness or even die. A 40-mg bolus of cocaine given intravenously to a human volunteer produces plasma concentrations of between 204 and 523 ng/mL at 10 minutes (Kumor et al., 1988). A 32-mg dose given to volunteers produced peak levels of approximately 250 ng/mL, with a maximum increase in heart rate at 7.3 minutes (Chow et al., 1985). Barnett et al. (1981) observed levels of 700–1000 ng/mL, 5 minutes after injecting 100 mg. The levels exceeded 2500 ng/mL after an injection of 200 mg. Blaho et al. (2000) reported that typical symptomatic emergency room patients, presenting after injecting unknown amounts of cocaine, had relatively low plasma cocaine concentrations of 170 ± 0.24 ng/mL, but much higher concentrations of BZE, with a median plasma concentration very near 2000 ng/mL.

Intravenous cocaine produces a more intense and immediate response than ingestion by any other route except for "crack" smoking, but it does require multiple frequent injections to maintain a "high." Narcotic users, by comparison, inject infrequently.

The increased number of injections places the cocaine user at greater risk for infection with human immunodeficiency virus, as well as all of the other infectious complications of intravenous drug use. In fatal cases of "speedballing" (combining cocaine and heroin), death-scene investigators generally find that the heroin has been injected and the cocaine smoked, though recently there have been more and more anecdotal reports of abusers injecting "crack" cocaine (Lankenau et al., 2004; Buchanan et al., 2006).

1.5.6 Genital Application

Cocaine is promptly and completely absorbed through the mucous membrane. High blood levels are achieved quickly. In addition, cocaine acts as a local anesthetic, which may make certain sexual practices more comfortable. However, the main cause of genital application today is smuggling, where drug couriers conceal packets of drugs in their vagina or rectum (though swallowing still remains the preferred route) (Mebane and DeVito, 1975; Gallup et al., 1991; Benjamin et al., 1994; Klein et al., 2000).

Fatalities have been reported after direct vaginal or rectal application during sexual activities (Doss and Gowitt, 1988; Greenland et al., 1989). Except for a pregnant woman who died of air embolism after her partner blew "crack" smoke into her vagina (Collins et al., 1994), the clinical histories in these patients suggest that death was due to arrhythmia, but, interestingly, reported plasma concentrations have not been high.

Toxicity from genital application is not limited to females. Priapism has been reported in men after application of cocaine to the glans (Mahler et al., 1988; Fiorelli et al., 1990; Rodriguez-Blaquez et al., 1990; Munarriz et al., 2003) and occasionally leads to serious surgical complications (Altman et al., 1999). Biopsy of the corpora in these individuals demonstrates fibrosis (Minardi et al., 2004). Drugs and alcohol, not just cocaine, are commonly introduced into the rectum to promote sphincter relaxation and to ease the discomfort of anal dilatation. Plasma cocaine concentrations after rectal application have never been measured.

1.5.7 Dermal Absorption

Cocaine adheres to the skin and can be absorbed through it. Controlled experiments have shown that cocaine can remain on the skin for at least three days after external exposure (Kidwell et al., 1997), and that it is not easily removed. The most reasonable explanation is that positively charged drugs will bond ionically to skin proteins, just as they bond to protein in hair (Levisky et al., 2000; Kidwell and Smith, 2001). That would explain why cocaine can be recovered from the skin of individuals who have handled "crack" cocaine, even after thorough hand washing, or swabbing with 70% isopropyl alcohol. It is quite unlikely that anyone could absorb enough cocaine via this route to cause a NIDA positive urine test (although that can occur when an individual has handled bulk cocaine) (Maloney et al., 1994).

In one very small study, where 5 mg of cocaine hydrochloride and 5 mg of cocaine free base, dissolved in alcohol, were painted on the forearm skin of a volunteer, the maximal urinary BZE concentration from the free base was 55 ng/mL at 48 hours. Much less of the cocaine hydrochloride was absorbed, with a peak urine level of only 15 ng/mL at 48 hours (Baselt et al., 1990). A similar study, done with cocaine paste, yielded much the same result (ElSohly, 1991).

In most instances, the testing of medical personnel is not federally regulated, which means that a zealous administrator might pursue charges against an individual with a urine BZE concentration well below federally mandated cutoffs. The concern is mostly academic, because two separate studies have shown that physicians, unless they violate all rules of infection control, are not likely to accidentally absorb sufficient quantities of cocaine via the skin, or even via an aerosol, to test positive.

While physicians may not be at risk for false positive tests, crime technicians may well be. In a systematic study of crime lab employees, laboratory procedures were examined by monitoring personal breathing zones (PBZ), ambient airborne cocaine levels in the laboratory spaces, and urinary levels of the primary cocaine metabolite, BZE. The study was performed when the technicians were using their standard laboratory procedures. A subsequent study was performed to determine the effectiveness of the follow-up procedure in reducing exposure. As a result of the changes, the 8-hour time weighted averages were 40–80% lower in the follow-up study as compared to the baseline assessment. Most of the exposure was attributed to airborne and dermal exposure (Gehlhausen et al., 2003).

Environmental skin contamination is not the only explanation for the presence of cocaine in or on the skin. Cocaine has a relatively large volume of distribution (V_{ss}). Various reports suggest values of 2.5–3.0 L/kg, which means that cocaine will distribute throughout the tissues in the body, including the skin. Studies of tissue obtained at autopsy have shown high concentrations of abused drugs in abdominal skin and subcutaneous fat, even of drugs that are generally not thought of as being highly lipophilic. The rate at which such drugs move from subcutaneous skin to the surface, if they do at all, is simply not known (Levisky et al., 2000).

Absorption through the skin is also of theoretical concern for convicted drug takers who are being monitored with sweat-collection patches. It has been suggested that exposure to low levels of drug in the environment could lead to skin absorption, entrance of very small amounts of drug into the bloodstream, subsequent secretion of the drug into the sweat, and eventual collection of that drug-containing sweat by the patch. The results of several studies suggest that this scenario, while logically possible, simply does not occur. However, the possibility of absorption through the patch has never been entirely ruled out (Kidwell et al., 2003). The body has a great deal of skin, and there is no reason why it should not act as a repository. Even though the amounts of cocaine released into the bloodstream at any one time remain below limits of detection, the drug would still be absorbed by a sweat detection patch (Yang et al., 2006).

1.5.8 Inhalation

By 1986, the practice of smoking cocaine free base extracted with volatile solvents gave way entirely to the practice of smoking "crack" (Washton and Gold, 1986). In order to make "free base," cocaine must first be dissolved in ether which is then heated, a practice even skilled chemists would approach with caution. Many of the less-skilled "freebasers" sustained life-threatening burns. Perhaps the most famous of these was the American comedian Richard Pryor.

The origins of "crack" smoking are not entirely clear. It has been alleged by conspiracy theorists that introduction of the drug was either (1) a genocidal plot to destroy the black community, or (2) a cynical approach towards fundraising, adopted by an administration badly in need of cash to support covert military operations in South America. Neither

theory is supported by any substantial body of evidence, though it must be admitted that the financing of wars by selling drugs is a very old tradition, first introduced into North America by the Spanish more than 500 years ago (Karch, 2005). Another popular theory, that "crack" is cheaper than cocaine hydrochloride, has been disproved by economists (Caulkins, 1997). The first medical reports of "crack" smoking came from the Bahamas in 1983 (Jekel et al., 1986), followed by the first mentions of "crack" smoking in New York City in 1985 (Gross, 1985).

"Crack" prepared on the streets contains variable amounts of bicarbonate and other contaminants. In order to produce "crack" for performing clinical experiments, cocaine hydrochloride is mixed with an equal weight of sodium bicarbonate in sterile water and the mixture placed in a boiling water bath. Cocaine base precipitates out and forms small pellets or rocks when the water is cooled. "Crack" prepared in this way is quite pure, and smoking 50 mg of base will deliver between 16 and 32 mg of cocaine to the subject (Foltin and Fischman, 1991). The composition of "crack" has a great deal of clinical significance; the salting out process removes many, if not most, of the adulterants and contaminants. Removal of the contaminants may make the occurrence of medical complications less likely. For example, the entity of eosinophilic myocarditis in cocaine abusers (an allergic disorder), all but disappeared after "crack" was introduced. There have been recent reports of "crack" cocaine containing alpha-methyl fentanyl, suggesting that agent is not removed in the process.

There have been many anecdotal reports of cocaine/fentanyl combinations being sold on the street, usually represented as pure cocaine. However, the traces of fentanyl found in some of these exhibits may actually be the result of contamination, either from reuse of the plastic "baggies," or contamination by the distributor during formulation (i.e. selling a cocaine/fentanyl mixture was never intended). Clearly, this explanation does not apply to all of the samples, because the percentage of fentanyl in some of the samples has been extraordinarily high—23 per cent (Anon., 2006a).

When faced with arrest, many "crack" smokers swallow the drug packets they are carrying. The act is referred to as "body stuffing" as opposed to "body packing," which is a means of smuggling. The chief risk to the first practice is that instead of swallowing the small packets dealers have aspirated and choked to death trying to hide the evidence. The fatality rate for "packing" (concealing large amounts of drug in the intestines) is much higher. A newspaper article published in 2006 described a transatlantic flight that had to be diverted because one of the passengers had fallen ill and was vomiting; he had swallowed more than 1.5 kg of cocaine and began to regurgitate the packets in mid-flight (Anon., 2006b). When cocaine is smuggled in this fashion it is usually wrapped in latex (see Figure 1.5.9.4), but if the package leaks, the results can be fatal (Bednarczyk et al., 1980; Wetli and Mittlemann, 1981).

If the "crack" has been formulated in such a way that it contains substantial amounts of bicarbonate, the rock is likely to pass through the stomach without dissolving and without producing symptoms. If the "crack" contains more cocaine than bicarbonate, it may dissolve rapidly and produce toxicity. Today "crack" is most often sold in small plastic vials and there are anecdotal reports of body-stuffers who have died not from cocaine poisoning, but from aspirating the plastic vials or small rocks covered with plastic wrapping (Zaas et al., 2002).

In controlled laboratory studies, plasma cocaine concentrations measured 6–12 minutes after smoking 50 mg of "crack" ranged from 250 to 350 ng/mL. In a second study from

the same laboratory, two 50-mg doses of free base were smoked 14 minutes apart; the peak plasma concentration was 425 ng/mL four minutes after smoking the last dose (Foltin and Fischman, 1991). In one subject, smoking a 50-mg dose every 14 minutes, for a total of four doses, produced a plasma concentration of over 1200 ng/mL. In both humans and experimental animals, changes in heart rate and blood pressure are dose dependent and correlate temporally with peak plasma cocaine concentrations (Boni et al., 1991), but there is a great deal of variation between experimental subjects, animal and human.

Drug concentrations in symptomatic "crack" smokers seeking emergency treatment are very similar to those reported in earlier controlled trials. In the study by Blaho et al. (2000), plasma cocaine concentrations in symptomatic "crack" smokers were indistinguishable from the plasma concentrations of individuals who prefer to insufflate their drug and, regardless of which route had been used, there was no correlation between blood concentrations and symptoms.

Side-stream exposure to cocaine vapor can cause measurable quantities of cocaine metabolite to appear in the urine. When a 73-kg adult male was confined in a closed space approximately the size of a closet and exposed to 200 mg of volatilized free base, urine concentrations over the next 24 hours ranged from 10 to 50 ng/mL (Baselt et al., 1991). Environmental exposure to cocaine is also a real hazard for inner-city children. Nearly 2.5% of children examined at a metropolitan emergency department tested positive for cocaine or cocaine metabolite. The number would probably have been higher, but children with signs of cocaine toxicity or a history of cocaine exposure were specifically excluded from the survey (Kharasch et al., 1991).

1.5.9 Gastrointestinal Absorption

Cocaine is well absorbed via the gastrointestinal tract. Chewers who swallow their saliva have higher plasma cocaine levels than those who do not. The hydrochloride salt is absorbed even more completely than masticated leaf (Wilkinson et al., 1980). Plasma levels in coca chewers have been measured (Paly et al., 1982), and the gastrointestinal absorption of cocaine hydrochloride has been studied in at least two controlled clinical trials.

In a decade-old trial with human volunteers, ascending doses of cocaine were given over the course of several weeks so that participants were eventually receiving up to 2000 mg of cocaine hydrochloride per day. Peak plasma concentrations occurred approximately one hour after administration. The maximum concentrations produced by doses ranging from 1250 mg (five separate doses of 250 mg each) to 2000 mg/day (five separate doses of 400 mg each), ranged from 653 to 1899 ng/mL (Jufer et al., 1998).

In a second trial, concerned mainly with psychological effects, oral doses of up to 300 mg of cocaine hydrochloride were well tolerated, producing only transient and insignificant changes in blood pressure. Interestingly, the subjects of the second trial rated the stimulant effects higher, and more pleasurable, after oral dosing than after smoking or insufflating (Rush et al., 1999).

Gastrointestinal absorption assumes particular importance in the "body packer" syndrome (Figures 1.5.9.1 and 1.5.9.2). Most packets are round to oval in form and are easily seen with plain x-ray, though CT scanning is generally considered a more sensitive diagnostic tool. The packet's content is suggested by the form of x-ray attenuation observed: hashish is denser than stool, cocaine appears similar to stool, and heroin has a gaseous transparence (Hergan et al., 2004). Asymptomatic packet ingestion is managed

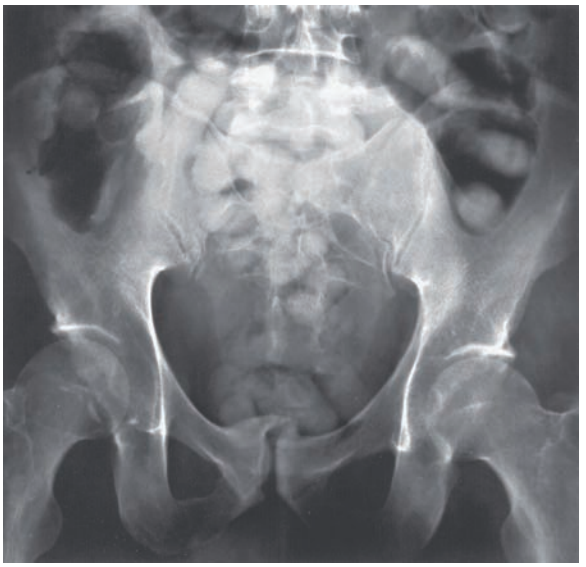

Figure 1.5.9.1 "Body packer" syndrome. Drug couriers can be diagnosed with plain abdominal x-rays, although occasionally CT scanning is required. This plain film clearly demonstrates cocaine-containing packets. (From *Abdom. Imaging,* 20, 339, 1995. With permission. Courtesy of Dr. M. Meyers, State University of New York, Health Sciences Center.)

conservatively, but leakage from the packets can constitute a surgical emergency. In a review of 17 cases collected over a decade in Jamaica, there were 11 cases of bowel obstruction, two of delayed passage of pellets, three of ruptured pellets with cocaine toxicity, and one patient who panicked and requested surgery. The distal ileum was the commonest site of obstruction. It appears that actual cocaine poisoning only occurs when the packets

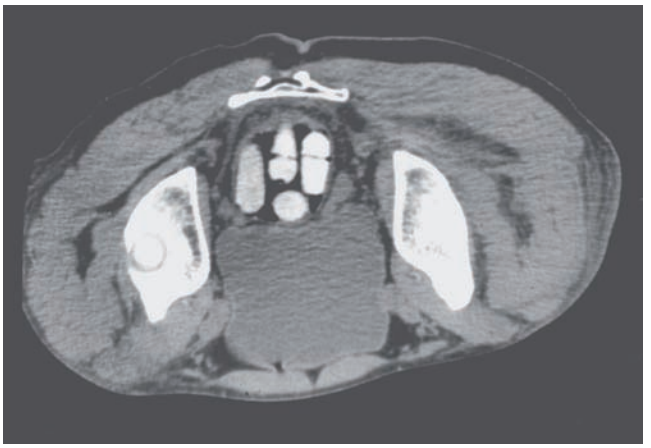

Figure 1.5.9.2 "Body packer" syndrome. This syndrome was first described in 1977. Smugglers who swallow multiple, rubber-coated packets of drugs are at grave risk for massive overdose. (From *Abdom. Imaging,* 20, 339, 1995. With permission. Courtesy of Dr. M. Meyers, State University of New York, Health Sciences Center.)

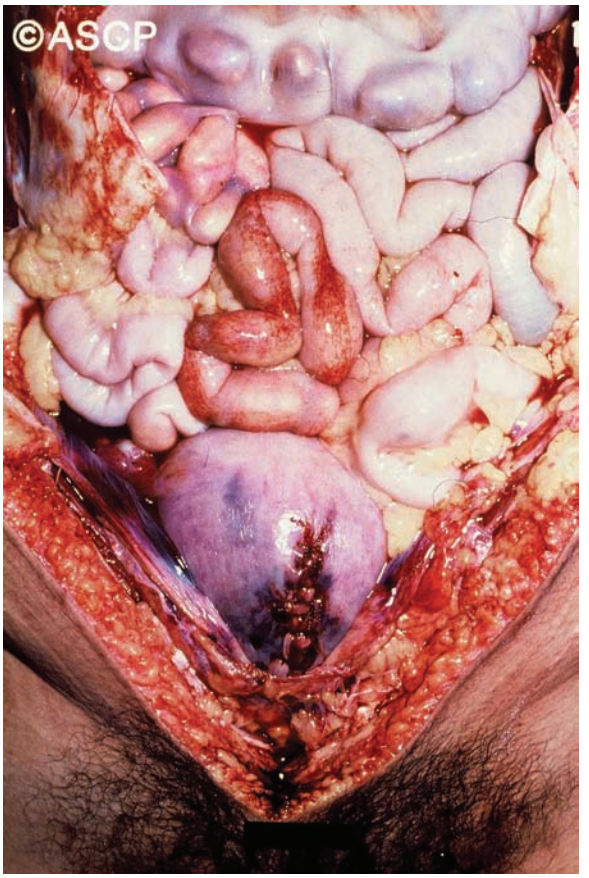

Figure 1.5.9.3 Pregnant drug courier. Pregnant uterus is visible in lower section of picture, while cocaine-filled condoms are apparent throughout the intestinal tract; see Figure 1.5.9.4. (Photograph courtesy of the College of American Pathologists, Northfield, IL.)

rupture in the upper gastrointestinal tract. Obstructing packets must, of course, be removed, but if unruptured, the packets may be allowed to pass spontaneously (East, 2005).

The practice of "body packing" was first described in 1977 (Suarez et al., 1977). Low-level smugglers ("mules") swallow packets containing hundreds of grams of cocaine. The drugs are wrapped in a condom, plastic bag, or aluminum foil, with each packet containing 3–6 g of drug; an individual courier may carry nearly two kilograms of drug. If a cocaine-containing packet should rupture, fatal seizures will result, usually with concomitant pulmonary edema and heart failure. If the drug courier happens to be regular user with some degree of tolerance, even a massive overdose may not produce the classical symptoms, and the outcome is not necessarily fatal (Bettinger, 1980; Howell and Ezell, 1990). Occasionally body packers may present first with toxic psychosis, rather than fever (Fernandez Moyano et al., 1998).

Plasma concentrations in body packer fatalities have ranged from 3 to 11 mg/L, well in excess of levels normally seen after intravenous abuse. Even if the cocaine-containing packets do not rupture, small amounts of cocaine may still appear in the urine, and urine testing may be diagnostic for the syndrome (Gherardi et al., 1990). Most major international airports are now equipped with facilities for on-site EMIT urine testing, and special

Figure 1.5.9.4 Drug packets. Cocaine packets removed from decedent shown in Figure 1.5.9.3. Reports suggest that some may ingest up to half a kilogram in this fashion. (Photograph courtesy of the College of American Pathologists, Northfield, IL.)

toilet facilities with which to collect the contraband. Gastrointestinal absorption can also occur via mother's milk (Dickson et al., 1994; Golding, 1997; Winecker et al., 2001).

Still another form of gastrointestinal absorption involves drinking coca-based teas and, more recently, coca-containing soft drinks. These are popular in many parts of South America where they are sold commercially. At the end of 2005, an Indian-owned company in Colombia began to sell its own brand of coca soda as an alternative to Coca-Cola™. It is called Coca Sek™, which, in the local dialect, means "coca of the sun." It is a carbonated drink made from the coca leaf extract and is said to taste like lemonade and ginger ale.

Coca is also consumed in South America as a tea. The average coca leaf tea bag contains approximately 1 g of dried coca leaves. The content of the commercial tea bags is quite variable, depending on where they are manufactured. A reasonable approximation is that 1 g of dried, shredded coca leaf wlll contain 4 to 5 mg of cocaine plus variable amounts of BZE and ecgonine methyl ester, along with trace amounts of *trans*-cinnamoylcocaine. Depending on the origins of the tea, urinary BZE concentrations in those who consume it range from 4000 ng/mL to almost 5000 ng/mL at 3.5–10 hours after ingestion (Jenkins et al., 1996).

Coca-containing tea has become an increasing problem for workplace testing programs. In one instance, an enlisted man who was not a cocaine user had to face courts martial because of a positive urine cocaine test. He claimed not to be a user, but did admit to drinking a tea called mate de coca. When a single tea bag was placed into 100 mL of

water and boiled for 10 minutes, 5.35 mg of cocaine, 0.64 mg of ecgonine methyl ester, and 0.26 mg of BZE were extracted. This would have been more than enough to result in a positive urine test (Anon., 2005). Similarly, the *British Journal of Sports Medicine* recently reported positive tests for BZE in jockeys who had been drinking mate de coca tea (Turner et al., 2005). Of course, even possessing coca tea in the U.S. is a crime.

In a recent study of five healthy adult volunteers who consumed coca tea and then underwent serial quantitative urine testing for cocaine metabolites, urine cocaine concentrations exceeded 300 ng/mL by 2 hours after ingestion. Three out of five participants' samples remained positive at 36 hours. Mean urine BZE concentration in all post-consumption samples was 1777 ng/mL (95% confidence interval: 1060–2495) (Mazor et al., 2006).

1.5.10 Special Maternal/Fetal Considerations

Little is known about maternal/fetal cocaine drug ratios, nor is it known whether such measurements have any meaning. By mid-pregnancy, the fetus may come into direct contact with high concentrations of cocaine that have been absorbed in the amniotic fluid (Woods, 1998). How much cocaine, if any, the fetus actually absorbs via this route is not known, nor is it known whether the amount absorbed has any medical significance, though there is some epidemiologic evidence that 20% of infants exposed to cocaine in utero will develop hypertension later in life (Salisbury et al., 2006). Cocaine, along with concentrations of nicotine, caffeine, and their metabolites, has been measured in the cord blood in 36 neonates. Eighteen neonates had detectable concentrations of BZE, and 50% of these were also positive for cocaine. Cocaethylene was not found in any case. The maximum plasma cocaine concentration measured in any newborn was 88 ng/mL (mean, 39 ng/mL). The maximum plasma BZE concentration observed was 3880 ng/mL (mean, 844 ng/mL). Among BZE-positive babies, the mean plasma drug levels were as follows: nicotine, 1.8 ng/mL; cotinine, 94 ng/mL; and caffeine, 1205 ng/mL. Among the BZE-negative babies, the mean plasma drug levels were as follows: nicotine, 5.2 ng/mL; cotinine, 97 ng/mL; and caffeine, 1440 ng/mL (Dempsey et al., 1998). In the same study the half-life of cocaine and BZE was 11.6 and 12.8.

Within the U.S. court system, the transfer of cocaine through breast milk has been alleged to be fatal and nursing mothers charged with abuse or even manslaughter. However, given the infant's daily consumption of milk, and given the cocaine concentrations that have been measured in human breast milk, it seems unlikely that toxic quantities of cocaine could be transferred in this fashion. When breast milk was collected from 11 cocaine-using mothers, cocaine was detected in six of the specimens. When cocaine and one or more of its metabolites were detected, the concentration of parent compound was greater than any of the metabolites. The highest cocaine concentration ever found in any report was a surprisingly high 12 mg/L (Winecker et al., 2001).

The result would suggest that breast-fed infants of cocaine-abusing mothers can be exposed to significant amounts of drug orally. Unfortunately, the sampling technique used in the last study discussed was inadequate. The study was performed before it was recognized that concentrations in the first milk expressed are very different from concentrations in the last milk expressed at the end of feeding (Stowe et al., 2003). The only way to be sure of the amount of drug delivered is to collect all the milk produced over a 24-hour period and measure the average concentration; having a woman express some milk and measuring the cocaine concentration, is simply unacceptable—the concentration of any drug

in breast milk tends to increase as more and more of the milk is expressed. Neither can breast milk drug concentrations be calculated by analogy to the behavior of other similarly structured molecules. Milk does concentrate drugs to higher concentrations than plasma, but how much depends on the actual molecule, and even though molecules may be related (e.g., methamphetamine and amphetamine), that does not guarantee that the same concentration will occur in the milk.

Recommendations for breast-feeding cocaine users have been developed (Sarkar et al., 2005). The National Academy of Pediatricians has also developed its own guideline for cocaine-using women who breast feed (Anon., 1995).

In vitro studies of the human placenta have demonstrated high-affinity binding sites for cocaine (Ahmed et al., 1990), and isolated perfused cotyledons of normal term human placenta passively, but rapidly, transport cocaine, though it appears they do not metabolize it. The same holds true for cocaethylene and norcocaine. In this *in vitro* model, the direction of transport seems to depend entirely upon the relative concentration of cocaine in the mother and fetus; when fetal levels are higher than maternal levels, equally rapid transport back across the placenta occurs (Schenker et al., 1993), but results are often unpredictable (Bailey et al., 1998).

When amniotic fluid from 450 women between 12 and 39 weeks of pregnancy was screened for cocaine or its metabolites, only five samples out of 450 were positive for cocaine when measured by GC/MS, and only one sample was positive for cocaethylene (Ripple et al., 1992). In a second study, cocaine or BZE was detected in 74% of amniotic fluid samples taken from 23 known cocaine abusers. In the 23 cases that were positive, concentrations in the amniotic fluid ranged from 400 to greater than 5000 ng/mL for BZE, and from trace amounts to 250 ng/mL for cocaine (Jain et al., 1993). Interestingly, BZE concentrations were significantly greater in the amniotic fluid than in the urine of the newborns (1800 and 280 ng/mL, respectively; $p = 0.0001$), suggesting that not a great deal of drug had been absorbed, either via the skin or through the gastrointestinal tract.

The results of at least two other studies suggest that, in spite of maternal use, fetal cocaine absorption does not necessarily occur in every case. A case report published in 1994 described a 26-year-old woman who was an admitted intravenous cocaine user. She had injected herself daily throughout the course of her pregnancy. She also used hashish on a weekly basis during the first trimester of the pregnancy, drank alcohol on occasion, and smoked one to two packs of cigarettes a day throughout the pregnancy. Hair samples from the mother, obtained two months after delivery, contained nicotine, cotinine, and BZE (concentrations in various segments of hair ranged from 0.8 to 2.3 ng/mg). Urine from the child was negative for BZE and cannabinoids, and only cannabinoids were detected in the meconium. Hair samples obtained from the child at birth were negative for cocaine and BZE, but did contain nicotine and cotinine (Potter et al., 1994).

Similar anomalies have been reported in other cases. When cocaine and its metabolites were measured in urine, meconium, and amniotic fluid specimens collected from 30 mother–infant pairs with histories of prenatal cocaine use, there was qualitative, but not quantitative, agreement between results in mother and child. This applied to maternal urine, amniotic fluid, infant urine, and meconium. However, even though all of the mothers in this study admitted to using cocaine during their pregnancy, cocaine or its metabolites were detected only in the 20 cases in which cocaine was used within three weeks before delivery (Casanova et al., 1994). Eyler et al. (2005) conducted private structured interviews with women who had a prior history of perinatal cocaine use. In most instances the

history provided by the mothers corresponded with the toxicological findings. However, in five cases of infants born to women who admitted using cocaine during their pregnancies, tests of hair, urine, and meconium were all negative (Eyler et al., 2005).

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1.6 Metabolism of Cocaine and Its Metabolites

1.6.1 Cocaine

Cocaine is rapidly cleared from the bloodstream at an estimated rate of 2.0 L per minute (Figure 1.6.1.1) (Inaba et al., 1978). In healthy human adults cocaine has a half-life that has variously been reported as between 0.5 and 4.0 hours, depending mainly on whether the individual is a chronic or naïve user (Chow et al., 1985; Moolchan et al., 2000). However, many other factors must be considered when attempting to evaluate postmortem measurements of any drug, including cocaine (Skopp, 2004). For example, the half-life of cocaine is much longer in the newborn than in adults—on the order of 11–12 hours (Dempsey et al., 1998).

The results of animal as well as human clinical and autopsy studies demonstrate that cocaine is stored in deep body compartments and that its rate of excretion changes as the drug accumulates (Weiss and Gawin, 1988; Cone and Weddington, 1989; Burke et al., 1990; Jufer et al., 1998; Levisky et al., 2000; Preston et al., 2002). Excretion rates are also altered by the amount of cocaine consumed; "crack" smokers consume multiple gram quantities of the drug, not just milligrams doses (Gossop et al., 1994), and even though clearance rates are substantial, traces of cocaine remain in the body for weeks, and in the hair for months (years in the dead). As previously discussed, ethical considerations prevent pharmacokinetic studies performed with realistic doses of cocaine.

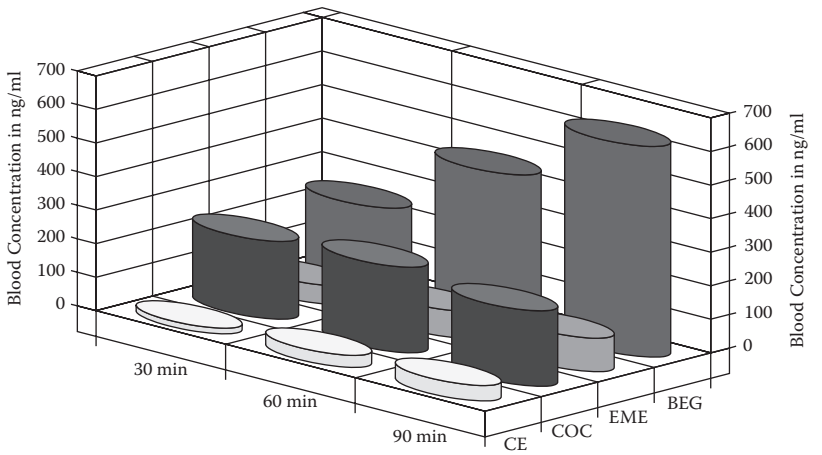

Figure 1.6.1.1 Blood concentrations of cocaine and its metabolites in humans. Average blood concentrations of cocaethylene (CE), cocaine (COC), ecgonine methyl ester (EME), and benzoylecgonine (BZE) in eight subjects given 2 mg/kg of intranasal cocaine and 5 mL/kg of 10% ethanol. (Data adapted from Pirwitz, M. J. et al., *Arch. Intern. Med.,* 155, 1186–1191, 1995.)

In analysis of 104 postmortem urine specimens, already tested and known to be positive for cocaine metabolite (either BZE or EME, or both), cocaine was found to be present in 66% of the specimens, sometimes in very high concentrations (0.07–78 mg/L). In this study, when the BZE concentration of the urine sample was greater than 2.0 mg/L, cocaine was detected in 83% of the specimens, but the detection rate dropped to only 30% when BZE levels were under 2.0 mg/L (Ramcharitar et al., 1995). In a study of 99 cocaine-related deaths, the mean urine cocaine concentration in 48 individuals actually dying of cocaine toxicity was 1.12 mg/L ± 2.71, but only 0.487 ± 0.75 mg/L in those where cocaine was an incidental finding (Karch et al., 1998). The difference was not statistically significant.

More than a dozen different cocaine breakdown products have been identified, but they are rarely measured, mainly because their presence seems to be of little clinical or forensic significance. In Blaho's series of 46 symptomatic "crack" smokers, the mean concentrations of cocaine and its principal metabolites, listed in decreasing order, were: BZE (1.4 ± 0.19 mg/L) > ecgonine methyl ester (0.53 ± 0.05 mg/L) > ecgonine (0.53 ± 0.07 mg/L) > cocaine (0.18 ± 0.06 mg/L) > norcocaine (0.04 ± 0.03 mg/L) > cocaethylene (0.02 ± 0.01 mg/L) (Blaho et al., 2000).

Most hospital laboratories use commercial immunoassay kits for urine screening. There are many products to choose from, but almost all of these screening kits are designed to detect only BZE. Other metabolites, even if present, go undetected or produce only minimally positive cross-reactions. Over the last decade researchers have begun to introduce other diagnostic techniques (tandem mass spectrometry or LC/MS/MS) that allow for the simultaneous measurement of cocaine and all of its metabolites, including even pyrolysis products, and do so all at the same time (Klingmann et al., 2001; Lewis et al., 2004). More importantly, the price of these measurements continues to decline (Cognard et al., 2006). The same situation applies to heroin and its metabolites (Rook et al., 2005). It seems likely that in the not too distant future, immuno-screening tests will be replaced with LC-tandem mass spectrometry. One implication of this development is that physicians trying to interpret laboratory results will require some knowledge of the role, if any, played by many different drug metabolites that can and will be identified. This will require a steep learning curve for the pathologists and considerable effort on the part of the toxicologists; it will also require a great deal of money. Funding these new technologies will prove to be a considerable challenge for even the most affluent of medical examiner's offices.

In the absence of alcohol, the principal breakdown products of cocaine are BZE (BEG) and ecgonine methyl ester (EME). Three distinct esterases (hCE-1, hCE-2, and hCE-3) are involved in the process. Cocaine is converted to BZE by hC-1, and EME by hC-2. BZE is the primary metabolite that appears in the urine. However, depending on storage conditions, cocaine will transform into BZE spontaneously. If ethanol and cocaine are both present, hC-1 will transesterify cocaine to form cocaethylene.

In cases of cholinesterase deficiency, more cocaine is shunted via the benzylecgonine route. There is very little evidence, however, that cholinesterase levels have any effect on toxicity, neither does it appear that either BZE or ecgonine methyl ester exerts any measurable activity at all in humans. A negligible amount of cocaine undergoes oxidative metabolism to form norcocaine. There are two alternate pathways by which this may occur. One route involves only cytochrome CYP3A4 (LeDuc et al., 1993). The alternative pathway also requires the participation of a flavin-containing monooxygenase in a two-step process; cocaine *N*-oxide is formed as an intermediate and then demethylated to form norcocaine

(Kloss et al., 1983). Unless the collection tube contains NaF as a preservative, any cocaine present in postmortem blood will be converted to benzyoylecgonine by esterases that continue to operate for some time after death. Similarly, unless it is collected with NaF preservative, anhydroecgonidine (a cocaine metabolite produced by "crack" smokers) also undergoes breakdown to cocaine (Fandino et al., 2002).

1.6.2 Benzoylecgonine (BZE) and Ecgonine Methyl Ester

In the absence of alcohol, the principal metabolites of cocaine are BZE and ecgonine methyl ester (Figure 1.6.2.1). In the living, the relative proportion of BZE and EME detected appears to have very little to do with the route of administration. In a study of 111 emergency room patients, BZE concentrations were consistently the highest (generally by a factor of 10 of 11) of any metabolite detected (1.4 mg/L in "crack" smokers, 1.9 mg/L in insufflators, 1.9 mg/L in intravenous users, and 1.6 mg/L in subcutaneous injectors) (Blaho et al., 2000).

Each of the different cocaine metabolites has a slightly different excretion rate and a markedly different steady-state volume of distribution. In fact, formal pharmacokinetic measurements have been performed for only one cocaine metabolite—BZE. The V_{ss} for BZE is only one third as high as that for cocaine (Ambre et al., 1991). Urinary detection times have been determined for all of the principal metabolites: BZE, ecgonine methyl ester (EME), norcocaine (NCOC), benzoylnorecgonine (BNE), *m*-hydroxy-BZE (*m*-HO-BZE), *p*-hydroxy-BZE (*p*-HO-BZE), *m*-hydroxy-COC (*m*-HO-COC), and *p*-hydroxy-COC (*p*-HO-COC). Results of studies performed in closed metabolic wards indicate that the excretion pattern is, at least in part, related to the pattern of ingestion. No matter which route was used, C_{max} values were BZE > EME > COC > BNE, and *p*-HO-BZE > *m*-HO-BZE > *m*-HO-COC > NCOC > *p*-HO-COC.

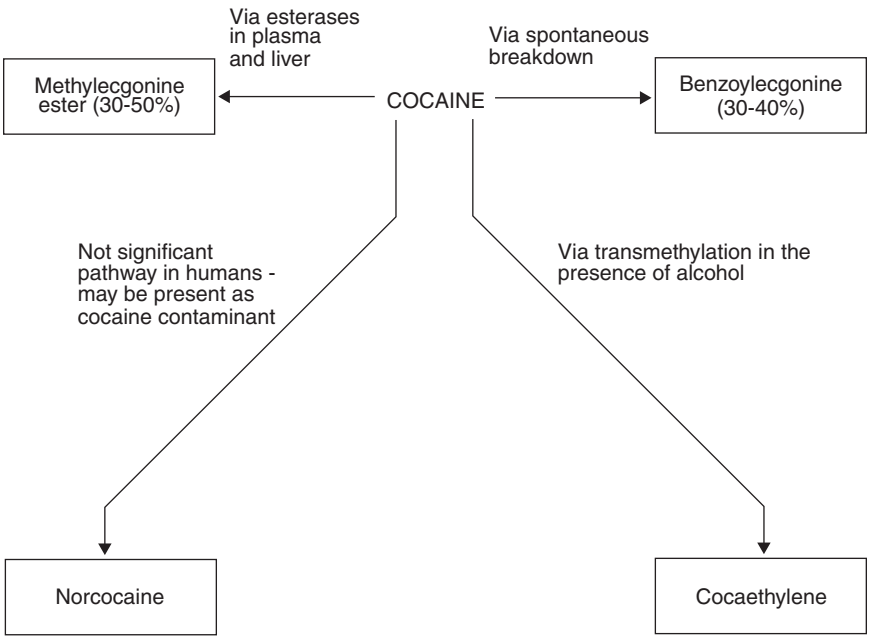

Figure 1.6.2.1 Metabolic fate of cocaine.

Elimination half-lives for cocaine and its metabolites are generally shorter following smoking, slightly longer after intravenous injection, and longest following "snorting." The metabolite with the longest half-life was *m*-HO-BZE (mean range 7.0–8.9 h). Cocaine itself displayed the shortest half-life (2.4–4.0 h). However, some of the difference may be more apparent than real; the result depends upon the cutoff level chosen, which is an arbitrary decision (Cone et al., 2003).

The half-lives of BZE and EME are both much longer than the half-life of cocaine (Brzezinski et al., 1994). EME has a half-life on the order of 4 hours, while BZE may be detected in the blood for 4–6 hours, and in the urine for 2–3 days after snorting 100 mg, or 1.5 days after injecting a single 20 mg dose. In neonates, the half-life of BZE appears to be 1.5 to 2.1 times longer than in adults (Dempsey et al., 1998). As a consequence, BZE is likely to still be detectable in plasma for at least 24 hours after ingestion (Javaid et al., 1983). In chronic users (> 8 g per day) a 20 mg dose of BZE given intravenously is likely to be detected for an even longer period. BZE can be detected in the blood of chronic users for at least 5 days (Verstraete, 2004). Measurement of the ratio of cocaine, the parent compound, to metabolite is not meaningful, because the volume of distribution of the parent compound is so much greater than that of the metabolites. Neither is it legitimate to combine the concentrations of the different metabolites to estimate the amount of cocaine ingested, or to calculate a "body burden," and for the very same reason: the V_{ss} of each metabolite is different, which means that a different percentage of each compound will reside in the blood/plasma at any given time.

Benzoylecgonine is stable in frozen specimens, but cocaine is not (Dugan et al., 1994), and the amount of BZE and EME measured in urine will vary depending on how the specimen is stored. It is also a function of the preservative used (Toennes and Kauert, 2001). EME is stable for as long as three years in urine samples with pH ranges of 3 to 5, but at pH 9, 100% will have disappeared in 30 days (Vasiliades, 1993). Under alkaline conditions, EME will hydrolyze to form ecgonine and thus will not be detected at all. Most postmortem urine samples contain more BZE than EME (Clark and Hajar, 1987), but changes in sample acidity can also lead to the measurement of inaccurately high ratios of EME to BZE in postmortem blood samples.

In life, circulating EME is rapidly converted to ecgonine, and EME levels generally remain quite low. After death, however, anaerobic metabolism continues and conditions are not suitable for spontaneous hydrolysis, so the conversion of cocaine to BZE and EME to ecgonine ceases. At the same time, enzyme-mediated hydrolysis continues, albeit at a slower rate, and EME continues to accumulate. The resultant high EME levels and relatively low BZE levels will thus provide a misleading picture of the situation before death (Logan and Peterson, 1994).

Cocaine is a weak base and a small molecule that diffuses freely across the placenta. BZE does not. It is highly ionized at physiological pH ranges and barely crosses the placenta and does not cross the blood–brain barrier at all. These physical properties have several important consequences for postmortem interpretation. In the case of fetal demise, all the BZE detected in a fetus will have been derived from cocaine metabolized in the fetus. The fetus cannot clear BZE from the system as quickly as the mother, so maternal/fetal ratios are just the opposite of those observed with cocaine. In Meeker's autopsy study of fetal and newborn deaths where cocaine was detected (but not the cause of death), the ratio in six cases was 2.44, with a range of 1.17–6.80 (Meeker and Reynolds, 1990).

Another possible source for BZE detected in a forensic urine sample is "spiking" (the purposeful contamination of a specimen in order to cause a false-positive test). Claims of spiking are sometimes made by athletes who test positive after a competition. Analyzing the specimen for other cocaine metabolites, particularly those that only occur *in vivo* (specifically, *m*-hydroxybenzoylecgonine, *p*-hydroxybenzoylecgonine, and *N*-desmethylbenzoylecgonine), easily disproves the spiking claim. Recovery of any of these compounds proves that cocaine was metabolized to BZE by the athlete, and that BZE was not maliciously added to the sample (Klette et al., 2000). Another variation on this theme, also used by some athletes, is to claim that cocaine was surreptitiously added to their food. In such an event, the presence of normal *in vivo* metabolites would be expected, but if they are present in high concentrations, it stretches credulity to suppose that the victim would not have noticed something wrong at the time the food was eaten.

Some authors have suggested that low plasma cholinesterase levels explain cocaine toxicity (Jatlow et al., 1979), but there is very little evidence to support this idea. Normal plasma cholinesterase (PCE) levels vary tremendously from individual to individual and these levels change depending on the physiologic state. In one study purporting to show that "complications" were more common in individuals with low PCE levels, some of the individuals with "complications" actually had higher PCE levels than controls (Om et al., 1993). Clearly, individuals with genetic defects and atypical forms of cholinesterase, as indicated by low dibucaine numbers (a measure of PCE activity), will metabolize cocaine more slowly than individuals without that defect, but that does not prove toxicity is any more likely. There is no evidence that a reduction in cholinesterase activity increases the chances for toxicity. Almost all the complications of chronic cocaine abuse occur after continuous, long-term use (Smart and Anglin, 1987; Karch et al., 1998). When an individual who has been using cocaine dies, there is, in fact, total overlap between blood cocaine concentrations in fatal cases of cocaine toxicity and in trauma deaths where the presence of cocaine is an incidental finding (Karch et al., 1998). Cholinesterase activity is not even necessary for EME production. Small amounts of EME continue to form in hepatectomized animals, and BZE concentrations continue to rise after hepatectomy, even when plasma cholinesterase inhibitors are given (Kambam et al., 1993).

Finally, it should be pointed out that, while the blood ratio of cocaine to BZE or any of its metabolites is meaningless, the same measurements made on brain homogenates might, in fact, be diagnostic. Almost 20 years ago, Spiehler showed that if brain, not blood, is the testing matrix, the ratios of cocaine/BZE in the toxic cases (brain mean 14.7 and blood mean 0.64) were clearly different from those found in cases where cocaine was obviously an incidental finding (brain mean 0.87 and blood mean 0.27). The brain/blood ratios of cocaine and BZE concentrations generally are characteristic of the time elapsed since cocaine dosing. In instances of cocaine overdose, the mean brain/blood ratio was 9.6 for cocaine and 0.36 for BZE (Spiehler and Reed, 1985).

The difference is explained by BZE's inability to cross the blood–brain barrier. Any BZE found in the brain would have to be derived from cocaine that had previously crossed the blood–brain barrier. It follows that brain ratios of cocaine to BZE are meaningful and do reveal important information about toxicity and time of ingestion. Spiehler's work has recently been repeated in a much larger study with the same results (Bertol et al., 2007), except that the blood/brain ratios in cases where cocaine was actually the cause of death were substantially greater than those reported by Spiehler. A very strong case could be made for the use of brain as a primary analyte.

1.6.3 Cocaethylene

The DAWN report for 2003 states that, of all drug-related emergency room visits, nearly a quarter were related to the consumption of alcohol, or alcohol in combination with other drugs. The most frequently listed "other" drug is cocaine (25,049 visits), which was detected nearly five times more frequently than heroin (5160 visits) (SAMHSA, 2004). The observation is important because when ethanol is consumed with cocaine it leads to the creation of a unique metabolite called cocaethylene (Hearn et al., 1991).

Cocaethylene is synthesized in the liver by a transesterification reaction that adds an extra ethyl group to cocaine (Figure 1.6.3.1). The reaction occurs in the microsomal fraction, and is catalyzed by a nonspecific carboxylesterase that not only catalyzes the transesterification of cocaine to cocaethylene, but also converts cocaine to BZE (Brzezinski et al., 1994). The enzyme that performs the conversion is a broad-spectrum bioscavenger; it also catalyzes the deacetylation of heroin to 6-acetylmorphine, and even the detoxification of organophosphate chemical weapons, such as sarin, soman, and tabun (Bencharit et al., 2003). Cocaethylene is detectable for much longer than cocaine, in both urine and blood, because it does not bind as strongly to the carboxylesterase (Brzezinski et al., 1997).

When cocaethylene was first discovered, many thought it might be the key to explaining why cocaine toxicity occurs in some, but not all, abusers. That is not the case. There is generally no evidence that the combination of alcohol and cocaine does more than enhance additively the already strong tendency of each drug to induce a variety of physical and psychological disorders, though there is some evidence that the combination of alcohol and cocaine tends to have greater-than-additive effects on heart rate (Pennings et al., 2002).

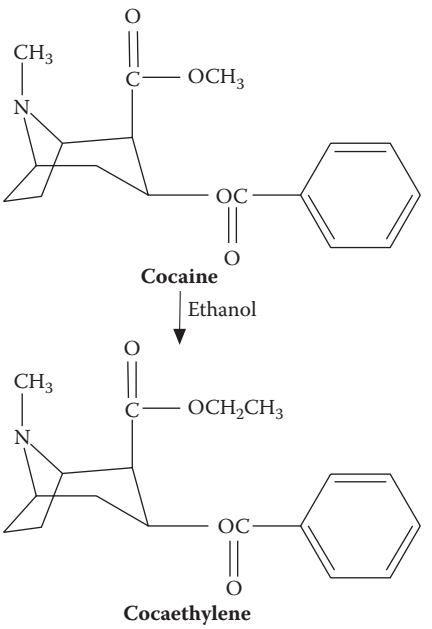

Figure 1.6.3.1 Cocaethylene formation. Cocaethylene is formed in the liver by a transesterification reaction that adds an extra methyl group to cocaine. Cocaethylene has a much longer half-life than cocaine, but cocaethylene binds to the dopamine receptor with the same affinity as cocaine.

In controlled studies, cocaethylene is less potent in elevating heart rate than equivalent doses of cocaine. Similar differences between cocaine and cocaethylene were also found for subjective measures. No matter the drug dose, there were significant increases in systolic blood pressure relative to placebo, but no significant effect on diastolic blood pressure. Cocaethylene has a slower rate of clearance and a larger volume of distribution than cocaine and, therefore, has a correspondingly longer elimination half-life.

When drug concentrations and autopsy findings were compared in a sample of 72 accidental deaths where only cocaine, cocaine metabolites, and no ethanol was detected in two thirds of the cocaine-related deaths. When ethanol was present, no other differences between the two groups could be identified. This suggests that acute cocaine toxicity is not enhanced by ethanol–cocaine interactions. However, ethanol concentrations were generally low in this study, and it is possible that increased toxicity only becomes apparent when much larger quantities of alcohol have been consumed (Karch et al., 1999).

In most postmortem studies, concentrations of cocaethylene are very modest, probably because the amount of alcohol present is the rate-limiting step in cocaethylene production. Most cocaine users simply do not ingest enough alcohol to produce significant amounts of cocaethylene. In the case of the developing fetus, it appears that, even when cocaethylene is produced in significant quantities, the placenta prevents its passage from mother to child (Morishima et al., 1999).

In Hearn's original autopsy study, cocaethylene was found in only 62% (77/124) of decedents testing positive for both cocaine and ethanol. Further analysis showed that, in the 47 cases where cocaethylene could not be detected, ethanol concentrations were usually significantly less than 0.1 mg/L (Hearn et al., 1991). Using a somewhat different but very sensitive technique, Jenkins and Goldberger (1997) found cocaethylene in the blood of only 1 of 13 decedents who tested positive for cocaine (range 23–2088 ng/mL), and that the individual with the highest cocaine level had died of a gunshot wound, not cocaine toxicity. In another study of 41 patients with detectable cocaethylene concentrations, there was no significant correlation between plasma ethanol and plasma cocaethylene concentrations. The lack of correlation was thought to be a consequence of the very high ethanol concentrations in most of the patients, which, contrary to the usual situation, made the cocaine concentration the rate-limiting step in cocaethylene formation (Bailey, 1996).

The relationship between cocaine and alcohol has been evaluated in healthy volunteers (Farre et al., 1993; McCance-Katz et al., 1993). In the first study, individuals with a history of recreational drug use were given cocaine alone or a drink containing 1 g/kg of vodka followed by a 100-mg dose of cocaine hydrochloride (snorted). Cocaethylene was detected only in the samples from the group that had been pretreated with alcohol. The peak cocaethylene concentration was 55 ± 8 ng/mL, and serial blood measurements were consistent with a half-life of 109 minutes. Norcocaine levels were also much higher in the group that had been pretreated with alcohol.

The pharmacologic properties of cocaethylene and cocaine, though largely similar, do differ in some important aspects. *In vitro* studies suggest that cocaethylene is a more potent blocker of the inward sodium channel than the parent compound (Xu et al., 1994), but a less potent blocker of the hERG potassium channel. If that is the case in humans, then high levels of cocaethylene would be more likely to produce cardiac conduction abnormalities than would high levels of cocaine. In fact, Brugada syndrome, a conduction abnormality due to the presence of an abnormal sodium conductance channel in cardiomyocytes, has

been reported after cocaine use, but never in a situation where cocaethylene was also present (Bebarta and Summers, 2007). This result is hardly surprising given that the cocaine concentrations normally encountered in regular cocaine users would be expected to interact with hERG and the sodium conductance channel and would very likely be proarrhythmic anyway, particularly if the abuser were heterozygous for hERG (Ferreira et al., 2001; Guo et al., 2006).

1.6.4 Anhydroecgonine Methyl Ester (Methylecgonidine)

Anhydroecgonine methyl ester (AEME) is the major pyrolysis product of cocaine. It is excreted only in the urine of "crack" smokers (Jacob et al., 1990), and it can also be detected in their blood as well, although plasma concentrations were generally quite low (3–34 ng/mL when measured in 13 admitted "crack" smokers) (Toennes et al., 1999). The pharmacology and pharmacokinetics of this compound have still not received very much attention.

Structurally, AEME shares features with other chemicals such as anatoxin and arecoline which have cholinergic properties, raising the possibility that anhydroecgonine may be toxic in its own right. Studies in animals confirm that AEME inhalation decreases airway conductance (Chen et al., 1995). AEME may, or may not, have something to do with the reported increases in incidence and severity of asthma within the inner city (Tartasky, 1999; Rome et al., 2000; Tashkin, 2001).

The detection of AEME is of questionable scientific value, at least for proving that "crack" was smoked, because the testing procedure cannot be relied upon, even in cases where AEME is known to be present. Pyrolytic production with pentoflouro-AECG (the derivitizing agent for BZE, ecgonine, and *m*-hydroxybenzoylecgoine), can completely mask any AEME originally present in a biological sample (Toennes et al., 2003; Cardona et al., 2006). AEME can also be formed as an analytic product if injection port temperatures are too high, but there are effective means of measurement that will survive forensic challenge, though they may not be available in the laboratories of many medical examiners (Cognard et al., 2006; Yang et al., 2006).

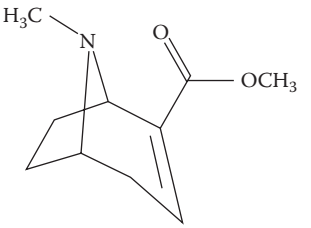

Figure 1.6.4.1 Anhydroecgonine.

1.6.5 Norcocaine

Oxidation of cocaine plays a minor role in human metabolism of cocaine, but there is a modicum of evidence that oxidized cocaine, in the form of norcocaine and norcocaine nitroxide, may play an important role in human cocaine toxicity. Norcocaine is metabolized by *N*-hydroxylation, a conversion catalyzed by several different members of the CYP family (1A, 2A, 3A, and possibly 3B) (Pellinen et al., 2000). Other minor pathways are known to be involved in the hydrolysis of hydroxybenzoylecgonine, but they have not been identified and their significance remains obscure. Animal brains and liver microsomes can reduce norcocaine nitroxide to form superoxide radicals, in turn leading to lipid peroxidation and lipid peroxyl radical formation. The result compromises the very antioxidant systems that are designed to protect the heart (Kovacic, 2005).

Whether this mechanism helps to explain the fibrosis normally observed in the hearts of chronic cocaine users, or even some of the hepatic damage that is also seen, remains

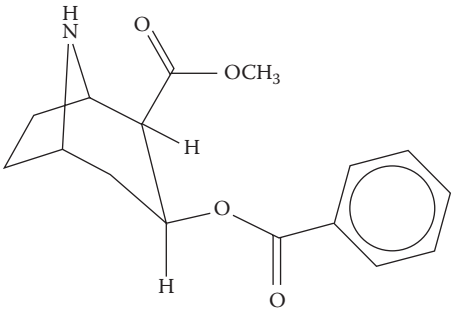

Figure 1.6.5.1 Norcocaine.

unknown. Myocardial fibrosis is a multifactorial process, and the most likely explanation is that the presence of norcocaine is just one more contributory factor to cardiac myotoxicity and repair. It also appears that cocaine itself, even in the absence of high levels of norepinephrine, can induce myocardial apoptosis (Zhang et al., 1999), and apoptosis appears to play a key role in cocaine-induced myocardial remodeling. It had been thought that humans produced only minute amounts of norcocaine, but Blaho et al. (2000) detected significant amounts in the plasma of symptomatic cocaine abusers, thereby raising the possibility that this route might actually be responsible for human toxicity. In their study of 111 cocaine users presenting for emergency room treatment, the mean norcocaine concentration was 30 ± 17 ng/mL.

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1.7 Fetal Metabolism

Like any other abused drug, cocaine may interfere with the placental transfer of endogenous compounds. *In vitro* studies have shown that cocaine, nicotine, and cannabinoids all can inhibit amino acid transport in the placenta. Specifically, cocaine decreases the activity of the placental amino acid transport systems A, N, and possibly others as well (Myllynen et al., 2005). Any interference with placental transporters may potentially have adverse effects on fetal development and placental handling of endogenous compounds by interfering with the placental blood flow through vasoconstriction (Woods, 1998; Lipton et al., 2002). Interestingly, this ability is not confined to cocaine. Nicotine and alcohol also can induce placental vasoconstriction. In fact, nicotine and alcohol exert very similar effects on the placenta (Rice et al., 1986).

There appears to be great intra-individual variation, but human placenta has considerable cholinesterase activity (Sastry, 1991). This variability is important because drugs that effectively block the cholinergic receptor can also block amino acid transport activity (and the transport of drugs such as morphine, cocaine, and nicotine). It does so by the activation of endothelial muscarinic receptors. For reasons that are not understood, *in vitro* inhibition of cholinesterase activity also leads to increased production of norcocaine (Little et al., 1995), a metabolite that is potentially more toxic than its parent compound (see above).

Infants born to cocaine-using mothers may have persistently elevated cocaine levels for days (Chasnoff et al., 1987). At least one case report of perinatal stroke and intraventricular hemorrhage in the newborn has been described (Wu et al., 2005), but it is not clear

that any of the adverse effects, in the fetus or mother, can be directly related to cocaine plasma concentrations, since this is an uncontrolled, anecdotal report, and similar reports in the modern literature are uncommon.

The fetus handles BZE differently than the mother. Because BZE is excreted primarily in the urine, and because both renal blood flow and glomerular filtration rates double in pregnant women, mothers clear metabolite much more quickly than their fetus. Though unproven, the possibility also exists that the enzymatic pathway for conversion of cocaine to methylecgonine may not be fully developed in the newborn. In newborns, the plasma half-life of BZE during the first day of life, based on measurements in 13 infants, was 16 hours. During the first week of life, the urine half-life of BZE measured in 16 subjects decreased to 11.2 hours (Dempsey et al., 1998).

Concentrations of cocaine and its metabolites in umbilical cord blood may vary considerably, and in some cases no cocaine may be detected at all even if the mother is a cocaine user. When umbilical cord blood from 36 neonates at risk for prenatal cocaine exposure was studied prospectively, only 18 of the samples were plasma positive for BZE, and only half of those (9, or 25% of the sample) were also positive for cocaine. The maximum plasma cocaine concentration in cord blood was 88 ng/mL (mean, 39 ng/mL). The maximum plasma BZE concentration was 3880 ng/mL (mean, 844 ng/mL). Other drugs were also detected. In infants testing positive for BZE, the mean plasma drug concentration of nicotine was 1.7 ng/mL; cotinine, 94 ng/mL; and caffeine, 1205 ng/mL. Mean plasma drug concentrations were not significantly different in the infants that were BZE negative (nicotine, 5.2 ng/mL; cotinine, 97 ng/mL; and caffeine, 1440 ng/mL). No cocaethylene was detected in any of the women (Dempsey et al., 1998).

The failure to detect cocaethylene is a good example of the difficulties involved in trying to generalize from animal or *in vitro* toxicity studies to humans. The results of animal studies strongly suggest that cocaethylene does not cross the placenta (Morishima et al., 1999), but *in vitro* studies with human placenta indicate that the placenta does not present any physical or metabolic barrier to cocaethylene transfer from mother to child (Simone et al., 1997). In humans, most studies have failed to detect this compound in the newborn. None was detected in a large group of children born to cocaine-using mothers (Dempsey et al., 1998) and even though good analytic methods exist that could detect cocaethylene in meconium (Pichini et al., 2005), it appears to be a very rare finding (Pichini et al., 2005).

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1.8 Problems of Cocaine Test Interpretation

1.8.1 Introduction

Modern techniques allow for the detection of drugs in quantities as small as parts per billion, in an ever-growing list of alternative tissue matrices, yet modern technology is seldom of any help in differentiating deaths due to drugs from those deaths where the presence of drugs is simply an incidental finding. Why are such precise measurements of so little value? Because, except for episodes of massive overdose (as might occur in a drug mule) where the mechanism of death is perfectly clear, most cocaine-related deaths occur in chronic drug users in whom death is a consequence of neurochemical and anatomic changes induced over a period of months or even years. Long-term cocaine users have changes in their hearts (Karch et al., 1998) and brains (Volkow et al., 1993) that favor the occurrence of sudden death. And, if the abuser is truly unlucky, he or she may be heterogeneous for one of several abnormal hERG ion channels (Guo et al., 2006). The existence of these changes explains why, in the living or the dead, it is absolutely impossible to correlate a specific blood or plasma concentration with a specific type of toxicity, or even speculate whether cocaine-related toxicity occurred at all (Jenkins and Goldberger, 1997; Karch et al., 1998; Blaho et al., 2000).

In addition to problems caused by direct cocaine toxicity, less privileged drug users, such as sex workers or those without access to sterile syringes, are at increased risk for a host of lifestyle diseases, such as hepatitis, tuberculosis, and HIV (Inciardi 1995; Figueroa et al., 2005). Given these realities, the accurate certification of a drug-related death requires knowledge of (1) the decedent's past medical history, (2) an account of what happened at the scene, (3) a thorough postmortem examination, and (4) the results of DNA testing to rule out hereditary forms of heart disease or even myocarditis; the cost of such testing is so great it is not likely to be available any time soon. Reliance upon only one of these elements, to the exclusion of the others, is very likely to result in misdiagnosis.

The definition of just what constitutes a "complete" autopsy is not as simple or clear as it once was. Does the examination of one section of myocardium constitute a "complete"

examination of the heart? When a young person dies suddenly, is it proper to refer to the heart as normal when cardiac ion channels have not been measured? In unexplained cases of drug death, should the examination be considered complete if the P450 metabolizer status is not determined? The answer to all of these questions is "no." As a consequence, cause of death determinations are often based solely on toxicological measurements, significantly raising the chances of missed diagnosis. Because cocaine is so widely used, cocaine-related deaths present a special set of problems.

There is seldom any reason for clinicians to measure plasma concentrations of cocaine or its metabolites. Unlike alcohol intoxication, where specific blood concentrations can generally be related to specific physiological and psychological states, cocaine blood concentrations do not relate to symptoms (Blaho et al., 2000), not even in the laboratory setting. Accordingly, treatment must be based on the patient's symptoms, not on the plasma level of cocaine.

When cocaine is given to volunteers, correlations can be drawn between the degree of mood elevation and peak blood levels, but only when cocaine concentrations are rising. If blood concentrations are falling, the exact same concentration that resulted in a "high" when concentrations were rising can be associated with a dysphoric reaction when concentrations are falling. Cardiovascular effects and feelings of euphoria decline more rapidly than do cocaine blood concentrations (Javaid et al., 1978), but the "rush" experienced by cocaine users follows a different time course than the cardiovascular changes; drug tolerance begins to emerge after the first dose (Foltin and Haney, 2004).

1.8.2 Tolerance

Postmortem blood concentrations are much more difficult to interpret than concentrations in the living. At one time, blood concentrations of more than 5 mg/L were thought to be uniformly fatal (Wetli and Mittlemann, 1981). With more experience, it has become apparent that isolated postmortem blood concentrations cannot be used to determine the cause of death at all. Tolerance on a massive scale occurs, and cocaine concentrations well in excess of 5 mg/L can be encountered in cases of trauma-related deaths where the presence of cocaine is clearly an unrelated finding (Pagel et al., 1994; Shannon et al., 1996). For example, one case report described a man who was shot while drinking in a bar. Prior to being shot, the man's behavior was said to have been normal. When he was autopsied several hours later, after having undergone extensive attempts at resuscitation, including aggressive fluid replacement, multiple blood specimens showed a blood cocaine concentration of 30 mg/L (Howell and Ezell, 1990). In a similar case, a young woman with a history of chronic cocaine abuse was found dead at home. The woman was not a body packer attempting to smuggle drugs, and there was no evidence that she had purposefully overdosed; the blood concentration was over 300 mg/L (Peretti et al., 1990).

On the other hand, individuals who are chronic abusers will already have established changes in their hearts and brains (and perhaps elsewhere). In these individuals, death and toxicity may occur after the use of trivial amounts of drug (Smart and Anglin, 1987; Jenkins and Goldberger, 1997; Karch et al., 1998), or even when no cocaine is detected. For example, a cocaine addict just released from a rehabilitation program could still die of an arrhythmia secondary to cocaine-induced myocardial fibrosis (Stephens et al., 2004a, b). These considerations would not apply in naïve users who have no underlying or undiagnosed heart or

brain changes. In a series of 99 cocaine-associated deaths, where roughly one half were a direct consequence of cocaine toxicity and one half in which the presence of cocaine was an incidental finding, blood and urine cocaine and BZE concentrations in the two groups were indistinguishable. The mean blood cocaine concentrations were 1.12 mg/L in the group where death was attributed to direct cocaine toxicity and 0.487 mg/L in the group for which cocaine was an incidental finding (not significantly different). Interestingly, concentrations of the principal metabolite, BZE, were significantly higher in the group dying of cocaine toxicity than the other group (1.54 vs. 0.946 mg/L) (Karch et al., 1998). Tolerance is certainly one explanation for the overlap; the other is the occurrence of postmortem redistribution.

1.8.3 Postmortem Redistribution

The concentrations of basic drugs, such as tricyclic antidepressants, some narcotic analgesics, local anesthetics, and stimulants such as methamphetamine and cocaine, are all likely to increase after death (Prouty and Anderson, 1990; Pounder, 1993). Provided that the blood remains liquid, drugs sequestered in the lungs rapidly redistribute into the pulmonary venous blood, and then into the left chambers of the heart. Because of the lung's very great blood supply, the absolute amount of drug in the pulmonary circulation will be much greater than in other organs. Postmortem, drugs temporarily sequestered in the pulmonary circulation may diffuse through the thin-walled pulmonary veins, falsely elevating the blood concentration within the left ventricle (Moriya and Hashimoto, 1999).

Accordingly, left ventricular blood should never be used for toxicological evaluation because the concentrations reported are likely to be considerably higher than they were at the time of death. Blood taken from the right ventricular cavity, however, is unlikely to be subject to the same sort of postmortem concentration increase seen in the left heart, and femoral artery blood even less so (Drummer, 2004). Regrettably, most autopsy reports still do not specify from which part of the body the blood sample was obtained, let alone from which side of the heart. This is an omission that pathologists completing a death certificate need to accept and consider before attributing death to a drug simply because the concentration of that drug is high. If the concentration of cocaine "falls in the toxic range" (a bizarre concept given that the "toxic range" is derived in humans, not cadavers!), knowledge of that number contributes very little to the interpretative process (Karch, 2006). In chronic abusers, changes in the heart and brain favoring sudden death would still be present, even if cocaine had not been used that day. Even without evidence of myocardial remodeling, the decedent may have a previously undiagnosed channelopathy, making them more vulnerable to sudden death in the presence of cocaine (Karle and Kiehn, 2002).

1.8.4 Cocaine-Related Deaths

Cocaine is directly toxic to the myocardium (Peng et al., 1989), and the process appears to be multifactorial. Cocaine induces apoptosis (Kajstura et al., 2006) and at the same time it increases production of calmodulin kinase II, both in the heart (Sun and Quamina, 2004) and brain (Zhang et al., 2005). The end result is that the hearts of chronic cocaine users undergo a process known as myocardial remodeling; myocardial collegen content increases and ventricular fibrosis becomes apparent. It has been known for nearly two decades that the hearts of cocaine users are enlarged and fibrotic (Tazelaar et al., 1987; Brickner et al., 1991) (see Section 1.10).

Fibrosis is hardly the only change that occurs within the myocardium. Growth initiators like angiotensin II, and even the mechanical strain produced by cocaine-related increases in blood pressure, lead to the generation of even more reactive oxygen species capable of damaging the myocardium, the death of additional myocytes, and the production of even more fibrosis. The role of activated metalloprotease enzymes in this process is not entirely clear, but it appears that their production leads to down-regulation of cardiac β receptors. If that is the case, it would ultimately prevent the release of calcium from the myocardium, resulting in decreased cardiac output (Opie et al., 2006).

Regardless of the underlying etiology, the presence of myocardial fibrosis and enlargement leads to electrical instability and favors the occurrence of arrhythmic sudden death. When cocaine is the cause of the remodeling, sudden cardiac death is even more likely, because cocaine binds to the hERG (rapid delayed potassium rectifier) channel (O'Leary, 2001). Under most circumstances, cocaine–hERG binding is probably of little consequence. However, cocaine interacts strongly with certain mutated hERG channels (Guo et al., 2006), which would favor the occurrence of arrhythmias.

If the appropriate morphologic changes can be identified in the heart of a known cocaine abuser, it would not be unreasonable to designate cocaine as the cause of death, even when little or no cocaine is detected in postmortem blood specimens (Stephens et al., 2004). Conversely, the same conclusions cannot be drawn about naïve cocaine users, or those with anatomically normal hearts. The finding of very low blood and tissue cocaine concentrations may just be a consequence of environmental contamination, and is very likely to be totally unrelated to the cause of death. Cocaine is universally present in our environment; even the currency of most countries is contaminated (Mirchandani et al., 1991; Oyler et al., 1996; Smith and Kidwell, 1996; De Giorgio et al., 2004). In the absence of any anatomic alteration, low levels of cocaine or its metabolites are the only evidence of cocaine exposure. In situations where the postmortem examination is totally unrevealing and modest amounts of cocaine are detected in the blood or hair, it is likely that a heritable channelopathy or other cardiac mutation is the cause of death, and genetic testing for these entities should be strongly considered (Karch, 2006).

1.8.5 Estimating Time of Ingestion

Although it is certainly an attractive idea, measurement of cocaine to BZE ratio in postmortem blood cannot be used as an indicator of when the cocaine was taken, nor can the concentrations of cocaine and benzoylegonine be combined together and then used to extrapolate dosage. These two compounds have very different volumes of distribution, invalidating such calculations. The V_{ss} constant for cocaine is thought to be between 2 and 3 L/kg (Chow et al., 1985; Cone, 1995), while that of BZE is only 1.0 (Ambre et al., 1991). What this means is that in a living person, at steady state, most cocaine resides in the tissues and most of the metabolite in the blood. Diffusion of cocaine back into the bloodstream after death makes accurate extrapolation to the immediate antemortem period impossible. Much the same situation pertains to morphine and its metabolites, where the steady-state volume of distribution of the metabolites is less than one tenth as high as morphine itself (see Section 5.6.3 for a fuller discussion of morphine).

Cocaine rapidly crosses the blood–brain barrier, but BZE does not; any BZE found in the brain is breakdown product of cocaine that has crossed the blood–brain barrier (Spiehler and Reed, 1985; Bertol et al., 2007). It follows that the ratio of cocaine to BZE

in the brain can be used to estimate time of ingestion: high brain cocaine concentrations with low BZE concentrations mean that ingestion was very recent, while the opposite finding indicates that use was remote. Postmortem redistribution is not an issue in the brain, because, except for the blood already present in the cerebral circulation, no additional drug can be delivered to the brain after death.

1.8.6 Low Cocaine Concentrations

Chronic cocaine users sequester cocaine in deep body stores. Small amounts of this sequestered cocaine can leach back into the bloodstream and saliva for days after the drug was last used (Cone and Weddington, 1989; Burke et al., 1990). There is also evidence that in chronic users of large amounts of cocaine the plasma half-lives of cocaine and benzoylegonine are longer than the times observed in occasional users (Preston et al., 2002). In studies performed in a closed metabolic ward, 63% of the volunteers studied tested positive for longer than the expected 48-hour window of detection. By self-report, the mean time to last positive urine after last use of cocaine was approximately 81 ± 34 (34–162) hours and small amounts of BZE were still present at 72 hours. For those reasons alone, attributing significance to very low cocaine levels is not a good idea unless, of course, appropriate anatomic changes are present as well.

Cocaine can be recovered from most of the currency in circulation in most industrialized countries (Oyler et al., 1996; Dressler and Muller, 1997; Jenkins, 2001; Furton et al., 2002) and it can also be detected in the sweat and hair of the children of drug abusers, even those in rehabilitation! In one study, 85% of the children living with cocaine-using parents had detectable levels of cocaine in their hair (Smith and Kidwell, 1996). Whether the positive tests were a result of inhaled cocaine being deposited within the hair or were a result of environmental cocaine deposited on the hair has not been determined.

Volatilized cocaine, just like cigarette smoke, can be passively absorbed. The process has been described in children and can even produce transient neurologic syndromes (Bateman and Heagarty, 1989). Whether such exposure can lead to serious consequences is not clear, but it certainly can lead to positive urine, blood, and hair tests. If parents use cocaine within their home environment, no matter what their wishes, it will end up in their children.

In general, the courts have tended to rule that the presence of detectable amounts of cocaine, or cocaine metabolite, is proof of willful child endangerment. One of the most frequently cited studies in this regard described 16 dead children who had cocaine or cocaine metabolite in their blood. Scene investigations documented that shortly before death these infants had been exposed to "crack" smoke. Most of the infants were under three months of age, none had revealing autopsy findings, and their mean cocaine blood level was 76 ng/mL, just barely over the level required to produce any measurable physiologic effects (Mirchandani et al., 1991). On the basis of this evidence alone, and in the absence of any plausible alternative mechanism, sudden infant death syndrome (SIDS) would appear to be the more likely diagnosis, especially given the absence of pathologic findings. Of course there are two problems with this interpretation. The first is that if drugs are detected in an infant who dies suddenly, the diagnosis is, by definition, not SIDS. The second is that these infants are rarely, if ever, tested for heritable channelopathy, which is not a rare disease.

In fact, low levels of cocaine detected in a fetus do not even constitute evidence of maternal cocaine use. Side-stream intake of volatilized cocaine can occur in innocent mothers (Cone, 1995) and if the mother is exposed to this vapor then cocaine and its metabolite could appear in the infant, although the mother herself was not a voluntary cocaine user. Thus, the

identification of cocaine in an infant is not necessarily proof of abuse by the mother, though it might very well be considered endangerment. Similar considerations apply to breast milk. There is evidence that cocaine becomes concentrated in breast milk (Bailey, 1998).

Because there is so much cocaine in the environment of industrialized countries, and because the possibilities of accidental contamination are so real, NIDA has promulgated regulations for drug testing that include "cutoffs." For BZE, the cutoff is 150 ng/mL; levels below that value are reported as negative. Of course, these "cutoffs" were formulated with living patients in mind, but the reasoning is still valid. In the absence of any other information, cocaine or cocaine metabolite levels of less than 50 ng/mL are chiefly of historic interest and do not provide evidence of very recent ingestion. Levels on the order of 50 ng/mL, or even less, are frequently seen in postmortem blood samples and must be interpreted with great care. Cocaine has a relatively large volume of distribution. After death, as the body decomposes, cocaine will be slowly released from deep tissue stores and concentrations can increase significantly from levels measured in the immediate antemortem period. Cocaine blood concentrations only rise after death (Hearn et al., 1991) and, depending on how and where the specimen is collected, the rise may be very considerable. These levels will stay elevated, provided that NaF preservative is added to the sample. If it is not, conversion of cocaine to BZE will continue and cocaine concentration will decrease. Substantial drops may occur in as little as a few hours.

1.8.7 Cocaine and Prescription Drug Interactions

Formal studies of cocaine–prescription drug interactions have rarely been undertaken, though some interactions of importance have been identified. Cocaine users who are treated with disulfiram have significantly higher plasma cocaine concentrations when they are taking disulfiram than when they are not. They also develop higher systolic and diastolic blood pressure and higher mean heart rates than when they are just taking cocaine (McCance-Katz et al., 1998). It is not known if this interaction has any clinical significance. Similar considerations apply to documented interactions with amitriptyline, procainamide, and quinidine, all of which inhibit human plasma butrylcholinesterase, slowing the breakdown of cocaine. Clinical measurements are lacking, but *in vitro* studies have shown that the breakdown of cocaine is slower in the presence of drugs that inhibit butrylcholinesterase (Bailey, 1999).

The *N*-demethylation product of cocaine is norcocaine, and the demythelation is performed mainly by hepatic CYP3A4. This is the same enzyme involved in the metabolism of various antiretrovirals, so cocaine use by individuals taking these drugs may lead to elevated cocaine concentrations; protease inhibitors and many other antiretrovirals are also CYP3A4 inhibitors (Ladona et al., 2000). The most potent inhibitors are ritonavir, indinavir, and efavirenz, but ketoconazole (Nizoral), nefazodone, erythromycin, and clarithromycin (Biaxin) are all CYP3A4 inhibitors (Wynn et al., 2005). On the other hand, antiretrovirals that induce CYP3A4 activity, such as nevirapine, may shift cocaine metabolism so that more of it undergoes *N*-demethylation and less undergoes hydroxylation, which means that production of norcocaine would increase, as would chances of liver toxicity (Roberts et al., 1991).

Cocaine interacts with the hERG K^+ channel (rapid delayed influx potassium channel) and can increase or decrease the channel's normal function (Karle and Kiehn, 2002). Much of the time this effect is more theoretical than real, but the hERG channel is polymorphic and, in the presence of the combination of the right drug and existing structural changes (such as fibrosis and cardiomegaly), there is enormous potential to disrupt the heart's electrical cycle.

Diverse drugs from many therapeutic classes, such as quinine and amiodarone, exert cardiotoxic side effects by inducing torsade de pointes (TdP), a life-threatening cardiac arrhythmia, due to interaction with hERG channels. Men are known to be at a lower risk for drug-induced TdP than women, suggesting a role of androgens and estrogens in modulating the sensitivity of cardiac K(+) channels, particularly those encoded by hERG (Zunkler and Wos, 2003). Neuroleptic agents haloperidol, pimozide, and fluspirilene are all capable of inducing TdP. Testosterone seems to oppose the effect. The action of these neuroleptics is voltage-dependent, an effect most consistent with an open-channel blocking mechanism (Shuba et al., 2001).

1.8.8 Adulterants

Table 1.8.8.1 Types of Cocaine Adulterants

A. Sugars
Dextrose
Lactose
Mannitol
Sucrose
B. Stimulants
Caffeine
Ephedrine
Phenylpropanolamine
Phentermine
C. Local Anesthetics
Lidocaine
Benzocaine
Procaine
Tetracaine
D. Inert Agents
Inositol
Corn starch
E. Others
Acetaminophen
Aminopyrine
Ascorbic acid
Aspirin
Boric acid
Diphenhydramine
Fentanyl
Niacinamide
Phenacetin
Quinine

Source: Based on information supplied by the Drug Enforcement Agency and Shannon, M., *Ann. Emerg. Med.,* 17(11), 1243–1247, 1988.

* During late 2006 and early 2007 there were numerous confirmed reports of alpha-fentanyl being added to cocaine. The reasons for this practice have never been clarified, but a number of unanticipated narcotic deaths occurred in cocaine users.

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1.9 Cocaine Tissue Disposition

Animal studies have identified low-affinity cocaine receptors in the heart, lungs, gut, kidney, and testes (Calligaro and Eldefrawi, 1987). Distribution of C^{11}-labeled cocaine has been studied in humans using positron emission tomography (PET) scanning. The rate of uptake and clearance of C^{11} cocaine varies from organ to organ: peak uptake in lung was at 45 seconds, but did not occur until 2–3 minutes later in the heart and kidneys, and not until 7–9 minutes later in the adrenal glands. Liver uptake began at 10 minutes and peaked at 15 minutes. Half-peak clearances were 90 seconds in the lungs, 10 minutes in the heart and kidneys, and 22 minutes in the adrenals. Lung radioactivity paralleled that of plasma, but active uptake was highest in the heart, kidneys, adrenal, and liver (Volkow et al., 1992). Unfortunately, this information tells us nothing about cocaine's postmortem distribution and allows no predictions.

As Prouty and Anderson (1990) were the first to observe, drug concentrations measured during life may bear little or no relation to drug levels measured after death. The differences are especially great for basic drugs, including popular drugs of abuse such as cocaine. Postmortem cocaine blood levels vary, depending on where the blood sample was drawn (Hearn et al., 1991), and may be considerably higher or lower than they were at the time of death (Sylvester et al., 1998; Flanagan et al., 2003; Crandall et al., 2006). The magnitude of the change depends on the postmortem interval, the means of collection, the temperature at which the cadaver was stored, the position in which the cadaver was lying, whether cardiopulmonary resuscitation (CPR) had been performed, the portion of the organ sampled, and the physical properties of the drug itself (Moriya and Hashimoto 1999; Pounder et al., 1996; Langford and Pounder, 1997).

Postmortem redistribution is the process after death by which drugs move from regions of higher concentration to regions of lesser concentration. Drugs that are hydrophilic will be released from cells as they die. Blood taken from the left side of the heart will yield higher concentrations than on the right (Pounder et al., 1996). This is a function of the large amount of blood resident in the pulmonary circulation and the thin-walled structure of the pulmonary veins. Drug concentrations are higher in the heart than the femoral vessels, partly because concentrations may not have equilibrated at the time of death, and partly because of migration of drug back into the heart from the lungs. Blood from the femoral vessels seems less subject to redistribution but, at autopsy, unless the

proximal vessels are first ligated, or if more than 25 mL of blood is collected, aspiration from the femoral vein is likely to yield blood from the liver, where drug concentrations would be expected to be much higher. After death, cocaine quickly disappears from blood and liver, but it can be detected in brain and muscle for some time. The same phenomenon has been observed in *in vitro* studies, suggesting that brain and femoral muscle may be the most suitable tissue for postmortem analysis (Moriya and Hashimoto, 1996), and that the brain/blood ratio may be a reliable indicator of overdose death (Spiehler and Reed, 1985). In fact, the only conclusion that can be reached with certainty about postmortem cocaine blood samples is that cocaine is present, and that the amount present may be large or small. Neither conclusion is particularly helpful in determining the cause of death.

1.9.1 Human Postmortem Measurement

More than 20 years ago, Poklis et al. (1985) analyzed the cocaine content in five individuals who died after taking cocaine (three by intravenous injection and two by smoking). Data from that study are reproduced in Table 1.9.1.1. Unfortunately, similar studies have not been repeated, though it is possible that as the technology of tandem mass spectrometry becomes more widely available, reporting values from multiple tissues may become more common.

1.9.2 Brain

Concentrations of cocaine in the brain may be very high, which is one reason why brain is the best matrix for postmortem cocaine determinations. Cocaine blood levels measured at autopsy bear little relationship to levels at the time of death (Spiehler and Reed, 1985), but cocaine is more stable in the lipid-rich environment of the brain, and there is reason to believe that cocaine brain levels more accurately reflect concentrations at the time of death than measurements made in blood or any other tissue (Hernandez et al., 1994).

Cocaine freely crosses the blood–brain barrier (Misra et al., 1975), as does cocaethylene (Hearn et al., 1991). Receptors with varying affinities for cocaine are found throughout the brain, particularly in the stratum. However, when cocaine is taken in doses that cause behavioral change, uptake can also be observed in other, lower-affinity sites within the brain (Volkow et al., 1995) such as the frontal and occipital cortices (Calligaro and Eldefrawi, 1987). In experimental animals and in autopsied cases of human cocaine-related deaths, the concentrations of cocaine found in the brain are almost always many times higher than in plasma, even if the measurements are made only hours after drug administration (Spiehler and Reed, 1985; Reith et al., 1987; Mari, 2007).

Table 1.9.1.1 Cocaine Content in Five Individuals Who Died After Taking Cocaine (Values shown in m/L)

Specimen	Blood	Bile	Brain	Heart	Kidney	Liver	Lung	Spleen	Skeletal Muscle	Adipose Tissue	Urine	Vitreous
Case #1	1.8	10.0	4.0	6.1	26.0	1.6	3.40	22.0	6.1	1.0	39.0	2.4
Case #2	6.9	18.0	24.0	—	26.0	17.0	—	25.0	—	—	41.0	—
Case #3	31.0	—	59.0	—	58.0	6.5	69.0	42.0	48.0	5.9	270.0	—
Case #4	13.0	25.0	83.0	—	53.0	10.0	24.0	—	30.0	—	—	14.0
Case #5	3.9	5.2	6.4	5.3	34.0	15.0	27.0	15.0	—	0.7	27.0	—

Benzoylecgonine, the principal metabolite of cocaine, crosses the blood–brain barrier with great difficulty (Misra et al., 1975). An autopsy study of 37 patients who had died of cocaine toxicity revealed a mean blood cocaine concentration of 4.6 mg/L (range 0.004–31.0 mg/L), while the mean BZE concentration was 0.88 mg/L (range 0–7.4 mg/L). The mean concentration of cocaine found in the brain was 13.3 mg/kg (range 0.17–31 mg/kg), while that of BZE was 2.9 mg/kg (range 0.1–22 mg/kg). In most cases, the blood/brain ratio was close to 4. In a second study of 14 deaths, where cocaine was only an incidental finding (instances of murder, accidental death, etc.), the average blood/brain ratio was only 2.5 (Spiehler and Reed, 1985). In a much large (85 brains analyzed) study published in 2007, ratios were twice as high, with brain/plasma ratios greater than 10 (Bertol et al., 2007).

Measurement of the brain cocaine and BZE concentration ratios generally provides a good indication of what the levels were at the time of death, and allows reasonably accurate estimates relating time of ingestion to death. Because any BZE detected in the brain had to have been formed in the brain, it can reasonably be inferred that an individual with a brain concentration of 8 mg/kg of cocaine and 0.5 mg/kg of BZE must have taken the drug just before death. Had a longer period elapsed, cocaine concentrations would be lower and BZE concentrations higher. Patients with excited delirium are usually found to have only modest cocaine concentrations but high concentrations of BZE, a result of "binging," where large amounts of cocaine are ingested over several days (Karch et al., 1998). Cocaine is stable in frozen brain for months (Moriya and Hashimoto, 1996) and can be recovered, along with its metabolites, using solid-phase extraction techniques (Bogusz et al., 1998).

A handful of human case reports suggest that brain concentrations are lower in the fetus than in the mother. In a case reported by Mittleman et al. (1989), the maternal-to-fetal brain cocaine ratio was 6.5:1. A study of fetal demise, which included 47 cases where both blood and brain cocaine levels were determined, disclosed mean blood cocaine concentrations were 800 ng/mL, while the mean brain concentration of cocaine was 1100 ng/mg (Morild and Stajic, 1990). Cocaethylene concentrations, both in the fetus and adult, remain poorly characterized, although there are now good methods for measurement of all the cocaine metabolites in this matrix (Lowe et al., 2006).

1.9.3 Hair

Disagreement continues to exist as to the route (or routes) by which cocaine is incorporated into hair, but melanin binding appears to be the most likely (Cone, 1996). There is good evidence for passive diffusion from blood into the hair follicle, but hair is coated with sebum, which may also contain drug, and the possibility of external contamination is ever present (Blank and Kidwell, 1993; Kidwell et al., 2000). Whether or not the color of hair or the race of the individual has any effect on the avidity with which hair binds cocaine is also disputed, but mounting evidence suggests that it does, although the results of other experiments suggest it does not (Hoffman, 1999; Kelly et al., 2000).

When deuterium-labeled cocaine is given to human volunteers, the parent drug, cocaine, is the predominant analyte detected in hair, just the opposite situation to blood, where BZE is the major analyte. The estimated minimum dose required for detection of cocaine in hair is 25–35 mg of drug administered intravenously; a single dose of cocaine is detectable for two to six months, although very large intra-individual variation exists, especially in the amount of cocaine detected in the hair. In controlled studies with non-Caucasians and Asians, the Asians generally exhibit much higher concentrations than

Caucasians, even though both racial groups had received the same amount of cocaine (Nakahara and Kikura, 1994; Henderson et al., 1996).

All cocaine metabolites can be detected in hair samples, but the parent compound predominates. Unlike heroin abuse, where heroin ingestion can be proved conclusively by demonstrating the presence of the unique heroin metabolite, 6-monoacetylmorphine, there are no unique cocaine metabolites that cannot also be produced externally. Cocaethylene can be produced *in vitro*, for example, when cocaine has been smuggled in bottles of alcoholic beverages (Casale and Moore, 1994).

Cocaine concentrations in the hair of active users range from 1 to 5 ng/mg of hair, or even higher (Henderson et al., 1996). Once cocaine is deposited in hair it is stable indefinitely (Baez et al., 2000), a fact that can be of considerable importance should questions about drug use arise after death. The question can be easily answered by exhumation. Cocaine has been detected in the hair of mummified Peruvian coca chewers who died more than 1000 years ago (Springfield et al., 1993). As a practical matter, hair storage requires very little space, and some medical examiners now routinely collect and store samples, analyzing them only should the need arise at a later date.

1.9.4 Heart

Positron emission tomography (PET) scanning studies of humans demonstrate a very high uptake of cocaine by the heart. Within two to three minutes after injection, 2.5% of the dose administered appears in the heart, clearing rapidly over the next 10 minutes. When pharmacologic doses of cocaine are given to baboons, the pattern of uptake and washout is similar to that seen in humans. Even though the cocaine rapidly disappears, inhibition of the norepinephrine transporter persists for some time after the cocaine is gone (Fowler et al., 1994; Volkow et al., 1996). This finding suggests that toxic levels of norepinephrine may persist in the heart for some time after the cocaine has been cleared. It may also explain the typical patterns of catecholamine-induced necrosis seen in the hearts of some abusers.

The relatively high uptake by the heart, in spite of the rapid rate at which cocaine is cleared, makes it possible that cocaine could be detected in myocardium at autopsy, especially in chronic users or those who have ingested large amounts of drug. Poklis described a case where death occurred after an intravenous dose of unspecified size, where the concentration of cocaine in the heart was 6 mg/L while the cocaine concentration in the blood was only 1.800 mg/L (Poklis et al., 1985). In a later report the same author described two other cases where myocardial cocaine concentrations exceeded 5 mg/L (Poklis et al., 1987). Neither report specifies the postmortem interval, so it is not clear whether myocardium actually accumulates and concentrates cocaine, or if the values measured are merely the result of redistribution.

1.9.5 Kidneys

In human studies of radioactive cocaine uptake, kidney uptake is greater than that of the heart. Kidney uptake occurs in the renal cortex only and, as in the heart, peak uptake occurs at two to three minutes; after 10 minutes half of the dose will have been cleared (Volkow et al., 1992). Autopsy measurements of renal cocaine levels are rarely reported: the values that have been ranged from 1 to 28 mg/kg (Lundberg et al., 1977; Di Maio and Garriott, 1978; Poklis et al., 1985, 1987). Comparison of the results is impossible because, in most cases, the postmortem interval is never mentioned.

1.9.6 Liver

Hepatic cocaine receptors are present in higher concentrations and have greater affinity for cocaine than those located in the brain (Calligaro and Eldefrawi, 1987). In Volkow's PET studies, hepatic accumulation of drug was very high, although uptake occurred after most of the other organs, but still within 10–15 minutes after intravenous injection. More than 20% of a dose reaches the liver and, once there, concentrations remain stable for more than 40 minutes. The findings of these dynamic studies are generally in agreement with autopsy studies that have also shown high concentrations in the liver.

In the autopsy study reported by Spiehler and Reed (1985), the mean hepatic cocaine concentration in patients dying of cocaine toxicity was 6.7 mg/L, and the BZE concentration was 21.3 mg/L. An earlier retrospective study of 15 cases gathered from several centers yielded slightly different results. More cocaine was detected in the blood than in the liver, with a blood/liver ratio of 1.4 (Finkle and McCloskey, 1977). The high concentrations of BZE reported are hardly surprising given that the major metabolic pathways of cocaine metabolism involve plasma and hepatic esterase activity. Cocaethylene is also synthesized in the liver, and hepatic cocaethylene levels are much higher than hepatic cocaine levels (Hearn et al., 1991). Whether or not this concentration difference explains why cocaethylene appears to be more hepatotoxic than cocaine (Odeleye et al., 1993) remains an open question.

Hepatic oxidation of the nitrogen atom in cocaine's tropane ring also occurs. The resulting products are *N*-hydroxynorcocaine and the free radical norcocaine nitroxide. Norcocaine can also be found as a contaminant in illicit cocaine, where it is a byproduct of the refining process. When potassium permanganate is added to crude cocaine mixtures, norcocaine can be formed. Norcocaine is believed to be responsible for the hepatotoxicity observed when cocaine is given to experimental animals (Thompson et al., 1979). Mice pretreated with phenobarbital, which activates their P-450 microsomal systems, develop a specific type of hepatic necrosis (Kloss et al., 1984).

Norcocaine can also be detected in humans, possibly as a cocaine contaminant, but only in very small amounts, and it would appear that most norcocaine is formed within the human body. This is somewhat surprising because hepatic oxidation of cocaine is certainly not a preferred route of human cocaine metabolism. When human volunteers are given both cocaine and alcohol they produce more norcocaine than controls given only cocaine. An explanation for this phenomenon is still wanting. It has been suggested that, given enough alcohol, blood pH will drop slightly and plasma cholinesterase will become less efficient, leaving more cocaine to circulate through the liver. No matter how the norcocaine gets into the body, its relationship to hepatic injury in humans is unclear (Inaba et al., 1978). Hepatic lesions histologically similar to those seen in mice have been described in man, but are quite rare (Marks and Chapple, 1967; Teaf et al., 1984; Perino et al., 1987; Charles and Powell, 1992).

1.9.7 Skin and Nails

Nails can prove a good forensic matrix for the detection of abused drugs. Indeed, the international literature reports the use of nail analysis in a number of settings, including postmortem drug detection, drug testing in the workplace, and drug screening to detect prenatal exposure. Basic drugs, including those that are not thought of as being very lipid soluble, accumulate in the epidermis, dermis, and subcutaneous fat. Even the stratum corneum, the outermost layer of the skin consisting entirely of keratinocytes that have lost their nuclei, still binds drugs.

Cocaine, for example, reaches the skin either through the circulation or via external contamination. In a controlled study of cocaine and heroin users housed in a locked ward, cocaine and BZE remained present in most stratum corneum specimens collected over a three-week "washout" period, during a period when the volunteers were not receiving any drugs at all. When drugs were given, low concentrations quickly appeared in the stratum corneum and remained there for at least two weeks (Joseph et al., 1998). In other studies, cocaine, BZE, and THC (or 11-*nor*-delta-9-tetrahydrocannabinol, THC-COOH), when applied directly to the skin, remained detectable there for up to three days and were not removed by simple cleansing with isopropanol (Kidwell et al., 1998).

Most cocaine metabolites, including anhydroecgonine, can be extracted from the nails (Ragoucy-Sengler and Kintz, 2005). Several methods have been used and all can simultaneously resolve cocaine, BZE, and norcocaine (Ragoucy-Sengler and Kintz, 2005). This methodology seems complementary to hair testing but, like hair testing, it is subject to outside contamination and false positive tests. Toenails provide a much better testing matrix than fingernails, because positive results from handling drug are unlikely.

Fingernails and toenails contain melanin and keratin which is basically indistinguishable from keratin found in hair. The results of preliminary studies suggest that nail drug testing may prove to be a more sensitive postmortem detector of cocaine use than either urine or blood. When fingernail and toenail specimens obtained from 18 suspected cocaine users were extracted in methanol and then purified by solid-phase extraction, nail analysis markedly increased detection of cocaine. Cocaine or one of its metabolites was present in 14 (82.3%) subjects, but only 5 (27.7%) were found positive by conventional postmortem drug analysis. As is the case with hair and sweat, cocaine itself is the main analyte detected, but smaller quantities of BZE were found in all the positive nail specimens. Other metabolites, including anhydroecgonine methyl ester, ecgonine methyl ester, cocaethylene, norcocaine, and norbenzoylecgonine, are inconsistently present. The ratio of cocaine to BZE ranged from 2 to 10:1 (Garside et al., 1998).

In a related study, the toenails of 46 decedents were tested for cocaine, BZE, norcocaine, and cocaethylene. Concentrations of cocaine and BZE ranged from 0.20 to 140.17 ($n = 20$) and 0.30 to 315.44 ng/mg ($n = 21$), respectively. Norcocaine concentrations of 6.78 and 0.66 ng/mg and cocaethylene concentrations of 2.60 and 0.73 ng/mg were detected in two specimens (Engelhart et al., 1998). Cocaine can also be detected in the finger- and toenails of infants and children. One case report described finding cocaine in the nails of a 3-month-old with SIDS (Skopp and Potsch, 1997).

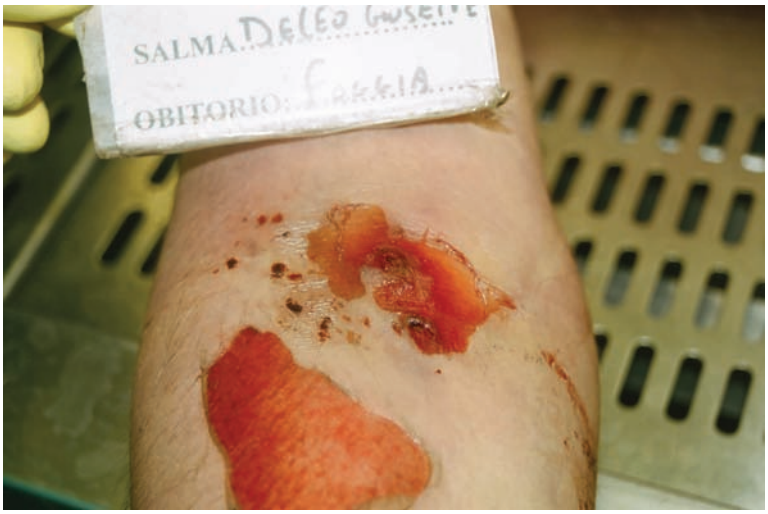
Basic drugs can also be extracted from the underlying dermis. The dermis is composed of fibrous, vascularized connective tissue, hair follicles, sweat and sebaceous glands. The number of sweat and sebaceous glands, and the output of sweat and sebum found in the dermis vary by location. The hands are the most richly supplied, but sweat glands in any location are capable of excreting drug-containing sweat and sebum onto any part of the skin. In autopsy studies, drug concentrations measured in the dermis were comparable to those measured in blood (Levisky et al., 2000). Values from a typical cocaine-related death are shown in Table 1.9.7.1.

The adipose layer, beneath the dermis, consists of lobules of fat separated by fibrous connective tissue septa. Lipophilic drugs including diazepam, nordiazepam, meprobamate, and alprazolam all have been detected in skin and adipose tissue. In the case of heavy marijuana smokers, THC has been shown to remain detectable in fat for up to 28 days after smoking (Johansson and Halldin, 1989). In the case of other drugs, the detection

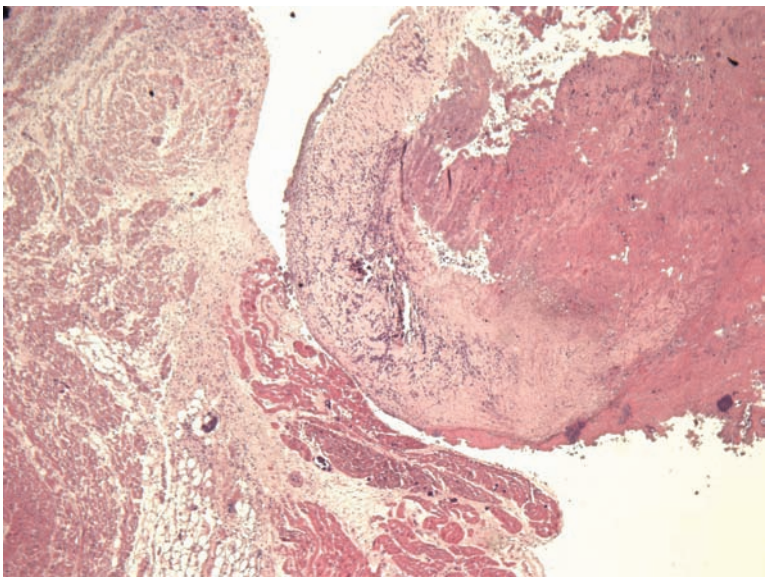
Table 1.9.7.1 Values from a Typical Cocaine-Related Death

	Adipose (ng/g)	Skin (ng/g)	Blood (ng/g)
Cocaine	220	259	341
Cocaethylene	348	188	209
Benzoylecgonine (BZE)	111	Negative	2903
Ecgonine methyl ester	Present	Negative	Present

Source: Data adapted from Levisky, J. et al., *Forensic Sci. Int.,* 110, pp. 35–46, 2000.



(a)



(b)

Figure 1.9.7.1 Subcutaneous injection of skin ("skin popping") and inflammatory response in underlying skin.

time may be even longer. Measurable amounts of the drug terbinafine can be found in plasma, serum, sebum, hair, nails, dermis/epidermis, and stratum corneum for more than six weeks (Faergemann et al., 1991).

Special considerations apply to the fetus. Human newborns rely on energy that is stored in brown fat, and that energy is liberated when catecholamines bind to the receptors on the fat. The brown fat of experimental rats avidly takes up cocaine. The high uptake is probably explained by rat nuchal brown fat which is richly supplied with sympathetic nerve terminals (Som et al., 1994). The children of cocaine-using mothers no doubt have detectable levels of cocaine in their fat stores, but measurements have not been reported, or at least not in humans. The actual mechanism of uptake is not completely understood, but leptin, which is produced in several organs in addition to white adipose tissue, brown fat, the placenta, and fetal tissues (such as heart and bone/cartilage), almost certainly play a role. It is known, however, that the production of leptin by white fat is at least partly controlled by inhibitory β adrenoceptor agonists that bind to β-3-adrenoceptors, and cocaine does not do that. Cocaine- and amphetamine-regulated transcripts (CARTs) are also integral to the process (Trayhurn et al., 1999).

1.9.8 Biofluids

1.9.8.1 Amniotic Fluid

Cocaine and its metabolites have been measured in amniotic fluid and umbilical cord tissue taken at birth from 32 cocaine-abusing women. The main analyte detected was BZE, which was found in 28.1 and 18.5% of the amniotic fluid samples and umbilical cord tissue specimens, respectively. Measurable concentrations of ecgonine methyl ester and *m*-hydroxybenzoylecgonine were also present in amniotic fluid specimens, while umbilical cord tissue specimens were found to contain mainly EME, norcocaine, and *m*-hydroxybenzoylecgonine (Winecker et al., 1997). In the only case report yet published on the subject, cocaine and BZE were quantitated in amniotic fluid, umbilical cord blood, and neonatal urine from children of cocaine-using mothers. Benzoylecgonine concentrations were 290 ng/mL and cocaine levels were 70 ng/mL in the amniotic fluid. Levels of BZE and cocaine were much higher in the newborns' urine, although cocaine levels were roughly similar. Neither cocaine nor BZE was detected in umbilical cord blood (Jain et al., 1993).

1.9.8.2 Breast Milk

An estimated 5–10% of American women use cocaine during pregnancy, yet the issue of cocaine in mother's milk is poorly studied. Cocaine certainly can be transferred to infants via mother's milk (Chasnoff et al., 1987), but the kinetics in humans are unclear and the relevance of experimental models, at least in terms of pathology and pharmacokinetics, has not been demonstrated. In human milk, both cocaine and cocaethylene are bound mainly to albumin. In fact, up to 55% of cocaine and up to 61% of cocaethylene found in milk is protein bound. It has been speculated that protein binding and the lower pH of milk relative to serum (6.9 vs. 7.4) may enhance the mammary secretion of cocaine and cocaethylene into the milk, exposing the child when it nurses (Bailey, 1998). Cocaine binds only weakly and nonspecifically to milk lipids.

Chasnoff et al. (1987) studied kinetics in a single case after a 0.5 g dose of cocaine. The peak cocaine concentration in the milk was 40 ng/mL occurring 12 hours after the drug

had been given, and it was completely cleared from the milk by 36 hours. In a second, more recent case report, the milk cocaine concentration was 8 ng in one woman six days after injecting an unknown amount of cocaine (Sarkar et al., 2005). Presuming that the measurements reported by Chasnoff were typical for all women, a mother who consumes half a gram of cocaine per day while producing one liter per day of milk would be delivering 0.48 mg per day to her child (0.09% of the dose consumed by the mother). Most experts agree, and clinical evidence confirms, that such a low dose poses little risk to a child (Sarkar et al., 2005). Similar measurements have been reported for other psychotropic drugs (Koren et al., 2006), but as a recent case report makes clear, the existence of genetic heterotropism may alter the picture (Madadi et al., 2007).

Winecker et al. (2001) reported finding milk concentrations of 12 μg/mL—100 times higher than earlier studies. If correct, this would amount to the delivery of much more substantial amounts of cocaine—a total dose of nearly 50 mg/day, enough to raise legitimate questions about toxicity—but the observation has not been repeated, the study is almost a decade old, and it may well be that methodology accounts for the differences. At the time, it was not appreciated that drug concentrations in the first milk produced tend to be much higher than in the "hind" milk. The only way to get an accurate concentration measurement is to collect and analyze all of the milk produced over a 24-hour period.

The consequences of such exposure, whether to 5 mg or 50 mg in 24 hours, have not been established and will be difficult to characterize. Women who use cocaine during their pregnancy also use ethanol, cigarettes, and other drugs, all of which may be excreted in the milk. Indeed, one case report describes finding nicotine, codeine, and oxycodeine along with cocaethylene in the milk of one admitted cocaine user, and no drug in the milk of another woman who was also an admitted drug user (Dickson et al., 1994). Nursing mothers have been charged with assault, endangerment, and even manslaughter for the administration of drug-tainted milk, but in none of the cases that have come to trial has the mother, or her milk, ever been tested for the offending drug (Ariagno et al., 1995). The most recent of these cases was tried in Southern California, where a methamphetamine-using woman was convicted of murder by breast feeding, even though she denied breast feeding, insisting that she was using formula. The formula was never tested.

1.9.8.3 Fetal Gastric Aspirates

The developing fetus swallows cocaine-containing amniotic fluid. Concentrations of cocaine measured in gastric aspirates taken from the newborn contain unpredictable amounts of cocaine and/or cocaine metabolite. In one study cocaine was detected in nearly half (45.5%) of gastric aspirate samples collected from infants in whom meconium was positive for cocaine. This approach would seem to have little to offer over meconium testing, though it will provide a specimen that is easier to handle (O'Connor et al., 1996).

1.9.8.4 Oral Fluid (Saliva)

Oral fluid is comprised of a mixture of saliva and gingival products, crevicular fluid, debris of the oral mucosa, and bacteria; however, the bulk of the fluid consists of the output of the submandibular glands (approximately 70%) and the parotid glands (25%). The total volume of fluid produced ranges from 500 to 1500 mL per day. Saliva contains very little protein, so unbound drugs in the plasma appear in almost the same concentrations

in both plasma and saliva. Because cocaine is weakly basic and saliva is normally more acidic than plasma, the concentration of ionized cocaine in saliva may be as much as five times higher than plasma cocaine concentrations. For the same reasons, concentrations of BZE are two to three times higher in plasma than in saliva (Thompson et al., 1987; Cone et al., 1988). Saliva cocaine concentrations correlate well with plasma concentrations. Concentrations in both saliva and blood correlate equally well with behavioral and physiological effects. The half-life of cocaine in both fluids is also the same, on the order of 35 minutes. Five hours after a 40-mg intravenous bolus of cocaine, levels in both saliva and blood are near the limits of detection (29 ng/mL for saliva and 8 ng/mL for plasma). When cocaine is detected in saliva it is very good evidence of very recent use (Cone and Menchen, 1988; Ferko et al., 1992).

Cocaine is the predominant analyte in saliva but, because BZE and EME both have much longer half-lives (2.3 to 6.5 hours) than cocaine, both of the metabolites will accumulate in saliva with repeated dosing. The relative proportions and absolute concentrations of cocaine and its metabolites are highly dependent on how the saliva is collected. Stimulated saliva (specimens collected after the donor has been given a piece of sour candy) tends to contain much less drug than nonstimulated samples (Kato et al., 1993). Cocaethylene can also be detected in saliva (Cognard et al., 2006). In general, oral fluid testing seems to produce results equivalent to those obtained with urine testing (Cone et al., 2002).

The same cautions apply to the interpretation of low cocaine concentrations in the saliva as those for blood. Chronic cocaine users may be found to have persistent low levels of cocaine even when they have abstained for several days or more. The presence of low concentrations of cocaine in the saliva is certainly consistent with past cocaine use, but it is not necessarily diagnostic of recent ingestion. During cocaine withdrawal, lipophilic storage sites in the brain continue to release cocaine. Small amounts of cocaine can appear in saliva and urine for weeks. Rats given 20 mg/kg of cocaine a day, twice a day for two weeks, have measurable cocaine levels in their fat for up to four weeks after the drug was discontinued (Misra et al., 1974). The same situation applies in humans. Chronic users who are monitored during withdrawal will continue to excrete unmetabolized cocaine, detectable by radioimmunoassay (RIA), for 10 days or more after their last dose (Cone and Weddington, 1989; Weddington, 1990).

1.9.8.5 Spinal Fluid

Measurements of spinal fluid might prove useful, especially since cocaine crosses the blood–brain barrier so readily, but there have been no systematic studies in humans. One case report described finding unmetabolized cocaine within the CSF at 24 hours, but there has been no follow-up to the original study (Rowbotham et al., 1990).

1.9.8.6 Urine

Cocaine is eliminated almost entirely by biotransformation with a renal clearance of less than 30 mL/min (Chow et al., 1985). The primary entities detected in the urine are cocaine and BZE. In a study of otherwise healthy drug addicts in treatment, the median concentrations of cocaine and BZE equivalents were 235 and 14,900 ng/mL, respectively, but in some instances the maximum concentrations were many times higher (112,025 ng/mL of cocaine and 1,101,190 ng/mL of BZE in at least one instance)

(Preston et al., 1998). Great intra-individual variation exists, and the route by which cocaine has been taken has an important effect on the proportion of metabolites produced and then excreted.

When single bioequivalent doses of cocaine were administered by intravenous, intranasal, and smoked routes to six volunteers, and all urine was collected for three days, peak cocaine concentrations occurred in the first specimen collected and thereafter fell to 1 ng/mL (the limit of detection) within 24 hours. Benzoylecgonine was the most common metabolite detected (39, 30, and 16%, after intravenous, intranasal, and smoked routes, respectively) (Cone et al., 2003). Other metabolites present in much smaller amounts were EME and six minor cocaine metabolites (norcocaine, benzoylnorecgonine, *m*-hydroxycocaine, *p*-hydroxycocaine, *m*-hydroxybenzoylecgonine, and *p*-hydroxybenzoylecgonine). Taken together, the minor metabolites accounted for as much as 18% of the original dose when it had been given intravenously, and as little as 8% when it had been smoked as "crack" (Weddington, 1990).

When six volunteers smoked 40 mg of cocaine, maximum urinary concentrations for cocaine, BZE, and ecgonine methyl ester occurred at 2.2, 6.6, and 5.6 hours, respectively. The last positive urine test for cocaine (10 ng/mL cutoff) occurred 55 hours after smoking, but BZE (20 ng/mL cutoff) and ecgonine methyl ester (10 ng/mL cutoff) continued to be detectable for 106 and 164 hours, respectively (Huestis et al., 2007).

Chronic abusers continue to excrete cocaine and its metabolites for much longer than occasional users. Cocaine's plasma half-life is longer in chronic users than it is in naïve ones, and the same holds true for urinary excretion. Most standard references indicate a 48-hour excretion time for BZE, cocaine's principal metabolite, but several published reports have described different results. In one study, performed with three volunteers, BZE remained detectable in the urine at concentrations above the 300 ng/mL cutoff for more than 120 hours, while cocaine itself was found in the urine for up to 24 hours (Preston et al., 2002).

In a second study, volunteers who had used cocaine daily for at least one month were observed on a closed metabolic ward. On average, the group had been regularly using cocaine for more than seven years, and consuming, on average, 1 g per day. All were "crack" smokers who neither injected nor snorted cocaine. The mean age was 36.7 years. The group included 10 women and eight men, with the last episode of cocaine use having occurred within 24 hours of admission to the closed unit. All urine samples (n = 953) were collected, frozen, and batch analyzed. As would be expected, all the participants tested positive for urine BZE at the start of the study, with concentrations ranging from 630 ng/mL to 277,709 ng/mL urine at Time 0. After the first 24 hours had elapsed, BZE concentrations had decreased to only one third (33.5%) of the concentrations at Time 0. At 48 hours, concentrations had dropped to 7.7% of the original value, and at 72 hours, BZE concentrations had fallen to 3.6% of the Time 0 levels.

BZE excretion fluctuates and does not decrease in a straight line. For example, at 48 hours, four of the volunteers in the second study had urine concentrations above the standard 300 ng/mL cutoff, but only two of these same individuals had tested positive 24 hours earlier. Sixteen of the study participants remained in the locked ward for the completion of the study. For those individuals, the elapsed mean time from admission, until the first urine that tested negative for BZE, was 43.6 ± 17 hours (range 16–75 hours). The mean time until the last positive test (i.e., when all further tests were negative) was 57.5 ± 31.6 hours.

In sum, chronic cocaine users who stop taking cocaine will continue to excrete cocaine metabolites for at least two days, and even after they finally do test negative for BZE, the next day they may well test positive again. Normalizing BZE to the creatinine concentration helps. Creatinine appears in the urine at a relatively constant rate. Normalizing BZE to creatinine will help correct for distortions introduced by dilution or concentration of urine. The process of normalization to creatinine will increase BZE detection time.

When urine samples from the previous study were normalized to creatinine content, 15 of the 16 participants had at least one positive test at between 48 and 72 hours. On the other hand, normalizing BZE to creatinine does nothing to change the fact that some negative tests are followed by some positive tests (Preston et al., 2002). The situation comes about because the half-life of BZE is relatively long, on the order of 6 hours, and it may appear in the urine for days. The presence of BZE is solid proof of past use, but the timing of the past use cannot be inferred from the urinalysis by itself.

In cases of cocaine-related sudden death, urinary cocaine concentrations may well exceed concentrations of BZE or that of the other metabolites (Ramcharitar et al., 1995; Karch et al., 1998). Most, but certainly not all, commercial screening tests are designed to detect the cocaine metabolite BZE and not cocaine itself. Some cross-reactivity may exist, but antibody-based screening tests generally do not detect cocaine or other metabolites such as EME in the urine, even if they are present, which explains the false general impression that cocaine does not appear to any significant degree in the urine. Actually, detection of cocaine in the urine is a sign of recent ingestion, especially in occasional users. The absence of cocaine, on the other hand, is only evidence that the drug has not been taken within the last few hours (Jatlow, 1988).

Hospitalized patients undergoing detoxification continue to excrete metabolite for weeks after their last dose of cocaine (Weiss and Gawin, 1988; Cone and Weddington, 1989; Burke et al., 1990). The same caveats that apply to saliva and blood testing also apply to urine. It should also be apparent that no conclusion may be drawn about the degree of impairment, if any, at the time of urine testing. The presence of metabolite indicates only that the drug was used in the past.

Similar considerations also apply to the newborn. The elimination half-life of cocaine and BZE in the newborn has been measured. The half-life of BZE during the first day of life, based on plasma measurements in 13 subjects, was found to be 16 hours (95% confidence interval [CI], 12.8–21.4 hours). The half-life of BZE during the first week of life, based on urine data from 16 subjects, was 11.2 hours (95% CI, 10.1–11.8 hours) (Dempsey et al., 1999). It should go without saying that there is no fixed relationship between plasma cocaine or cocaine metabolite concentrations and the amount that appears in the urine. The blood/urine ratio may be much greater or much less than 1, and the concentrations measured in the urine may vary greatly depending on the individual's state of hydration and renal function. Attempts at relating urinary concentrations to impairment or toxicity have been characterized as "pure folly" (Jones, 1998).

1.9.8.7 Vitreous Humor

When swine were injected with massive cocaine overdoses of (10 mg/kg) and euthanized eight minutes later, vitreous humor (VH) uptake substantially lagged plasma concentrations, but by eight hours vitreous cocaine concentrations had risen by 300% and were

comparable to those measured in femoral blood after eight hours (McKinney et al., 1995). There are conflicting data about vitreous uptake in humans. Hearn et al. (1991) measured vitreous cocaine concentrations in one eye just after death, and then measured concentrations in the other eye 18 hours later. The cocaine level, which was 1.0 mg/L just after death, rose to 3.5 mg/L after 18 hours. Benzoylecgonine levels also rose from 1.1 to 1.7 mg/L. Just the opposite results were observed by Duer et al. (2006), who used liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) to measure cocaine and all of its principal metabolites in approximately 50 autopsy samples. They found a strong correlation between blood and vitreous concentrations (correlation coefficients of 0.88–0.94), suggesting rapid distribution of cocaine and its metabolites and even of its hydrolysates in the blood and vitreous. In an unspecified number of decedents, the mean femoral blood cocaine concentration was 0.7 mg/L. Samples of vitreous, obtained at the same time, had a mean concentration of 1.0 mg/L. Unfortunately, the value of this later study is limited by the unknown postmortem interval. The postmortem behavior of cocaine cannot be generalized to other drugs. In another, recently published *in vitro* study, free morphine concentration in the vitreous of dogs sacrificed by massive morphine overdose was found to rise rapidly after death and then slowly decline (Crandall et al., 2006).

In the first large series of vitreous measurements in cocaine users ever to be published, cocaine, BZE, ethanol, and cocaethylene concentrations were quantitated in 62 medical examiner cases. The mean concentrations of cocaine, cocaethylene, and ethanol measured in vitreous were not significantly different from the mean concentrations of the same drugs in blood: 0.613 mg/L (standard deviation [SD] 0.994) vs. 0.489 mg/L (SD 1.204) for cocaine; 0.027 mg/L (SD 0.59) vs. 0.022 mg/L (SD 0.055) for cocaethylene; and 0.092 g/dL (SD 0.12) vs. 0.058 g/dL (SD 0.091) for ethanol. There were, however, significant differences between BZE concentrations in the two matrices; they were much lower in the vitreous than in the blood: 0.989 mg/L (SD 1.597) vs. 1.941 mg/L (SD 2.9) (Mackey-Bojack et al., 2000).

In two other published series, no cocaine could be detected in the vitreous. Chronister et al. (2001) screened 392 consecutive vitreous humor specimens using the CEDIA DAU cocaine assay and compared the vitreous cocaine levels to those in other tissue specimens including blood. Twenty-two cases were confirmed by GC-MS. Routine analysis of blood, urine, bile, and/or bladder wash specimens by gas chromatography–nitrogen phosphorus detection revealed the presence of cocaine/cocaine metabolites in only seven (31.8%) of the 22 confirmed to have taken cocaine. The concentration of cocaine and BZE in the blood specimens ranged from 0 to 337 ng/mL and 17 to 8598 ng/mL, respectively. Cocaethylene was not detected in these cases.

In the most recently published study, a very good correlation was found between blood and vitreous cocaine concentrations (correlation coefficients of 0.88–0.94), but only weak correlations were observed between the urine and blood concentrations (correlation coefficients of 0.61–0.64), and correlations were weaker still between urine and vitreous concentrations (correlation coefficient of 0.59). Ecgonine is a significant cocaine hydrolysate with concentrations on the same order of magnitude as BZE and it also very rapidly distributes into the vitreous. With such a strong correlation between the blood and vitreous, measurement of vitreous concentrations could prove to be an important element in the evaluation of cocaine-related deaths (Duer et al., 2006).

1.9.8.8 Sweat

Cocaine and its metabolites are excreted in sweat. Cocaine first appears in sweat within one to two hours of administration (Huestis et al., 1999), and concentrations of up to 100 ng/mL of cocaine have been recorded. Sweat testing is a noninvasive technique for monitoring drug exposure and it is used increasingly in an assortment of medico-legal settings. Proprietary sweat collection devices are available for this purpose. Cocaine is the main analyte found in sweat, but ecgonine methyl ester and BZE can also be detected, with ecgonine methyl ester generally detected in higher concentrations than BZE. In experimental studies, cocaine and EME were found to be detectable within two hours; however, BZE is not detected until four to eight hours after low doses and slightly sooner after high doses. The majority of drug is cleared from the sweat within 24 hours (Kacinko et al., 2005).

1.9.8.9 Semen

Cocaine appears in semen and may enter the circulation of both mother and child. There is evidence that the fetus may be exposed to chemicals in semen, either (1) by access of chemicals to the maternal circulation after absorption from the vagina, or (2) by delivery to the egg of chemicals, including cocaine, that have become bound to the sperm cell. Direct chemical exposure following transport from the vagina to the uterine cavity has not been demonstrated in humans.

Seminal fluid chemical concentrations are typically similar to, or lower than, plasma concentrations. Assuming total absorption of a seminal dose of a chemical with a high semen/blood concentration ratio, blood concentrations in the woman would be many orders of magnitude lower than in the man. The presence of cocaine in or on human sperm cells has been demonstrated. Based on *in vitro* studies, cocaine oocyte concentrations would be five orders of magnitude lower than blood concentrations associated with cocaine abuse (assuming of course that cocaine-laden sperm were capable of fertilizing) (Klemmt and Scialli, 2005).

The forensic value of semen testing is questionable. Prostatic fluid is more acidic than plasma and is likely to cause ion trapping of cocaine. On the other hand, vesicular fluid is more alkaline than plasma and the effects may cancel each other out. Only one controlled study has ever been performed and it is now over a decade old. Five volunteers were given variable amounts of cocaine (from 1 to 42 mg) IV and via insufflation. In most cases the semen cocaine to plasma cocaine ratio approached unity. Ejaculate volumes ranged from 1.8 to 2.7 g, while the semen cocaine content ranged from 0 to 81 ng/g. In no case did the total of cocaine and BZE in the ejaculate exceed 0.001 mg at one hour (after which the value would be declining because of cocaine's short half-life). Thus, it is extremely unlikely that enough cocaine and BZE could be transferred to a sexual partner for them to test positive. Other studies have shown positive tests can be expected after a dose of 1–2.5 mg (Cone et al., 1996).

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1.10 Electrophysiology of Sudden Death in Cocaine Abusers

Cocaine-related myocardial infarction and stroke are now so common that their occurrence is no longer reportable; neither is the most common cause of cocaine-related death, cardiac arrhythmia, which is likely to be electrical and not mechanical in origin. In fact, cocaine-related deaths are almost always arrhythmic in nature. For an arrhythmia to occur, (1) a susceptible myocardial substrate must be present and (2) a potent triggering mechanism must be applied. The former is provided by alterations in the heart's electrophysiological properties or anatomic structure produced by chronic cocaine use. Chemical toxins, disease (such as myocarditis), or genetic polymorphism can provide other sorts of substrates. Genetic polymorphisms can alter the ionic currents that constitute the action potential. What makes cocaine such a fascinating drug is its ability to interact with both sodium and potassium ion channels. Cocaine cardiotoxicity cannot, therefore, be understood without some appreciation of cardiac electrophysiology and the molecular biology of myocyte hypertrophy (Shah et al., 2005). A brief introduction follows. Section 1.10.2 describes specific forms of heart disease encountered in cocaine abusers, including coronary artery disease, myocardial infarction, valvular disease, and coronary dissection.

1.10.1 Myocardial Remodeling

This term was first introduced to describe the changes seen in the heart after recovery from myocardial infarction, but it is now used to describe alterations that accompany stimulant abuse, ischemia, hypertension, and even aging. Remodeling involves individual myocytes, the collegen network that supports them, and the ion channels that penetrate them. Remodeling is the way the heart adapts to new working conditions, either volume or pressure overload. Part of the remodeling process is initiated by the occurrence of preprogrammed cell death, also called apoptosis. No matter what initiates the process, the result is that myocardial collagen content increases and the ventricle becomes fibrotic (Figure 1.10.1.1) (Abbate et al., 2006; Lafontant and Field, 2006).

One element of the remodeling process is electrical. It begins with the activation of genes in the nucleus and extends to the level of the ion channel. Activation of the gene for calmodulin kinase II leads to myocyte hypertrophy (Henning and Cuevas, 2006) (see Figure 1.10.2.1). While that process is occurring, the predominant form of myosin in the heart shifts from a faster to a slower isoform, and there is increased production of atrial natriuretic factor. The renin–angiotensin system is activated, and calcium levels within the endoplasmic reticulum decrease (Henning et al., 2000), generally reducing cardiac

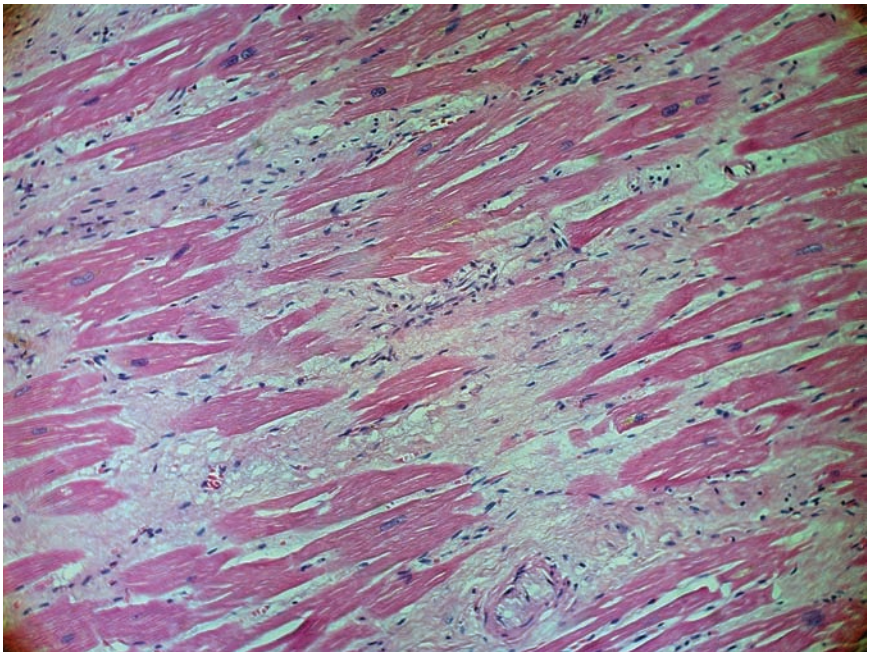

Figure 1.10.1.1 Myocardial fibrosis in the heart of a chronic cocaine user who died suddenly. (Courtesy of Dr. Vittorio Finnechi, Sienna.)

output. Additional changes occur in the number and function of β receptors (to compensate for the decreased output) while, at the same time, potassium channels controlling myocardial depolarization begin to function less efficiently (Swynghedauw, 1999; Furukawa and Kurokawa, 2006).

Myocytes depolarize whenever the potassium ions contained in their interior move outward to the interstitum during what is known as phase Ik of the depolarization cycle. Ik has two components, Ikr and Iks—the first acting rapidly, the second much more slowly. Abnormalities of this channel may lead to QT prolongation and increased vulnerability to sudden cardiac death, especially if the Ik channel is in some way blocked by a drug like astimazole or cocaine (Guo et al., 2006). More than 30 years after this relationship was discovered, the genes underlying these currents have also been identified. The Ikr current is generated because of the expression of a gene known as KCNH2 (otherwise known as the hERG channel). Iks is generated by the co-expression of a pore forming unit, the gene for which was formerly known as *KvLQTI*, but is now referred to as *KCNQ1*. It interacts with a KvLQT1 subunit called KCNE1 (older books refer to this subunit as "MINK"). Mutations of *KvLQT1* are the most common cause of Type I long QT syndrome (LQTS1) (Zhang et al., 2001).

Two genes (*KCNQ1* and *KCNE1*) function together to produce an ion channel. There is no such thing as a single unitary potassium channel, nor any one gene for its creation. An ion pore is actually composed of many different molecular complexes, each with different functions. Some of these strucures really do behave as pores, while other molecules hold the pore in place or in some way modify the channel's behavior. One of the molecules that independently alters ion channels is a calcium-dependent phosphate called calmodulin; it

binds to L-type calcium channels, sodium channels, and most of the potassium family of channels (Wu et al., 2002). It also binds to KCNQ1. When calmodulin binds to the *KCNQ1* channel, flow within that channel is modified. If a mutation occurs, which happens with some frequency, then flow through the channel could be exaggerated or, alternatively, stopped completely.

An enzyme that requires calmodulin as a cofactor (calmodulin kinase II, or CaMKII) is responsible for causing cardiac dysfunction and arrhythmias in patients (and experimental animals) with structural heart disease (Kirchhof et al., 2004). This is a consequence of activated calcium signaling dysfunction within the cell, or entry of excessive calcium into the cell, or increased release of calcium from the sarcoplasmic reticulum into the cytosol, or perhaps some combination. What is known is that both cocaine and methamphetamine directly activate the gene that produces CaMKII (Ouchi et al., 2004). It has also been shown that activation of that gene leads to myocardial hypertrophy and myocardial remodeling (McKinsey, 2007). Of course, we also know that myocardial hypertrophy is a prime risk factor for sudden cardiac death (Kannel and Abbott, 1986).

1.10.2 Hypertrophy

Left ventricular hypertrophy and alteration in the shape of the left ventricle are the most obvious consequences of CaMKII activation in cocaine abusers (Karch et al., 1995), but recognition of the results of the remodeling process long antedates the arrival of the current cocaine pandemic. When a myocardial infarction expands and heals by fibrosis, the surrounding normal muscle becomes hypertrophic. When these two changes occur together it makes the ventricle less distensible, causing diastolic pressure to rise. The process is slightly different depending on whether remodeling is the result of hypertension (pressure overload) or direct gene activation (as it appears to be for cocaine). For clinicians the important issue is that the enlarged left ventricle assumes a concentric shape. Aerobic conditioning causes the heart to enlarge eccentrically, and none of the processes normally associated with remodeling occur; even the myocardial blood supply remains normal (de Simone, 2004). Physiological hypertrophy of the type that occurs in trained athletes is characterized by normal organization of cardiac structure with normal and perhaps even enhanced cardiac function. This situation is in stark contrast with pathological hypertrophy of the heart that is commonly associated with up-regulation of fetal genes; fibrosis, cardiac dysfunction and increased mortality. Completely different signalling molecules control the processes of pathological and physiological cardiac hypertrophy. Because cocaine and methamphetamine directly activate the gene producing calmodulin kinase II, use of either drug results in pathological concentric cardiac remodeling with resultant enlargement of the ventricle (the same is true for meth MDMA abusers) (Karch et al., 1999; Patel et al., 2005). The pattern of enlargement differs very little, if at all, from the pattern seen in untreated hypertensives.

Concentric hypertrophy confers an increased risk for sudden death (Haider et al., 1998), but eccentric hypertrophy does not (de Simone, 2004). There are conflicting theories as to why that should be, but the most likely explanation seems to be that concentrically hypertrophied myocardium is ischemic. In general, the process of angiogenesis seems to lag the process of hypertrophy. This lag in vessel production is often apparent if the zone of the subendocardium is closely examined. Morphometric studies have shown that the

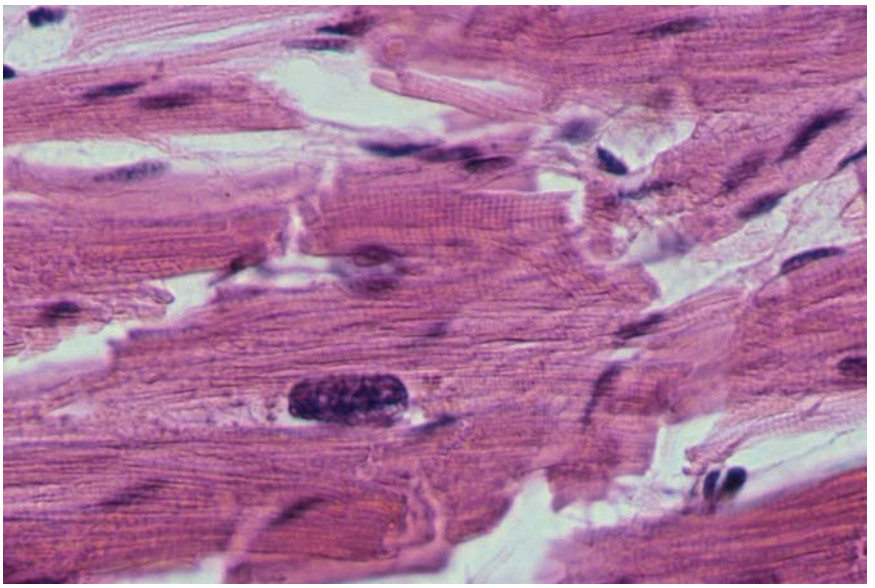

Figure 1.10.2.1 Myocardial hypertrophy. Modest, and occasionally massive, degrees of myocardial hypertrophy are common in cocaine and methamphetamine abusers. The nuclei in hypertrophic myocytes become elongated and squared. They are sometimes referred to as "boxcar" nuclei. A typical "boxcar" nucleus is illustrated in this section of myocardium from a cocaine user with sudden arrhythmic death. (H&E stain.)

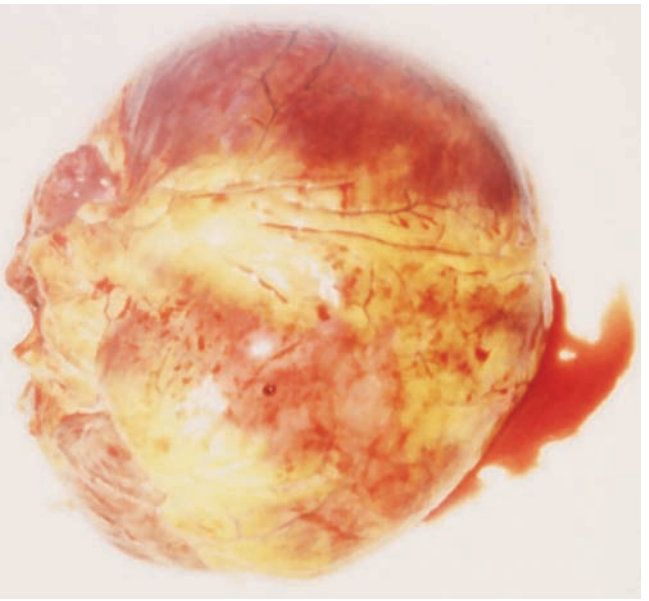

Figure 1.10.2.2 Myocardial hypertrophy. The occasional cocaine user is found to have massive myocardial hypertrophy, sometimes referred to as "cor bovinum." The heart shown here weighed over 1200 g. The decedent succumbed during his second episode of excited delirium. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

distance between myocytes and the nearest blood vessel is increased in various forms of cardiomyopathy, including ischemic, and that that distance is much greater than in a normal heart (Mosseri et al., 1986, 1991; Yarom et al., 1990). There is simply less blood to supply more muscle.

The difference between what blood flow is needed and what is available is referred to as coronary flow reserve (CFR). It is a measure originally derived to assess the severity of coronary artery disease. More specifically, CFR is defined as the ratio of hyperemic flow to resting flow for a given epicardial coronary artery. CFR decreases with increasing severity of arterial stenosis. It is possible to calculate CFR by dividing hyperemic flow by resting blood velocity (Bishop and Samady, 2004). This ratio gives a measure of how much both epicardial blood flow and microvascular resistance limit hyperemic blood flow. Ultrasound catheters are used to perform the measurements, but this technique has not yet been widely adopted by clinicians.

Any condition that causes microvascular disease (such as cocaine and methamphetamine abuse), along with other conditions such as left ventricular hypertrophy resulting from whatever cause, decreases CFR, and this occurs independently of whether epicardial coronary disease is present or absent (Bishop and Samady, 2004). The important issue here is that, even in the absence of significant epicardial disease, cocaine abusers with left ventricular hypertrophy have ischemic myocardium, even when they are at rest. This may explain some cases of sudden death, especially those that occur in confrontations with police—the catecholamine surge generated by an altercation will make the heart work harder, increasing oxygen requirements to a level that simply cannot be met because of the pre-existing microvascular disease.

Myocardial hypertrophy often goes undiagnosed during life, particularly in patients who are significantly overweight (body mass index > 30). Obesity limits the sensitivity of the ECG voltage criteria used to make the diagnosis of left ventricular enlargement. In particular, the older Sokolow Lyon voltage criteria significantly underestimate the size

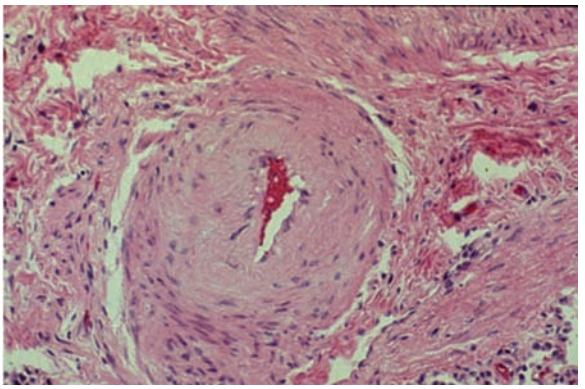

Figure 1.10.2.3 Small vessel disease. Methods now exist for the invasive measurement of myocardial flow reserve. These techniques make it possible to diagnose this abnormality even in living drug abusers (see Figure 1.10.2.3). This profoundly narrowed small vessel is from the heart of a chronic cocaine abuser.

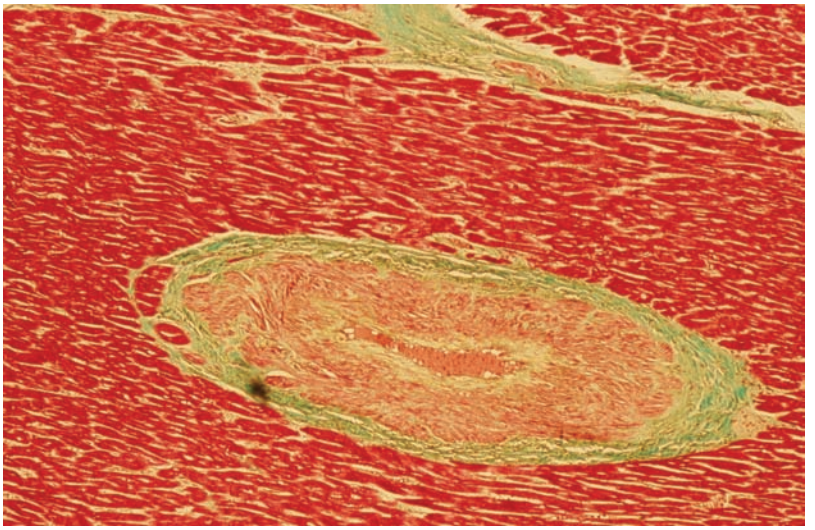

Figure 1.10.2.4 Perivascular fibrosis.

of the left ventricle (Okin et al., 2001). The importance of accurately assessing left ventricular mass during life is difficult to overstate (particularly in the obese hypertensive, cocaine user or not), as heart size is an independent risk factor for sudden cardiac death (Kannel and Abbott, 1986; Kozakova et al., 1997; Frohlich, 1999; Messerli, 1999). As the heart enlarges, perfusion of individual myocytes decreases, as does CFR (Kozakova et al., 1997); the result is decreased endocardial perfusion (Chen et al., 1994), especially during situations where there is a high demand for oxygen.

A 10% increase in heart weight is likely to go unrecognized at autopsy. Similarly, in life, in the absence of serial studies, an increase in heart weight of only 40 to 50 g will not be disclosed by ultrasonography, nor would such a modest weight increase cause wall thickness to increase beyond generally accepted limits. Even if wall thicknesses were fastidiously measured at autopsy, which is seldom the case, the increase would most likely go undetected. Weighing of the heart could disclose a large increase in weight, but because there is no universally accepted way to determine heart weight, differences in methodology are likely to obscure the presence of small increases.

Several different systems for determining normal heart weight are in use. Some pathologists use arbitrary cutoffs: 380–400 g for men and 350 g for women. Others consider heart weight to be normal provided the heart weighs less than 0.4% of the body weight (or 0.45% for women) (Ludwig, 1979). The most reliable approach is the Mayo Clinic nomogram relating heart weight to body height (see Appendix 4). This nomogram is based on measurements made in 890 autopsies of individuals found to be free of heart disease (Kitzman et al., 1988). Hearts weighing significantly more than predicted by the nomogram are abnormal, even if the heart weighs less than 400 g or 0.4% of body weight. The only problem with this widely used nomogram is that it was derived from hospitalized patients. Even though their hearts were found to be normal, all of the patients had some other fatal disease, which probably explains why the range of values observed was relatively wide. A new nomogram based on drug-free trauma patients is very much needed, but it may

be some years in the making because most trauma fatalities have positive, not negative, drug screens!

1.10.3 QT Dispersion

QT dispersion is defined as the difference between the longest and shortest QT interval in each lead of a 12-lead electrocardiogram. The greater the degree of QT dispersion across the myocardium, the greater the probability that torsade de pointes, a lethal form of ventricular tachycardia, will occur (see below) (Anderson, 2003).

The effect is quite striking. The corrected QT interval (it must be corrected for rate, because the faster the rate, the shorter the QT interval) should be less than 440 ms. Dispersion of more than 80 ms is associated with 3.5 times the normal mortality rate, and a QTc > 440 ms is associated with 8 times the normal mortality rate (Antzelevitch, 2005). The simplest explanation for QT dispersion is that it takes longer for the electrical depolarization front to traverse a thicker ventricular wall than a wall of normal thickness. Clearly, more is involved because the mycoardium is thicker in some places than in others, and the process of repolarization begins at different times in different cells (Kang, 2006; Schillaci et al., 2006).

Electrical heterogeneity within ventricular myocardium is partly dependent on the synchronized operation of different ion channels that open and close in sequence, but it is also due to the presence of myocytes with different electrical properties. There are three main myocardial cell types: endocardial cells, M cells, and epicardial cells. If the net repolarizing current is reduced, there is prolongation of the M cell's action potential. Conversely, if there is an increase in net repolarizing current, the action potential of the M cell becomes shorter. The interposition of the M cell between the endocardial and epicardial cells results in amplification of transmural repolarization heterogeneities. These heterogeneities predispose to the development of potentially lethal re-entrant arrhythmias. The initial cause really matters very little, because all of the different etiologies share a common final pathway leading to sudden death—increased spatial dispersion of repolarization currents within the ventricular myocardium (Antzelevitch, 2005).

1.10.4 Ion Channel Remodeling and Interactions

Electrical signals in all biological systems are transmitted by the flow of inorganic ions (Na^+, K^+, Ca^{2+}) through pores that penetrate the cell membrane. Each pore is composed of proteins that rapidly open and close in response to a train of biological signals (usually a change in transmembrane voltage, or interaction with a neurotransmitter such as norepinephrine). This process of opening and closing is referred to as "gating," literally because the pore acts as a gate that opens and closes, allowing the ingress and egress of different ions during the various phases of electrical depolarization. When a gate remains open, ions continue to flow and the gate is described as activated. The term "inactivation gating" is applied when the channel remains closed (Swynghedauw, 1999).

All protein structures, including ion gates, are polymorphic; because of their molecular structure, some channels work better than others and some do not work at all. Ion channel defects underlie a series of disorders known as long QT syndromes, or LQTS. LQTS defects prolong the time it takes cardiomyocytes to recycle after each heartbeat,

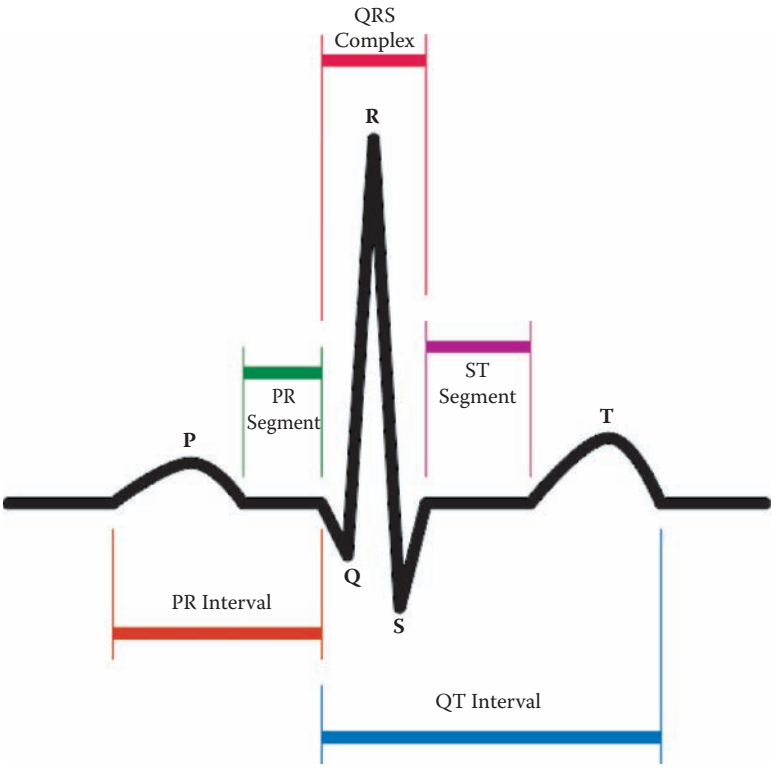

Figure 1.10.3.1 "The QT interval is a measure of the time required for repolarization to occur. When the QT interval exceeds 440 ms the probability increases that a lethal arrhythmia may occur. Myocardial hypertrophy can lead to QT prolongations, as can some inherited diseases and some drugs, including cocaine." (From Wikipedia.)

leading to prolongation of the QT interval. When the QT interval is longer than normal, it increases the risk for torsade de pointes (Figure 1.10.3.1) (Shah et al., 2005).

The phase of myocardial repolarization that has received the most attention, from researchers and drug regulators alike, is called Ikr, "the rapid repolarizing inward potassium channel" which is also known as the delayed potassium repolarization current. The channel controlling this current is produced by a gene called *hERG* (a contraction of "human-ether-related-a-go-go channel," so called because when the gene is inserted into fruit flies and the flies anesthetized with ether, their legs make motions that appeared, to the experimenters at least, like go-go dancing). Interactions between *hERG* and cocaine have been recognized for several years, but there appear to be unique differences between the way cocaine interacts with *hERG*, and what happens when other drugs interact with the same channel. The other drugs interact with *hERG* only when it is open, but cocaine's ability to bind to the *hERG* channel has little if anything to do with whether the channel is open or closed (O'Leary, 2001; Guo et al., 2006).

1.10.5 The Theory of "Multiple Hits"

If millions of people use cocaine every month, and they do, and if cocaine interacts with the *hERG* channel, and it does, why then do so few people die? The answer is that more

than simple *hERG* dysfunction is required for death to occur. There must also be abnormal signal dispersion, and that generally requires the existence of acquired structural heart disease, as well as complex gene–environment interactions. The most common form of structural disease to be encountered is likely to be an area of healed myocardial infarction. As a consequence of the injury there will be ventricular dysfunction, electrical and structural remodeling, and abnormal impulse propagation, all in combination. Should there be an electrolyte imbalance (for example, diuretic therapy for hypertension), or neurohumoral activation (for example, elevated levels of norepinephrine from stimulant abuse or an altercation), then either of these other abnormalities might serve as a trigger for generating an arrhythmia (Shah et al., 2005). Death is more likely if the *hERG* channel itself is heterogeneous and in some way abnormal, which is much more common than had previously been thought.

Cocaine-induced sudden death is a disease with an incubation period. Cocaine has the ability to interfere with sodium and potassium channel function as soon as it is used, but that seldom leads to illness, let alone lethal arrhythmias. Structural alterations are required before arrhythmias can occur, and such alterations take months, or perhaps years, of chronic use. Deaths that occur after the first or second use (barring substantial overdose) are due to pre-existing structural abnormalities, such as coronary artery disease, hypertension-induced hypertrophy, and small vessel disease, as might be seen in a diabetic or poorly treated hypertensive.

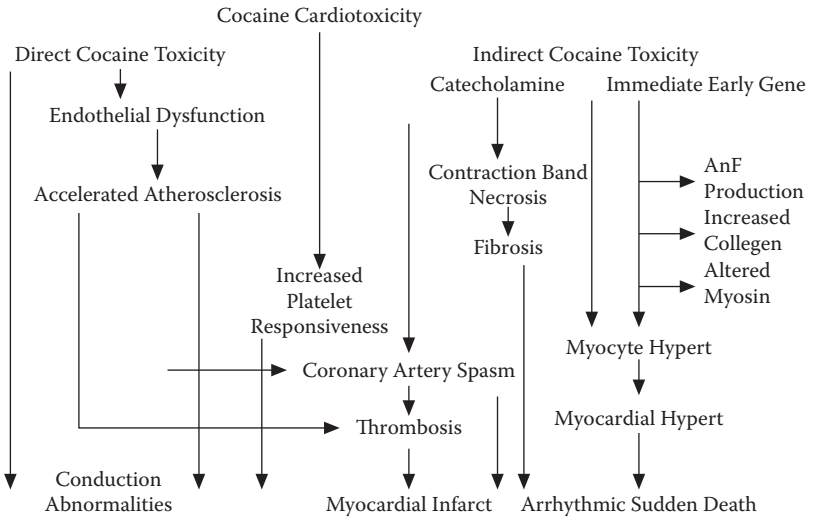

Figure 1.10.5.1 Mechanisms of cocaine cardiotoxicity. This flow chart has been constructed from both human and experimental data, and many of the mechanisms remain unclear. Toxicity may be the result of direct or indirect actions of cocaine on the heart. Direct effects include myocardial infarction and conduction abnormalities secondary to the local anesthetic effects of cocaine; however, the latter are only seen when massive amounts of cocaine are consumed. (From Kolodgie, F. D. et al., *Hum. Pathol.*, 26(6), 583–586, 1995. With permission.)

1.10.6 The Role of Catecholamines

The following sequence of events leads to cardiac myocyte contraction. Norepinephrine (NE) binds at both α and β receptor sites but has much greater affinity for the α receptor. Calcium enters via voltage-dependent channels (known as "slow channels") and through other calcium channels that open when NE binds to a receptor. Calcium is also released from storage sites within the myocyte. Once the level of calcium within the cell has risen 100-fold, myofilaments are able to contract. If cytosolic calcium levels become too high, for whatever reason (this would include the administration of inotropes that would raise intracytosolic calcium concentrations and even nuclear polymorphisms where excessive calcium is released from the endoplasmic reticulum), irreversible damage occurs to the myofilaments, a condition known as contraction band necrosis (Figure 1.10.6.1).

Cocaine abusers have elevated concentrations of circulating catecholamines. This effect has been demonstrated both in experimental animals and in humans (Gunne and Jonsson, 1964; Chiueh and Kopin, 1978; Ozaki et al., 1994; Dixon et al., 1989; Kiritsy-Roy et al., 1990; Mahlakaarto et al., 1998). Even the infants born of substance-abusing mothers have evidence of abnormal sympathetic function (Ward et al., 1991). It was once thought that cocaine toxicity and catecholamine toxicity were nearly interchangeable terms, but it is becoming increasingly apparent that they are not. In light of what is now known about hereditary channelopathies, and myocardial remodeling, it is obvious that the process is more complex.

Human β receptors belong to a group of receptors known as seven-transmembrane receptors (because the structure of the receptor traverses the plasma membrane seven times). Genes for these receptors are located on human chromosome five. They are classified

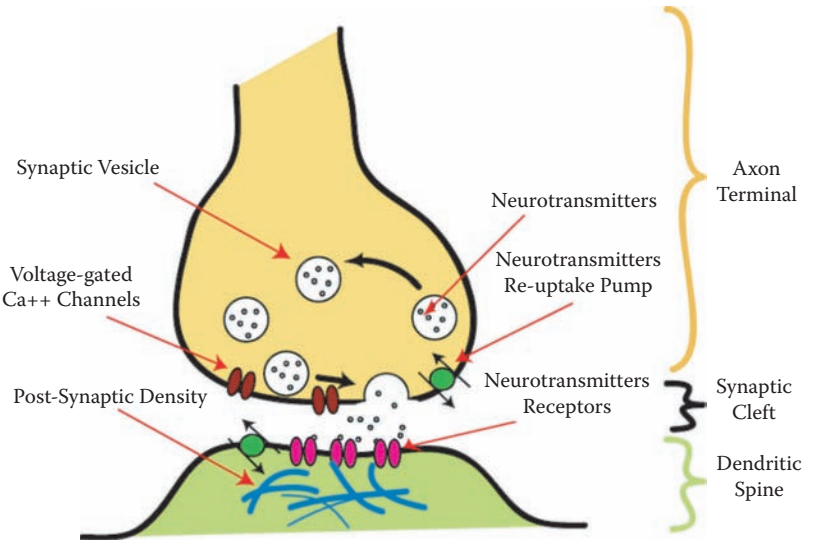

Figure 1.10.6.1 Norepinephrine (NE) is the main neurotransmitter in the heart. NE is stored within small vesicles at the end of nerve terminals. When an impulse traverses the nerve, NE is released into the synaptic cleft, then crosses the cleft, thereby activating the adjoining cell. The impulse is terminated when the NE is pumped out of the cleft back into the nerve ending. Cocaine prevents the re-uptake of NE, and toxic amounts of NE may accumulate.

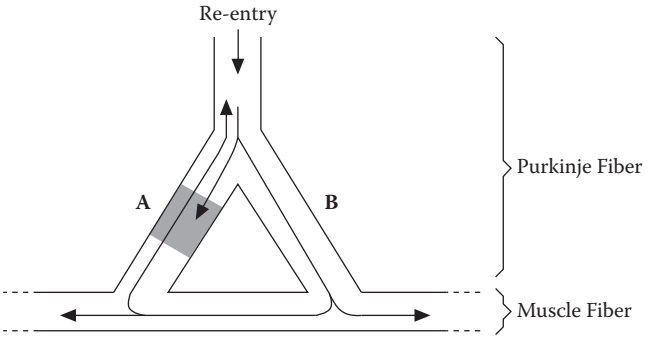

Figure 1.10.6.2 Unidirectional heart block. Zones of patchy myocardial fibrosis may provide the anatomic substrate for re-entry arrhythmia. The mechanism is thought to account for many cases of cardiac sudden death. (From *Textbook of Advanced Cardiac Life Support,* American Heart Association, Dallas, TX, 1987. With permission.)

into three main groups: β_1, β_2, and β_3. The β_2 receptors are found mainly in the respiratory tract, particularly in airway smooth muscle. Cyclic-AMP, which is formed when any β agonist binds to a β_2 receptor, causes airway relaxation, which is why this group of compounds is so widely used to treat asthma (Hoffman and Taylor, 2001). Ephedrine also binds to the β_2 receptor explaining why, until the 1930s, it was a mainstay in the treatment of bronchial asthma. Ephedrine also has the unique property of binding to β_3 receptors that, some believe, may account for ephedrine's ability to induce weight loss.

The principal catecholamine of the heart is norepinephrine (NE) (Figure 1.10.6.1), and within the heart NE functions as a neurotransmitter. It is released into the synaptic cleft each time an impulse is transmitted. Impulse transmission stops only when NE is pumped back into the presynaptic nerve ending. Cocaine prevents the re-uptake of NE and thereby exaggerates its effect. Unmetabolized NE overflows into the systemic circulation and acts as a circulating hormone (at α_1, α_2, and β_1 receptor sites). Once NE enters the general circulation it acts as a hormone, not as a neurotransmitter. Epinephrine and NE bind to both α and β receptors, but they differ in their relative affinities for each type of receptor. Epinephrine elicits a greater response at β_2 receptors than does NE.

Not only does calmodulin kinase II cause the hearts of cocaine users to increase in size, it also elevates intracytosolic calcium concentrations and causes alterations in the myosin isoforms within the heart. The result is myocardial hypertrophy and remodeling (Henning and Cuevas, 2006). NE also causes the heart to enlarge, but via a different pathway—it signals the heart by two very distinct G-coupled receptor systems. On the one hand, modest stimulation of β_2 receptors improves cardiac function, while excessive stimulation leads to dilated congestive cardiomyopathy. Excessive stimulation of adrenergic receptors sets off the process of myocyte apoptosis (auto-destruction), further exaggerating the remodeling process. In fact, adrenergic signaling causes at least two separate types of myocardial damage—(1) activation of destructive mitogen-activated protein kineases, and (2) increased mitochondrial toxicity—which both result in generation of reactive oxygen species (Singh et al., 2001). It matters very little whether the remodeling is secondary to catecholamine excess or direct gene activation. The result is the same: apoptosis, cell death, and remodeling.

Very limited data suggest that cocaine users respond abnormally to elevated catecholamine concentrations, and this too may be the result of genetic heterogeneity. Chronic catecholamine excess is usually associated with down-regulation of β receptors, but it appears that cocaine users do not down-regulate. Several groups have made measurements of the adrenergic receptors found on lymphocytes (which mirror those in the heart) and have found no change in binding sites or receptor affinity for either α or β adrenoreceptors after treatment with cocaine, in spite of elevated circulating levels of catecholamines (Costard-Jackle et al., 1989; Trouve et al., 1990; Conlee et al., 1991). Failure to down-regulate has also been observed in infants born to substance-abusing mothers, in spite of the fact that they, too, have increased circulating levels of norepinephrine.

1.10.7 Mechanisms of Catecholamine Toxicity

Persistently elevated catecholamine concentrations damage vascular tissue. Increased α-adrenergic stimulation of coronary vascular smooth muscle causes vasoconstriction and ischemia (Mathias, 1986; Ascher et al., 1988). The simultaneous stimulation of both α and β receptors also means that cocaine-induced vasoconstriction is accompanied by increased oxygen demand. Cocaine-induced increases in catecholamine concentrations almost certainly explain most cases of myocardial infarction in cocaine abusers, the majority of whom have undiagnosed, pre-existing coronary artery disease. An individual with an undiagnosed, previously asymptomatic, 70% left anterior descending lesion could become symptomatic, or even experience a fatal arrhythmia, just by virtue of the increased demand created by catecholamine-stimulated increased exertion and oxygen demand.

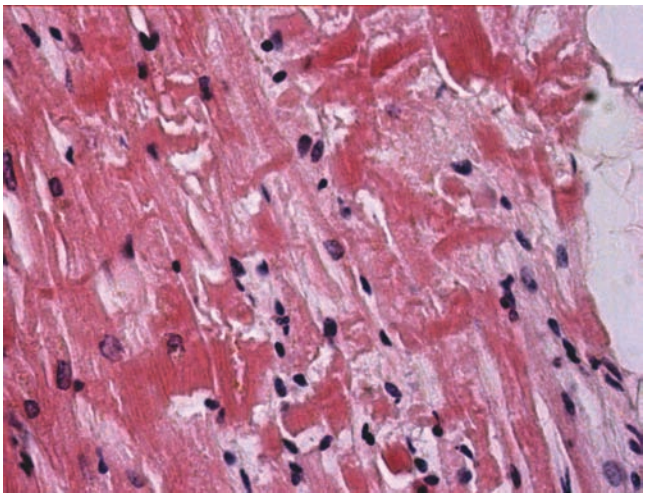

Figure 1.10.7.1 Intense catecholamine contraction band necrosis in a cocaine abuser with sudden death. Calcium overload in the cytosol leads to destructive contraction of the myofilaments. (Courtesy of Vittoria Finnechi.)

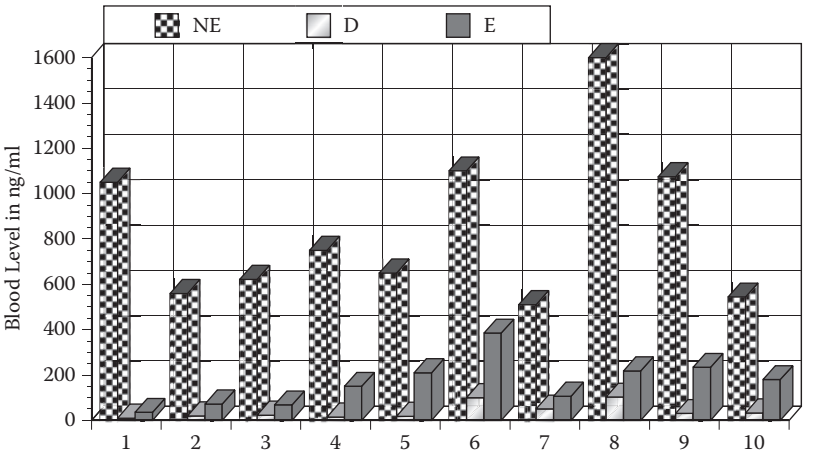

Figure 1.10.7.2 Elevated catecholamine levels in cocaine users with chest pain. Catecholamine levels were measured in symptomatic "crack" smokers. The large, checked columns represent NE levels, which are markedly elevated. Modest elevations in epinephrine could be seen (dotted columns), but not in dopamine. These levels are comparable to those seen in patients with pheochromocytoma.

At the subcellular level, an acute rise in the concentrations of epinephrine and NE can cause myocardial dysfunction (Bosso et al., 1994; Powers et al., 1994). Membrane potentials are altered in such a way as to favor the occurrence of malignant ventricular arrhythmias. This sequence was first suggested more than 50 years ago (Bozler, 1943). In human clinical studies, epinephrine administration increases the probability that ventricular fibrillation will occur and decreases the probability of spontaneous defibrillation (Tovar et al., 1998). In patients prone to sustained ventricular tachycardia, mental stress can alter the cycle length and the amount of energy required to terminate ventricular tachycardia, even when there is no evidence of ischemia (i.e., as in primary heart muscle disease where scarring from a previous infarct greatly increases the likelihood of lethal arrhythmias). In other words, mental stress may lead to sudden death through the facilitation of lethal ventricular arrhythmias (Lampert et al., 2002, 2005; Brotman et al., 2007).

1.10.8 Histopathology of Catecholamine Toxicity

The specific morphologic changes induced by catecholamine excess are essentially the same as those associated with cocaine and methamphetamine (Bravetta and Invernizzi, 1922; Karch and Billingham, 1986; Tazelaar et al., 1987). The changes associated with cocaine and catecholamine toxicity are, in turn, the same as the morphologic changes associated with intracellular calcium overload. It follows that, depending on the experimental design, the morphologic changes induced by cocaine and methamphetamine, like the changes associated with experimental catecholamine toxicity, or even pheochromocytoma, can be prevented by lowering intracellular calcium. Whether that is accomplished by calcium channel blockade (Nahas et al., 1985), or by preventing or facilitating release from the endoplasmic reticulum, or by even by gene transplants designed to repair leaky ryanodine

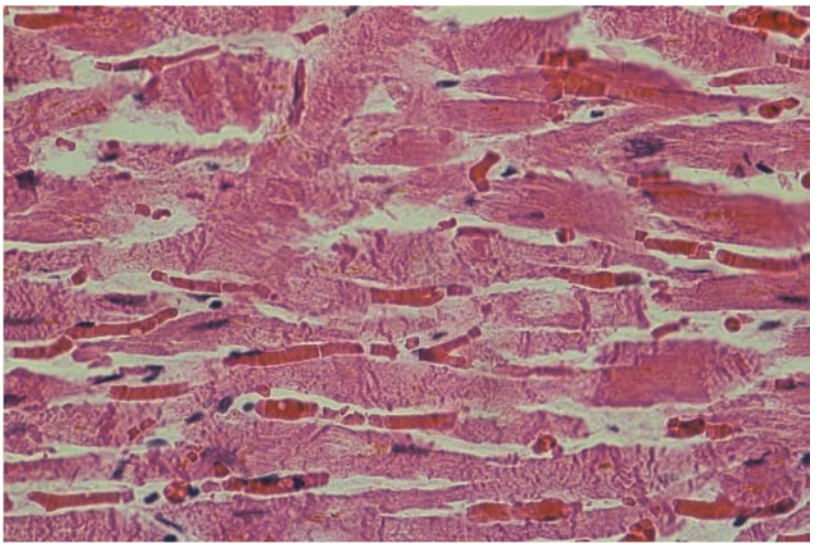

Figure 1.10.8.1 Contraction band necrosis (CBN) in myocardium of cocaine user with sudden arrhythmic death (H&E stain). Decedent was aggressively resuscitated, which probably accounts for the areas of interstitial hemorrhage and may have made the process of contraction band necrosis more intense.

receptors, remains to be seen. It is important to remember that calcium overload is not synonymous with cocaine toxicity and neither is contraction band necrosis. Anything that disrupts membrane integrity, including ischemia, can result in calcium overload (Rona, 1985).

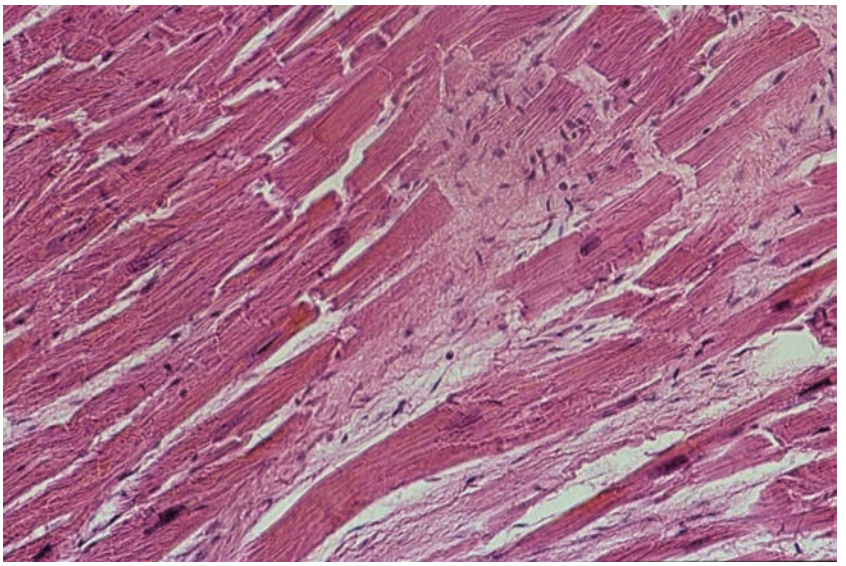

Figure 1.10.8.2 Microfocal fibrosis. Replacement of damaged CBN myocytes takes weeks or months, and lesions in various stages of evolution may be seen in chronic stimulant abusers. Neither CBN nor the resultant fibrosis is a specific finding. The occurrence of either abnormality simply indicates catecholamine toxicity.

Catecholamines cause recognizable histologic changes within the myocardium (Szakacs and Cannon, 1958; Szakacs et al., 1959), and these are easily distinguished from those produced by ischemia. The most widely recognized change is the lesion known as contraction band necrosis (CBN). This lesion has both pathologic and forensic significance. CBN is sometimes also called coagulative myocytolysis and sometimes myofibrillar degeneration. Whatever the nomenclature, it is a nonspecific finding, seen in a variety of apparently unrelated disorders. The most common setting for CBN is in the zone bordering an area of reperfused myocardium salvaged with angioplasty (Bouchardy and Majno, 1974) but CBN also occurs in the hearts of patients who have been subjected to multiple defibrillation attempts (Karch and Billingham, 1984), and is present in almost every myocardial biopsy. The presence of CBN in myocardial biopsies is probably explained by the disruption of local norepinephrine-containing nerve terminals. CBN is also a common finding in cases of intracerebral hemorrhage, drowning (Lunt and Rose, 1987), pheochromocytoma, the "stone heart syndrome," and other conditions known to be associated with catecholamine excess (Table 1.10.8.1) (Karch and Billingham, 1986). CBN is an extremely frequent finding in cases of sudden cardiac death.

Contraction band necrosis is the earliest recognizable lesion of catecholamine excess. Catecholamine-induced necrosis and ischemic necrosis can be distinguished by their pattern of distribution (Table 1.10.8.2). In cases of ischemic injury, all the cells supplied by a given vessel will be affected. When the injury is due to catecholamine excess, individual necrotic cardiomyocytes are found interspersed between normal cells. Distribution is, in fact, one of the principal diagnostic features of catecholamine injury. Another feature that separates the two is the arrangement of the myofilaments within the cells. When the insult is ischemic, the myofilaments within the cardiomyocytes remain in register. When the damage is due to catecholamine excess, the filaments are disrupted.

The reason that the same lesion is seen in such diverse conditions is that the underlying mechanism is always the same: calcium overload. Calcium enters cells when calcium channels are opened by catecholamine stimulation, but both myocardial ischemia and loss of cell membrane integrity can lead to the same result, and the cell floods with calcium. Nor does that exhaust the list of possibilities. Individuals born with abnormal ryanodine receptors can develop the same kinds of lesions (Williams et al., 2007). Whatever the mechanism of entry, a continuum of morphologic alterations can be observed; these may range

Table 1.10.8.1 Conditions Associated with Contraction Band Necrosis

Reperfusion	Norepinephrine
Steroid therapy	Cobalt poisoning
Electrocution	Starvation
Defibrillation	Myocardial infarction
Drowning	Free-radical injuries
Cocaine	Brain death
Amphetamine	Phenylpropanolamine
Epinephrine	Intracerebral hemorrhage
Isoproterenol	MDMA

Source: Modified from Karch, S. B. and Billingham, M. E., *Hum. Pathol.*, 17, 9–13, 1986. With permission.

Table 1.10.8.2 Histological Differences Between Ischemic and Catecholamine Necrosis

Ischemic Necrosis	Catecholamine Necrosis
Involves many cells in area supplied by a single vessel	Very focal; necrotic cell may be surrounded by normal cells
Myofilaments remain in register	Myofilaments are destroyed, forming eosinophilic clumps
Mitochondria remain neatly packed, uniform size	Mitochondria are translocated with distorted shapes

from hypereosinophilia to total disruption of the cell. The lesions have no apparent relationship to blood supply. CBN can, and does, occur in the absence of significant coronary artery disease.

Contraction band necrosis is a prominent feature of all myocardial biopsies, including those taken from cocaine users, making etiology difficult to assess (Adomian et al., 1978; Karch and Billingham, 1986; Peng et al., 1989). Clinical experience suggests that the presence of nuclear pyknosis may be one way to distinguish pre-existing contraction band lesions from those produced by the biopsy process itself; however, that has never been proven in a controlled study. In some cardiac biopsies, Z-band remnants can be seen with electron microscopy. This particular finding is classically associated with dilated congestion cardiomyopathy, and is not generally associated with the type of necrosis resulting from catecholamine toxicity. While it has not been observed in other patients with cocaine-related heart disease, it has been seen in patients with amphetamine toxicity (Smith et al., 1976). Its presence probably signifies only that necrosis was very severe.

Unlike the picture seen in ischemic infarction, where the myofibrillar apparatus remains visible and in register, in CBN the sarcomeres become hypercontracted and distorted (Figure 1.10.8.4). The contractile apparatus may not even be visible. Milder forms of the lesion consist of eosinophilic transverse bands separated by areas containing fine eosinophilic granules. With electron microscopy, it is apparent that the myofilaments are completely out of register and the mitochondria translocated. The dense bands visible with light microscopy are seen as amorphous gray material. This material is all that remains of both the thick and thin filaments. This exact change has been observed in the hearts of rats chronically treated with cocaine (Trouve et al., 1990). Z-band remnants, the hallmark of dilated, congestive cardiomyopathy, are generally not seen; however, if the process were ongoing and particularly severe, then the presence of Z-band remnants would not be particularly surprising. In severe instances, as in open-heart defibrillation, the sarcomeres look as if they have been torn apart, and dehiscence of the intercalated disks can occur (Karch and Billingham, 1986).

Initially, and probably for at least 12 hours, inflammatory cells are not in evidence around the contraction bands. Occasionally, a mononuclear infiltrate may appear. Eventually, the injured cells are reabsorbed and replaced with fibrous tissue. The pattern is classically seen in patients (and experimental animals) with pheochromocytoma. Illustrating the progression of lesions in humans is quite difficult, but lesions corresponding to each stage in the evolution of catecholamine injury have been reported in experimental animals. The resultant fibrosis, which is often quite prominent in the hearts of cocaine users, may supply the substrate for lethal arrhythmias (Merx et al., 1977). The catecholamine

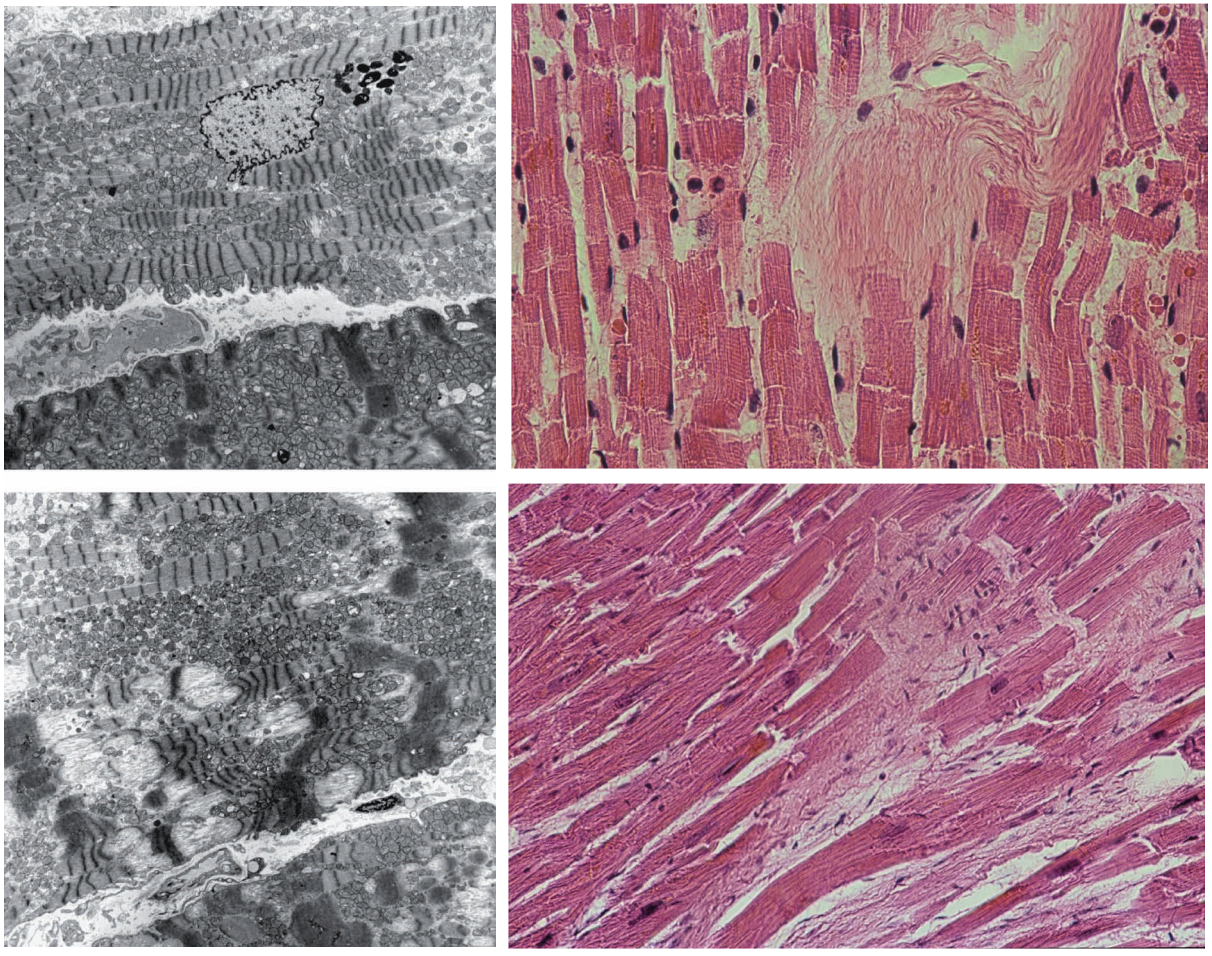

Figure 1.10.8.3 Effects of catecholamines on cardiac myocytes. The electron micrograph on top shows normal human myocardium. The myofilaments are in register; the mitochondria are of uniform size and are neatly packed between the filaments. The bottom micrograph illustrates the changes seen in contraction band necrosis. The dark electron-dense material is all that remains of the myofilaments; the mitochondria are swollen and translocated. (Original magnification 4320×, top and bottom.) (Micrographs courtesy of Dr. Margaret Billingham and Marilyn Masek, Stanford University School of Medicine.)

levels required to produce necrosis have been determined, largely as a result of research in the field of heart transplantation. Until adequate preservation techniques were introduced, hearts from donors maintained with pressor therapy frequently failed after surgery. In the course of research designed to explain the failure, experimenters found that a surge of catecholamine accompanies brain death, and that this surge is associated with the presence of CBN (Novitzky et al., 1987).

In experimental models of brain death, cardiac lesions can be prevented either by denervation or beta blockade. The occurrence of myocardial contraction bands must, in some way, be related to β receptor number, density, and regulation. These parameters, in turn, depend on whether any drugs have been taken, which ones they were, and the duration of use. The impact of cocaine and chronic catecholamine excess on receptor physiology still remains, for the most part, unstudied. The limited number of studies that have addressed this question have all reached the same conclusion. In the heart, at least, there is no indication of β receptor down-regulation in cocaine users (Trouve et al., 1990; Conlee et al., 1991; Trouve et al., 1991; Vitullo et al., 1993). This failure of down-regulation distinguishes cocaine abuse from all other chronic hyperadrenergic states.

1.10.9 Contraction Band Necrosis and Sudden Death

Contraction band necrosis is a common feature in cocaine-associated sudden death (Tazelaar et al., 1987). CBN and microfocal fibrosis have been observed in autopsy studies of cocaine users (Simpson and Edwards, 1986; McKelway et al., 1990; Roh and Hamele-Bena, 1990), and even observed in tissue cultures of myocardium exposed to cocaine (Welder et al., 1993).

The incidence of CBN in various autopsy studies of other diseases is over 80% (Reichenbach and Moss, 1975; Baroldi et al., 1979; Cebelin and Hirsch, 1980). In stimulant-related deaths, the incidence of CBN may be even higher (Rajs and Falconer, 1979; Tazelaar et al., 1987). CBN heals by fibrosis, and postmortem studies of addicts in general, and stimulant users in particular, confirm the presence of reparative microfocal fibrosis (Rajs and Falconer, 1979; Oehmichen et al., 1990a, b). This picture is not always as clear as might be desired. The process of myocardial hypertrophy also leads to the deposition of collagen and scarring (Laviades et al., 1998; Varo et al., 1999).

Contraction band necrosis never occurs as a fixation artifact (Karch and Billingham, 1986). The presence of these lesions always indicates some underlying abnormality, usually catecholamine excess. By themselves, contraction bands constitute only an indicator for cocaine use, especially if they are seen in biopsy specimens (Adomian et al., 1978). Stronger inferences can be drawn if there are other supporting findings. For instance, if microfocal fibrosis is present, the differential diagnosis then becomes quite limited. Very few conditions produce CBN with microfocal fibrosis. In fact, the only real alternative diagnosis is pheochromocytoma, which should not be all that difficult to rule out.

1.10.10 Hereditary Channelopathies

In one way or another, the investigation of sudden death in infants will eventually involve legal authorities. If *any* cocaine is found at autopsy, the parents will, at a minimum, be charged with endangerment, and possibly with homicide. It is, or should be, a basic principle

of forensic toxicology that alternative causes of death are ruled out. A number of alternative causes are not ruled out by "unremarkable" autopsies, because the lesions of LQTS cannot be seen with the naked eye or even with the microscope and, therefore, the autopsy should, in no way, be considered unremarkable but merely as incomplete. One important cause of SIDS is congenital long QT syndrome. Until the very late 1990s, congenital long QT syndromes were classified as rarities. That is no longer true and the number of SIDS cases attributable to genetic aberration seems to be rising every day (Roden, 2008).

Genetic screening of SIDS victims confirms that this disorder has a fairly high incidence. Arnestad and his collegues performed genetic screening in 201 Norwegian SIDS victims. Mutations of rare genetic variants were identified in 10% of cases (Arnestad et al., 2007). Roughly half the mutations involved variants of the *SCN5A* gene (Wang et al., 2007). On further analysis there was evidence that the children suffered from defects in the voltage-dependent inactivation of sodium currents, leading to long QT syndrome. The editors of *Circulation*, where the papers were published, concluded that this disease is sufficiently common to warrant the EKG screening of all newborn children (Berul and Perry, 2007). If a disease is sufficiently common to require newborn screening, then it should certainly be considered as a possible cause of death. Fortunately, techniques are now available by which long QT syndromes can be ruled out by analysis of postmortem materials.

In a very recent study DNA-based PCR and cycle sequencing analysis was used to detect nucleotide changes in 42 infants previously diagnosed with SIDS/SUDS. The pathogenic mutation rate was found to be 28% (12/42), and the most frequent mutation found was in the SGN5A gene (21%) (Tang, 2008). The apparent frequency of the mutation will pose grave problems for pathologists and toxicologists in the very near future. Suppose the decedent was also taking a pediatric cough formula and modest levels of drug were detected. There might be a temptation to blame the drug, which would not be legitimate unless lots were ruled out.

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1.11 External Markers of Cocaine Abuse

Certain external markers for cocaine abuse may be of clinical value. None of these changes is particularly common, as they are only seen with intense and compulsively repeated use. The absence of these external signs has little, if any, significance, but their presence provides confirmation that the individual has been a chronic user for some time.

1.11.1 Perforated Nasal Septum

Septal perforation is the best-known external manifestation of cocaine abuse. The first cases were described in the early 1900s, shortly after the practice of snorting cocaine became popular (Hutant, 1910; Maier, 1926). The presence of this lesion, however, is not pathognomonic. Perforations of the nasal septum can also result from chronic abuse of nose drops containing vasoconstrictors (Vilensky, 1982).

Septal perforation occurs as a consequence of cocaine's ability to constrict blood vessels, which is one of the reasons it remains popular with ear, nose, and throat surgeons—it controls bleeding. With chronic use of intranasal cocaine, septal cartilage becomes deprived of its blood supply and breaks down (see Figure 1.11.1.1) (Kridel, 1999;

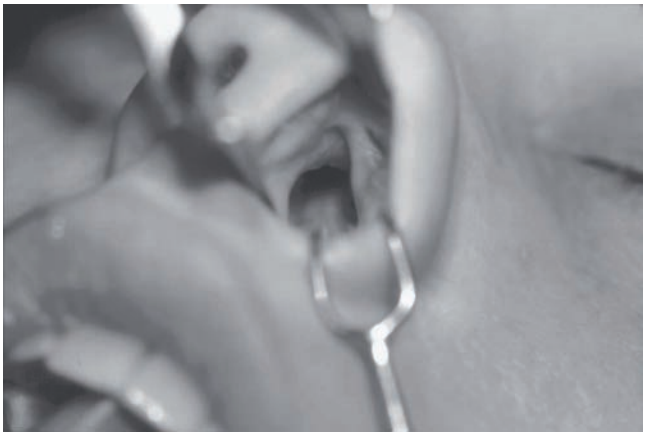


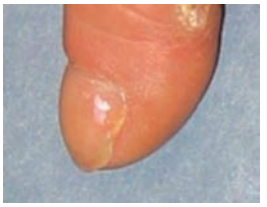
Figure 1.11.1.1 Perforated nasal septum. This lesion was first reported in conjunction with cocaine use in 1904. It is not absolutely diagnostic for cocaine abuse, as the same defect can be produced by the chronic use of vasoconstrictive nose drops. (Photograph courtesy of Dr. Russel Kridel, University of Texas Health Sciences Center, Houston.)

Trimarchi et al., 2003; Goodger et al., 2005). Other, much more severe complications have also been reported as a consequence of chronic cocaine use.

These include nasolacrimal duct obstruction with orbital cellulitis (Alexandrakis et al., 1999), severe avascular necrosis of all of the nasal chambers (Braverman et al., 1999), and even perforation of the palate (Sastry et al., 1997). A type of central facial necrosis of the nasal septum, maxillary sinus, ethmoidal sinus, sphenoidal sinus, and soft palate also occurs (Sittel et al., 1998; Caravaca et al., 1999). This constellation of symptoms is sometimes confused with Wegener's syndrome (Armstrong and Shikani, 1996; Helie and Fournier, 1997). After a brief hiatus, new cases of Wegner's-like diseases continue to be reported (Helie and Fournier, 1997; Smith et al. 2002; Trimarchi et al., 2006). Some of these cases may be the result of impacted cocaine providing a nidus for infection (Tierney and Stadelmann, 1999). Occasionally the reaction may be sufficiently extreme to simulate angiosarcoma. A recent case report described an exuberant ulcerative angiomatoid nasal lesion in a cocaine abuser. Microscopic examination showed polymorphous endothelial cells with occasional mitoses, arranged in a lobular pattern with infiltrative-looking areas. Extensive areas of thrombosis with focal recanalization were also seen, but intravascular proliferation was not observed (Alameda et al., 2000).

1.11.2 "Parrot Beak" Nails

A pseudosclerodermatous triad of perniosis, pulp atrophy, and "parrot-beaked" clawing of the nails is a newly recognized syndrome seen primarily in female chronic "crack" cocaine users. Some "crack" cocaine users develop coarsening changes in the appearance of their hands after prolonged use of the drug. The changes are thought to be the result of ischemia that results from the peripheral vasoconstriction induced by "crack" cocaine. Early changes may resolve with abstinence. The syndrome does not appear to be related to intravenous drug usage, nor is concomitant use of heroin a requirement for its occurrence. Since these changes only occur in a small subset of abusers, it is hypothesized that individuals with a



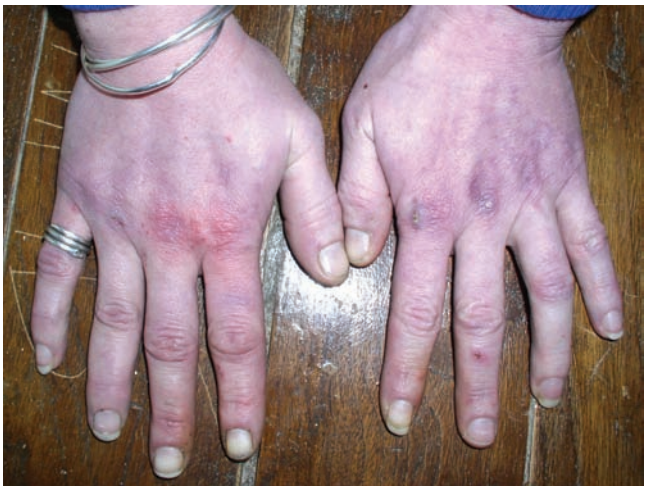


Figure 1.11.2.1 Some "crack" users develop coarsening of their hands after prolonged use of the drug, more often in women than men. The changes include perniosis with cold, numb hands, finger pulp atrophy of the distal part of the pulps of some digits, and claw-like curvature of the nails. As the distal pulp is lost, it can no longer splint the nail straight and so the nail curves, claw-like, and reminiscent of a parrot's beak as it clings to the new contour. The syndrome consisting of the triad of perniosis, pulp atrophy, and parrot-beaked clawing of the nails should alert clinicians to the possibility of prolonged "crack" cocaine use. (Courtesy of Dr. Jason Payne James, London.)

vasoreactive circulation (i.e., those with vasomotor instability/perniosis) are more susceptible to this reaction pattern (Payne-James et al., 2007).

1.11.3 "Crack Thumb"

"Crack thumb" was first described in 1990. It is a repetitive-use type of injury. Crack smokers often use disposable cigarette lighters to heat their crack pipes. They may do this many times a day, and a callus can result from repeated contact of the thumb with the serrated wheel that ignites the lighter. The callus is usually located on the ulnar aspect of the thumb (Larkin, 1990; Gatof and Albert, 2002). Constant handling of a heated crack pipe can lead to superficial burns on the palmar aspect of the hands. The same type of injury happens in methamphetamine smokers. A typical case is illustrated in Figure 1.11.3.1.

1.11.4 "Crack Lips"

"Crack" is often smoked with improvised pipes using pieces of steel wool to support the "rock." Hot steel wool may burn the lips or even be inhaled. Even the ubiquitous glass pipes may become so hot that they burn the lips.

1.11.5 "Track" Marks

The adulterants most commonly found in cocaine are water-soluble. Repeated injection tends not to produce the chronic inflammatory reactions and the type of granulomas

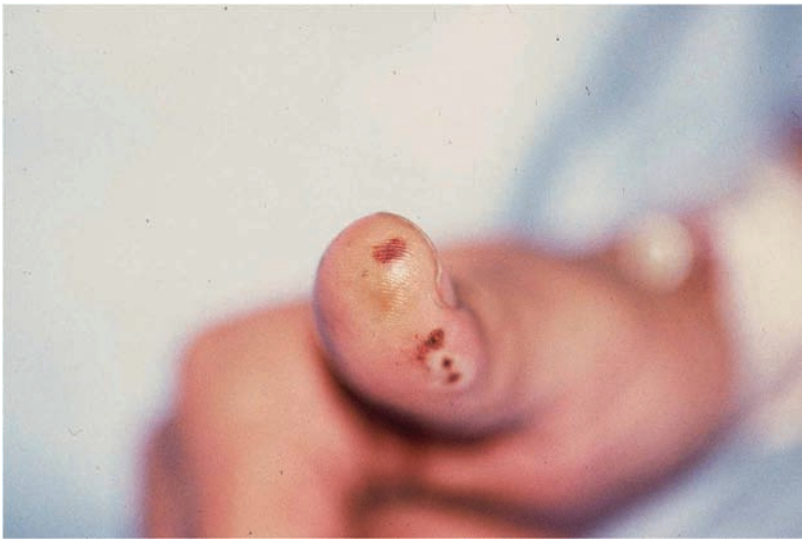


Figure 1.11.3.1 "Crack thumb." A repetitive-use injury from using disposable butane lighters to heat crack pipes. (Photograph courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

associated with opiate abuse. Recent injection sites appear as salmon-colored bruises, sometimes with a clear central zone about the needle puncture site. Typical lesions are illustrated in Figure 1.11.5.1. As lesions become older, they turn blue and yellow, eventually disappearing without leaving any scar. In one fairly recent series of mixed drug deaths, nearly half the decedents were found to have track marks (Gatof and Albert, 2002).

Slowly healing cutaneous ulcers are occasionally seen. The base of the ulcer may be red to gray, and the margins of the ulcers will have a pearly white appearance consistent

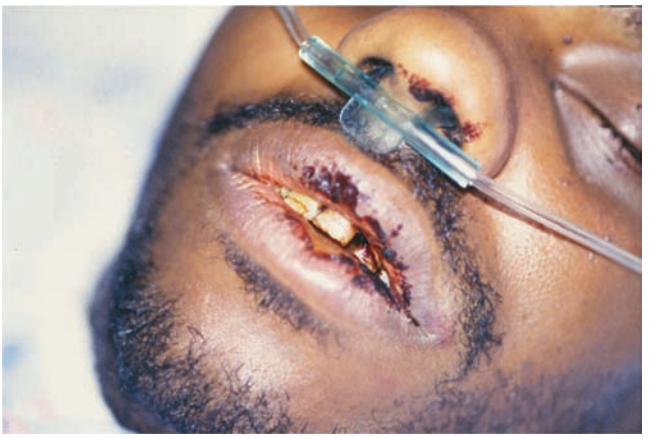


Figure 1.11.4.1 "Crack lips".

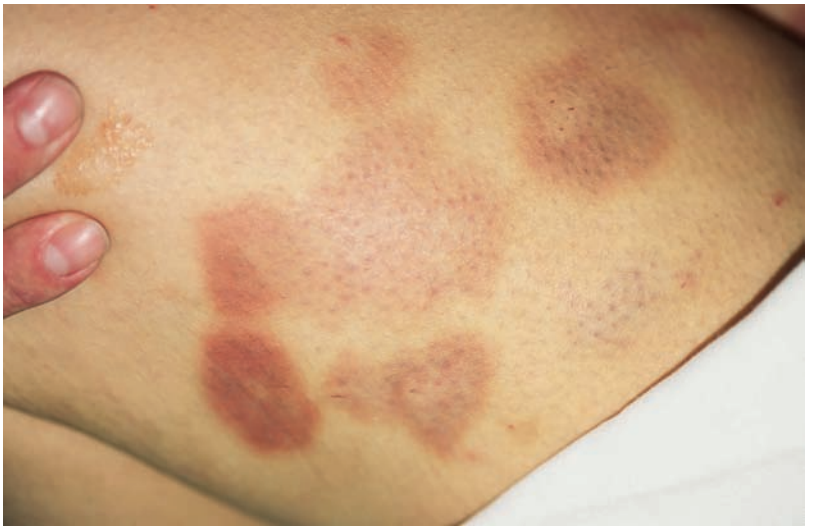


Figure 1.11.5.1 Cocaine injection sites. Injection with cocaine causes a distinctive salmon-colored bruise, sometimes with a clear zone around the needle puncture. (Photograph courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

with epidermal overgrowth (Yaffe, 1968). In experimental animals, healing of lesions is relatively rapid and complete. The histopathological effects of subcutaneous cocaine injection have been studied on a limited scale (Bruckner et al., 1982). In one study, subcutaneous injections of 0.1 mL of 2.0% cocaine solutions were found to cause blanching and hemorrhage. However, other workers have found no histological damage, even after rats were repeatedly injected with large subcutaneous doses (32 mg/kg twice a day) of cocaine over a two-week period (Durazzo et al., 1994). If changes do occur, more is involved than cocaine-induced vasoconstriction and ischemia. Epinephrine is a more powerful vasoconstrictor than cocaine but does not produce similar lesions, and it seems likely that there is an infectious component.

1.11.6 "Crack" Keratitis

"Crack" cocaine exposure has been reported to cause corneal disturbances ranging from subtle superficial punctate keratitis to perforation (Pilon and Scheiffle, 2006; Ghosheh et al., 2007). The corneas of "crack" smokers may inadvertently become anesthetized. When the smoker rubs his or her eyes, too much pressure may be applied and a sizable piece of the cornea may be rubbed off. This complication appears to occur with some frequency. In a five-year review of cases of microbial keratitis at an urban county hospital in north Texas, nearly 5% of the patients were cocaine users (Pachigolla et al., 2007). This type of corneal abrasion/infection/injury is often referred to as "crack eye" (Figure 1.11.6.1) (Ravin and Ravin, 1979; Zagelbaum et al., 1991; Colatrella and Daniel, 1999; Parmar et al., 1999). The same mechanism may lead to keratitis with corneal ulcer formation and infection (Strominger et al., 1990; Parmar et al., 1999).

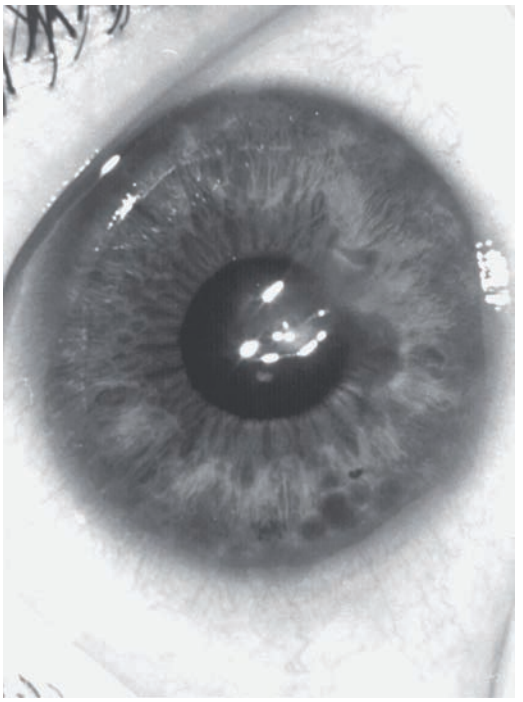


Figure 1.11.6.1 "Crack" keratitis. Volatilized cocaine anesthetizes the cornea so that abusers cannot feel how hard they are rubbing their eyes. Evidence indicates that crack smokers may be less able to resist corneal infection, and infected ulcers with corneal clouding may be the result. (From *Am. J. Ophthalmol.*, 111(3), 247–248, 1991. With permission. Photograph courtesy of Dr. Peter S. Hersh, Chairman, Department of Ophthalmology, Bronx-Lebanon Hospital, New York.)

1.11.7 Dental Erosions and Oral Lesions

Chronic intranasal cocaine users may have erosions on the enamel of the upper front teeth. The erosions occur when the teeth are bathed with acid cocaine hydrochloride that has trickled down from the sinuses and the posterior oropharynx (Krutchkoff et al., 1990). This does not happen with "crack" abusers and may not happen with methamphetamine abusers at all (although they are often edentulous, the cause appears to be poor hygiene). Rapid gingival recession and dental erosion secondary to local cocaine application have also been reported (Kapila and Kashani, 1997; Ronderos et al., 2001; Vilela et al., 2002; Driscoll, 2003; Khocht et al., 2003a, b; Blanksma and Brand, 2004, 2005; Shibli et al., 2005). Whitish lesions of the oral mucosa are said to be common in "crack" smokers (Parry et al., 1996; Blanksma and Brand 2005), and leukoplakia is a recognized consequence of coca leaf chewing (Hammner and Villegas, 1969; Parry et al., 1996). HIV-infected patients who also use cocaine may manifest atypical ulcers of the mouth that may be difficult to identify (Mitchell-Lewis et al., 1994).

1.11.8 "Crack Hands"

This lesion has much in common with "crack thumb." Examination of chronic "crack" smokers may disclose blackened, hyperkeratotic lesions on the palmar aspect of the hands.

The pipes used to smoke cocaine can become quite hot, and chronic users are likely to sustain multiple small burns (Feeney and Briggs, 1992). In some cases they may be extreme (Dhawan and Wang, 2007).

1.11.9 Evidence of Terminal Seizures

Bite marks of the lips and tongue may occur. A minority of cocaine users may experience seizure activity as a terminal event (Wetli, 1987). However, because seizures do not always occur, even in conjunction with massive overdose, and because many other agents can cause terminal seizure activity, the usefulness of this sign is somewhat limited.

1.11.10 Marks and Mutilation

Wetli et al. (1997) described a series of 10 heroin "body packers". In two of the cases, the drug couriers died after reaching their destinations, and their accomplices made abdominal incisions to remove the drug packets. A similar case was reported from the U.K., where the back and buttocks of a deceased courier were marked with a number of superficial lacerations, corresponding to the number of drug-containing packets that the deceased had swallowed, a sort of living invoice. Similar markings have not been reported in cocaine smugglers but they are certainly possible.

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1.12 Skin Toxicity

Subcutaneous drug injection (called "skin popping") is much more common among heroin than cocaine users. Cocaine users who elect this route generally experience fewer complications than heroin users. In the past the adulterants found in cocaine were likely to be water-soluble, though this situation seems to be evolving. Toward the end of 2005 the first reports of heroin adulterated with diltiazem (an antihypertensive calcium channel blocker) emerged (Anon., 2005), and it appeared that a shift in adulterant patterns may be occurring. During the last few years there have been reports from the United States and Europe of exotic substances beings used as adulterants. Fucci (2007), for example, found hydroxyzine and levamisole in wholesale quantities cocaine found in Rome.

Adulterants can produce subcutaneous skin abscesses that are sometimes accompanied by cellulitis, lymphangitis, and lymphadenopathy (Hoeger et al., 1996). Infection is generally the result of infection with oral flora that are sensitive to multiple antibiotics, but surgical debridement is often required. Necrotizing fasciitis has occasionally been reported in cocaine users (Jacobson and Hirschman, 1982) but the connection between that disorder and illicit drug injection is much stronger for heroin than cocaine (Dunbar and Harruff, 2007; Smeets et al., 2007).

Soft tissue infection is rapidly emerging as one of the most widespread and pernicious complications of illicit drug abuse. Many hospitals have established diversion clinics in order to segregate cases of skin infections from other complications of drug abuse. Most of these infections are indolent and superficial (Sen et al., 2005), but infection in the deep spaces of the neck, groin, and scrotum have been reported (Lautermann et al., 2005; Sen et al., 2005). As evidenced by multiple outbreaks of necrotizing fasciitis secondary to *Clostridium sordellii* in black-tar heroin users, it is clear that the risk of serious infection is much greater with some drugs than others (see Chapter 5).

Scleroderma is an uncommon disease, and there have been a handful of new reports of cocaine-related scleroderma since this book was first published. The estimated annual incidence is between 4 and 12 new cases per 1,000,000 per year. Scleroderma is 3 times more common in females, but when it occurs in young people it is 15 times more common in women than men (Poormoghim et al., 2000). The median age of onset for scleroderma is between 40 and 50. Less than half a dozen cases in the English literature have involved cocaine users, all of which involved men, with two only in their 40s (Trozak and Gould, 1984; Kerr, 1989; Attoussi et al., 1998; Foidart et al., 2003).

The principal abnormality in scleroderma is the deposition of pathologic amounts of normal collagen. Excessive fibrosis, vascular injury, autoimmunity, and inflammation are permanent features of the disease process and lead to irreversible organ damage (Kowal-Bielecka, 2006). There is general agreement that primary myocardial involvement is common in this disorder, strongly suggesting that involvement is in some way related to repeated focal ischemic injury causing irreversible myocardial fibrosis.

The underlying mechanism appears to be microcirculatory impairment accompanied by abnormal vasoreactivity, with or without structural vascular abnormalities. Clinically evident cardiac involvement portends a poor outcome. Pericardial involvement is frequent but usually asymptomatic. Conduction system abnormalities also appear to be common and life-threatening arrhythmias may occur. Significant valvular involvement is not associated with systemic sclerosis. Treatment for myocardial involvement includes long-term systematic administration of calcium channel blockers and possibly angiotensin-converting enzyme inhibitors (Allanore and Kahan, 2006).

Both cocaine users and scleroderma victims may develop isolated cerebral vasculitis, but it is an uncommon complication of either disorder. In the two biopsy-proven cases of cocaine-associated vasculitis, the vessels were infiltrated with lymphocytes. In the one case of scleroderma-associated vasculitis, the biopsy was nondiagnostic (Pathak and Gabor, 1991; Andonopoulos et al., 1998).

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1.13 Cardiovascular System, General Overview

Cocaine causes vascular disease, the most obvious manifestation being sudden death. In general, there is little to distinguish cocaine-induced vascular disease from naturally occurring vascular disease, and no single abnormality is absolutely diagnostic for cocaine. Changes in the myocardium have already been discussed (see Section 1.10).

1.13.1 Myocardial Infarction

It is well accepted that cocaine users, even those without other risk factors, experience large, transient increases in the risk for acute myocardial infarction (AMI) immediately after using cocaine (Mittleman et al., 1999). Why this should be the case is not clear. A great deal of attention has been focused on the sympathomimetic effects of the drug and coronary artery spasm, but other mechanisms, including vasculitis, accelerated atherosclerosis, exacerbations of pre-existing fixed lesions of the epicardial arteries, disease of the microvasculature, and interaction with polymorphic ion channels are all possible contributors.

In various case series, the incidence of fixed lesions found in cocaine-related deaths, presumably atheromatous but possibly thrombotic, has been anywhere from 0% (Virmani et al., 1988) to well over 50% (Minor et al., 1991; Virmani, 1991). Only a handful of published reports describing cocaine-related AMI have included autopsy findings (Young and Glauber, 1947; Kossowsky and Lyon, 1984; Nanji and Filipenko, 1984; Simpson and Edwards, 1986; Stenberg et al., 1989; Isner and Chokshi, 1991; Karch et al., 1998; Coskun et al., 2006). There is, unfortunately, no published registry for cases of drug-induced AMI, and no systematic study of angiograms in cocaine users, let alone a cohort of studied younger people—those who could be presumed to be free of coronary artery disease or risk factors for that disease that could be used as controls.

However, the results of the most recent published reports in the English and non-English literature, from 1970 to 2005, suggest that drug-induced coronary spasm is a

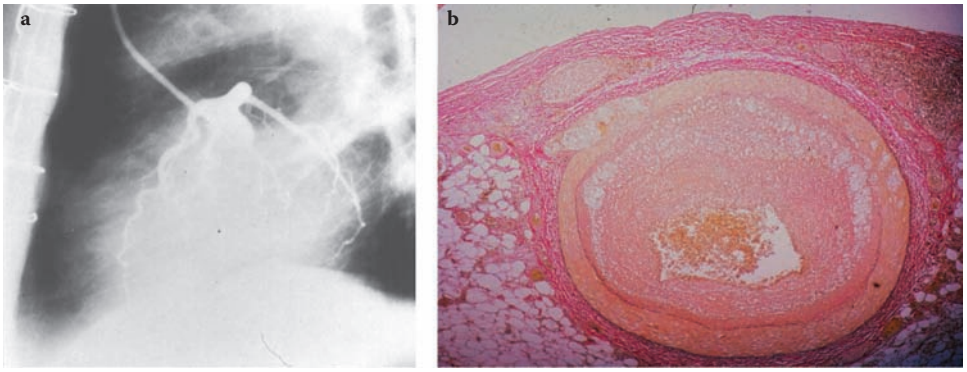

Figure 1.13.1.1 Coronary artery disease in cocaine users. The coronary arteries of cocaine users may undergo the same type of intimal hyperplasia as seen in transplant recipients. Because this sort of lesion concentrically involves the entire length of the involved vessel, obstructions may not be apparent unless earlier studies are available for comparison. The normal-appearing study on the left was obtained just two weeks before the patient died of myocardial infarction. On the right is a cross section of the left anterior descending coronary artery (LAD) from the same patient. Concentric intimal hyperplasia has almost entirely obstructed the lumen. (H&E stain.) (Courtesy of Margaret Billingham, Stanford University School of Medicine.)

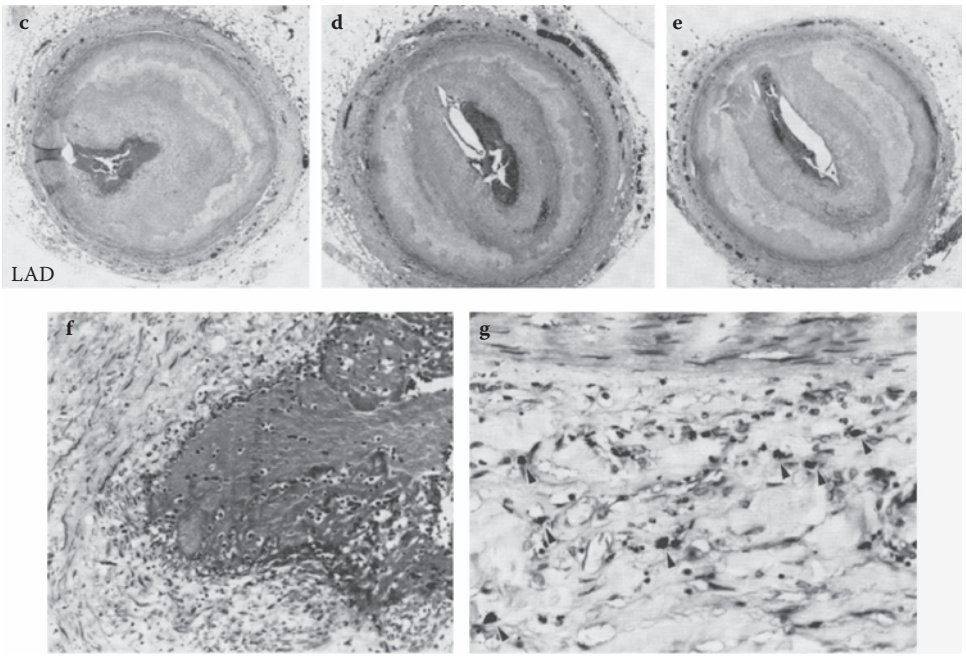

Figure 1.13.1.2 Adventitial mast cells in cocaine users. Compared to age- and sex-matched controls, more mast cells are present in the adventitia of the coronary arteries of cocaine users, and the degree of luminal narrowing correlates well with the number of mast cells present. On top are three cross sections of severely diseased LAD from a chronic cocaine user. On the bottom are higher power views of the adventitia in this vessel. Toluidine blue staining demonstrates the presence of numerous mast cells. (Original magnification 150×.) (Courtesy of Dr. Rene Virmani, Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Bethesda, MD.)

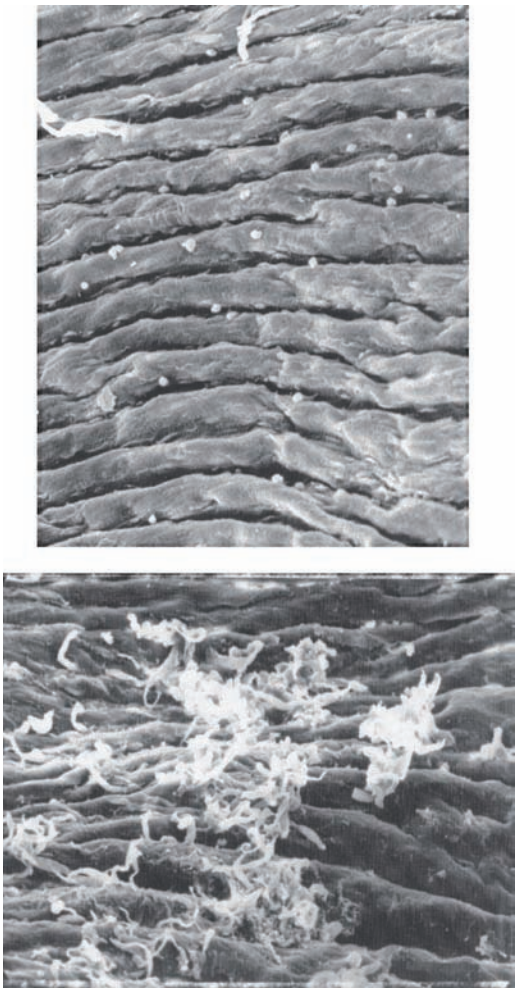

Figure 1.13.1.3 Effects of cocaine on endothelium. Both scanning micrographs are of a canine coronary artery. The photograph on top is from a control animal (original magnification 312×). The lower photograph is from a dog that received 1 mg/kg/day of cocaine for 4 weeks; sloughing of endothelial cells is evident (original magnification 520×). (Courtesy of Dr. Randall L. Tackett, Department of Pharmacology and Toxicology, University of Georgia, Athens.)

frequent complication of cocaine abuse. In 220 articles (> 12,000 cases) dealing with cocaine-associated AMI, there were approximately 100 cases where AMI was thought to be secondary to coronary artery spasm (CAS). The diagnosis in most of those cases was based on the clinical and laboratory findings, not angiography, and is of not much value, at least in terms of understanding the pathophysiology of the problem. Further complicating the picture is that cocaine was not the only illicit drug present in many of these cases; most were also cigarette smokers (El Menyar, 2006), yet cocaine is usually blamed for the event.

Cocaine users are rarely found to have coronary artery lesions resembling those seen in the hearts of transplant patients with chronic rejection. The first such case was described

by Simpson and Edwards in 1986 when a 21-year-old construction worker was found to have multivessel blockage due entirely to intimal hyperplasia. There was no sign of collagen or elastin deposition. This type of lesion is routinely seen in transplanted organs, and also occurs in some connective tissue disorders (Dawkins et al., 1985). Similar alterations have been observed in the hearts of other cocaine users (Pamplona et al., 1990; Roh and Hamele-Bena, 1990). However, this complication remains so rare that it is still reportable, and its etiology is unknown.

1.13.2 Microvascular Disease

Chronic cocaine use also produces changes in the smaller coronary vessels, and they are highly reminiscent of the changes seen in hypertension: a decrease in the lumen of the arterioles (a consequence of either vasoconstriction or wall thickening), along with the deposition of an abnormal amount of collagen within the ventricular wall (Gavin et al., 1998) results in vessels with diminished caliber. The acute administration of cocaine raises both pulse and blood pressure, so it is hardly surprising that endomyocardial biopsies from 11 cocaine users with symptoms of myocardial ischemia demonstrated marked medial thickening of small intramyocardial arteries (20–40 mm) in 7 of the 11 patients (Majid et al., 1990).

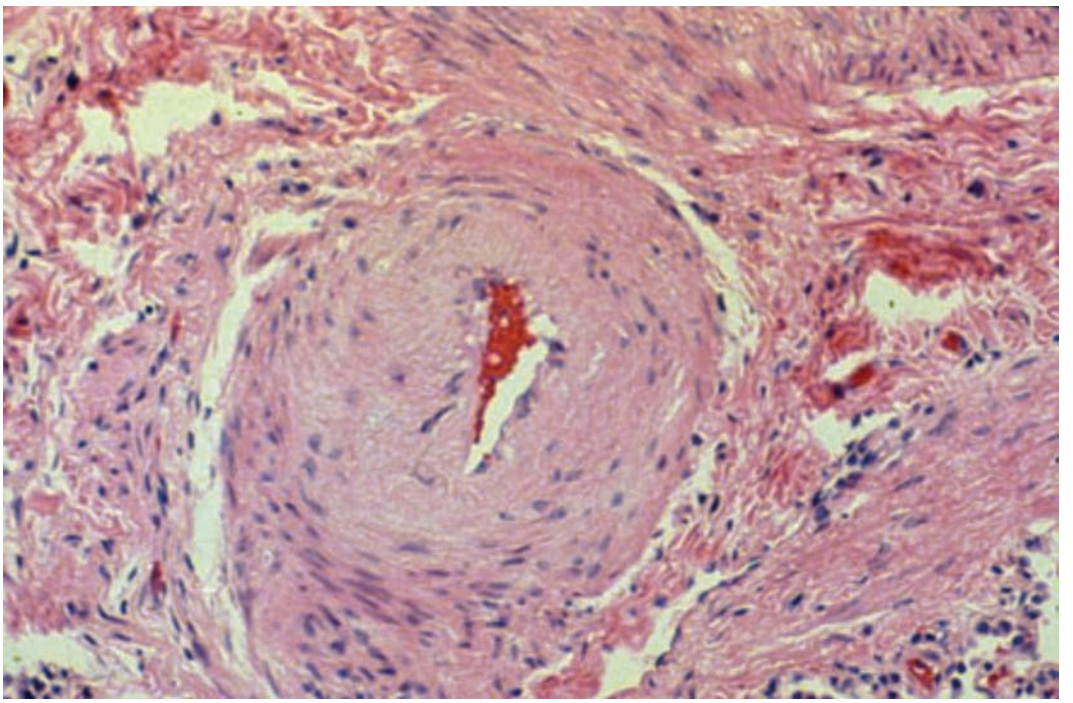

Figure 1.13.2.1 Medial hypertrophy of small resistance vessel in subendocardium of a cocaine abuser. This type of change can be widespread, leading to ischemia even at rest and even in the absence of overt epicardial disease. (Photograph by S.B. Karch.)

Thickening of the media together with intimal hyperplasia has also been seen in the nasal submucosal vessels of chronic cocaine addicts (Chow et al., 1990), suggesting that in susceptible individuals similar changes occur throughout the body. It has also been suggested that myocardial infarction in young people, without apparent epicardial disease, is probably a result of microvascular disease (Kelly et al., 2003; Turhan et al., 2007), but the picture probably is not that simple. It is not uncommon for individuals to suffer both from epicardial and microvascular disease (Kelly et al., 2003), nor is damage limited to the myocardium. Furthermore, there is autopsy evidence that the pulmonary vessels may be involved as well (Baldwin et al., 2003).

1.13.3 Atheromatous Coronary Artery Disease

Cocaine is atherogenic. This fact became apparent almost as soon as scientists started doing systematic studies on the subject (Karch et al., 1995). Tissue factor (TF) has been implicated in acute coronary syndromes, and the balance between TF and tissue factor pathway inhibitor (TFPI) determines whether or not thrombi will form. The effect of cocaine on endothelial TF and TFPI expression has been confirmed in tissue culture studies and experimental animals. Cocaine transiently increases thrombin-induced TF expression by nearly 25%. Cocaine also reduces endothelial tissue factor pathway expression, and thrombin reduced TFPI concentrations. These changes are seen at cocaine concentrations comparable to those in active drug users.

Given the importance of TF in the pathogenesis of acute coronary syndromes, TF induction in conjunction with TFPI suppression may explain the increased frequency of myocardial infarction observed in cocaine consumers (Steffel et al., 2006). In one two-decade-old study, over 60% of the patients with cocaine-associated sudden death were found to have moderate to severe coronary atherosclerosis (the patients had a mean age of 47). In such a young age group, a much lower percentage of significant lesions would be expected (Dressler et al., 1990). Other autopsy studies have also noted the increased incidence of significant atherosclerotic lesions (Virmani et al., 1988; Farb et al., 1990).

When the coronary arteries of cocaine abusers dying of thrombosis are compared to those of cocaine users without thrombosis, and those dying of other causes, as well as to cases of sudden death not associated with cocaine use, the average age for the cocaine-thrombosis group was only 29 years, and the degree of luminal narrowing was much higher than would be expected in this age group. In the patients with thrombosis, moderate to severe coronary atherosclerosis is seen, as well as increased numbers of adventitial mast cells (Figure 1.13.1.2) (Kolodgie et al., 1991).

One plausible explanation is that the incidence of AMI is time-related with circadian, circaseptan, and circannual variation. Triggering of an AMI by heavy exertion, sexual activity, anger, mental stress, cocaine, marijuana use, and exposure to air pollution have all been reported (Servoss et al., 2002). There is no reason not to suppose that stress, superimposed on pre-existing lesions, may well trigger infarction (Servoss et al., 2002). Not infrequently, cocaine users die of AMI during sex play. This leaves medical examiners the nearly impossible task of determining whether death was accidental or homicidal (Kloner, 2006).

The role of histamine in atherosclerosis remains controversial (Born, 1991). Increased numbers of histamine-rich mast cells have been noted in atherosclerotic coronary vessels,

even in non-drug-using populations. Fibroblasts, mast cells, macrophages, and ganglionic cells are all present within the coronary artery adventitia. After infarction, most of the mast cells in coronary arteries are found in the outer layer of the adventitia. It would not be unreasonable to suppose that neurogenic stimulation of these adventitial mast cells might lead to the release of vasoactive compounds, such as histamine (Varty and Hey, 2002) and leukotrienes, which can contribute to the complex neurohormonal response that leads to abnormal coronary vasoconstriction (Hu et al., 2006).

Of course there are other plausible ways to explain infarction in cocaine abusers. Lymphocytes and bacteria are also usually found to be present, mainly in the adventitial layer. They are subject to the development of adventitial and plaque inflammation (pan-arteritis), and thence to plaque rupture. The leading candidate for causative agent in this process is excess production of oxidized catecholamines; all cocaine abusers, in fact, have elevated plasma concentrations of catecholamines, and free radicals generated from catecholamine breakdown would seem a likely candidate (Hu et al., 2006). Uptake of LDL by the arterial wall is accelerated in the presence of epinephrine and norepinephrine, and cocaine raises concentrations of both (Born, 1991). But as attractive as the theory may sound, most cocaine users are actually polydrug abusers who also smoke cigarettes and there is no very good way to determine which toxic agent is responsible for the process.

Uncomplicated cases of AMI can occur in cocaine users who already have extensive coronary artery disease. If underlying fixed lesions are present, cocaine use can make them symptomatic. In controlled human studies, intranasal cocaine (2 mg/kg body weight) increased arterial pressure and the rate pressure product. At the same time that the rate pressure product was rising, coronary sinus blood flow was significantly falling (Lange et al., 1990). The end result is that cocaine increases myocardial work and oxygen demand while at the same time decreasing blood flow (Lange et al., 1989, 1990). If asymptomatic lesions are already present, the extra workload imposed by the cocaine can lead to infarction, even without coronary spasm. Increased oxygen demand in the presence of preexisting lesions is sufficient to cause AMI.

Failure to demonstrate lesions with angiography does not necessarily mean that they are not there. Studies have shown that angiography usually underestimates the severity of lesions, especially when they are in the 50–75% range and when multi-vessel disease is present (Gruberg et al., 1999). The discrepancy is mostly explained by the false assumption, made by many, that segments of artery adjacent to an area of stenosis are normal. In fact, compensatory dilation of the vessel usually occurs in response to the accumulation of lesser degrees of plaque. The opposite situation occurs when the obstruction is due to intimal hyperplasia. That process tends to involve vessels along the entire length in a concentric fashion. The lesions may not be noticed on angiography unless earlier films are available for comparison (Tazelaar et al., 1987). An arteriogram that looks normal may actually be masking serious underlying heart disease.

1.13.4 Coronary Artery Spasm

Cocaine-mediated coronary artery constriction occurs in humans. In one clinical trial, 2 mg/kg of cocaine was given intranasally to 45 patients undergoing cardiac catheterization. The dose given did not cause chest pain, but it did reduce the diameter of the left coronary artery by at least 8–12% (Lange et al., 1990). In related studies, it was observed that vasoconstriction is more intense in atherosclerotic vessels (Flores et al., 1990). It has also

been shown that cocaine and cigarettes act synergistically on diseased arterial segments to produce even greater degrees of vasoconstriction: 19% for cigarettes and cocaine combined vs. 9% after cocaine and 5% after cigarette smoking (Moliterno et al., 1994). Just the opposite happens when cocaine is combined with alcohol. When patients evaluated for chest pain were given ethanol and cocaine in combination, significant increases in myocardial oxygen demand occurred. However, there were also concomitant increases in epicardial coronary artery diameter, suggesting that no net decrease in myocardial oxygen supply occurred (Pirwitz et al., 1995).

The mechanism responsible for spasm is not really known, but there are a number of established factors that could contribute. Endothelial dysfunction is a strong candidate (Kawano and Ogawa, 2005). Nitric oxide (NO) production is largely responsible for vasodilatation, and damaged endothelium (as it is in cocaine users, smokers, and patients with atherosclerosis) is incapable of producing sufficient NO required for vessels to dilate normally.

Another possibility is increased smooth muscle hypersensitivity. Contraction of vascular smooth muscle depends on intracellular calcium levels (Kandabashi et al., 2000; Henning and Cuevas, 2006). Catecholamines are elevated in cocaine users, and increased concentrations of norepinephrine lead to increased concentrations of calcium within the cytosol. Even when catecholamine concentrations are kept constant, the application of cocaine by itself causes cellular calcium concentrations to increase—in both the heart and brain. As with atherosclerotic lesions in cocaine users, oxidative stress is still considered a likely factor. Treatment of coronary arteries with superoxides and free radicals, such as those contained in cigarette smoke, causes increased contraction (Boelsterli et al., 1993), but here, too, identifying one individual cause is nearly impossible because so many cocaine users are also cigarette smokers.

Autonomic tone is increased in cocaine users (Mehta et al., 2002; Vongpatanasin et al., 2004), and even in normal coronary arteries, spasm is induced by the application of acetylcholine and blocked by the application of atropine. Genetic susceptibility is also another possible etiology. The production of NO needed to cause vasodilation is under the control of a gene with multiple polymorphisms. It may well be that the genetic disposition of some cocaine users predisposes them to spasm, while that of others makes them resistant.

Unless spasm occurs at the site of pre-existing coronary artery narrowing, it would seem unlikely that it could account for very many episodes of infarction, at least in cocaine users. In humans, anything less than a 75% cross-sectional coronary obstruction is unlikely to produce symptoms, so constriction of an epicardial vessel amounting by only 10–12% should be an asymptomatic event unless, of course, severe atherosclerotic disease is already present. In fact, in another human study, doses of 1.2 mg/kg of cocaine administered intravenously to 20 human volunteers (resulting in mean cocaine levels of 709 ng/mL vs. levels of only 120 ng/mL in the Lange et al. studies cited earlier) produced only nonspecific T- and R-wave changes with no changes in the left ventricular ejection fraction or wall motion score index (Eisenberg et al., 1995).

1.13.5 Decreased Flow Reserve

Within the last few years it has become increasingly apparent that myocardial perfusion may be decreased even in the absence of occlusive epicardial disease. The degree

of cross-sectional narrowing of the large epicardial vessels, as assessed by routine angiography and by direct measurements made at autopsy, cannot be relied upon to provide an accurate assessment of myocardial perfusion. However, recent technical advances make assessment of perfusion possible. Myocardial fractional flow reserve (FFR) is a new index of the functional severity of coronary stenosis. It is calculated from pressure measurements made during coronary arteriography. In patients with moderate epicardial stenosis, this measurement may provide a great deal of important information (Pijls et al., 1996). Thickening of the media of the smaller, intramyocardial arteries has already been demonstrated in cocaine users and can lead to coronary insufficiency (see Figures 1.10.2.3 and 1.10.2.4).

Unfortunately, this technique can only be applied in the living. Fractional flow reserve is determined by placing an ultrasound flow probe into a coronary artery and measuring flow and resistance at baseline and after maximal vasodilation (Kern, 2000). The difference between the two measurements allows for an accurate assessment of perfusion (Frohlich, 1999). These measurements have not been made in cocaine abusers, in spite of their known propensity for disease localized to the small intracardiac vessels. A significant decrease in flow reserve could explain some of the very large number of emergency room visits by cocaine-using young men who present with chest pain but with little or no obvious evidence of ischemia.

1.13.6 Centrally Mediated Vascular Disease

The sympathetic axis plays an important role in the vascular adjustments to cocaine use. Cocaine-related pressor effects (and, therefore, cocaine-related vasoconstriction) are mediated by norepinephrine released from neurons of the sympathetic nervous system. Other changes, such as heart rate, are mediated by release of epinephrine from the adrenal medulla (Tella et al., 1993). In intact organisms, cocaine's net effects are closely linked to the underlying level of sympathetic adrenergic activity (Perreault et al., 1991).

The first suggestion of a relationship between coronary vasospasm and alterations in adrenergic function came from studies of Prinzmetal's angina. In that disorder, repolarization abnormalities (QT prolongation) precede episodes of spasm (Ricci et al., 1979; Roberts et al., 1982). Of course, at the time the studies were performed, no one realized that QT interval prolongation might be due to other factors besides increased sympathetic discharge such as ion channelopathy, myocardial hypertrophy, or other drugs that alter myocardial repolarization (see Section 1.10.2).

In animal studies, unilateral stellate ganglion stimulation causes selective coronary spasm, QT prolongation, and a marked increase in coronary artery resistance. These changes can all be prevented with adrenergic blockade (Randall et al., 1972) and all of these changes can be produced by giving cocaine. Both PR and QT prolongation are easily induced in animals infused with cocaine (Beckman et al., 1991). Torsade de pointes (reciprocating ventricular tachycardia associated with QT interval prolongation) has been reported in number of cocaine-intoxicated patients (Schrem et al., 1990; Khan et al., 1999; Perea et al., 2000; Deamer et al., 2001; Singh et al., 2001; Bauman and DiDomenico, 2002; Khan, 2002; Riaz and McCullough, 2003; Portale et al., 2004; Krantz et al., 2005; Sticherling et al., 2005). In one group of 45 hospitalized cocaine users, those with chest pain had

much longer QT intervals than those hospitalized for noncardiac complaints, and lethal ventricular arrhythmias occurred in three of the individuals (Gamouras et al., 2000).

1.13.7 HIV-Related Myocardial Disease

Infiltrates in the hearts of drug users may be a sign of HIV infection. A variety of opportunistic infections occur as a result of HIV infection, and, as more effective therapies have been introduced and survival times have lengthened, new complications of late-stage HIV infection have emerged. Almost any agent that can cause disseminated infection in patients with acquired immunodeficiency syndrome (AIDS) may involve the myocardium, but clinical evidence of cardiac disease is usually overshadowed by disease in other organs, primarily the brain and lungs. Cardiac abnormalities are found at autopsy in two thirds of patients with AIDS. More than 150 reports of cardiac complications had been published by 1998 (Milei et al., 1998). Recently, evidence has been published suggesting a link between treated HIV infection and ischemic heart disease (Zangerle et al., 2007; Carr et al., 2008).

Today, the probability is that any obvious infiltrate in the heart of an HIV-positive cocaine user represents an opportunistic infection and not a cocaine-related injury. Similar considerations apply to pericardial effusion. HIV-associated pericardial effusion is now the most common type of pericardial effusion seen in inner-city hospitals. The presence of any kind of effusion in an HIV-infected patient, especially pericardial, predicts a poor prognosis (Chen et al., 2000).

The first report describing AIDS-related myocardial disease was published in 1985. An assortment of opportunistic agents was found in 10 of the 41 hearts studied (Commarosano and Lewis, 1985). In a different series of 82 patients dying of AIDS, 17% were found to have infectious agents in their hearts. The usual pathogens associated with decreased immune function, including *Toxoplasma*, mycobacteria, *Histoplasma*, *Cryptococcus*, cytomegalovirus, and *Pneumocystis*, have all been reported (Anderson et al., 1988). There is also evidence that the HIV virus itself invades the myocardium (Grody et al., 1990).

When it invades the heart, Kaposi's sarcoma usually involves the pericardium (Chyu et al., 1998), as does lymphomatous infiltration of the heart. The incidence of both primary and secondary lymphomatous involvement of the heart of HIV patients is increasing, and, because the hematogenous route is the most common pattern of involvement, even extrathoracic lymphomas can present with heart dissemination (Sanna et al., 1998). Thus, a high level of suspicion is indicated in lymphoma patients with cardiac symptoms.

A very high percentage of intravenous drug takers (the percentage varies by location) are infected with HIV. The risk of HIV transmission makes intravenous cocaine users unlikely candidates for organ donation. However, the outcome in patients who receive hearts from nonintravenous cocaine users (and it appears that fairly large numbers of donors fall into that category) is comparable to that observed in those receiving hearts from non-drug users (Freimark et al., 1994). A positive history for nonintravenous cocaine abuse should not disqualify possible donors.

The most recent longitudinal study of this problem found little reason to avoid use of these organs. Eleven liver and 18 kidney transplant recipients were followed for a

median of 3.4 years (IQR [interquartile range] 2.9–4.9). One- and 3-year liver recipients' survival was 91% and 64%, respectively; kidney recipients' survival was 94%. One- and 3-year liver graft survival was 82% and 64%, respectively; kidney graft survival was 83%. Kidney patient and graft survival were similar to the general transplant population, while liver survival was similar to the older population. CD4+ T-cell counts and HIV RNA levels were stable in these transplant recipients and there were only two opportunistic infections. The 1- and 3-year cumulative incidence (95% confidence intervals) of rejection episodes for kidney recipients was 52% (28–75%) and 70% (48–92%), respectively. Two thirds of hepatitis C virus (HCV)-infected patients, but no patient with hepatitis B virus (HBV) infection, experienced reoccurrences of those diseases (Roland et al., 2007). Good transplant and HIV-related outcomes among kidney transplant recipients, and reasonable outcomes among liver recipients, suggest that transplantation is an option for selected HIV-infected patients when they are cared for at centers with adequate expert facilities.

1.13.8 Valvular Heart Disease

As intravenous drug users, cocaine abusers are, of course, at risk for the development of valvular heart disease. However, such events must be very rare, with only an occasional case report appearing in the literature. In theory, some of the amphetamine analogues should be injurious to heart valves. Very little has been written on the subject, but echocardiographic studies have failed to demonstrate increased risk (Filipattos et al., 2002; Gullone et al., 2003).

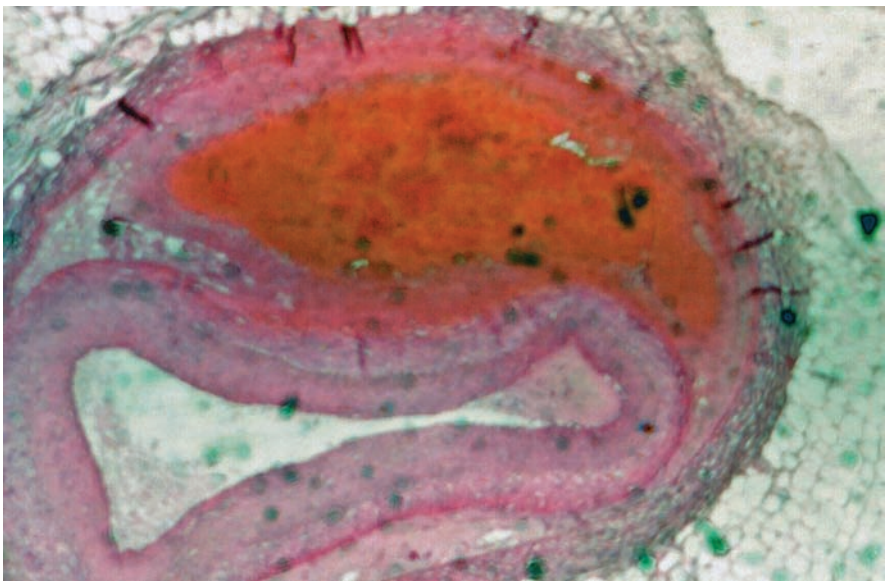

Figure 1.13.9.1 Coronary artery dissection. Dissection in the left anterior descending artery of a 38-year-old woman with a history of chronic cocaine abuse (H&E stain). Dissection is a rare, but increasingly more common complication of cocaine abuse. The underlying mechanism remains unknown.

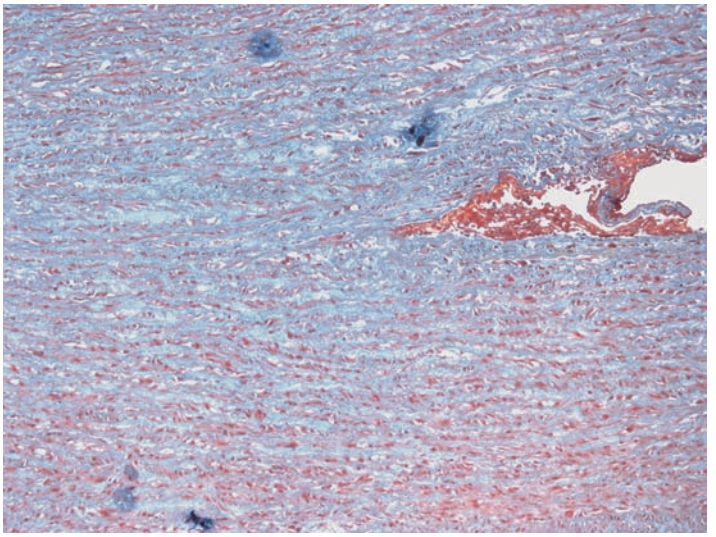

Figure 1.13.9.2 An example of acute aortic dissection. (From the files of Steven B. Karch, MD.)

1.13.9 Aorta and Peripheral Vessels

Some retrospective data suggest that, in an inner-city population, acute aortic dissection in the setting of "crack" cocaine use is common, presumably as a consequence of abrupt, transient, severe hypertension and catecholamine release (Hsue et al., 2002). While that

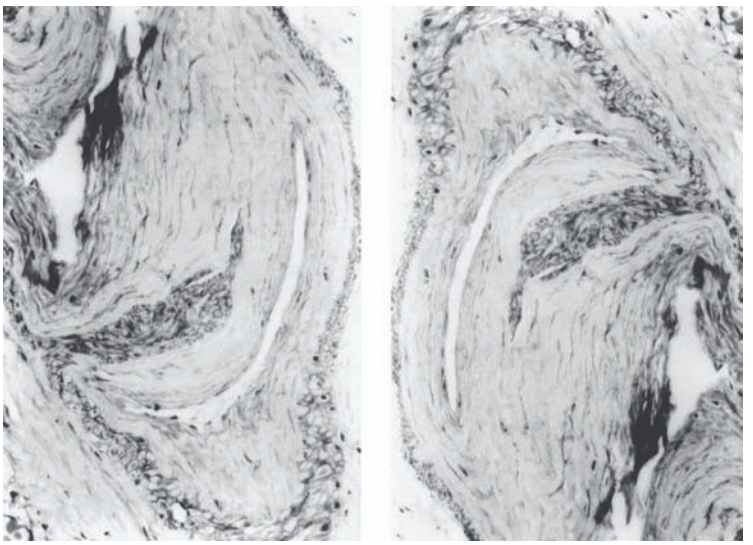

Figure 1.13.9.3 Accelerated atherosclerosis is not confined to the coronary arteries. This section of segmental artery, demonstrating severe intimal fibrosis and medial thickening, was obtained from a cocaine user with renal failure (PAS stain). (From Fogo, A. et al., *Am. J. Kidney Dis.*, 20(5), 513–515, 1992. With permission.)

may well be the case, it has never been proven in any systematic study that they relationally exist, and the only evidence available consists of anecdotal case reports. Fewer than 30 cases have been reported since the mid-1980s (Mehta et al., 2004). Most have been type I dissections with the process extending from the ascending aorta to the iliac vessels. Only one of these individuals was found to have the typical pattern of medial degeneration associated with Marfan's syndrome, and even then, none of the other stigmata of the disorder were present (Cohle and Lie, 1993).

Two principal risk factors contribute to aortic dissection: aortic medial disease and hypertension. Cocaine use is certainly associated with one, and possibly both of the disorders. Transient hypertension occurs in virtually all users, and some preliminary studies have shown damage to the media and elastic layers in the aortas of rats chronically treated with cocaine (Langner and Bement, 1991). A third, though seldom considered, predisposing factor is pregnancy, and dissecting aneurysm has been described in pregnant cocaine users (Madu et al., 1999). Like coronary artery aneurysms, aortic aneurysms in pregnancy are thought to be the result of progesterone excess. The high concentrations of progesterone associated with pregnancy may lead to destruction of elastic fibers and fragmentation of reticular fibers in the wall of the aorta, ultimately resulting in loss of structural integrity (Madu et al., 1994). Aortic dissection is initiated by transverse tears in the aortic wall. For dissection to occur, tears must extend through the intima and at least halfway through the media (Crawford et al., 1988).

1.13.10 Eosinophilic Myocarditis

The presence of an eosinophilic infiltrate suggests a hypersensitivity phenomenon. Hypersensitivity myocarditis is distinguished from toxic myocarditis by several important features: (1) it is not dose related, (2) the lesions are all of the same age, (3) hemorrhages are rare, and (4) myocyte necrosis is not present. The list of drugs causing hypersensitivity myocarditis is increasing (Billingham, 1985). When eosinophils have been observed in the myocardium of cocaine users, it has often been as an incidental finding, either at autopsy or in biopsy specimens obtained to evaluate chest pain, heart failure, or arrhythmia. Most of the time, the clinical manifestations of this disorder are so nonspecific that the diagnosis is rarely suspected during life (Taliercio et al., 1985).

None of the cocaine users with eosinophilic infiltrates have had signs of extracardiac involvement such as polyarteritis nodosa or eosinophilic leukemia. In general, these patients do not match the picture classically associated with acute necrotizing myocarditis (Herzog et al., 1984) nor, with the exception of one case report, do they resemble patients with eosinophilic coronary arteritis (Churg–Strauss syndrome, also called allergic granulomatous angiitis) (Orriols et al., 1996). In one case report a female "crack" smoker first presented with relapsing fever, bronchoconstriction, arthralgias, and weight loss. She then went on to develop pulmonary infiltrates, arthritis, microhematuria, skin rash, and mononeuritis multiplex. Both skin and muscle biopsies showed eosinophilic angiitis.

Many agents can cause toxic myocarditis, and even though the purity of cocaine sold in the U.S. is increasing (generally > 60%), a variety of adulterating agents are still in use with new agents added to the list monthly (see Table 1.8.8.1). A review paper published

in 1988 listed sugars (lactose, sucrose, mannitol) as the most common cocaine adulterants, followed by stimulant drugs (caffeine, amphetamines) and local anesthetic agents (Shannon, 1988). In Europe, and in many parts of the U.S., caffeine and lidocaine are the two agents most frequently encountered (Fucci and De Giovanni, 1998).

However, adulterants are subject to all the vagaries of the market, and vary from market to market. In 2005 smugglers began adding papain to cocaine in hopes of foiling urine screening tests (Burrows et al., 2005). However, most adult drug abusers are polydrug abusers, so even if they were all taking pure drug, proving whether a particular drug or an adulterant co-ingested with it was responsible for a particular finding would be a difficult undertaking. More recently there have been confirmed reports of diltiazem (Anon., 2005) and even fentanyl (Anon., 2006) being used to adulterate cocaine. The reasons for diltiazem adulteration remain unclear, as diltiazem would counteract many of the desired effects of cocaine. The extent of the practice remains unknown, but the suspicion is that diltiazem was chosen only because it was white, looked rather like cocaine, and was easily purchased or stolen. On the other hand, the addition of alpha-fentanyl would enhance the value of the product, as it would be equivalent to a "premixed speedball."

After an initial flurry of reports in 1986 and 1987, recent mentions of eosinophilic infiltrates have become uncommon. One explanation may be that most cocaine users are now "crack" smokers, and "crack," while it may contain large amounts of bicarbonate, is otherwise largely free of other chemical contaminants. Finally, it must be emphasized that the mere presence of cells in the myocardium does not necessarily mean that active myocarditis is present. The lymphocytic infiltrates seen in cocaine users are generally not

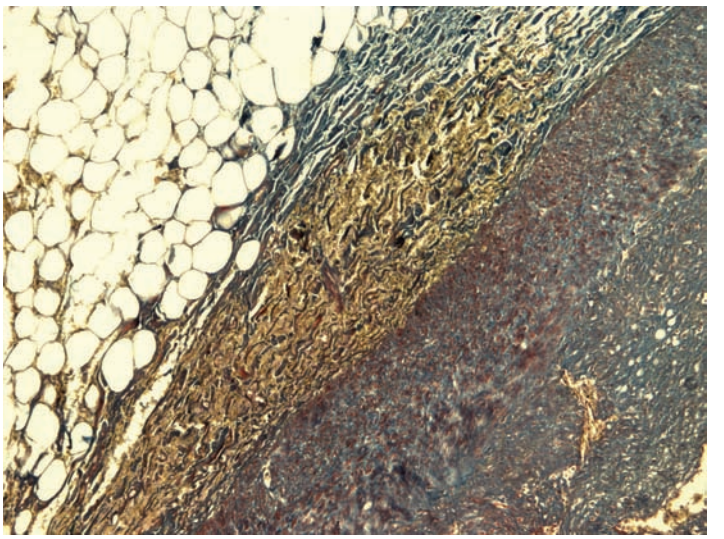

Figure 1.13.11 Dissection of the LAD artery in a 28-year-old regular cocaine user. Note that in addition to the area of dissection there is significant pre-existing plaque formation with nearly 50% occlusion of the vessel. Note dissolved cholesterol crystals and complete lack of any inflammatory infiltrate. (Courtesy of Dr. Vittorio Finnechi, Sienna.)

accompanied by myocyte necrosis and, according to the Dallas criteria, infiltrates without necrosis do not prove myocarditis (Aretz, 1987). What these infiltrates represent is not clear, but similar infiltrates are also seen in experimental animals with catecholamine toxicity.

Confusing the issue even further is the recent discovery that many cases of myocarditis (proven positive by DNA analysis) are not accompanied by infiltrates (Baughman, 2006). Of course, such an occurrence would be irrelevant in a cocaine abuser. Since nothing would be seen at autopsy, the diagnosis would not be considered.

1.13.11 Coronary Artery Dissection

Spontaneous coronary artery dissection remains a rare cause of acute coronary syndrome or sudden death. A connection with cocaine is recognized (Cohle and Lie, 1992; Castro and Nacht, 2000; Eskander et al., 2001; Steinhauer and Caulfield, 2001; Bizzarri et al., 2003), but not really understood. This disease usually affects young women during the peripartum period and those using oral contraceptives. Unlike atherosclerotic intimal dissection, the dissection plane in the spontaneous coronary dissection lies within the media or between the media and adventitia. An eosinophilic periadventitial inflammation has been commonly observed in such cases (Gowda et al., 2005).

1.13.12 Nonatheromatous Coronary Artery Disease

One of the major complications of cardiac transplantation is allograft failure, which is caused by the process of chronic rejection. Recent animal and human studies show that cardiac lymphatic obstruction leads to significant myocardial fibrosis and depression in contractile forces, and it appears that lymphatic interruption accounts for these changes (Kong et al., 2007). Most of the studies that have addressed this subject have found evidence of a complex interplay of inflammation, primitive donor-derived myocardial angiogenesis, and arteriosclerosis in transplanted hearts, and that the vascular endothelial growth factors play an important role in the process.

It is not known if cocaine use alters vascular endothelial growth factor production, but it is known that the coronary arteries of an occasional cocaine user will display exactly the same histological abnormalities seen in transplant patients (Simpson and Edwards, 1986; Nykänen et al., 2006). The reasons remain unknown.

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1.14 Excited Delirium and the Neuroleptic Malignant Syndrome

1.14.1 History and Overview of Excited Delirium

Lewis Bell, an American physician, first described excited or agitated delirium more than 150 years ago. The *American Journal of Insanity* published his lengthy paper describing a syndrome titled "On a form of disease resembling some advanced stages of mania and fever, but so contra distinguished from any ordinarily observed or described combination of symptoms as to render it probable that it may be an overlooked and hitherto unrecorded malady." All victims died suddenly after they had experienced a brief period of mania and fever (Bell, 1849). Fifty years after Bell's paper was first published, similar reports began to appear in the popular press. These reports were not exactly spontaneous; they were, in fact, deeply interwoven with elements of racist hysteria. They were published in part by opponents of the prohibitionist movement who wanted to keep alcohol available. Otherwise, it was argued, people would just start using other drugs, like cocaine, and the situation would just become much worse. The prohibitionists feared that cocaine users might become deranged and start killing people.

A physician writing for the *New York Times* (Williams, 1914) penned the most notorious, and certainly the most racist, of these reports. His article described a series of murders and violent crimes, allegedly committed by black men under the influence of cocaine. Williams claimed that cocaine not only made the men crazed and resistant to bullets, but it gave them a temporary immunity to shock. He too attributed the new menace to the restriction of alcohol sales (Knopf, 1924). When prohibition ended, so did concerns about cocaine-related violence, and reports of new cases stopped appearing in medical journals and newspapers. Some years after the end of prohibition, new case reports finally began to reappear in the early 1980s, at the beginning of the new cocaine pandemic. The first modern mention of cocaine-associated excited delirium was in 1985 (Wetli and Fishbain, 1985).

The syndrome is comprised of four separate components, with each component appearing in stereotypical sequence: hyperthermia, delirium with agitation, respiratory arrest, and death, although hyperthermia may be absent in some cases (see below). As a rule, individuals succumbing to this disorder, if they are drug users and not schizophrenics, will be found to have low to modest blood levels of cocaine or methamphetamine. Their clinical course is entirely different from that seen in body packers with massive cocaine overdose (continuous seizures, respiratory depression, and death). The incidence of this disorder is not tracked by any government agency (although the National Association of Medical Examiners has begun to maintain a database separately from the government, it is not available to the public), but there is very little doubt that the number of cases has increased markedly since the late 1980s. Deaths from excited delirium now account for a significant number of in-custody deaths both in the U.S. and in Europe. There is good reason to think that the number of newly reported cases is an accurate indicator of the cocaine/methamphetamine supply (Karch and Stephens, 1999).

In the early stages of the syndrome, which rarely last for more than a few hours, victims are hyperthermic, sweaty (even in frigid weather), paranoid, grossly psychotic, and very agitated. They often perform amazing feats of strength, usually while they are fleeing from imaginary threats, but sometimes when they are fleeing from the police. What happens next is not entirely clear. After a relatively short interval, agitation ceases and the patient "quiets." This episode of "quiet" often occurs shortly after the victim has been restrained, but it may well occur with no one else in the vicinity. Death occurs shortly afterward, and victims are almost inevitably found in asystole, not ventricular fibrillation. Victims who do not come to police attention are often found dead in their bathrooms, surrounded by wet towels and clothing, sometimes even with empty ice trays scattered about, all in a vain attempt to treat their fevers, which may be as high as 108°F.

Epidemiologic studies have shown that victims of this syndrome are much more likely to be men than women. They are also more likely to die in custody, and more likely to live for one hour after onset of symptoms. In Miami, men with excited delirium account for 10% of cocaine-related deaths. The syndrome is more common in summer, especially when the weather is warm and humid. Indeed, all types of cocaine-related death, not just excited delirium, seem to be more common when temperatures are elevated (Ruttenber et al., 1997; Marzuk et al., 1998). Two thirds of the victims die on the scene or while being transported by paramedics to the hospital. The few who live long enough to be hospitalized almost always succumb to disseminated intravascular coagulation, rhabdomyolysis, and renal failure. The patients reported from Miami had an average temperature of 104°F at the time of their first medical encounter (Ruttenber et al., 1997).

In 1985, Wetli described seven cases. All had fairly stereotyped histories, such as the 33-year-old man who was found pounding on the door of a house he had moved out of some time previously (Wetli and Fishbain, 1985).

> He was shouting that he wanted to see his wife and daughter. The occupants informed him that nobody by that name resided there, yet he pursued his actions. Four bystanders finally restrained him and assisted police units upon their arrival. The subject was handcuffed and put into a police car, whereupon he began to kick out the windows of the vehicle. The police subsequently restrained his ankles and attached the ankle restraints and handcuffs together. He was then transported to a local hospital. While en route, the police officers noted he became tranquil (about 45 minutes after the onset of the disturbance). Upon arrival at the

hospital a few minutes later, the subject was discovered to be in a respiratory arrest. Resuscitative attempts were futile. A postmortem examination was performed 1 hour and 45 minutes later (about 3 hours after the onset of the disturbance), and a rectal temperature of 41°C (106°F) was recorded. He had the needle marks typical of intravenous drug abuse and was also found to have pulmonary and cerebral edema. Abrasions and contusions of the ankles and wrists were also evident from his struggling against the restraints. Toxicologic analysis of postmortem blood disclosed 52.3 mg/L of lidocaine and 0.8 mg/L of cocaine. No lidocaine was administered to the victim during resuscitative attempts.

1.14.2 Excited Delirium and the Redefinition of "Positional Asphyxia"

If police restrain a violently agitated individual who is under the influence of drugs, and that person dies, questions will be raised about the type and level of force applied. If the force is deemed inappropriate, litigation will ensue. There is no question that some methods are clearly harmful and can cause death, such as the baton choke hold (Reay and Eisele, 1982), but these obviously inappropriate approaches are no longer permitted. There is, however, a general perception that any form of police restraint may be fatal, especially when prisoners have been bound while lying prone, with the arms behind their backs ("the hobble restraint," or "hog tying"). This belief is erroneous and runs counter to all established principles of medical physiology, but it endures nonetheless. The situation is not helped by the number of case reports published on the topic by well-meaning pathologists untrained in the general principles of exercise physiology.

Beginning in the late 1980s, pathologists started publishing anecdotal case reports describing the deaths of drug users who were in custody (Reay et al., 1988, 1992; O'Halloran and Lewman, 1993; Pollanen et al., 1998; O'Halloran and Frank, 2000; Belviso et al., 2003). Because they were only case reports, and not controlled scientific studies, they served little value except to draw the attention of the medical community. But even though a number of reports appeared, there is no strength in numbers, at least not when the numbers referred to are case reports. These reports are incomplete, uncontrolled, retrospective, and lack operational criteria for identifying when an adverse event has actually occurred. No matter how many cases are included in the "case series", each case, individually, is subject to the same weaknesses and flaws as all of the others, including any pre-existing biases affecting the authors (Kelly, 2003; Hollingsworth and Lasker, 2007). A case report is, in effect, passively collected anecdotal material. In court, such material could be considered "hearsay."

Beginning in the late 1980s, some medical examiners began applying the term "positional asphyxia" whenever they were confronted with an agitated psychotic, transported prone, who died suddenly. If the autopsy was said to be unrevealing (Reay et al., 1992), the term positional asphyxia was applied. In fact, the autopsies were rarely unrevealing. The prosecutors had simply failed to recognize key anatomic and histochemical changes. Worse, the autopsies were often incomplete (no heart weights, or heart weight not normalized, or no cardiac histology, no brain neurochemical testing). The omissions were not confined to the autopsy suite. More often than not, paramedics and even medical examiners failed to record the victim's temperature, either at the scene or at the time of postmortem examination. If the temperature has not been recorded, proving that a decedent suffered from excited delirium and hyperthermia becomes much more difficult.

More recently the whole concept of positional asphyxia has been reviewed, and the underlying hypothesis (that death may occur simply as a result of restraint in a prone

position) tested, as required by the scientific method. The results of these controlled clinical studies have discredited the theory. Nonetheless, these cases are still litigated, so the history and physiology of this non-disease is worthy of detailed review. The term positional asphyxia was originally used to describe what happens when alcoholics, or the otherwise infirm, fall into a confined space unaware that their chests are not expanding enough to support respiration (DiMaio and DiMaio, 1989; Purdue, 2000). The mechanism in such cases is easily identified because the autopsy will disclose marked skin congestion, cyanosis, and showers of petechiae.

Efforts made during pre-hospital care require precise documentation. Attempts at endotracheal intubation and cardiopulmonary resuscitation may produce petechiae, contusions, and even damage to the tracheal mucosa and strap muscles of the neck (Raven et al., 1999). Any one of these artifacts may mistakenly be attributed to the effects of neck compression or application of a choke hold. If the resuscitative attempts go undocumented, false accusations of brutality may result. In recognition of at least some of these problems, one forensic pathologist has proposed an immediate scene recreation, with all players participating (O'Halloran, 2004).

The *de facto* adoption of this new definition for positional asphyxia, and the flood of litigation that followed, occurred before the neurochemical changes of excited delirium had been characterized (Staley and Mash, 1996; Mash and Staley, 1999), before it was apparent that stimulant abusers have enlarged hearts (Karch et al., 1995) and, perhaps more important, before it was widely recognized by pathologists that myocardial hypertrophy was an independent and potent predictor for sudden cardiac death (Zipes and Wellens, 1998). It was also before it had been demonstrated that "hog-tying" of normal-sized individuals (body mass index [BMI] < 30), has no significant effect on respiratory function (Chan et al. 1997, 1998; Schmidt and Snowden, 1999; Elfawal, 2000; Meredith et al., 2005), at least not those with normal hearts and lungs.

As a consequence of these discoveries, and the admission by the originator of the theory of positional asphyxia that he had been mistaken (Reay and Howard, 1999), there has been a name change. Instead of ignoring all the other contributing factors and attributing death to position, death is now attributed to the act of "restraint asphyxia" or, alternatively, "death during a restraint procedure." The argument is that pressure applied to the back in some way disrupts ventilatory mechanics, asphyxiating the victim. It is also argued that obese individuals (BMI > 30) placed in a prone position will have upward pressure exerted on their diaphragm, contributing to their own asphyxiation.

1.14.3 The Exercise Physiology of "Positional Restraint" and "Restraint Asphyxia"

In order for tissue to receive an adequate supply of oxygen, two things must occur: (1) the blood must be oxygenated (blood flowing through the lungs must absorb oxygen from, and release carbon dioxide into, the air being pumped through the bronchi), and (2) the oxygenated blood must flow normally to the tissues. At rest a normal human being exchanges approximately 500 mL of air with each breath, and they do so 12–16 times a minute. Put another away, each minute the normal lungs of a normal person move between 6 and 8 L of air, just enough to supply all of the body's oxygen needs. If there were a greater

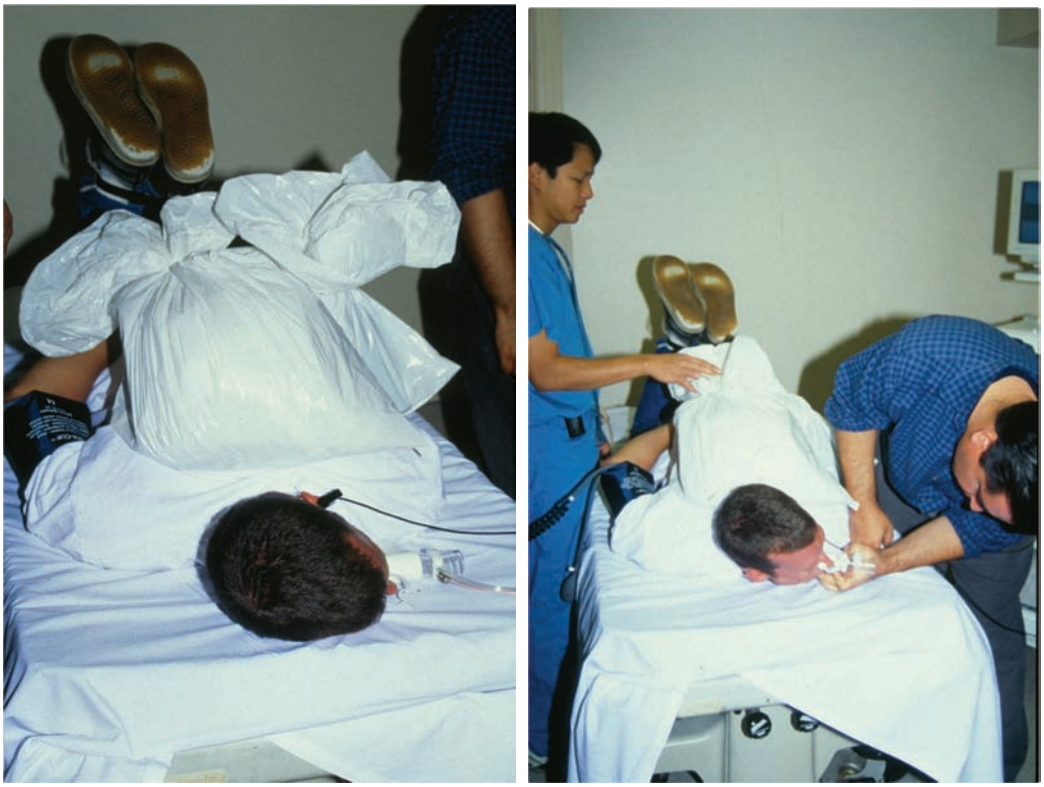

Figure 1.14.3.1 "Restraint asphyxia" is a term used by some to describe the mechanism of death in patients who actually are suffering from a distinct neurological disorder called excited delirium. As the photographs illustrate, hog-tying and even applying more than 200 pounds of weight to the backs of healthy volunteers (BMI < 30) does not cause a clinically significant decrease in tidal volume or SaO_2. (Courtesy of Dr. John Eisle.)

need for air, for example if someone wanted to compete in a 1000 m relay, the normal body could easily increase the airflow to 160–180 L per minute.

This means that the body has enormous reserves of oxygen and is capable of getting more. In fact, the maximal breathing capacity is about 50% greater than ventilation during maximal exercise (Guyton and Hall, 2000)! This excess is what protects athletes, because it gives them extra ventilation that can be called on when there are extreme demands. Even a person working as hard as they can (technically referred to as VO_2 max) would be unable to use up all of the oxygen available to them.

Careful measurements have been made, and the act of "hog-tying" a normal individual has only negligible effects on the amount of oxygen consumed. As the results of these studies have become better publicized, supporters of the concept of positional asphyxia (i.e., those people who think that hog-tying can be a fatal exercise) have morphed into supporters of the concept of "restraint asphyxia." These individuals argue that, during an intense struggle, placing enough weight on a victim's back is sufficient to cause asphyxial death and/or that the diaphragm is forced into the chest, thereby decreasing respiratory capacity.

Is weight on the back sufficient to prevent blood and oxygen delivery to the tissues? There is nothing contradictory about the suggestion, and it certainly seems possible, but it must be borne in mind that the body contains a great deal of oxygen (both in the lungs and in the blood), and death would be delayed until all of these oxygen reserves were used up, a process that would take several minutes and would almost certainly be accompanied by florid cyanosis and ventricular fibrillation—not asystole which is usually observed in these situations (Stratton et al., 2001). Further, the limiting factor in delivering oxygen to the tissues is not the ability of the lungs to exchange air (maximal ventilatory capacity supplies twice the oxygen that can be consumed during maximal exercise) but, rather, the ability of the heart to pump oxygen-containing blood.

If it were possible to place enough weight on the back to prevent respiratory exchange (short of preventing the chest from moving entirely, which was what the term "positional asphyxia" was originally meant to describe), how much weight would be needed? Evidence from numerous sources suggests that a reduction in breathing capacity of nearly 80% would be required (Rochester and Esau, 1994; Neuman, 2006). This number is not arbitrary, but rather derives from observations made in numerous medical conditions where oxygenation/ventilation is disrupted.

The question then becomes, "How much weight would be required to cause asphyxia?" The simplest answer is "Weight sufficient to reduce ventilation by 80%" (the majority of patients are not considered eligible for a lung transplant until 80% of their lung capacity has been lost). Can a policeman, or even two policemen, placing their feet on a prisoner's back, exert enough force to prevent chest movement, and, if so, how many pounds of pressure would that be? Controlled clinical studies have shown that placing up to 225 pounds on the backs of restrained volunteers produces no significant decrease in maximum voluntary ventilation (Michalewicz et al., 2007), so whatever that number is, it must be greater than 225 pounds (100 kg) to produce any significant clinical effect.

1.14.4 The Neurochemistry of Excited Delirium

The abnormalities in this syndrome have to do with the number and type of dopamine receptors present and their location within the brain. Cocaine use alters the number of D1, D2, and D3 receptors. When compared to the brains of drug-free trauma victims, the brains of nonpsychotic cocaine users have more places for cocaine to bind in the striatum. That is not the case in cocaine users with excited delirium. It appears that these individuals become psychotic because they have no way to clear their synapses of dopamine.

In nonpsychotic cocaine users, striking increases also occur in the density of D1 receptor subtypes throughout the striatal rewards areas. Similar increases are not seen in individuals with excited delirium. Tolerance is also explained by changes in the number of dopamine binding sites. In nonpsychotic cocaine users the number of D2 receptors remains relatively unchanged, but in excited delirium there are marked decreases. Excited delirium victims have temperature elevations because there are marked reductions in the number of D2 receptors in the hypothalamus. These receptors mediate temperature control. With fewer D2 receptors available, D1-mediated temperature increases are unopposed (Staley et al., 1994). Whether or not hyperthermia occurs, and the degree of severity, depend upon the absolute decrease in D2 receptors; if it is not very great, then hyperthermia may or may not occur.

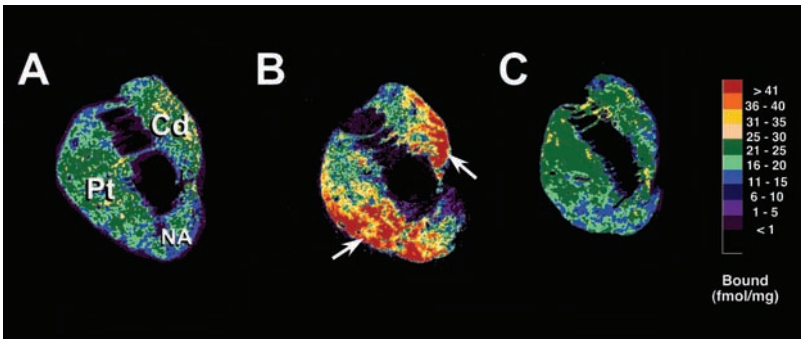

Figure 1.14.4.1 Excited delirium. Adaptive increases in the number of dopamine transporters can be seen in the brains of cocaine users dying of overdose but not in the brains of patients with excited delirium. Shown here are *in vitro* autoradiographic maps of [^{3}H]WIN 35,428 labeling of the dopamine transporter in coronal sections of the human brain from (A) a representative age-matched and drug-free subject, (B) a cocaine overdose victim, and (C) a cocaine-related excited delirium victim. Color codes are presented at the right and are matched for the range of density values across the groups (red = high densities; yellow = intermediate; blue = low to background densities). Abbreviations: Cd, caudate; NA, nucleus accumbens; Pt, putamen. (Courtesy of Debra Mash, University of Miami School of Medicine.)

The significance of changes in the D3 receptor has only recently become apparent (Mash and Staley, 1999). Compared to drug-free controls, the brains of nonpsychotic cocaine users contain an increased number of D3 binding sites, with a one- to threefold increase measurable in the nucleus accumbens and in the ventromedial sectors of the caudate

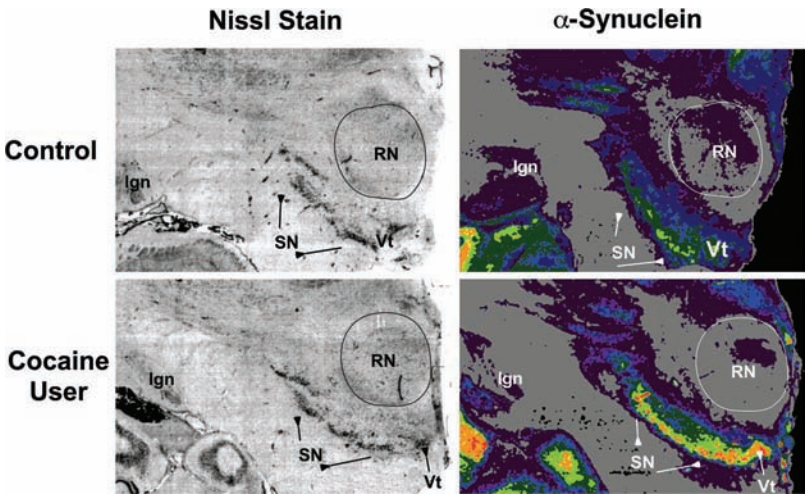

Figure 1.14.4.2 Alpha-synucleins, seen in the brain of a patient dying from excited delirium. Cocaine blocks dopamine re-uptake, but its actions are modulated by alpha-synuclein. Cocaine causes concentrations of alpha-synuclein to increase, especially in the ventromedial sectors of the striatum other than in the dorsal caudate nucleus. Thus, overexpression of alpha-synuclein may play a role in cocaine-induced plasticity and regulation of dopamine synaptic tone. (Courtesy of Debra Nash, University of Miami School of Medicine.)

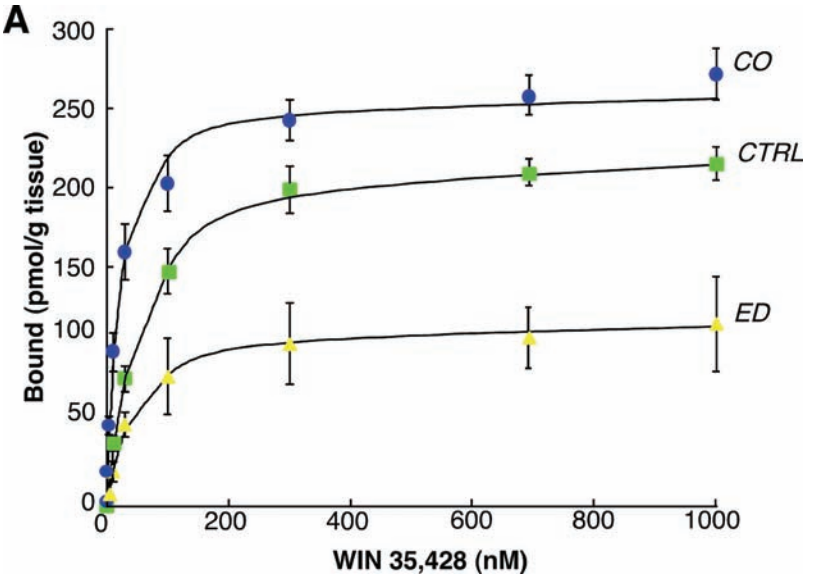

Figure 1.14.4.3 A graphical representation of the same information displayed in the autoradiogram shown in Figure 1.14.1.1. It is apparent that, compared with controls, WIN binding (a marker for dopamine transporters), is elevated in occasional cocaine users, but is markedly reduced in patients with excited delirium.

and putamen. The nucleus accumbens is a collection of brain stem neurons deeply implicated in the process of addiction to all drugs. Within this nucleus, cocaine exposure also causes increased production of D3 receptors.

By mechanisms yet to be determined, the increase in D3 receptors is related to an increase in the number of κ-opioid receptors. Nonpsychotic cocaine users, when compared to drug-free controls, have twice the number of κ receptors in the nucleus accumbens and other corticolimbic areas. Unlike nonpsychotic cocaine users, cocaine users who die of excited delirium have a selective up-regulation of κ receptors in the amygdala (Staley et al., 1997; Mash and Staley, 1999).

Serotonin (5-HT) regulation also plays a role because it modulates dopaminergic neurotransmission. Chronic use of cocaine may cause a "serotonin deficit", resulting in a form of 5-HT dysregulation. In patients with simple cocaine overdose, levels of 5-HT transporters are elevated within the nucleus accumbens and throughout the anterior and posterior sectors of striatum. A much different picture is seen in patients with excited delirium where there are increases in the number of 5-HT transporters in the anterior striatum, but not the posterior sectors. Chronic cocaine exposure up-regulates 5-HT transporter densities in the substantia nigra in victims of cocaine overdose, but not in excited delirium victims. Some speculate that the lack of 5-HT up-regulation in the substantia nigra and posterior striatum may identify a distinct phenotype for excited delirium victims who have an acute onset of bizarre and violent behavior prior to death (Mash et al., 2000).

Some of the neurochemical effects of cocaine seem to be gender related. Studies utilizing proton magnetic resonance spectroscopy have shown that the brains of cocaine users, when compared to those of non-drug-using controls, contain decreased amounts of *N*-acetyl

compounds, an indicator of neuronal damage. Production of myoinositol, an indicator of glial activation, is increased. Both of these alterations are most prominent in the frontal lobes, and both changes are much more pronounced in men than in women. Whether these neurochemical alterations explain why nearly all excited delirium victims are men is not known (Chang et al., 1999).

1.14.5 Autopsy Findings

The presence of petechiae is often cited as proof of death from "positional asphyxia" (Reay et al., 1992), but petechiae around the eyes are not infrequently seen in individuals with heart failure, for whom there is no question of drug abuse or strangulation having occurred (Rao and Wetli, 1988). Petechiae can, and do, occur as a result of resuscitative attempts (Maxeiner and Winklhofer, 1999; Raven et al., 1999) and they may not be apparent until some time has elapsed after death (Kondo et al., 1997; Burke et al., 1998). Thus, photographic documentation of the absence of petechiae is just as important as documentation of their presence.

If it is examined appropriately, the heart will invariably be found to be abnormal, if not grossly enlarged, then at least enlarged above the predicted weight (Mayo Nomogram—see Appendix 3). Recent evidence suggests that cocaine has the ability to induce the production of calmodulin kinase II (Henning and Cuevas, 2006), in turn leading to myocyte hypertrophy and increased concentrations of calcium within the cytosol. Increased cytosolic calcium favors electrical instability and the occurrence of cardiac arrhythmias.

Methamphetamine may or may not share this ability. There is clear evidence that methamphetamine can induce calmodulin kinase II production (Dipace et al., 2007), but whether it also induces production in the heart is not known, even though myocardial hypertrophy certainly occurs in most methamphetamine abusers. In the case of methamphetamine and other stimulants, cardiac enlargement seems to be secondary to catecholamine-induced effects. Whatever the case, myocardial remodeling occurs, and the myocardium itself becomes fibrotic, if not grossly so, then in a microfocal pattern easily discernable under the microscopic. Increased myocardial mass has a greater oxygen demand than normal myocardium, and a decreased ability to meet that demand (remodeling in these individuals also involves medial hypertrophy of small myocardial vessels, and a greater distance from muscle to vessel lumen), which explains why increased heart size is a well-established risk factor for sudden cardiac death (Zipes and Wellens, 1998).

1.14.6 The Toxicology of Excited Delirium

The mean cocaine concentration in 45 cases seen by the Miami Dade County Medical Examiner was 1.32 mg/L (range 0.05–11.8 mg/L, $n = 34$), while the BZE level was 3.78 mg/L (range 0.08 ± 14.75 mg/L, $n = 38$). In these same deceased individuals, the mean brain cocaine concentration was 1.90 mg/kg (range 0.05 ± 4 mg/kg, $n = 10$), while the mean BZE concentration was 2.69 mg/kg (range 0.85 ± 3.5 mg/kg, $n = 6$) (Wetli et al., 1996). By comparison, cocaine blood concentrations in a group of 51 trauma victims, where the presence of cocaine was an incidental finding, were not much lower than in victims of excited delirium (Karch et al., 1998; Stephens et al., 2004).

1.14.7 Cause of Death Determination

Chronic cocaine use leads to myocardial hypertrophy; surges in catecholamines produce myocyte damage (contraction band necrosis and damage to vessel walls) and, at the same time, lower the threshold for ventricular fibrillation. The microvasculature changes seen in the hearts of patients with excited delirium are highly reminiscent of those seen in hypertensive individuals with decreased arteriolar lumens either as a direct consequence of vasoconstriction or wall thickening (O'Halloran and Lewman, 1993; Gavin et al., 1998). These changes all favor ischemia, which can be expected to be even more severe in patients with enlarged hearts. Thus, the cause of death in virtually all the positional asphyxia cases can generally be presumed to be previously unrecognized heart disease. Nonetheless, alternative causes of death must be ruled out.

Obviously, direct trauma must be excluded, but other perceived possibilities often cloud the issue. The two alternative causes cited most to explain excited delirium deaths are (1) use of pepper spray and/or (2) the application of electrical control devices (Taser®). Since most fatalities associated with Taser use have been in patients with excited delirium (Kornblum and Reddy, 1991; Strote and Range Hutson, 2006), this is the explanation most likely to be adopted by the media and the public at large. While there is no question that the Taser produces an electrical charge sufficient to cause intense pain and immobilize skeletal muscle, there is no evidence that it can disrupt the electrical function of cardiomyocytes (Holden et al., 2007; Sun and Webster, 2007).

A case report published in 2006 (Haegeli et al., 2006) described a 51-year-old woman (height, 170 cm; weight, 75 kg) who had undergone placement of a single chamber ICD (internal cardiac defibrillator: Guidant Prizm 2VR, model 1860, Guidant Inc., St. Paul, MN, U.S.A.) five years earlier for idiopathic ventricular fibrillation (presumably from a channelopathy, though the paper never stated as much). The lead had been placed in the right ventricular apex. The patient was "Tased" because of uncontrolled violent behavior (the case report does not specify the circumstances). The Taser darts struck the sternum directly. When the Taser trigger was activated, current was delivered for 5.36 seconds. After the initial immobilization, the woman recovered and suffered no immediate adverse effects. Two months later, the patient presented for regular follow-up at the ICD clinic. Interrogation of the ICD device revealed one episode of what appeared to be VF, which corresponded to the time the Taser had been activated. What had happened was that the ICD interpreted the Taser discharge as an episode of VF, causing the capacitor in the ICD to charge so that the woman could be defibrillated. But, by the time the ICD had charged, the Taser was no longer firing and the ICD turned itself off without ever delivering a defibrillator shock. It was apparent from interrogation of the device that at no time during the Taser discharge had there been any change to the underlying rhythm.

Similar considerations apply to the pepper sprays used by some police departments. All adult deaths associated with pepper spray have been in individuals with excited delirium, usually cocaine users. In the absence of laryngeal edema, it is difficult to conceive of a mechanism, or any connection at all, other than that violently psychotic individuals are more likely to be exposed to pepper spray than people who are not psychotic. However, because of low cocaine blood levels at autopsy, because of general misunderstandings about cocaine blood concentrations and the probability of death, because core temperatures are generally not recorded, because heart weights are not being measured, let alone normalized for size, and because hearts are not examined microscopically, it is hardly surprising that

Table 1.14.7.1 Protocol for Investigation of Excited (Agitated) Delirium Deaths

1. *Training:* Establish protocols specifying that:
   a. Pepper spray should be avoided when excited delirium is suspected. It will not subdue the individual, and will only create needless liability.
   b. Avoid hog-tying the victim. If the heart is abnormal, doing so may hasten death. If the heart is normal, and death results, the act of restraint alone will be considered as grounds for litigation.
   c. Avoid multiple Taser applications. If there are multiple applications, document fully the distance from which the darts were fired. The greater the dispersion of the darts, the greater the area of muscle immobilized. If multiple darts are fired it may be impossible to pair the impacts accurately, a failure that could be of forensic significance.
   d. Make every effort to transport the patient by ambulance, not police car, and use pulse oximetry if it is available. It cannot be argued that an individual died of positional asphyxia if their oxygen saturation was normal.
   e. Never transport an excited delirium patient unattended in a police van. Better still, never transport an excited delirium patient. This should be done by paramedics.
   f. Always take patients with excited delirium to a hospital, never to a jail.
   g. Notify the medical examiner immediately of any excited-delirium-like death. Tissue for certain tests must be obtained as rapidly as possible.
   h. Document that each officer has learned the management protocol for this type of patient.
2. *Neurochemical testing:* Make arrangements with a local university or medical school to process the brain. The University of Miami brain endowment bank has done extensive research in this area and can always be consulted (1-800-UMBRAIN). Under most circumstances, only half the brain need be submitted for testing.
3. *Temperature:* Take and record the core temperature of the deceased at the scene. Take and record the ambient air temperature at the scene as well, and take it again at the time of autopsy.
4. Interview all witnesses; verify the method of restraint and time to loss of consciousness.
5. If the deceased was transported by ambulance, review paramedic records for temperature and oxygen saturation measurements that well may have been recorded and overlooked.
6. If pepper spray was used, confiscate the unit and weigh it to estimate the amount remaining (as an indication of how much was used).
7. Autopsy protocol to be completed within 24 hours of death:
   a. Remove brain, place 1-cm slices on baking sheet, rinse with saline, freeze with dry ice, and ship to neurochemistry reference lab.
   b. Remove heart and fix prior to examination. Consider consultation with a university-based cardiac pathologist.
   c. Obtain urine, blood samples from the clamped femoral vessels and the right heart, and also brain tissue for toxicology testing; record sites of sampling.
8. Always remove the brain and thoracic organs before performing and photographing the neck dissection (prevents artifacts simulating neck trauma).
9. Consider asking family of decedent to designate an independent forensic pathologist to be present at time of autopsy.
10. Perform a scene recreation and enactment as soon as is feasible. Videotape the re-enactment. If the decedent has been "Tased" by multiple officers with multiple darts, there is no way for the Medical Examiner to determine which dart strikes are paired. Taser darts are designed to diverge 10 inches when fired at 6 feet. The greater the dispersion of the darts, the greater the effect, which may be important in the Medical Examiner's deliberations.

death is often attributed to use of a choke hold or pepper spray or "hog-tying" or the Taser. The other alternative, attributing death to a trivial head injury (minor cerebral contusions or subdural hematomas) is still another obvious temptation best avoided (Mirchandani et al., 1994). Another possibility, yet to be investigated, is that both respiratory and cardiac

arrest are centrally mediated, perhaps because of some receptor imbalances in tractus soliterus or the Red Nucleus.

In some cities in the U.S., medical examiners have taken the sensible approach of contacting the deceased's family and asking them to retain their own pathologist to witness the autopsy. In the U.K., this is standard practice. Even the presence of an independent observer, however, may not be enough to prevent litigation or to prevent individuals from confusing temporal proximity of an action, such as "hog-tying," with causality. Aristotle identified this type of logical error more than 2000 years ago. One would hope that, in the interim, pathologists would have learned to avoid this mistake and base their decisions on factual analysis, not flawed reasoning.

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1.15 Cocaine-Associated Pulmonary Disease

Chronic coca leaf chewers may develop stomatitis, glossitis, and buccal mucosal leukoderma (Hamner and Villegas, 1969; Grattendick et al., 2000). The practice of "snorting" probably did not begin until shortly before 1903, the year when the first cases of septal perforation were reported (Maier, 1926). Septal perforation is now a well-known complication of drug abuse (Pearman, 1979), but surgery for its repair is much more effective than it was a decade ago (Meyer, 1994; Heller et al., 2005). Many of these cases present as midline granulomas that look, for all the world, like Wegener's granulomatosis, but histological examination will disclose necrosis and atrophy of the inferior and middle nasal turbinates bilaterally, along with prominent naso- and oropharyngeal ulcers (Trimarchi et al., 2006; Scheenstra et al., 2007). Biopsies generally reveal focal areas of chronic inflammation and necrosis, but no evidence of vasculitis or granuloma formation (Becker and Hill, 1988; Deutsch and Millard, 1989; Daggett et al., 1990; Allbery et al., 1995; Sevinsky et al., 1995; Heller et al., 2005). One controlled autopsy study compared histological findings in septal mucosa from 20 individuals with proven histories of chronic nasal inhalation of cocaine, and 15 controls. As might be expected, chronic inflammatory disease was seen in the cocaine users. The glandular elements were in total disarray, and mononuclear cells, particularly lymphocytes, were seen surrounding arterioles and glands (Chow et al., 1990). Even if sections of the septum are not obtained, the mucosa should be swabbed with saline because cocaine may be recovered for some time, possibly days, after it was last used.

Biopsies of a posterior oropharyngeal ulcer in one patient showed only necrosis and a mixed inflammatory cell infiltrate, and there is nothing diagnostic about the tissue changes. The causative role of cocaine is usually confirmed by the resolution of the lesions with cocaine abstinence. In the living, computed tomography remains the preferred imaging modality for evaluating nasal masses that contain calcification, or that originate from bone or cartilage.

Pott's puffy tumor, an old name for subperiosteal abscess of the frontal bone associated with underlying frontal osteomyelitis, has rarely been reported in stimulant abusers. This complication of frontal sinus infection was once fairly common, but the introduction of antibiotic medications has made it a rarity. When it does occur in association with cocaine use, the underlying mechanism presumably is recurrent vasospasm and ischemia, favoring the spread of infection (Noskin and Kalish, 1991).

Black sputum is reported by nearly half of all cocaine smokers and is thought to be secondary to the practice of some of smoking the tarry residue that coats the "crack" pipe (Taylor and Bernard, 1989; Tashkin et al., 1992; Laposata and Mayo, 1993). The inhaled particles can be seen as black particles within collections of macrophages. Some individuals may even sustain upper airway burns, caused by the inhalation of hot particulate matter from inadequate filters used in their "crack" pipes, which are often composed of steel wool (Bezmalinovic et al., 1988; Snyderman et al., 1991; Reino and Lawson, 1993). Others will experience severe stridor, but some may present with uvular edema unaccompanied by any apparent respiratory distress. No predictable pattern of symptoms suggests upper airway injury as a consequence of cocaine use (Reino and Lawson, 1993; McQueen et al., 1995). Strangely, there have been no new reports in the last decade. It is almost as if the disorder had disappeared.

1.15.1 Barotrauma

The general classification of barotrauma includes disorders where increased intra-alveolar pressure or decreased interstitial pressure leads to rupture of alveoli with leakage of air. Whether pneumothorax or pneumomediastinum results will depend on the location of the alveolus. Increased intra-alveolar pressure is usually the result of coughing or performing the Valsalva maneuver, which "crack" smokers routinely do. There are, however, other possibilities. Pulmonary inflammation could weaken the alveolar wall and lead to leakage of air. Alternatively, vasoconstriction in the vessels adjacent to an alveolus could cause decreased interstitial pressure, leading to alveolar rupture without any great increase in intra-alveolar pressure (Maklin and Macklin, 1944; Seaman, 1990; Chan et al., 1997; Uva, 1997; Maeder and Ullmer, 2003).

Another possible cause for pneumo- and hemothorax is injection into central veins, although this practice is much more common in heroin abusers, because heroin tends to be adulterated with material that is not water-soluble. Repeated injections of adulterated heroin can lead to sclerosis of peripheral veins. When that happens, the users are forced to inject central veins. The two most popular central sites are the great vessels in the neck ("pocket shot") (Lewis et al., 1980) and the vessels of the femoral triangle ("groin shot") (Pace et al., 1984). Injections are also made into the general area of the supraclavicular fossa (Figure 1.15.1.1), either by the addict himself or by a hired "street doc." Because the lung apex is directly contiguous with the area, pneumothorax commonly results (Kurtzman, 1970; Butterfield, 1972; Yellin, 1977; Merhar et al., 1981; Feldman and Berguer, 1983;

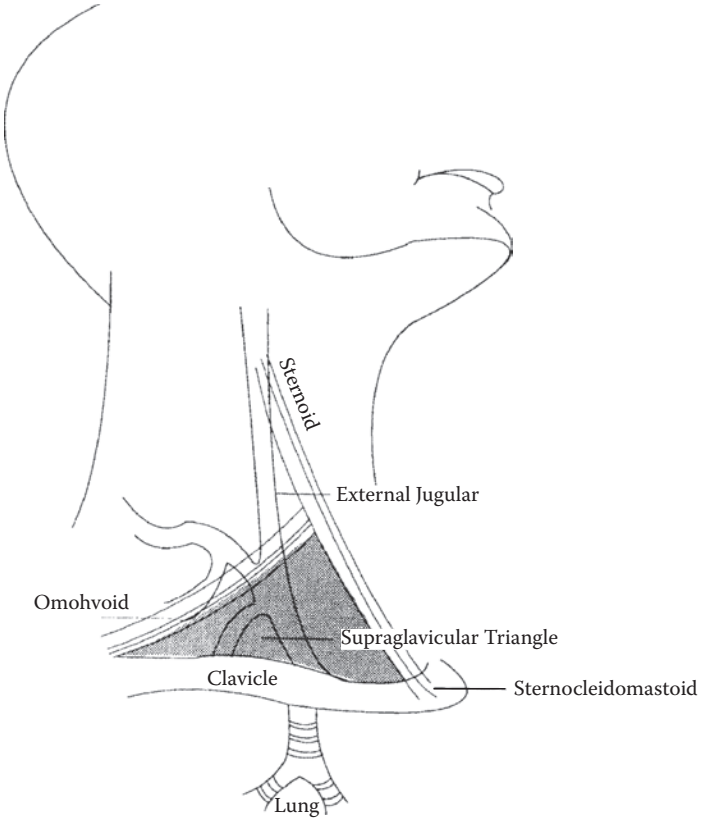

Figure 1.15.1.1 The supraclavicular fossa. As peripheral veins become sclerosed, chronic abusers resort to injecting themselves in the supraclavicular fossa and in the femoral triangle. The supraclavicular fossa overlies the great vessels and the apex of the lung. Pneumothorax and hemothorax are the predictable results.

Douglass and Levison, 1986; Reddy et al., 1986; Reddy, 1988; McIlroy et al., 1989; Patel et al., 1989; Peretti et al., 1990; Welch et al., 1990; Cheng et al., 1992).

Cocaine-associated pneumomediastinum occurs with some frequency (Shesser et al., 1981; Bush et al., 1984; Morris and Shuck, 1985; Aroesty et al., 1986; Hunter et al., 1986; Mir and Galvette, 1986; Schweitzer, 1986; Luque et al., 1987; Salzman et al., 1987; Brody et al., 1988; Leitman et al., 1988; Savader et al., 1988; Christou et al., 1990; Sullivan and Pierson, 1997; Gotway et al., 2002; Janes et al., 2004; Mortelmans et al., 2005; Viswanathan and Navaneethan, 2007). Pneumomediastinum is a generally benign condition; no fatal cases have been reported, and no autopsy studies have been performed. Presumably, the mechanism has to do with the performance of a Valsalva maneuver by a deeply inhaling smoker. No cases have been reported after intravenous or intranasal use. This is another entity that almost disappeared over the last decade, but which seems to have re-emerged in this decade. Perhaps its occurrence is some sort of marker for population-wide cocaine abuse.

Surprisingly, barotrauma has not been proposed as the mechanism for some cocaine-related strokes (see Section 1.16.3), but it might offer just as good an explanation as cocaine-induced vasospasm. Air from ruptured alveoli may diffuse into pulmonary capillaries and

veins, then pass through the left side of the heart and embolize via the systemic arteries to the brain. This possibility seems especially likely, now that the role of atrial septal defect in stroke is increasingly understood (Berthet et al., 2000). The diagnosis would be particularly difficult to make because, if the patient survives for more than a few hours, the air bubbles will have dissolved and typical morphologic changes (multiple small, well-circumscribed foci of cortical necrosis, sometimes associated with laminar necrosis) will not have had time to develop (Wolf et al., 1990).

1.15.2 Parenchymal Disease

In additional to having carbonaceous sputum, "crack" smokers not infrequently have emphysematous changes in their lungs. The pattern is readily apparent in microscopic sections, even before they are placed under the microscope; it is highly reminiscent of the pattern seen in "coal miner's lung." Sputum from these individuals is usually turbid, gray or even black, and considerably darker than sputum seen in heavy tobacco smokers dwelling in the same urban environment. Microscopic examination of sputum smears from "crack" smokers will disclose excessive carbonaceous material in the cytoplasm of pulmonary alveolar macrophages and also in the extracellular compartment (Figure 1.15.2.1) (Klinger et al., 1992; Greenebaum et al., 1993; Barsky et al., 1998; Janjua et al., 2001; Ali et al., 2002; Hirche et al., 2002; Restrepo et al., 2007).

Many, if not most, "crack" smokers also smoke cigarettes, though pulmonary symptoms are similar in both groups. However, the percentage of hemosiderin-positive alveolar macrophages in lavage fluid is markedly increased in the "crack" smokers (whether or not they also smoke tobacco), but not in the tobacco smokers. In addition, levels of endothelin-1 (ET-1) are significantly increased in bronchoalveolar fluid recovered from "crack" smokers, and the percentage of hemosiderin-positive alveolar macrophages tends to correlate with ET-1 concentrations. This suggests that clinically unapparent alveolar hemorrhage

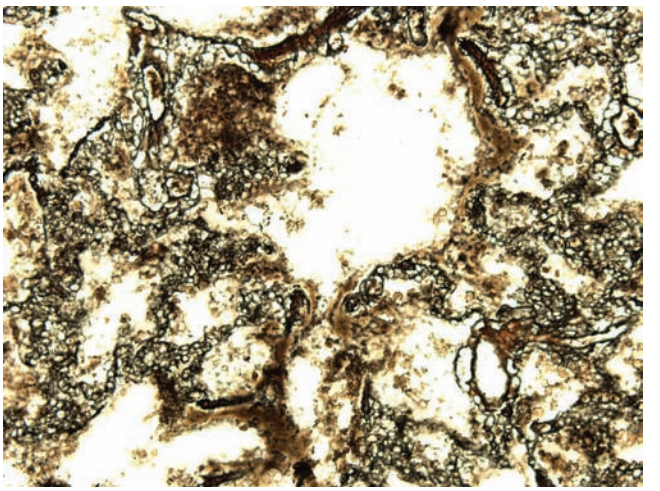

Figure 1.15.2.1 Pulmonary anthracosis. The lungs of "crack" smokers often are emphysematous and contain dense carbonaceous deposits. The changes can be apparent to the naked eye. Hemosiderin-laden macrophages are often present, probably reflecting recurrent bouts of focal hemorrhage. (Courtesy of Dr. Vittorio Finnechi, Sienna.)

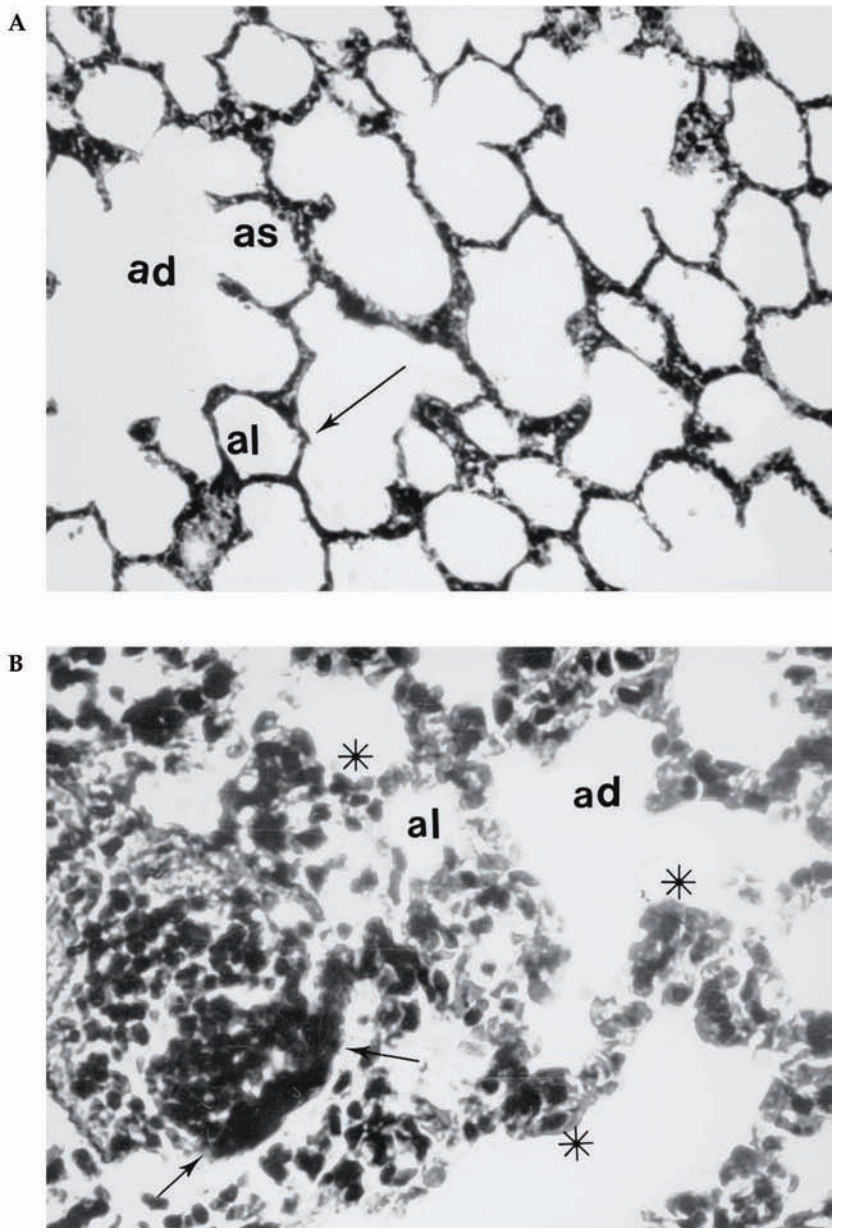

Figure 1.15.2.2 Typical alveolar changes. (A) Control rat in which the alveolar ducts (ad), sacs (as), and alveoli (al) are all normal; the arrows point to an alveolar wall of normal thickness. (B) Alveolar hemorrhage (arrows) in a rat after 30 days of treatment with 30 mg/kg/day of intraperitoneal cocaine; the lumen of the ducts and alveoli are narrowed by fibrous wall thickening. (C) After 45 days of treatment, intense cellular proliferation and increasing thickness of the alveolar walls result; arrows in the upper left show a collection of macrophages with cytoplasmic granulation. (D) After 75 days of treatment, the alveoli are deformed and the interstitial space is filled with necrotic cells; arrows point to occluded and collapsed capillaries. All four sections were stained with Masson's Trichrome, 100×. (From Barroso-Moguel, R. et al., *Toxicol. Lett.*, 110(1–2), 113–118, 1999. With permission.)

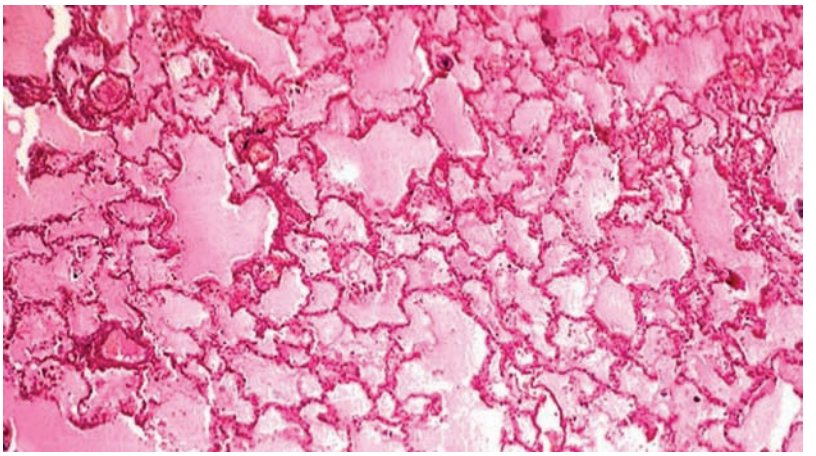

Figure 1.15.2.3 Pulmonary edema.

occurs frequently in otherwise healthy "crack" cocaine smokers and these hemorrhages are in some way associated with elevated levels of ET-1, suggesting that a cocaine-induced pulmonary microvascular injury has occurred (Baldwin et al., 2002; Terra Filho et al., 2004). Retrospective autopsy studies of cocaine users have disclosed hemorrhages and hemosiderin-laden macrophages in 27–58% of the patients (Murray et al., 1988; Bailey et al., 1994). Bailey et al. (1994) found evidence of acute or chronic hemorrhage in 71% of cases, even in the absence of any clinical history of hemoptysis, and concluded that relying on that particular historical clinical sign would lead to serious underestimation of how frequent alveolar hemorrhage actually was in "crack" smokers. Diffuse alveolar hemorrhage has been described, and clinical reports suggest that spontaneously resolving hemoptysis is not that uncommon among cocaine smokers (Murray et al., 1988; Forrester et al., 1990; Bouchi et al., 1992; Garcia-Rostan y Perez et al., 1997; Gallouj et al., 1999; Baldwin et al., 2002).

Pulmonary congestion in cocaine-related deaths was first recognized at the turn of the twentieth century, and it can occur even in nonfatal cases (Purdie 1982; Cucco et al., 1987; Efferen et al., 1989; Hoffman and Goodman, 1989; Bakht et al., 1990; Kline and Hirasuna, 1990; Batlle and Wilcox, 1993; Raijmakers et al., 1994; Kuczkowski, 2005; Diskin et al., 2006; Ksienski et al., 2007). The etiology of cocaine-associated pulmonary edema is obscure; however, the relatively low protein content of the edema fluid (it does not froth like the edema fluid seen with heroin overdose) suggests that it is of cardiogenic, not neurogenic origin (Robin et al., 1989; Simon, 1993). Alternatively, pulmonary edema in cocaine users could just be another manifestation of catecholamine toxicity of the lungs, the heart, or both (Kurachek and Rockoff, 1985; Karch, 1989; Arfi et al., 2005; Rassler, 2007).

Cocaine itself, and the catecholamine excess that occurs in association with cocaine use, both decrease myocardial contractility (Perreault et al., 1993). If contractility is depressed enough to lower cardiac output, heart failure and pulmonary edema will develop. A direct effect of cocaine on the lungs may also be possible. It has been suggested that the local anesthetic action of cocaine impairs the movement of sodium and fluid across the alveolar epithelium (Raijmakers et al., 1994).

The lungs of chronic cocaine smokers usually display thickening in some of the interalveolar septa, along with interstitial hemorrhages, progressive thrombosis, and transformation of reticular and elastic fibers into diffusely fibrotic tissue. These findings are indicative of severe cocaine-induced microvascular disease and are consistent with the findings of Baldwin and others. They have been reproduced in animals chronically treated with cocaine (Barroso-Moguel et al., 1999). The typical alveolar changes seen in this animal model are seen in Figure 1.15.2.2.

Prior to the advent of "crack" cocaine, mentions of cocaine-related pulmonary disease were rare. As smoking cocaine became more popular, reports of patients with inflammatory infiltrates, sometimes associated with fever, hypoxia, hemoptysis, and even respiratory failure, began to appear (Forrester et al., 1990). Specimens from some of these patients have demonstrated diffuse alveolar damage with hyaline membrane formation and type II cell hyperplasia, as well as intra-alveolar and interstitial inflammatory infiltrates with eosinophilia. Some, with x-ray demonstrated inflammatory infiltrates, have had peripheral eosinophilia (Mayron et al., 1972; Murray et al., 1988) while others did not (Cucco et al., 1987; Kissner et al., 1987; Patel et al., 1987; Forrester et al., 1990; Talebzadeh et al., 1990; Oh and Balter, 1992; Nadeem et al., 1994; Opalka et al., 2002; Strong et al., 2003).

1.15.3 Vascular Adaptations

Hypertrophy of the smooth muscle of the pulmonary arteries with proliferation of the elastic fibers can occur. This pattern is consistent with the diagnosis of pulmonary hypertension. This sort of anatomic alteration is of increasing interest to electrophysiologists, who believe that the abnormal impulses that drive atrial fibrillation arise in muscle fibers located at the insertion of the pulmonary artery (Mavroudis et al., 2007).

Hypertrophy of the pulmonary artery smooth muscle is also seen in the lungs of heroin abusers. It is the result of intravascular deposition of foreign materials that have been injected along with the heroin (see Chapter 5, Section 5.10.2.1). The formation of foreign body granulomas sets in motion a series of events that eventually leads to pulmonary hypertension. The specific particles causing the granulomas are easily seen with polarizing microscopy, but they can also be differentiated by their staining properties (Tomashefski and Hirsch, 1980; Tomashefski et al., 1981). These alterations are much more common in the subpopulation of abusers who inject crushed pills (Ritalin™, oxycodone, hydrocodone, etc.). In autopsy studies of heroin and polydrug abusers, the incidence of medial hypertrophy of small- and mid-sized pulmonary arteries has ranged from 8% (Hopkins, 1972) to as high as 40% (Rajs et al., 1984).

It seems likely that other mechanisms are operative among cocaine users: excessive stimulation of α_1 receptors causes smooth muscle to contract and also induces the proliferation of smooth muscle growth in vessel walls. Proliferation could also be the result of excessive 5-HT2 stimulation. Cocaine prevents platelet re-uptake of 5-HT (Patkar et al., 2003). Platelet re-uptake is one of the mechanisms by which the body normally maintains 5-HT concentrations within physiological ranges. Many abused drugs and SSRI antidepressants influence circulating 5-HT concentrations. Although the effects of cocaine have not been specifically studied, amphetamine analogs (which also block 5-HT re-uptake) have, and they evoke large dose-dependent increases in plasma 5-HT. At least in experimental animals, the rise in 5-HT concentrations is not sufficient to cause contraction of

pulmonary arteries, but they approach concentrations reported to stimulate mitogenesis in pulmonary artery smooth muscle cells (Zolkowska et al., 2006), which could explain the changes seen in chronic "crack" smokers, and which might place chronic cocaine users at higher risk for developing atrial fibrillation (Merigian, 1993; Fenelon et al., 2003; Mehta et al., 2003).

Without more data, the significance of medial hypertrophy of blood vessels in the lungs of cocaine users is impossible to assess, especially because granulomatous changes can also be seen in the lungs of individuals who only sniff cocaine. Cellulose granulomas were identified in a patient who denied intravenous drug use and who had no occupational exposure to cellulose products (Cooper et al., 1983). Talc granulomas have been identified in two other patients (Buchanan et al., 1981; Oubeid et al., 1990).

Mycotic aneurysm formation, local cellulitis, and abscess formation have all been described, usually in conjunction with injection of the neck or groin, although the incidence is much higher in heroin than in cocaine users (Roszler et al., 1989; Henriksen et al., 1995; Raso et al., 2000; Gotway et al., 2002; Maliphant and Scott, 2005; Chan and Burnand, 2006; Coughlin and Mavor, 2006; Yegane et al., 2006).

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1.16 Neurological Disorders, Introduction

Like all other psychostimulants, cocaine inhibits dopamine transporters (DAT) located in the striatum; alterations in this region are deeply implicated in the process of addiction. The striatum is especially rich in dopamine transporters, and their blockade by cocaine leads to elevated brain dopamine concentrations, transient euphoria, and addiction (Kahlig and Galli, 2003). At the same time that dopamine re-uptake is blocked, so is the re-uptake of other catecholamines, including norepinephrine, which is critical to the function of many parts of the brain, including the prefrontal cortex, the area implicated in attention deficit disorder. In addition to blocking 5-HT re-uptake, some of the selective 5-HT re-uptake inhibitor (SSRI) antidepressants (like paroxetine) act like cocaine and prevent norepinephrine re-uptake as well. There is still debate about whether the prevention of re-uptake adds to or detracts from SSRIs' antidepressant effects, though it is beginning to appear that it detracts (Nemeroff and Owens, 2004). Finally, cocaine elevates the calcium concentration within the brain (Du et al., 2006). While this effect could be the result of raised norepinephrine concentrations, the most recent studies indicate that it is cocaine itself, and not norepinephrine, that produces the calcium elevation. Elevated brain calcium concentrations favor the occurrence of vasospasm and seizure, two disorders known to be associated with cocaine abuse.

The results of clinical studies suggest that a high percentage of cocaine abusers exhibit symptoms of paranoia and even hallucination (Brady et al., 1991). Heavy users often believe they are being watched and/or followed. This complaint is not confined to cocaine users but is also well recognized in methamphetamine abusers (Brecht et al., 2004; Urbina and Jones, 2004). Psychosis is more likely to develop in men, and appears to be dose related (Brady et al., 1991). Intravenous abusers are more prone to develop paranoia and hallucinations than nonintravenous abusers (Kaye and Darke, 2004). Cocaine abusers with psychosis become sensitized—their disease becomes more and more severe the more drug they use (Brady et al., 1991).

1.16.1 Cocaine Neurotoxicity

Within minutes of cocaine administration, there is increased expression of several different genes; *c-fos*, the transcriptional regulator, is one of the first genes to be up-regulated (Graybiel et al., 1990), followed by an increase in production of mRNA coding for tyrosine hydroxylase and tryptophan hydroxylase. These two enzymes catalyze the rate-limiting steps in the production of both dopamine and 5-HT, the neurotransmitters most obviously involved in the ability of cocaine to cause both euphoria and seizures.

Postmortem studies have shown that, in humans, the numbers of both D1 and D2 dopamine receptors are altered by cocaine use (Seeman and Van Tol, 1994). The brains of cocaine abusers contain elevated numbers of cocaine recognition sites on striatal dopamine transporters, although no such increase is seen in victims of excited delirium. Chronic cocaine abuse also produces striking decreases in the density of the D1 receptor subtype throughout the striatal reward centers, probably as a result of receptor down-regulation, which also probably explains why cocaine users quickly become tolerant to the euphoriant effects of cocaine (Staley et al., 1994; Staley and Mash, 1996). Similar changes in D1 receptor sensitivity and gene expression are also seen in experimental animals (Laurier et al., 1994).

Positron emission tomography (PET) scanning studies show that even low doses of cocaine given intravenously cause cerebral hypoperfusion. Hypoperfusion is maximal at 8 minutes and is mostly dissipated by 32 minutes after infusion. Hypoperfusion occurs throughout the brain, but the left hemispheric dopamine-rich sublobar region is the most severely affected (Johnson et al., 2005). The decrease correlates with the density of the dopamine transporters that are blocked by cocaine, and there is strong evidence that dopamine concentrations play an important part in the control of blood flow (Choi et al., 2006). Magnetic resonance imaging (MRI) studies of human volunteers have also shown that cocaine administration induces dose-related vasoconstriction, even when low doses of cocaine are given, and even in the absence of other risk factors (Kaufman et al., 1998). These changes can only make ischemic stroke more likely.

At the same time, studies with transcranial Doppler sonography, a technique that can be used to continuously measure cerebral blood flow velocity, show a significant increase in mean and systolic blood flow velocity after intravenous cocaine injection. This change lasts only for a few minutes, but it is seen even with relatively low doses of cocaine. Increases in systolic velocity in the large vessels of the brain only occur when they are constricted, demonstrating that cocaine, apparently in all users, induces a transient period of cerebral vasoconstriction (Herning et al., 1999). These study results have been confirmed by many others. The only question to be answered is whether they explain the occurrence of ischemic stroke in cocaine users, or whether other factors such as 5-HT-depleted platelets are involved (Heesch et al., 2000).

1.16.2 Psychiatric Syndromes

The early workers in the field recognized cocaine-induced paranoid psychosis. Maier, Magnan, and Lewin (Magnan and Saury, 1889; Maier, 1926; Lewin, 1931) all wrote on the subject and took pains to distinguish cocaine psychosis from symptoms induced by alcohol and other drugs. More recent studies have tended to confirm the earlier observations (Siegel, 1978; Gawin and Kleber, 1986). Transient or "binge" paranoia is common among heavy users; the incidence in one study was nearly 70% (Satel et al., 1990). What distinguishes the cocaine-associated syndrome from the schizophrenic symptoms induced by amphetamines is that the paranoia occurs only for a very brief period (Janowsky and Risch, 1979). The development of paranoia among cocaine abusers is unpredictable and is not dose related. Some individuals appear to be more vulnerable than others.

When Magnan first reported on cocaine psychosis, over 120 years ago, the three patients he described all thought they had "bugs" under the skin. All three were covered with cuts and scratch marks made in an attempt to remove the parasites. This particular paranoid manifestation came to be known as Magnan's syndrome, and for a time it was thought to be diagnostic for cocaine abuse. The syndrome is now referred to as "delusional parasitosis," and it is now obvious that these symptoms are not confined to cocaine abusers. They may occur as a component of many different organic disorders (such as parkinsonism), or as a result of drug toxicity. It has been suggested, though not proven, that the disorder is a result of decreased striatal dopamine transporter (DAT) functioning, leading to elevated concentrations of dopamine in the striatum (Huber et al. 2007).

Cerebral glucose metabolism, as accessed by (^{18}F)-fluorodeoxyglucose PET scanning of cocaine abusers in early withdrawal, increases. This increase in glucose metabolism involves all areas of the brain, but is particularly noticeable in the basal ganglia and orbitofrontal cortex. The increase in the latter two areas correlates with clinical measures of cocaine craving and is consistent with the notion that the changes are due to changes in brain dopamine activity (Volkow et al., 1990, 1991a, b).

Cocaine-induced changes in cerebral perfusion and glucose utilization appear to be gender related. Brain scans of cocaine-dependent women failed to disclose the abnormalities seen in the men (Levin et al., 1994). Longer-lasting episodes of psychosis due to chronic cocaine abuse can occur. When they do, chances are good that the victim will be misdiagnosed as a schizophrenic. Because drug users, schizophrenic or not, often deny drug use, routine drug screening of such patients is prudent (Shaner et al., 1993). Another important diagnosis to consider in cocaine users with psychiatric symptoms is stroke. Cocaine-induced ischemic infarcts have occasionally been mistaken for acute-onset psychosis (Reeves et al., 1995).

Cocaine-related impairment is frequently an issue in court proceedings, but few satisfactory answers are to be had. Regular cocaine users rapidly become tolerant to cocaine's stimulant effects, but whether or not this tolerance extends to performance and impairment is not known, though it is beginning to appear that it does (Verdejo-Garcia et al. 2006a, b). The majority of studies done in human volunteers suggest that, taken in small doses, both cocaine and methamphetamine may increase energy and alertness while, at the same time, improving mood. Both drugs can increase the ability to sustain attention over prolonged periods of time during the performance of monotonous tasks, and both drugs have also been shown to improve performance on auditory and visual reaction time tests, other tests of psychomotor skills and attention, and tests of selective and divided

attention. These findings suggest that moderate cocaine use should enhance driving performance, but that supposition has never been tested directly (Higgins et al., 1990; Farre et al., 1993; Stillman et al., 1993). Modest performance improvement on a number of cognitive performance measures has also been observed after intravenous dosing (0.325 mg or 0.650 mg/kg) (Johnson et al., 1998).

1.16.3 Ischemic Stroke

There was more than a 100-year hiatus between the first reports of cocaine-associated stroke in the 1880s and Brust's report in 1977 (Brust and Richter, 1977), but now several new case reports appear each year, some very exotic. There have been reports of mesencephalic infarcts (Rowley et al., 1989), lateral medullary syndrome and anterior spinal syndrome (Mody et al., 1988), embolization from a left atrial thrombus (Petty et al., 1990), central retinal infarction (Devenyi et al., 1988; Zeiter et al., 1992; Libman et al., 1993; Sleiman et al., 1994), massive cerebellar infarcts (Aggarwal and Byrne, 1991), and even one case of apparent embolism (Petty et al., 1990). Nonetheless, the etiology of most cocaine-associated strokes remains obscure.

During the late 1980s, cocaine-related stroke emerged as a significant medical problem, but its incidence seems to be decreasing. Most cases of ischemic stroke in young adults (15–45 years) are of undetermined etiology. In a recent retrospective study reviewing the records of patients 15–45 years old who were experiencing their first-ever stroke, the etiological diagnoses were: undetermined in 36%, large-artery atherosclerosis in 21%, cardioembolism in 17%, non-atherosclerotic vasculopathy in 17%, and other specific etiologies in 9% (Varona et al., 2007). These results are in conformity with a now decade-old retrospective study from Hong Kong that failed to find that crack use (historical or acute) had any significant association with stroke or cerebral infarction (Qureshi et al., 1997).

Whether smoking free base is more dangerous than insufflation, and what type of cerebral catastrophe is most likely to occur, is not known. The use of free base is generally accepted as a risk factor, especially when stroke occurs in the young, although no controlled study, retrospective or prospective, clinical or autopsy, has ever demonstrated any such relationship. In spite of the massive and ongoing cocaine pandemic, stroke remains a disease affecting mainly the elderly. Nonetheless, data derived from MRI scanning suggest that patients with a history of crack smoking are at risk for white matter damage mediated by unknown mechanisms (Bartzokis et al., 1999a), and cerebral flow studies do show transient hypoperfusion (Johnson et al., 2005).

More recently, MRI studies of cerebral blood vessels in human volunteers have clearly shown that cocaine administration causes dose-related vasoconstriction, even when low doses of cocaine are given and even in the absence of other risk factors (Kaufman et al., 1998). An example of cocaine-induced vasoconstriction is shown in Figure 1.16.3.2. It is not clear whether vasospasm in cocaine users is a result of some direct action exerted by cocaine on cerebral blood vessels or is secondary to catecholamine elevation (Brust and Richter, 1977; Levine et al., 1987; Covert et al., 1994).

Increased platelet responsiveness leading to thrombosis may be the etiology for cerebral infarction in some cocaine users, but the case is far from clear, and platelet responsiveness is only one aspect of the problem. *In vitro* studies have provided conflicting results (Heesch et al., 1996), with some studies suggesting increased responsiveness and others just the opposite. Whole blood from some cocaine users has been found to contain higher

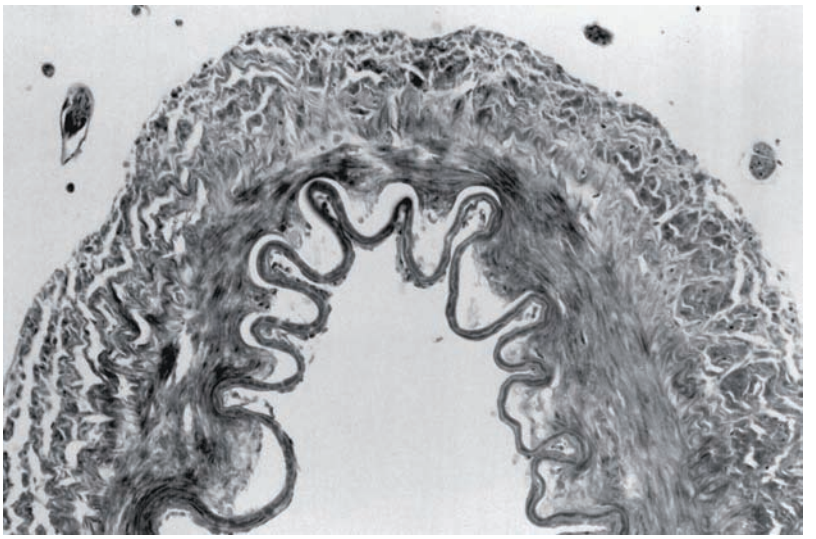

Figure 1.16.3.1 Markedly infolded, irregular internal elastic lamina in the anterior cerebral artery of cocaine with ischemic stroke. The irregularity of the elastic lamina may be a marker for cocaine-induced vasospasm. (From Konzen, J. P. et al., *Stroke,* 26, 1114–8, 1995. With permission.)

levels of activated platelets than in non-users (Rinder et al., 1994; Kosten et al., 2004) and even higher levels of tissue plasminogen activator inhibitor (Moliterno et al., 1994). Others have found variable changes in platelet aggregation after administration of cocaine to healthy volunteers (Rezkalla et al., 1990). In one of the few *in vivo* studies to evaluate hematologic parameters and blood viscosity in chronic users, transient erythrocytosis was observed, as were increases in blood viscosity and in von Willebrand factor, all changes that could favor intravascular thrombosis (Siegel et al., 2002).

Thus, cocaine users may be subject to decreased cerebral flow, even in the face of a normal cardiac output. Putting aside the issue of CNS atherosclerosis, there is no question

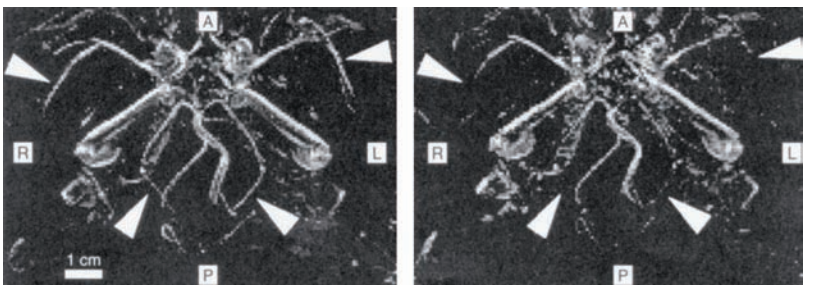

Figure 1.16.3.2 Cocaine-induced vasoconstriction. Axial maximum intensity projection images at baseline (left) and 20 minutes following intravenous cocaine (0.4 mg/kg) administration (right). Cocaine induced a signal loss at distal segments of the middle cerebral arteries (upper arrowheads) and in the posterior cerebral arteries (lower arrowheads), indicative of vasoconstriction. A indicates anterior; P, posterior; L, left; R, right. Scale bar = 1 cm. (From Kaufman, M. J. et al., *JAMA,* 279(5), 379, 1998. With permission.)

that cocaine users are subject to accelerated atherogenesis (Dressler et al., 1990; Kolodgie et al., 1991; Karch et al., 1995). If cardiac output is reduced, blood pressure fluctuations could also lead to cerebral infarction, especially in the face of pre-existing CNS atherosclerotic lesions. Cocaine-associated cardiomyopathy (Duke, 1986; Lathers et al., 1988; Williams, 1990) and arrhythmias are both recognized occurrences, and either of them could result in sudden blood pressure fluctuations. A sudden drop in blood pressure combined with asymptomatic stenotic lesions could lead to infarction. One report describes a woman with cardiomyopathy (presumably, cocaine-related) who sustained a cerebral embolism (Petty et al., 1990). The situation is somewhat analogous to cocaine-associated myocardial infarction. The presence of pre-existing lesions may exacerbate transient flow decreases which otherwise would have been asymptomatic.

Vasospasm remains another popular candidate, but vasospasm itself is a multifactorial process. It might be the result of endothelial dysfunction, smooth muscle hypersensitivity, oxidative stress, genetic susceptibility, or some combination thereof. Smooth muscle hypersensitivity is a possible explanation, since the contraction of vascular smooth muscle depends on the concentration of intracellular calcium (Somlyo and Somlyo, 1994), which is increased in the presence of cocaine (Lattanzio et al., 2005). Without further studies, the mechanism underlying stroke in this group of drug abusers remains somewhat mysterious.

1.16.4 Cerebral Vasculitis

The frequency of cerebral vasculitis in cocaine users is very low, but episodes of biopsy-proven vasculitis continue to be reported at the rate of one or two a year (Krendel et al., 1990; Fredericks et al., 1991; Scully et al., 1997; Diez-Tejedor et al., 1998; Kumar and Smith, 2000; Spittell and Spittell, 2001; Gertner and Hamlar, 2002; Ruiz Martinez et al., 2004), and authors continue to cite cocaine-induced vasculitis as a cause of stroke. Yet in virtually all of these reports microscopic proof of causation is lacking and/or multiple drugs have been ingested (Mockel et al., 1999). Autopsy reports of cocaine users with stroke are rare (Klonoff et al., 1989; Konzen et al., 1995; Nolte and Gelman, 1989), but in the few cases that have been examined histologically, vasculitis has been conspicuously absent.

In the first reported case of vasculitis, a biopsy showed that the small vessels within an area of infarction had a transmural infiltrate of acute and chronic inflammatory cells. Occasional multinucleated giant cells were also present. In the second case, there was also lymphocytic infiltration of the small vessel walls with multiple cystic, necrotic, and gliotic areas in the cerebral white matter, especially in the frontal lobes. Multinucleated giant cells were seen in the gliotic areas. The process was most intense in the frontal lobes (Figures 1.16.4.1 and 1.16.4.2) (Krendel et al., 1990). Fredericks et al. (1991) described a second case with marked endothelial swelling and small vessel lymphocytic infiltrates. In a third report, describing a 32-year-old hypertensive man who had became hemiplegic, surgical specimens disclosed no evidence of fibrinoid necrosis or giant cells, but there was vasculitis involving venules and arterioles, which were infiltrated with neutrophils, lymphocytes, and foamy macrophages. The endothelial cells were enlarged and, in addition, there was evidence of white matter damage.

In the fourth case report, a 21-year-old male cocaine user with encephalopathy, apraxia, left hemiparesis, and hemisensory loss had a cerebral angiogram that showed a lack of vascularization in the left precentral and central arterial groups. A corticomeningeal cerebral biopsy demonstrated perivascular cell collection and transmural lymphomonocytic

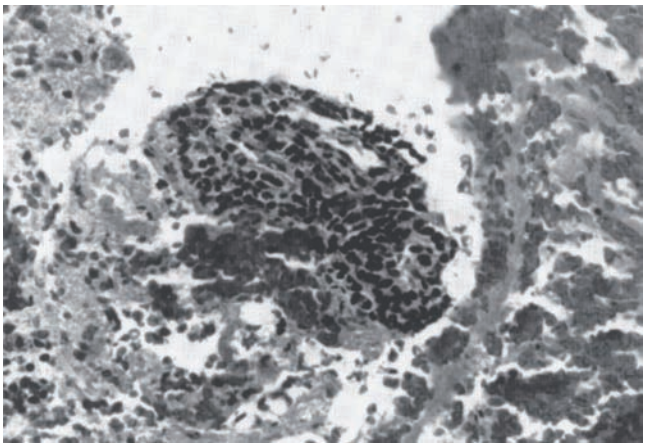

Figure 1.16.4.1 Cerebral vasculitis in a cocaine user. Biopsy specimen from patient surviving episode of vasculitis. Transmural infiltration of a small cortical vessel. Both acute and chronic inflammatory cells are present. (Original magnification 800×.) (Courtesy of Dr. David A. Krendel, Section of Neurology, The Emory Clinic, Atlanta, GA.)

infiltration of the small cortical vessels. Although the symptoms remitted with steroid therapy, the patient returned again, four years later, with severe encephalopathy. A cerebral MRI showed subcortical and periventricular lesions suggesting ischemic damage in small-sized vessel areas as well as cortical atrophy (Martinez et al., 1996).

Even when a specific effort has been made to detect vasculitis, it has been hard to find. A study published in 1996 described selected brain samples from 14 autopsy cases of cocaine-related cerebrovascular disease. Intracerebral or subarachnoid hemorrhage was present in 12 cases, but in each case the intracranial arterioles were either normal or showed only nonspecific changes (Aggarwal et al., 1996).

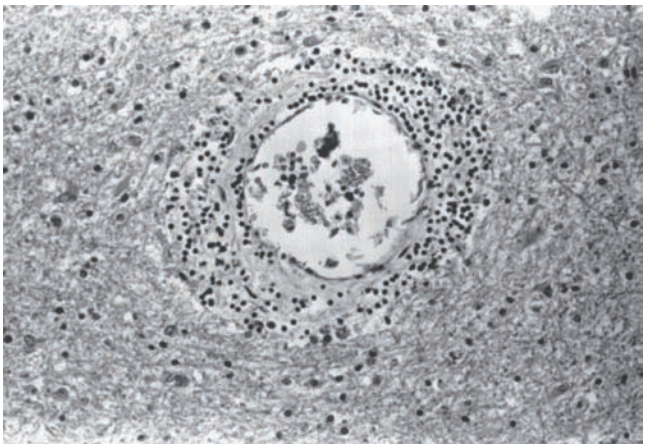

Figure 1.16.4.2 Cerebral vasculitis in a cocaine user. Autopsy specimen from another patient with cerebral vasculitis. Illustration shows a lymphocytic infiltrate around a small cerebral vessel. (Original magnification 800×.) (Courtesy of Dr. David A. Krendel, Section of Neurology, The Emory Clinic, Atlanta, GA.)

If cocaine does, in fact, cause cerebral vasculitis, it probably has nothing to do with catecholamine toxicity. Patients with pheochromocytoma and animals treated with exogenous catecholamines generally do not show signs of CNS inflammation. Small, perivascular hemorrhages can be induced in animals by giving massive amounts of epinephrine, but in this model the cerebral vessel wall remains normal, with no necrosis and no infiltrates (Stief and Tokay, 1935).

Necrotizing angiitis is a form of periarteritis nodosa associated with the abuse of amphetamine and other stimulant drugs (Citron et al., 1970; Mockel et al., 1999). It has never been seen in cocaine users, except insofar as they used cocaine along with intravenous amphetamines and heroin, and/or the user suffers from hepatitis B infection (Guo et al., 2001). Necrotizing vasculitis in stimulant abusers was first described in the early 1970s, but its incidence seems to have steadily declined over the last 30 years. The fact that this disorder has essentially disappeared, while intravenous abuse of cocaine and amphetamine has not, suggests that the originally reported cases may have been due to a contaminant introduced into the amphetamine during the course of manufacture and/or distribution. The current practice of referring to cocaine "pseudovasculitis" (Friedman and Wolfsthal, 2005; Bhinder and Majithia, 2007), applied whenever an ill patient has symptoms and/or laboratory findings that mimic true vasculitis but with a negative biopsy, is particularly unhelpful.

1.16.5 Subarachnoid and Intraventricular Hemorrhage

The relationship between cocaine and cerebral hemorrhage is much clearer than the relationship with ischemic stroke. Case reports have been appearing since the mid-1980s (Mangiardi et al., 1988). In a retrospective review of 42 cocaine abusers with stroke (mean age 38 ± 8.5 years) aneurysmal bleeding was found in 15 patients, but there were multiple risk factors and confounders and many of the victims, nearly one third, were known hypertensives (Nanda et al., 2006). Nine other cases of intracranial hemorrhages related to cocaine usage were also described in the same paper. In the most conclusive study to date, Nolte et al. (1996) performed a prospective autopsy study of all cases of fatal non-traumatic intracranial hemorrhage seen over a one-year period in a large metropolitan medical examiner's office. Ten of 17 (59%) of all non-traumatic intracranial hemorrhages were found to be associated with the presence of cocaine. Seven (70%) individuals had sustained parenchymal hemorrhages, and the remaining three (30%) subarachnoid hemorrhages from ruptured berry aneurysms. No vasculitis or other vasculopathy was identified in any of the cases. Nolte et al. concluded that the relationship between severe cocaine-induced hypertension and the development of subarachnoid or intracerebral hemorrhage "seems fairly clear and is apparently related to sudden transient increases of blood pressure related to cocaine use." Nothing published in the last decade would seem to contradict this conclusion.

Cocaine users seem to be particularly at risk for dying of subarachnoid hemorrhage. Nearly half the strokes associated with cocaine abuse are due to either intracerebral or subarachnoid hemorrhage (Nanda et al., 2006). Subarachnoid hemorrhage is more common than intracerebral hemorrhage by a ratio of 4:3. As is the case with cocaine-related infarction, individuals are in their early thirties. Most (80%) subarachnoid hemorrhages are the result of saccular aneurysms involving the anterior communicating artery, with the posterior communicating system being the next most frequent site. Intracerebral hemorrhage is most often the result of an arteriovenous malformation, although in half of the cases no

underlying lesions are demonstrable. Bleeding into the basal ganglia and thalamus is the most common pattern seen in cocaine users (Green et al., 1990; Nolte et al., 1996).

Saccular aneurysms involving the arteries at the base of the brain occur in 1–2% of the adult population and are often an incidental finding at autopsy. Usually they are located at arterial bifurcations. They form as a result of multiple factors, including atheroma, degenerative changes, and secondary flow abnormalities (Sekhar and Heros, 1981). The role of hypertension in the formation and rupture of saccular aneurysms is still unclear, but the role of hypertension in cocaine-associated subarachnoid bleeding is becoming increasingly well recognized (Kibayashi et al., 1995).

Intracerebral hemorrhage is usually due to hypertension, although in some series the number of cases due to vascular malformation roughly equals the number due to hypertension (Gras et al., 1991). Intracerebral hemorrhages occur as a consequence of structural changes in the small perforating vessels of the cerebral hemispheres and brain stem (Figures 1.16.5.1 and 1.16.5.2). They produce deeply situated hemorrhages in the cerebral hemispheres (basal nuclei and thalamus) and brain stem (Kase, 1995). Much less often, bleeding may occur in the subcortical white matter and cerebellum. Hemorrhage in the white matter is usually the result of amyloid angiopathy and probably has little to do with hypertension. The most common site for hypertensive hemorrhage is the basal ganglia, outnumbering the second most common site, the cerebral white matter, by a ratio of 7:1 (Adams et al., 1984).

In one study (Kibayashi et al., 1995), autopsy findings in 26 individuals with cocaine-induced intracerebral hemorrhage were compared with autopsy findings in 26 cases of cocaine-induced cerebral aneurysm rupture. Hypertensive cardiovascular disease was much more common in the former (mean heart weights of 497 vs. 380 g), suggesting very strongly that hypertensive cardiovascular disease, which itself can be a consequence of cocaine use, predisposes to cocaine-induced intracerebral hemorrhage. A 1997 study reviewed the findings in 33 cocaine abusers with neurologic deficits who presented at a

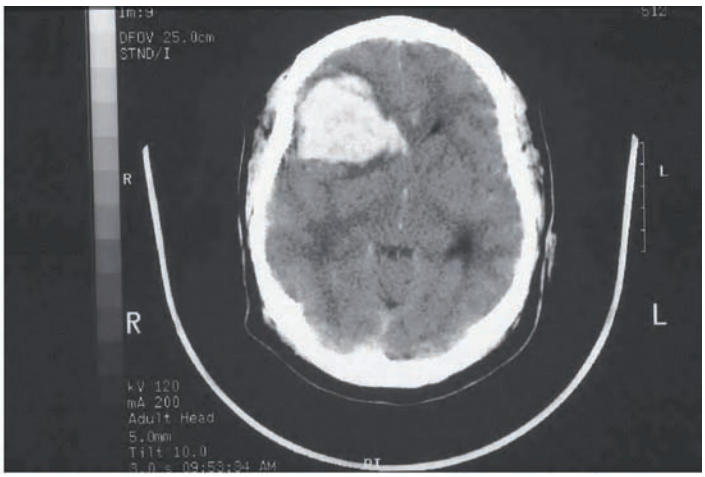

Figure 1.16.5.1 Intracerebral hemorrhage in a young "crack" cocaine smoker. Stimulant abuse is becoming an increasingly common cause of stroke in young people. Scan shows massive hemorrhage in the temporal–frontal region. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

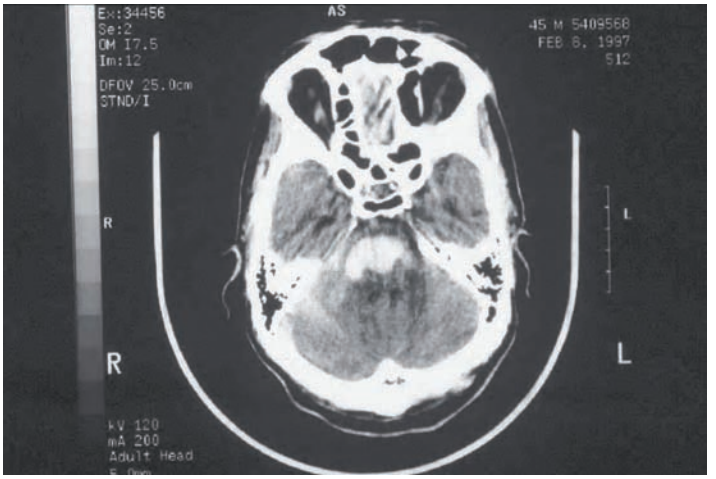

Figure 1.16.5.2 Intracerebral hemorrhage involving the brain stem of a young "crack" cocaine smoker. Brain hemorrhages in young drug abusers frequently involve pre-existing, previously undiagnosed, AV malformations and aneurysms. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

large inner-city hospital (Fessler et al., 1997). Sixteen of those patients were diagnosed with subarachnoid hemorrhage, and 12 of them subsequently underwent four-vessel cerebral arteriography, which revealed 14 aneurysms. Six patients presented with intracerebral hemorrhage and seven patients with evidence of ischemic stroke. More than half of the patients noted onset of their symptoms while they were using cocaine, and in almost all cases symptom onset was within six hours of use. Delayed onset of symptoms and delayed presentation at the emergency room seem to be more characteristic for patients with ischemic infarction. Perhaps the most interesting findings of that study were that, among the patients with aneurysm, the cocaine users were much younger than a control group of non-drug users (32.8 vs. 52.2 years) and the size of the aneurysms in the cocaine-using group was much smaller (4.9 vs. 11.0 mm).

Long-term cocaine use may be necessary before hypertensive cardiovascular disease and intracerebral hemorrhage occur, but even occasional use can lead to transient blood pressure elevations sufficient to cause the rupture of pre-existing malformations or bleeding into a tumor (Yapor and Gutierrez, 1992). Experimental evidence shows that cocaine potentiates the increases in blood pressure and cerebral blood flow produced by the administration of norepinephrine (Muir and Ellis, 1993). Because cocaine users have elevated circulating levels of norepinephrine, potentiation of the normal response to catecholamines may account for much of the reported pathology. Hemorrhage in individuals without underlying lesions, as in a recently reported case of spinal epidural hematoma (Huff, 1994), remains unexplained.

1.16.6 Seizures

Grand mal seizures in cocaine users are an uncommon occurrence, and very little is known about them (Winbery et al., 1998). The most current animal evidence shows that hippocampal norepinephrine transporters are up-regulated in the chronic presence of

cocaine. Inhibition of $Na^{(+)}$ channels by local anesthetics may also play a role in norepinephrine transporter down-regulation (all local anesthetics can induce seizures—the more potent the local anesthetic, the worse the seizures) (Kitayama et al., 2006). Other evidence suggests that it is the blockade of dopamine re-uptake and the resulting elevation of excitatory agonists that leads to cocaine-induced seizures.

Another possibility is that other neurotransmitters, especially γ-aminobutyric acid (GABA), may be involved (Ye et al., 1997). When seizures do occur, they may be a consequence of stroke, intracerebral hemorrhage, or even of massive overdose. There is also the possibility that cocaine use may simply exacerbate a pre-existing seizure disorder. Published case series have placed the incidence of this complication at somewhere between 2 and 10% (Lowenstein et al., 1987; Derlet and Albertson, 1989). In one series of nearly 1000 patients treated for acute medical complications of cocaine use, seizures were noted in nearly 10%. Only four of these patients had status epilepticus, and all of them were victims of massive overdose (Dhuna et al., 1991). Interestingly, in that same report, seizures were three times as common in women as in men (18.4 vs. 6.2%). This finding is consistent with the results of other studies suggesting that pregnancy and other hormonal alterations can exacerbate cocaine toxicity (Woods and Plessinger, 1990; Sharma et al., 1992).

"Kindling" is a term used to describe the development of generalized convulsions in response to repeated subconvulsive brain stimuli in animals, and cocaine-induced kindling can be induced in animals. Whether this process also occurs in humans as a consequence of cocaine or any other kind of drug use has been debated for some time. For example, it has been speculated, but without proof, that kindling, or some similar process, is the mechanism responsible for seizures in chronic cocaine abusers. The possibility that cocaine kindling could occur in humans is suggested by the well-described case of a 37-year-old woman who experienced generalized tonic clonic seizures immediately after smoking "crack". She then went on to develop generalized seizures even when she was not using cocaine (Dhuna et al., 1991). The latest data suggest that cocaine kindling is associated with increased NMDA receptor binding activity in the striatum, amygdala, and hippocampus (Itzhak and Martin, 2000).

Results from animal experimentation indicate that different mechanisms are responsible for seizures and lethality. Cocaine-induced seizures are a consequence of the effect of cocaine on the 5-HT transporter in concert with effects on muscarinic neurons and sigma (σ) receptors, while interactions with the dopamine transporter determine lethality (Ritz and George, 1993). It is also quite possible that other neurotransmitters such as GABA may be involved in the process. Cocaine noncompetitively inhibits GABA-generated currents in neuronal membranes, suggesting that the GABA receptor/channel complex is also a target for cocaine and may contribute to cocaine-induced seizures (Ye et al., 1997). Additional support for GABA involvement comes from experimental animal studies showing that drugs that enhance GABA-related neuronal inhibition, via mechanisms that are totally distinct from the mechanisms accounting for the effectiveness of barbiturates and benzodiazepines, offer the best protection against cocaine-induced seizures. Conversely, Na^{+} and Ca^{2+} channel blockers offer the least protection (Chynn, 1975).

The limbic system plays a major role in the process. When the effects of procaine, cocaine, and placebo were compared using single photon emission computed tomography (SPECT) to estimate regional cerebral blood flow (rCBF), the cocaine-addicted subjects demonstrated bilateral activation of the orbitofrontal cortex after the procaine challenge, whereas the comparison subjects showed activation of the anterior cingulate, bilateral

insula, and right amygdala regions. After receiving placebo, the cocaine-addicted subjects showed markedly lower rCBF in the bilateral orbitofrontal cortex than the comparison subjects. The pattern of hypoperfusion in the placebo state followed by heightened activation with procaine in the cocaine-addicted subjects bears a very strong similarity to the pattern of interictal hypoperfusion and ictal hyperperfusion that is observed in epileptics, and may represent a type of sensitization (Adinoff et al., 2001).

1.16.7 Movement Disorders

Movement disorders, including choreoathetosis, akathisia, and parkinsonism with tremor, have all been described in cocaine users (Daras et al., 1994; Bonime, 1995; Catalano et al., 1997; Riley et al., 2001; Supervia et al., 2006; Kamath and Bajaj, 2007). This phenomenon has become so common that it has even been given the slang name of "crack dancing." Symptoms are generally self-limiting and do not bring the victims to medical attention. However, one recent controlled study using MRI scanning demonstrated an increased incidence of basal ganglia abnormalities that were not seen in controls (Bartzokis et al., 1999b).

Dystonic reactions are extrapyramidal motor abnormalities that occur whenever there is an insufficient supply of nigrostriatal dopamine. The main symptom is spasm within isolated muscle groups. Neuroleptic drugs are a known cause of dystonia and are the most frequently encountered trigger, but the same symptoms can be caused by cocaine (Hegarty et al., 1991; Cardoso and Jankovic, 1993; Fines et al., 1997; Van Harten et al., 1998). Similar reasons may explain why cocaine users are also prone to multifocal tics, which cocaine precipitates (Pascual-Leone and Dhuna, 1990; Pascual-Leone et al., 1990, 1991) in addition to exacerbating the clinical manifestations of Gilles de la Tourette syndrome, and why cocaine users are at increased risk for developing neuroleptic-induced acute dystonia (Van Harten et al., 1998).

1.16.8 Blood–Brain Barrier Alterations

Aquaporin-4 (AQP4) is the predominant channel by which water enters the brain; it controls water movement at the blood–brain barrier and at the brain–cerebrospinal fluid interface. In experimental mice, deletion of the gene for AQP4 causes an increase of amino acid and monoamine levels in some brain regions, suggesting that AQP4 may participate in region-specific alterations in brain amino acid and monoamine metabolism that have been observed in experimental animals. In "knockout" mice unable to produce AQP4 there is decreased locomotor activity after acute and repeated cocaine exposure. At the same time, there is a decrease in extracellular dopamine and glutamate levels in the nucleus accumbens. The nucleus accumbens is known to be critically involved in the addictive properties of cocaine. Thus, it is speculated by some researchers that AQP4 may play a role in regulating extracellular cocaine-induced dopamine and glutamate release in the brain reward center. If that were the case, it would mean that AQP4 deletion attenuates cocaine reinforcement and dependence (Li et al., 2006).

Some believe that cocaine facilitates HIV-1 invasion through brain microvascular endothelial cells. Cocaine binds to a site on these cells that is not a transporter of biogenic amines, but, rather, is a binding site for estrogen. It also appears to act as a muscarinic receptor. Cocaine treatment of knockout mice disrupts intercellular junctions and induces cell ruffling, accounting for the observed increase in cellular permeability and

decreased electrical resistance. Once HIV-1 enters brain microvascular cells by macropinocytosis, it is transported to lysosomes and inactivated. In cocaine-treated animals, the microvascular cells allow the virus to enter and persist in large cytoplasmic "lakes." At the same time, exposure of these microvascular cells to cocaine up-regulates transcription of genes important in cytoskeleton organization, signal transduction, cell swelling, vesicular trafficking, and cell adhesion. All of these actions damage the blood–brain barrier and may lead to increased virus neuroinvasion and some, if not all, of the observed neurovascular complications of cocaine abuse (Fiala et al., 2005).

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1.17 Renal Disease

The results of some animal studies raise the possibility that cocaine is directly nephrotoxic (Barroso-Moguel et al., 1995) (Figure 1.17.1). Whether it is directly toxic or not, there is no questioning that cocaine users are subject to renal disease. The pathophysiology of cocaine-related renal injury is multifactorial, involving renal hemodynamic changes, alterations in glomerular matrix synthesis, oxidative stress, and perhaps even accelerated renal atherogenesis. Renal thrombosis occurs with some frequency (Bemanian et al., 2005) and numerous cases have been reported (Wohlman, 1987; Killam, 1993; Korzets et al., 1995; Webber et al., 1999; Volcy et al., 2000; Mochizuki et al., 2003; Edmondson et al., 2004). However, only two cases of cocaine-associated hemolytic uremic syndrome (HUS) have ever been described, and it is not clear whether they occurred as complications of cocaine use or whether cocaine was an incidental finding (Tumlin et al., 1990; Ito and Komatsu, 1993).

The most commonly reported cocaine-related renal disorder is acute tubular necrosis secondary to rhabdomyolysis. Rhabdomyolysis was recognized as a complication of both narcotic abuse (Richter et al., 1971) and stimulant abuse (Kendrick et al., 1977) long before the current wave of cocaine popularity ever began. The first case of rhabdomyolysis directly related to cocaine was described in 1987 (Merigian and Roberts, 1987), and hundreds of case reports have appeared since (Gitman and Singhal, 2004; Vets et al., 2006). In a large percentage of these cases, rhabdomyolysis was not the primary disorder; it occurred as a component of the excited delirium syndrome, where very high core temperatures and extreme physical activity combined to cause muscle breakdown.

Except for cases of excited delirium, the underlying process by which stimulant drugs produce rhabdomyolysis is poorly understood. In some cocaine-related cases, the relationship to prolonged seizure activity is clear; however, seizures are rarely reported in recreational users. In other settings, pressure-related injury seems to be the most likely explanation (Singhal and Faulkner, 1988; Singhal et al., 1989; McCann et al., 2002; Gitman and Singhal, 2004; Vets et al., 2006). Cocaine-induced vasospasm leading to myocyte necrosis has also been proposed as a mechanism (Roth et al., 1988), but this mechanism has never been reproduced in the laboratory or even described in other case reports. Accelerated renal artery arteriosclerosis, with histological changes reminiscent of those

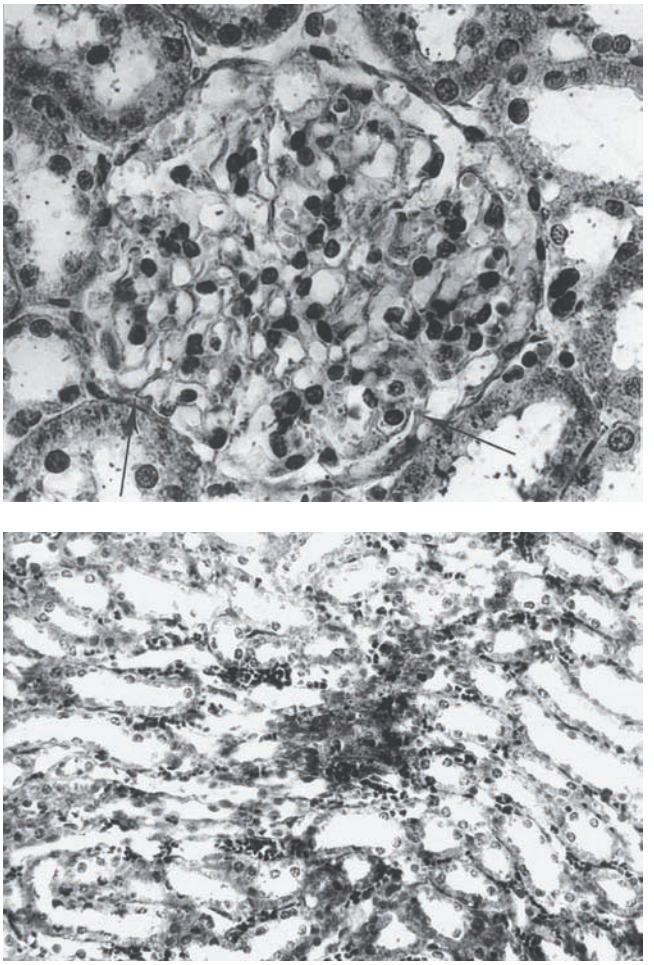

Figure 1.17.1 Glomerular and tubular lesions. In experimental models, long-term treatment with cocaine causes both glomerular and tubular lesions. These photographs are from rats sacrificed after 60 days of treatment. In the top figure, the glomerular tufts are distended and have few mesangial cells remaining. Capillary lumens are reduced, and numerous adhesions to Bowman's capsule can be seen. In the bottom figure, foci of hemorrhage and necrosis are evident in the distal tubules. (From Barroso-Moguel, R. et al., *Toxicology*, 98(1–3), 41–46, 1995. With permission.)

occasionally observed in the coronary arteries of cocaine users, has also been reported (Bacharach et al., 1992; Fogo et al., 1992; van der Woude and Waldherr, 1999), but there have been no similar reports in the last decade.

A common thread in many, but not all, cases of rhabdomyolysis is hyperthermia (Rosenberg et al., 1986; Campbell, 1988; Menashe and Gottlieb, 1988; Pogue and Nurse, 1989; Lomax and Daniel, 1990). Nonetheless, there is some evidence that cocaine may be directly toxic to skeletal muscle. In one *in vitro* study, exposure to moderate levels of cocaine caused an increased leakage of creatinine kinase from slow-twitch muscle, such as soleus, but not from fast-twitch muscle, such as extensor digitorum (Pagala et al., 1993). Given the rarity of these isolated reports, and in the absence of any obvious pressure symptoms, the explanation for most cases appears to be the syndrome of excited delirium.

Repeated exposure to electro-muscular incapacitating devices has also been proposed as a possible etiology in cocaine-associated rhabdomyolysis. Repeated Taser applications could, in theory, result in repetitive, sustained muscle contraction, with little or no muscle recovery period, especially if exposures are longer than 5 milliseconds. However, Taser application has not produced rhabdomyolysis in any plausible experimental setting.

The relationship between hyperthermia and excited delirium has been examined using meta-analysis. Data from 150 previously reported cases of cocaine-associated rhabdomyolysis were compared with data from an autopsy registry of 58 victims of fatal excited delirium and 125 other victims of fatal acute cocaine toxicity. Patients with rhabdomyolysis and fatal excited delirium were found to be similar with regard to age, sex, race, route of cocaine administration, degree of temperature elevation, absence of seizures, and presence of excited delirium. The same overlap was seen when the rhabdomyolysis patients were compared with victims of fatal acute cocaine toxicity. Because cocaine-associated rhabdomyolysis and excited delirium have similar clinical features, risk factors, and demographics, and because they can be explained by the same pathophysiologic processes (changes in dopamine metabolism), it is reasonable to conclude that both hyperthermia and excited delirium represent different stages of the same syndrome (Ruttenber et al., 1999).

The histological changes in cocaine-associated rhabdomyolysis have not been characterized. In one report of two cases, skeletal muscle was seen to be necrotic, but no signs of vasculitis were apparent, nor were any polarizable foreign bodies or other specific lesions seen, although contraction band necrosis was very prominent in some fibers (Nolte, 1991).

Cocaine-associated tubular necrosis is a multifactorial disorder. Hypovolemia, renal arterial vasoconstriction, and myoglobinuria all combine to produce the syndrome. Except for one case report (Turbat-Herrera, 1994), morphologic alterations in cocaine users have not been described. In the one case where a renal biopsy was performed, no abnormal antibody deposition or myoglobin was identified in the tubules, and the picture was otherwise typical for acute tubular necrosis, with vacuolation, fragmentation, and desquamation of the proximal lining tubular epithelial cells and pigmented casts in some distal nephrons (Turbat-Herrera, 1994).

Renal failure without rhabdomyolysis also occurs and has been reported by Tumlin et al. (1990) and Leblanc et al. (1994). In the first case, a 28-year-old woman with nausea, vomiting, and severe abdominal pain developed anuria, hemolytic anemia, and thrombocytopenia (i.e., HUS). Renal biopsy showed patchy cortical necrosis associated with the characteristic changes of thrombotic microangiopathy. Electron microscopy demonstrated extensive detachment of the endothelium from the basement membrane, with the accumulation of electron lucent material and red cell debris in the subendothelial area. However, no additional cases have been reported.

Acute renal failure in cocaine users can also be the result of microangiopathy, although such instances are very rare. One case report described a 38-year-old woman who developed hemolytic anemia, thrombocytopenia, and acute renal failure after smoking "crack" cocaine. A renal biopsy demonstrated thrombotic microangiopathy and glomerular ischemia. Whether the underlying mechanism involved direct injury to the epithelium or some as yet uncharacterized antiplatelet or procoagulant activity is not known (Volcy et al., 2000). Two cases of cocaine-induced malignant hypertension associated with morphologic features of thrombotic macroangiopathy have recently been reported. Kidney biopsies revealed thrombotic microangiopathy with fibrinoid necrosis of arterioles and

glomerular tufts (Gu and Herrera, 2007). Finally, several cases of hemolysis and thrombocytopenia mimicking thrombotic thrombocytopenic purpura have been reported in association with cocaine usage (Keung et al., 1996).

In theory, catecholamine toxicity and other well-known sequelae of cocaine use could lead to HUS or microangiopathy. After an initial endothelial injury, intravascular coagulation and all the other elements of HUS could result. This possibility is supported by the observation that not all cocaine users with hemolysis and thrombocytopenia have demonstrable histological lesions.

The focal type of glomerulosclerosis associated with heroin-related nephrotic syndrome has not been reported in cocaine or stimulant abusers, but similar lesions have been produced in rats (Barroso-Moguel et al., 1995), and the results of several *in vitro* studies suggest that cocaine use may be a risk factor for this disorder (Mattana et al., 1994). Mesangial cell expansion is generally considered to be a precursor for glomerulosclerosis and, at least *in vitro*, cocaine modulates mesangial cell proliferation via interaction with the secretory products (interleukin-6 and transforming growth factor-β) produced by macrophages after cocaine exposure. The confounding issue here is that substantial numbers of heroin users also inject themselves with cocaine (Diaz et al., 1994; Karch et al., 1998), so that when glomerulosclerosis is seen in a cocaine abuser it is impossible to tell whether the glomerular changes are due to cocaine or heroin, or both.

The presence of glomerulosclerosis in cocaine abusers should also raise the suspicion of HIV infection, as the most common renal lesion in AIDS patients is a similar sort of focal segmental glomerulosclerosis (Sanders and Marshall, 1989). Sometimes the picture becomes very confusing because cocaine users, who may be HIV positive, can present with refractory hypertension and renal failure, but only modest proteinuria and no renal shrinkage or cardiomegaly (Dunea et al., 1995). Because renal biopsies are no longer routinely performed in patients with end-stage renal disease and evidence of accelerated hypertension, the etiology in such cases may never be determined.

Cocaine-related progressive glomerulonephritis due to antiglomerular basement membrane (anti-GBM) antibodies occurs. A 1999 case report described a 35-year-old man who was an occasional intranasal cocaine user who developed acute renal failure. No evidence of rhabdomyolysis was present, but circulating anti-GBM antibodies were found and a renal biopsy showed linear IgG and C3 deposits, a sure diagnostic sign for antiglomerular basement membrane disease (Peces et al., 1999).

Cocaine has been implicated as a potential teratogen since the early 1990s when a few case reports describing congenital abnormalities of the genitourinary tract were published (Chavez et al., 1989). This relationship has never been substantiated by a controlled surgical or autopsy study. However, a prospective study using ultrasound to evaluate 100 consecutive infants exposed to cocaine *in utero* failed to find any consistent teratogenic effect (Rosenstein et al., 1990). A similar study repeated in 1995 yielded almost identical results. Renal ultrasound scans performed on 79 infants born to cocaine-using mothers demonstrated abnormalities in 11 of the babies, including one case each of horseshoe kidney, unilateral abnormal small kidney, duplex kidney, and hypospadias. Renal tract dilation was seen in several of the children. The authors of the study concluded that the risk of urogenital malformation might be slightly increased, but a much larger study would be needed to reach any conclusion (Battin et al., 1995). Such a study has never been undertaken and, indeed, it has been more than a decade since the last paper was even published on this subject.

Finally, even though cocaine use might seem a contraindication to organ donation, it is not. One-year survival rates for individuals receiving kidneys from cocaine abusers appear to be no different than rates for drug-free donors (Leikin et al., 1994). Donor hearts from cocaine abusers are similarly unaffected, with survival rates comparable to those for drug-free donors (Freimark et al., 1994; Caballero et al., 2003).

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1.18 Hematologic Abnormalities

1.18.1 Thrombocytopenic Purpura

Thrombocytopenic purpura seems to have a weak association with cocaine use. One study (Koury, 1990) described seven HIV-seronegative intravenous cocaine abusers with extensive cutaneous petechiae, ecchymoses, and heme-positive stools. The patients all had normal bone marrows or, at most, increased numbers of megakaryocytes. Platelet counts in each of the individuals all improved promptly after steroid administration. No other etiology for their condition could be identified. A handful of other cases have been reported (Savona et al., 1985; Gallup et al., 1991; Klein et al., 1991; McDonough and Nolte, 1991; Freimark et al., 1994; Valenza et al., 1995; Freimark et al., 1996; Keung et al., 1996; Takkenberg et al., 1997; Inbal et al., 1999; Volcy et al., 2000; Caballero et al., 2003; Alcazar-Guijo et al., 2005; Burke et al., 2005). As with many of the other cocaine-associated syndromes, possible etiologies include toxic contaminants or metabolites, as well as immune reactions to the cocaine itself. There are many other ways cocaine could affect platelet function. The most obvious is cocaine-related catecholamine excess. Circulating catecholamines are elevated in cocaine users, and elevated catecholamine levels can alter α and β receptors located on circulating lymphocytes and platelets (Maki et al., 1990). Perhaps more important, 5-HT uptake by platelets is one of the body's homeostasis mechanisms, and cocaine disrupts the process.

In vitro studies suggest another possible explanation. There is evidence that platelets contain the very same dopamine transporter found in the brain. Microarray and PCR data from pooled human blood platelets express a dopamine transporter protein (DAT), identical to a type of DAT that was first identified in neurons, which surely would have an effect on clotting (Frankhauser et al., 2006). There is also a real possibility that genetic polymorphisms, particularly in the 5-HT transporter, may also play a role (Patkar et al., 2004). Drug interaction is another factor that must be considered, particularly in polydrug abusers. Testosterone, at subphysiologic concentrations, is capable of potentiating cocaine's effect on endothelial and platelet functions; concomitant use of testosterone and cocaine could result in enhancement of the thrombotic risk ascribed to both drugs (Togna et al., 2003).

1.18.2 Thrombosis

In vitro, cocaine increases thromboxane generation; however, the consequences of this fact have not been clinically confirmed (Togna et al., 1985, 1996). Studies of platelet and clotting mechanisms in cocaine users have yielded what can only be described as conflicting results (Cook and Randall, 1996), but *in vitro* studies of platelet behavior cannot always be

relied upon to give a valid picture of what actually happens in humans. In the pig model, the administration of cocaine increases the reactivity of platelets exposed to cardiac subendothelium, a result that suggests that, in pigs at least, cocaine has a prothrombotic effect by virtue of its ability to facilitate the interaction of platelets with damaged arteries (Zurbano et al., 1997).

1.18.3 Erythrocytosis

In a 1999 study, changes in hemoglobin concentration, hematocrit, and red blood cell counts were measured in a group of chronic cocaine users, both before and after cocaine administration. Hemostatic parameters, including von Willebrand factor, fibrinolytic activity, fibrinogen, plasminogen activator inhibitor antigen, and tissue-type plasminogen activator antigen, were also measured. Hemoglobin levels, hematocrit, and red blood cell counts all increased significantly within 30 minutes or less after the cocaine had been given. At the same time, there was no change in white blood cell or platelet counts, but concentrations of von Willebrand factor increased by 40% over baseline levels. Thus, it is apparent that cocaine induces a transient erythrocytosis that may increase blood viscosity and concentrations of von Willebrand factor (Siegel et al., 1999). In a separate study of 79 consecutive chest pain patients presenting at an emergency room for treatment, hemoglobin and hematocrit levels were significantly elevated in the cocaine-using subjects compared with controls, but there was no corresponding elevation in reticulocyte count. Multivariate logistic regression revealed that male chest pain patients were significantly more likely to be exposed to cocaine than females ($p = 0.001$), and that all of the relative increases in hemoglobin concentration in the cocaine-exposed group were attributable to gender. Cocaine exposure was not significantly associated with reticulocyte count (Weber et al., 2003).

An epidemiologic survey of patients with myocardial infarction (Determinants of Myocardial Infarction Onset Study, DMIOS) showed that, among the subset of patients who were cocaine users, the risk for onset of myocardial infarction was elevated 23.7 times over baseline (95% CI, 8.5 to 66.3) in the 60 minutes after cocaine ingestion, but within the first hour the risk rapidly returned to that of the general population (Mittleman et al., 1999). Because the observed hematologic changes seem to precisely match the timing of the transient increases in von Willebrand factor, platelet aggregability, and the risk for acute myocardial infarct, it is tempting to suppose that all of these events are related.

1.18.4 Methemoglobinemia

Another hematologic abnormality associated with cocaine use, at least indirectly, is methemoglobinemia. Street-level cocaine is occasionally diluted with benzocaine or other related local anesthetics, and oxidation of ferrous (Fe_2) hemoglobin to the ferric (Fe_3) state is a well-recognized complication of benzocaine administration. One case report described a 27-year-old man with a massive overdose who developed classic methemoglobinemia. Blood cocaine levels were not measured; however, urine cocaine levels were 106 mg/L, while benzocaine levels were 3.8 mg/L (Tada et al., 1987; McKinney et al., 1992). Cocaine itself has never been implicated as a cause of this disorder, and additional reports of this complication are lacking.

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1.19 Hormonal Alterations

1.19.1 Overview

Both opiates and cocaine exert effects on adrenal and gonadal function. Opiates suppress the hypothalamic–pituitary–adrenal (HPA) axis, but cocaine use leads to HPA activation. During withdrawal from either opiates or cocaine, the HPA axis is also activated and it is speculated that reactivation of the HPA may reinforce relapse behavior (Brown et al., 2006). Cocaine-and-amphetamine-regulated transcript (CART) is a neuropeptide, but it also acts as neurotransmitter. It is a potent anorexigen and can be found in most parts of the body. It is also expressed in pituitary endocrine cells, adrenomedullary cells, islet somatostatin cells, and in rat antral gastrin cells. CART is regulated by leptin. CART is an object of interest to addiction professionals because fasting animals show a pronounced decrease in CART mRNA expression within the arcuate nucleus, the same brain nucleus deeply involved in the process of cocaine addiction (Dun et al., 2006; Fekete and Lechan, 2006). However, there is no known connection between CART production and addiction, though CART production is clearly involved in feeding behavior.

Men and women respond differently to cocaine. Even though cocaine is classically thought of as a re-uptake inhibitor exerting its effects on tissue and organs that respond to norepinephrine and 5-HT, it also acts on the endocrine system. In many ways, cocaine's effects resemble the effects exerted by monoamine oxidase inhibitors. In particular, acute cocaine administration stimulates the release of gonadotropins, adenocorticotropic hormone (ACTH), and cortisol or corticosterone, while at the same time it suppresses prolactin concentrations (Mello and Mendelson, 1997).

1.19.2 Prolactin

Prolactin is episodically secreted by the hypothalamus. During sleep, the amplitude of the secretory pulses increases. Unlike other pituitary hormones, hypothalamic secretion of prolactin is under tonic inhibition by dopamine and possibly by GABA. Release of prolactin is favored by increasing concentrations of thyroid-releasing hormone, vasoactive

intestinal polypeptide, and 5-HT (Molitch, 1992; Van de Kar et al., 1996). Initially, it had been thought that acute administration of cocaine produced a drop in prolactin levels, followed later by rebound hyperprolactinemia (Mello et al., 1990; Teoh et al., 1990). However, the most recent studies suggest that, in humans, intranasal cocaine increases plasma cortisol but not prolactin, and there is no evidence that tolerance changes the situation at all. The explanation is thought to be in some way related to concomitant increases in plasma 5-HT concentrations (Ghitza et al., 2007).

Even if changes in prolactin concentration do occur, they may not be of very great clinical significance. Under normal circumstances, the main function of prolactin is to stimulate postpartum lactation. It does not appear to play any other role in normal gonadal function, even though prolactin secretion can be altered in different physiologic states. Many drugs, especially dopamine antagonists, are notorious for causing changes in prolactin secretion. Nonetheless, measuring changes in prolactin levels could be of some clinical value. Markedly depressed levels are a good confirmation of recent drug use. High levels, which have been noted in detoxification patients, are consistent with withdrawal.

1.19.3 Sex Hormones

Effects on other human hormonal systems have been difficult to demonstrate, mainly because cocaine users also use alcohol and other drugs that alter hormone production. However, experimental studies have consistently shown neuroendocrine function is altered in rats and rhesus monkeys, with disruptions of the estrous cycle in rats and the menstrual cycle in rhesus monkeys. These changes appear to mimic those that have been observed in human female cocaine abusers (Mello et al., 1997). Animal studies also show that cocaine causes increases in progesterone production and increases in plasma concentrations of progesterone. Because progesterone is a precursor of cortisol/corticosterone, and because dopamine agonists and antagonists affect progesterone secretion by the adrenal glands, cocaine may alter progesterone secretion via activation of the hypothalamus. Alternatively, cocaine may cause rapid non-genomic alterations such as the modulation of extracellular monoamines and opioids (Becker, 1999).

It appears that gonadal hormones and cocaine may interact via the production of new proteins through transcriptional factors. For example, cocaine may induce steroid DNA-binding regulated transcription, which in turn may produce changes in expression of early genes that have been recognized for many years (e.g., *c-fos* and dynorphin). There is also evidence that cocaine may affect late genes (e.g., opioid and monoamine receptors) and even produce long-lasting adaptive changes within the organism, though these data are only just beginning to accumulate (Quinones-Jenab, 2006).

Drug abuse and HIV infection alter the production of female sex hormones. Luteinizing hormone levels are significantly higher in women with low CD4 cell counts, and current methadone use is associated with lower levels of total testosterone ($p = 0.03$) and higher levels of prolactin ($p = 0.002$). Mean estradiol levels are 43% lower in women using intravenous drugs than in those who do not ($p < 0.001$). There is, at present, no explanation why female alcoholics and "crack" smokers seem to have normal concentrations of sex hormones (Cofrancesco et al., 2006).

The explanation why there are so many more men than women drug abusers with cardiovascular disease may also have its basis in hormonal differences. Female sex hormones,

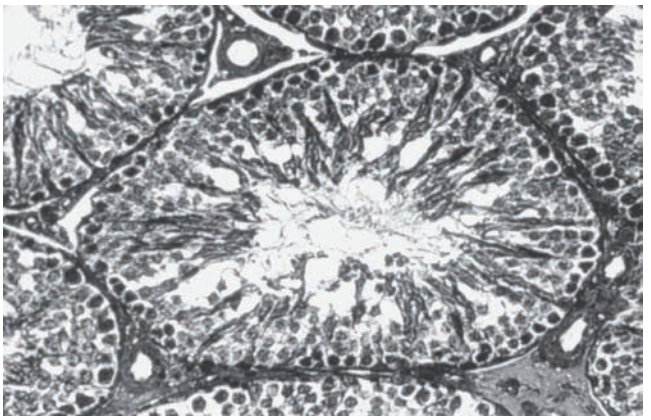

Figure 1.19.3.1 Testicular atrophy in chronic drug abusers is generally attributed to lifestyle and dietary deficiency. However, rats chronically exposed to moderate doses of cocaine undergo Leydig cell degeneration. Whether this is also true for humans is not known. (From Barroso-Moguel, R. et al., *J. Appl. Toxicol.,* 14(1), 37-41, 1994. With permission.)

even when present in normal concentrations, cause decreased ET-1 release, whereas testosterone increases endothelin production. In addition to classic steroid hormone receptors, σ_1/cocaine receptors also mediate the effects of female sex hormones on ET-1 release (Wilbert-Lampen et al., 2005).

Testosterone levels in chronic cocaine abusers have not been systematically characterized, and laboratory studies on gonadal uptake have produced conflicting results. However, there is real concern that combining cocaine with supplemental testosterone (as body builders may do), places them at increased risk for thrombosis—greater than the risk conferred by the single use of either agent (Togna et al., 2003).

Mice testes avidly bind labeled cocaine (Yazigi and Polakoski, 1992) but rat testes do not show high levels of cocaine uptake (Som et al., 1994). Even so, chronic cocaine administration, at least in rats, produces testicular lesions (Figure 1.19.3.1), which result in decreased testosterone production and depressed spermatogenesis (Barroso-Moguel et al., 1994). Depressed sperm production may be the result of cocaine-induced apoptosis, a process that has been demonstrated in rat testes, but not in humans. On the other hand, human sperm have multiple receptor sites for cocaine that very likely affect the substantial transfer of cocaine to any fertilized egg (Klemmt and Scialli, 2005).

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1.20 Immune System Abnormalities

1.20.1 Overview

Chronic cocaine use alters the immune response, but the exact mechanism in humans is not understood. There is some evidence that the control of cytokine production by σ receptors plays an important role. Sigma receptors are found in neuronal tissues (and some tumors) and they interact with many different kinds of drugs, including cocaine, dextromethorphan and benzomorphans (Wang and deHaseth, 2003). Based upon their physiologic and pharmacologic actions, two subtypes of σ receptors are recognized—σ_1 and σ_2.

Drugs that bind to σ receptors have important regulatory effects on cytokine production, including the induction of IL-10 and other cytokines that suppress the immune response. In animals, σ ligands prevent graft-versus-host disease and they also prevent delayed-type hypersensitivity granuloma formation (Carayon et al.. 1995). Cocaine is a σ_1 receptor ligand. It down-regulates the production of interferon (IFN) by human peripheral blood leukocytes and increases the production of transforming growth factor (TGF) by

endothelial cells and macrophages (Mattana et al., 1994). Alveolar macrophages collected from "crack" smokers have decreased antimicrobial activity when compared to similar cells from nonsmokers (Baldwin et al., 1997). Cocaine also enhances HIV-1 replication in stimulated peripheral blood mononuclear cells, and the process is known to involve TGF (Peterson et al., 1991). Acting via the σ_1 receptor pathway, cocaine has the ability to alter the balance of T helper type 1 (Th1) and type 2 (Th2) cytokines, which should mean, based on many animal studies at least, that cocaine suppresses anti-tumor immune activity (Gardner et al., 2004), but how and to what extent is debatable.

1.20.2 Immune Responses

The results of animal studies suggest that Th1-type lymphokines are central to the causation of organ-specific autoimmune diseases, such as experimental allergic encephalomyelitis or insulin-dependent diabetes mellitus. The same process appears to happen in man.

Th2-cell predominance is found in the skin of patients with chronic graft-versus-host disease, progressive systemic sclerosis, systemic lupus erythematosus, and allergic diseases. Both types of response are required for normal immune function, and a balance between the two is required; otherwise, protective responses are converted to pathologic ones (Singh et al., 1999). Cocaine enhances Th1-type immune responses and inhibits Th2-type responses, which is why it poses such a threat to the immune system (Gan et al., 1998).

Of major concern is the close link between cocaine use and HIV infection, and evidence for a connection continues to accumulate. When microglial cells are treated with cocaine the result is a concentration-dependent increase in viral expression (Gekker et al., 2006). Other evidence suggests that cocaine facilitates HIV-1 invasion through the brain's microvascular endothelial cells. Cocaine binds to these cells at the same sites where estrogens have their greatest affinity. HIV-1 enters the endothelial cells by macropinocytosis and is transported to lysosomes, where the virus is normally inactivated. But HIV viruses are not inactivated in endothelial cells that have been treated with cocaine. In addition, cocaine causes these same cells to up-regulate transcription of genes important in cytoskeleton organization, signal transduction, cell swelling, vesicular trafficking, and even cell adhesion. Thus, the balance of evidence suggests that cocaine enhances the risk of HIV-1 invasion by disrupting the blood–brain barrier (Fiala et al., 2005).

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1.21 Gastrointestinal Disorders

1.21.1 Introduction

Most of the gastrointestinal disorders associated with cocaine are due to its catecholamine-mediated effects on blood vessels. However, cocaine metabolites, and possibly even cocaine itself, may be directly toxic to the liver. Norcocaine is hepatotoxic in experimental animals, and so is cocaethylene, and both are synthesized by the human liver in the presence of ethanol. The overall toxicity of cocaethylene seems to be quite similar to that of cocaine itself. In spite of convincing animal studies, there is no evidence that cocaine use causes any significant damage to the humans liver, and when liver disease is observed, it can be presumed to be the result of lifestyle disease (hepatitis, HIV, or polydrug abuse). The other disorder seen with some frequency in the gastrointestinal tracts of cocaine users is an unintended side effect of the smuggling process: smugglers with intestines full of cocaine or other illicit drugs.

1.21.2 "Body Packing"

The practice of "body packing" has increased drastically in the last 20 years, and complications are ever more common. Most of these cases are managed with laxatives or bowel irrigation, but surgery is occasionally required, either because of drug toxicity and/or small bowel obstruction. If clinically indicated, drug-containing packets can be retrieved using a combination of milking and multiple enterotomies, but this generally leads to a high rate (40%) of postoperative wound infection (Khan, 2005; Silverberg et al., 2006).

1.21.3 Ischemic Bowel and Stomach Injuries

Ischemic colitis due to cocaine abuse is a well-recognized entity (Fishel et al., 1985). It was first described in 1985 (Nalbandian, 1985) and reports have been published regularly ever since (Mizrahi et al., 1988; Wattoo and Osundeko, 1999; Osorio et al., 2000; Herskowitz et al., 2002; Comay et al., 2003; Sanders and Dalsing, 2003). The disease process tends to involve the proximal colon (Ellis and McAlexander, 2005). Cocaine-associated enterocolitis usually presents within three days of cocaine use. The majority of patients will recover with nonoperative therapy; however, those who do develop peritonitis and undergo laparotomy have a 50% mortality (Ellis and McAlexander, 2005). Microscopic examination

of ischemic bowel removed from cocaine users will demonstrate findings consistent with pseudomembranous colitis, with some areas of the bowel resembling acute ischemic colitis more closely than others. Otherwise there are no distinctive features.

In the largest series published to date, which was comprised of seven patients, endoscopy revealed lesions restricted to the left colon, including hemorrhagic edema of the mucosa, pseudopolyps, and ulcerations. Rectal involvement, which is not generally considered a feature of ischemic colitis, was seen in five patients. The histologic changes were classified as acute/subacute in two of the five patients and as subacute/chronic in the other three (Niazi et al., 1997). Given that genital cocaine application is not uncommon, it could be that the rectal involvement noted in two of the cases had as much to do with sex practices as with drug-induced ischemia.

Perforation from any cause is said to occur in seven to 10 patients per 100,000 population annually, and is thought to be a complication in 5–10% of peptic ulcers. "Crack"-related gastroduodenal perforations are typically prepyloric and usually presumed to be ischemic, though motility disorders, increased air swallowing, platelet-related thrombosis, and increased ACTH and corticosterone secretion could all play a role (Yahchouchy et al., 2002). The incidence of this complication is thought to be rising, but there is no real documentation. A report from one inner-city hospital, published in 1999, described 50 consecutive patients with juxtapyloric perforations related to "crack" smoking over a four-year period. All but two of the patients were men, with a mean age of 37 years. However, in addition to being "crack" smokers, every one of the patients also had a history of chronic alcohol abuse (Feliciano et al., 1999).

During the beginning of the "crack" pandemic it was thought that maternal cocaine use might, in some way, be related to necrotizing enterocolitis in the neonates (Czyrko et al., 1991; Downing et al., 1991), but the last report was more than five years ago. The etiology of necrotizing enterocolitis is not known, and cocaine abuse is certainly not the only factor thought to be related to its occurrence (Downing et al., 1991). Millions of pregnant women have taken cocaine in the last 15 years, but the only reported cases are from the early 1990s, when cocaine use was highly publicized. It seems likely that cocaine is simply an incidental finding in these cases. In 1998, Myles performed a multivariate analysis of possible cases and found that this disorder had no associations with use of tobacco, alcohol, other drugs of abuse, respiratory distress syndrome, or intraventricular hemorrhage.

When bowel obstruction and ischemia occur in cocaine users, the pathologic findings are similar to those seen in patients with pheochromocytoma (Bravo and Gifford, 1993). In fact, catecholamine-mediated gastrointestinal lesions have been recognized since the 1930s, when treatment of asthmatics with nebulized epinephrine came into fashion. Treatment was occasionally complicated by tracheal hemorrhages and ulceration of the gastrointestinal mucosa (Galgaini et al., 1939).

Szakacs et al. (1959) systematically studied the effects of chronic catecholamine administration in experimental animals and humans. They observed that fibrinoid degeneration and necrosis could be seen in the arteriolar walls of vessels, both in the heart and the gastrointestinal tract. Prolonged norepinephrine infusion induced endothelial proliferation, occasionally sufficient to cause complete obstruction of small arteries of the gastrointestinal tract, leading to infarction and perforation of the bowel (Szakacs et al., 1959). Similar lesions are observed in experimental animals and in patients with pheochromocytoma. More than 40 years after Szakacs first presented his observations, precisely the same lesion has been identified in cocaine users (Garfia et al., 1990). Thrombotic lesions have also been

described, presumably caused by the same sequence of events that leads to thrombosis in the heart and other blood vessels (Ottolini and Foster, 1994). The bowel is not the only part of the gastrointestinal tract subject to ischemic injury. There is at least one report of spontaneous hepatic rupture in a pregnant cocaine user, presumably a result of the same mechanism responsible for ischemic gut injury (Moen et al., 1993).

1.21.4 Hepatic Disease

Most of cocaine's toxic effects, real or feared, are cardiovascular or neural. Hepatotoxicity has been repeatedly demonstrated in man and animals (Marks and Chapple, 1967; Perino et al., 1987; Kanel et al., 1990; Wanless et al., 1990), but the recent decrease in the number of reports raises the question of whether the frequency of this disorder has not been exaggerated. Alternatively, it may well be that the "crack" production process removes potential hepatic toxins.

Apart from contamination by toxins, another process that causes hepatotoxicity is the formation of reactive oxygen species. These are generated by cytochrome P-450 and flavin adenine dinucleotide (FAD) containing monooxygenase (Boelsterli et al., 1993). *N*-demethylation to norcocaine (which is only formed in small amounts by humans) leads to the formation of *N*-hydroxynorcocaine and norcocaine nitroxide (Bornheim, 1998). It has been proposed, though hardly proven, that redox cycling between the oxidation of *N*-hydroxynorcocaine to norcocaine nitroxide ultimately leads to membrane damage and cell death (Bornheim, 1998). Cells are protected from the damaging effects of free radical oxygen by superoxide desmutase conversion to peroxide.

Oxidative cocaine metabolism plays a very minor role in humans, and in most controlled human studies the amount of norcocaine formed has been found to be quite small. In a recently published study of 18 healthy volunteers given a 150 mg/70 kg dose of subcutaneous cocaine, concentrations of the cocaine and its major metabolites were in the hundreds of ng/mL, while that of norcocaine (and all of the other minor metabolites) was less than 18 ng/mL (Kolbrich et al., 2006).

In the one clinical study where there was simultaneous measurement of cocaine and its metabolites in living patients, only very low concentrations of norcocaine were detected in most individuals. Some of the patients in the study had consumed more than 3 g of cocaine before seeking emergency medical treatment. In 46 of these "crack" smokers, the mean norcocaine concentration was 40 ± 3 ng/mL compared to BZE concentrations that were more than 33 times higher (1400 ± 40 ng/mL) (Blaho et al., 2000). However, in some individuals, for reasons that still remain entirely obscure, norcocaine concentrations in the 400- to 500-ng/mL range were observed, indicating that, under appropriate circumstances, humans are capable of oxidative cocaine metabolism. The fact that this ability is limited to a small percentage of cocaine users suggests the presence of a genetic link, possibly a CYP polymorphism.

Animals, however, convert significant amounts of cocaine to norcocaine. Further enzymatic breakdown yields *N*-hydroxynorcocaine and norcocaine nitroxide (Shuster et al., 1977). Norcocaine nitroxide, once thought to be a highly reactive free radical, is now known to be stable. It does not react with either proteins or glutathione (Rauckman et al., 1982). However, further oxidation to the norcocaine nitrosodium ion yields a compound that is highly reactive with glutathione (Ndikum-Moffor et al., 1998). This reaction has the potential to cause hepatotoxicity because it ultimately leads to a reduction in body glutathione stores. In the absence of glutathione, lipid peroxidation goes unopposed, allowing

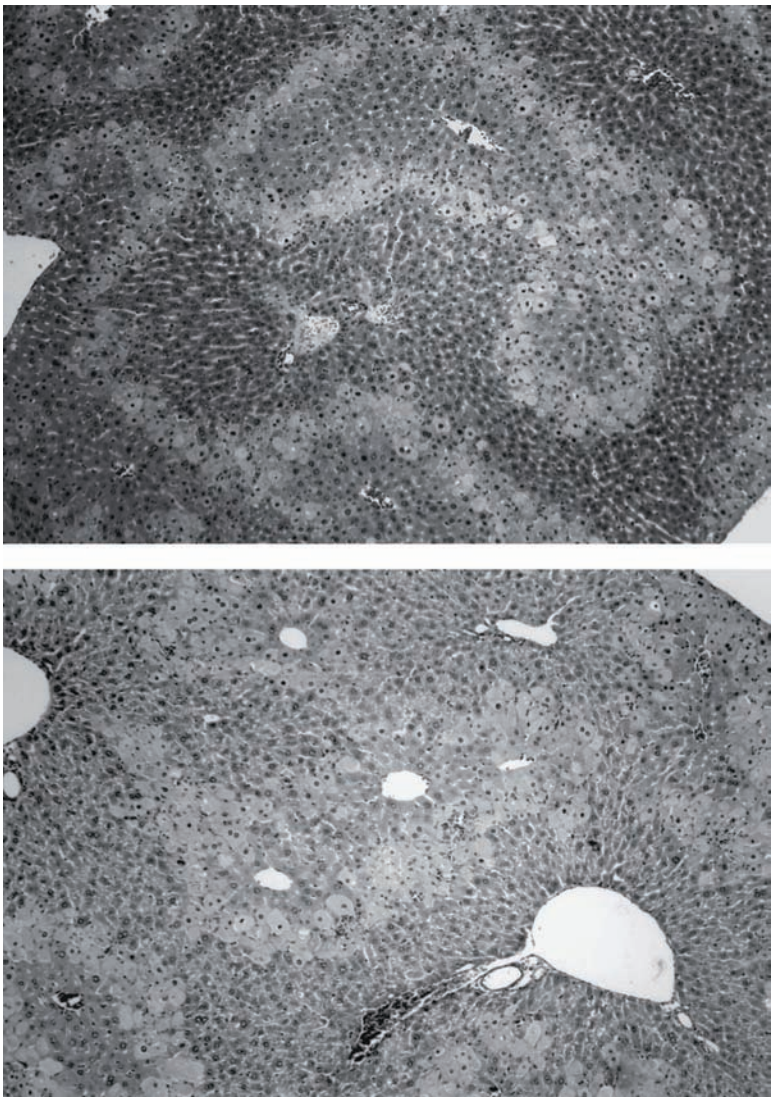

Figure 1.21.4.1 Effects of cocaine and cocaethylene on the rat liver. The upper microphotograph is from a rat treated with cocaine; the lower one is from a rat treated with cocaethylene. The patterns of injury are the same. (Courtesy of Stephen M. Roberts, Center for Environmental and Human Toxicology, University of Florida, Gainesville.)

norcocaine and other minor cocaine metabolites to damage hepatic proteins and destroy hepatocytes and eventually leads to cell death (Ndikum-Moffor et al., 1998).

When hepatic toxicity occurs in humans it is usually just manifested as enzyme elevation. When fatal cases occur they usually involve polydrug abusers, but the pattern of damage seems to vary from report to report, probably because different combinations of drugs are being used. One case report describes zone 1 necrosis with periportal necrosis and sparing of the centrozonal hepatocytes (Perino et al., 1987). Another report describes fulminant liver failure in a 24-year-old cocaine user (no other drugs detected) with coagulative-type perivenular and midzonal necrosis, as well as periportal microvesicular fatty

change (Kanel et al., 1990). In a series of four patients, two had well-demarcated zone 3 necrosis identical to that seen in acetaminophen poisoning (Wanless et al., 1990). Most cytochrome P-450 activity is located in zone 3 of the liver, so it is not surprising to find that acetaminophen and cocaine would cause a similar pattern of injury. Because humans use multiple drugs, and these drugs can induce, or block, the P-450 system (Bornheim, 1998), different patterns of injury may be the result. In spite of these suggestive case reports, at least two separate autopsy studies of cocaine-related deaths found that, except for a tendency to steatosis, the livers of the cocaine users are no more likely to show evidence of damage than controls (Copeland, 1989; Karch et al., 1998). There are still no case reports or controlled clinical series suggesting that liver disease is a regular occurrence among cocaine abusers.

It has also been suggested that hepatic injury could be secondary to cocaethylene production. This compound is produced in the liver by transesterification of cocaine, but only in the presence of large amounts of ethanol (Kanel et al., 1990). In animal experiments, cocaethylene is nearly as toxic as cocaine itself and, when experimental animals are simultaneously treated with ethanol and cocaine, tissue necrosis, presumably secondary to lipid peroxidation, is much worse than when the animals are treated with cocaine alone (Figure 1.21.4.1) (Odeleye et al., 1993). Cocaethylene given to mice produces dose-dependent hepatic zone 2 (midlobular) necrosis. Pretreatment with P-450 inducers makes the necrosis worse and shifts the zone of necrosis to zone 1 in the periphery. Treatment with inhibitors, such as cimetidine, reduces toxicity. This is essentially the same pattern seen in mice given cocaine, suggesting that both cocaine and cocaethylene share common mechanisms of toxicity (Roberts et al., 1992; Roth et al., 1992). Nonetheless, cocaethylene liver damage in humans has never been reported, even in autopsy studies where its occurrence was specifically sought (Karch et al., 1999).

There is some evidence that cocaine may interact with ketamine to cause illness, at least in experimental animals. Animal studies have shown that pretreatment of mice with ketamine (100 mg/kg) produced a 76-fold increase in serum alanine aminotransferase activity level and a 260-fold rise in those mice pretreated with 80 mg/kg ketamine for 4 days. This strongly suggests that ketamine can induce multiple forms of P-450 in rat liver microsomes, thereby increasing CCl_4-induced liver toxicity and cocaine-mediated acute toxicity. The observation is particularly worrying because young people in the "club" setting often combine the two drugs (Rimsza and Moses, 2005; Halkitis et al., 2007). In experimental mice, cocaine, given alone, caused focal inflammatory cell infiltrates, but when the cocaine was given after ketamine pretreatment there was sub-massive hepatic necrosis, apparently because of glutathione depletion. Still, human case reports of toxicity are lacking.

There are rare anecdotal case reports of hepatic amyloidosis in cocaine and other polydrug abusers, but it is not clear that cocaine is responsible. A report published in 1993 described clinical findings in four liver biopsies and 12 autopsies of individuals who had developed chronic suppurative skin ulcers as a consequence of both intravenous and subcutaneous cocaine and heroin use. Nearly one third (five of 16 patients) also had AIDS at autopsy. The diagnosis was made antemortem in only one third of the cases. The amyloid protein was found to be type AA in 14, and type AL in one case. None of the individuals had multiple myeloma or plasma cell dyscrasias. Amyloid distribution in the liver was both parenchymal and vascular. The histological pattern of amyloid distribution within the liver did not predict the type of amyloid protein that was identified (Osick et al., 1993). There have been no additional reports since the original index report was published, although

one case report was published in 1995 describing another subcutaneous cocaine injector who developed renal amyloid (Tan et al., 1995).

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1.22 Pregnancy Interactions

Early surveys of maternal cocaine abuse were based largely on the results of urine-testing programs, and these tended to understate the extent of use; cutoff concentrations built into commercial workplace urine screening systems were set far too high to detect many cases. In the early 1990s, studies utilizing meconium and hair testing yielded results suggesting that prevalence rates for cocaine use at inner-city hospitals were in the 12–20% range (Forman et al., 1992). The findings of more recent studies tend to suggest that the real prevalence of exposure is much lower. In a pilot study to determine the local prevalence of maternal drug misuse, cocaine was detected in the meconium of 2.75% of 400 infants tested (Williamson et al., 2006). In a similar, but much larger study from Spain, the rate was only 1.8% (Pichini et al., 2005).

Newborns exposed to drugs *in utero* can suffer from a varying degree of transient, usually benign, withdrawal syndrome a few days after birth. Cocaine and the other stimulants seem to present little problem, but mothers addicted to opiates often deliver children who undergo full-blown withdrawal syndrome (Lachenmeier et al., 2006).

Data derived from a population-based adverse pregnancy outcome registry (Hawaii, 1986–2002) indicate that the prenatal use rate for cocaine use was 0.18% and that it was associated with an increased risk for birth defects, primarily those associated with the central nervous system, cardiovascular system, oral clefts, and limbs (Forrester and

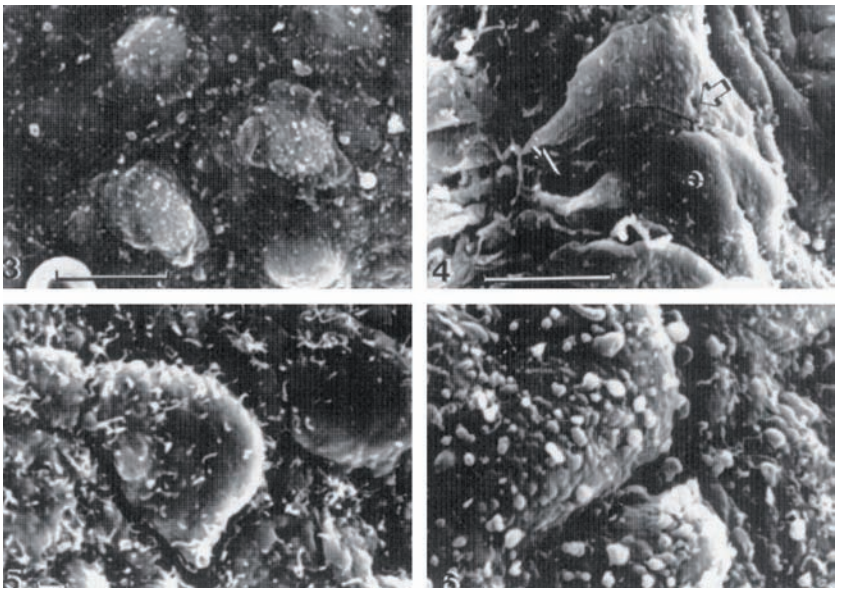

Figure 1.22.1 Transplacental cardiotoxicity. Whether or not cocaine exerts cardiotoxic effects in humans remains an open question. In animal models, toxicity is easily demonstrated. This pair of scanning micrographs shows endothelial sloughing in hamster neonatal right atrium. The figure on the left is a scanning micrograph of control right atria; the one on the right is from a neonate whose mother received cocaine on the 6th, 7th, and 9th days of gestation. The endothelium is abnormally flattened and no longer completely covers the underlying myocytes. Both scans are at the same magnification (scale bar = 10 μm). (Courtesy of Dr. Jacques Gilloteaux, Department of Anatomy, College of Medicine, Northeastern Ohio Universities, Akron.)

Merz, 2007). There are also data suggesting that, when compared to their non-cocaine-exposed peers, children with prenatal cocaine exposure are at increased risk for developing a learning disability by age seven years (Morrow et al., 2006). On the other hand, there is no evidence that children cared for by cocaine-using parents are mistreated at any greater rate than the rest of the population (Doris et al., 2006).

Women who use cocaine during pregnancy are likely to be older (Richardson and Day, 1994), less likely to have sought prenatal care (Cherukuri et al., 1988), more likely to be malnourished (Knight et al., 1994), and more likely to be suffering from HIV infection, syphilis, and hepatitis (Ellis et al., 1993). They are also more likely to be cigarette smokers, the apparent explanation for the lower birth weight of children born to cocaine-using mothers (Shiono et al., 1995). A recent multi-center trial confirmed that low birth weight, preterm birth, and intrauterine growth restriction were all more common among children whose mothers were cocaine users, but that the effects exerted by tobacco were greater than those exerted by cocaine (Bada et al., 2005).

Cocaine also stimulates human myometrial contraction, both *in vitro* and *in vivo*. Strips of uterus obtained at the time of Caesarean section contract much more forcefully when they are exposed to modest concentrations of cocaine (Monga et al., 1993). This increased force of contraction is mediated both by α-adrenergic stimulation and other factors that have yet to be identified (Hurd et al., 1998). Cocaine use during pregnancy is also associated with down-regulation of myometrial β-adrenergic receptors, a change that could inhibit uterine relaxation and speed labor (Smith et al., 1995; Wang et al., 1996).

Whether or not this increased force of contraction actually translates into accelerated labor is a matter of some debate, but the debate seems to have largely died out over the last decade. In fact, there have been few controlled studies of the subject, and no new ones. In the first study, published in 1994, the reported mean duration of labor in 16 cocaine mothers was 7.9 hours vs. 14.7 hours in 14 cocaine-free women (Konkol et al., 1994). In a second study involving 1000 women, cocaine-using women who were found to be older, of greater parity, and were admitted to the hospital with greater degree of cervical dilatation (4.63 vs. 3.96 cm, $p = 0.05$). The time elapsed from admission to birth was substantially shorter in the cocaine users, (336 vs. 565 minutes, $p = 0.001$), but after controlling for type of delivery, parity, birth weight, and prenatal care, the difference proved to be insignificant (Wehbeh et al., 1995).

It has also been suggested that cocaine users are at increased risk for placenta previa (Cherukuri et al., 1988; Macones et al., 1997) and there is some clinical evidence that cocaine may constitute an individual risk factor, but this is another problem that today is largely ignored. The last study is more than a decade old (Wehbeh et al., 1995), and the increased risk, if real, is trivial compared to the greater than 2.3-fold increased risk of placenta previa seen in cigarette smokers (Kistin et al., 1996; Slotkin, 1998).

Maternal cocaine use has also been linked with placental abruption, but there are very few case reports, and many other factors are capable of causing abruption (including prior abruption, smoking, trauma, multifetal gestation, hypertension, pre-eclampsia, thrombophilias, advanced maternal age, preterm premature rupture of the membranes, intrauterine infections, and hydramnios) (Oyelese and Ananth, 2006).

Still, cocaine does interact with the placenta. Cocaine binds to 5-HT and norepinephrine transporters located in the brush-border membrane of human term placenta (Prasad et al., 1994; Ganapathy et al., 1999). Depending on the physiologic status of the vascular receptors, elevated levels of 5-HT (Wehbeh et al., 1995), epinephrine, or norepinephrine

could cause constriction of uterine blood vessels, resulting in decreased uteroplacental blood flow. In addition, human placenta exposed to cocaine produces more thromboxane and less prostacyclin than controls, which could ultimately decrease uteroplacental blood flow (Monga et al., 1994) which would, in turn, lead to growth retardation and lower birth weights. In spite of the theoretical debate, it is clear that infants exposed *in utero* are more likely to have a lower birth weight (Bateman et al., 1993) and smaller head circumference than controls (Nulman et al., 1994). Controlled studies have also shown that maternal cocaine plasma levels during the third trimester correlate inversely with birth weight and head circumference (Knight et al, 1994).

Histopathological studies of both the cocaine-exposed fetus and placenta are rare. Detailed examination of placentas from 13 pregnancies with cocaine-related complications failed to demonstrate any specific changes (Gilbert et al., 1990). Vascular changes have, however, been documented in the human fetus by noninvasive means. Doppler studies have shown renal artery vasoconstriction and a simultaneous decrease in urine output (Mitra et al., 2000). Neonatal myocardial infarction and reversible myocardial calcification have both been described (Bulbul et al., 1994; Yap et al., 1994) and the incidence of arrhythmia in the neonatal period seems to be increased (Lipshultz et al., 1991; Frassica et al., 1994). All of these abnormalities could be explained by exposure of the fetal heart to high circulating levels of catecholamines *in utero*, but it is difficult to draw any firm conclusion based solely on isolated clinical and anecdotal reports, especially in the virtual absence of histopathologic studies. There are several other possibilities. Death might be due to cocaine-induced neurologic dysunction, which is well documented in animal and *in vitro* studies (Azmitia, 2001); heart rate variability, an indicator of autonomic stability and predictor for sudden death, is decreased in infants exposed to cocaine (Mehta et al., 2001). Another possible explanation might be hereditary channelopathy. A 1991 study from the office of the Los Angeles Medical Examiner found that nearly half of 43 newborns with no obvious cause of death were positive for cocaine or one of its metabolites (Rogers et al., 1991). Tests for Brugada syndrome and other channelopathies were not yet available, and it was not known that cocaine binds to the hERG channel. It is probable that a large number of these deaths were the results of other diseases, not direct cocaine toxicity (Berul and Perry, 2007; Wang et al., 2007).

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1.23 When Is Cocaine the Cause of Death?

It is distressing to see how often deaths caused by cocaine are misclassified. Misconceptions about cocaine-related deaths persist, largely because death certification practices are not standardized. Sometimes, use of the ICDM 9 classification system may even obscure important aspects of cocaine-related deaths, leading to both misdiagnosis and inaccurate mortality statistics (Young and Pollock, 1993). Cases of excited delirium comprise a large proportion of the misclassified cases. Well-meaning pathologists may conclude that cocaine users suffering from excited delirium only die because of the way they were restrained, or because they were exposed to pepper spray, or because a Taser has been applied. They either are unaware of, or cannot accept, the notion that chronic changes in the heart and brain, caused by long-term cocaine use, can prove fatal, even when postmortem blood levels are not very high. The situation is not at all helped by the fact that the diagnosis of excited delirium is not included in the American Medical Association's billing system (Current Procedural Terminology or CPT). Treatment of excited delirium does not involve any billable procedures performed by doctors, since patients with excited delirium are invariably treated by police and/or pathologists who do not bill insurance companies for their services!

The mere presence of cocaine, or any other drug for that matter, does not prove it was the cause of death or even the cause of toxicity. Drug use is pervasive in most societies and postmortem testing frequently reveals the presence of low levels of cocaine and its metabolites. The existence of these compounds only proves environmental exposure or, at most, use of cocaine within the last week or so of life. There is convincing evidence of prolonged cocaine excretion in the urine of chronic users (Weiss and Gawin, 1988; Cone and Weddington, 1989; Burke et al., 1990; Preston et al., 2002); cocaine is stored in reservoirs, such as skin or fat (Levisky et al., 2000). Very low concentrations of cocaine or cocaine metabolites measured in postmortem samples are the result of drug released from these reservoirs. The greater the steady state volume of distribution for a given drug, and the

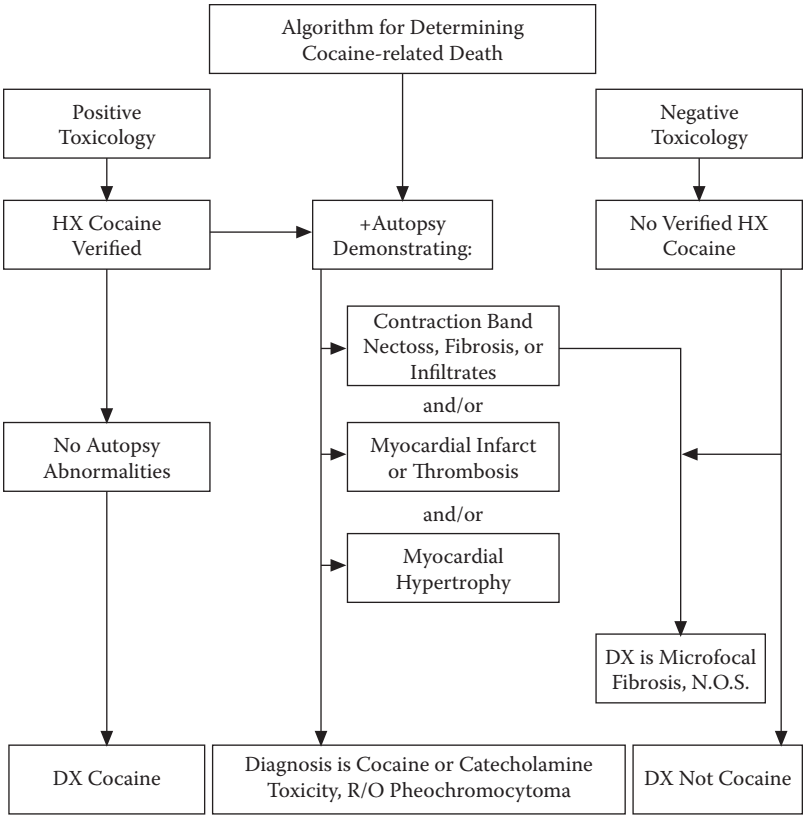

Figure 1.23.1 When is cocaine the cause of death? Suggested algorithm.

V_{ss} for cocaine is fairly high, the more likely it is to be present in fat and other deep tissue stores (Drummer, 2004; Flanagan and Connally, 2005) (Ferner, 2008).

In the absence of any confirmatory histopathological changes, cocaine levels of less than 50 ng/mL should not be deemed the cause of death. However, if there is myocardial hypertrophy, microfocal fibrosis, and microvascular disease, then cocaine may well be the cause of death, even when blood cocaine levels are only 1 ng/mL. To ensure the correct diagnosis, physical and laboratory findings must be integrated with information from detailed case histories and meticulous scene investigations.

There is no reliable methodology by which an isolated postmortem measurement can be relied upon to predict antemortem concentrations. The half-life of cocaine varies greatly from individual to individual, while the V_{ss} for only one metabolite (BZE) has ever been measured (roughly 1.0 L/kg—less than one half that of cocaine) (Ambre et al., 1991). It follows it is not legitimate to argue that, just because cocaine concentrations are high and metabolite concentrations are low in postmortem blood, ingestion occurred in close proximity to the time of death. However, such conclusions are warranted if brain is the analysate. Benzoylecgonine does not cross the blood–brain barrier, but cocaine crosses freely; any BZE detected in the brain was produced there. It follows that very high cocaine/BZE ratios suggest remote use, while low ratios suggest just the opposite (Spiehler and Reed, 1985; Bertol et al., 2007).

Another reason that blood concentrations taken in isolation cannot be used to determine cause of death is that tolerance occurs (Smart and Anglin, 1987). The rapid emergence of tolerance explains why cocaine-related deaths are not dose-related (Karch et al., 1998). Blood levels of over 5000 ng/mL may be present as an incidental finding. No upper concentration limit can be guaranteed fatal and, in chronic users with abnormal hearts, no lower concentration limit can be guaranteed safe. Anatomic alterations resulting from chronic cocaine use may persist indefinitely, even after drug use is discontinued. These changes may be the cause of death, even when no cocaine or metabolite is detectable.

In some cases postmortem blood concentrations can reasonably be used to identify those deaths resulting from acute toxicity and those due to chronic toxicity. The very first dose of cocaine might produce myocardial infarction from coronary spasm, particularly if significant underlying coronary artery disease is present. Cocaine-induced rises in blood pressure may lead to the rupture of a pre-existing berry aneurysm or AV malformation, which explains why most strokes in cocaine users are hemorrhagic (see Section 1.16.5). Cardiac standstill can be another manifestation of acute toxicity, but usually only at the very high blood concentrations (> 20 mg/L) seen in drug smugglers with massive amounts of cocaine sequestered in their bowels. All local anesthetics have toxic effects on the myocardium and can cause marked depression of cardiac output (Rhee et al., 1990), leading to infarction or asystolic arrest secondary to ion channel blockade (Nademanee, 1991; Guo et al., 2006; Ma et al., 2006).

Chronic cocaine abuse initiates a type of myocardial remodeling that favors sudden cardiac death. Cocaine activates calcium/calmodulin kinase II and causes cardiomyocyte hypertrophy, as well as elevating intracytosolic calcium—two actions that favor arrhythmic sudden death. Part of the remodeling process, whether due to cocaine or hypertension, involves alterations in sodium and potassium conductance channels that also favors sudden death (Guo et al., 2006; Ma et al. 2006). In the brain, chronic cocaine exposure produces alterations of norepinephrine transporter function that destabilize the autonomic nervous system in such a way as to favor sudden death. Changes in the sensitization to seizures induced by cocaine also favor sudden death (Kitayama et al., 2006), as do changes in striatal dopamine and 5-HT transporters, which is the apparent explanation for the syndrome known as excited delirium (Wetli et al., 1996; Mash et al., 2000). Cocaine induces apoptosis (Zhang et al., 1999), and apoptosis heals by fibrosis (Reddy et al., 2005), favoring the occurrence of re-entrant arrhythmias and sudden death. The list is almost endless.

The degree of myocardial hypertrophy seen in cocaine users, while highly significant, is nonetheless modest (less than 10% above predicted weight). Because the increase is small, it is likely to go unrecognized. The only way to make the diagnosis is by comparing the heart weight of the deceased to a standard nomogram (Kitzman et al., 1988) (see Section 1.10.2). Myocardial hypertrophy, taken in isolation, need not increase the chances of sudden death. It is only when the hypertrophic muscle is relatively underperfused, as it is in individuals with concentric hypertrophy. Eccentric hypertrophy, of the variety seen in athletes, is not ischemic, and hypertrophy in athletes does not constitute an increased risk for sudden death (Maron and Pelliccia, 2006). The situation is far different from that seen in hypertensives and cocaine users (concentric hypertrophy), and the two situations are easily distinguishable.

In many jurisdictions, the heart is not even examined microscopically or, if it is, only one or two sections may be reviewed, and mild thickening of the media of the smaller,

intramyocardial arteries, with a proportional reduction in luminal size, is likely to go unrecognized. This abnormality occurs in cocaine users and can lead to myocardial ischemia just as surely as obstruction of the large arteries, albeit by a somewhat different mechanism (Turhan et al., 2007).

Small vessel disease almost certainly accounts for some of the in-custody deaths that occur when police confront psychotically agitated stimulant abusers. Given myocardium that is already underperfused, even in the absence of gross epicardial disease decreased microvascular circulation combined with increased myocyte size could lead to sudden cardiac death (Holden et al., 2007; Sun and Webster, 2007).

In summary, the existence of a strong history of cocaine abuse in the presence of typical myocardial pathology, strongly suggest that cocaine is the cause of death, even in the face of negative toxicology. Presuming that appropriate measures have been taken to rule out pheochromocytoma, there simply is no other diagnosis except, perhaps, chronic methamphetamine abuse. If typical pathologic findings are present, but toxicology and history are both negative, the diagnosis must be microfocal fibrosis or microvascular disease (perhaps syndrome X) (Picano, 1999), etiology not otherwise specified. In the event that additional information becomes available at a later date (for example, exhumation with hair testing), the diagnosis can be revised. However, the mere presence of isolated myocardial alterations is not sufficient for diagnosis. Many states (California is an important exception) simply list the cause of death as "drug-related." The designation covers all deaths not considered to be suicide, but rather unexpected complications of chronic drug usage. It is unnecessary, therefore, to attempt to make the artificial separation between toxicity and poisoning.

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Natural Stimulants

2

At least four different alkaloid-containing plants are capable of producing amphetamine-like effects: absinthe, caffeine, khat, and ephedra. Europeans stopped using absinthe at the turn of the 19th to 20th century, but it is now making a comeback. The cessation of absinthe abuse in the early 1900s occurred almost entirely in step with the decline in the popularity of cocaine. Until 2007 United States law prohibited the importation and sale of absinthe, but it is sold over the counter in European Union liquor stores. In the U.S. it can be purchased in stores and over the Internet. Alternatively, the key herbal ingredients contained in absinthe can be purchased as "health food supplements" and then added to vodka or pure alcohol. The U.S. government rescinded its prohibition after nearly a century when it was discovered that the drink contained smaller amounts of potentially toxic thujones than had previously been supposed, although it is not entirely clear that the Drug Enforcement Agency agrees with this position.

Khat (Qat) has been used in the sub-Sahara for more than 1000 years, but it is now used in many parts of Africa, and legally used in the U.K., although there is an increasing movement to ban the plant. Khat chewing is illegal in the U.S. because it contains restricted drugs. Use is increasingly prohibited in Europe, not so much because chewing khat is associated with toxicity, but because distribution has fallen into the hand of organized crime. Khat usage has grown clandestinely in many areas of the U.S., though the amounts consumed are relatively insignificant. Xanthine derivatives, especially caffeine, are the world's most widely consumed natural stimulants and massively caffeinated drinks are very popular, both in the U.S. and Europe, particularly among the young. The other important naturally occurring stimulant is ephedrine. A ruling by the FDA caused it to be withdrawn from the herbal supplement market in 2004 (Thompson, 2004). The ruling was appealed and overturned, but now the FDA has won its appeal, and ephedra-containing products can no longer be sold (though ephedrine, its active ingredient, is still a legal drug used daily, on a large scale, by hospital anesthesiologists). Pharmaceutical grade ephedrine still remains, arguably (Lee et al., 2004), one of the preferred drugs for the treatment of anesthetic-related hypotension, especially in cardiac and obstetric surgery, where its use seems rarely to cause complications.

Outside of the hospital setting, ephedrine can be an abused drug: when smoked, or injected intravenously, ephedrine is a potent stimulant. Ephedrine was widely abused in Asia during World War II (it was injected into Kamikaze pilots), and was considered a major threat to public health in Japan during the 1950s (Karch, 2005). Sales of pseudoephedrine remain legal, but they are strictly controlled for fear that, once sold, the drug will be used

to make methamphetamine. Nonetheless, pseudoephedrine continues to be used routinely as a cold medicine and decongestant. Methylephedrine, which is not sold in the U.S., is a potent cough suppressant widely abused in Japan, and small amounts are occasionally found in ephedra plants. Except for caffeine and ephedrine, little is known about the human pharmacotoxicology and kinetics of these drugs, and knowledge of the pathologic changes associated with the chronic abuse of any of these agents remains very limited.

2.1 Absinthe

Thujone

Systematic name: (1S-(1-,4-,5-alpha))4-methyl-1-propan-2-yl-bicyclo[3.1.0]hexan-3-one bicyclo[3.1.0]hexan-3-one
Formula: $C_{10}H_{16}O$
Molecular weight: 152.23 daltons
Bioavailability (oral): not known
C_{max}: unknown
T_{max}: unknown
$T_{½}$: unknown
Metabolism: CYP3A4
Volume of distribution: unknown
$T_{½}$: not known
Drug interactions: None reported. Some important drugs, such as statins, are also metabolized by CYP3A4, but no inhibition or competition has been shown. There is some concern that interactions with cyclosporine (also metabolized by CYP3A4) might occur.

2.1.1 Incidence and Epidemiology

Absinthe is not even mentioned in any of the various iterations of Drug Abuse Warning Network (DAWN) reports. The lack of DAWN mentions does not necessarily mean that no episodes of toxicity have occurred. It just means that, except for alcohol, which is present in high concentrations, standard urine toxicology screens, either in the emergency room or at autopsy, detect none of the other ingredients contained in absinthe. The true incidence of toxicity, if any, remains unknown. Absinthe contains the same toxic monoterpene ketones, called thujones, present in the essential oils of eucalyptus, fennel, hyssop, pennyroyal, rosemary, sage, savin, tansy, thuja, and other popular herbal remedies. Published case reports have described seizures and even status epilepticus following the use of some of these oils (Burkhard et al., 1999). In the late 1990s, the E.U. voted to allow absinthe back on the market (Directive 88/388/EEC), provided that the total content of α and β thujone did not exceed a concentration of 35 mg/kg. Hundreds of different brands of absinthe, easily recognized by their pale green color (see Figure 2.1.1.1), are now available in E.U. liquor stores and pubs. Analysis shows that the thujone content of all the commercial products remains below the mandated 35 mg/kg standard. More or less the same restrictions apply in the U.S. The total sales volume is not known, so even if cases of alleged toxicity were reported, there would be no way to determine the incidence of the problem.

Figure 2.1.1.1 Photograph of a glass of absinthe. (From Wikipedia, with permission.)

2.1.2 History

Absinthe is a French word for wormwood (*Artemisia absinthium* and *Artemisia pontica*), a perennial herb related to sage (*Salvia officinalis*). The Egyptians used wormwood for medical purposes. Pliny, in the first century A.D., recommended it as a vermifuge, and wormwood is mentioned in several of Shakespeare's plays (Karch, 2005). In *Romeo and Juliet*, Act I, Scene 3, the nurse discourses:

> For I had then laid wormwood to my dug,
> Sitting in the sun under the dove-house wall;
> My lord and you were then at Mantua: —
> Nay, I do bear a brain: — but, as I said,
> When it did taste the wormwood on the nipple
> Of my dug, and felt it bitter, pretty fool…

Late in the 1700s, techniques for the mass production of grain alcohol were introduced, and shortly afterward herb-based liqueurs appeared on the market. A French general practitioner named Courvet, working in Switzerland, is credited with first devising the formula (Lachine, 1967). In early 1797, he sold the formula to Henri-Louis Pernod, who ushered in the era of absinthe abuse when he opened his factory in Pontarlier. Pernod's liquor became

Figure 2.1.2.1 Absinthe drinkers. These gentlemen were obviously intoxicated, but whether from the terpenes or the alcohol in their drinks is not entirely clear. Early evidence suggested that the active ingredients in this drink may have been very similar to those in marijuana, but this suggestion has been disproven. (From *Harper's Magazine*, April 1889.)

immensely popular in France and throughout Europe (Lachenmeier et al., 2006a). By the time of the Parisian Exposition Universelle in 1867, most boulevard cafes in Paris had their equivalent of a "happy hour," except that it was called the heure verte ("green hour") because of absinthe's green color.

Absinthe drinking became popular only a few years before Angelo Mariani started selling his coca-fortified wines, and the popularity of both coca and absinthe rose almost in parallel. French impressionist painters left an enduring record of just how popular the drink was (see Figure 2.1.2.1). During the 1860s and 1870s, Degas and Manet immortalized

Figure 2.1.2.2 Absinthe abuse was common in the late 1800s. Individuals who were intoxicated with it were said to be in possession of the "green faire" illustrated here. (From Wikipedia.)

Figure 2.1.2.3 Advertisement for the Pernod brand of absinthe. The inventor of absinthe sold the formula to Henri-Louis Pernod in 1797. (From Wikipedia.)

images of absinthe drinking. Toulouse-Lautrec painted van Gogh with a glass of absinthe (Morrant, 1993). Some even speculate that van Gogh's mental illness was related to his abuse of absinthe, either as a consequence of its direct toxicity (Hughes, 2005), or because it exacerbated an undiagnosed (and at the time not even recognized) case of acute intermittent porphyria (Bonkovsky et al., 1992).

Toulouse-Lautrec's painting of van Gogh was completed just three years after Freud published his infamous paper *Über Coca*. Baudelaire used both cocaine and absinthe, though he only wrote about the latter. Valentine Magnan studied the medical complications of both cocaine and absinthe (Magnan, 1874) and sounded warnings about the potential toxicity of both drugs. Just as American and European manufacturers of cocaine-containing patent medicines minimized the medical problems associated with cocaine use, so did the manufacturers of absinthe cordials.

Public relations campaigns mounted by the absinthe makers and the coca wine industry were very similar. Manufacturers minimized the risks, and sales boomed. From 1875 to 1913, annual consumption of absinthe per French citizen increased by 1500% (Arnold, 1989). However, the success of the advertising campaigns was short lived, and, just two years before the Harrison Narcotic Act banned cocaine from patent medications in the U.S., the French government passed legislation limiting the alcohol and absinthe content of commercial products. In 1915, the sale and manufacture of absinthe was banned entirely. Since the breakup of the former Soviet Union, absinthe production has resumed in several Eastern European countries, particularly the Czech Republic, although the E.U. and now

the U.S. have followed suit. Regulatory agencies in both Europe and the U.S. limit the beta thujone content. The results of periodic government monitoring suggest that the limits are being followed.

The thujone content of absinthe produced in the 1930s and product manufactured today has been measured and compared. The thujone content of the older samples was relatively low (mean: 1.3 ± 1.6 mg/L, range: 0–4.3 mg/L), but it is impossible to say whether this is the result of deterioration or the original manufacturing process (Lachenmeier et al., 2006b).

2.1.3 Manufacture

Absinthe is prepared either as a distillate of aromatic herbs or as a solution made by steeping the herbs in alcohol, so the physical characteristics of any particular sample will depend on the production techniques used by the manufacturer. It will also vary from batch to batch, particularly if the absinthe is home brewed or if the liqueur is made with components purchased from a "head shop." A fairly high concentration of alcohol is required to keep the various essential oils in solution. According to the older classifications, absinthe ordinaire contained 47.6% alcohol, absinthe demi-fine contained 68% alcohol, and premium grade, also known as absinthe Suisse, contained 80.66% ethanol (Vogt and Montagne, 1982). Some of the components, such as thujone, are found in other plants (sage, in particular) (Ishida et al., 1989; Loza-Tavera, 1999). It has been suggested that thujone concentrations might have been as high as 260 mg/L in the 19th century versions, but testing of product from that era has not shown levels even approaching that magnitude. Either thujone deteroriates with time or, more likely, the colormetric methods used then simply were not that accurate.

The typical formula used in the 1890s to produce a premium grade absinthe is given below (Fritsch, 1891). Kits for home production usually also contain star anise and use caramel and food dyes for coloring (Lachenmeier et al., 2006a).

Classic absinthe production formula

a. Combine 2.5 kg Wormwood + 5 kg, Anise 5 kg, and 5 kg Fennel with 91 liters of 85 percent ethanol
b. Allow mixture to sit for 12 hours (the process is called maceration)
c. Add 45 liters of water
d. Distill to 95 liters of colorless distillate
e. Add coloration consisting of 1 kg Roman Wormwood + 1 Kg Hyssop + 500 gm lemon balm
f. Add water to a final volume of 100 liters, yielding 74 proof Absinthe

2.1.4 Routes of Administration

Absinthe is only taken orally. Resultant blood concentrations of the individual herbal components are not known. The ethanol content can be exceedingly high, but whether or not the herbal components have any effects that would alter the rate of absorption or excretion has not been determined. Sale of absinthe in the U.S. is now legal, but even when it was not, human exposure still occurred because thujone diastomers of the active ingredient were contained in 20 different approved food flavorings, as well as perfumes and fragrances, all

allowed for sale within the U.S. The best known of these products is Vicks VapoRub® (Hold et al., 2001).

2.1.5 General Pharmacology

Three different types of terpenoids are found in absinthe: thujones (α and β) (see Figure 2.1.5.1), camphor, and pinenes. Thujone is a monoterpene composed of two isoprene units with the molecular formula of $C_{10}H_{16}$. Thujone has two stereoisomeric forms: (+)-3-thujone or α-thujone and (–)-3-thujone or β-thujone. Thujone is the principal terpene extracted from wormwood, and its structure was first published in 1900. Both the α and β forms of thujone are noncompetitive blockers of the GABA-gated chloride channel, which explains their proconvulsant activity (Hold et al., 2000). The α form is also more likely to trigger episodes of porphyria in those with a genetic susceptibility (Bonkovsky et al., 1992).

There are no human metabolic studies, but in animals, enzymatic reduction (possibly by a cytosolic ketone reductase) of thujone to thujol and neothujol, has been demonstrated in rabbit, but not mouse, liver. Mouse liver CYP3A4 rapidly converts thujone to 7-hydroxythujone, to smaller amounts of the 4-hydroxythujone diastomer, and other hydroxythujones. Dehydrothujone is also formed. It is presumed that the various hydroxythujones then undergo conjugation and excretion. In animal toxicity studies, brain concentrations of 7-hydroxythujone metabolite are several times greater than concentrations of thujone, suggesting that the metabolite may also be toxic (Hold et al., 2000).

In the absence of more definitive studies, it would be a mistake to dismiss the potential toxicity of all the other absinthe components. In addition to wormwood, absinthe also contains the essential oils of angelica, anise, marjoram, and calamus. Some of these other plants contain pharmacologically active compounds. Angelica (*Angelica archangelica* L., Umbelliferae) contains ferulic acid, which acts both as a cyclooxygenase and as a thromboxane A2 synthetase inhibitor (Kuenzig et al., 1984; Lanhers et al., 1992).

Calamus (*Acorus calamus* L. var. *americanus Wulff* or *A. calamus* L. var. *vulgaris* L., Araceae) is a hallucinogen and a potential carcinogen (Vohora et al., 1990). The β-asarone in calamus causes cancer in experimental animals but is found only in the calamus grown in Europe and Asia; α-asarone, also found in calamus, is similar in structure to reserpine. The structures of both α- and β-asarone both bear a strong resemblance to the structure of "Ecstasy" (3,4-methylenedioxymethamphetamine, or MDMA) (Vohora et al., 1990). Asarones tend

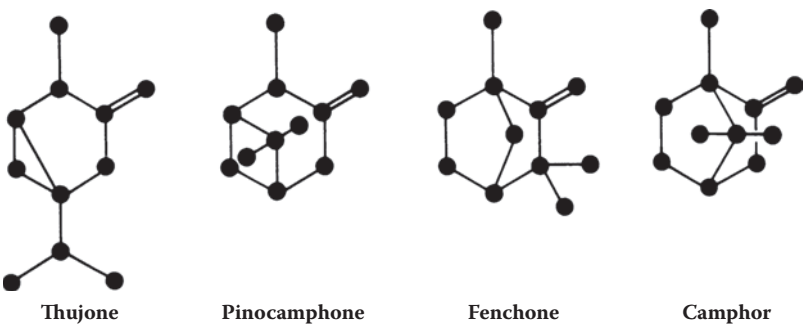

Figure 2.1.5.1 Terpenes. Absinthe contains many different compounds; thujone is the principal agent.

to decompose over time, losing their psychoactive properties within a few months of harvesting. Once asarones have been dissolved in alcohol, their psychoactivity may be longer lasting. Calamus is still used as a "recreational" hallucinogen in the U.S., although its popularity is somewhat limited by the nausea that accompanies its use (Karch, 1999).

2.1.6 Tissue Concentrations

Tissue concentrations of thujone have never been measured, nor have blood and tissue concentrations for camphor-associated deaths ever been reported in humans.

2.1.7 Toxicity by Organ System

Without knowing the thujone, camphor, pinene, or asarone content of the absinthe being consumed, or even what other herbs and secret ingredients have been added, it is difficult to say what, besides ethanol, absinthe drinkers are actually consuming, let alone whether that amount is sufficient to cause toxicity. It seems likely that the amount actually required would be far less than the 30 mg/kg suggested as the fatal dose in the older literature (Amory, 1868).

The molecular structures of thujone and tetrahydrocannabinol are, in some respects very similar, and in the past it had been suggested that the psychological effects ("high") experienced by absinthe drinkers was a variety of marijuana intoxication (del Castillo et al., 1975). More recent studies have shown that not to be the case. Thujone is the only component of wormwood oil that has any affinity at all for the CB1 cannabinoid receptor, and then only in massive doses far exceeding those that could conceivably be encountered in any absinthe drinker (Meschler and Howlett, 1999). A more plausible explanation for the intoxicant effects of absinthe may have to do with the recent finding that thujones are non-competitive blockers of the γ-aminobutyric acid gated chloride channels (Hold et al., 2000). On the other hand, the alcohol content of these beverages is so high that the neurological symptoms observed are likely to be alcohol related. Drugs in this category are known to cause seizures by disrupting calcium homeostasis within neurons (Weiergraber et al., 2006).

Questions about absinthe-related impairment are not uncommon within the E.U., where there have actually been controlled studies assessing the impact of absinthe on attention, performance, and mood. The administration of alcohol containing a high concentration of thujone has a negative effect on attention performance. In controlled studies subjects tended to direct their attention to signals in the central field of attention, to neglect peripheral signals, and their reaction times increased significantly. However, when alcohol was combined with low doses of absinthe, performance was actually better than when alcohol was consumed alone (Dettling et al., 2004).

Whether absinthe has any effect on the cardiovascular system is not known. One case report describes a 29-year-old absinthe-drinking man with no risk factors, a plasma ethanol concentration of 198 mg/dL, but otherwise negative toxicology, who developed Mobitz type-I atrioventricular block that converted to a rapid junctional rhythm (Benezet-Mazuecos and de la Fuente, 2006). No similar cases have been reported. Stomach upset was a common complaint of absinthe drinkers in Paris during the late 1800s. Vincent van Gogh wrote several letters to his brother Theo complaining of stomach upset after bouts of absinthe drinking (Morrant, 1993). This appears to be a rare complaint among van Gogh's modern cousins.

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2.2 Caffeine

2.2.1 Incidence

Caffeine is present in many different plants and goes by many different names depending on the plant source. It is sometimes called guaranine when extracted from the guarana plant, mateine when found in yerba mate, and theine when found in tea. The leaves and beans of the coffee and tea plants are the main sources of caffeine in tea, yerba mate, and guarana berries. Only small quantities of caffeine are found in cocoa, the kola nut, and the Yaupon Holly. Smaller amounts of caffeine can be detected in the beans, leaves, and fruit of over 60 different plants, where its primary purpose appears to be to act as a natural pesticide. No matter the name used, caffeine remains the most widely used stimulant in the world. Citizens of the U.S., with an estimated consumption of more than 100,000 tons in 2002, are its largest consumers. According to testimony before the U.S. Senate, the coffee market is grossly oversupplied. Total global supply in 2002–03 was forecast to reach 143.6 million bags, up nearly 6% from the previous year, largely as a result of increasing production in Brazil. Coffee supplies have not reached this level since 1991–92. This oversupply is not likely to lessen anytime soon (Lee and Service, 2002).

The United Nations states that world tea production continues to increase at rates parallel to those of coffee. Since 2004, tea production has grown by 2% a year to reach an estimated 3.6 million tons. In China, tea output for 2004 approached the 800,000 tons, as policy initiatives to promote production, passed years earlier, finally began to have an impact (Anon., 2005).

Estimates from many different sources suggest that formidable amounts of caffeine are also consumed in soft drinks, cold medications, and pain-relief formulas. In spite of caffeine's widespread use, neither the Medical Examiner's component nor the Emergency Room component of the most recent DAWN survey makes any mention of caffeine, suggesting that episodes of serious toxicity are very uncommon (Ball and Duchama, 2005).

Guarana, officially known as *Paullinia cupana*, is the primary source of caffeine added to commercial products, both in the U.S. and Europe. Unlike other sources of caffeine, guarana comes only from the Amazon, with Manaus the exporting center. In Brazil it is used mainly as a soft drink and has some traditional uses in folk medicine, where it is used to treat fever and diarrhea. The seeds contain 4–5% caffeine as well as theophylline and theobromine (Carlson and Thompson, 1998), making it the richest source of caffeine.

Guarana production figures are sketchy but, thanks to modern growing techniques, the average production is thought to be on the order of 1200 tonnes per year (Hernándo Bermejo and León, 1994). Yerba mate (Rioplatense Spanish) and erva mate (Portuguese) (*Ilex paraguariensis*) both belong to a species of holly (family Aquifoliaceae) that is native to subtropical South America, particularly in northern Argentina, Paraguay, Uruguay,

southern Brazil, and Bolivia. Steeping the dried leaves in hot water rather than boiling water like tea or coffee prepares an infusion called mate. It is slightly less potent than coffee and said to be much gentler on the stomach. The flavor is grassy, but much stronger than green tea, to which it is generally compared (Dickel et al., 2007).

2.2.2 Epidemiology

Table 2.2.2.1 shows the caffeine content of some commonly consumed beverages and medications. The average American adult consumes 2.4 mg/kg/day of caffeine. Intake for children between the ages of 5 and 18 is thought to be half that amount. European consumption is said to be even higher: 3.5 mg/kg/day (Scientific Committee for Food, 1983). An average cup of coffee contains 40–100 mg of caffeine, and the average American drinks two cups a day, the average European, three. The caffeine content of cola drinks is lower, ranging from 30–65 mg per 8-ounce serving, but the caffeine intake of some cola drinkers is substantially higher than that of coffee or tea drinkers.

Table 2.2.2.1 Caffeine Content (in mg) of Some Common Beverages and Medications

Carbonated beverages (12 oz can)	
A&W Root Beer®	0
Barq's Root Beer®	23.0
Coca-Cola®	64.7
Coca-Cola Classic®	34.0
Diet Coke®	45.6
Diet Mountain Dew®	55.0
Diet Sunkist Orange®	41.0
Dr. Pepper®	60.9
Diet Dr. Pepper®	54.2
Jolt®	71.2
Lipton Brisk, All Varieties®	9
Mellow Yellow®	52.8
Mountain Dew®	54.7
Mug Root Beer®	0
Nestea Sweet Iced Tea®	26.5
Pepsi-Cola®	43.1
Pepsi One®	55.5
RC Cola®	33.7
Red Bull (8.2 oz)®	80.0
Snapple Sweet Tea®	12.0
Sunkist Orange®	40.0
Tab	46.8
Tea bags (average per 8 oz cup)	
Black teas	21–33
Green teas	9–19
Coffee (average per 8 oz cup)	
Instant	65–100
Electric percolator	80–135
Stove percolator	105

(*Continued*)

Table 2.2.2.1 Caffeine Content (in mg) of Some Common Beverages and Medications (Continued)

Drip	115–175
Starbuck's tall latte®	375
Starbuck's grande® (470 mL)	> 500
Starbucks® expresso decaffeinated (per short)	3–15.8
Starbucks® brewed decaffeinated (16 oz)	12–13.4
Cocoa	10–17
Medications	
Norgesic Tablets®	30.0
Darvon Compound 65®	32.4
Fiorinal Capsules®	40.0
Excedrin Extra Strength®	65.0
Caffergot Tablet®	100.0
NoDoz Tablets®	100.0
NoDoz Maximum Strength®	200.0
Common prescription and over-the-counter (OTC) drugs containing caffeine	
Actamin Super®	65.4
Anacin Maximum Strength®	32.0
Anacin Tablets and Caplets®	32.0
Aspirin-Free Excedrin Caplets®	65.0
Headache Pain Relief	65.4
Cafergot Suppositories (other names: Cafertrine®, Cafetrate®, Migergot®, Wigraine®)	100
Cafergot Tablets (other names: Ercaf®, Ergo-Caff®, Gotamine®, Wigraine®)	100
Darvon Compound 65 Puvules®	32.4
Dristan Capsules®	16.0
Excedrin Caplets®	65.0
Excedrin Caplets Extra Strength®	65.0
Excedrin Extra Strength Caplets and Tablets®	65.0
Fiorinal Capsules and Tablets®	40
Fiorinal with Codeine No. 3®	40
Goody's Extra Strength Tablets®	16.25
Goody's Headache Powder®	32.5
Midol Maximum Strength Caplets®	60
Midol for Cramps Maximum Strength Caplets®	32.4
NoDoz®	100
Norgesic Forte; Norphadrine Forte®	60
Norgesic; Norphadrine Forte®	30
Triaminicin with Codeine Tablets®	30
Vanquish Caplets®	65.0
Vivarin®	200

Data for caffeine-containing beverages taken from Bunker and McWilliams, 1979. Data on decaffeinated coffee from McCusker et al., 2006. Additional data from National Soft Drink Association and US Food and Drug Administration. Current labeling requirements do not require manufacturers to list caffeine content. Values may have changed. Data for medications taken from current PDR, WebMD, and the Cleveland Clinic (Anon., 2006).

2.2.3 History

The origins of coffee drinking are a mystery. According to legend, the prior of a Muslim convent observed that goats eating beans from certain trees tended to stay up all night. He assumed that the beans were responsible and concluded that using the beans might help him and his followers stay awake during their long prayer vigils in the mosque. The prior brewed a beverage called "kahweh" and was said to have been quite pleased with the results. The first convincing evidence of coffee's widespread popularity is from the 16th century. In 1511, when a new Egyptian governor arrived in Mecca, he noticed people sitting around the mosques drinking coffee. He asked what they were doing, and he was told that they were drinking coffee to give them the energy they needed to pray all night.

The governor had his doubts about the propriety of the practice, and convened a meeting of clerics and elders to discuss the subject of coffee drinking. The governor feared that coffee might be some sort of intoxicating agent and, therefore, its use would be prohibited by the Koran. The assembly concluded that coffee was indeed an intoxicant, and therefore should be banned. Sales of coffee were prohibited and stocks were burned. Had the new governor bothered to check with his superiors, he would have found that the Sultan of Cairo was an avid coffee drinker; the Sultan promptly overruled the governor's decision, and coffee drinking in Mecca has been legal ever since.

Venetian traders introduced coffee to Europe. In London, the first coffee shop opened in 1652 and was located in St. Michael's Alley, Cornhill. Its owner, Pasqua Rosee, advertised extensively, making mostly medicinal claims for the drink. According to Rosee, coffee was "a very good help to the digestion…and makes you fit for business" (Thompson, 1928). In spite of Rosee's claims, coffee drinking was at first considered highly suspect among the Europeans. Coffee drinkers were said to have a haggard appearance and to be "subject to fits of agitation and depression." Coffee drinking had been introduced into France nine years earlier and by 1690, 250 coffee houses were registered in France; by 1782, that number had risen to 1800. Some of the coffee houses were quite opulent, with marble tables and crystal chandeliers. Like the English, the French also had some doubts about the habit. Medical literature from that period contains reports both praising and condemning the effects of coffee. It was alleged that coffee caused inflammation of the liver and spleen, and that it even caused kidney stones.

Suspicions that coffee drinking is unhealthy have never entirely disappeared. Even Virchow classified caffeine, along with alcohol, as an addictive substance. Lewin (1931), who generally thought that coffee drinking was a good thing, accepted reports of "delirium, vertigo, trembling, and even convulsions" as an occupational disease in coffee roasters. In modern times, epidemiological investigations have focused on possible links between caffeine intake and myocardial infarction, sudden death, and fibrocystic disease and arrhythmias. Alleged links to cancer have never been proven (Stavric, 1988a), and the histopathological changes associated with caffeine treatment in animals have never been confirmed in man (Strubelt et al., 1976). Interestingly, the same suspicions have never been entertained about other caffeine-containing beverages such as cocoa, and certainly never about tea, even though both contain substantial amounts of caffeine. That may be because it has become increasingly apparent that tea consumption may actually protect against cancer (Hirose et al., 1999; Okabe et al., 1999).

During the 1990s a great deal was written about the dangers of combining caffeine and ephedra/ephedrine in athletic supplements, and the increased risk of such combinations for producing cardiovascular disease (Haller and Benowitz, 2000; Haller et al., 2004b). The caffeine concentrations in these products ranged from 40 to 200 mg (the equivalent of one half to two cups of coffee) (Haller et al., 2004a). Since the beginning of the decade there has been a virtual explosion in caffeine research into new areas, perhaps the best publicized being the apparent ability of caffeine consumption to modify or even reverse some of the changes associated with Parkinson's disease (Aguiar et al., 2006; Alisky, 2006; Deleu et al., 2006) and Alzheimer's disease (Dall'Igna et al., 2003). There has also been diminished interest in coffee consumption and coronary artery disease, as large epidemiologic studies have shown that no such relationship exists. The lack of correlation is attributed to the tolerance that rapidly emerges to caffeine's effects (Shi, 1997; Lopez-Garcia et al 2006). However, data published in early 2008 strongly suggest that caffeine may exert deleterious effects on pregnant women (Savitz et al., 2008).

2.2.4 Chemical Constants

Systematic name: 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione, also alternatively called, 3,7-trimethylxanthine, trimethylxanthine, theine, mateine, guaranine, methyltheobromine

Formula: $C_8H_{10}N_4O_2$

Molecular weight: 194.19

Metabolism: CYP1A2

Pharmacokinetic data

Bioavailability:

Intravenous: 100%

Oral: 100% ($n = 4$) (Bonati et al., 1982)

Inhalation: 60% ($n = 10$) (Zandvliet et al., 2005)

Half-life:

a. Healthy male adults, 3–4 hours, 2–8 hours (Bchir et al., 2006), 3–7 hours (Levy and Zylber-Katz, 1983)
b. Women taking oral contraceptives, 6–10 hours
c. Pregnant women, 9–11 hours
d. In presence of severe liver disease, 96 hours (Sanchez-Alcaraz et al., 1991)
e. Newborns, 30–80 hours
f. Premature, at birth, 65–102 hours
g. 3–4.5 months old, 14.4 hours
h. 5–6 months old, 2.6 hours

Clearance: 1–3 mg/kg/min (both men and women) (Kaplan et al., 1997)

V_{ss}:

a. Intravenous: 0.55 ± 0.13 L/kg ($n = 10$) (Sanchez-Alcaraz et al., 1991)
b. Inhalation: 0.65 L/kg ($n = 10$) (Zandvliet et al., 2005)

C_{max}: oral, 15–120 minutes

Urine detection time: The elimination time is 2.5 to 10 hours depending upon the p450 status and whether other drugs being taken (Magkos and Kavouras, 2005; Rengelshausen et al., 2007)

Known interactions: serotonin re-uptake inhibitors (Prozac®), antiarrhythmic drugs such as mexiletine and propafenone, antipsychotics (clozapine), psoralens, and phenylpropanolamine all compete for CYP1A2 and have the potential to cause dangerous interactions

2.2.5 Sources

Depending on the type of bean, chemical extraction of roasted coffee beans yields from 8 to 20 mg of caffeine per gram of coffee (Zuskin et al., 1983). Teas made from the leaves of *Camellia sinensis* also contain caffeine, but herbal teas made by soaking other plant leaves, such as mint, in hot water do not contain caffeine, nor does it appear that they contain the antioxidants thought to prevent cancer, or any of the other recently discovered potential benefits associated with coffee and tea consumption. Green teas, such as gunpowder tea, are made from tea leaves that are heated immediately after they are picked, then rolled and crushed, thereby preserving the natural constituents of the leaves, including their color. Black teas, such as pekoe, are picked, allowed to dry, and then packaged. Fermentation partly digests some of the components of the leaf, giving black tea its reddish-brown color (Karch, 1999). The caffeine content of a cup of tea depends partly on which leaves are used and on how the leaves are brewed; however, the caffeine content of *Camellia sinensis* is not high enough to make extraction for other purposes worthwhile.

Guarana seeds contain more caffeine (4–5%) than any other plant and are the main source of commercial caffeine. In addition, the leaves contain large amounts of theobromine (Carlson and Thompson, 1998), a close relative of caffeine. Guarana also contains a number of tannins, some very similar to those found in tea (the same ones that are thought to provide beneficial antioxidant effects) (Morton, 1992). At least nine different antioxidants/tannins have been identified in the oil extracted from guarana; two of them, estragole and anethol (Benoni et al., 1996), are thought to be psychoactive. In Brazil, guarana is used to make an extremely popular carbonated soft drink. In laboratory studies, low concentrations (1.2 mg/mL) of guarana inhibit lipid peroxidation. No histopathological changes secondary to guarana ingestion have been detected, even in animals treated with very large amounts (250–2000 mg/kg) of this drug (Mattei et al., 1998).

Two main varieties of the coffee plant are used for brewing coffee: robusta and arabica. As its name implies, the robusta plant is the hardier of the two, but at a price. Beverages produced from it do not have nearly the flavor of arabica beans, which is why most robusta beans are used to make instant coffee or are used in the least expensive coffee blends. While robusta beans may be lacking in flavor, their caffeine content is about twice that of arabica.

The caffeine content of cocoa is substantially less than that of coffee. Cocoa trees only grow in a limited geographical area: 10 degrees to the north and south of the equator. Accordingly, almost 70% of the world crop is grown in West Africa. The estimated annual world production is approximately 3,000,000 tons. Chocolate derived from cocoa contains a small amount of caffeine, and the limited stimulant effects possessed by this plant are mostly due to its content of theobromine and theophylline (Smit et al., 2004). Still, cocoa contains too little of these compounds for a reasonable serving to create effects in humans, or at least none that are on par with coffee. A typical 28-g serving of a milk chocolate bar has about as much caffeine as a cup of decaffeinated coffee.

2.2.6 Routes of Administration

Most caffeine is consumed orally, either in beverages or in medications, especially those used to treat headache and migraine (Pradalier et al., 1985). When ingested orally, caffeine is rapidly absorbed, distributes throughout total body water (including the fetus), and reaches a peak plasma level between 30 and 75 minutes. Animal studies have demonstrated that the caffeine concentration in mouse brain is about 80% that of plasma (Kaplan et al., 1997) and that value probably also obtains in man. Plasma levels of caffeine after the consumption of up to about six cups of coffee per day generally ranged between 2 and 6 mg/L (Lelo et al., 1986). In another study, plasma caffeine levels peaked at about 3 mg/L after 4.2 mg/kg/day of caffeine added to decaffeinated coffee, and reached 13 mg/L after 12 mg/kg/day of caffeine was added.

When a capsule containing 2 mg/kg of caffeine (corresponding roughly to two cups of coffee for an adult) was given to volunteers, the plasma level reached a value of about 3 mg/L and plateaued at 7.5 mg/L after a 4-mg/kg dose of caffeine (Benowitz et al., 1995). This mode of administration is convenient and precise, but does not precisely mirror the absorption of caffeine after drinking sufficient cups of coffee to contain the same quantity of caffeine. Caffeine is also given intravenously to help prevent headache after spinal anesthesia (Yucel et al., 1999) and to treat apnea in pre-term infants (Tobias, 2000). The pharmacokinetics of caffeine remains the same, regardless of the route of administration (Fredholm and Lindstrom, 1999). Caffeine can also be inhaled, and is frequently added to pharmaceutical grade heroin, both on the streets and in replacement programs. The addition of caffeine results in a decreased sublimation temperature of the heroin and a slightly higher recovery after it has been smoked. Perhaps most important, pyrolytic decomposition of the heroin is reduced (Huizer, 1987). Caffeine is rapidly and effectively absorbed after inhalation with a bioavailability of 60%. The volume of distribution for the central compartment is estimated to be 0.65 L/kg (Zandvliet et al., 2005).

2.2.7 Metabolism

The first step in caffeine metabolism involves demethylation into dimethylxanthines, specifically paraxanthine, theobromine, and theophylline. In humans the metabolic pathway for demethylation of caffeine into paraxanthine and 1-methylxanthine predominates (Brice and Smith, 2001). Other pathways are recognized in animals. Human caffeine metabolism is controlled by the CYP1A2 enzyme, which is a genetically polymorphic enzyme. CYP1A2 activity is influenced by a variety of factors, especially smoking, which induces CYP1A and therefore controls the rate of caffeine breakdown to 1-methylxanthine (Tang et al., 1991; Caubet et al., 2002). Inhibiting this enzyme prolongs caffeine's half-life and diminish clearance.

Caffeine and theophylline both convert entirely to other xanthines and are then excreted in the urine. At least 14 different caffeine metabolites have been identified in human urine (Rodopoulos and Norman, 1994). On average, 14% of ingested caffeine is excreted as theophylline and 60% as the demethylation product paraxanthine (1,7-dimethylxanthine). Paraxanthine is not found in man but is found as a metabolite in many different species (Ullrich et al., 1992); it has sympathomimetic effects comparable to those of caffeine itself (Benowitz et al., 1995). In humans, paraxanthine is either acetylated or further demethylated to a compound devoid of sympathetic activity (Sawynok and Yaksh, 1993).

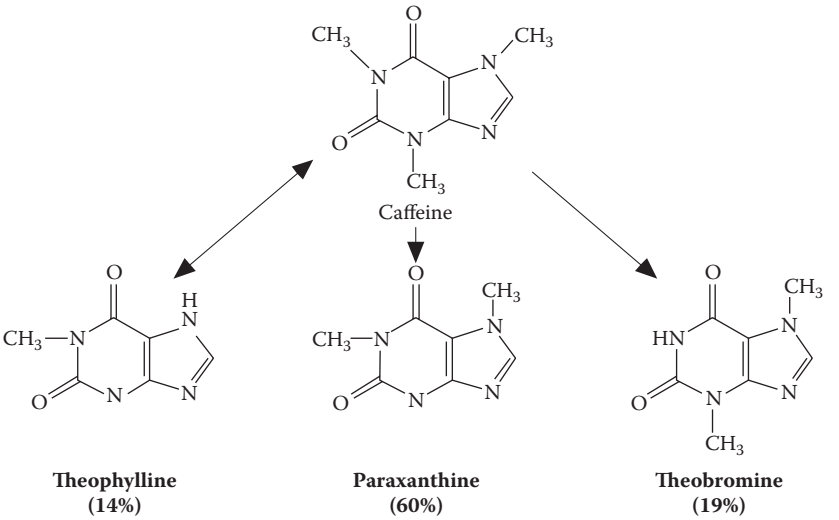

Figure 2.2.7.1 Caffeine metabolism. Assuming an average caffeine intake of roughly 500 mg per day, 60% will be excreted as paraxanthine, 19% as theobromine, and 14% as theophylline (small amounts of minor metabolites account for the remainder). The results may be quite different in smokers and patients with cirrhosis.

Many commonly prescribed medications are potent CYP1A2 inhibitors. It is not known whether the other ephedrine isomers are CYP1A2 inhibitors, but this interaction could have important clinical implications, resulting in higher than anticipated caffeine concentrations. It has been suggested that unsuspected interactions might inadvertently cause athletes to exceed the 12-mg/L urinary caffeine concentration limit set by the International Olympic Committee (IOC) and other sports regulatory bodies (Carrillo and Benitez, 2000).

2.2.8 Mechanisms of Action

For many years, caffeine's cardiovascular effects were assumed to be a consequence of its ability to act as a phosphodiesterase inhibitor, leading to increased formation of cyclic AMP and cyclic GMP (Wells and Kramer, 1981). That explanation is almost certainly incorrect because caffeine is a relatively nonspecific phosphodiesterase inhibitor, and very high caffeine concentrations, substantially higher than those that result after a few cups of coffee, are required to produce measurable vasoconstriction in humans (Casiglia et al., 1992). However, even low doses of caffeine antagonize adenosine receptors present in brain, blood vessels, kidneys, heart, the gastrointestinal tract, and the respiratory tract (Chou and Benowitz, 1994; Daly and Fredholm, 1998). It now appears that the stimulatory effects of caffeine are a result of its ability to block adenosine type 2A receptors. Blockade of these receptors activates adenylcyclase, increases concentrations of cyclic AMP, and causes the closing of K^+ channels that indirectly increase calcium concentration within cells. In the brain this leads to stimulation of GABAergic neurons that inhibit the dopaminergic reward system.

When herbal supplement makers began combining caffeine and ephedrine, some expressed concern that blockade of A2 receptors would lead to systemic and coronary

artery vasoconstriction. In addition, adenosine blockade would favor platelet aggregation. More recent work has tended not to confirm these fears, largely because the number of A2 receptors is so great that the caffeine levels achieved with anything like normal caffeine consumption cannot block critical numbers. Most prospective cohort studies have not found coffee consumption to be associated with significantly increased risk for cardiovascular disease (Higdon and Frei, 2006).

The results of epidemiological research suggest that coffee consumption may help prevent several chronic diseases, including type 2 diabetes mellitus, Parkinson's disease and liver disease, including both cirrhosis and hepatocellular carcinoma (Higdon and Frei, 2006). Adenosine antagonists, such as caffeine, are under active development as adjunctive symptomatic treatment for advanced parkinsonism. There is preclinical evidence that A(2A) antagonists favorably alter the course and symptoms of the disease, while epidemiological and laboratory data suggest that A(2A) blockade may prevent dopaminergic neuron degeneration (Xu et al., 2005). Some of coffee's effects have nothing to do with caffeine. For example, coffee generally stimulates the gastrointestinal tract and causes the gallbladder to contract, even when the caffeine has been removed (Boekema et al., 1999).

The underlying mechanism of caffeine-induced diuresis is not known, but it has been shown that the process does not involve increased production of atrial natriuretic factor (Nussberger et al., 1990). In a double-blind controlled study, 642 mg of caffeine given to 12 healthy volunteers led to an increase in 24-hour urine excretion of 753 ± 532 mL, a cor-responding negative fluid balance, and a concomitant decrease in body weight of 0.7 ± 0.4 kg. Total body water decreased by 1.1 ± 1.2 kg (or 2.7%), and urinary excretion of sodium and potassium increased by 66 and 28%, respectively (Neuhauser et al., 1997).

Under controlled laboratory conditions caffeine itself has no effect on body mass, urine osmolality, urine specific gravity, urine color, 24-hour urine volume, 24-hour Na^+ and K^+ excretion, 24-hour creatinine, blood urea nitrogen, serum Na^+ and K^+, serum osmolality, hematocrit, or total plasma protein, and there is no evidence of dehydration (Armstrong et al., 2005). These results are in conformity with earlier clinical studies showing that caffeine exerts no effect on the production of atrial natriuretic peptides (Nussberger et al., 1990).

2.2.9 Pharmacokinetics

A caffeine dose of 1 mg/kg (roughly equivalent to a 70 kg man drinking a cup of coffee) will produce peak plasma concentrations of 500–1000 ng/mL (Carrillo and Benitez, 2000). Caffeine is taken up mainly by lean body tissue. The same dose of caffeine will produce much higher blood levels in older than in younger adults (Massey, 1998). It will also produce plasma concentrations 20% higher than saliva, though there is excellent correlation between the two matrices (Carrillo et al., 2000). In the newborn, lean body mass is reduced in proportion to the amount of fat present (Anderson et al., 1999). The half-life of caffeine is extremely variable: during the first three hours after ingestion there is a 5–11-fold inter-individual variation in plasma caffeine concentrations (Bonati et al., 1982). Among the factors accounting for the variation are the age of the individual, lean body mass, and CYP1A2 activity. Smoking enhances CYP1A2 activity, while some drugs decrease the rate at which caffeine is metabolized (Faber et al., 2005).

The half-life for caffeine in healthy adults is 3–7 hours (Levy and Zylber-Katz, 1983) but even wider ranges have been reported (Magkos and Kavouras, 2005). In adults, but not necessarily in children, caffeine has a low volume of distribution, 0.4 L/kg. Because

Table 2.2.9.1 Half-Life of Caffeine vs. Age

Age	Half-Life of Caffeine (hr)
Premature, at birth	65–102
Term, at birth	82
3–4.5 months old	14.4
5–6 months old	2.6
Adult	3–7.5

of the higher fat content of neonates and the hydrophilic nature of caffeine, the volume of distribution may be more than three times as high in neonates (Anderson et al., 1999). Caffeine's metabolism is saturable. Saturation occurs at a value of roughly 8000–9000 ng/mL (Mandel, 2002). Human trials have shown the caffeine kinetics to be nonlinear; clearance decreases and the elimination half-life is prolonged when larger doses (500 vs. 250 mg) of caffeine are given (Troger and Meyer, 1995; Kaplan et al., 1997).

Theophylline (1,3-methylxanthine), the caffeine metabolite, initially undergoes demethylation followed by acetylation (Troger and Meyer, 1995). Its volume of distribution is also low (0.46–0.90 L/kg) (Sanchez-Alcaraz et al., 1991). When theophylline clearance is corrected for body weight it is substantially higher in young adults than in the elderly — 0.52 mL/min/kg for those over age 56 vs. 0.72–0.77 mL/min/kg in individuals aged 20–50 years). The pharmacokinetics of caffeine is essentially the same, no matter whether the caffeine is given orally or intravenously (Fredholm et al., 1999).

Over the last several years, caffeine has become increasingly used as a probe with which to assess CYP1A2 activity. Caffeine clearance, 3-*N*-demethylation, measurement of the amount of ^{13}C-caffeine expired in the breath, and calculation of the ratio of different xanthine metabolites can all be used to indirectly assess CYP1A2 activity. The ability to do so is of more than academic interest. A number of drugs besides caffeine, some potentially quite toxic (phenacetin, clozapine, imipramine, tacrine), are metabolized by this same enzyme system, and CYP1A2 activity is deficient in part of the human population (Spigset et al., 1999).

2.2.10 Tissue Concentrations

A healthy adult drinking two cups of very strong coffee would be expected to have urine caffeine levels no greater than 3–6 mg/mL, which is not very much different than levels seen in heroin smokers who are "chasing the dragon" (Zandvliet et al., 2005). Plasma measurements made one hour after drinking two cups of coffee showed a peak caffeine value of 5.3 mg/mL (Marks and Kelly, 1973), though peak levels can be expected to occur anywhere from 30 to 45 minutes after ingestion. The clearance rates for both theophylline and paraxanthine decrease in chronic users. Tissue measurements in rats have shown that, after dosing with caffeine, concentrations of caffeine and theophylline are equal in most tissues except the brain, where caffeine levels are 25% higher than theophylline levels (Stahle et al., 1991). If this is also the case in humans, it might explain the different clinical profiles of theophylline and caffeine.

What really matters to caffeine drinkers is getting the caffeine to the A1 adenosine receptors where it may act to provide the desired effects. This issue has been studied by

using the technique of modern positron emission tomography (PET) scanning. Measurements were made in 36 healthy volunteers, aged 22–74 years, and compared. There was no significant association between regional uptake, age, gender, caffeine consumption or sleep duration and adenosine receptor binding, but there was a significant age-dependent decrease of adenosine receptor binding in all regions of the brain except the cingulate gyrus. Declines ranged from –17% (striatum) up to –34% in the postcentral gyrus. The average cortical decline was –23%. The decrease in uptake was not affected by gender, caffeine consumption, or sleep duration. Although as yet unproven, researchers speculated that the decrease in A1 binding could be a general marker for neurodegenerative disease (Meyer et al., 2006).

Newborns, like adults, can convert caffeine to theophylline and theophylline to caffeine, but the direction and degree of conversion are not always predictable. Measurements of cord blood caffeine levels in children born to cocaine-abusing mothers have shown that these women are likely to be abusing caffeine and nicotine as well; caffeine may be present in substantial concentrations (up to 10 mg/L) (Dempsey et al., 1998). In three newborns treated with therapeutic doses of intravenous aminophylline, the highest levels were observed in the blood and then the brain. Decreasing levels were found in the heart, liver, lung, and kidney. Brain theophylline levels ranged from 6 to 30 mg/g, while caffeine levels ranged from 2.1 to 3.7 mg/g. Caffeine can be detected in most biofluids, including saliva, semen, and breast milk (Bonati, 1982), but levels have not been systematically studied.

Ingestion of even modest amounts of caffeine by naïve mothers can produce significant effects on maternal and fetal circulation (Miller et al., 1994). Infants born to heavy coffee drinkers have high caffeine levels at birth (Khanna and Somani, 1984) and generally manifest intrauterine growth retardation. A recent large epidemiologic investigation (n = 1606) measured the association between caffeine and its primary metabolites in umbilical cord blood and attempted to correlate them with intrauterine growth restriction. Using an adjusted model including caffeine only, levels in all growth quartiles were associated with risk of intrauterine growth restriction. In adjusted analyses including paraxanthine and caffeine, serum paraxanthine levels in the highest quartile were associated with increased risk of the same problem. The findings suggest that cytochrome CYP1A2 metabolic activity may play a key role in growth retardation. No associations were observed between caffeine or any metabolites and/or pre-term delivery (Grosso et al., 2006).

Substantially similar results have been obtained in other recent studies. Children born to coffee-drinking mothers who did not smoke had statistically significant lower birth weights and smaller placentas ($p < .05$), but there was no difference between groups according to body lengths, head circumferences, and diameters of placentas. On the other hand, birth weight and placenta size in pregnant smokers ($p < .05$) were even lower (Balat et al., 2003).

Two special situations are of clinical and forensic interest. The CYP1A2 system is immature in infants (Tanaka, 1998), and the plasma half-life of caffeine is 17 times longer than in healthy adults (Labow, 1983). Infants being treated with aminophylline run a real risk of toxicity from caffeine, which continues to accumulate in their blood as aminophylline is converted to caffeine. Similar results can occur in patients with hepatic insufficiency or decreased cardiac output (Lacroix et al., 1985; Bechtel et al., 2000). Treatment with aminophylline under these circumstances runs the risk of caffeine toxicity. Measurement of both theophylline and caffeine levels in individuals at risk would be prudent.

Altered caffeine metabolism is also observed in children with cystic fibrosis, but the alterations remain poorly characterized. That disease is caused by defects in the gene for cystic fibrosis transmembrane conductance regulator (CFTR), which encodes for a chloride channel and is regulated by cyclic adenosine monophosphate (cAMP). Mutations in the gene for CFTR (*CFTR*) result in abnormalities of cAMP-regulated chloride transport across epithelial cells on mucosal surfaces. The mucus that is produced is abnormally thickened and susceptible to bacterial infection. There is mounting evidence that caffeine, if not some other designer xanthine, may help reverse the problem (Bulteau et al., 2000).

2.2.11 Toxicity by Organ System

Reactions to low doses of caffeine are widely variable and unpredictable by the interconversion of theophylline and caffeine in humans. The ratio of plasma theophylline to caffeine after caffeine administration is 8:6, and it is not clear whether toxic reactions, when they are observed, are really the result of caffeine or theophylline excess. After theophylline administration, the ratio of theophylline to caffeine is nearly the same (Stavric, 1988b).

2.2.11.1 Neurologic

A 250-mg dose of caffeine (approximately 2.5 cups of coffee) reduces cerebral blood flow for 90 minutes. The decrease in cerebral flow is unexplained. It is not due to changes in the general circulation or in CO_2 levels, but it might be the result of the ability of caffeine to block adenosine receptors (see earlier). Adenosine is a powerful cerebral vasodilator and it may be that adenosine receptor blockade results in decreased cerebral flow. Interactions with the adenosine receptor have also been suggested as a possible mechanism in caffeine-related seizures, though this suggestion also remains unproven (Morgan and Durcan, 1990), as does the role of adenosine receptors in caffeine-related hypertension (Nurminen et al., 1999). These earlier studies have been confirmed in more recent studies done with functional magnetic resonance imaging (MRI). Because chronic caffeine use causes an upregulation of adenosine receptors, the differential effects of caffeine observed in occasional and regular coffee users are to be expected. The blood flood decrease in the visual cortex is significantly greater in heavy coffee drinkers than in more modest users. In addition, the magnitude of the change is significantly correlated with caffeine consumption. This correlation is thought to be the result of upregulation of adenosine receptors in high users (Laurienti et al., 2002).

The elderly are more sensitive to the psychological effects of caffeine, including increased alertness and improved performance on certain psychological tests (Massey, 1998; Kallus et al., 2005). Older adults also seem to be more likely to experience insomnia after consuming caffeine than are younger individuals (Brezinova, 1976). The suggestion has also been made that a caffeine dependence syndrome exists, and that this syndrome meets all the generic criteria for substance dependence, including the fact that affected individuals continue to use caffeine in spite of persistent problems related to its use (Holtzman, 1990). In one controlled study, dependence was diagnosed in 16 of 99 individuals who were evaluated. The median daily caffeine consumption in this group was only 357 mg per day (Strain et al., 1994).

Since this observation was first published, caffeine addiction has been added as an official diagnosis in ICDM 9. This decision is disputed by many and is not supported by

any convincing body of experimental evidence. For example, other abused drugs lead to predictable increases in cerebral function and dopamine release in the shell of the nucleus accumbens. Caffeine does not. Except in massive doses, caffeine does not cause an increase in nucleus accumbens glucose utilization, as do drugs such as heroin, cocaine, and methamphetamine (Fredholm et al., 1999; Nehlig, 1999). All of these observations strongly suggest that caffeine does not act on the dopaminergic structures related to addiction, nor does it improve performance by alleviating any symptoms of withdrawal (Hewlett and Smith, 2006).

Neurological researchers are now focused, to a very large degree, on the possibility of treating, or at least mitigating, the symptoms of Alzheimer's and Parkinson's disease with caffeine. Epidemiological studies have conclusively shown that a higher coffee and caffeine intake is associated with a significantly lower incidence of parkinsonism, probably as a result of the caffeine and not of any of the other compounds contained in that drink (Ross et al., 2000). Recent studies have shown that administration of caffeine shortens the time until maximal plasma concentrations of levodopa are reached, decreases the latency to levodopa walking and tapping motor response, and increases the magnitude of walking response. Caffeine administered before levodopa may improve its pharmacokinetics in some parkinsonian patients (Deleu et al., 2006). Because adenosine A(1) and A(2A) receptors are expressed in the basal ganglia (structures involved in motor control, including Parkinson's disease) and because caffeine acts as an antagonist to both types of receptors, it is possible that caffeine's stimulating effects are exerted via a particular group of projection neurons located in the striatum — the main area that receives input from the basal ganglia, cells expressing very high levels of adenosine A(2A) receptors. These receptors are involved in many intracellular processes, and alterations in just one of them may be sufficient to help patients with Parkinson's disease (Chen, 2003; Fisone et al., 2004).

The other area of intense interest is Alzheimer's disease, where adenosine receptors also seem to play a role. In laboratory animals the pharmacological blockade or gene disruption of adenosine A(2A) receptors confers neuroprotection in several different neurotoxic brain disorders. These disorders can be reversed either by giving coffee or a specific A(2A) antagonist, suggesting that A(2A) is the molecular target responsible for the observed beneficial effects of caffeine consumption in the development of Alzheimer's disease (Dall'Igna et al., 2003).

2.2.11.2 Cardiovascular

Caffeine, regardless of the source, acutely raises blood pressure in naïve individuals, but only for a short time and not to a very great degree (Cameron et al., 1990). When a large (44,005 men and 84,488 women) cohort of American coffee drinkers were followed over a 20-year period, there were 2173 cases of myocardial infarction among the men (724 fatal) and 2254 (693 fatal) among the women. Results of the study strongly suggest that individuals who drank two cups of coffee per day experienced no increase in risk for heart attack. Intake of decaffeinated coffee, tea, and the total caffeine intake were all completely unrelated to the occurrence of coronary artery disease. Even individuals who drank six or more cups of coffee per day did not experience any significant risk in coronary artery disease. At the same time, neither caffeinated nor decaffeinated coffee had any effect on individual lipid profile. It appears that tolerance to caffeine's vascular effects emerges so quickly that caffeine's undesirable effects (such as slight elevation in pulse and blood pressure) are only transient. Another possibility not to be dismissed is that coffee is a very rich source of

antioxidants; it is, in fact, the principal antioxidant in most Americans' diet. It may well be that any damage done by the caffeine is more than offset by the protective antioxidants contained in coffee.

Results are hard to predict when physiologic studies are done with individuals who consume caffeine on a regular basis, presumably because of tolerance (James, 1997). Evidence exists that increasing age is associated with increasing response to the pressor effects of caffeine (Massey, 1998). Some epidemiologic studies suggest that regular coffee consumption may be harmful to those with established hypertension (Nurminen et al., 1999). Even if coffee intake is not associated with coronary artery disease (see earlier), that does not mean that it may not be associated with the occurrence of sudden cardiac death. Of course, a very large intake of caffeine by individuals with coronary artery disease substantially increases the risk for sudden cardiac death (de Vreede-Swagemakers et al., 1999). In some cases death may be due to the presence of an abnormal ryanodine (RyR2) receptor. Point mutations in *RyR2* lead to abnormal Ca^{2+} release following cardiac stimulation which, in turn, can lead to the occurrence of sudden cardiac death (Thomas et al., 2005). In any individual case, such a nexus could only be proven by DNA sequencing.

The results of early studies suggested that caffeine caused the release of catecholamines from the adrenal medulla (Robertson et al., 1978), but the results of more recent research suggest that caffeine-related catecholamine perturbations are minimal. Human volunteers given a mean dose of 250 mg of caffeine exhibited only insignificant increases in catecholamines (Cameron et al., 1990). Rises did occur, but were so trivial that the clinical significance, if any, would have been negligible (Table 2.3.7.3.1 shows catecholamine levels in a number of situations.

All methylxanthines cause the release of calcium ions from the sarcoplasmic reticulum into the cytoplasm, where the calcium acts as a second messenger, altering myofilament contraction and electrical conduction. Some methylxanthines exert more potent effects than others. The differences in potency appear to be a function of differences in membrane permeability to the different methylxanthines (Donoso et al., 1994). A relationship between caffeine intake and ventricular ectopy has always been presumed, but electrophysiologic studies of patients with recurrent ventricular tachycardia have failed to confirm any such action. In fact, some patients with ventricular ectopy who have been treated with caffeine had fewer extra heartbeats after drinking coffee than at baseline (Chelsky et al., 1990). Signal-averaged electrocardiograms (ECGs) of normal subjects before and after administration of 5 mg/kg of caffeine show small but statistically significant prolongation of the signal-averaged QRS complex. The finding is consistent with, but far from proof of, the notion that excessive caffeine intake might be a risk factor for serious arrhythmias (Donnerstein et al., 1998). Similarly, dogs given caffeine intravenously can be made to fibrillate, but only with massive doses of caffeine. After low doses, comparable to those seen in coffee drinkers, either no arrhythmias or only inconsequential arrhythmias occurred, suggesting that the arrhythmogenicity of caffeine is dose related (Mehta et al., 2004).

Cardiac alterations similar to those reported in animals have not been mentioned in the few published human autopsies. In a case of one overdose, with a postmortem caffeine level of 113.5 mg/L and clinical evidence of acute heart failure, there was right atrial dilation, acute pulmonary edema, and passive congestion of the liver, but no specific cardiac lesions could be identified (Bryant, 1981). No anatomic basis could be found in a second case report where there were even higher caffeine levels (181 mg/L), pulmonary edema, and passive congestion of the liver, but the heart was not specifically described (Alstott et al.,

1973). Even though heart failure occurred in a 1860-g 31-week-old child who was accidentally given a caffeine overdose as a treatment for apnea, the child nonetheless survived. Its initial serum concentration was 2175 mg/L 36.5 hours after dosing. Toxic manifestations included heart failure, pulmonary edema, gastric dilatation, metabolic acidosis, and hyperglycemia. Nonetheless, the child made an uneventful recovery (Anderson et al., 1999).

Several case reports of alleged caffeine-related infarction and arrhythmia have been published, but it is difficult to know how they should be interpreted. One case involved a 20-year-old bulimic woman who ingested 20 g of caffeine in a suicide attempt. After being evaluated and discharged from the emergency department, she was re-admitted with ECG changes, and ultimately found to have sustained a subendocardial infarction. Angiography was not performed (Forman et al., 1997).

2.2.11.3 Hematologic

Although the claim is still disputed, some reports have shown that chronic caffeine consumption may lead to a reduction in platelet aggregability due to upregulation of A2A adenosine receptors located on the platelet surface, disrupting normal platelet aggregation and thrombogenesis (Biaggioni et al., 1991). Others have found no such evidence (Cavalcante et al., 2000). In the most recent studies of the subject, mean platelet aggregability after exposure to epinephrine was 11.8 ± 5.7%, significantly lower than those of nontreated group (85.7 ± 9.5%, $p < .01$). There were no significant differences in the mean values of collagen- or ristocetin-induced platelet aggregability between caffeine-treated and nontreated groups. Based on this study, it seems likely that caffeine selectively inhibits the platelet aggregability both to epinephrine and ADP, and disturbs the release of endogenous ADP from platelets in response to exogenous ADP (Choi, 2003).

2.2.11.4 Ergogenic Effects

Caffeine is frequently used by athletes as an ergogenic aid. It improves performance and endurance during prolonged, exhaustive exercise. When caffeine is consumed before prolonged running or cycling (30–60 min), the time to exhaustion is improved by 20–50% at 60–80% of $V0_{2max}$. In one controlled study, elite marathon runners given 9 mg/kg of caffeine before testing were able to increase their time on a treadmill by an average of 70% (Graham and Spriet, 1991). This improvement was achieved without evidence of toxicity, and without exceeding the requirement of the IOC that testing reveal no more than 12 mg/mL of caffeine or the National Collegiate Athletic Association's even more generous limit of 15 mg/mL. In short-term competition, with intense aerobic exercise at greater than 90% of $V0_{2max}$, improved time to exhaustion has been repeatedly confirmed, though the performance increment has not been so great (Magkos and Kavouras, 2005).

Caffeine improves concentration, reduces fatigue, and enhances alertness. Habitual intake does not diminish caffeine's ergogenic properties. Several mechanisms have been proposed to explain the physiologic effects of caffeine, but adenosine receptor antagonism most likely accounts for the primary mode of action. Caffeine is relatively safe and has no known on effects performance, nor does it cause significant dehydration or electrolyte imbalance during exercise. Routine caffeine consumption may cause tolerance or dependence, and abrupt discontinuation is said to produce irritability, mood shifts, headache, drowsiness, and fatigue. Major sport governing bodies ban excessive use of caffeine, but current monitoring techniques are inadequate, and ethical dilemmas persist regarding caffeine intake by athletes (Paluska, 2003).

2.2.11.5 Maternal/Fetal Effects

Caffeine and theobromine cross the placental and the blood–brain barrier, and caffeine ingested during gestation does cause a dose-dependent decrease in body weight, but only when large doses of coffee have been consumed (>7 cups/day of coffee); it has no effect at moderate doses, and thus appears not to have the potential to cause toxicity (Eteng et al., 1997). Investigators do not agree on the quantities of the methylxanthine found in breast milk, but caffeine does not change breast milk composition and, rather, stimulates milk production; maternal caffeine consumption in moderate amounts during gestation and lactation has no measurable consequences on the fetus and newborn infant.

Lingering doubts exist as to whether the consumption of coffee and caffeine is associated with an increased risk of miscarriage. In the most recent study to be published on the subject, women were recruited before or early in pregnancy and interviewed regarding sources of caffeine. The interview included an assessment of changes that had been noted by the mothers during the perinatal period. Two hundred and fifty eight of the 2407 women enrolled lost their child. The researchers examined the relationship of coffee and caffeine to pregnancy loss occurring within the first 20 weeks of gestation. The authors found that consumption was unrelated to total miscarriage risk. The authors concluded there was very little indication of possible harmful effects of caffeine on miscarriage, at least among those women drinking moderate amounts of coffee. They also concluded that their result supported a reporting bias among women with losses, and that their results were more indicative of exposure misclassification and unmeasured heterogeneity of pregnancy losses (Savitz et al., 2008). This finding would be in agreement with the findings of other scientists who have speculated that caffeine only appears to increase miscarriage risk because women with morning sickness, who are more likely to carry a pregnancy to term, avoid coffee and other drinks that contain it, giving the false appearance of a causal relationship.

Given the degree of controversy, it would seem prudent for pregnant mothers to consume coffee and caffeinated beverages in moderation, especially because of the prolonged half-life of caffeine both during the last trimester of pregnancy and in the newborn infant (Nehlig and Debry, 1994).

2.2.12 Autopsy Studies

A 1980 case report described two patients who expired after using repeated coffee enemas. Both had underlying malignancies and both appeared to have succumbed to fluid and electrolyte abnormalities, not to any toxic effect of caffeine. In fact, both of these women had negligible caffeine levels at the time of death (Eisele and Reay, 1980). Blood concentrations in cases of fatal intoxication have ranged from 79 to 1560 mg/L (McGee, 1980; Mrvos et al., 1989). In 1985, Garriott reported on five fatalities — three cases of combined caffeine and ephedrine and two cases of caffeine only. Blood concentrations ranged from 130 to 344 mg/L. The report did not comment on histological findings, if any (Garriott et al., 1985). Another case report describes a 22-year-old woman who committed suicide by taking an unknown number of caffeine tablets. Death appeared to have been the result of cardiac arrhythmia. Blood obtained during attempted resuscitation had an extraordinarily high caffeine concentration of 1560 mg/L. As is true in experimental animals, postmortem findings in this case consisted mainly of pulmonary edema and visceral congestion (Dimaio and Garriott, 1974). Mrvos described a 19-year-old woman who also died of a

ventricular arrhythmia. At autopsy, her caffeine blood level was 181 mg/L, and no histopathologic alterations could be identified (Mrvos et al., 1989).

The more recently reported cases have only contained toxicological data. Four new cases were reported in 2004 — two suicides and two causes undetermined. All four victims had psychiatric or polydrug histories. No autopsy findings were reported, but blood caffeine ranged from 153 to 200 mg/L with many other drugs present (Holmgren et al., 2004). More recently Kerrigan and Lindsey (2005) described two more cases. One decedent was a polydrug user and the other an obese diabetic. Autopsy findings were not discussed, but the blood caffeine level was 597 mg/L in one and 192 mg/L in the other (Kerrigan and Lindsey, 2005). The failure to demonstrate myocardial lesions is consistent with the fact that caffeine toxicity is not associated with marked elevations in circulating catecholamines.

Other studies where caffeine has been the sole agent have all reported caffeine concentrations in comparable ranges. In an 81-year-old female suicide, caffeine concentrations in the heart and stomach were almost identical (180 and 190 mg/L, respectively) (Reisselmann et al., 1999). As with all of the abused drugs, tolerance occurs (although the mechanism is not clear), and high caffeine levels have been recorded in patients who survived massive caffeine overdoses. Blood levels of 200 mg/L were recorded in a woman who took 24 g of caffeine in an unsuccessful suicide attempt. Her theophylline level was 17.2 mg/L (Benowitz et al., 1982). Another report described the case of a 27-year-old man who regularly ingested coffee grounds in order to get "high." On one occasion, he doubled his usual dose and swallowed half a kilogram of ground coffee. He arrived at the hospital comatose, febrile, hypertensive, tachycardic, and seizing. He survived but required intense treatment with beta blockers and anticonvulsants. His caffeine blood concentration was 29 mg/L (Wurl, 1994). There remain a number of other cases in the literature, but all involve multiple drugs, and there is no way to attribute toxicity to one or the other or any possible interaction that may have occurred.

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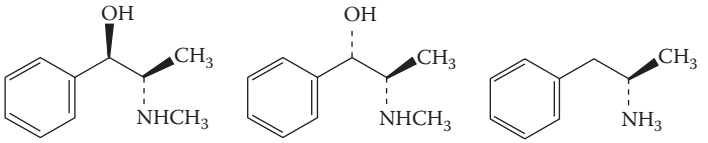
2.3 Ephedrine

Name: Ephedrine, isomeric forms include (±)-ephedrine and (±)-pseudoephedrine. The two naturally occurring isomers are (–)-ephedrine and (+)-pseudoephedrine.
Systematic name: [1-(methylamino)ethyl]benzene-methanol]
Formula: $C_{10}H_{15}NO$
Molecular weight: 165.23 daltons



L-(−)ephedrine D-(+)-pseudoephedrine Amphetamine

Figure 2.3.1 Ephedrine and pseudoephedrine. The principal importance of ephedrine is its role as a precursor in the illicit production of methamphetamine; however, ephedrine is a potent stimulant in its own right and has significant abuse potential.

Metabolism: mostly unmetabolized, some undergoes *N*-demethylation, but enzyme responsible is not known

V_{ss}:

a. epinephrine: 1.71–3.70 L/kg, mean 3.08 (22 mg, $n = 10$) (Pickup et al., 1976)

b. pseudoephedrine: 1.5–4.32 L/kg, mean 2.64 (129 mg, $n = 16$) (Dickerson et al., 1978), 2.4 ± 4 L/kg (dose 50 mg, children, $n = 21$) (Simons et al., 1996)

Half-life:

a. ephedrine: 4.48–11.48 hours (22 mg, $n = 10$) (22 mg, $n = 10$) (Pickup et al., 1976)

b. pseudoephedrine: 2.2–107 hours, mean 5.9 (129 mg, $n = 16$) (Dickerson et al., 1978), 3.1 ± 0.4 (dose 50 mg, children $n = 21$) (Simons et al., 1996)

C_{max}:

a. ephedrine: 52.7–138.8 ng, mean 79.4 ng (22 mg, $n = 10$) (Pickup et al., 1976)

b. pseudoephedrine: 116–649 ng/mL, mean 447 (129 mg, $n = 16$) (Dickerson et al., 1978), 492 ng/mL (dose 50 mg, $n = 21$) (Simons et al., 1996)

Time to maximum concentration:

a. ephedrine: 1.81 hours (22 mg, $n = 10$) (Pickup et al., 1976)

b. pseudoephedrine: 2.4 ± 0.2 hours (dose 50 mg, $n = 21$) (Simons et al., 1996)

Clearance:

a. ephedrine: 9.2 ± 0.4 mL/min/kg (dose 50 mg, children, $n = 21$) (Simons et al., 1996)

Interactions: may precipitate acute angle glacouma (Lachkar and Bouassida, 2007)

Dickerson, J., Perrier, D. et al. (1978). Dose tolerance and pharmacokinetic studies of L (+) pseudoephedrine capsules in man, *Eur. J. Clin. Pharmacol.*, 14(4), pp. 253–9.

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2.3.1 General

In spite of the complete absence of controlled clinical trials, the FDA concluded that ephedrine-containing food supplements were too dangerous to remain on the market, and all OTC products containing ephedrine were banned in April 2004. However, the FDA continues to allow prescription use of ephedrine, and possession of ephedrine is not illegal. Though sometimes used to treat narcolepsy and attention deficit disorder, the main use for

ephedrine today is in the production of methamphetamine. The latter can be synthesized from ephedrine via reduction of chloroephedrine with hypophosphorous acid. International controls on ephedrine have been increased in an effort to control methamphetamine production. As a consequence, illicit methamphetamine is now made using pseudoephedrine as the starting material.

2.3.2 Epidemiology

Ephedrine can be extracted from plants (primarily those grown in Pakistani and China), or it can be synthesized, though most of the drug for sale is made from natural products. In recent years Chinese production of ephedra extract powder (6%, 8%, 10% strengths) has been increasing. Most of this output is or was exported to the U.S., though now diversion to the Mexican super-labs or other illicit methamphetamine producers, such as Burma, is more likely.

Since the dismantling of the DAWN report, there is no single source that can be relied upon for epidemiological information. The U.S. Government's National Drug Intelligence Center no longer follows trends in ephedrine production, except as they relate to the use of ephedrine as a methamphetamine precursor. Ephedrine is not mentioned in the U.S. Department of Justice annual report on drug intelligence, nor does it rate a mention in the National Survey on Drug Use and Health for 2006.

2.3.3 History

Ephedra plants have been identified at European Neanderthal burial sites from 60,000 B.C. (Lietava 1992). Traditional Chinese healers used ephedra extracts thousands of years before Pliny, and the ancient Romans accurately described both the ephedra plant and its medical uses. Chinese texts from the 15th century recommended ephedra as an antipyretic and antitussive. At about the same time that the Chinese began using ephedra, Russian herbalists used ephedra extracts to treat joint pain, and recent laboratory studies confirm that ephedra might be useful for that purpose (Ling et al., 1995). In the 1600s, Indians and Spaniards in the American Southwest used ephedra as a treatment for venereal disease (Grinspoon and Hedblom, 1975). Settlers in the American West brewed ephedra teas, which were referred to by a variety of names, including teamsters' tea, Mormon tea, and chaparral tea (Max, 1991).

The modern rediscovery of ephedrine can be attributed to the work of Nagayoshi Nagi, a Japanese-born, German-trained chemist, who first isolated and crystallized ephedrine in 1885 (Holmstedt, 1991). Nagi's original observations were confirmed by Merck chemists, who thought that ephedrine might have commercial value, but sales were never very great and ephedrine production was all but abandoned until 1930, when Chen and Schmidt published a paper recommending ephedrine as a primary treatment for asthma. Following the publication of Chen and Schmidt's report, ephedrine quickly replaced epinephrine as the first-line treatment for asthma.

Ephedrine became such a popular drug that there were concerns that demand would exceed supply. The possibility of an ephedrine shortage fostered research on methods to synthesize it. Amphetamines were created largely as a byproduct of those efforts. The anticipated ephedrine shortage never emerged, but ironically ephedrine sales soared during the 1990s because ephedrine was the preferred precursor for use in the illicit manufacture of methamphetamine. Because government controls now limit the use of ephedrine

for this methamphetamine production, ephedrine largely has been replaced by its enantomers, phenylpropanolamine (now withdrawn from the market) and pseudoephedrine, as the precursors of choice in clandestine laboratories.

In addition to being an effective bronchodilator, ephedrine in large doses is a potent CNS stimulant (Martin et al., 1971). Ephedrine injections called *philopon* (which means "love of work") were given to Japanese Kamikaze pilots during World War II. During the 1940s the Japanese government distributed ephedrine pills to almost anyone who wanted them (in hopes of reducing combat fatigue and increasing industrial output). After 1945 large stocks of the drug, either looted from military supplies or sold by the army in hopes of raising cash, flooded the market. In 1952 ephedra was finally made illegal and immediately became a revenue generator for the criminal underground (yakuza gangs). During the epidemic of the 1950s, abusers in Japan injected themselves with ephedrine, then called *hiropon*, in much the same way that methamphetamine is injected today (Deverall, 1954).

Filipinos have, for many years, smoked a mixture of ephedrine and caffeine called *shabu* (in Japan the same word is used to describe amphetamines in general). In the late 1980s, shabu smoking gave way to the practice of smoking methamphetamine ("ice"). In what is perhaps a tribute to the past, some "ice" is sold under the *hiropon* name today. After the passage of the DSHEA act in 1994 hundreds of "food supplement" producers came into being. Mainly they sold ephedrine combined with caffeine. That industry no longer exists, and ephedrine has been largely replaced by more effective decongestants and treatments for asthma, but it is still widely used for the prophylaxis and treatment of hypotension caused by spinal anesthesia (Flordal and Svensson, 1992; Yap, 1998).

2.3.4 Sources

Ephedrine (ephèdre du Valais in French and Walliser Meerträubchen in German) can be extracted from a group of closely related species of plants that grow in Asia, Western Europe, Southeastern Europe, and even the New World. The alkaloid content of these plants varies quite considerably. The best known species, *Ephedra sinica* (average 1.3% alkaloid content) and *E. equiseti* (average 2.2% alkaloid content) are collectively known as *ma huang* and are grown mainly in China, Northern India, and Pakistan (Cui et al., 1991). *E. gerardiana, E. intermedia*, and *E. major* grow in South West Asia, while other members of the family Ephedraceae can be found in Europe and the U.S. (*E. distachya, E. vulgaris*).

The most common Chinese cultivar (called China 3) contains 1.39% ephedrine, 0.361% pseudoephedrine, and 0.069% methylephedrine (Sagara et al., 1983). This mix is fairly typical for commercially grown ephedra plants (Zhang et al., 1989; Cui et al., 1991; Gurley et al., 1998). Only *L*-ephedrine occurs naturally.

Ephedrine can now be produced synthetically (benzaldehyde is fermented with brewer's yeast, followed by reductive condensation with methylamine, yielding pure (–)-ephedrine), but there is no evidence that clandestine drug makers are utilizing this approach (Dewick, 1997).

2.3.5 Routes of Administration

Ephedra may be taken orally, injected, or smoked. The latter route is reserved for abusers, primarily in the Philippines, where the practice has been popular for many years. No data on the pharmacokinetics of smoked ephedra or smoked pure ephedrine have been

published. Peak ephedrine levels after an oral dose of 400 mg of *ma huang* (equivalent to 20 mg of pure ephedrine) result in blood concentrations of 81 ng/mL (White et al., 1997). Very nearly the same peak ephedrine levels were seen after giving an equivalent amount of pure ephedrine (25 mg) or the equivalent amount of ephedrine given in combination with other botanicals (Gurley et al., 1998).

In a separate study, 50 mg of ephedrine given orally to six healthy 21-year-old women produced mean peak plasma concentrations of 168 ng/mL (Vanakoski et al., 1993). The results are comparable to those obtained in studies done nearly 30 years earlier (Wilkinson and Beckett, 1968). In a study performed to assess the effectiveness of caffeine/ephedrine combinations as performance-enhancing agents in combat troops, volunteers ($n = 20$) were treated with 375 mg of caffeine, 75 mg of ephedrine, 375 mg of caffeine combined with 75 mg of ephedrine, or placebo. Modest elevations in pulse and blood pressure were seen in all the treatment groups, with peak effects occurring one to two hours post administration. Maximal ephedrine concentrations of approximately 300 ng/mL occurred at three hours. Maximal caffeine concentrations were also reached at three hours and ranged from 7 to 8 mg/L. Drug concentrations when the two agents were taken together were no higher than when they were taken separately, and there was no significant measurable increase in catecholamine levels (Bell et al., 1998, 2001, 2002; Jacobs et al., 2003).

Methylephedrine is a minor component of most ephedra plants, but in Japan it is produced synthetically and used in cough and cold remedies. One of these products (called BRON) is very widely used (Tokunaga et al., 1989; Ishigooka et al., 1991; Levine et al., 1993; Nakahara and Kikura, 1997). Blood concentrations of methylephedrine in patients taking BRON for legitimate therapeutic purposes are usually less than 0.3 mg/L (Kunsman et al., 1998). Higher concentrations appear to produce toxic effects, usually psychiatric.

2.3.6 Metabolism and Pharmacology

Ephedrine stimulates β_1 and β_3 receptors. The net result of β_1 stimulation is a modest, somewhat unpredictable increase in pulse and blood pressure. The degree of increase is somewhat unpredictable because of concomitant, but variable, increases in peripheral resistance that occur at the same time — the phenomenon is known as diastolic runoff (Webb and Shipton, 1998). In some situations, administration of ephedrine may result in decreased systemic blood pressure, simply because β-induced vasodilation occurs concurrently in the extremities.

Ephedra extracts contain a complex mixture of phenylpropanolamines (Rothman et al., 2003; Ma et al., 2007) with several isomers including (+)- and (–)-ephedrine and (+)- and (–)-pseudoephedrine. In fact, all of the agonists had their highest affinities as norepinephrine transporter substrates. Most of the compounds also had modest activity as dopamine transporter substrates. None of the tested compounds displayed any functional activity at cloned human α_{1A}-adrenergic or cloned human α_2-adrenergic receptors (Rothman et al., 2003). Taken together, these results are consistent with the notion that the main cardiovascular actions of ephedrine and related phenylpropanolamines are due to an indirect sympathomimetic action (Roth et al., 2004).

Ephedrine is one of the few naturally occurring drugs that is an agonist at β_3 receptors. This receptor mediates various pharmacological and physiological effects such as lipolysis, thermogenesis, and relaxation of the urinary bladder. Investigations continue into the possibility that the β_3-AR might be one way to cure obesity, type 2 diabetes

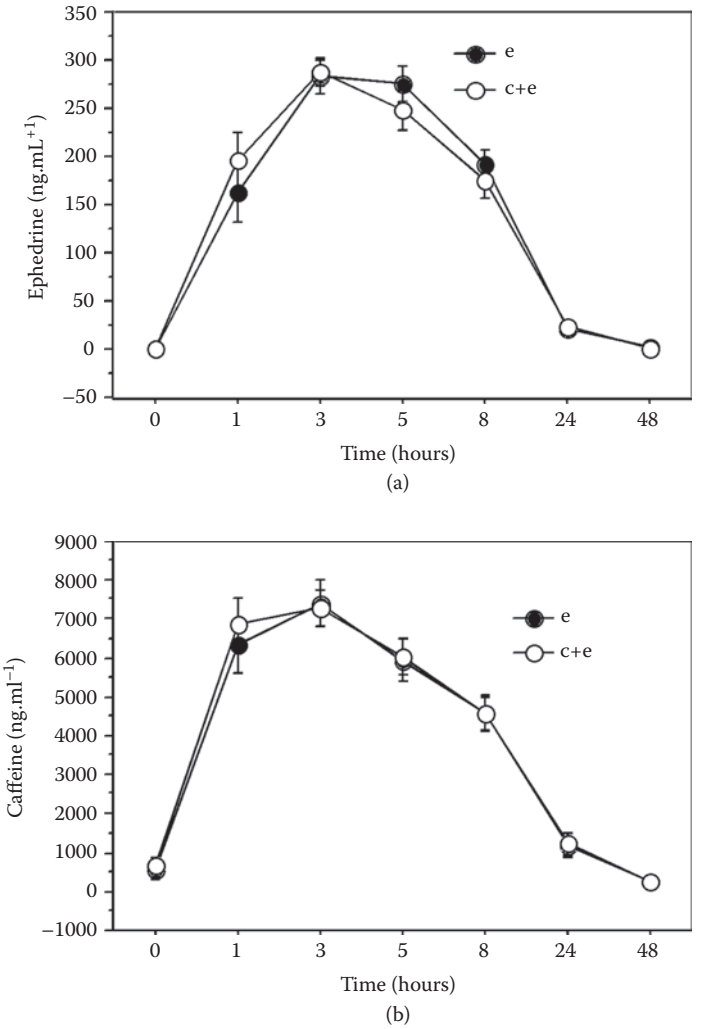

Figure 2.3.6.1 Plasma ephedrine levels after ephedrine and caffeine/ephedrine ingestion. The level of ephedrine in the plasma after ephedrine alone and after ephedrine combined with caffeine had no effect on clearance rates. Peak levels occurred between two and four hours after drug ingestion. Caffeine concentrations peaked at between one and two hours, regardless of whether the caffeine was given alone or in combination with ephedrine. (Courtesy of Douglas Bell, Defense and Civil Institute of Environmental Medicine, the Department of National Defense of Canada, Toronto, Ontario.)

mellitus, and frequent urination (Sawa and Harada, 2006). Investigation is difficult because the β_3-AR gene is highly polymorphic, making it impossible to predict just what effect β_3 agonists will exert upon patients. It has been reported that one of these mutations is correlated with the occurrence of diabetes and hypertension in obese individuals. Other studies suggest a relationship between polymorphism and carcinogenesis (Babol and Blasiak, 2005). Other clinical studies have produced results suggesting that ephedrine can produce peroxisome proliferators (and therefore weight loss) via β_3 stimulation (Bogacka et al., 2007).

Ephedrine's usefulness as a bronchodilator is limited by the number of β receptors located on the bronchi. The number of β receptors located on human lymphocytes correlates with the number found in the lungs, and it has been observed that they decrease rapidly after the administration of ephedrine; the density of β binding sites drops to 50% of normal after 8 days of treatment, and returns to normal 5–7 days after the drug has been withdrawn (Neve and Molinoff, 1986). The down-regulation of receptors renders ephedrine useless as a bronchodilator after a few weeks, which explains why ephedrine is no longer used as a first-line drug in the treatment of asthma.

Each of the ephedrine isomers has different pharmacokinetic and toxicokinetic profiles. Phenylpropanolamine, now withdrawn from the U.S. OTC market, is readily and completely absorbed, but pseudoephedrine (the sale of which is now much restricted in hopes of limiting methamphetamine manufacture) is subject to gut-wall metabolism and has a bioavailability of only 38% (Kanfer et al., 1993). Pure ephedrine is well absorbed from the stomach, but absorption is slower when ephedrine is given along with other botanicals rather than when it is given in its pure form (Gurley, 2000). Peak plasma concentrations occur 2.5–3 hours after administration. The volume of distribution of ephedrine appears to be the same whether or not pure drug is given or equivalent amounts are given in ephedra mixtures: 2.5–3.0 L/kg (Gurley et al., 1998).

Ephedrine is eliminated in the urine largely as unchanged drug, with a half-life of about 3–6 hours. Peak concentrations for the other enantomers, specifically phenylpropanolamine and pseudoephedrine, are shorter (0.5 and 2 hours, respectively) than for ephedrine, but both drugs are extensively distributed into extravascular sites, with apparent volumes of distribution that are greater than that of ephedrine (2.6 L/kg for phenylpropanolamine and 5.0 L/kg for pseudoephedrine). No protein-binding data in humans are available. Urinary excretion of all three enantomers is pH dependent. Excretion may be much more rapid in children, and a greater dosage may be required to achieve therapeutic effects. Unlike amphetamines, acidification of the urine has no effect on ephedrine excretion (Wilkinson and Beckett, 1968).

Patients with renal impairment are at special risk for toxicity because ephedrine isomers may accumulate (Kanfer et al., 1993). None of the enantomers is easily removed by dialysis, and the only treatment is supportive, using pharmacologic antagonists to counter the α- and β-adrenergic effects of these drugs (Lyon and Turney, 1996). Because excretion is pH dependent, patients with renal tubular acidosis, a rare disorder, are also at particular risk (Brater, 1980).

Traditional Chinese herbalists have always claimed that *ma huang* could be used to treat arthritis and, although Western-style clinical trials are still lacking, it appears that these claims could have a scientific foundation. One problem in establishing efficacy is that traditional herbalists usually combine ephedra with other herbs, or even acupuncture. In animal models of arthritis, mRNA expression of TNF-α and interleukin (IL)-6 genes, which are stimulated in arthritic rat joints, return to normal levels after treatment with ephedrine (Yeom et al., 2006).

2.3.7 Toxicity by Organ System

Judged by reports in the peer-reviewed literature alone, the most frequent complications of ephedrine abuse appear to be behavioral. However, in non-abusers case reports describing toxicity are simply too few to permit generalizations. A large collection of controlled

clinical ephedrine trials were undertaken in the 1960s and 1970s when drug makers began to introduce new, more effective anti-asthmatics. The side effect profile that emerged was not very different than that of pseudoephedrine — generally benign.

2.3.7.1 Neurological

Ephedrine-induced psychosis has been reported with some regularity (Herridge and a'Brook, 1968; Roxanas and Spalding, 1977; Whitehouse and Duncan, 1987; Ishigooka et al., 1991; Capwell, 1995; Doyle and Kargin, 1996; Jacobs and Hirsch, 2000; Boerth and Caley, 2003; Kim and LeBourgeois, 2004; Miller, 2005). Ephedrine psychosis closely resembles amphetamine psychosis: paranoia with delusions of persecution, auditory and visual hallucinations, but consciousness remains unclouded. Typically, patients with ephedrine psychosis will have ingested more than 1000 mg per day. Recovery is rapid after the drug is withdrawn (Kalix, 1991; Nakatani and Hara, 1998). The results of neurochemical studies suggest that the basis for ephedrine-induced behavioral changes may be altered dopamine metabolism.

Intracranial hemorrhage has been reported, but almost always in the setting of drug overdose (Loizou et al., 1982; Wooten et al., 1983; Stoessl et al., 1985; Glick et al., 1987; Forman et al., 1989; Bruno et al., 1993; Baker et al., 2005; Kendirli et al., 2006; Kunieda et al., 2006). Only a handful of peer-reviewed reports describing cerebral infarction in ephedrine users have been published, and most contained so little detail that causation assessment is impossible (Gorey et al., 1992; Haller and Benowitz, 2000; Vahedi et al., 2000; du Boisgueheneuc et al., 2001; Chen et al., 2004).

2.3.7.2 Renal

Chronic ephedrine use has occasionally been implicated as the cause of renal calculi (Schweisheimer, 1976; Powell et al., 1998; Assimos et al., 1999; Hoffman et al., 2003; Bennett et al., 2004; Song et al., 2005). A large commercial laboratory that analyzes kidney stones found that 200 of 166,466 stones (0.064%) contained either ephedrine or pseudoephedrine (Blau, 1998). Unfortunately, the analytic technique utilized by that laboratory could not distinguish between ephedrine and pseudoephedrine. Except for the possibility of renal stones, no direct effect on the kidney or altered renal function has ever been demonstrated, nor is there any evidence that ephedrine exerts diuretic effects. Urinary retention can occur as a consequence of drug overdose (Glidden and DiBona, 1977; Lindberg, 1988) but has not been reported when recommended doses are consumed.

2.3.7.3 Cardiovascular

Even though it has never been observed by anesthesiologists, who use the drug frequently, it has been suggested that ephedrine causes dangerous QT prolongation. Researchers, using a double-blind controlled study design, found that participants who received ephedrine/caffeine mixtures were more likely to experience a QTc interval increase of at least 30 milliseconds vs. placebo (8 individuals — 53.3%), which would place them at higher risk of developing torsade de pointes (McBride et al., 2004). A later study showed that the Bazett correction (the formula used most often by hospital computers to correct the QT interval for rate) overestimates the corrected QT interval: the higher the heart rate increase, the greater the increase in calculated QT interval duration (Milic et al., 2006). Intraspinal ephedrine has no effect on QTc (Sen et al., 2006), and there is actually evidence that in severely pre-eclamptic women, spinal anesthesia may actually normalize the QT interval

Table 2.3.7.3.1 Catecholamine Concentrations

Activity/Condition	Ephedrine (pg/mL)	Norephedrine (pg/mL)
Resting	35 (Eisenhofer et al., 2005)	200–300 (Eisenhofer et al., 2005)
Normal exercise	700 (Bell et al., 2001)	299–300 (Bell et al., 2001)
Exercise and ephedrine	700 (Pott et al., 1996; Bell et al., 2001)	300 (Bell et al., 2001)
Heart failure	35–75 (Yan et al., 2005)	500–800 (Yan et al., 2005)
Pheochromocytoma	35 (Eisenhofer et al., 2005)	3000–5000 (Eisenhofer et al., 2005)
Cocaine	30–40 (Sofuoglu et al., 2001)	1000–2000 (Sofuoglu et al., 2001)
Cardiac arrest	10,000–100,000 (Wortsman et al., 1984)	500–600 (Wortsman et al., 1984)

(Sen et al., 2006). Thus, it appears that concerns over ephedrine-related QT prolongation were actually based on a mathematical artifact.

It has also been suggested that ephedrine causes increased plasma catecholamine concentrations. However, catecholamine concentrations in exercising ephedrine users are not altered by catecholamine administration.

A handful of case reports describe heart failure in ephedrine abusers. One was a 35-year-old asthmatic taking 4000 mg of ephedrine per day and "liberal doses of prednisolone" for 14 years. Another involved a woman who had been abusing ephedrine (300–600 mg/day) for 10 years, and a third case involved a 28-year-old, cigarette-smoking, 321-pound woman taking 2000 mg of ephedrine every day for 8 years (To et al., 1980; Gaulteri, 1996; Schafers et al., 1998; Naik and Freudenberger, 2004; Mark et al., 2005). The difficulty in interpreting these reports is that histological findings were not described, and angiography was not performed, making it virtually impossible to establish the diagnosis of cardiomyopathy.

Similar considerations apply to the possible relationship, if any, between myocardial infarction and ephedrine use. One case report describes a 25-year-old man who injected himself intravenously with an unknown amount of what he believed was amphetamine. It was, in fact, ephedrine, and he sustained a posterior wall infarction. Blood ephedrine concentrations were not determined (Cockings and Brown, 1997). No case report in the peer-reviewed literature has ever linked the use of ephedrine to actual clinical episodes of myocardial infarction. That is not the case, however, for ephedrine isomers. Myocardial necrosis and arrhythmias have been reported both in humans and experimental animals after administration of phenylpropanolamine (Pentel et al., 1982) and, more rarely, after pseudoephedrine (Wiener et al., 1990). The relative paucity of ephedrine-related infarcts (Forte et al., 2006), but the much more common occurrence of infarction with the other ephedrine isomers, may be explained by the fact that the latter are both more effective α agonists than ephedrine.

If, in fact, any clinical trial were to link ephedrine use to myocardial infarction, the connection would probably have to do with increased calmodulin kinase II activity. Increased activity of this enzyme is linked to arrhythmias (Wu et al., 2002; Kirchhof et al., 2004), sudden death, and mechanical dysfunction (Zhang et al., 2003). Unlike cocaine, which causes increased production of calmodulin kinase II, leading to myocardial hypertrophy and elevated intracytosolic calcium, thereby increasing the likelihood of lethal arrhythmia (Henning and Cuevas, 2006), ephedrine has never been demonstrated to have any such effect.

2.3.7.4 Gastrointestinal

Chronic ephedrine abusers are prone to develop hepatic steatosis. In the only published autopsy series fatty liver infiltrates were found in approximately one fifth of the decedents, but since almost all the decedents were polydrug abusers, attributing causation is impossible (Blechman et al., 2004), especially as there is evidence that, in animal studies at least, ephedrine may be hepatoprotective (Yamada et al., 2008).

2.3.7.5 Dermatological

Use of ephedrine (Catlin et al., 1993; Villas Martinez et al., 1993) and its enantiomers is occasionally associated with the occurrence of nonpigmented fixed drug eruptions (Tomb et al., 1991; Garcia Ortiz et al., 1997; Anibarro and Seoane, 1998; Vega et al., 1998; Moreno-Escobosa et al., 2002). Similar eruptions have been reported in cocaine users (Hofbauer et al., 1999).

2.3.8 Drug Testing

The IOC, while not entirely banning ephedrine consumption, has ruled that urine levels of over 1000 ng/mL indicate abuse and are grounds for disqualification. The 1000-ng/mL level set by the IOC is probably unrealistically low, since ephedrine is still used as a nasal decongestant in Europe and other countries. IOC rules consider each ephedrine enantiomer separately. However, under its new rules the World Anti-Doping Agency (WADA) can issue TUEs (therapeutic use exceptions). In order to obtain such an exemption, pulmonary function testing is required. It seems unlikely that ephedra users would ever be granted a TUE since healthy volunteers given realistic doses of ephedrine-containing nasal spray (roughly 14 mg) were found to have urine levels ranging from 0.09 to 1.65 mg/mL (Lefebvre et al., 1992).

Occasionally, innocent non-abusers may find themselves falsely accused of ephedra abuse. A Dutch professional cyclist who thought he was using a perfectly legal, ephedra-containing food supplement found to his surprise that he was taking cathine, a weak stimulant present in both khat and ephedra (Ros et al., 1999). When tested after a competition, the bicyclist's urine was found to contain 20.2 mg/mL of norpseudoephedrine (cathine). No species of ephedra contains more norpseudoephedrine than ephedrine, and most contain substantially less. Obviously, the makers of the supplement had been spiking their product with norpseudoephedrine. Ignorance of the law is not a sufficient excuse for the IOC or WADA, since both organizations enforce a policy of strict liability.

2.3.9 Postmortem Tissue Measurements and Autopsy Findings

There is only one controlled study of the postmortem toxicology findings in ephedrine-related deaths. The Office of the San Francisco Medical Examiner undertook a review of all cases from 1994 to 2001, where ephedrine or any its isomers were detected (Blechman et al., 2004). The anatomic findings in ephedra-positive cases were compared to those in a control group of drug-free trauma victims. Of 127 ephedra cases identified, 33 were due to trauma. Decedents were mostly male (80.3%) and mostly Caucasian (59%).

Blood ephedrine concentrations were < 0.49 mg/L in 50% of the cases, but ranged from 0.07 to 11.73 mg/L in trauma victims, and 0.02 to 12.35 mg/L in non-trauma cases. Norephedrine (NE) was present in the blood of 22.8% (mean of 1.81 mg/L, SD = 3.14 mg/L) and

in the urine of 36.2% (mean of 15.6 mg/L, SD = 21.50 mg/L). Pseudoephedrine (PE) was present in the blood of 6.3% (8/127). More than 88% (113/127) of the decedents also tested positive for other drugs, the most common being cocaine (or its metabolites) and morphine. The most frequent pathologic diagnoses were hepatic steatosis (27/127) and nephrosclerosis (22/127). Left ventricular hypertrophy was very common and coronary artery disease was detected in nearly one third of the cases. The most common abnormalities in ephedra-related deaths were those generally associated with chronic stimulant abuse. There were no cases of heat stroke and no cases of rhabdomyolysis. In most instances, norephedrine was not detected, suggesting it plays no role in ephedrine toxicity.

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2.4 Khat

Synonyms: Khat, qat, quat, chat, miraa
Chemical name: (*S*)-(–)-α-aminopropiophenone, (*S,S*)-(+)-norpseudoephedrine (cathine), and (*R,S*)-(–)-norephedrine
Formula: $C_9H_{11}NO$
Molecular weight: 165.23 daltons

Metabolism:
Bioavailability: > by chewing 36–59 g (Toennes et al., 2003)
a. cathinone: 45% (Toennes et al., 2003)
b. cathine: 45% (Toennes et al., 2003)
c. norephedrine: 59% (Toennes et al., 2003)

T_{max}: After chewing whole leaf, the mean half life for cathinone, cathine, and norephedrine should be 2.31 ± 0.65, 2.62 ± 0.77, and 2.84 ± 0.42 hours, respectively (Toennes et al., 2003).

Average C_{max}: (chewing, 0.8 mg/kg, $n = 6$; 127 ± 53 [SD] ng/mL) (Widler et al., 1994); cathinone: range 58.9 ± 18.8 ng/mL; cathine, range 71.2 ± 19.0; norephedrine 72.7 ± 12.2

Terminal half-life:
a. (chewing, 0.8 mg/kg, $n = 6$), 127 ± 30 minutes (Widler et al., 1994)
b. (chewing 0.64 to 1.7 g)
Cathinone $T_{\alpha} = 0.39 \pm 0.07$ hours
Cathinone $T_{\beta} = 1.50 \pm 0.081$ hours
Cathine $T_{\alpha} = 0.24 \pm 0.17$ hours
Cathine $T_{\beta} = 5.22 \pm 3.36$ hours

Apparent V_{ss}: (chewing, 6 g, $n = 4$) cathinone, 2.765 ± 1.6 L/kg; cathine 0.7 ± 0.35 L/kg (Toennes et al., 2003)

Interactions: none known

Toennes, S. W., Harder, S. et al. (2003). Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves, *Br. J. Clin. Pharmacol.*, 56(1), pp. 125–30.
Widler, P., Mathys, K. et al. (1994). Pharmacodynamics and pharmacokinetics of khat: a controlled study, *Clin. Pharmacol. Ther.*, 55(5), pp. 556–62.

2.4.1 Incidence and Epidemiology

Khat is native to the sub-Sahara and is cultivated on the mountain slopes of Yemen, where use is endemic. Khat also grows well in California, the desert southwest of the U.S., Oregon, and Florida where its popularity seems to be increasing. Khat chewing is prohibited in most European countries, but is legal in the U.K. With the exception of immigrants from the sub-Sahara, the practice of khat-leaf chewing has not been adopted by the remainder of the U.S. population. Khat does not even rate a mention in any of the standard government surveys, including the Annual Household Survey and DAWN reports. According to some estimates, 5–10 million people around the world chew khat on a daily basis (Balint et al., 1991).

2.4.2 Cultivation and Manufacture

Although it grows in the U.S. (Wallace, 1998), most of the khat consumed in the U.S. is illegally imported. According to the United Nations, 15 different nations reported khat seizures, amounting to 19 tons, in 2005 (seized cannabis amounted to 115 tons). The rate of use appears to be declining, at least in Africa where use has dropped by more than 7% in the last several years. On the other hand, there are reports that popularity is increasing in Scandinavia (Al-Samarraie et al., 2007).

2.4.3 History

Khat is an evergreen that grows at high altitudes in East Africa and the Arabian peninsula. Its leaves contain a naturally occurring psychostimulant closely related in structure to ephedrine and amphetamine. Khat first came to the notice of Europeans in 1762, when the botanist Peter Forskal found it growing on the mountain slopes in Yemen (Pantelis et al., 1989). The habit of chewing khat leaves is much older. Historical references date to the 13th century, when the Arab physician Naguib Ad-Din gave khat leaves to soldiers to relieve fatigue (Giannini et al., 1986). Ad-Din might not have been the first ever to give soldiers psychostimulants, but he was certainly one of the earliest to experiment with performance-enhancing drugs. Since Ad-Din's pioneering experiments, the practice has been repeated many times. Aschenbrant gave cocaine to Prussian recruits during the Franco-Prussian war, while both Japan and the Allies issued amphetamines to their troops during World War II (and apparently still do — see Section 2.3 and Chapter 1).

In 1852, James Vaughn, an English surgeon, published an illustration and an account of khat chewing in the *Pharmaceutical Gazette* (Vaughn, 1852). Figure 2.4.3.1 is from

Figure 2.4.3.1 Khat leaves. This drawing from 1852, published in the *Pharmaceutical Journal* of London, was the first illustration of khat to appear in the English literature. Khat abuse is still a problem in Africa, where some of the gratuitous violence in areas such as Somalia is attributed to it.

Figure 2.4.3.2 Fresh khat leaves. Because they contain amphetamine-like substances they are illegal in the U.S., but use is still permitted in the U.K. and parts of Europe and Africa. (From the DEA website.)

Vaughn's paper. Vaughn speculated that the principal reason for the popularity of khat was that, unlike alcohol, the Koran did not forbid its use. Khat chewing is usually a social event, with sessions often lasting for hours. In some areas of Africa where khat chewing is still popular (the World Health Organization estimates that there are still millions of khat users), houses often have a special room, called a *muffraj*, just for that purpose.

The normal dose is 100–200 g of leaves and stems chewed over a 3–4-hour period (Max, 1991). An occasional solitary individual will chew to increase his work capacity, and ever since the period of almost continuous warfare in the region, soldiers have begun consuming prodigious quantities prior to combat. Users describe increased feelings of alertness and an improved ability to concentrate. Use is also said to make people friendlier and improve the flow of ideas (Kennedy et al., 1983). Nonetheless, use of this material conforms to most definitions of addiction. Chewers attempting to secure their daily supply of leaves will do so to the exclusion of all other activities. In Yemen, 4% of all arable land is used to grow khat, and 10% of the revenues in Djibouti are derived from taxes on khat (Max, 1991).

2.4.4 General

Khat is a large, slow-growing, evergreen shrub; in the right environment it can grow to a height of 10 meters. In certain areas it is grown mixed in with coffee plants (the same method is sometimes used to conceal coca crops in South America). Khat leaves lose their potency with aging and the tips of young branches are preferred for chewing. The principal psychoactive agent, cathinone, is slowly absorbed. In a controlled setting maximal plasma concentrations occur at approximately 2 hours. Cathinone is the ketoanalog of cathine, and as such penetrates the blood–brain barrier far more quickly than cathine — hence its greater psychoactivity.

The primary constituents of khat leaves are norpseudoephedrine, norephedrine, 3,6-dimethyl-2,5-diphenylpyrazine, and 1-phenyl-1,2-propanedione (Szendrei, 1980;

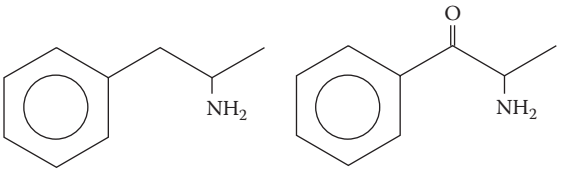

Figure 2.4.4.1 Cathinone molecule. Many of the effects of khat are similar to those produced by amphetamine. The structures of both molecules bear a strong resemblance to each other.

Brenneisen et al., 1986). The first two compounds occur in the leaves and are also produced by metabolic breakdown, so that any measurement of their blood concentration will include some drug that is ingested and some that is metabolized. This makes pharmacokinetic studies difficult and uncommon (Widler et al., 1994). Maximal plasma concentrations of norephedrine and norpseudoephedrine are achieved at about 3.3 and 3.1 hours, respectively. These two drugs have a much longer duration of action than cathinone, where terminal half-lives could not be calculated after 10 hours.

If many of the mood alterations induced by khat resemble those produced by amphetamine, it is not by chance. The active ingredient, cathinone, has the same basic configuration as amphetamine (Figure 2.4.4.1). A second active component, cathine, is much less active because its lipid solubility is much lower than that of cathinone. During storage and transport, cathinone is rapidly converted to cathine, and the result is a considerable loss of potency. Only fresh leaves have any commercial value, and the fragile nature of the product probably explains why it is not more widely distributed (Giannini et al., 1986).

Analysis of khat leaves seized at the airport in Basel, Switzerland, showed the leaves contained, on average, 1 mg of cathinone, 0.86 mg of norpseudoephedrine, and 0.47 mg of norephedrine per gram of leaf (Widler et al., 1994). Absorption of cathinone from the leaves is a slow process. When volunteers were given leaves containing a total of 0.8 mg cathinone per kilogram body weight, maximal plasma concentrations (127 ± 53 ng/mL) were not reached until more than 2 hours after the subjects started to chew the leaves (127 minutes). The elimination half-life is on the order of 4.5 hours (206 ± 102 minutes). Peak norephedrine levels in this study were 110 ± 51 ng/mL; for norpseudoephedrine, 89 ± 49 ng/mL (Widler et al., 1994).

Urine levels were measured in six volunteers 2, 4, 6, and 8 hours after taking 0.5 mg/kg of optically pure (*S*)-(–)-cathinone. Resultant levels were from 0.2 to 3.8 mg/mL for the parent compound, 7.2 to 46 mg/mL for (*R,S*)-(–)-norephedrine, and 0.5 to 2.5 mg/L for (*R,R*)-(–)-norpseudoephedrine (Brenneisen et al., 1986). It is not known if the normal antibody-based screening tests for amphetamine would be sufficiently cross-reactive to detect this compound, but it seems unlikely.

2.4.5 Clinical Studies

Khat chewing produces symptoms consistent with sympathetic activation, displaying both inotropic and chronotropic effects; use also causes elevations in blood pressure, temperature, and respiratory rate, and exerts inconsistent effects on heart rate. In isolated heart preparations, cathinone causes increased release of norepinephrine (Hassan et al.,

2000). When khat is chewed in a controlled setting, cathinone is barely detected, with concentrations of 20 ng/mL at 30 minutes and 0.5 ng/mL at 7.5 hours. Peak plasma levels occur some time between 1.5 and 3.5 hours with a mean of 83 ng/mL observed in five test subjects (Halket et al., 1995).

Khat chewing causes chronic constipation and reduced milk production in nursing mothers (Makonnen, 2000). Most of these effects are transient. It has been reported that in some parts of Saudi Arabia the only patients seen with oral cancers are those with long histories of khat chewing (Soufi et al., 1991) although two biopsy studies of khat chewers show that chewing-related changes (acanthosis 97.5%, parakeratosis 50%, and orthokeratosis in 25%) are innocuous, rarely, if ever, showing signs of malignancy (Ali et al., 2006).

Papers in the older literature described cerebral hemorrhage, myocardial ischemia, and pulmonary edema (Halbach, 1972). Even though published data are sparse, there does seem to be some truth to the earlier reports. Khat is an amphetamine, and in sufficient doses it should produce typical catecholamine-related injuries. However, catecholamine concentrations in khat users have not been measured, though it is known that urinary catecholamine excretion is increased after khat chewing (Nencini et al., 1984), and other hormonal alterations normally associatied with the amphetamines have also been seen, at least in experimental animals. When rabbits were fed various doses of khat leaves, and periodic blood samples collected, hormonal changes were detected with even the lowest doses given. Khat significantly lowered the pulse frequency of luteinizing hormone, the area under the LH curve, as well as mean plasma LH and mean plasma testosterone levels. In addition, plasma cortisol levels were significantly elevated and the elevation occurred in a dose-dependent manner. The findings raise the question of decreased sexual function in habitual users (Nyongesa et al., 2007).

Epidemiologic studies show that there is a dose-dependent relationship between khat chewing and the occurrence of AMI. This relationship persists even after the effects of smoking by multivariate analysis are removed. The risk of chewing for a short period of time (less than 3 hours) and sustaining an AMI is no greater than not chewing at all. However, users who chew continuously for 6 hours or longer have an odds ratio of 39.33! The mean age of those with infarction was 48.6 ± 9.0 years and 67% of those who experience khat-related AMI are under age 50. Over 90% are men (Al-Motarreb et al., 2005; de Ridder et al., 2007). There are also anecdotal case reports describing stroke (Vanwalleghem et al., 2006) and cardiomyopathy in khat chewers, but there has never been a systematic study of either disease in this population (Saha and Dollery, 2006).

Animal studies and at least one human case report suggest hepatotoxicity, with elevated liver enzymes and histopathologic evidence of acute hepatocellular degeneration seen after six months of continuous exposure (Al-Habori et al., 2002; Brostoff et al., 2006). Just how these findings should be reconciled with other six-month animal studies that demonstrate a significant decrease in plasma cholesterol, accompanied by significant increases in plasma HDL-cholesterol with significant decreases in plasma glucose and triglycerides concentrations, is somewhat difficult to understand (Al-Habori and Al-Mamary, 2004). Chewing some types of khat leads to increased levels of nitrosamines in the gastric fluid. It has been speculated that this might account for the observed high incidence of esophageal and gastric carcinoma in Yemen. The autopsy findings in chronic khat users, if any, are unknown. Postmortem measurements of cathinone and cathine have never been published.

2.4.6 Detection

Khat detection is a relatively simple matter and several alternative methods exist. Hair testing has become increasingly possible, and there appears to be good correlation between the amount of cathinone detected in the hair and the amount that is actually consumed (Sporkert et al., 2003). However, other perfectly good methods for detection with GC/MS are available (Paul and Cole, 2001). While there do not as yet exist antibody-based detection systems for khat and its components, the structural similarities with amphetamine make it likely that there would be at least some cross-reaction in systems designed to detect amphetamine.

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Synthetic Stimulants

3

The term *amphetamine* denotes a class of chemicals that share a common structural backbone. Methamphetamine, though it does have some clinical applications, is primarily a drug of abuse. Dextroamphetamine, which generally lacks the intense psychostimulant effect of methamphetamine, is the primary drug used for the treatment of attention deficit-hyperactivity disorder (ADHD). The most popular of the dextroamphetamines are various amphetamine salts combined together to form Adderall®, used to treat ADHD. Dextroamphetamine abuse is uncommon in the U.S., but still very popular in Europe, though use of methamphetamine is growing there as well. In Europe, methamphetamine is spelled metamfetamine, while dextroamphetamine is spelled dexamfetamine. Methamphetamine and amphetamine share a number of characteristics, both in terms of structure and effect produced. The problems associated with ADHD will be considered separately.

3.1 Amphetamines

Methamphetamine

Synonyms: (+)-(*S*)-deoxyephedrine; (+)-methamphetamine; (+)-methylamphetamine; (+)-*N*-methylamphetamine; (*S*)-*N*,α-dimethylbenzeneethanamine; 1-phenyl-2-methyl-amino-propan (German); benzeneethanamine; *N*-α-dimethyl-, *d*-(*S*)-methamphetamine; *d*-1-phenyl-2-methylaminopropan; *d*-1-phenyl-2-methylaminopropane; *d*-deoxyephedrine; *d*-desoxyephedrine; *d*-methamphetamine; *d*-methylamphetamine; *d*-*N*,α-dimethylphenethylamine; *d*-*N*-methylamphetamine; *d*-phenylisopropylmethylamine; *L*-methamphetamine; metamphetamine; methyl-β-phenylisopropylamine; methylamphetamine; *N*-methylamphetamine; Norodin; (*S*)-(+)-methamphetamine

Brand names: Desoxyn® (Abbot, USA), Methampex® (Lemmon, USA), Methedrine® (Wellcome UK), Pervitin® (Trenker Bldg.), Temmler® (Germany)

Chemical name: *N*-α-dimethyl benzenethanamine, *d*-*N*-α-dimethylphen ethylamine, and *d*-deoxyephedrine.

Molecular weight: 149.24 deltons

Metabolism:

Bioavailability:

Oral: 67.2 ± 3

Smoked: 90.3

C_{max}:

IV: (*n* = 6, 15.8 mg), 3–6 hours (Cook et al., 1993); *n* = 8, 30 mg = 108.4 ng/mL (Newton et al., 2005); *n* = 12, IV 0.25 mg/kg, 60–92.8 (Mendelson et al., 2006)

Oral: ($n = 8$, 10 mg), 14.5–33.8 ng/mL (Schepers et al., 2003); ($n = 8$, 125 mg/kg) = 19.8 ± 2.7; ($n = 8$, 250 mg/kg) = 37.2 ± 1.3 (Cook et al., 1993)
Vapor: ($n = 6$, 22 mg), 47.1 ± 5.6 (Perez-Reyes et al., 1991)

T_{max}:
IV: $n = 8$, 30 mg = 17 minutes (Newton et al., 2005)
Oral: ($n = 8$, 10 mg), 2–8 hours (Schepers et al., 2003); ($n = 8$, 250 mg/kg) = 3.23 ± 0.38 ($n = 8$, 125 mg/kg) (Cook et al., 1993)
Vapor: ($n = 6$, 22 mg), 2.5 ± 5 hours (Perez-Reyes et al., 1991)

$T_{1/2}$:
IV: 11.1 hours (Cook et al., 1993), $n = 12$; $n = 8$, 30 mg = 9 hours (Newton et al., 2005) = 9.1 hours and after a dose of 0.25 mg/kg, the range was 6.6–11.7 hours (Mendelson et al., 2006)
Oral: ($n = 8$, 10 mg), 2.1–14 hours (Schepers et al., 2003); 10.2 hours ± 2.3
Vapor: ($n = 6$, 22 mg), 11.8 ± 3 hours 2.5 ± 5 minutes (Perez-Reyes et al., 1991)

V_{ss}:
IV: ($n = 1$) 3.4 L/kg (Cook et al., 1993); $n = 8$, 30 mg = 5.8 L/kg (Newton et al., 2005), 3.6 ± 4.6 L/kg (Mendelson et al., 2006)
Oral: ($n = 8$, 10 mg), 1.6–8.9 L/kg (Schepers et al., 2003); ($n = 12$, 0.25 mg/kg) = 3.73 ± 0.94 L/kg; ($n = 12$, 0.50 mg/kg) = 4.15 ± 0.76 L/kg (Mendelson et al., 2006)
Vapor: ($n = 6$, 15.8 mg), 17 ± 8.1 hours (Cook et al., 1993)

Urine detection times: 23.6 ± 6.6 hours

Interactions: methamphetamine induces production of CYP2C6, which could conceivably change the kinetics of tolbutamide and dextromethorphan (Dostalek et al., 2007)

Amphetamine

Synonyms: 1-(+/-)-benzedrine, (+/–)-desoxynorephedrine, (+/–)-β-phenylisopropylamine, 1-methyl-2-phenylethylamine, 1-phenyl-2-aminopropane, 3-methoxy-α-methylbenzeneethanamine, 3-methoxyamphetamine, 3-methoxyphenylisopropylamine, actedron, adipan, allodene, α-methylbenzeneethaneamine, amphetamine (narcotics), amphetamine base, amphetamine sulfate, anorexide, anorexine, benzebar, benzedrine, benzolone, β-aminopropylbenzene, *dl*-α-methylphenethylamine, *dl*-amphetamine, *dl*-benzedrine, desoxyn, dexampex, dexedrine, dextroamphetamine sulfate, dextrostat, *dl*-1-phenyl-2-aminopropane, elastonon, fenamin, fenyloizopropylaminyl, ferndex, finam, isoamycin, isoamyne, isomyn, mecodrin, methampex, *m*-methoxy-α-methylphenethylamine, *m*-methoxyamphetamine, [1-(3-methoxyphenyl)-2-propylamine, norephedrane, norephedrine, deoxy-novydrine, oktedrin, ortedrine, paredrine, percomon, phenamine, phenedrine, phenylisopropylamine, profamina, propisamine, psychedrine, racemic-desoxynor-ephedrine, raphetamine, rhinalator, simpatedrin, simpatina, sympamin, sympamine, sympatedrine, weckamine

Brandnames: Adderall® (amphetamine + dextroamphetamine), Adderall XR® 10–25 mg (amphetamine aspartate + amphetamine sulfate dextroamphetamine saccharate + dextroamphetamine sulfate)

Chemical name: 1-phenylpropan-2-amine

Formula: $C_9H_{13}N$

Molecular weight: 135.206 daltons

Metabolism: P450 enzymes CYP2D and CYP3A form 4-hydroxyamphetamine and amphetamine (Dostalek et al., 2005)

Protein binding: 23–26% (Franksson and Angaard, 1970)

Bioavailability:

T_{max}: (15 mg, $n = 2$) 1.2 hours for acidified urine, 5.7–25.8 hours alkalinized (Anggard et al., 1970)

Oral: 67.2 ± 3%

Smoked: 90.3%

C_{max}:

IV: (n = 6, 15.8 mg), 3–6 hours (Cook et al., 1993); n = 12, IV 0.25 mg/kg, 60–92.8 (Mendelson et al., 2006)

Oral: ($n = 8$, 10 mg), 14.5–33.8 ng/mL (Schepers et al., 2003)

Vapor: ($n = 6$, 22 mg), 47.1 ± 5.6 (Perez-Reyes et al., 1991)

T_{max}:

IV: not known

Oral: (n = 8, 10 mg), 2–8 hours (Schepers et al., 2003); (n = 8, 125 mg/kg) 3.6 ± 0.63

Vapor: ($n = 6$, 22 mg) 2.5 ± 5 hours (Perez-Reyes et al., 1991)

$T_{½}$:

IV: 11.1 hours (Cook et al., 1993), $n = 12$, IV 0.25 mg/kg 6.6–11.7 (Mendelson et al., 2006)

Oral: ($n = 8$, 10 mg), 2.1–14 hours (Schepers et al., 2003)

Vapor: ($n = 6$, 22 mg), 11.8 ± 3 hours 2.5 ± 5 minutes (Perez-Reyes et al., 1991)

V_{ss}: 2.5–4.6 L/kg (Rowland, 1969), 6.1 L/kg (Anggard et al., 1970), 4.8–7.6 L/kg (Franksson and Angaard, 1970)

Urine detection time: 20.7 ± 7.3 hours

Interactions: Amphetamines as a group are substrates for both P-gp and CYP3A4. They may alter the transport and metabolism of protease inhibitors (PIs) and NNRTIs if administered in combination with azole antifungals, macrolide and fluoroquinolone antibiotics, statins, some cardiovascular agents, immune modulators, and even other abused drugs, in particular benzodiazepines, cocaine, lysergic acid diethylamide (LSD), marijuana, amphetamine (Meth), 3,4-methylenedioxymethamphetamine (MDMA), and some opiates (Pal and Mitra, 2006).

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3.1.1 Incidence and Availability

The Medical Examiner's component of the 1988 Drug Abuse Warning Network (DAWN) reported 501 methamphetamine-related deaths. By 1999, that number had risen to 690, accounting for not quite 6% of all reported drug-related deaths. In just one decade, methamphetamine had moved from the ninth most common cause of drug-related death to the number six position, just after diazepam (811 cases), and just ahead of marijuana (670 cases) (Kissin and Ball, 2000). The current situation is difficult to assess. Since the new DAWN report was released, it has become impossible to determine on a countrywide basis how much drug is being produced, how much is used, how many users become ill, or even how many die. The only agency with any real credibility on this matter is the United Nations, and even its figures are difficult to interpret, because the U.N. lumps together amphetamine, methamphetamine, and designer amphetamines into one category. Based upon consumption estimates, and the amount of precursor chemical seized, the United Nations Office on Drugs and Crime (UNODC) estimates that total worldwide amphetamine production amounted to just less than 500 tons (range 285–1184 tons) in 2004 (UNODCCP, 2006).

The National Survey on Drug Use and Health ("The NSDUH Report") stated in 2005 that use among the noninstitutionalized population aged 12 or older had been declining for the last three years. The number of persons who used methamphetamine for the first time in the prior 12 months did not differ significantly between 2002 (299,000 persons) and 2004 (318,000 persons) but did decrease significantly between 2004 and 2005. In 2004, an estimated 318,000 persons aged 12 or older first tried methamphetamine in the year prior to the survey compared with 192,000 persons in 2005. Combined data from the annual National Survey on Drug Use and Health from 2002 to 2005 were used to examine demographic differences in methamphetamine use. Persons in large metropolitan areas (0.5%) were less likely to have used methamphetamine in the past year than those in small metropolitan areas (0.7%) and in non-metropolitan areas (0.8%) (Anon., 2007).

The majority of the amphetamines produced consist of methamphetamine and amphetamine, amounting to 353 tons. The amount of MDMA on the streets is much smaller, with, according to the U.N., an annual production of only 126 metric tons. Worldwide methamphetamine production seems to have peaked in the year 2000, and actually may have begun to fall in 2001–2003. The new increases that have been reported by various international agencies are thought to reflect the worldwide increase in MDMA production. At the same time, there are reports of record seizures of amphetamine precursors, and an increasing number of clandestine laboratories are being discovered, suggesting that production is expanding. The best guess, which is all the data permit at this time, is that levels of use of the traditional amphetamines remain relatively constant (UNODCCP, 2006).

The upward trend in Ecstasy use, however, seems genuine. Production may well have declined in the Netherlands (the world's largest Ecstasy-producing country), and evidence points to decreasing consumption in the U.S. Nonetheless, UNODC estimates suggest that Ecstasy production increased from between 34 and 141 tons in 2003 to between 81 and 206 tons in 2004. UNODC prevalence estimates rose by 22 percent, Ecstasy seizures rose by 87 percent, and seizures of Ecstasy precursor chemicals rose by 113 percent in 2004, largely due to increased seizures of 3,4-MDP-2-P (also known as PMK), the main Ecstasy precursor. Most amphetamine production takes place in Europe, most methamphetamine production occurs in North America and East and South East Asia. Most Ecstasy is produced in Europe and North America (UNODCCP, 2006).

Methamphetamine that is produced in the Americas is not exported. The U.S. continues to dismantle the largest number of methamphetamine laboratories worldwide (17,199 laboratories in 2004). U.S. production has traditionally been concentrated in California and neighboring states but production has steadily expanded eastward, and large numbers of laboratories are now being seized in rural states between Texas and Illinois, as well as small towns along the Mississippi River. Most of the "super-labs," that is, laboratories capable of manufacturing more than 5 kg of methamphetamine in 24 hours, continue to be located in California. The number of "super-labs" seized in the U.S. has, however, shown a downward trend in recent years, from 245 in 2001 to 55 in 2004 (–22%) and had declined even further, by 34%, in the first half of 2005, at least as compared to the same values a year earlier. The decline in "super-lab" seizures may well have to do with the availability of precursor chemicals. To produce 100 kg of methamphetamine, 150 kg of ephedrine or pseudoephedrine are required and the sale of both these substances is highly controlled. Alternatively, methamphetamine can be just as easily produced using phenyl-2-propanone, but, within the U.S. at least, sales of this compound are even more tightly controlled than sales of ephedrine and pseudoephedrine (International Narcotics Control Board, 2005). A frightening prospect is that alternative routes are always being introduced.

3.1.2 Epidemiology

DAWN estimates that in 2004 there were 940,953 (confidence interval [CI]: 773,124 to 1,108,782) emergency room visits related to methamphetamine use, accounting for just over 11% of drug-related ER visits involving a major abused drug. By comparison, cocaine was involved in 383,350 (CI: 284,170 to 482,530), marijuana was involved in 215,665 (CI: 175,930 to 255,400), and heroin was involved in 162,137 (CI: 122,414 to 201,860) ER visits.

In 1998, the old DAWN survey estimated that the number of persons who had tried methamphetamine in their lifetime was 4.7 million (2.1% of the population). The 1998 estimate was similar to the 1997 estimate (2.5%) and the 1994 estimate (1.8%) (Kissin et al., 2000). However, other data sources indicate a substantial increase in methamphetamine use during the 1990s. For example, the Treatment Episode Data Set (TEDS) of the Substance Abuse and Mental Health Services Administration (SAMHSA) indicates that methamphetamine-related admissions to publicly funded treatment programs rose from 14,000 in 1992 to 53,000 in 1997.

The National Household Survey on Drug Abuse continues to reflect the aging of the drug-using population (Green and Marsden, 2000). Of the methamphetamine users who were teenagers and young adults in the 1960s and 1970s, most no longer use drugs, but a

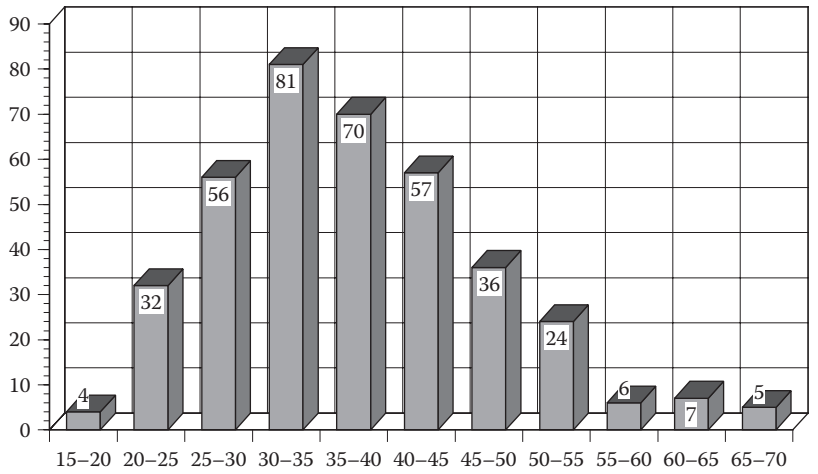


Figure 3.1.2.1 An analysis of 413 methamphetamine-related deaths in San Francisco (1985–2006). Since the DAWN report has been reconfigured there is no way to determine whether a similar distribution still applies, though some epidemiologic projects indicate wider use among the general population.

significant number continue with their habits, which explains why the number of users aged 35 and older, as reported by the National Household Survey, continues to increase, and why methamphetamine also accounts for an ever larger proportion of drug-related deaths (from 10% of users in 1979 to 32% of users in 1998). Projections indicate that the number of people aged 50 and older needing treatment for a drug problem will increase fivefold in the next 20 years (Gfroerer and Epstein, 1999). Similar trends seem to be emerging in the Medical Examiner's component of the DAWN report, as indicated by the 1999 DAWN report, or at least such trends were evident until the Medical Examiner's component of DAWN was reformulated. In 1999 methamphetamine was found in 6–8% of deaths involving decedents aged 6–54, and in 2% of deaths of individuals aged 55 and older (Kissin and Ball, 2000).

The most recent survey published by the U.S. government indicated that in 2002–2005 an estimated 1.4 million persons (0.6% of the population) aged 12 or older had used methamphetamine in the past year. Rates of past year methamphetamine use were highest in Nevada (2%), Montana (1.5%), and Wyoming (1.5%). The lowest rate of past year use was about 0.1%, with similar low values being reported from Connecticut, Maryland, Massachusetts, New Jersey, and New York. Among youths aged 12–17, rates of past year methamphetamine use were highest in South Dakota (2.3%), Montana (2.2%), North Dakota (1.6%), and Wyoming (1.6%). The use rate was lowest among youths in the District of Columbia (0.1%), New York (0.2%), and Maryland (0.2%) (SAMHSA, 2006).

Young adults aged 18–25 were the most likely to have used methamphetamines in the past year. Past year rates of use among adults aged 18–25 were highest in Wyoming (4.6%), Arkansas (4.4%), Minnesota (3.8%), and Nevada (3.8%). Very small numbers of methamphetamine users were reported among young adults in New York (0.3%), Connecticut (0.4%), and Vermont (0.4%). If these figures are valid, they would seem to confirm the impression of U.N. investigators that methamphetamine abuse is either stable or decreasing (Anon., 2006b).

There is a paucity of epidemiologic evidence regarding the use of methamphetamine by pregnant or nursing mothers. The evidence that is available indicates that among pregnant women, methamphetamine abuse is more common than cocaine use, especially in cigarette-smoking Caucasian women (Vega et al., 1993). Reports of methamphetamine-related pregnancy complications, in mother or child, are uncommon, although decreased birth weight is a generally recognized consequence of maternal methamphetamine abuse (Catanzarite and Stein, 1995; Plessinger, 1998; Chomchai et al., 2004).

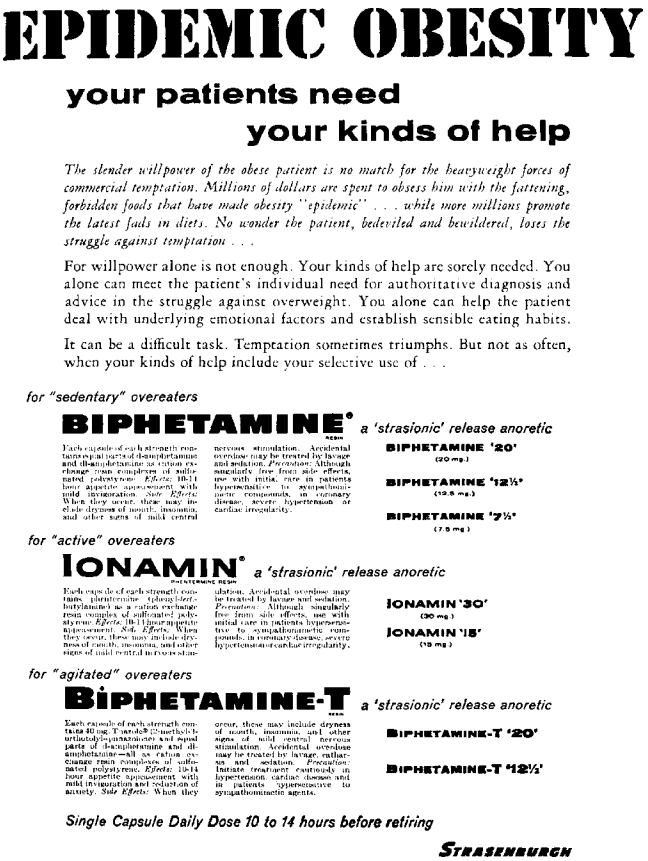
3.1.3 History

In the 1920s, concerns that the supply of naturally occurring ephedrine might not be sufficient to meet the needs of asthma sufferers prompted laboratories around the world to attempt the synthesis of ephedrine. A graduate student at the University of California at Los Angeles (UCLA), Gordon Alles, was assigned the task as his thesis project. Alles reviewed the older literature and discovered previous research carried out by an Italian chemist named Edeleano, who had synthesized the basic phenylisopropylamine molecule in 1887. Alles took the phenylisopropylamine molecule as a starting point from which to synthesize ephedrine. Alles never succeeded, at least not in his attempts to produce ephedrine. He did, however, produce a molecule called phenylisopropylamine, later named dextroamphetamine. He gave samples to laboratory animals, and when he saw little evidence of toxicity he tried it on himself. The mood-altering properties of this novel molecule quickly became apparent. A Japanese chemist named Ogata had also been trying to synthesize ephedrine, but Ogata ended up producing a different amphetamine, *d*-phenyl-isopropylmethylamine hydrochloride, later known as methamphetamine. Hermann Emde finally managed to synthesize ephedrine in 1929, but the anticipated ephedrine shortage never occurred.

Ogata licensed his process for making methamphetamine to the Burroughs Wellcome Company, which sold methamphetamine in the U.S. under the brand name Methedrine® until it was taken off the market in 1968. In 1932, the Smith Kline & French Company sold a nasal inhaler containing Benzedrine®, their patented name for racemic β-phenylisopropylamine (*d,l*-amphetamine). The inhaler effectively relieved nasal congestion as well as drowsiness and fatigue. The latter qualities, along with exaggerated claims by both drug manufacturers and the popular press, led to widespread interest and even more widespread abuse.

The medical community responded to the introduction of amphetamine in almost exactly the same way it had responded to the introduction of cocaine 50 years earlier. Amphetamines were recommended for the same assortment of unrelated conditions that had been treated with cocaine when it was first introduced. Given what is known today, some of the earlier recommended uses for the amphetamines appear bizarre. For example, amphetamine was recommended as a "valuable adjunct" in the treatment of seizures and schizophrenia. Bearing in mind that amphetamine-induced psychosis is still thought by some (Janowsky and Risch, 1979; Machiyama, 1992; Sato et al., 1992) to be a useful model for the study of schizophrenia, it is difficult to imagine what type of improvement clinicians were observing!

Amphetamines were also said to be useful in treating barbiturate overdose, "caffeine mania," smoking, multiple sclerosis, myasthenia, head injuries, cerebral palsy, migraine, urticaria, seasickness, dysmenorrhea, ureteral colic, obesity (Figure 3.1.3.1), irritable colon, radiation sickness, Ekbom's syndrome, and other seemingly unrelated conditions—even



EPIDEMIC OBESITY

your patients need
your kinds of help

The slender willpower of the obese patient is no match for the heavyweight forces of commercial temptation. Millions of dollars are spent to obsess him with the fattening, forbidden foods that have made obesity "epidemic" . . . while more millions promote the latest fads in diets. No wonder the patient, bedeviled and bewildered, loses the struggle against temptation . . .

For willpower alone is not enough. Your kinds of help are sorely needed. You alone can meet the patient's individual need for authoritative diagnosis and advice in the struggle against overweight. You alone can help the patient deal with underlying emotional factors and establish sensible eating habits.

It can be a difficult task. Temptation sometimes triumphs. But not as often, when your kinds of help include your selective use of . . .

for "sedentary" overeaters

BIPHETAMINE® *a 'strasionic' release anoretic*

BIPHETAMINE '20' (20 mg.)
BIPHETAMINE '12½' (12.5 mg.)
BIPHETAMINE '7½' (7.5 mg.)

for "active" overeaters

IONAMIN® *a 'strasionic' release anoretic*

IONAMIN '30' (30 mg.)
IONAMIN '15' (15 mg.)

for "agitated" overeaters

BIPHETAMINE-T® *a 'strasionic' release anoretic*

BIPHETAMINE-T '20'
BIPHETAMINE-T '12½'

Single Capsule Daily Dose 10 to 14 hours before retiring

STRASENBURGH

Figure 3.1.3.1 Medical use of amphetamine. For many years, amphetamine was promoted as a treatment for obesity. When first introduced to the market, amphetamine was claimed to be something of a wonder drug. The same claims were made for amphetamine as were made for cocaine when it was first introduced. This advertisement was published in a 1961 issue of *JAMA*.

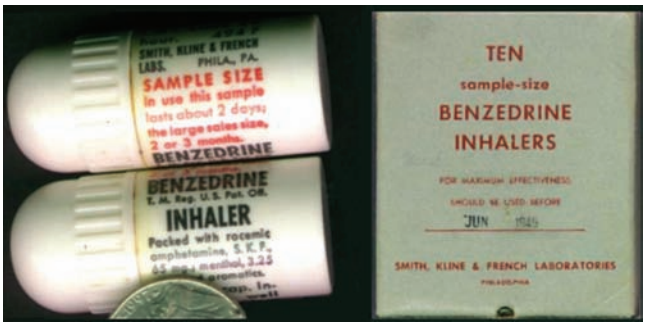


Figure 3.1.3.2 Benzedrine® Inhaler made by Smith Kline & French Laboratories. A regulatory lapse allowed continued over-the-counter sales until 1949. Each inhaler contained eight folded paper sections impregnated with 250 mg of amphetamine.

impotence and loss of libido (Bett, 1946). It should come as no surprise that amphetamine was even recommended for use in the treatment of morphine addiction. By the time amphetamine arrived on the scene, Freud's disastrous cocaine experiments of 1885 apparently had been completely forgotten (Wax, 1997).

Moderate doses of *d*-amphetamine increase the ability to sustain attention over prolonged periods of time, especially when performing monotonous tasks. Like cocaine, *d*-amphetamine improves performance on auditory and visual reaction time tests, and on the digit symbol substitution test (DSST), a measure of psychomotor skills and attention (Heishman, 1998). These actions were recognized very soon after amphetamine became commercially available, which probably explains why, during World War II, troops of both the Allied and Axis forces were supplied with amphetamines.

Soon after World War II, laws limiting amphetamine distribution were enacted, but a regulatory lapse allowed the continued sale of the Smith Kline & French's nasal inhaler. Inside each inhaler were eight folded paper sections impregnated with 250 mg of amphetamine. Abusers opened the inhaler and chewed the papers. Friends mailed the strips to prison inmates, and abuse within the prison system became a problem (Monroe and Drell, 1947). In an escalating battle with would-be abusers, amphetamine manufacturers tried adding denaturants such as emetine and picric acid to the strips, but abusers found ways to extract the amphetamine, or simply put up with the transient side effects produced by the denaturants.

The Benzedrine® inhaler was reformulated in 1949, and the new product's name was changed to Benzedrex®. The new formulation contained propylhexedrine, also a potent vasoconstrictor, but with only one twelfth the central nervous system (CNS) stimulant potency of amphetamine. Smith Kline & French's patents expired in 1953, and almost immediately Wyeth, Rexall, Squibb, Eli Lilly, and W. S. Merrell brought competing products to market. Inhaler abuse continued until the amphetamine inhaler was finally classified as a prescription item.

The first amphetamine-related deaths were reported within a few years of the introduction of amphetamine. The serious complications associated with amphetamine abuse are essentially the same as for cocaine: arrhythmic sudden death (Jacobs, 2006), stroke, psychosis, and rhabdomyolysis, but they seem to occur much less frequently than with methamphetamine. Most of the case reports are from the 1950s and 1960s. Mentions of toxicity were uncommon during the 1980s, when use was largely confined to the desert Southwest.

With the introduction of smokable "ice," a pure form of (+)-methamphetamine hydrochloride, interest in methamphetamine as a drug of abuse revived, and new case reports of toxicity began to appear (Cho and Wright, 1978). Methamphetamine becomes "ice" when it is crystallized out of a saturated solution. Depending on how methamphetamine is initially prepared (a number of ways are possible, see Skinner, 1990), solvent is captured within the structure of the crystals. The type of solvent is a clue to which processes were used in the manufacture, and may also suggest where the illicit drug was made. The volatility of the solvent in which the methamphetamine is dissolved determines how large the resultant crystals will be. With very volatile solvents, such as Freon®, crystallization is rapid and only very small crystals form. With less volatile solvents, such as methanol, larger crystals are produced. No matter the size of the crystals, they can all be smoked and all produce exactly the same effects.

Figure 3.1.3.3 "Ice" crystals. Crystal size depends on how rapidly the solvent evaporates and has nothing to do with the effect observed. If methamphetamine were powdered and smoked it would exert the same effect. (From the website of the DEA.)

The first illicit "ice" laboratories were located in Japan. The Japanese have referred to this particular form of methamphetamine by a number of different names, including *kaksonjae, hanyak, batu,* and *hiropon*. The use of the name *hiropon* is doubly ironic because that was the name the Japanese used for ephedrine during the epidemic of ephedrine abuse that swept Japan just after World War II. Today, ephedrine is the universally preferred starting material for making methamphetamine.

Large-scale "ice" production began in the early 1980s. Enforcement efforts by police convinced the illegal chemists to transfer their operations out of Japan to Korea. To this day, Korea remains the principal manufacturer of "ice." At first, the market for this form of amphetamine was confined to Taiwan, Japan, and the Philippine Islands. Japanese and Korean abusers took it intravenously, but the Filipinos began smoking it. The Filipinos were already used to smoking stimulants, having smoked *shabu* (a mixture of ephedrine and caffeine) for years. Demand within the Filipino community was also thought to be responsible for the introduction of "ice" into Hawaii (Skinner, 1990).

In the late 1980s, Korean chemists emigrated and established illicit laboratories in Portland, Oregon, and Los Angeles, Most of their production was shipped back to the Philippines. In 1988, sporadic seizures of "ice" took place across the U.S., but no laboratories were seized in 1989. By 1990, the Drug Enforcement Agency (DEA) had seized seven laboratories in California alone. Impressive amounts of "ice" continue to be seized in China and Korea, but not in the U.S. No "ice" laboratories have been raided in the U.S. for several years, nor do any of the thousands of clandestine "meth" laboratories raided each year appear to be producing "ice." During the last decade, the Myanmar Republic has begun mass production of methamphetamine, producing huge quantities of the drug, but mostly for local consumption. It is not clear what form — large crystals for smoking or small crystals for oral ingestion — is being produced.

Amphetamine trafficking has spread beyond its traditional regions. Increases have been reported, inter alia, from South Africa, while use of methamphetamine has increased in parts of Asia not traditionally affected, and this trend is likely to continue. The European market for methamphetamine, which at one time was nearly nonexistent, is

now much greater. Methamphetamine abuse is a major problem in Germany (where amphetamine was always the drug of choice) (UNODCCP, 2006).

Taking into account the enormous amount of illicit methamphetamine produced and consumed in the U.S., episodes of toxicity are surprisingly uncommon, with less than one methamphetamine-related death for every ten attributed to cocaine.

3.1.4 Illicit Manufacture

As legitimate medical indications for methamphetamine and amphetamine became fewer and fewer, and the dangers of long-term use more apparent, legal production fell off. However, the recent dramatic rise in the number of illicit methamphetamine laboratories seized, from only 263 in 1994 to 1627 in 1998 and 2252 in 1999, suggests a thriving market for the product (Tichacek and Napolitano, 1999) in spite of an apparent decline in the number of "super-labs" seized that has been observed since the early 2000s. More clandestine laboratories are now seized in Missouri (371 in 1998) than in any other state, but most of these "laboratories" are small, with very modest production. In the mid-1990s, illegal Mexican laboratories, operating in Southern California, constructed "super-labs" capable of processing 10-lb (and occasionally 100-lb) batches of methamphetamine (Tichacek and Napolitano, 1999).

Transportation of methamphetamine from Mexico appears to be increasing, as evidenced by increasing seizures along the U.S.–Mexico border. The amount of methamphetamine seized at or between U.S.–Mexico border ports of entry (POEs) increased more than 75% overall from 2002 (1129.8 kg), to 2003 (1733.1 kg), and 2004 (1984.6 kg). The effect of the North America Free Trade Act (NAFTA), which allows the unimpeded traffic of Mexican tractor-trailors into the U.S. has, no doubt, made the condition worse.

Another fairly recent change in methamphetamine production is the entrance of new overseas illicit manufacturers. The Myanmar Republic, in addition to being a poppy grower and heroin manufacturer, has also become a large-scale methamphetamine producer. Ephedra is grown commercially in both India and Pakistan and sold to clandestine laboratories in Myanmar (which produces mainly for export) and Thailand (which produces mainly for local consumption). Occasional batches of methamphetamine from both countries have been confiscated by U.S. Customs, but the amount of methamphetamine being exported to the U.S. from South East Asia is not really known. Similarly, clandestine laboratories have sprung up in Poland and the Czech Republic, but data from these locations are quite limited and the true magnitude of production there is not known either (International Narcotics Control Board, 2005).

When phenyl-2-propanone (P2P) sales were not controlled, it was the precursor of choice for "meth cooks." Once P2P became a controlled substance, clandestine chemists in the U.S. were forced to first make P2P before they could make methamphetamine. P2P can be synthesized in several ways. The most frequently used approach starts with phenylacetic acid, acetic anhydride, and sodium acetate. P2P is then converted to methamphetamine by reductive amination (Skinner, 1990; International Narcotics Control Board, 2005).

Methylamine, aluminum foil, mercuric chloride, diethyl ether, and isopropanol are required. High yields can be obtained via this synthetic route. Formulas for production using readily available materials are easily found on the Internet. Legislation has been introduced in the U.S. Congress that would make the act of disseminating information

about drug manufacture illegal, and the Patriot Act was amended in 2006 to severely limit the sales of ephedrine, pseudoephedrine, and phenylpropanolamine.

Regardless of the source, methamphetamine made from P2P yields a racemic mixture. Because the (+) form of methamphetamine is five times as potent as the (–) isomer, the potency and yield of the final product can be variable. Not only can the potency vary, but an assortment of contaminants can also be introduced. Some of the contaminants have strong stimulant properties themselves (Soine, 1986), while others may be quite toxic, possibly more toxic than amphetamine. In the U.S., the P2P synthetic route has been entirely replaced by the "red phosphorus" route (Figure 3.1.4.1), and P2P toxicity is no longer an issue.

As an alternative, either (–)-ephedrine or (+)-pseudoephedrine can be converted to methamphetamine by reductive dehalogenation using red phosphorus as a catalyst. If (–)-ephedrine is used as the starting point, the process generates (+)-methamphetamine. Pseudoephedrine also yields dextromethamphetamine. Regardless of the isomer produced, contaminants will be present. As is true with the P2P route, some of these contaminants, particularly 2-(phenylmethyl)phenethylamine, may also be toxic in their own right. Unfortunately, the subject has not been studied in any detail (Soine, 1986).

The popularity of the red phosphorus route created an unprecedented demand for ephedrine, which has now been removed from the market — not because of its use in methamphetamine manufacture but, rather, because the FDA believes that use of ephedrine is dangerous. Now pseudoephedrine is largely used in its stead, and, if used as a starting material, it yields pure *l*-methamphetamine. Occasionally, methamphetamine "cooks" have resorted to the use of assorted cold remedies in place of ephedrine. Mixtures of diphenhydramine, chlorpheniramine, dextromethorphan, doxylamine, and even guaifenesin have been used. All of these chemicals, except for chlorpheniramine, react with

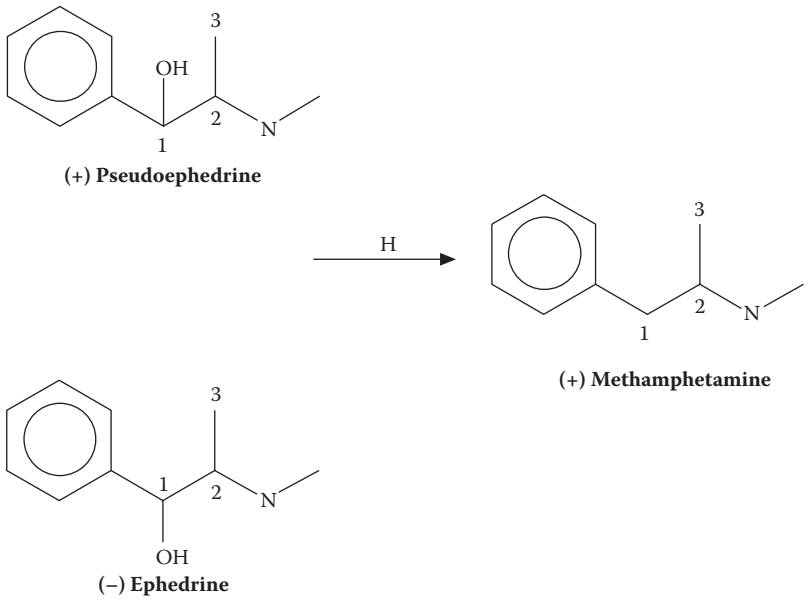


Figure 3.1.4.1 Making methamphetamine. The most popular formula for making methamphetamine starts with ephedrine and uses red phosphorus as a catalyst. Ephedrine used to be inexpensive and easily available, but now its sales are controlled and availability limited.

red phosphorus and hydroiodic acid to form an assortment of by-products that may be detected in the finished product. Diphenhydramine is converted to diphenylmethane, but because it does not crystallize, at least not with the techniques used to crystallize methamphetamine, it is unlikely to appear in the final product. Other by-products generated by the hydroiodic acid/red phosphorus reduction method include 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene (Lurie et al., 2000). Whether any of the other intermediates and by-products produced in this fashion are toxic in their own right is not known.

Given that phenylpropanol, ephedrine, and pseudoephedrine are all now controlled in one way or another, the phenylacetone route (because phenylacetone is easy to make) is now the precursor of choice among illicit methamphetamine producers. Unlike the other methods, this synthetic route yields a racemic mixture, and the effects of a synthetic mixture are not necessarily benign. The *l*- form of methamphetamine has always been considered benign and sold as a nasal decongestant (Vicks™), however, its presence creates problems. For one thing, it poses a forensic challenge, since *l*-methamphetamine is a legal drug and *d*-methamphetamine is not. For another, the pharmacokinetics of the two forms may diverge, and not doing chiral separation could prove a thorny issue in court. Lastly, some recent evidence indicates that *l*-methamphetamine may not be quite so benign as once thought (Mendelson et al., 2006).

Another increasingly popular alternative for production is the use of HI hypophosphorous acid, an industrial chemical that is used legally for a variety of commercial purposes. This approach works as well as red phosphorus for the purpose of methamphetamine manufacture. Although hypophosphorous acid is a List I chemical under the Controlled Substances Act, methamphetamine producers typically purchase the chemical via the Internet or from associates who also are engaged in methamphetamine production. Unlike red phosphorus, the use of hypophosphorous acid in methamphetamine production is an extremely dangerous practice. Deadly gases can be generated and there is significant risk of fire or explosion.

The most comprehensive agreement on international chemical control is the 1988 UN *Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances*. While the convention covers methamphetamine's precursor chemicals such as ephedrine and pseudoephedrine, it exempts finished pharmaceutical preparations containing them. This situation continues to allow criminal organizations to circumvent the convention by purchasing uncontrolled pharmaceutical preparations on the international market, instead of the regulated bulk precursor chemicals. Furthermore, many countries have simply been reluctant to share information regarding their trade in these substances, because much of the data is commercially sensitive. Complicating matters further, in some countries these chemicals are regulated by health officials, rather than law enforcement agencies (Patterson, 2006).

3.1.5 Routes of Administration

Methamphetamine can be swallowed, injected, smoked, or "snorted." Recently it appears that more users prefer to smoke than inject it, and there is some evidence that the smoked route is more addictive (McKetin et al., 2006). An oral dose of 10 mg results in 30-ng/mL plasma concentrations after 1 hour (Lebish et al., 1970). Ten subjects given a 12.5-mg dose had peak plasma concentrations of 20 ng/mL at 2 hours, decreasing to 10 ng/mL at

24 hours (Lebish et al., 1970). Similar studies with amphetamine have yielded comparable results, at least in terms of resultant blood levels.

The pharmacokinetics of smoked and intravenously injected methamphetamine have been compared in male volunteers acting as their own controls. The average dose smoked was 21.8 mg (bioavailability was > 90%), and the dose injected intravenously was 15.5 mg. The mean plasma half-life was 11.1 hours for the smoked methamphetamine and 12.2 hours when the drug was injected. Peak methamphetamine blood levels after smoking and injecting were comparable, ranging from 50 to 100 ng/mL. Amphetamine concentrations were much lower, reaching peak values of only 4 ng/mL after 3.3 hours. Methamphetamine levels in saliva were very high after smoking, but saliva amphetamine levels were negligible (Cook et al., 1993). In other studies, larger doses of amphetamine have been given intravenously, again with comparable results. Volunteers given 160–200 mg of amphetamine intravenously had a one-hour plasma concentration of 269 ± ng/mL (Anggard and Hankey, 1969). In seven patients presenting at an emergency room with evidence of amphetamine toxicity, plasma concentrations were found to range from 105 to 560 ng/mL (Lebish et al., 1970).

3.1.6 Metabolism

If there are important differences in the way that humans handle the different chiral forms of methamphetamine, not much has been written about it. Humans excrete the *l*-enantiomers of both amphetamine and methamphetamine more slowly than the *d*-isomers. The half-life of *d*-amphetamine is 7 ± 1.2 hours versus 11 ± 2.1 hours for *l*-amphetamine, but the values are closer to 5 hours and 6 hours for *d*- and *l*-methamphetamine, respectively (Beckett and Shenoy, 1973). There is some evidence that *d*-methamphetamine is metabolized more extensively than *l*-methamphetamine in humans (Rowland and Beckett, 1966) with the urinary excretion of *d*-methamphetamine being lower than *l*-methamphetamine.

In a recently published study (Mendelson, 2006), the different effects of the two isomers were compared after intravenous dosing using chiral separation and gas chromatography/mass spectrometry (GC/MS). A number of differences were observed between the two forms of drug, but none of great magnitude. The AUC for the *l*-form was slightly greater (i.e., the amount absorbed), but the C_{max} (*d* = 60.6–92.8 ng/mL, *l* = 53.9–76.9 ng/mL), $T_{½}$ (10.2 vs. 13.6 hours), and volume of distribution (3.3–4.3 vs. 3.66–4.63 L/kg) of both forms were similar, no matter whether the isomers were given separately or as a mixture. The clearance rates for both isomers were also similar. For amphetamine, the C_{max} was roughly a tenth of that for methamphetamine (an observation that has been repeated in postmortem studies), and the half-life considerably longer (18.4–46 hours). With pharmacodynamic testing, much stronger effects were exerted by the *l*-form than had previously been suggested.

Methamphetamine metabolism is catalyzed by cytochrome P-450, mainly by the CYP2D and CYP3A subfamilies, to produce 4-hydroxyamphetamine and amphetamine. Animal studies have shown that the administration of methamphetamine significantly stimulates the metabolic activity of CYP2D2 as well as that of CYP3A1/2, and the same very likely occurs in humans (Dostalek et al., 2005).

Amphetamine is occasionally detected in clandestinely produced methamphetamine, so the mere demonstration of amphetamine in hair or sweat samples does not necessarily prove that methamphetamine was ingested and demethylated to amphetamine within the

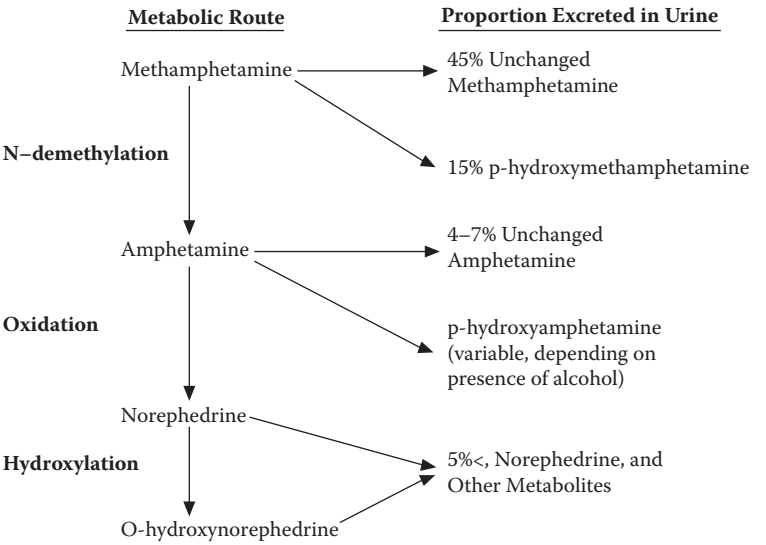


Figure 3.1.6.1 Methamphetamine metabolism. Methamphetamine is demethylated to produce amphetamine. Ephedrine and other analogs are not converted to amphetamine. Thus, the presence of amphetamine in a sample containing methamphetamine is proof that methamphetamine, and not some harmless analog, has been taken.

body. Its presence could equally well be explained by contact (innocent or otherwise) and environmental contamination, such as might be found in a clandestine laboratory or in the home of a drug user or drug dealer, or even the ingestion of amphetamine. Of course, this would matter little for NIDA urine-testing purposes, but it could make a great deal of difference to probationers or those involved in child-custody lawsuits.

Over a period of several days, 35–45% of a given dose of methamphetamine is excreted unchanged in the urine (Cook et al., 1993). If the urine is acidic, that amount may increase to over 75%. On the other hand, when the urine is extremely alkaline the amount excreted unchanged may drop to as little as 2% (Beckett et al., 1965). In carbon-14 tracer studies of two volunteers, 23% was excreted in the urine within the first 24 hours. Other metabolites also appear in substantial quantities, including 4-hydroxymethamphetamine, norephedrine, and 4-hydroxynorephedrine (Caldwell et al., 1972). The (+) isomer of amphetamine is metabolized more rapidly than the (–) isomer and appears in the urine sooner.

The situation has become more complex now that most methamphetamine abusers smoke the drug. When smoked, thermal degradation of the methamphetamine occurs, and there are several decomposition products. These include *trans*-phenylpropene, allylbenzene, amphetamine, phenylacetone, dimethyl-amphetamine, and other products (Sato et al., 2004). One of the main alkenylbenzene breakdown products is *trans*-phenylpropene, formed by elimination of methylamine in a Hoffman-like degradation reaction that converts an amine into an alkene. This compound is a marker for smoked methamphetamine (Shakleya et al., 2006). *Trans*-phenylpropene is structurally similar to styrene analogs, which are known to be carcinogens. They are formed by the activity of three different P-450 enzymes — CYP2E1, CYP1A2, and CYP3A4 (Sanga et al., 2006). The resultant end products are cytotoxic in tissue culture. The situation in humans is unclear, but no one has ever reported an increased rate of hepatic cancer in methamphetamine abusers, although

hepatic steatosis in this subgroup is extremely common. It may be that smoking is a means of harm reduction for these abusers. Virtually all intravenous drug users in California (and very large percentages in other states) are infected with the hepatitis C virus, and chronic infection with this virus can lead to liver malignancy.

Daily oral dosing with methamphetamine appears to have little effect on either metabolism or peak blood levels. No significant metabolic changes were noted in six volunteers given 10 mg of methamphetamine per day for 2 weeks, nor was there any change in blood levels that ranged from 25 to 50 ng/mL. Interestingly, saliva concentrations were much higher than concentrations measured in plasma, with an average saliva-to-plasma ratio of 7:8 (Cook et al., 1993). Other studies have shown that both the *d*- and *l*- forms of amphetamine appear in the saliva in concentrations that are two to three times higher than those measured in plasma. Detectable concentrations remain present for at least 48 hours (Wan et al., 1978). While methamphetamine clearly appears in saliva, its presence is unpredictable. In a different study of 25 methamphetamine abusers, methamphetamine was found in the hair of 73%, in the nails of 65%, and in the sweat of 50%, but in the saliva of only 16% of the participants (Suzuki et al., 1989).

If the urine is alkaline, the differences in metabolic rates among the methamphetamine enantiomers assume significance, because the (+) form is cleared about 5 hours more rapidly than the (–) isomer (17 hours vs. 12.7 hours) (Wan et al., 1978). Concomitant alcohol consumption appears to have relatively minor effects on methamphetamine pharmacokinetics, although evidence indicates that the simultaneous consumption of both drugs produces a more intense euphoria than either drug used alone (Mendelson et al., 1995).

3.1.7 Tissue Disposition

Rabbits sacrificed one hour after intravenous injection of methamphetamine were found to have hepatic drug concentrations that were twice as high as blood concentrations. Amphetamine concentrations measured at the same time were eight times higher in the liver than in the blood. In the same rabbit model, skeletal muscle concentrations of both methamphetamine and amphetamine were equal to the concentration in the liver (Nagata et al., 1990). Histochemical studies of methamphetamine-treated mice confirm the results of the rabbit studies. Amphetamine also localizes in the epithelial cells of the distal part of the renal tubule, transitional epithelial cells of the bladder, liver parenchymal cells, epithelial cells of the striated duct of the salivary gland, parietal cells of the gastric gland, part of epithelial cells of the distal portion of the large intestine, secretory cells and part of the epithelial cells of the ductal portion of the sweat gland, alveolar cells of the mammary gland, and secretory cells of the sebaceous gland and hair, both in the medulla and cortex (Kajitani et al., 1989).

There have been no comparable studies in humans, but the results of functional MRI scanning (fMRI) suggest that methamphetamine concentrates in certain parts of the brain and not others. Abnormal metabolic activity and structural deficits in limbic and paralimbic cortices have also been demonstrated. Even in the recently abstinent, dysfunction in the cingulate gyrus and insular cortices seems to persist (London et al., 2005).

The results of drug distribution studies in humans suggest that skin and blood methamphetamine concentrations are comparable, and that methamphetamine may persist in

the skin for some time. In the mammary gland, methamphetamine combines with casein and is excreted by exocytosis. Accumulation of methamphetamine in the hair is thought to be the result of drug derived from tissue fluid and sebum penetrating the shaft of the hair. It could also be due to blood perfusing the hair follicle (Nakahara and Kikura, 1997).

In experimental animals the disposition kinetics of amphetamine are stereoselective, with significant differences in pharmacokinetic parameters for *d*- and *l*- forms (Hutchaleelaha et al., 1994). It is not known whether or not the different isomers possess different enough toxicity to make any difference in humans, nor even whether disposition is the same in humans. Several postmortem studies have been published, but the issue of postmortem redistribution makes any generalization from their results difficult, if not impossible.

Amphetamine concentrates in human breast milk. There exists only one report containing measurements made in the milk of one amphetamine-using woman. When tested at 10 days and again at 42 days after delivery, amphetamine concentrations were much higher in her milk than in her plasma (Steiner et al., 1984). These measurements were made at a time when it was not appreciated that milk expressed early has much lower concentrations of fat than milk expressed later from the same breast (Suri et al., 2002). There is, however, no doubt that amphetamine is transferred to the baby by breast milk. A study published in 2006 studied four maternal–infant pairs. The median maternal dexamphetamine dose was 18 mg/day (range 15–45 mg/day). Median (interquartile range) descriptors were 3.3 (2.2–4.8) for milk/plasma ratio, 21 μg/kg on day 1 (range 11–39) for absolute infant dose, and 5.7% (4–10.6%) for relative infant dose. No adverse effects were seen. In three infants tested, dexamphetamine in plasma was undetected in one (limit of detection 1 μg/L) and present at 18 μg/L and 2 μg/L in the other two. Thus, the relative infant dose of amphetamine was <10% and within a range that is generally accepted as being 'safe' in the short term (Ilett et al., 2007).

Neither random nor systematic measurements of methamphetamine concentrations in human breast milk have ever been reported. And, in spite of obvious similarities between the amphetamine and methamphetamine molecules, these structural similarities do not insure that the two different molecules will be incorporated into breast milk in the same way. For one thing, the charges on the two molecules are different (amphetamine has a pKa of 7.23, while that of methamphetamine is 10.1). Neither is there any evidence that amphetamine use during pregnancy, or excretion of amphetamine into breast milk, directly harms the fetus. Some studies have found evidence for prematurity and lower birth weight (Oro and Dixon, 1987) in children born to women using amphetamines. Also arguing against the toxicity of methamphetamine transferred by breast milk are a number of other case reports describing women who took methamphetamine, either for narcolepsy or as abusers, throughout pregnancy and while nursing, with no detectable ill effects in their children (Milkovich and van den Berg, 1974; Briggs et al., 1975; Eriksson et al., 1978; Billing et al., 1980; Little et al., 1988; Joffe and Kasnic, 1994; Little et al., 1999). Nonetheless, at least two California methamphetamine-using mothers have been convicted of child endangerment for administering drugs by breastfeeding (Ariagno et al., 1995).

3.1.7.1 Interpretation of Infant Postmortem Blood Concentrations

When cases of infanticide (or at least endangerment) involving amphetamines come to trial, the prosecution is generally forced to rely on anecdotal case reports. The most often

cited series of case reports was published in 1997. It reported methamphetamine blood concentrations in eight cases of fetal and infant demise. The mean fetal blood concentration of methamphetamine was 0.36 μm/mL (range, 0.03–1.20 μm/mL), and the mean concentration of amphetamine was 0.05 μm/mL (range, 0–0.08 μm/mL). The problem is that in all eight cases, the pathologist who determined the cause of death (Stewart and Meeker, 1997) considered the presence of drug an incidental finding. Nonetheless, if blood concentrations in an alleged murder victim fall within the ranges observed in the eight reported cases, the prosecution's expert will argue that methamphetamine was the cause of death. The line of reasoning may seem plausible to the jury, because it supplies an interpretable value range, spurious though it may be.

A handful of other anecdotal reports have described blood levels in dead infants. One case involved a 24-year-old chronic amphetamine abuser who delivered a premature, low-Apgar-score, 2-lb, 7.5-ounce child who expired at 4 hours. Autopsy findings were consistent with intrauterine anoxia. Methamphetamine concentration was highest in the lungs and lowest in the liver. The concentration in the lungs was nearly three times that in the blood (Garriott and Spruill, 1973). In a second case, a methamphetamine-injecting mother injected amphetamine a few hours prior to giving birth to twins. The highest amphetamine concentrations were in the kidney and liver, and the lowest concentrations were in the blood and brain. Methamphetamine concentrations ranged from 4.53 to 11.0 mg/kg. Amphetamine concentrations were less than 15% of the methamphetamine concentrations, which ranged from 0.18 to 1.40 mg/kg (Stek et al., 1993).

As the ability to detect nanogram quantities of drugs improves, drugs are being detected in more and more sick children (Kharasch et al., 1991; Dusick et al., 1993; Smith and Kidwell, 1996; James et al., 1998; Lustbader et al., 1998). The mere presence of these drugs is not sufficient reason to implicate them as a cause of illness or death, either in adults or in children; it just proves that the drug is present. In order to prove that death was the result of drug toxicity, there should be some plausible explanation of the mechanism of toxicity and, preferably, anatomic or histologic evidence of toxicity. In the case of methamphetamine and cocaine, such evidence might be provided by the presence of infarction, cardiac enlargement, myocardial fibrosis, or contraction band necrosis. At the same time, other possible causes of death must be proven absent. For example, a child with a modest blood concentration of methamphetamine might well die of a heritable long QT syndrome or some other genetic disorder (Sarkozy and Brugada, 2005). Without doing DNA testing, there simply is no way to determine the cause of death, at least not with any level of certainty. At a minimum, the autopsy itself must be meticulous and complete, and the state's mandated sudden infant death syndrome (SIDS) protocol completed; even then a meticulous autopsy is not sufficient to rule out a genetic defect.

Another factor complicating the interpretation of postmortem blood and tissue levels in neonates and infants is that they may be more resistant to drug effects than the mother. The birthing process is associated with a massive surge of catecholamines (partly to facilitate the mobilization of brown fat), and yet the hearts of newborns never display any histologic evidence of catecholamine toxicity. This situation arises because at birth adrenergic receptors in the heart are down-regulated (Robinson, 1996; Hata et al., 1997). If adrenergic receptors are down-regulated (Fanaroff and Fanaroff, 2006), then it becomes increasingly difficult to imagine how catecholamine-mediated amphetamine toxicity could occur.

3.1.8 Interpretation of Adult Postmortem Blood Concentrations

3.1.8.1 Autopsy Series

Postmortem methamphetamine measurements have been reported in two large autopsy series (Logan et al., 1998; Karch et al., 1999), and the problem of postmortem redistribution addressed in one other (Barnhart et al., 1999). The value of postmortem methamphetamine measurement is questionable, primarily because both tolerance (McLeman et al., 2000) and postmortem redistribution occur (Moriya and Hashimoto, 1999). Many, if not most, methamphetamine-using decedents are polydrug users (Karch et al., 1999), and because methamphetamine concentrates in heart muscle, from which it is slowly released after death (Barnhart et al., 1999), measurements made on left-heart blood inevitably cause spurious elevations in concentration. In the largest autopsy series reported to date, drug concentrations were compared in a group of 132 decedents where methamphetamine toxicity was clearly not the cause of death (trauma victims), and 232 patients for whom methamphetamine was the cause of death (Karch et al., 1999). Seventy-five percent of both had blood methamphetamine concentrations of less than 1.32 mg/L.

The mean blood methamphetamine concentration was 1.84 mg/L in the trauma group, and 2.11 mg/L in the methamphetamine-induced group. Blood amphetamine concentration was 0.24 mg/L in the incidental finding group, and 0.161 mg/L in those dying of drug toxicity. These concentrations were not significantly different. Measurement of urinary methamphetamine and amphetamine concentrations revealed similar overlap; no difference was observed between cases in which methamphetamine was the cause of death and cases where it was not (38.6 vs. 27.5 for methamphetamine and 8.0 vs. 4.5 mg/L for amphetamine). Ethanol was present in one quarter of all the cases, and cocaine or cocaine metabolite in 24% of the decedents. However, the drug most often used in combination with methamphetamine was morphine, which was present in nearly one third of the cases (Karch et al., 1999). In the absence of a national database, it is impossible to determine whether the co-abuse of methamphetamine and heroin is a local phenomenon, or whether some common mechanism of addiction is involved. Comparable results were also reported from a second autopsy series in Seattle (Logan et al., 1998).

3.1.8.1.1 False Positives The presence of methamphetamine can also be explained by the conversion of certain drugs, such as selegiline (Eldepryl®, Deprenyl®) to amphetamines. Selegiline is a monoamine oxidase (MAO) inhibitor used in the treatment of parkinsonism. It is a derivative of phenethylamine, and two of its principal metabolites are amphetamine and methamphetamine. Both may accumulate in substantial amounts in patients receiving anti-Parkinson therapy. In such cases, the clinical history will be necessary to make the correct diagnosis. Other drugs that can be converted to methamphetamine include benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, and prenylamine (Musshoff, 2000).

3.1.8.1.2 Tolerance In most methamphetamine-related deaths, blood concentrations fall between 0.5 and 2 mg/L. But, just as in children, methamphetamine concentrations alone cannot be used to determine the cause of death. Long-term methamphetamine abuse sets in motion a complicated series of interactions affecting both physiologic and behavioral responses. As is true for cocaine, death from methamphetamine may be

associated with very low or very high postmortem blood concentrations (Karch et al., 1998; Jenkins et al., 2002). Tolerance to stimulant drugs cannot be assessed at autopsy so it is not possible to attribute any particular significance to isolated high-concentration measurements (unless, of course, no methamphetamine is detected in the hair, which would prove that the decedent was naïve and, therefore, not tolerant). This is especially true for methamphetamine, where the measured concentration is highly dependent on where in the body the sample is obtained. Low concentrations are equally difficult to interpret. If significant methamphetamine-related heart disease is present (enlargement, fibrosis, coronary artery disease, dissection), and there is a documented history of long-term methamphetamine abuse, death could be attributed to methamphetamine even when blood drug concentrations are low or nonexistent.

3.1.8.1.3 Alternate Testing Matrices There is some hope that the problems posed by the issue of tolerance may eventually be resolved. Studies of hair morphine concentrations suggest that addicts can be separated from occasional, or even non-users, by the concentration of morphine in their hair (Tagliaro et al., 1998; Berankova et al., 2005). It may well be that a similar situation applies to stimulant abusers, but this possibility has never been systematically studied. Methamphetamine addiction is a chronic, relapsing disorder, characterized by an uncontrollable motivation to seek and use the drug. There is evidence that chronic use leads to changes in the corticolimbic glutamate system, but only in those with a genetic predisposition to addiction. Members of the Homer family of proteins regulate signal transduction through the brain, controlling glutamate receptors as well as maintaining and regulating extracellular glutamate levels in corticolimbic brain regions (Szumlinski, 2008). With every passing month the brain's response to abused drugs becomes better characterized and receptors easier to measure (Staley and Mash, 1996; Chang and Haning, 2006). Receptor measurements are already used to identify stimulant abusers who die of excited delirium, and it could possibly be adapted to other types of stimulant-related deaths as well. However, the most important and potentially useful technique, one that could be implemented overnight, would be to measure brain drug levels. There is substantial experimental evidence that brain concentration measurements provide a more accurate portrayal of the situation at the time of death than is achievable by isolated blood drug measurements (Spiehler and Reed, 1985).

3.1.8.1.4 Methamphetamine Stability and Measurement Animal studies suggest that, over the long term, amphetamines are stable in most tissues, no matter the degree of environmental exposure. Nagata et al. (1990) found that concentrations of both drugs in whole blood, liver, and skeletal muscle were nearly unchanged after two years of storage in sealed tubes, and that concentrations only decreased by half in samples of bone exposed to the air over a two-year period. The amphetamine content of marrow submerged in tap water for two years barely decreased from baseline (Nagata et al., 1990). Levels in blood and urine do not decrease significantly with storage (Jimenez et al., 2006), but after exposure to formalin, methamphetamine is converted into its *N*-methyl derivative. The rate of conversion is dependent upon pH and upon the formalin concentration; the greatest conversion occurs under alkaline conditions and the higher the formalin concentration the greater the rate and degree of conversion. Conversion begins within 30 minutes of exposure to formalin and, under certain conditions, the conversion may be complete (Tirumalai et al., 2005). Other studies have shown that after the formalin fixation, methamphetamine

concentrations in fixed organ tissues decrease by 1.3–3.1% per day, partly because the drug elutes into formalin fixative (Takayasu et al., 1994).

There is also the problem of Vicks® decongestant inhaler which contains the levorotatory isomer of methamphetamine (Poklis et al., 1993). This isomer has minimal CNS activity but, unless special precautions are taken, it may give false-positive test results for methamphetamine during both screening and confirmatory testing. Few laboratories are equipped to do the testing required to discriminate between the *d*- and *l*- forms of methamphetamine. In fact, immunoassay-based screening for amphetamines as a group still has a variably positive predictive value for detecting amphetamine abuse, which makes confirmatory testing a necessity. Unfortunately, not all urine screening is done under federal rules requiring confirmatory testing, and not all laboratories are equipped with GC/MS, let alone LD/MS/MS, so false positives are still reported with some frequency. There is, however, no substitute for confirmation using alternative testing modalities.

3.1.8.1.5 Site Dependence Concentrations measured at autopsy are site dependent, and concentrations in left-heart blood may be many times higher than concentrations measured in right-heart blood (Miyazaki et al., 1993; Moriya and Hashimoto, 1999). Concentrations in samples collected from other sites may also differ. The difference is at least partly explained by the diffusion of methamphetamine out of lung tissue into the pulmonary circulation, which occurs more rapidly than diffusion from the liver into the vena cava. As a consequence, methamphetamine concentrations in blood from the pulmonary artery and left ventricle may be many times higher than in blood collected from the right side of the heart (Nagata et al., 1990; Moriya and Hashimoto, 1999). Results may also be altered by the size of the specimen collected. If large quantities of blood (c. 50 mL) are drawn from the inferior vena cava, the values measured may really be more a reflection of hepatic drug concentration than of the amount circulating in the blood at the time of death.

3.1.9 Measurements in the Living

Methamphetamine detection in the living is equally problematic. Under federally regulated workplace testing programs, a urine test is not considered to be positive for methamphetamine unless immunologic screening tests demonstrate that the specimen contains amphetamine or methamphetamine in concentrations of 1000 ng/mL or more, and subsequent GC/MS analysis shows a concentration of at least 500 ng/mL. First-generation amphetamine screening tests often cross-reacted with compounds such as ephedrine and phenylpropanolamine, but the problem was largely eliminated when these products were removed from the market. Still, the degree of cross-reaction with other amphetamines (MDMA for example) remains substantial but unpredictable. It goes without saying that if a methamphetamine user does die, and there is a hospital specimen available, it, rather than any postmortem blood, should be relied upon for cause of death determination.

3.1.10 Impairment

There is no evidence that low oral doses of amphetamine and methamphetamine impair psychomotor performance. In fact, there is a good deal of evidence suggesting quite the opposite (Newhouse et al., 1989; Koelega, 1993; Mills et al., 2001; Caldwell et al., 2003; Kelly et al., 2004; Van Dongen et al., 2006). However, it is generally accepted that the intake of

higher doses may impair traffic-related skills. Analysis of data derived from 878 Norwegian amphetamine-abusing drivers arrested for "driving under the influence" (DUI), and examined by a police physician, disclosed that 27% of the drivers were judged as not impaired, while 73% were, and there was a positive relationship between blood amphetamines concentrations and impairment. However, the relationship had limits, and only applied when blood amphetamines concentrations were in the range 0.27–0.53 mg/L. At the same blood concentrations, the diagnosis of impairment was made more often in younger drivers than old (Gustavsen et al., 2006). In another very large study of amphetamine abusers arrested for driving under the influence, the median concentration of amphetamine in males was 740 ng/mL and 880 ng/mL in women (Jones, 2008). Whether a test that is wrong nearly one third of the time meets forensic requirements is open to question.

3.1.11 Toxicity by Organ System

The number of methamphetamine abusers has increased considerably in the last decade, but the number of reported deaths and medical complications remains surprisingly low. The explanation may be that the most important complications are cardiovascular, and that the production of cardiovascular damage only occurs after protracted use. Exact figures are not available, but SAMHSA estimates that from 2002 to 2005 1.4 million Americans (0.06% of the total population) took methamphetamine and that in 2004 alone, some 600,000 had used in the previous month (Anon., 2006b). Table 3.1.11.1 shows the ten most frequently seen disorders in an autopsy study of 413 methamphetamine-related deaths. Liver disease, ranging from steatosis to cirrhosis, was present in nearly 40% of the cases, followed by heart and lung disease. There have been similar surveys since the original was published, with roughly similar results.

3.1.11.1 Cardiovascular

The hearts of chronic methamphetamine and cocaine users have the same microscopic features: hypertrophy, interstitial fibrosis, and microvascular disease. Both drugs produce

Table 3.1.11.1 Top Ten Abnormalities in Methamphetamine Abusers at Autopsy

Abnormality	Percent (%)
1. Fatty liver	16.2
2. Moderate coronary artery disease	10.3
3. Cirrhosis	9.0
4. Pneumonia	8.2
5. Myocardial fibrosis	6.7
6. Triaditis	6.1
7. Severe coronary artery disease	6.1
8. AIDS	5.4
9. Emphysema	5.1
10. Hepatitis	4.1

Source: From Karch, S. B. et al., *J. Forensic Sci.,* 44(2), 359–368, 1999. With permission.

a pattern of fibrosis that is perimyocytic in distribution. Stimulant abusers in general are also prone to accelerated coronary artery disease (CAD), but it is not at all clear whether the stimulant or polydrug abuse and cigarette smoking, or some combination is responsible (Karch et al., 1999).

In spite of the morphologic similarities, the underlying mechanisms producing these changes may be different in cocaine and methamphetamine abusers. Catecholamine excess is certainly a common factor and both drugs activate calmodulin (which indirectly leads to myocardial hypertrophy), but even acute cocaine administration activates myocardial genes favoring hypertrophy (including angiotensinogen, C-reactive protein, and calmodulin kinase), and increases intracellular calcium in both heart and brain (Ouchi et al., 2004; Lattanzio et al., 2005; Du et al., 2006; Henning and Cuevas, 2006). None of these changes has been demonstrated in the hearts of methamphetamine abusers, though this is not an area of active research; the changes may be present but going unrecognized. Another important difference between the two drugs is that cocaine is both a sodium and potassium channel (HERG) blocker, but methamphetamine is not.

Still another difference between the two drugs is in the incidence of symptomatic coronary artery disease. As Table 3.1.11.1 clearly illustrates, multivessel coronary artery disease occurs at a much higher rate in methamphetamine users than in age-matched controls, or even, apparently, cocaine users (Karch et al., 1998). Yet, surprisingly, reports of methamphetamine-related myocardial infarction remain so uncommon as to still be reportable, while acute coronary syndrome among cocaine users is a common occurrence. Recent advances in molecular biology may explain the difference; the rise in body temperature produced by amphetamine abuse leads to the increased production of myocardial heat-shock proteins (Maulik et al., 1994). Cells produce these proteins in response to stressors such as ischemia and cellular injury (Lindquist, 1986). Animals treated with amphetamine are resistant to ischemia. If the same set of responses occurs in humans, it would account for the apparent difference in cardiotoxicity observed between methamphetamine and cocaine.

Cocaine and amphetamines cause norepinephrine to accumulate in the synaptic cleft and overflow into the circulation, but amphetamines exert additional effects over and above those produced by cocaine. Amphetamine is transported into the pre-synaptic terminal, where it inhibits MAO and prevents further storage of catecholamines within nerve ending (Figure 3.1.11.1.1). Taken together, the result is increased sympathetic stimulation and increased circulating levels of catecholamines in the periphery (Fukunaga et al., 1987).

High circulating catecholamine levels, regardless of their origin, result in cardiotoxicity. The very same morphologic alterations produced by amphetamine abuse have been seen in patients with pheochromocytoma (Szakacs and Cannon, 1958; Szakacs et al., 1959) and cocaine abusers (Tazelaar et al., 1987). They are easily reproduced in experimental animals by infusing catecholamines (Rona, 1985; Todd et al., 1985a, b). Japanese researchers first described signs typical of catecholamine toxicity in methamphetamine-related fatalities in the early 1980s (Matoba, 2001). Methamphetamine abuse has been a problem in Japan since the drug was first invented, and methamphetamine-induced arrhythmic sudden death is a recognized entity in that country. Myocardial alterations in stimulant abusers with sudden cardiac death include focal subendocardial hemorrhage, usually surrounding areas of myocyte disruption, sometimes with lymphocytic infiltrates (Fukunaga et al., 1987; Tazelaar et al., 1987). Interstitial fibrosis with myocyte hypertrophy is the pattern most commonly seen.

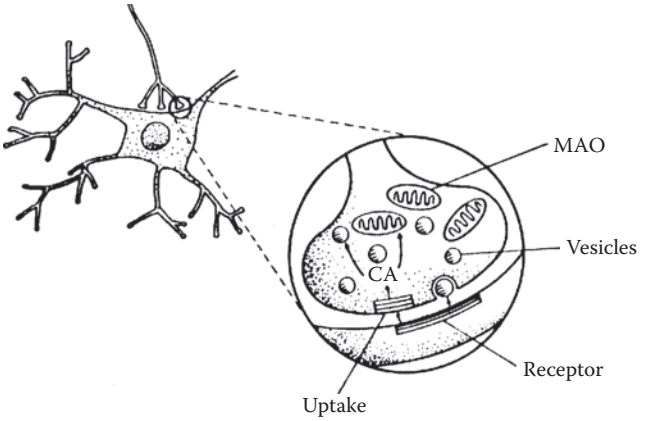


Figure 3.1.11.1.1 Effects of amphetamine on nerve endings. The effects of amphetamine on catecholamine metabolism are more complex than those of cocaine. In addition to blocking re-uptake, amphetamine also causes increased release of neurotransmitters. (Courtesy of Dr. Arthur K. Cho, Department of Pharmacology, UCLA School of Medicine.)

In recent years, a new cardiac syndrome with transient left ventricular dysfunction has been widely reported in Japan where it is referred to as "tako-tsubo cardiomyopathy." It occurs in Western countries as well. This new entity is characterized by "apical ballooning," for the shape of the left ventricle at end systole which resembles an octopus trap, hence its Japanese name. The syndrome has also been reported to occur in the Western population as stress-induced cardiomyopathy, or broken heart syndrome. This syndrome is characterized by transient dysfunction of the apical portion of the left ventricle, with compensatory hyperkinesis of the basal walls, producing ballooning of the apex in systole even though there is complete absence of significant coronary artery disease.

Tako-tsubo is more common in women than men, and more common in menopausal women. In a review of seven different case studies, postmenopausal women accounted for 82–100% of cases, with a mean age of 62–75 years.

Onset is typically triggered by acute medical illness or intense emotional or physical stress (e.g., death of relatives, particularly if unexpected, domestic abuse, arguments, catastrophic medical diagnoses, devastating financial or gambling losses, natural disasters) — in short, a situation that would lead to an outpouring of catecholamines, but almost always in the absence of coronary artery disease. Reports in the clinical literature suggest that patients presenting with this disorder are often mistaken for individuals sustaining myocardial infarction (Cattaneo et al., 2008; Prasad et al., 2008).

A unifying mechanistic explanation responsible for this type of acute but rapidly reversible contractile dysfunction is still lacking. The results of several investigations suggest a variety of possible etiologies, including catecholamine-mediated cardiotoxicity, coronary artery vasospasm, microvascular injury, impaired fatty acid metabolism, or even transient obstruction of the left ventricular outflow tract. The optimal treatment of patients presenting with this syndrome may depend on the stage of the condition, since various pathophysiological mechanisms underlie the final clinical picture (Nef et al., 2006a, b). The same disorder has been observed in cocaine users, strongly suggesting that the underlying

disorder is catecholamine-related (Arora et al., 2006). The first report of methamphetamine and tako-tsubo was published in 2007 (Reuss et al., 2007).

Inducible nitric oxide synthase (iNOS)–mediated stress is the putative mechanism to catecholamine cardiotoxicity. Chronic treatment of mice with isoproteronol induces an up-regulation of iNOS. Serum levels of C-reactive protein, an inflammatory mediator, rise at the same time. The up-regulated iNOS produces a significantly increased amount of nitric oxide and its byproduct, peroxynitrite. When this occurs, myocardial apoptosis develops at an accelerated rate, but the apoptosis can be prevented by pre-treatment with nitric oxide blockers. Chronic β-receptor stimulation, as would occur in amphetamine and cocaine users, up-regulates iNOS expression and increases nitric oxide production in the heart, enhancing the formation of reactive nitrogen species/peroxynitrite within the heart, resulting in myocardial apoptosis and cell death (Hu et al., 2006).

Medial hypertrophy of myocardial arterioles has also been described, both in cocaine and methamphetamine abusers (Matoba et al., 1986). Until recently, the significance of microvascular disease had gone unrecognized. It is now apparent that the combination of microvascular disease and myocyte hypertrophy almost certainly provides the underlying substrate necessary for arrhythmic sudden death, because the enlarged myocytes (whether from DNA activation or secondary to catecholamine excess) are relatively undersupplied with oxygen at all times, and suffer from decreased coronary artery reserve (Karch et al., 2005). The most recent experimental evidence suggests that, given the pre-existing anatomic changes, elevated concentrations of catecholamines provide the trigger for these arrhythmias.

Endomyocardial biopsy of one methamphetamine abuser with heart failure disclosed patchy interstitial fibrosis along with the presence of scattered mononuclear cells (Jacobs, 1989). Another report described autopsy findings in a 45-year-old female abuser of oral amphetamine who died of heart failure. Her heart was enlarged (530 g) but the coronary arteries were widely patent. Widespread interstitial edema, with scattered lymphocytic and histiocytic infiltrates, was evident, along with degeneration of individual fibers and patchy myocardial fibrosis. In still another case, patchy myocardial fibrosis, without infiltrates, was the principal finding in a young "ice" smoker who died of an acute posterior wall infarct (Smith et al., 1976). The pattern described in all of these cases is very much like the pattern produced by catecholamine toxicity in general and by cocaine in particular. Similar lesions have been observed in experimental animals treated with methamphetamine (Smith et al., 1976).

Electron microscopic studies of autopsy material from a chronic amphetamine abuser were first carried out more than a quarter century ago; myofilament rupture and disarray could be seen, and the mitochondria contained many large electron-dense granules (Smith et al., 1976). The latter finding is a marker for mitochondrial calcium overload, the typical response seen in myocytes after ischemia and/or excessive catecholamine stimulation.

All phenylisopropylamines can produce catecholamine-mediated cardiotoxicity, and all the features associated with catecholamine toxicity are seen in stimulant abusers. It has been known for more than 40 years that the same pattern of injury can be induced by infusing large amounts of norepinephrine (Szakacs and Cannon, 1958). Since the last publication of this book considerable evidence has been published describing cardiomyopathy in methamphetamine (but not amphetamine) abusers (Wijetunga et al., 2003; Reuss et al., 2007; Yeo et al., 2007).

Myocardial infarction has been reported after "snorting" methamphetamine (Furst et al., 1990), after intravenous injection (Carson et al., 1987), and after the oral use of various amphetamine analogs, including propylhexedrine (Marsden and Sheldon, 1972), dextrofenfluramine (Evrard and Allaz, 1990), and pseudoephedrine (Wiener et al., 1990). None of these case reports has included histological findings, but in several instances angiography was performed and found to be normal (Chen, 2007). The absence of fixed lesions suggests that the infarcts were due to coronary spasm, which, we now know, might actually be the result of endothelial viral infection (endothelial tropic myocarditis) (Kuhl et al., 2003). Still, reports of methamphetamine-related myocardial infarction remain quite rare and are still considered reportable.

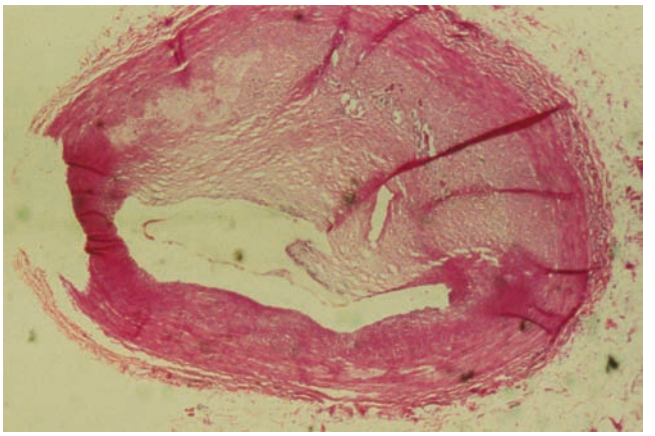
A number of cases of aortic dissection have also been reported, and aortic dissection is now a well-recognized complication of methamphetamine abuse (Davis and Swalwell, 1994; Swalwell and Davis, 1999; Anzalone et al., 2002; Gotway et al., 2002; Wijetunga et al., 2003). The mechanisms for coronary artery disease and aortic dissection in methamphetamine abusers (Figure 3.1.11.1.2) are not known, but elevated plasma and tissue concentrations of catecholamines lead to free radical generation, and metabolites of these agents, called *o*-quinones, contribute to redox cycling, toxicity, and apoptosis. Cyclized *o*-quinones, including aminochrome, dopachrome, adrenochrome, and noradrenochrome (formed from dopamine, dopa, adrenaline, and noradrenaline, respectively), are all highly reactive compounds capable of producing damage to the endothelium of large and small vessels, not to mention the destruction of neurons (Baez et al., 1997).

3.1.11.2 Pulmonary

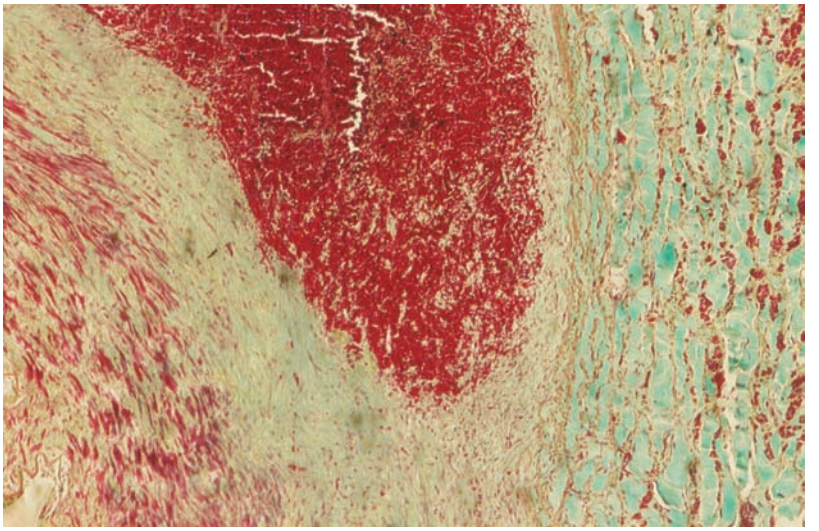
In the only large autopsy series of methamphetamine-related deaths, pulmonary edema was present in over 70%, pneumonia in 8%, and emphysema in 5%. Birefringent crystals were noted in 11% (Karch et al., 1999). When drug tablets are crushed and injected intravenously, the insoluble fillers (microcrystalline cellulose, corn starch, or cotton fibers) contained in the tablet become trapped in the pulmonary microvasculature, where they are easily visualized as birefringent crystals. If the process is repeated enough times, the smaller vessels become thrombosed, and foreign body granulomas form. Eventually, some of the foreign material will work its way into the perivascular spaces, leading to further granuloma formation and more fibrosis (Tomashefski and Hirsch, 1980; Tomashefski et al., 1981).

Repeated amphetamine injections result in a net reduction in the size of the pulmonary vascular bed and an increase in pulmonary vascular resistance. At autopsy, organizing and recanalizing thrombi will be seen, along with easily identifiable birefringent material (Rajs et al., 1984; Kringsholm and Christoffersen, 1987). Histologically, this type of pulmonary hypertension can be distinguished from the much rarer primary variety by the presence of plexiform lesions, seen at branching points of the obstructed small arteries (Pietra, 1991). This complication seems to be associated more with some abused drugs than with others. In general, heroin abusers are much more prone to thromboembolic arteriopathy than stimulant abusers, and individuals who injected crushed pills seem to show the worst lesions, often with giant cell formation and birefringent crystals.

During the last decade our understanding of the pathogenesis of amphetamine-induced pulmonary disease has increased considerably. Elevations in plasma 5-HT (serotonin) have been implicated in the pathogenesis of both cardiac and pulmonary disease. Under normal circumstances, plasma 5-HT concentrations are kept at low levels by transporter-mediated



(a)



(b)

Figure 3.1.11.1.2 (a) Cross section of left anterior descending coronary artery in a gunshot wound victim, where methamphetamine abuse was unrelated to the cause of death. Extensive coronary artery disease is common among methamphetamine abusers and occurs at a much younger age than coronary artery disease in the general population. (b) Dissecting femoral artery aneurysm in a methamphetamine abuser. Aortic dissection is a recognized complication of methamphetamine abuse, although the mechanism is not known. Special staining procedures are unrevealing, and none of the reported cases has involved individuals with Marfan's syndrome. (From the office of the San Francisco Medical Examiner.)

uptake of 5-HT into platelets, and also by metabolism to form 5-hydroxyindoleacetic acid (5-HIAA). Many abused drugs, including the amphetamines, target 5-HT transporters and, indirectly, increase the amount of circulating 5-HT. Studies of animals have shown that drugs like amphetamine and methamphetamine raise 5-HT levels sufficiently to initiate mitogenesis in pulmonary artery smooth muscle cells (Zolkowska, 2006). Additional studies are needed to determine the effects of chronic administration of amphetamines on circulating 5-HT, but it seems likely that the elevated 5-HT concentrations may also

account for the smooth muscle hypertrophy that is always evident in the hearts of chronic stimulant abusers (Shannon and Chaudhry, 2006).

Finally, there is emerging evidence, or at least a strong suspicion, that methamphamine abuse could play a role in the development of pulmonary arterial hypertension (PAH). This suspicion arises largely because of the structural similarity between methamphetamine and fenfluramine. In a recent retrospective study of 340 patients with idiopathic pulmonary hypertension, a history of stimulant use was found in 28.9% of patients with this diagnosis, compared with 3.8% of patients with PAH and a known risk factor, and 4.3% of patients with chronic thrombotic embolism (including those who inject crushed pills not meant for injection) (Chin et al., 2006). After adjustment for differences in age, patients with idiopathic PAH were 10.14 times (95% confidence interval, 3.39 to 30.3; $p < 0.0001$) more likely to have used stimulants than patients with PAH and known risk factors, and 7.63 times (95% confidence interval, 2.99 to 19.5; $p < 0.0001$) more likely to have used stimulants than patients with chronic thromboembolic pulmonary hypertension. More and more young people are injecting crushed tablets and the findings of this study are disturbing. Even though the study is only retrospective, it raises serious concern.

3.1.11.3 Central Nervous System

With the exception of attention deficit-hyperactivity disorder (ADHD), the only other legitimate use for drugs in this group is appetite suppression. Amphetamine and phentermine are anorectic drugs by virtue of their ability to cause the release and/or prevent the re-uptake of noradrenaline and dopamine. In drug abusers (as opposed to individuals taking pharmacologic doses of methamphetamine), the most obvious manifestations of toxicity are psychosis and stroke. Large doses of methamphetamine (10–15 mg/kg) given to experimental animals quickly alter the serotonergic and dopaminergic systems of their brains. Tyrosine hydroxylase activity, the rate-limiting enzyme in the synthesis of dopamine and norepinephrine, decreases in a dose-related fashion, and so does the content of dopamine and homovanillic acid in the brain (Koda and Gibb, 1973).

The pattern of injury associated with chronic amphetamine treatment is similar to that seen with methamphetamine, though less severe (Sachdeva and Woodward, 1989; Ellison and Switzer 1993; Karch et al., 1999). Both hemorrhagic (Yen et al., 1994) and ischemic (Perez et al., 1999; Ohta et al., 2005; Miller and Coon, 2006) stroke have been reported as a consequence of methamphetamine abuse, but the pathology is not understood, except for the fact that those with pre-existing malformations are obviously at increased risk, and that amphetamine-related hemorrhages are more often intracerebral, or simultaneously intracerebral and subarachnoid, than pure subarachnoid. Hemorrhage is most often confined to the frontal lobes, though it occasionally involves the basal ganglia. This distribution is in contrast with the pattern seen in hypertensive hemorrhages that usually involve the basal ganglia and hypothalamus. The pattern is, however, almost exactly the same as that seen in cocaine abuse where the frontal lobes are most often involved. Rarely, the etiology may be embolic (Imanishi et al., 1997), and occasionally there is evidence for vasculitis.

Much has been learned about the neurotoxic potential of methamphetamine. Whether or not neurotoxicity occurs depends on the dose, dosing interval, route of administration, and temperature. The availability and proper function of dopamine and 5-HT transporters is a requirement for the expression of amphetamine-related neurotoxicity. Still, the mechanisms by which amphetamine leads to selective damage to cells that produce dopamine and 5-HT is not yet known, nor are the mechanisms, time course, and features of recovery.

One reality that makes experimental work difficult are the very wide differences in species response. Finally, it is becoming clear that the neurobiology of monoaminergic neurons plays a key role in neurodegenerative diseases such as Parkinson's disease. Elucidating this mechanism is key if clinicians are ever to understand any of the neurodegenerative diseases, including psychosis (Ricaurte et al., 2005).

Whatever the mechanisms, there is very little doubt that methamphetamine psychosis exists, and that it may remain for months after the drug has been discontinued (Young and Scoville, 1938). Amphetamine-related psychotic reactions were recognized soon after the drug was first introduced, with the first paper on the subject appearing in 1938 (Iwanami et al., 1994). A 1958 paper reviewed 36 cases from the world's literature and concluded that there were striking similarities between the symptoms of amphetamine-induced psychosis and schizophrenia (Connell, 1958), and at one time, large numbers of amphetamine abusers were admitted to mental hospitals with the mistaken diagnosis of schizophrenia.

Chronic cocaine abuse can also cause acute psychosis, but it seems to do so less frequently than methamphetamine. The reason amphetamine-related psychosis appears to be more common than psychosis in cocaine abusers may be a function of the affinity of methamphetamine for sigma (σ) receptors. The ability to bind σ receptors is clearly related in some way to the occurrence of psychosis but just what that connection is remains unknown. In animal studies, chronic methamphetamine administration leads to up-regulation of σ receptors in the substantia nigra, frontal cortex, and cerebellum (Gardner and Connell, 1972); enhances catecholamine-related, cortical-event-related potentials (Takeuchi et al., 1999); and even leads to the expression of some early genes (c-*fos*) (Namima et al., 1999). Cultural determinants may also have some bearing on the psychiatric manifestations of amphetamine abuse; even though methamphetamine psychosis is responsible for large numbers of psychiatric hospitalizations in Japan (Iwanami et al., 1994), disease on a similar scale has never occurred in the U.S., or at least it had not before the current methamphetamine pandemic, and this situation may change. The remarkable feature of psychosis in Japanese methamphetamine users is that it may reoccur, even when they have been abstinent for some time.

Quite recently researchers have shown that there are really two types of methamphetamine psychosis: transient and prolonged. Dysfunction of central dopaminergic neurotransmission has been implicated in the pathogenesis of both psychiatric states. To a large extent, the polymorphisms of catechol-*O*-methyl transferase (COMT) are responsible for control of synaptic dopaminergic activity. When compared to nonpsychotic methamphetamine abusers and controls, the patients prone to spontaneous relapse have a nearly 1.7-fold less active form of COMT than controls. In other words, patients with less COMT activity are both more likely to experience methamphetamine psychosis and more likely to suffer from relapse (Suzuki et al., 2006).

Even if they do not become psychotic, amphetamine users may be restless, tense, and fearful. Some develop delusions of persecution and ideas of reference. They may also have auditory, tactile, and visual hallucinations. Strangely, most are not disoriented and will act appropriately, given their paranoid state. The frequencies with which hallucinations are visual, and the relative preservation of orientation in amphetamine users, are believed by some researchers to differentiate amphetamine psychosis from true schizophrenia (Iwanami et al., 1994).

The syndrome of excited delirium, which also occurs in chronic cocaine users, has been reported in amphetamine abusers (O'Halloran and Lewman, 1993; Wetli et al., 1996; Stephens et al., 2004), though cocaine appears to be a much more frequent cause.

Amphetamine-related vasculitis was first described by Citron et al. in 1970, and there have been intermittent reports ever since (Forman et al., 1989; Perez et al., 1999; Zhu et al., 2000; Ohta et al., 2005). Additional cases continue to be reported, but none of these new reports includes the histopathologic findings, so there is no way to determine whether vasculitis or vasospasm is being demonstrated by non-invasive studies. In the cases first described by Citron et al., the histological appearance was identical to that seen in polyarteritis nodosa, with fibrinoid necrosis of the intima and media, and mixed cellular infiltrates. With longer periods of survival, intimal proliferation and marked luminal narrowing, especially at the bifurcation of vessels, occurred. Characteristically, giant cells were in absent in Citron's report and the veins spared. Other reports described involvement of smaller (Stafford et al., 1975) and larger vessels (Bostwick, 1981; Shibata et al., 1991).

In the case described by Shibata et al. (1991) the smaller vessels were spared but virtually all of the other major vessels were necrotic, with destruction of the smooth muscle layer and scarring of the elastic layer. No leukocytic infiltration of the vessels was seen, but additional reports are extremely rare. A possible explanation for the apparent decline in the number of cases is that the original case may have been the result of some contaminants or adulterants introduced during the manufacture of methamphetamine. The other problem is that methamphetamine abusers tend to be polydrug abusers, and attributing vasculitis to just one of the drugs is probably not possible.

One of the most likely contaminants, one which would certainly be toxic to blood vessels, is hydrochloric acid. In the summer of 2005 the German government noted that its €50 notes were falling apart, with a frayed moth-eaten appearance, even if they were nearly new. Methamphetamine has now surpassed amphetamine in popularity among Germans and it turns out that the €50 note is the perfect size for snorting methamphetamine. Users crush crystal methamphetamine on the bank notes, then roll them up and insert into a nostril — exactly the same way that most Americans took cocaine before crack arrived on the scene. American abusers have an advantage over their German counterparts because all U.S. currency is exactly the same size; euro notes are not.

3.1.11.4 Genitourinary Tract

Except for episodes of rhabdomyolysis, methamphetamine-related kidney damage is almost always secondary to a disease somewhere else in the body. Renal complications of amphetamine and methamphetamine abuse are uncommon. In the series of 413 methamphetamine-related deaths reported from San Francisco, the incidence of renal disease was less than 2%. When renal disease was detected, most often it consisted of typical nephrosclerotic lesions of the sort that are usually seen in hypertensives (Luke, 1999).

There are only a few experimental studies of any relevance. Renal damage and peroxidative injury occur after the subacute treatment of experimental animals with methamphetamine. Immunohistochemical analysis disclosed evidence suggesting that chronic methamphetamine exposure may lead to oxidative DNA damage (Tokunaga et al., 2006). For the moment, there is no way to determine whether nephrosclerosis observed in a methamphetamine abuser is a consequence of the drug or untreated hypertension. The first report linking amphetamine ingestion and reversible renal failure was published in 1970 (Ginsberg, 1970), but few additional mentions have appeared since then. Most recently, reported cases have involved the use of "designer" amphetamines, particularly MDMA (3,4-methylenedioxymethamphetamine, also known

as Ecstasy) (Sultana and Byrne, 1996) and PMA (paramethoxyamphetamine) (Byard et al., 1998).

Methamphetamine abuse is becoming an increasingly common cause of rhabdomyolysis, and must always be considered in the differential diagnosis of that disorder. Occasionally it is seen as a complication of "body packing" (Hendrickson et al., 2006), but more often it is seen in "ravers" and in users of MDMA. In a recent retrospective review of 367 emergency room patients with rhabdomyolysis, nearly half were found to be methamphetamine users (Richards, 2000), probably a result of concomitant hyperthermia. Hyperthermia in amphetamine users can occur for a number of reasons. Increased motor activity, even without seizures, raises body temperature, especially when heat loss from the skin is inhibited because of catecholamine-induced vasoconstriction. Altered thermoregulation may also be the result of the direct actions of amphetamine on the hypothalamic temperature centers. However, a number of other unrelated insults can also lead to rhabdomyolysis; alcoholism, drug toxicity, hypokalemia, muscle ischemia, hypotension, and prolonged immobilization have all been implicated as possible factors (Scandling and Spital, 1982; Terada et al., 1988).

When rhabdomyolysis does occur, myoglobin, potassium, and phosphorus are released into the plasma. The presence of these substances in the plasma sets into motion a series of metabolic derangements and fluid shifts. The resultant damage to the kidneys can be indirect, resulting from hypotension and renal ischemia, or direct, as when myoglobin or its decomposition products cause tubular obstruction. Much of the damage may be mediated by free radical formation (Odeh, 1991).

Another possible explanation is that amphetamines themselves are myotoxic. After use of amphetamine, prolonged elevations in creatine phosphokinase can occur, even in patients who do not go on to develop full-blown rhabdomyolysis (Williams and Unwin, 1997). In the retrospective review of Richards (2000), individuals with methamphetamine-related rhabdomyolysis had much higher initial mean concentrations of creatinine phosphokinase than individuals with rhabdomyolysis from other causes (12,439 vs. 5678 U/L ($p = 0.02$)). How amphetamine interacts with muscle sarcolemma to release cell contents is not known.

3.1.11.5 Oral

Chronic methamphetamine use has been associated with severe oral health effects; rampant caries being the most notable of these abnormalities (Damm and Fantasia, 2006; Klasser and Epstein, 2006). There is even now a term, "meth mouth," used to describe the process. The explanation for these changes has not been accessed in anything like a controlled study. Methamphetamine abusers report subjective perception of xerostomia, which cannot be explained by the direct peripheral action of methamphetamine on the secretory acini. The possibility exists that chronic methamphetamine use may result in decreased salivary flow rate by centrally inhibiting salivatory nuclei via stimulation of α_2 receptors in the brain. A decreased salivary flow rate, either secondary to a central inhibitory action of methamphetamine or generalized dehydration, likely contributes to the increased occurrence of dental caries (Robinson et al., 2005; Saini et al., 2005). Although the issue has not been raised in any of the dental journals, it does seem possible that some of the dental disease is secondary to hydrochloric acid carried over from the production process, but the most likely explanation for these changes would still seem to be the combination of trauma, neglect, and poor diet (Laslett and Crofts, 2007).

3.1.11.6 Gastrointestinal Tract

Chronic methamphetamine abuse is associated with liver damage (Karch et al., 1999). In one very large autopsy series, fatty liver was evident in 15.4% of all cases, cirrhosis in nearly 9%, cellular infiltrates of the portal triads ("triaditis") in 6%, and hepatitis in 5%. Hepatitis and infiltration of the portal triads are both common findings in intravenous drug users, and their occurrence in methamphetamine drug users probably is coincidental, having nothing to do with the basic pharmacologic properties of methamphetamine. Dual drug abuse is the rule, not the exception, and a very high percentage of heroin users in California are infected with hepatitis C (Hahn et al., 2001). Viral infection could well explain the infiltrates seen in the portal triads of many methamphetamine users.

A relationship between gastrointestinal ulcers, particularly of the duodenum, and methamphetamine has been reported to exist, but in spite of the current methamphetamine pandemic, new reports of this disorder simply have not appeared. If a connection does exist, it is not nearly so striking as that seen with cocaine abuse (Pecha et al., 1996). Presumably, the same mechanisms are operative with both cocaine and methamphetamine: vasospastic ischemia leading to ulceration. Unfortunately, no animal studies of the process have been undertaken.

Nor is the evidence for a connection with pancreatitis and methamphetamine any stronger. There are no clinical reports or trials, but the results of animal studies suggest that regular administration of methamphetamine to rats can result in the occurrence of scattered edematous lesions and moderate vacuolization within the pancreas. Four of the eight rats in the study (Ito et al., 1997) developed severe regional hemorrhage, partial acinal cell necrosis, and destruction of the acinal cells, neutrophil infiltration, interstitial vessel dilatation, interstitial edema, and fatty cell invasion. In every case the Langerhans' islets were spared. Hemorrhagic pancreatitis has occasionally been noted at autopsy of methamphetamine users, but only in chronic users. The etiology is not known, but a relationship to decreased blood flow seems reasonable (Ito et al., 1997).

3.1.12 Attention Deficit/Hyperactivity Disorder

Amphetamine can be synthesized by the sequential alkylation of methyl acetoacetate with dimethyl sulfate and benzoyl chloride, followed by hydrolysis and deacetylation to give 2-phenylpropionic acid, which is then reacted with benzyl chloride and ammonia to form 2-phenylpropionamide. This mixture is treated with sodium hypochlorite and undergoes Hoffman rearrangement to form a racemic mixture.

According to the DEA, 2096 kg of *d,l*-amphetamine were sold at retail in 2002, along with 3097 kg of *d*-amphetamine, compared with only 17 kg of *d*-methamphetamine. The U.N. reports that the U.S. produced 18,856 kg of *d,l*-methamphetamine in 2000 falling to 7447 kg in 2002. During that same period, production of *d*-amphetamine was reported as 12,306 kg in 2000, dropping to 5962 kg in 2002. Reported exports were minimal. The failure to export is not difficult to understand. The DEA estimates that nearly 8 million amphetamine prescriptions are written each year, almost all for the treatment of ADHD (National Toxicology Program, 2005). The recommended starting dose for the treatment of narcolepsy is 2.5 g/day for children aged 6–12.

In 2006 the U.S. Food and Drug Administration (FDA) announced changes to the labels of Dexedrine® timed-release capsules and, the following year, to methylphenidate. The package insert must now state "Misuse of amphetamines may cause sudden death

and serious cardiovascular adverse events." The prescription information area of the insert now includes the warning "Sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems; Children and adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug." The label change was made on the advice of an FDA advisory committee (Nissen, 2006).

The FDA move followed a Canadian decision made and reversed in 2005. Health Canada suspended sales of Adderall XR®, a relatively low-dose, time-release formulation of dextroamphetamine and amphetamine salts. After reviewing safety data collected over the last 10 years, Health Canada felt that at least 12 and as many as 20 cases of sudden death could be related to Adderall® and Adderall XR®. Later that year the government appointed an independent external committee to review the Health Canada decision. This second committee felt that that the decision should be reversed, and it was. At present it is estimated that 700,000 U.S. residents take Adderall XR® and another 300,000 take Adderall®, while the number taking methylphenidate is even greater, estimated at between 1.5 and 2.5 million children.

Health Canada reported to the FDA that of 12 cases for which there were adequate data, five occurred in patients with underlying structural heart defects (abnormal arteries or valves, myocardial hypertrophy, history of arrhythmias, etc.), all conditions that increase the risk for sudden death. One of the decedents came from a family with a history of ventricular tachycardia. Another of the cases was associated with heat exhaustion, another with dehydration and another with near drowning. Others were associated with very rigorous exercise, fatty liver, heart attack, and type 1 diabetes mellitus. One case was reported three to four years after the event and another had above-toxic blood levels of amphetamine. The duration of treatment varied from one day to eight years. At the time this book went to press, details of the autopsy findings in the 12 children were available at the manufacturer's website (www.adderallxr.com).

The number of cases of sudden deaths reported for Adderall® is only slightly greater, per million prescriptions, than the number reported for methylphenidate products (Ritalin®, Concerta®, Methylin®, Metadate®), which are also commonly used to treat pediatric patients with ADD/ADHD. Presumably that is why an advisory committee of the FDA has recommended a black-box warning on methylphenidate products. According to the FDA, methylphenidate products are the most frequently prescribed ADHD medications. Approximately 1.5 million adults and 2.5 million children in the U.S. take ADHD medications. The rate of sudden death in pediatric patients treated with Adderall® products (assuming 30 million prescriptions were written during the 10-year review) does not appear any greater than the number of sudden deaths that would be expected to occur in this population even without treatment.

The FDA is advising that children with ADHD be screened with an EKG or echocardiogram before commencing therapy. This is unrealistic because an echocardiogram costs more than $1500 and most parents do not have the funds. The FDA is correct in stating that people with heart disease should avoid the drug, but the incidence of heart disease in

children with ADHD is so low as to be of little concern, and myocardial infarction secondary to amphetamine is so rare that new cases are still considered reportable events. Even if a family could pay for echocardiography screening it would not be much of a guarantee of safety. Some forms of hypertrophic cardiomyopathy cannot be seen with an echocardiogram, even though there is a lethal cardiac defect and, with the exception of children with Brugada syndrome, most children with heritable channelopathies will have normal EKGs as well.

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3.2 Methylphenidate (Ritalin®)

Brand names: Ritalin® (Ritalina®, Rilatine®, Ritalin LA (Long Acting)®), Attenta®, Concerta® (a timed-release capsule), Metadate®, Methylin® and Rubifen®. Methylphenidate administered via a transdermal patch (under the brand name Daytrana®).

Chemical names: ([*d,l*]-threo-α-phenyl-2-piperidine acetic acid methyl ester)

Formula: $C_{14}H_{19}NO_2$
Molecular weight: 233.306 daltons
Bioavailability:
d- form: 22± 8, *n* = 19 (Aoyama et al., 1993)*
l- form: 5 ± 3, *n* = 19 (Aoyama et al., 1993)
C_{max}: after 15 mg, 4.7 ng/mL racemic (Modi et al., 2000); *n* = 1, 0.3 mg/kg = 15.7 (Hao-Jie Zhu et al., 2007)
d- form: 18.1 ng/mL (Aoyama et al., 1993)
l- form: 3.0 ± 0.94 ng/mL (Aoyama et al., 1993)
T_{max}: 6 hours, racemic (Modi et al., 2000)
d- form: 2.4 ± 0.8 hours (Aoyama et al., 1993)
l- form: 2.1 ± 0.6 hours (Aoyama et al., 1993)
$T_{½}$: 3 hours racemic (Modi et al., 2000)
d- form: 5.96 ± 1.71 hours (Aoyama et al., 1993)
l- form: 3.61 ± 1.12 hours (Aoyama et al., 1993)
V_{ss}:
d- form: 2.6 5± 1.11 (Aoyama et al., 1993)
l- form: 1.80 ± 0.91 (Aoyama et al., 1993)
Interactions: interactions with other drugs are unlikely as methylphenidate is not metabolized by the P-450 system. Most is excreted unchanged as ritilanic acid.

Aoyama, T., Sasaki, T. et al. (1994). Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia, *Clin. Pharmacol. Ther.,* 55(3), pp. 270–6.
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3.2.1 Incidence and Epidemiology

Methylphenidate (Ritalin®) is used extensively for the treatment of ADHD (Robison et al., 1999). Clandestine methylphenidate labs have never been encountered. Because Ritalin® is so widely available, diversion and illicit sales do occur, mostly to teenagers and young people. Based on the findings of the DAWN report, the amount of drug diverted to the black market cannot be very great. Twelve methylphenidate deaths were reported in the Medical Examiner's component of the 1999 DAWN report (0.01% of all drug-related deaths), but no mentions were found in the Emergency Department component of the same DAWN report or in the National Household Survey (Green and Marsden, 2000). On the other hand, prescribing of methylphenidate for adults with persistent symptoms of ADHD is increasing. Some feel this is cause for concern given the increased risk for substance abuse disorders in this subgroup of patients (Lindsay et al., 1999). These concerns were first raised over a decade ago.

* Although this drug is usually administered as a racemate, the *d*- form of methylphenidate is much more active than the *l*-form, and both forms have different pharmacokinetics.

3.2.2 Names and Drug Constants

Methylphenidate ([*d,l*]-threo-α-phenyl-2-piperidine acetic acid methyl ester) has two chiral centers, but the drug used in therapy comprises only the threo pair of enantiomers. *d*-Threo-methylphenidate is more potent than the *l*- enantiomers. Methylphenidate is administered as a racemic mixture that undergoes stereoselective clearance (Kimko et al., 1999), and the different isomers have profoundly different tissue distributions (Thai et al., 1999). In the U.S., it is only sold under the brand name Ritalin®, either as immediate or timed-release tablets. Skin patches are also available.

3.2.3 Routes of Administration

Like the other amphetamines, methylphenidate is rapidly absorbed after oral administration, reaching peak levels between 1 and 3 hours after ingestion (Wargin et al., 1983; Volkow et al., 1995). In cases of methylphenidate abuse, ground tablets are injected (Levine et al., 1986; Sandi Esquivel and Avila Corrales, 1989; Parran and Jasinski, 1991; Gautschi and Zellweger, 2006) or occasionally snorted (Jaffe, 1991; Garland, 1998; Teter et al., 2006). Neither the transnasal bioavailability nor the resultant blood concentrations have ever been determined. However, transdermal methylphenidate is now being sold by Noven/Shire pharmaceuticals. After application of the patch no methylphenidate is detected in plasma for at least 3 hours (range 1–6 hours), and concentrations of the *d*-isomer (which is the more active form) are not seen until 7–9 hours have elapsed. In children, at 9 hours, plasma concentrations of methylphenidate are comparable to those seen after taking the oral, timed-release form.

3.2.4 Mode of Action

The reinforcing effects of methylphenidate are a consequence of its ability to block dopamine transporters. Even though cocaine and methylphenidate have similar in vitro affinities for the dopamine transporter, abuse of methylphenidate is extremely uncommon, at least when compared to cocaine. It has been suggested that the difference has to do with the persistence of methylphenidate within the striatum. Unlike cocaine, which is washed out in a matter of minutes, methylphenidate remains localized in the striatum for several hours (Volkow et al., 1999). Similarly, even though cocaine and methylphenidate cause comparable increases in heart rate and blood pressure, these increases persist for much longer with methylphenidate than cocaine (Volkow et al., 1999).

Even though methylphenidate binds to and blocks dopamine and norepinephrine transporters, it differs from cocaine and amphetamine in that it has a very low affinity for the 5-HT transporter. When methylphenidate is administered, extracellular levels of dopamine in the striatum, nucleus accumbens, and prefrontal cortex all increase. Methylphenidate also raises concentrations of norepinephrine levels in many parts of the brain, including the prefrontal cortex and hippocampus. However, unlike other psychostimulants, which have a high affinity for the 5-HT transporter, methylphenidate produces no 5-HT overflow in the striatum and nucleus accumbens, which may explain its extremely low potential for significant abuse. Even though self-administration studies in animal models suggest that exposure to methylphenidate, particularly at a young age, might increase the likelihood of subsequent substance abuse in humans, there is no clinical evidence that any such process occurs (Yano and Steiner, 2007).

3.2.5 Pharmacokinetics

Methylphenidate has a much shorter half-life (2–4 hours on average) than other amphetamines. First-pass hydrolysis to ritalinic acid occurs in the intestine, and 80% is excreted in the urine as ritalinic acid. Peak plasma levels of both methylphenidate and ritalinic acid occur at the same time. In vitro studies indicate that methylphenidate metabolism is not P-450 dependent (DeVane et al., 2000), which suggests minimal intra-individual variation in rates of metabolism.

A range of values has been reported for the pharmacokinetic parameters of methylphenidate. In one controlled study, after a 15-mg dose of immediate-release drug was given to 35 healthy volunteer adults, the mean average peak concentration (C_{max}) was 4.17 ± 1.0 ng/mL, reached at 6.5 ± 1.8 hours (T_{max}). The observed half-life ($T_{½}$) was 3.0 ± 0.5 hours (Modi et al., 2000). Somewhat different results were obtained in a second study where 40-mg doses of immediate-release drug were given to 26 healthy volunteers; very substantial differences were observed between the *d*- and *l*- isomers, with the *l*- isomer eliminated at nearly three times the rate of the *d*- isomer (Wong et al., 1998).

When methylphenidate and ethanol are co-ingested, a new, active metabolite, ethylphenidate (ritalinic acid ethyl ester), is formed by a mechanism analogous to that responsible for production of cocaethylene: hepatic-carboxylesterase-dependent transesterification. Only very small amounts of ethylphenidate are produced after clinically relevant doses and, unlike cocaethylene, which has a much longer apparent half-life than cocaine, the half-life of ethylphenidate is much shorter than that of the parent compound (Markowitz et al., 1999).

3.2.6 Methylphenidate Blood Concentrations

In therapeutic settings, peak concentrations of methylphenidate may reach 0.07 mg/L (Gualtieri et al., 1984) but treatment is not generally guided by plasma drug concentrations. Interestingly, in studies designed to determine whether differences in plasma concentration of the *d*- and *l*-threo enantiomers had any bearing on clinical response, researchers found that nonresponders (based on electrophysiological testing) had significantly higher plasma concentrations of both isomers than responders, and that plasma concentrations of the *d*- enantiomers were always higher than the *l*- enantiomers, regardless of the response (Jonkman et al., 1998).

3.2.7 Breast Milk Concentrations

Methylphenidate is excreted in breast milk, but in such low concentrations that mothers with narcolepsy have no need to discontinue the drug. A case report published in 2007 described the values seen in a woman taking 15 mg of Ritalin® per day. Maternal serum and breast milk were obtained at five time points: immediately before the morning dose at 8 a.m., just before the dose at noon, and 4, 8, and 21 hours after the dose at noon. The first three samples were from foremilk, whereas the two last samples were from hindmilk. Concentrations of methylphenidate were analyzed by liquid chromatography–mass spectrometry with a limit of quantification of 0.3 ng/mL. The maternal serum concentrations in the five samples were < 0.3, 2.3, 3.8, 1.7, and < 0.3 ng/mL, respectively. The corresponding milk concentrations were < 0.3, 2.4, 5.9, 1.4, and < 0.3 ng/mL. Presuming that the infant

ingested the standard volume of 150 mL of milk per kilogram of body weight per day, the authors estimated the daily infant dose at 0.38 μg/kg of body weight, or less than 0.2 μg per day (Spigset et al., 2007).

3.2.8 Methylphenidate Tissue Disposition

Tissue disposition in humans has been poorly studied. In rats, after doses of 1 mg/kg (Kotaki et al., 1988), 10 mg/kg (Thai et al., 1999), or 20 mg/kg, (Patrick et al., 1984) the tissue distribution was the same: kidney > lung > brain > heart > liver.

3.2.9 Urine Concentrations

At least 80% is excreted in the urine, primarily as ritalinic acid, within 24 hours of administration. The remainder is excreted as 6-α-phenylpiperidine-2-acetic acid. A very small proportion is excreted unchanged (Srinivas et al., 1992). The testing of stored samples may be problematic because ritalinic acid is unstable and nearly half will be lost during the first month of storage (Collins et al., 2008).

3.2.10 Postmortem Measurements

Data on the tissue disposition of the amphetamine analogs are sparse. A woman who died after injecting 40 mg of methylphenidate intravenously had a blood concentration of 2.8 mg/L (Levine et al., 1986). In that same case, the concentration in the liver was 2.1 mg/kg, while the bile contained 5.7 mg/L and the kidneys 3.0 mg/kg. Little accumulation of methylphenidate occurs in the body. The blood level of a woman who died during a Cesarean section, who presumably had not had any drug for a number of hours, was only 9 ng/mL (Lundquest et al., 1987). A paper published in 1999 described the findings in two individuals who had died after intentional methylphenidate overdose. Ethanol had also been consumed and, as a consequence, ethylphenidate was also detected, although in extremely small quantities (8 ng/mL and 1 ng/mL) (Markowitz et al., 1999).

3.2.11 Toxicity by Organ System

3.2.11.1 Overview

Information about methylphenidate toxicity is confined to anecdotal case reports. These can be divided into two separate groups: (1) complications related to catecholamine toxicity, and (2) complications related to the intravenous injection of talc-containing pills meant for oral consumption. The lungs and eyes bear the brunt of the latter insult, and, except in the case of drug abusers, medical complications are rare.

3.2.11.2 Integument

Occasionally, drug users will grind up methylphenidate tablets and inject them subcutaneously (Zumwalt and Franz, 1983). Superficial skin abscesses are the result, but they appear to be no different than the type of infection produced by "skin popping" heroin or cocaine. Myositis has also been reported as a consequence of injecting crushed pills (Gautschi and Zellweger, 2006), as has arterial thrombosis due to injection of the wrong vessel (Still et al., 2001).

3.2.11.3 Cardiovascular

A recent case report described the cardiac findings in a 19-year-old who died after snorting powder methylphenidate tablets. The myocardium displayed foci of localized, microfocal necrosis with infiltration by histiocytes and polymorphonuclear leukocytes — typical changes associated with catecholamine toxicity (Massello and Carpenter, 1999). A second case describes spontaneous multivessel coronary vasospasm leading to anterior myocardial infarction and cardiogenic shock in a man who was taking methylphenidate and, at the same time, being withdrawn from beta-blockers and calcium channel antagonists. Attributing the event to methylphenidate abuse seems something of a stretch (Bromberg-Marin et al., 2007). Still another case report describes an infarct in a mentally disturbed child being treated with bupropion, erythromycin, and methylphenidate (George et al., 2005). In animals bupropion causes dose-dependent increases in central nervous system stimulation. It also blocks the re-uptake of 5-HT, norepinephrine, and dopamine, thereby giving any methylphenidate present the same net effect as taking cocaine or methamphetamine.

3.2.11.4 Pulmonary

Granuloma formation and pulmonary fibrosis have been recognized as complications of methylphenidate abuse for many years (Hahn et al., 1969; Waller et al., 1980; Levine et al., 1986). If anything is unique about the histopathology of methylphenidate abuse, it remains to be identified. Presumably, the deposition of birefringent material contained in the methylphenidate preparations is followed by a granulomatous inflammatory reaction and focal thrombosis (Byers et al., 1975). The situation has never been studied experimentally, and nothing has been found to distinguish granuloma formation in stimulant abusers from the same alterations seen in opiate addicts.

Panacinar emphysema, more pronounced in the lower lung fields, has been described in a group of young intravenous methylphenidate Ritalin® abusers who died of severe obstructive lung disease (Sherman et al., 1987; Schmidt et al., 1991; Stern et al., 1994; Ward et al., 2000) and repeatedly confirmed in a series of case reports. Autopsy findings included variable degrees of vascular involvement by talc granulomas, but no interstitial fibrosis. X-rays of these individuals show a distinctive picture with prominent, or even massive, fibrosis in the upper lobes and with translucence and bullae formation in the lower lobes (Pare et al., 1989). In most respects, the clinical and pathologic findings are the same as those associated with α_1-antitrypsin deficiency, though tests for that disorder are negative. Obstructive lung disease is an uncommon complication of intravenous drug abuse, regardless of the type, and its mechanism remains to be evaluated (Groth et al., 1972; Vevaina et al., 1974; Ward et al., 2000). It is unclear whether the apparent connection of lung disease with methylphenidate has to do with the drug itself or with the way it is compounded.

3.2.11.5 Gastrointestinal Tract

Methylphenidate-associated hepatocellular injuries, unlike those reported in pemoline users, have mostly involved intravenous abuse (Mehta et al., 1984; Lundquest et al., 1987). In the case described by Mehta et al. (1984), portal inflammation with hepatocellular disarray was diagnosed in the liver biopsy of an intravenous abuser who survived a bout of liver failure. In a second case, the autopsy findings in a polydrug user who died of amniotic fluid embolus included biventricular hypertrophy and multiple granulomas in the liver and lungs. Autopsy findings in a third polydrug abuser, known to have repeatedly injected

methylphenidate and hydromorphone, are best explained by the injection of tablets meant for oral use, and probably have nothing to do with the pharmacologic effects of either drug. Pulmonary hypertension is the expected outcome of this practice but, because this particular individual had a patent foramen ovale, the elevated pulmonary pressure caused a right-to-left shunt. Talc granulomas were found throughout the body, including the brain and kidneys (Lundquest et al., 1987).

3.2.11.6 Nervous System

Psychosis occurs, even in nonabusers. In one recent study, 6 of 98 children diagnosed with ADHD and treated with stimulant drugs developed psychotic or mood-congruent psychotic symptoms during treatment (Cherland and Fitzpatrick, 1999). Individuals who inject ground tablets of methylphenidate may experience ophthalmologic complications. The pills are compounded with talc (magnesium silicate) and cornstarch. When they are crushed and injected they lodge in the pulmonary bed, obstructing flow and ultimately causing pulmonary hypertension. Elevated pressure, in turn, leads to collateralization of blood vessels, allowing part of the venous return to bypass the lung and directly enter the left side of the heart. Once the talc particles have gained access to the left heart, they are then distributed in the arterial circulation throughout the body. Particles entering the retinal circulation usually settle out in the posterior pole, the portion of the globe with the richest supply of capillaries. These particles are easily visualized on routine fundoscopic examination (Lederer and Sabates, 1982). The presence of retinal talc emboli occasionally leads to the process of neovascularization, depriving the retina of its normal blood supply and leading to vasoproliferation. The underlying mechanism and the appearance of the retina are much the same as seen in patients with sickle cell disease (Schatz and Drake, 1979).

In contrast to methamphetamine, which is an increasingly common cause of stroke in young people, stroke in methylphenidate users is exceedingly rare and still reportable (Sadeghian, 2004; Thomalla et al., 2006). One stroke involved an 8-year-old boy being treated for ADHD. Arteriography showed no congenital malformations, but did show evidence of cerebral vasculitis. An extensive hematologic evaluation failed to disclose any coagulation abnormalities (Schteinschnaider et al., 2000). Since the original case report, a second case of vasculitis in a methylphenidate user has been described (Thomalla et al., 2006). Because only two such cases have been reported and millions of children take methylphenidate, it would appear that the associated risk is exceedingly low and, in fact, there may not be any connection at all. There are even ongoing experiments where methylphenidate is being used as an adjunct in the rehabilitation of stroke patients (Paolucci and De Angelis, 2006; Barrett et al., 2007).

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Hallucinogens

4

4.1 Introduction

Criteria for this group are difficult to define. Hallucinogens are said to share five common features: (1) changes in mood and perception dominate in proportion to any other effects the drugs might exert, (2) minimal memory or intellectual impairment occurs, (3) use is not associated with either stupor or excessive agitation, (4) side effects from autonomic nervous system stimulation are minimal, and (5) craving and addiction do not occur (Hollister, 1967). Traditionally, hallucinogens have been divided into two groups: phenylalkylamines (drugs such as mescaline, methylene-2-5-dimethyoxyamphetamine [DOM], 4-bromo-2-5-dimethyoxyamphetamine [DOB]) and the indoylalkylamines (psilocybin, bufoteine, LSD, harmaline). But to a certain extent, disassociative anesthetics and amphetamine derivatives also share some properties with the hallucinogens, making their classification somewhat problematic, especially because their ingestion can cause severe medical complications or even death. Now that the receptor mechanisms for these drugs are known, it seems to make more sense to group the drugs by the receptor to which they bind. Still, the original classification by chemical family is widely used and it will more or less be followed in this chapter. Table 4.1.1 lists the drugs. With the exception of the designer amphetamines, specific pathologic changes are not associated with any of these agents.

4.2 Incidence

The 2005 National Survey on Drug Use and Health (NSDUH; Kissin et al., 2006) reports that in 2004, 19.1 million Americans, or 7.9% of the population aged 12 or older, were current users of illicit drugs. The term "current drug use" means use of an illicit drug during the month prior to the survey interview. In 2004, an estimated 934,000 persons reported having used hallucinogens for the first time within the past 12 months. This was not significantly different from the estimate in 2003 (886,000), but it was lower than the estimate in 2002 (1.2 million).

Although there was little change between 2003 and 2004 in the number of past year initiates to LSD or Ecstasy, there were declines between 2002 and 2003. The number of past year LSD initiates was 338,000 in 2002, 200,000 in 2003, and 235,000 in 2004. Initiation of Ecstasy use was 1.2 million in 2002, 642,000 in 2003, and 607,000 in 2004. Most (57.7%) of the recent Ecstasy initiates in 2004 were aged 18 or older at the time they first used Ecstasy. The average age at initiation for Ecstasy users was 19.5 years. A total of 929,000 persons used hallucinogens. The types of drugs used differed between age groups. Among young

Table 4.1.1 Hallucinogens

A. Tryptamine derivatives
Mescaline
Substituted amphetamines
TMA
DOM
PMA
DOB
4-bromo-2,5-dimethoxyphenethylamine
Nutmeg
DOC
2,5-dimethoxy-4-iodophenethylamine
Piperazines
BZP
TFMPP
mCPP
B. Hallucinogenic amines
MDMA
MDA
MDEA
4-MAX (U4Euh, EU4EA, U4EA), aminorex
Methcathinone
C. Phenylalkylamines
Simple tryptamines
DMT
Ayahuasca (harmine and harmaline)
Bufotenine
5-MeO-DMT (5-methoxy-*N*,*N*-dimethyltryptamine)
D. Psilocybin
E. Ergolines
LSD

adults, aged 18–35, 1.5% reported having used hallucinogens. Only 0.15% of those aged 26 and older reported use of hallucinogens.

The 2005 NSDUH survey also provides specific results for LSD and PCP. Some 22.4 million Americans (9.2% of the population aged 12 or older) reported lifetime use, 563,000 (0.2%) reported past year use, and 104,000 (0.1%) reported past month use. For PCP, 6.6 million (2.7%) reported lifetime use, 164,000 (0.1%) reported past year use, and 48,000 (0.0%) reported past month use (Kissin et al., 2006).

The 2006 NSDUH report on hallucinogens states that in that year, young adults aged 18–25 were more likely than younger (aged 12–17) or older people to be past-year users of LSD, MDMA, and *Salvia divinorum*. In the younger age group, women were more likely than men to have used one of these drugs in the last year, although males were more likely to have experimented with *Salvia divinorum* than women. Young adult males were also more likely than young adult females to have used one or more of these drugs in the past (Anon., 2008).

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4.3 Tryptamine Derivatives

The most popular hallucinogens are mescaline derivatives, and MDMA is by far the most widely used mescaline analog. Evidence suggests that these compounds may be more toxic than had previously been appreciated, and increasing numbers of deaths attributable to MDMA and MDEA are being reported. But in the absence of an effective, worldwide database it is impossible to tell how much more popular these drugs have become. Experimental studies are difficult because different experimental animals respond differently from other animal models and from humans.

4.3.1 Mescaline

Synonyms: *Lophophora williamsii* is the name of the plant that produces mescaline
Chemical name: 3,4,5-trimethoxybenzeneethanamine or 3,4,5-trimethoxyphenethylamine
Formula: $C_{11}H_{17}NO_3$
Molecular weight: 211.26 daltons
Metabolism: CYP2D6
Bioavailability: unknown
C_{max}: 3.88 mg/L after hallucinogenic dose
T_{max}: hallucinogenic effects after 2 hours
$T_{½}$: not known; approximately 6 hours
V_{ss}: not known
Interactions: potential interaction with other CYP2D6 dependent drugs

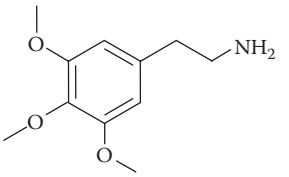

Figure 4.3.1.1 Mescaline molecule.

4.3.1.1 History

Louis Lewin was one of the first to systematically study mescaline. Mescaline comes from the cactus referred to as either *Lophophora williamsii* or *Anhalonium lewinii*. This small cactus can be found growing in dry places and on rocky slopes throughout the southwestern U.S. (Figure 4.3.1.1.1). It grows singly or in clusters. It is an inconspicuous plant that can be difficult to find. Unless it is in flower, it tends to look like a small rock. Indian shamans have used the dried tops of the plants, known as peyote buttons, for centuries. In the early 1800s, the Apaches, Kiowas, and Comanche of the Great Plains began to chew the buttons and incorporate them into their religious rites. The practice quickly spread among the Plains Indians, who combined its use with elements of Christianity. Today, their ceremonies still begin with the chewing of peyote buttons, followed by nights of prayers and singing. The sect is now known as the Native American Church and has more than 200,000 members

Figure 4.3.1.1.1 Peyote buttons. Even though it grows wild throughout the American Southwest, the cactus can be very difficult to find. Except when it is in bloom, it tends to resemble a small rock. This photograph is from *Microgram*, the monthly bulletin of the Drug Enforcement Agency.

(Barron et al., 1964). The emblem of this church is shown in Figure 4.3.1.1.2. Mescaline, or 3,4,5-trimethoxy-β-phenethylamine, is the active principle found in peyote cactus. The average mescaline content is 6%. No mescaline-related deaths or emergency room visits have ever been reported in any DAWN survey, either in the "new" or original versions.

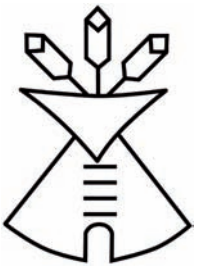

Figure 4.3.1.1.2 The emblem of the Native American Church.

Lewin and Henning reported the first systematic chemical and pharmacologic studies in 1888. Lewin's work attracted the attention of the famous American neurologist S. Weir Mitchell (Lewin and Henning, 1888). Mitchell, who was a prolific writer and a pioneer in the study of peripheral nerve injuries, was also interested in toxicology and psychiatry (Metzer, 1989). He obtained some peyote buttons and used them himself. He then went on publish an account of his experiences in the *British Medical Journal* (Metzer, 1989). He believed that the plant might be of great value in the study of psychological disorders, but he also warned of the abuse potential. The famous sexologist Havelock Ellis also dabbled with mescaline and described the many benefits to be derived from its use (Mitchell, 1896). Neither the benefits nor the epidemic of abuse ever really materialized. Similar claims now being made for MDMA have considerably more substance.

4.3.1.2 Production

Mescaline is extracted from the cactus by first drying and then grinding the plant tops. The ground material is then soaked in methanol for a day, filtered, and acidified. After the alcohol has evaporated, the solution is neutralized and the mescaline extracted with chloroform. Less sophisticated chemists "cook" the cactus in a pressure cooker, producing a tarry material that can be formed into small pills. Some clandestine producers may even

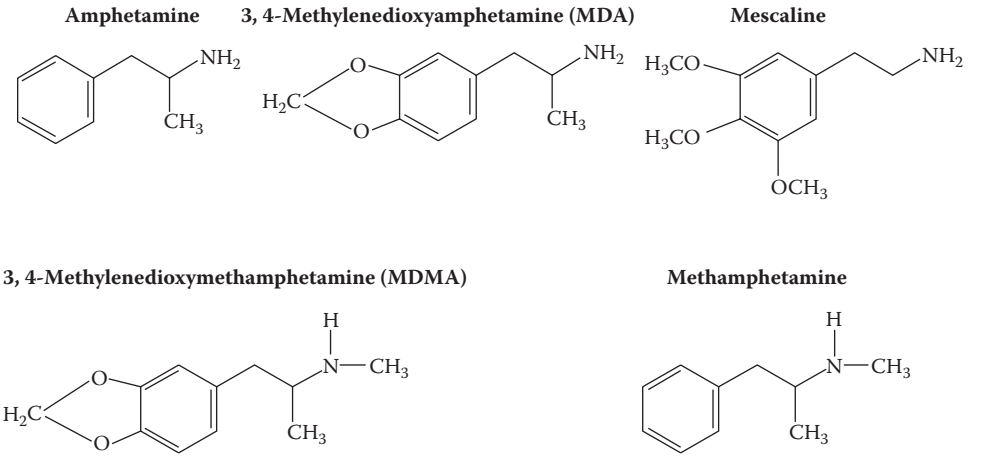

Figure 4.3.1.3.1 Mescaline and the "designer" amphetamines. Whether small recreational doses of these drugs are hallucinogenic is difficult to say, but all of these agents can impair judgment, and their use occasionally leads to fatal accidents.

apply an enteric coating or place the tarry material in gelatin capsules with the hope of reducing the nausea induced by mescaline use.

4.3.1.3 Mechanism of Action

Very little has been written about mescaline's mode of action. It has been proposed that the two major classes of psychedelic hallucinogens, the indoleamines (e.g., LSD) and the phenethylamines (e.g., mescaline), have a common site of action in the central nervous system and act as partial agonists at 5-HT2A and other 5-HT2 receptors, but this view appears overly simplistic. It is true that all of these drugs are 5-HT (serotonin) agonists, but the results of in vitro studies and of animal studies all suggest that phenylisopropylamines and their phenethylamine counterparts can actually be distinguished by their activity at the 5-HT(2A) receptor; most hallucinogenic compounds behave as partial agonists. However, at 5-HT(2C) receptors, all phenylisopropylamines are more effective than their phenethylamine counterparts. The differentiation is the result of differing abilities of the two compounds to activate the enzyme phospholipase (Moya, 2007). The noradrenergic neurons of the locus caeruleus and others located in the cerebral cortex are among the regions where hallucinogens exert their most prominent effects via their actions upon 5-HT2A receptors (Aghajanian and Marek, 1999).

4.3.1.4 Metabolism and Tissue Levels

When dogs are injected subcutaneously with mescaline, the highest concentrations are found in the liver and kidneys. Concentrations in the liver, spleen, and kidneys are three to six times the concentration found in the bloodstream. Brain levels tend to parallel the blood levels (Kapadia and Fayez, 1970). Animals metabolize mescaline differently than humans, and it may be that the resultant tissue concentrations vary as well. Human tissue levels have been measured in a handful of cases: one mescaline user, who died of a head injury, was found to have had a blood concentration of 9.7 mg/L, a concentration eight times higher than that in the liver (Reynolds and Jindrich, 1985). In 2003, a report

described blood and tissue levels in another mescaline user who had been shot. Concentrations of the drug were 2.95 mg/L, 2.36 mg/L, 8.2 mg/kg, and 2.2 mg/kg in blood, vitreous, liver, and brain, respectively (Henry et al., 2003).

4.3.1.5 Clinical Syndromes

Healthy volunteers given a 0.5-mg dose of mescaline exhibited symptoms of psychosis indistinguishable from those normally associated with acute schizophrenia. Neuropsychological measurements made during mescaline intoxication have suggested that the observed behavioral changes result from right-hemispheric striato-limbic hyperactivity, with associated left-hemispheric dysfunction (Oepen et al., 1989). Single photon emission computed tomography (SPECT) imaging of human volunteers during mescaline-induced psychosis showed increased regional flow in the frontal lobes bilaterally (Hermle et al., 1998). Otherwise the symptoms associated with mescaline abuse are mostly those of sympathetic nervous system stimulation. Transient rises in pulse, blood pressure, and temperature may occur (Kapadia and Fayez, 1970), but episodes of clinically significant hyperthermia and/or excited delirium have not been reported with this drug.

4.3.1.6 Pathologic Findings

Lethal overdoses of mescaline have never been reported, nor have there been any reports of medical complications associated with its use. Reported deaths have been accidental, usually occurring as a result of drug-induced confusion (Reynolds and Jindrich, 1985).

4.3.2 Substituted Amphetamines

Phenethylamines are compounds in which the core chemical structure is a benzene ring substituted with a 2-aminoethyl chain. Although phenethylamine itself is not a controlled substance, it has a chemical structure that constitutes the skeleton of many phenethylamines listed in Schedule I of the Controlled Substances Act (CSA), and they are all classified as hallucinogenic substances. Phenethylamines also appear on the CSA's list of Schedule II and IV drugs. Phenethylamine is sometimes substituted on the benzene ring or the 2-aminoethyl chain, or both, with various moieties and various results leading to the production of different physiological and psychological effects.

Many of the mescaline type analogs that have been substituted at the 4 position (e.g., escaline, proscaline, buscaline) are, on a weight-for-weight basis, much more potent than mescaline. Alkoxylated mescaline homologs (e.g., metaescaline, metaproscaline) are less potent. A series of thiomescaline analogs have also been synthesized, with substitutions at both the 3 and 4 positions. The clinical effects of these agents have never been systematically studied, and virtually nothing is known about their pharmacology, either in humans or animals. Since 1947, when researchers produced the first psychoactive mescaline analog (TMA), molecular manipulations have been used to produce a long list of psychoactive derivatives. With the exception of MDMA, considerably more is known about the conformational chemistry of these molecules (Kovar, 1998) than about their clinical effects.

4.3.2.1 TMA

2,4,5-Trimethoxyamphetamine (TMA) was the very first synthetic phenethylamine found to be active in man. It has twice the psychoactive potency of mescaline (Shulgin,

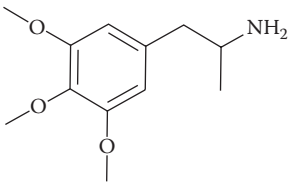

Figure 4.3.2.1.1 TMA molecule.

1973). It was first synthesized in 1933 but was not used as a psychedelic until 1962. It produces all the same effects as mescaline but is said to have a lower therapeutic index. The amount required to cause hallucinatory or psychedelic experiences is not very different from the amount needed to produce toxicity (Chesher, 1990). Its structure is essentially the same as that of the mescaline molecule, except that it has a one carbon side chain. After it was first synthesized, a series of mescaline molecules with longer and longer side chains were introduced. All are hallucinogens of varying potency, but very little is known about their metabolism or toxicokinetics. GC/MS of urine from rats given TMA has shown that the drug is metabolized by several routes: oxidative deamination to the corresponding ketone followed by reduction to the corresponding alcohol, *O*-demethylation followed by oxidative deamination, and finally O,O-bis-demethylation (Ewald et al., 2006). In Shulgin's studies, all metabolites carrying hydroxy groups were at least partly excreted in urine as glucuronides and/or sulfates. According to Shulgin, the dosage is 100–250 mg and the effects last for 6–8 hours (Shulgin and Shulgin, 1991).

4.3.2.2 DOM

Methyl-2,5-dimethoxyamphetamine (DOM) was first synthesized in 1963, shortly after TMA (Shulgin, 1979). Abuse was first reported in 1967. Due to a fluke of marketing (two different clandestine labs started producing the same compound at the same time) DOM was also referred to as STP ("serenity, tranquillity, and peace"). In doses of less than 3 mg, the effects of DOM are said to be similar to those of mescaline. Higher doses cause hallucinations and unpleasant side effects that may last for as long as eight hours (Snyder et al., 1968). DOM disappeared rather quickly from the street, probably because when it was used in excessively high doses it caused a very unpleasant experience. Regardless of the dose, approximately 20% appears unchanged in the urine with peak excretion occurring at between three and six hours, the period when intoxication is most intense. Hallucinations produced by higher doses are associated with nausea, diaphoresis, and tremor. Some of these symptoms may be attributable to the fact that the makers of STP recommended higher doses than did the makers of DOM. Moderate elevations in pulse and systolic, but not diastolic, pressure occur in DOM users. Blood and tissue levels have never been determined, and the pathologic changes associated with its use, if any, are unknown. The closely related drug 2C-T-7, which Shulgin ranks nearly as high as mescaline for its pleasurable effects (Shulgin and Shulgin, 1991), has been linked with at least one fatality (Curtis et al., 2003). 2,5-Dimethoxy-4-n-propylthiophenethylamine (also referred to as 2C-T-7) shares structural and pharmacodynamic features with MDMA. In one case report it was initially identified on routine screening of postmortem urine from a 20-year-old male who died in a local emergency room after reportedly insufflating 35 mg of 2C-T-7. Postmortem testing revealed the following concentrations: heart blood, 57 ng/mL; femoral blood, 100 ng/mL; urine, 1120 ng/mL; and liver, 854 ng/g (Curtis et al., 2003).

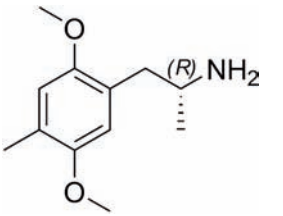

Figure 4.3.2.2.1 DOM molecule.

4.3.2.3 PMA

Paramethoxyamphetamine (PMA) is a potent hallucinogen, and the only member of this group that qualifies as a truly dangerous drug; a number of deaths have been reported, mostly due to the sympathomimetic properties of the drug (Kraner et al., 2001; Chodorowski et al., 2002; Galloway and Forrest, 2002; Becker et al., 2003; Dams et al., 2003; Johansen et al., 2003). It is not one of the compounds created by Shulgin, perhaps because he was aware of the dangerous sympathetic side effects.

The first PMA-related deaths were reported in Canada in the mid-1970s (Cimbura, 1974), followed not too long thereafter by a series of fatalities in Australia (Byard et al., 1998; Felgate et al., 1998; James and Dinan, 1998; Ling et al., 2001). The first PMA-related death in the U.S. was not reported until the summer of 2000. In Australia, 22 patients with PMA poisoning were admitted to a major metropolitan teaching hospital between 1 January 1996 and 31 December 1998. These patients presented with tachycardia (64%), hyperthermia (temperature > 37.5°C; 36%), coma (41%), seizures (32%), arrhythmias (23%), and QRS intervals ≥ 100 ms (50%). Two patients with PMA poisoning had severe hypoglycemia (blood glucose level, < 1.5 mmol/L) accompanied by hyperkalemia (K^+ concentration, > 7.5 mmol/L). It may be that hypoglycemia and hyperkalemia are specific to PMA poisoning (Ling et al., 2001).

In another Australian study PMA poisonings accounted for most of the severe reactions among people who believed they had taken Ecstasy. MDMA and PMA both disrupt autonomic components of thermoregulation (this subject is discussed in more detail in the section dealing with MDMA), while behavioral complications seem to occur to a much lesser degree (Jaehne et al., 2005). PMA and MDMA both facilitate the release, and prevent the re-uptake, of 5-hydroxytryptamine (5-HT), but, in addition, PMA is also a potent inhibitor of monoamine oxidase type A (MAO-A), an enzyme responsible for the catabolism of 5-HT, and this characteristic may contribute to its increased toxicity. In humans, co-administration of MDMA with the reversible MAO-A inhibitor moclobemide has led to increased evidence of toxicity with ensuing fatalities (Freezer et al., 2005).

Animal studies from the early 1960s suggested that the hallucinogenic potency of PMA is nearly as great as that of LSD (Byard et al., 1998), but, unlike LSD, PMA may cause instances of marked hypertension and hyperthermia and, in fact, most of the reported fatalities have been as a consequence of extreme temperature elevation. Decedents are always young, usually in their mid-20s, but with a different sex distribution than other abused drugs, PMA fatalities are just as likely to be female as male. In six fatalities reported from Australia, femoral blood PMA concentrations ranged from 0.24 to 4.9 mg/L (mean, 2.3 mg/L), while liver PMA levels ranged from 1.4 to 21 mg/kg (mean, 8.9 mg/kg). Other amphetamines were found in five of the six cases, confirming the impression that, when PMA is detected, it is probably present as an adulterant. Blood PMA concentrations in nonfatal cases are usually less than 0.5 mg/L (Felgate et al., 1998).

PMA toxicity should be suspected when severe or atypical reactions occur in individuals who believe they have taken Ecstasy. The evidence strongly suggests that many who think they are buying MDMA are actually purchasing material contaminated with PMA (Byard et al., 1998). PMA poisoning should also be considered

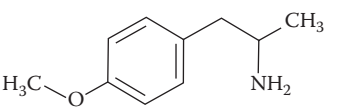

Figure 4.3.2.3.1 PMA molecule.

as the possible etiology in hallucinating individuals who present with both hypoglycemia and hyperkalemia (Ling et al., 2001). The same can probably be said of a related compound, para-methoxymethamphetamine, that is now being sold in Italy (Genoa), and probably elsewhere in Europe. Analysis of a few confiscated samples has shown that the drugs were actually a mixture of 14% PPMA and 14% para-methoxymethamphetamine (PMMA) calculated as their bases. PMA has been scheduled in Italy since 1988, while PMMA has been scheduled since 2002; however, criminal penalties are not applicable for possession of either substance if the amount confiscated is under 450 mg.

4.3.2.4 DOB

4-Bromo-2,5-dimethoxyamphetamine (DOB, also called bromo-DMA) is another potent hallucinogenic sympathomimetic, though one that is not nearly so often associated with death as PMA. Compared to MDMA (and most of the other mescaline derivatives), the effects are longer lasting. Reports of DOB abuse are becoming more frequent, though use still seems largely confined to Australia (Buhrich et al., 1983). It is occasionally sold as MDMA or found as an adulterant in MDMA tablets, but it is also sold and used under its own name. Occasionally it is sold as blotter acid (Figure 4.3.2.4.2), both in the U.S. and

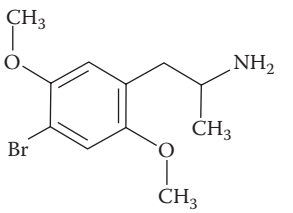

Figure 4.3.2.4.1 DOB molecule.

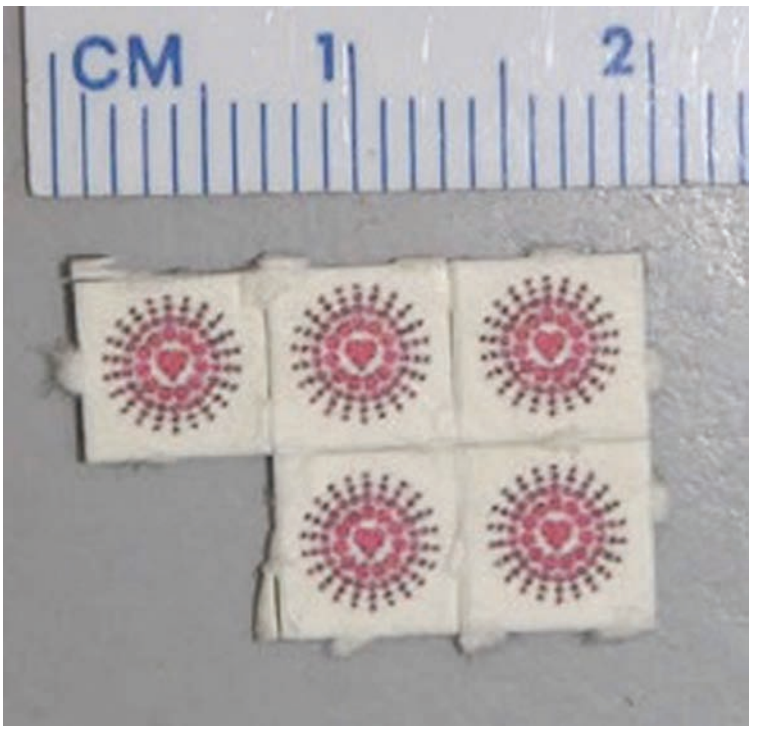

Figure 4.3.2.4.2 DOB impregnated in a blotter. This dosage form is only occasionally reported. (From *Microgram,* November 2006.)

Caribbean. Because it is so potent, DOB can be absorbed into blotter paper and misrepresented as LSD (Shulgin, 1981). The problem with distributing DOB in the form of postage stamps is that DOB is considerably more toxic than LSD. During manufacture, the drug may migrate to the corners or bottom of the sheet of stamps. Users buying squares from the center of the sheet often receive less DOB than they paid for, while those buying squares from the margins of the sheet often get more than they bargained for. This may explain why so many bad experiences have been associated with use of the drug (Delliou, 1980, 1983).

In 1991 Shulgin wrote that the *d*- isomer of this drug is much more potent than the *l*-isomer, but pharmacokinetic and pathology studies are lacking, and chiral separation has never been performed in any forensic setting.

Symptoms of intoxication occur three to four hours after ingestion and may take 24 hours to resolve. Pupillary dilatation, increased pulse and blood pressure, and increased temperature may be present. The effective dose is said to be between 2 and 3 mg. DOB is associated with more morbidity than other mescaline analogs (Winek et al., 1981; Buhrich et al., 1983). Diffuse vascular spasm, identical to the classic picture of ergotism, has been reported after DOB use (Bowen et al., 1983), and grand mal seizures have also been described (Delliou, 1983). This syndrome has not been reported in conjunction with other "designer" amphetamines, but it is a well-known complication of LSD use. Scant autopsy information about DOB is available. In one reported case (Winek et al., 1981) a 21-year-old woman was found dead at the wheel of her parked car. Gross autopsy findings included cerebral edema with uncial herniation. The lungs were minimally congested. Microscopic findings were not reported. Blood and tissue concentrations for this particular case are shown in Table 4.3.2.4.1. Another case reported from Germany described two men who took what they thought was LSD; it was not, and in one the serum DOB concentration was 13 ng/mL, while the other, who died, had a concentration of 19 ng/mL (Balíková, 2005).

Human data are limited, but some of the experimental animal studies may be of relevance. In 2007 the metabolism of DOB, and its phenolic metabolite, 2-methoxy-5-hydroxy-4-bromoamphetamine (2M5H4BA), were measured in blood and biological tissues of experimental rats. The rats were administered a 20 mg/kg dose of DOB hydrochloride, either orally or by subcutaneous injection. Plasma, brain, liver, and lung tissues were collected at 0.5, 1, 2, 4, 8, 16, and 32 hours after dosing (three animals per time point). A rapid phase of DOB absorption, and 2M5H4BA formation tissue distribution occurred during the first two hours after ingestion and was followed by a slow decrease in the rate of

Table 4.3.2.4.1 Blood Levels in a Case of Fatal DOB Intoxication

Tissue	Concentration (mg/L)
Blood	0.90
Bile	0.64
Vitreous	0.51
Brain	0.25
Liver	9.00
Kidney	1.10

Source: Winek, C. L., Collom, W. D. et al., *Clin. Toxicol.,* 18(3), 267–271, 1981. With permission.

elimination until 32 hours had passed. After subcutaneous injection, high plasma levels of the unchanged parent drug, and relatively reduced formation of its metabolite 2M5H4BA, were observed. The maximum plasma concentration of DOB was 1143 ng/mL, one hour post ingestion, whereas peak levels of the metabolite occurred after 8 hours, and were only 213 ng/mL. With oral administration there was evidence of a significant first pass effect. DOB tissue concentrations exceeded plasma concentrations and the highest values were found in the lungs, where drug accumulation occurred with prolonged retention until 32 hours after subcutaneous dose. Although the plasma/tissue transfer was more effective for the lipophilic parent drug than for its hydroxylated metabolite 2M5H4BA, the metabolite tissue levels were still significant. The hallucinogenic potential of 2M5H4BA appearing in brain remains unclear as nothing is yet known about its pharmacological activity.

4.3.2.5 4-Bromo-2,5-Dimethoxyphenethylamine

The Drug Enforcement Agency first reported having encountered this drug in Florida, in 1979. In Florida, and it is not clear if this is true elsewhere, 4-bromo-2,5-dimethoxyphenethylamine is also referred to as 2-C-B, bromo, or toonies, as well as by such street names as Venus, Bromo, Erox, and XTC. To add further confusion, this same drug was once popularly known as Nexus. Since it was first introduced, 4-bromo-2,5-dimethoxyphenethylamine has been found in material seized in California, Arizona, Louisiana, Pennsylvania, Iowa, Oregon, Georgia, Tennessee, and Florida. Nexus-producing clandestine laboratories were seized in California in 1986 and in Arizona in 1992, but no further reports have been published.

4-bromo-2,5-dimethoxyphenethylamine is very closely related to DOB and is sometimes referred to as α-desmethyl DOB. 2C-B shares common properties with 2,5-dimethoxy-4-methylamphetamine (DOM) and DOB, including a high affinity for central 5-HT receptors. 2C-B produces dose dependent psychoactive effects. Threshold effects are noted at approximately an oral dose of 4 mg. The drug is said to produce euphoria with increased body awareness and enhanced receptiveness of visual, auditory, olfactory, and tactile sensation. Oral doses of 8–10 mg produce stimulant effects. Doses in the range of 20–40 mg are said to produce LSD-like hallucinations. It is also reported that doses greater than 50 mg lead to the occurrence of extremely frightening hallucinations and morbid delusions. Onset of subjective effects following 2C-B ingestion occurs between 20 and 30 minutes after ingestion, with peak effects occurring at 1.5–2 hours. Effects of 2C-B can last up to 6–8 hours. Detection of this drug can be problematic because it does not react with the usual ELISA screening tests for amphetamines.

4.3.2.6 Nutmeg

Myristica fragrans Houtt. is a large tropical evergreen tree, the fruit of which contains a large central seed, called the nutmeg. Even though nutmeg is used as a spice, it also acts as a hallucinogen. For many years it was postulated that these hallucinogenic effects were explained by the metabolic formation of amphetamine derivatives of the compounds contained in the nutmeg, specifically elemicin, myristicin, and safrole. Nutmeg is, for that reason, included here with the other substituted amphetamines, despite the fact that it is now known that no amphetamines are detected in the urine of abusers, even though elemicin, myristicin, and safrole are all easily enough detected (Beyer et al., 2006).

Nutmeg's effects are long lasting and they are considered unpleasant by most who experience them. However, it has been known since the Middle Ages that moderate doses of nutmeg are psychoactive (Beck and Marty, 2001). There are sporadic reports of nutmeg

intoxication, but deaths are rare (Lavy, 1987; Demetriades et al., 2005; Forrester, 2005). Intoxication produces a typical anticholinergic syndrome (Abernethy and Becker, 1992). It appears that the CNS activity of this plant results directly from plant components, without their undergoing any biotransformation (specifically elemicin, myristicin, and safrole) to

Figure 4.3.2.6.1 Nutmeg. (From Wikipedia.)

amphetamine-like compounds (Sangalli and Chiang, 2000). Nutmeg has little significance as a drug of abuse, but ever since Alexander Shulgin synthesized MDMA from myristicin in 1962 (Shulgin, 1966), safrole from nutmeg has been used by some clandestine drug makers to produce MDMA.

4.3.2.7 4-Chloro-2-5-Dimethoxyamphetamine (DOC)

According to Shulgin (1991), the three halo-amphetamine derivatives of this compound all share roughly the same potency, however, there are no controlled experiments. All have long half-lives, but little else is known about them. They can be smoked or insufflated. A normal average dose of DOC is said to range from 1.5 to 3.0 mg. Doses as low as 10 mg have been known to cause restless stupor. Onset of drug effect requires one to three hours, with a peak and plateau at four to eight hours, and a gradual resolution. Some users may still remain symptomatic 24 hours later. As with many of the drugs in this group, the mechanism of action is not known, but like DOB and DOI, its effects seem to be mediated by a partial agonist activity at the 5-HT2A serotonin receptor, and by its high binding affinity for the 5-HT2B and the 5-HT2C serotonin receptor. This molecule is unscheduled in the U.S., but it is likely that it would be considered an analog (of DOB), in which case, sales for human consumption or possession with the intent to ingest could be prosecuted under the Federal Analog Act. DOC is scheduled in many other countries including Canada, Germany, New Zealand, Sweden, and the U.K. In the U.S., the other analogs, including 2,5-dimethoxyamphetamine, 4-bromo-2,5-dimethoxyamphetamine, and 4-methyl-2,5-dimethoxyamphetamine are Schedule I controlled substances. This analog seems to be particularly popular on the eastern and southern coasts of the U.S. It is sometimes misrepresented as LSD.

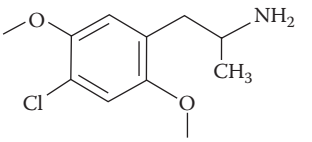

Figure 4.3.2.7.1 DOC molecule.

4.3.2.8 2,5-Dimethoxy-4-Iodophenethylamine

Like all amphetamine analogs that possess a chiral center, the *d*- isomer of this drug is more potent than the *l*- isomer. In common with the other members of this group, animal studies suggest that it exerts its main effects by preventing monoamine re-uptake (Nagai et al., 2007).

4.3.3 Piperazines

BZP (*N*-benzylpiperazine) is a Schedule I controlled substance commonly substituted for MDMA. TFMPP (3-trifluoromethylphenylpiperazine monohydrochloride) is currently not controlled but it too has been substituted for MDMA. It was first encountered in the U.S. in 2006, but it has been in fairly widespread use in Europe and Australia/New Zealand for more than 5 years. Piperazines are colorless crystalline compounds used around the world as hardeners for epoxy resins, but also as antihistamines and antihelminthics. Interestingly, they are also used in the manufacture of Viagra® and Marzine® (cyclizine). Piperazines of various sorts are now available online or in "head shops" across the U.K. and, by extension, via the Internet in the U.S. Head shops commonly sell this drug under the brand name of "p.e.p. pills." These chemicals present such

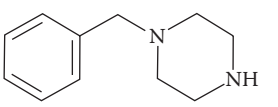

Figure 4.3.3.1 BZP molecule.

a problem that New Zealand has established a new drug classification, called "Class D," which requires certain drugs to be placed on a "restricted list" to be sold only under various strict licensing conditions.

The main legal supplier of piperazines in the U.K., called "Spiritual Highs," sells four different products: two containing just BZP (in two strengths) and two containing BZP and TFMPP combined (again, in two strengths). The different mixtures allow the products to be sold under separate, more lenient laws (de Boer et al., 2001). In some areas BZP gained popularity during the early 2000s, when it was sold as a legal alternative to amphetamine, methamphetamine, and MDMA. At the time of this printing, the company that produces "p.e.p" claims they are selling more than 3600 doses every day.

Piperazines share the same molecule at their core (they are *not* derived from plants of the *Piper* genus). The action of the most widely known piperazine, BZP, could be described as falling somewhere between amphetamines and MDMA, or even yohimbine. BZP has two main actions. It is an antagonist at the α_2-adrenoreceptor, disrupting negative feedback at the synapse, resulting in a larger stimulation-evoked release of an as yet to be specified neurotransmitter, most probably dopamine. However, BZP has only 1/1000 the potency of yohimbine. BZP also prevents the re-uptake of norepinephrine (just like cocaine and some antidepressants). BZP acts as a stimulant in humans and produces euphoria and cardiovascular effects, namely increases in heart rate and systolic blood pressure. BZP is about 10–20 times less potent than amphetamine in producing these effects (Staack and Maurer, 2005).

TFMPP is a more potent drug than BZP. The minimal dose is thought to be 25 mg with a maximum of 100 mg, which is much lower than that of BZP. Both BZP and TFMPP have an effect on the 5-HT receptors and users report that the mix of the two drugs produces an effect that is similar to the euphoric high of MDMA, although neither BZP nor TFMPP appears to have this effect when used alone (Maurer et al., 2004). This has led some to conclude that the two drugs have a yet-to-be-characterized synergistic relationship. No deaths from the use of either agent have been reported.

Whether or not either product is addictive is an open question. An article in the *New Scientist* reported on studies showing that monkeys will self-administer BZP (the criteria for addiction), but no one has ever encountered a human addict (Vince, 2006). Piperazine side effects are known to include severe agitation, nausea (lessened if taken on a full stomach), seizures, paranoia, hyperthermia, abdominal pain, and cardiac arrhythmias. Effects from longer-term use are not known. Both agents act as diuretics and extensive use may lead to dehydration, especially if consumed with alcohol.

BZP is hydroxylated in the liver, but TFMMP undergoes demethylenation. *N*-dealkylation to piperazine, followed by further degradation to form the corresponding ethylenediamine or aniline derivatives to complete the process. As a rule the phenylpiperazines are more extensively metabolized than the benzylpiperazines and virtually no unchanged drug is excreted. Glucuronidation occurs, but not to any great extent (Maurer et al., 2004).

One of the piperazines, 1-(3-chlorophenyl)piperazine (mCPP), is of particular interest. It is sometimes sold as an MDMA substitute. It is a metabolite of trazodone (an antidepressant) and in many U.S. jurisdictions it is sold legally, however it is being increasingly encountered as an MDMA look-alike. Recent reports indicate that, in some areas, it is also being used as a cocaine adulterant (Staack et al., 2007). More is known about the pharmacology of mCPP than any of the other drugs in this group. It causes neuronal release of 5-HT, and prevents re-uptake of 5-HT by, in some way, interfering with the 5-HT

transporter (Baumann et al., 1995). There is also evidence that it causes the release of dopamine (Hamik and Peroutka, 1989). There is only one published pharmacokinetic study. It showed that, compared to placebo, the drug causes increased plasma concentrations of ACTH, cortisol, and prolactin. Maximum mCPP concentrations varied 2.3-fold after intravenous infusion and 8-fold after oral administration, and absolute bioavailability ranged from 12% to 84%. The drug's elimination half-life ranges anywhere from 2.4 to 6.8 hours after intravenous infusion, and from 2.6 to 6.1 hours after oral administration. This enormous degree of variation is attributed to P-4502D6 polymorphism (Feuchtl et al., 2004). This drug will not be detected by any of the standard immunoscreening assays, though it can be detected with full scan GC/MS, and the presence of tramadol metabolite should serve to raise suspicion of its presence.

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4.4 Hallucinogenic Amphetamines

4.4.1 MDMA

Synonyms: XTC, Adam, MDM
Chemical name: *N*-α-dimethyl-1,3-benzodiaoxole-5-ethanamine or 3,4-methylenedioxymethamphetamine
Formula: $C_{11}H_{15}NO_2$
Molecular weight: 193.25 daltons
Metabolism: COMT and CYP2D6 & CYP3A4
Bioavailability:
$\mathbf{C_{max}}$ (ng/mL), n = 17,
Mean ± SD

1.0 ng/mL: 162.9 ± 39.8
1.6 ng/ml: 291.8 ± 76.5

Median value
1.0 ng/ml: 148.5 range
1.6 ng/ml: 275.8

Range
1.0 ng/ml: 115.4-248.8
1.6 ng/ml: 190.0-465.3

T_{max} hours
Mean ± SD
1.0 ng/ml: 2.4 ± 6
1.6 ng/ml: 2.4 ± 7

Median value
1.0 ng/ml: 2.3
1.6 ng/ml: 2.3

Range
1.0 ng/ml: 1.8-3.5
1.6 ng/ml: 1.5-4.0

V_{ss}: 6.7 L/kg (Kolbrich et al., 2008; n = 17) = 5.5 L/kg

Interactions: SSRI antidepressants (serotonin syndrome); antiretrovirals (Henry and Hill, 1998) and any drug that competes for CYP2D6; plasma concentrations increase slightly when taken with ethanol. Slight plasma concentrations also occur when taken with paroxetine. Results with other SSRIs are not known.

Note: (1) The half-life for MDMA is significantly longer after a larger dose. Note also the enormous range for $T_{½}$ and C_{max}. This presumably reflects a high degree of CYP2D6 polymorphism. (2) MDMA is a chiral molecule and the different forms display different pharmacokinetic patterns. The values above (and the values likely to be reported in any medical examiner's office) will reflect the total of (+) and (–), and it must always be considered that the two forms do NOT exert equivalent activity.

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4.4.1.1 History

It is widely supposed that MDMA (3,4-methylenedioxy-*N*-methylamphetamine, or Ecstasy) was synthesized by Merck with the goal of creating a new anorectic, but they never took it to market because of its side effects. That turns out not to be the case. When an

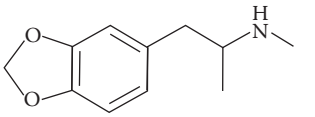


Figure 4.4.1.1 MDMA molecule.

interdisciplinary working group analyzed the original documents in Merck's historical archive in Darmstadt, they found that MDMA was actually first produced in 1912 and that it was called "Methylsafrylamin." Merck did apply for a patent, but only to protect an alternative chemical method for synthesizing styptic hydrastinine; MDMA was a precursor. MDMA was never intended for use as an appetite suppressant. There is also evidence that Merck's scientists did not perform any serious or fundamental pharmacological testing with MDMA (which they had renamed "Safrylmethylamin") until 1927. These tests were halted for economic reasons, but some testing was done in the 1950s, and then abandoned (Bernschneider-Reif et al., 2006). Later in the 1950s the U.S. Army contracted with a group of researchers at the University of Michigan to perform MDMA toxicity studies. The results of the Michigan study remained classified until 1973, when they were finally released. The studies showed that MDMA was somewhat less toxic than MDA but more toxic than mescaline (Hardman et al., 1973). MDMA was classified as a Schedule I drug in 1985.

MDMA causes the release of dopamine, 5-HT, and norepinephrine within the central nervous system. There is also evidence that it interferes with 5-HT re-uptake transporters (Eisner, 1989; Green et al., 2003). All of these compounds have an effect on behavior, and in the case of MDMA, the result is said to be increased empathy, hence the naming of it as an "empathogen" or "entactogen" (from the Greek *en* meaning "inside" and *gen* meaning "to produce" and the Latin term *tactus* for "touch") (Nicholas, 1986). MDMA is immensely popular in Europe, where the number of MDMA tablets seized has increased from less than 500,000 in 1997 to more than 30 million tablets in the year 2000 (Interpol, 2006). The latest published report from Interpol, which contains data for 2003, indicates declining use, but total seizures were still an astonishing 17,892,940 tablets (Interpol, 2006). The amount of MDMA seized by federal law enforcement agencies in the U.S. has increased 186%, from approximately 1.92 million dosage units seized in 2004 to nearly 5.5 million dosage units in 2005. This trend seems likely to continue (DEA, 2006).

Since 2004 MDMA trafficking has increased significantly. Canada-based Asian drug trafficking organizations have recently gained control over most MDMA distribution in the U.S. and have expanded distribution of the drug to a level similar to that of 2001, when availability peaked under the control of Israeli gangs that have since been largely dismantled. Asian gangs trafficking in MDMA distribute wholesale quantities of MDMA produced in Canada. MDMA production by Canada-based Asian groups is increasing. Moreover, the Asian gangs have established much wider distribution networks than their Israeli predecessors. Whereas Israeli MDMA distributors operated primarily in the Los Angeles, Miami, and New York City areas, the Asian gangs have strong distribution networks operating in most states throughout the country.

4.4.1.2 Incidence and Epidemiology

No MDMA-related deaths are listed in the DAWN report for 1999 (Kissin et al., 2000). The Emergency Room component of the most current DAWN report lists 8621 MDMA-related visits (CI: 5985–11,257) (SAMHSA, 2006). The last reliable medical examiner "component" to be issued by DAWN was for 2002, and it does not mention any MDMA-related deaths. The situation is far different in Europe and Asia. A 2006 U.K. survey based upon medical death certificates (coroners' reports in the U.K. tend to underestimate the problem)

of MDMA, MDA, and MBDB deaths occurring from 1994 to 2003 found a total of 394 deaths. In 42% of the deaths identified, MDMA was the only drug detected. The remainder were all polydrug abusers. The study also found that the number of MDMA-related deaths was increasing yearly, as were the number of offenders arrested for MDMA possession and the actual number of users. The number of users was definitely related to MDMA prices, which have been consistently falling: the lower the cost, the greater the number of people experimenting with the drug (Schifano et al., 2006).

4.4.1.3 Illicit Production

Safrole, the active ingredient in nutmeg, can be used to prepare the starting ketone (3,4-(methylenedioxy)phenylpropanone) by oxidization with hydrogen peroxide in an acid medium. However, safrole can no longer be bought without authorization, though it is still available via the Internet. If safrole can be obtained and oxidized it is then combined with methylamine in alcohol. Aluminum powder, freshly treated with mercuric chloride in ethanol, is added to the mixture, which is then boiled for several hours. MDMA is then distilled off under pressure (Verweij, 1991a, b). The final product is compressed into a tablet that is usually embossed with a logo (Figure 4.4.1.3.1). Other routes of synthesis are possible.

In Southeast Asia, MDMA is made by reductive amination of 3,4-methylenedioxyphenylacetone (MDP2P or PMK) with methylamine and sodium borohydride; gassing an acetone solution of the free base with commercial hydrochloric acid gas produces the hydrochloride salt. The amphetamine is then synthesized via the Leuckart reaction, and crystallized as the sulfate salt. Some of these laboratories may produce a remarkable amount of drug. There is evidence that the same synthetic route is favored in Europe as well as the U.S. and Asia (Palhol et al., 2002). In 2005 a laboratory seized outside of Jakarta was found to be producing 60–90 kg of MDMA per batch, corresponding to 428,000 to 642,000 tablets per day, based on a standard dosage unit of 140 mg of MDMA per tablet.

Figure 4.4.1.3.1 Tablets confiscated from a mega-lab located outside of Jakarta. Tablets are colorful and tend to carry logos, but the logo is no guarantee of quality. Forensic labs have noticed that the percentage of MDMA contained in each tablet tends to decrease with time and that the MDMA is replaced with other drugs, especially methamphetamine. (From the website of the DEA.)

In 2005 the DEA discovered large quantities of *Ocotea cymbarum* (also referred to as Brazilian sassafras, Ocotea cymbarum oil, Ocotea cynbarnum, Ocotea cymbarium, and Oil of Ocotea) at several clandestine laboratories located in the northeastern U.S. *Ocotea cymbarum* is made by distilling the trunk bark of a tropical tree native to Brazil, Colombia, and Paraguay. The distillate typically contains between 80 percent and 94 percent safrole (see above) plus small amounts of MDA (3,4-methylenedioxyamphetamine). Sales of *Ocotea cymbarum* are not controlled.

Ocotea cymbarum is available via the Internet, even at online auction sites, and also through the mail from chemical, aromatherapy, and perfume companies. It is also occasionally diverted from legitimate domestic businesses, such as the manufacture of fragrances, flavoring agents, and insecticides. The DEA estimates that a 5-gallon drum of *Ocotea cymbarum*, if used correctly as a precursor, would yield an estimated 49,000 to 108,000 tablets containing 120 mg of MDMA each.

Much of the MDMA available in the U.S. is still produced in clandestine laboratories located in the Netherlands and Belgium. MDMA is transported from Europe to the U.S. by couriers on commercial flights, via mail and package delivery services, and even by air cargo and maritime vessels. The amount of the drug available for distribution may be increasing slightly but no major new producers have been identified.

Once MDMA is produced, it is converted into tablets, each with a recognizable logo (see Figure 4.4.1.3.1) and the tablets quickly develop names based upon the imprinted logo. Brand loyalties develop, and users ask for particular tablets by name (tablets with the Mitsubishi label were once particularly popular, with a very loyal following). Some of the logos often have whimsical themes, ranging from an imprint of McDonald's Golden Arches to the Rolex trademark symbol, the Mercedes symbol, and even the skull and crossbones. A recognized logo is, however, no guarantee of quality, safety, or purity. Once the makers have developed a following for a pill with a particular logo, they then begin substituting cheaper ingredients in the pill such as methamphetamine or even PMA (a much more dangerous drug than MDMA) (Lora-Tamayo et al., 2004).

4.4.1.4 Metabolism

At least 16 different MDMA-related compounds have been discovered. Part of the reason for proliferation of metabolites is this drug's complex metabolism, which involves two main metabolic pathways: (1) *O*-demethylenation (leading to the formation of MDA), and then both MDMA and MDA are *O*-demethylenated to form 3,4,-dihydroxymethyamphetamine (usually abbreviated as HMMA and HMA), followed by further *O*-demethylenation and then catechol-*O*-methyltransferase (COMT)-catalyzed methylation and/or glucuronide/sulfate conjugation; and (2) *N*-dealkylation, deamination, and oxidation giving the corresponding benzoic acid derivatives conjugated with glycine. The fact that the polymorphic enzyme CYP2D6 partially regulates the *O*-demethylenation pathway suggests that "poor metabolizers" (possessing an abnormal CYP2D6) phenotype may be at higher risk of acute toxicity than normal individuals. The fact that such occurrences are seldom reported is explained by MDMA-induced inhibition of CYP2D6, which occurs in all users after the second dose of MDMA. Thus all people who take MDMA are, in effect, "poor metabolizers." In the case of MDMA, CYP2D6 pharmacogenetics have little effect on acute toxicity, but it is quite possible that MDMA-induced CYP2D6 inhibition could enhance the toxicity of other drugs (Kraemer and Maurer, 2002; de la Torre et al., 2004; Schifano, 2004). One of the interesting features of MDMA metabolism is its potential involvement in the

development of mid- to long-term neurotoxic effects as a result of progressive neurodegeneration of the serotonergic neurotransmission system.

The results of studies in experimental animals indicate that even a single dose of MDMA can significantly alter the cellular antioxidant defense systems and produce oxidative stress. The latter is associated with increased formation of reactive oxygen species capable of oxidizing phospholipids and proteins via interaction with their thiol groups and by lipid peroxidation. Oxidative stress may cause depression of sarcolemmal Ca^{2+} pump ATPase and Na^{+}-K^{+} ATPase activities, leading to decreased Ca^{2+} efflux and increased Ca^{2+} influx, respectively. There is evidence also that MDMA has an effect on the noradrenergic system in the periphery. Users of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) have been found to have elevated plasma catecholamine levels, and that could lead to myocardial toxicity (Carvalho et al., 2004).

CYP2D6 is not the only polymorphic enzyme involved in MDMA metabolism. The activity of COMT is subject to the same sort of genetic polymorphism as the P-450 enzymes, and has never been characterized in MDMA users or in cases of MDMA toxicity. It has been known for some time that catecholamines accelerate their own metabolic clearance, but whether this occurs via enzyme induction, and what effect, if any, MDMA or any other sympathetic amine has on this process is simply not known. The picture is further confused by the recent discovery of the enzyme called renalase, which also contributes to catecholamine homeostasis (Li et al., 2008). Whether this mechanism is altered by drug abuse is simply not known.

The half-life of MDMA is somewhere between 4 and 7 hours, but the greater the dose administered, the longer the half-life. In other words, the more drug that is taken, the more slowly it is broken down. The half-life for MDA is substantially longer than that of the parent compound, with peak plasma concentrations that are only one tenth as great. MDA itself is psychoactive. Illicitly produced MDMA is a racemic mixture, and clinical evidence indicates that the different enantiomers are metabolized at different rates (Moore et al., 1996). Enantiomeric effects on tissue distribution are known, and it is clear that the racemic form of the molecule has an enormous impact on drug distribution.

Not all of MDMA's actions can be explained by the effects it exerts on catecholamines. MDMA also causes the increased release of cortisol, prolactin, adrenocorticotropic hormone, dehydroepiandrosterone, and antidiuretic hormone (Henry and Hill, 1998; de la Torre et al., 2004). Some believe the presence of increased prolactin concentrations explains the feelings of closeness that users cite as one of the reasons for taking the drug (Hall and Henry, 2006). Some of the observed effects may be attributed to changes in the 5-HT receptor. In animals long-term self-administration of MDMA may lead to the development of chronic tolerance to the reinforcing effects of MDMA, but *S*(+)-MDMA is somewhat less susceptible to this effect than the racemate or the *R*(–)-enantiomer. The results of non-human primate studies suggest that any results obtained in vivo with the MDMA enantiomers may not be particularly informative with regards to the racemate and vice versa (Fantegrossi, 2008).

4.4.1.5 Clinical Syndromes

The two most feared complications of MDMA use are serotonin syndrome and hyperthermia with rhabdomyolysis. The first disorder is characterized by the rapid onset of confusion, diaphoresis, diarrhea, increased muscle tone, and cardiac arrhythmias. There may also be shivering, myoclonus, and increased deep tendon reflexes. If severe, the outcome may be hyperthermia, rhabdomyolysis, multisystem failure, and death. Risks for developing

the syndrome are higher in individuals taking SSRIs and MAOI type drugs. Most adult drug users take multiple drugs, and it is worth remembering that many of these other drugs have weak, but quite real, SSRI and MAO activity (methadone, tramadol, dextromethorphan, meperidine — see individual sections).

However, hyperthermia can occur in the absence of serotonin syndrome, occasionally with lethal outcome. MDMA increases core body temperature regardless of ambient temperature in humans, and it also causes substantial increases in metabolic rate (Freedman et al., 2005). The results of animal studies suggest that the higher the ambient temperature when MDMA is taken, the greater the increase in metabolism that results (Goni-Alto, 2007). Even in the absence of overt evidence of significant hyperthermia, MDMA (and amphetamines in general) can induce brain hyperthermia. Just how great an increase occurs depends upon an individual's state of activity and on prevailing environmental conditions. MDMA exacerbates drug-induced hyperthermia via mechanisms that are not fully understood (Kiyatkin, 2007).

Laboratory results suggest that MDMA has the ability to uncouple skeletal muscle mitochondria (leading to heat generation); in combination with hypothalamic–pituitary–adrenal activation, this causes body temperature to increase via a series of complex neurological mechanisms (Hargreaves et al., 2007). Just as recent animal studies suggest that MDMA produces more hyperthermia when it is used in a warm environment than in a cold one (Brown and Kivatkin, 2004), so too does some of the human experimentation. In one of the few controlled human studies ever performed, the physiological and subjective effects of MDMA were measured in 18 volunteers under both cold (18°C) and warm conditions (30°C). MDMA produced significant elevations in core body temperature under both conditions, even without any exercise; the metabolic rate in both warm and cold conditions also increased, and significant elevations in blood pressure and heart rate were noted (Freedman et al., 2005). MDMA increased core body temperature regardless of ambient temperature in humans. Animal studies have shown that MDMA administration decreases blood flow to the skin (Pedersen and Blessing, 2001). In short, MDMA causes heat to be produced, while, at the same time, it prevents heat dissipation.

In addition to hyperthermia and rhabdomyolysis, all of the usual complications associated with amphetamine abuse have been reported in association with MDMA abuse. There have been reports of cerebral sinus thrombosis, subarachnoid and intracerebral hemorrhage (De Silva and Harries, 1992; Gledhill et al., 1993), and even aplastic anemia (Marsh et al., 1994).

The occasional chronic MDMA user may develop compartment syndrome when attempting to inject crushed tablets into the femoral or other major vessels (Swan et al., 2006). Pneumothorax and pneumomediastinum have also been reported, but would not be an expected regular feature of MDMA use (Rejali et al., 2002). When intracranial bleeding does occur, it is usually as a consequence of pre-existing malformation, undiagnosed aneurysm, or AV malformation (Hughes et al., 1993; Selmi et al., 1995; Auer et al., 2002). Several reports of cerebral infarction were published in the early 1990s (Manchanda and Connolly, 1993; Hanyu et al., 1996), but no new cases have been published recently. Given the very great number of users today, and the absence of new case reports describing either cerebral or myocardial infarction, any connection with MDMA abuse must be considered unproven. Similar considerations apply to the one report of MDMA-related spongiform encephalopathy (Bertram et al., 1999), where the victim may have used other drugs in the past.

Finally, myocardial hypertrophy has been documented as a complication of regular MDMA use (Patel et al., 2005). Hypertrophy has been recognized as a complication of cocaine use for years (Karch et al., 1995) although it was only recently that the mechanism became apparent — cocaine combines with DNA leading to increased production of calmodulin kinase II, leading,

in turn, to elevated intracytosolic calcium and myocyte hypertrophy (Henning and Cuevas, 2006). Both abnormalities favor the occurrence of sudden cardiac death (Ruan et al., 2007).

4.4.1.6 Blood and Tissue Concentrations

Postmortem measurements are unreliable indicators of toxicity. For one thing, MDMA is usually sold as a racemic mixture, the (*S*)-enantiomer is metabolized faster than the (*R*)-enantiomer (roughly 5 hours versus 15 hours), and both of the isomers have different pharmacologic properties (Brunnenberg and Kovar, 2001). The fact that there is complete overlap in blood concentrations between users who are experiencing symptoms and those who are not (Henry, 1992) further complicates the picture. Drug concentrations in MDMA fatalities may be extremely high, often as much as four or five times higher than concentrations measured in controlled studies with doses of MDMA comparable to those used by "recreational" users. This has partly to do with the fact that MDMA has a high volume of distribution (> 5 L/kg), and partly with the fact that MDMA almost certainly undergoes extensive postmortem redistribution. In addition, concentration measurements are site dependent, and the origin of the blood sample is not always mentioned in autopsy reports.

MDMA postmortem redistribution is described in a paper by Elliot, published in 2005. He analyzed multiple tissues taken from five MDMA users who were treated at the hospital just before they died, so that both admission and postmortem blood samples were available. Admission MDMA concentrations ranged between 0.55 and 4.33 mg/L, while those of MDA ranged from 0 to 0.10 mg in antemortem serum/plasma. Postmortem blood samples of MDMA and MDA from the same individuals ranged from 0.47 to 28.39 mg/L and 0.02 to 1.33 mg/L, respectively. In every single case the postmortem values were higher than the antemortem values. Selected values from this study are shown in Table 4.4.1.6.1.

In one case, the MDMA concentration in femoral blood was 2750 ng/mL, while the concentration measured at the same time in "heart" blood was 9100 ng/mL. Although not shown in the table, the concentrations in the brain were even higher: 10,000 ng/g in the medulla and 14,000 ng/mL in the cerebellum.

Still another factor that complicates postmortem interpretation is the presence of MDA. It is produced as a minor metabolite of MDMA, but it is also manufactured and sold in its own right (see Section 4.4.2). Determining the origin of the MDA can usually be accomplished by looking at the other drugs found in the gastric contents. If MDA is found in isolation that is good evidence that its presence has nothing to do with MDMA degradation.

Blood concentrations in recently published case series seem to be higher than in those cases described in the early 1990s. Table 4.4.1.6.2 is composed of data from a 2006 paper on MDMA use in Taiwan.

Table 4.4.1.6.1 Selected Values from MDMA Postmortem Redistribution Study by Elliott

	MDMA/MDA	MDMA/MDA
Specimen	Case 4	Case 5
Antemortem serum	4.33	1.08
PM, L femoral	7.25/0.21	NA
PM, R femoral	6.19/19	2.6/.02 (side?)
PM, Heart	28.39/1.33	NA

Adapted from Elliott, S. P., *J. Anal. Toxicol.*, 29(5), 296–300, 2005.

Table 4.4.1.6.2 Postmortem MDMA Concentrations

	Matrix	Highest MDMA	Range	Mean	SD	Mean ± 2 SD
1.	Urine (n = 10)	67.115 µg/mL	<0.011–0.174	0.061	0.049	0.038–0.160
2.	Bile (n = 8)	130.952 µg/mL	<0.011–0.146	0.057	0.045	0.000–0.147
3.	Gastric (n = 12)	40.515 µg/mL	<0.004–0.046	0.086	0.130	0.000–0.346
4.	Heart (n = 15)	40.412 µg/mL	<0.014–0.045	0.069	0.053	0.000–0.174
5	Antemortem urine (n = 22)	33.31 µg/mL	0.128–0.211	0.101	0.052	0.000–0.205
6.	Hair (n = 6)	55.91 ng/mg	0.128–0.211	0.160	0.032	0.096–0.224

Data adapted from Liu et al., *J. Anal. Toxicol.*, 30(8), 545–50, 2006.

In still another study, MDMA concentrations in five patients who survived serious bouts of toxicity were said to have ranged from 200 to 970 ng/mL, while concentrations in five car-accident victims varied from 50 to 340 ng/mL (Henry et al., 1992). Several authors have reported plasma concentration measurements in suspects arrested for driving while intoxicated (DWI). The concentration ranges are so wide as to be non-diagnostic, ranging from less than 50 ng/mL to nearly 600 ng/mL, and as high as 2140 ng/mL in one traffic fatality attributed to MDMA; it appears that in all of these cases MDMA was almost always co-ingested with other drugs. Nonetheless, elevation in postmortem concentrations of MDMA and MDA should always be anticipated. Furthermore, the degree of elevation cannot be reliably predicted, except to say that blood collected from the heart always has much higher concentrations than blood from peripheral sites. Postmortem MDMA measurements bear no predictable relationship to antemortem values (Gamma, 2004; Elliott, 2005). It also bears repeating that MDMA is chiral, and that both chiral forms have different volumes of distribution and different activity. It is entirely possible that a reported MDMA plasma concentration may not reflect the presence of any psychoactive MDMA in the plasma.

The possibility always exists that the presence of MDMA may just be an incidental finding. Dowling et al. (1987) described one asthmatic with a blood MDMA concentration of 1.1 mg/L, but severe chronic lung disease was the cause of death. MDMA users are very likely to be using more than one drug (see above); if death is to be attributed to MDMA, then at least some plausible mechanism, such as water intoxication or hyperthermia with rhabdomyolysis, should be demonstrable.

4.4.1.7 Neurotoxicity

Like other amphetamines, MDMA acts on both the heart and the central nervous system, causing release of catecholamines (including 5-HT) and preventing their re-uptake. Neurotoxicity in animals is manifested by damage to serotonergic neurons. In the rat model, even one dose of MDMA causes degeneration of 5-HT-containing neurons, but animals treated with massive and repeated doses of MDMA eventually recover and at one year after treatment have no apparent lesions (Battaglia et al., 1987). Interspecies variation in the response to MDMA is considerable. The monkey is much more sensitive to the 5-HT-depleting effects of MDMA than is the rat (Ricaurte et al., 1985), while the mouse experiences dopamine-related changes without any alteration of the serotonergic system. Another difficulty with extrapolating from animal experiments is that, histologically, animal models never demonstrate any evidence of gliosis, which is an important anatomic

marker for tissue damage in man. It remains a matter of some contention whether the findings in animal models can reliably be extrapolated to human beings (Burgess et al., 2000; Curran, 2000; Turner and Parrott, 2000).

In 2002 a paper was published claiming to have demonstrated that multiple studies from the same laboratory over a span of approximately 2 years had demonstrated that MDMA produced not only serotonergic neurotoxicity, but that in addition MDMA also caused severe dopamine neurotoxicity in two different nonhuman primate species (Ricaurte et al., 2002). This conclusion was met with disbelief by most of the research community and subsequently the paper was withdrawn (Ricaurte et al., 2003). The authors found that they were unable to reproduce their original research, leading them to investigate their laboratory records. They discovered the controversial studies had mistakenly been performed with methamphetamine (which does damage dopaminergic neurons) and the study was retracted (Ricaurte et al., 2003). No one now suggests that MDMA has the potential to damage dopaminergic cells.

Brain lesions have not been demonstrated in humans and the results of functional MRI imaging show no evidence of injury (Jager et al., 2007), but chronic paranoid psychosis has been reported on a number of occasions, even though the mechanism remains unexplained (Creighton et al., 1991; Schifano, 1991; Williams et al., 1993; Van Kampen and Katz, 2001; Landabaso et al., 2002; Vecellio et al., 2003). The experience in Europe has been that MDMA abusers may present with a diverse group of psychiatric syndromes including, but not limited to, toxic psychosis (Morland, 2000). Nothing distinguishes the psychotic symptoms of MDMA users from symptoms seen in individuals with any other type of toxic psychosis.

Even though there is a wealth of experimental evidence suggesting that MDMA is toxic to serotonergic neurons, there is no clinical evidence that humans ever develop the typical symptoms of 5-HT depletion (disorders of sleep, mood, appetite), and the most recent evidence suggests that depressive symptomatology simply does not occur in occasional users (Falck et al., 2008). On the contrary, MDMA users are at risk for serotonin syndrome (Padkin 1994; Parrott, 2001), suggesting 5-HT excess, not deficiency.

Functional MRI has shown the brain areas that are significantly activated by the low oral doses of MDMA; these include the midbrain raphe nuclei, hippocampus, hypothalamus, amygdala, and the corticostriatal circuit composed of the dorsal thalamus, sensory motor cortex, and basal ganglia. The onset of brain activation correlates well with the rise in plasma MDMA concentrations (measured in monkeys) (Meyer et al., 2006).

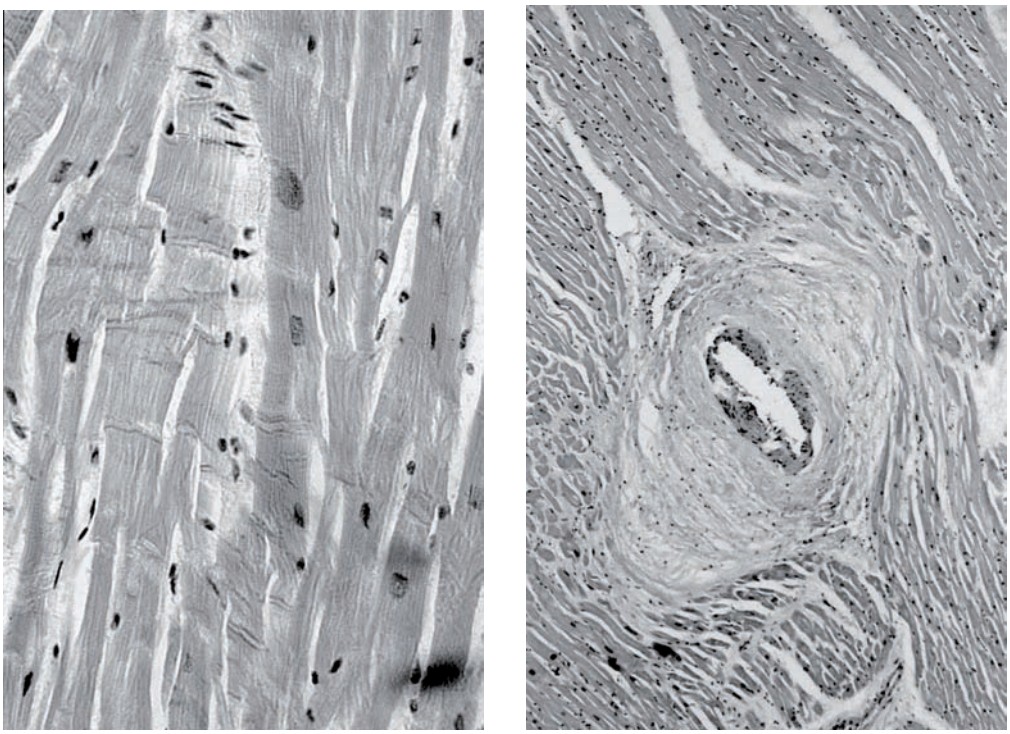
Users of MDMA are also at increased risk for seizure activity. Seizure onset after MDMA is thought to be related mainly to its acute systemic effects (e.g., hyponatremia and hyperthermia). However, additional mechanisms may be involved. Amphetamines exert profound effects on different monoaminergic systems, which might participate in lowering the seizure threshold. Unfortunately, the chronic effects of MDMA abuse on seizure threshold really have not been explored (Giorgi et al., 2006).

4.4.1.8 Cardiovascular Toxicity

Modest oral doses of MDMA cause increases in heart rate (increases of up to 30 beats per minute), blood pressure (average increase of 7 mm in diastolic pressure), and myocardial oxygen consumption. These increases are comparable to those induced by a dobutamine infusion of 20–40 mg/kg per minute. But, unlike dobutamine, MDMA has no measurable inotropic effects (Lester et al., 2000). In the only large, controlled, large postmortem study

of MDMA cardiotoxicity, it was determined that heart weights were significantly higher in MDMA-related deaths than those in controls (Patel et al., 2005). The results are comparable to the changes seen in the hearts of cocaine and methamphetamine abusers, which generally are 10–12% greater than predicted (Karch et al., 1998, 1999). In a 1996 report, Milroy et al. described the findings in seven MDMA-related fatalities. Hepatic damage was the most frequent finding (see below), but one of the decedents, who was assumed to have suffered a sudden cardiac death, was also found to have myocardial fibrosis, a very common finding in methamphetamine abusers (Figure 4.4.1.8).

Some MDMA users have shown classic signs of amphetamine/catecholamine toxicity with hyperadrenergic symptoms, including fever, tachycardia, and hypertension, as well as rhabdomyolysis, renal failure, and disseminated intravascular coagulation (Chadwick et al., 1991; Campkin and Davies, 1992). A report published in 1988 described an MDMA user, previously diagnosed with Wolff–Parkinson–White syndrome, who died a sudden cardiac death. At autopsy, in addition to the presence of an aberrant conduction pathway,



(a) (b)

Figure 4.4.1.8 (a) Myocardium of a 28-year-old man with sudden cardiac death. He was thought to be a chronic MDMA user. Note areas of extremely intense contraction band necrosis. CBN is a common lesion in stimulant abusers because of their increased plasma catecholamine concentrations. (b) Zone of perivascular fibrosis from the same heart showing contraction band necrosis in (a). The combination of perivascular fibrosis, microvascular disease, and contraction band necrosis is nearly diagnostic for chronic exposure to high concentrations of catecholamines, which can only be explained by the presence of a pheochromocytoma or by chronic stimulant abuse. (a, b, H&E stain; courtesy of Professor Chris Milroy, Sheffield Forensic Centre, U.K.)

myocardial fibrosis was also evident, so it is impossible to say whether it was pre-excitation or re-entry, or both, that led to the individual's demise (Suarez and Riemersma, 1988). One factor that may favor re-entry is that amphetamine analogs increase plasma 5-HT levels that, at least in theory, could cause contraction of pulmonary arteries and/or stimulate mitogenesis in pulmonary artery smooth muscle cells (which would favor the occurrence of atrial fibrillation) (Zolkowska et al., 2006).

Two cases of aortic dissection in MDMA users have been reported (Suarez and Riemersma, 1988; Duflou, 2000). Dissection is a known complication of methamphetamine abuse, but the mechanism in these cases remains unknown. Special stains are generally unrewarding, and evidence of medial degeneration is conspicuously absent. Presumably, the MDMA-related cases and the methamphetamine-related cases share common mechanisms, but since so few cases have been reported, it is impossible to say.

MDMA strongly binds the 5-HT-2_B receptor. It is known that chronic exposure to high levels of 5-HT, either from metastatic carcinoid tumors or the anorectic drug fenfluramine, is associated with proliferative disease and thickening of cardiac valves, mediated through 5-HT-2_B receptors. Whether this applies to MDMA remains debatable, but in a recent controlled study of chronic MDMA users (29 subjects each with two age-matched controls) there was a significantly higher incidence of very mild tricuspid regurgitation (Droogmans et al., 2007).

4.4.1.9 Hepatotoxicity

Reports, mainly from Europe, continue to describe patients with severe hepatitis, sometimes with fulminant liver failure (Brauer et al., 1997; Hellinger et al., 1997; Andreu et al., 1998; Friebe and Kindler, 1998; Jones and Simpson, 1999; Schwab et al., 1999; Brncic et al., 2006). The etiology is not clear. Liver failure may occur as a complication of hyperthermia and multi-organ failure, but there are other possibilities. Genetic polymorphism, at least of the P-450 systems, seems an unlikely cause; cases present with symptoms of liver damage indistinguishable from those of infectious hepatitis, with centrolobular necrosis and microvascular steatosis (Milroy et al., 1996). While a great deal of laboratory work has been undertaken, almost all has been in rats, and it is not certain that these findings can be generalized to humans. Some animal studies suggest that MDMA may be hepatotoxic because use leads to lipid peroxidation and decreased reduced glutathione levels, suggesting that MDMA induces a state of oxidative stress in the liver (Ninkovic et al., 2004). Other data suggest a possible association of specific human leukocyte antigen (HLA) phenotypes and MDMA-induced hepatotoxicity (Brncic et al., 2006).

4.4.2 MDA (3,4-Methylenedioxyamphetamine)

MDA is produced as a minor metabolite of MDMA, but it is also manufactured and sold in its own right. It is frequently misrepresented as MDMA. Even moderate doses of MDA can produce marked sympathetic stimulation, with resultant tachycardia and hypertension (Gunn et al., 1939).

Synonyms: tenamfetamine, "the love drug"
Chemical name: 3,4-methylenedioxyamphetamine, 1-(benzo[1,3]dioxol-5-yl)propan-2-amine
Formula: $C_{10}H_{13}NO_2$

Molecular weight: 179.22 daltons
Metabolism: CYP2D6, CYP3A4
Bioavailability: not known
C_{max}: After 100 mg MDMA, *n* = 8; 13.4 ± 4.5 ng/mL (de la Torre et al., 2004)
T_{max}: After 100 mg MDMA, *n* = 8; 6.7 ± 2.6 hours
$T_{½}$: After 100 mg MDMA, *n* = 8; 24.9 ± 14.5 hours
Interactions: no clinically significant interactions have been reported

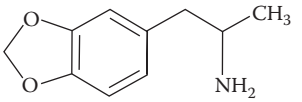


Figure 4.4.2.1 MDA molecule.

de la Torre, R., Farre, M. et al. (2004). Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition, *Ther. Drug Monit.,* 26(2), pp. 137–44.

4.4.2.1 History

Shulgin writes,

> There is a broad and checkered history concerning the use and abuse of MDA, and it is not the case that all the use was medical and all the abuse was social. One of the compulsive drives of both the military and the intelligence groups, just after World War II, was to discover and develop chemical agents which might serve as "truth serums" or as incapacitating agents. These government agencies considered the area of the psychedelics to be a fertile field for searching. The giving of relatively unexplored drugs in a cavalier manner to knowing and unknowing subjects was commonplace. There was one case in 1953, involving MDA and a psychiatric patient named Howard Blauer that proved fatal. The army had contracted with several physicians at the New York State Psychiatric Institute to explore new chemicals from the Edgewood Arsenal and one of these, with a chemical warfare code number of EA-1298, was MDA. The last and lethal injection into Blauer was an intravenous dose of 500 milligrams. (Shulgin and Shulgin, 1991)

MDA was also explored for commercial value by Smith Kline & French under the code name SKF-5, trade name Amphedoxamine, for use as an anorectic. The drug enjoyed some popularity in the early 1960s, before MDMA became widely available. MDA was even patented as an anorectic agent and as an antitussive (Lukaszewski, 1979), though it never saw commercial distribution. Today it is important only because it is a major metabolite of MDMA. No evidence indicates that MDA is currently synthesized or sold in the U.S. or Europe.

4.4.2.2 Clinical

MDA is a chiral compound and, according to Shulgin's unpublished studies, the *d*- form is substantially more potent than the *l*- form. Since chiral separation is rarely carried out in medical examiners' offices, MDA chirality can be a source of forensic confusion. The pharmacokinetics of MDA have never been seriously studied, and what is known about its pharmacokinetics is largely a function of the study of MDMA metabolism. Nonetheless, based upon the behavior of other chiral drugs (methadone comes to mind immediately) it seems likely that chirality has an effect on both MDA metabolism and the effects that it exerts. There simply is no way a pathologist (or toxicologist) can look at an isolated postmortem measurement and be sure he or she is looking at mostly active or mostly inactive drug.

The effects of a 150-mg dose of MDA peak at 1.5 hours and may last for as long as 8 hours. The half-life of MDA is on the order of 24 hours. One report compared MDMA and MDA concentrations in a case of polydrug overdose. These results are shown in Table 4.4.2.2.1. MDA undergoes oxidative cleavage of the methylenedioxy ring, producing

Table 4.4.2.2.1 Postmortem Distribution of MDMA and MDA Found in One Polypharmacy Death (Cocaine and Heroin Were Also Present)

Bile
MDMA (*d*) 58 ng/mL
MDMA (*l*) 15 ng/mL
MDA (*d*) 0.5 ng/mL
MDA (*l*) 1.2 ng/mL
Blood
MDMA (*d*) 1.6 ng/mL
MDMA (*l*) 1.3 ng/mL
MDA (*d*) 0.8 ng/mL
MDA (*l*) 0.8 ng/mL
Liver
MDMA (*d*) 5.0 ng/mL
MDMA (*l*) 1.4 ng/mL
MDA (*d*) 0.3 ng/mL
MDA (*l*) 0.4 ng/mL
Urine
MDMA (*d*) 302 ng/mL
MDMA (*l*) 227 ng/mL
MDA (*d*) 8 ng/mL
MDA (*l*) 18 ng/mL
Vitreous
MDMA (*d*) 1.2 ng/mL
MDMA (*l*) 0.7ng/mL
MDA (*d*) 0.2 ng/mL
MDA (*l*) 0.04 ng/mL

Adapted from Moore et al., *Forensic Sci. Int.,* 83(2), pp. 111–9, 1996.

methoxy and/or hydroxy metabolites, which then undergo conjugation (Marquardt and DiStefano, 1974). The results of pharmacokinetic studies in human volunteers have been reported from at least three separate studies.

In rats, the (*d*)-isomer of MDA is extremely arrhythmogenic, and even moderate doses can provoke ventricular tachycardia. This may explain some reported cases of MDA-associated sudden death. Illicitly manufactured MDA is always a racemic mixture (Lukaszewski, 1979), but the proportions of each isomer present may vary. Blood and tissue concentrations reported in several fatalities have ranged from 6 to 26 mg/L (Cimbura, 1972). In one driving fatality, the deceased was a 29-year-old man with no known history of drug abuse. The concentrations of MDMA in clotted blood, sodium fluoride–potassium oxalate anticoagulated blood, vitreous humor, and urine were 2.32 mg/L, 2.14 mg/L, 1.11 mg/L, and 118.8 mg/L, respectively. The concentrations of the metabolite MDA were less than 0.25 mg/L in blood and vitreous, and 3.86 mg/L in the urine (Crifasi and Long, 1996). In another case report, it appeared that MDA was actually the cause of death. The decedent was a 26-year-old individual whose clinical history suggested arrhythmia. At autopsy, fresh thrombosis was found in a severely obstructed (75%) left main coronary artery. Microscopic features were not described (Nichols et al., 1990).

4.4.3 MDEA (Eve)

4.4.3.1 Introduction

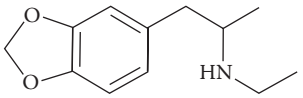


Figure 4.4.3.1.1 MDEA molecule.

Chemically, drugs like MDEA fall between amphetamines on the one hand and phenylethylamine hallucinogens on the other, with considerable overlap between the effects exerted by both groups of drugs. Until 1997 the rates of MDEA use in Europe and the U.K. were roughly similar. Now, except for some isolated pockets in Germany, survey results suggest that MDEA is rarely used any more (Schifano et al., 2006). As clinical and postmortem screening techniques improve, and there are now a number of very comprehensive methods for measuring all of the drugs in this group in most matrices, MDEA may prove to be more popular than is commonly thought (Casteele, 2005; Concheiro et al., 2005). Taiwanese chemists analyzed 181 MDMA tablets sampled from confiscated drugs received over a 3-year period ending in 2005. The MDMA content of the tablets varied from 16 to 193 mg/tablet, and 66–71% of the tablets seized each year contained only MDMA, with tablet concentration varying from 89 to 133 mg/tablet. As has been observed here and in Europe, MDMA content in these tablets decreased over time. As the MDMA content begins to drop, other drugs begin to appear. Components commonly found besides MDMA included caffeine (18%), methamphetamine (7%), 3,4-methylenedioxyethylamphetamine (MDEA) (7%) and amphetamine (4%), 3,4-methylenedioxyamphetamine (MDA), ketamine, ephedrine, diazepam, chlorzoxazone and nicotinamide (Teng et al., 2006).

4.4.3.2 Physiologic Effects in Humans

Brain glucose utilization in human volunteers given MDEA has been studied using functional magnetic resonance imaging (fMRI). Both MDMA and MDEA cause similar neurochemical alterations, most marked in the frontostriatocerebellar regions, areas implicated in the actions of most psychotropic drugs (Schreckenberger, 2006). One fatality in an individual with an enlarged heart and some nonspecific histological changes has been described. The subject's blood contained 2.0 mg/L of MDEA (Milroy et al., 1996). A second report described the findings in a 19-year-old who died after taking 10 tablets of pure MDEA. His symptoms progressed from apparent intoxication to profuse sweating, followed by aggressive behavior and hallucinations. Respiratory failure quickly supervened. The only significant autopsy finding was passive congestion. The serum MDEA was 12 mg/L in femoral vein blood, 22 mg/L in "heart" blood, and 201 mg/L in the urine (Weinmann and Bohnert, 1998). As with MDA and MDMA, the S(+) isomers of MDEA have a much higher affinity for the dopamine transporter and, therefore, more activity. The dispositions of the different enantiomers in humans are not known.

Some, but not all, of MDEA's effects have been duplicated in animals. For example, MDMA, MDA, and MDEA all cause an initial drop in the temperature of experimental animals, then predictable elevations in core temperature. That is not always the case for human MDEA users. MDEA also produces a transient fall in the diastolic pressure of experimental animals that is not seen in humans. MDEA is an α_1-adrenoceptor antagonist with a pK(B) of 4.79 ± 0.12 and this action is thought to explain the run up in temperature seen after the initial hypothermia (Bexis and Docherty, 2006).

4.4.3.3 Illicit Synthesis

MDEA is relatively easy to make, especially as production requires no expensive or bulky equipment. More than 20 different synthetic pathways are known, and just about all source materials are available over the Internet. The simplest methods start with the alkylation of MDMA. Other popular precursors include safrole from sassafras, nutmeg, and dill. The final product is usually mixed with expients like sorbitol or glucose. Pills are finally stamped from the same dyes that clandestine drug makers used to make MDMA tablets (Freudenmann and Spitzer, 2004). Depending on the intent of the manufacturer, any number of active agents, such as opiates or cocaine, may also be added to the mix, making this a particularly dangerous recreational drug. The average dose of MDEA in an illicit pill is said to be between 64 and 176 mg (Freudenmann and Spitzer, 2004).

4.4.4 4-MAX (U4Euh, EU4EA, U4EA), Aminorex

4-Methylaminorex (4-MAX) and aminorex belong to a group of compounds known as oxazolines (Figure 4.4.4.1). Aminorex was sold in Europe by McNeil Laboratories during the 1960s under the brand names Menocil® and Apiquel®. It was promoted for appetite suppression and weight reduction, but had to be withdrawn from the market when its use was linked with the development of fatal pulmonary hypertension (Ioannides-Demos et al., 2006). The first reports of 4-methylaminorex as an abused drug came from Florida during the mid-1980s. Since then, sporadic seizures have continued, but only rarely (Gaine et al., 2000). Instead of being sold under its own name, aminorex has more often been misrepresented as methamphetamine. Based largely on concerns that aminorex had the potential to become a low-cost substitute for cocaine or methamphetamine, aminorex was classified as a Schedule I substance in April 1989. No deaths or emergency room visits have been attributed to this drug since then, at least within the U.S. There is evidence that 4-MAX continues to be a problem in the former Soviet Republics. Unfortunately, nothing new about the abuse of this drug, either in the U.S. or Europe, has been written in the last five years.

The *cis*-(+)-isomer is the form of the drug found in most clandestine drug laboratories. It is synthesized in a one-step reaction by condensing phenylpropanolamine with cyanogen bromide. It could also be produced starting with norpseudoephedrine, although with the tight controls on this agent in the U.S. that seems increasingly unlikely, especially since phenylpropanolamine has been withdrawn from the market entirely. Aminorex produces the same effects as the other amphetamines, causing substantial increases in brain dopamine release, and decreases in tryptophan hydroxylase activity (Hanson and Magill, 1962). The discovery that aminorex could cause fatal pulmonary hypertension effectively stopped all further research on this substance (Seiler, 1975; Frank et al., 1993).

Pharmacokinetic studies of aminorex were done before sophisticated measurement techniques became available. Aminorex absorption is rapid; a single 15-mg oral dose produces a peak plasma concentration of 40 ng/mL at 2 hours. Concentrations decline slowly after that, dropping to

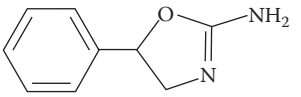


Figure 4.4.4.1 Aminorex molecule. 4-Methylaminorex differs from MDMA and other ring-substituted amphetamines. It is classified as an oxazoline and has a side-chain substitution that resembles pemoline, a potent stimulant.

5 ng/mL at 24 hours. The reported half-life for aminorex in humans is 7.7 hours. Studies have not been done on 4-MAX, but the similarities to aminorex are so great that it should behave in much the same way. Most of a given dose is eliminated unchanged in the urine (WHO, 1991).

The chemistry of aminorex is now a bit better understood than a decade ago. Three metabolites have been identified by high-performance liquid chromatography-tandem mass spectrometry with thermospray ionization: norephedrine, 5-phenyl-4-methyl-2-oxazolidinone, and 2-amino-5-(*p*-hydroxyphenyl)-4-methyl-2-oxazoline. Stability studies have shown that in aqueous solution aminorex degrades very slightly to norephedrine upon standing. There is no evidence for glucuronidation, which means that P-450 plays only a negligible role in its metabolism; rather, it is excreted primarily unchanged but undergoes some slight oxidative deamination and aromatic hydroxylation. Hydrolytic degradation back to the synthetic precursor can also occur (Henderson et al., 1995).

4.4.5 Other MDMA Homologs

The 2-butanamine-2-homolog of MDMA (*N*-methyl-1-1(3,4-methylenedioxyphenyl)-2-butanamine) has been produced by German clandestine chemists. Use of the drug is said to result in a pleasant, introspective state, devoid of hallucinogenic effects. Nothing is known about the pharmacology of this drug (Rosner and Ouednow, 2005).

4.4.6 *N*-Methylcathinone

This drug is also known by a number of street names, including Kat, Jeff, and Cat or *N*-methylcathinone, or methcathinone. It has no relationship with cathinone, the active ingredient of khat (see Chapter 2). In the 1950 the Parke-Davis Company considered selling *N*-methylcathinone as an appetite suppressant, and even went so far as to file a patent in 1957. However, subsequent studies disclosed that only the pure *l*-form had any activity and, with storage, this form of the drug rapidly deteriorated. Because of the drug's limited shelf-life, attempts at developing a commercial product were abandoned. Very recent new evidence indicates that ingestion of this drug causes manganese poisoning, and that can lead to parkinsonism (Glennon et al., 1987). For a brief period in the late 1990s *N*-methylcathinone enjoyed some popularity as a drug of abuse, particularly in the Midwest, probably because it was very simple to make. Many officials feared that, because of ease of illicit production, use would become widespread. That event never materialized.

N-methylcathinone is a structural analog of methamphetamine and cathinone. When it is sold, it is almost exclusively as the stable, and highly water-soluble hydrochloride salt. It is most commonly snorted, although it can be taken orally by mixing it with a beverage, or diluted in water and injected intravenously (Kamata et al., 2006). *N*-methylcathinone has an abuse potential that is considered the equivalent to methamphetamine, and it produces amphetamine-like activity. It was placed in Schedule I of the CSA in 1993.

N-methylcathinone is synthesized directly from ephedrine by oxidation with potassium permanganate. The required chemicals (battery acid, sodium dichromate, lye, paint thinner, and Epsom salts) are easy to come by. Even though it is rarely, if ever, used in the U.S., it remains popular in Eastern Europe, where abuse has resulted in fairly frequent cases of manganese poisoning and outbreaks of full-blown parkinsonism in young people who have been injecting the drug. Once the symptoms of parkinsonism have become

apparent, full recovery is rare. The pharmacokinetics of this drug have not been studied, although the urinary excretion pattern has. There appears to be two major metabolic pathways in humans and rats. The first is side chain degradation by *N*-demethylation to the corresponding primary amine methylenedioxycathinone (MDC), which is partly conjugated; and, second, demethylenation followed by *O*-methylation of either a 3- or 4-OH group on the benzene ring to produce 4-hydroxy-3-methoxymethcathinone (HMMC) or 3-hydroxy-4-methoxymethcathinone (3-OH-4-MeO-MC), respectively, most of which is conjugated. Of these metabolites, HMMC is the most abundant in humans and rats. The cumulative amount of urinary HMMC excreted within the first 48 hours in rats was approximately 26% of the dose, and the amount of the parent methylone was not more than 3% (Kamata et al., 2006). Thus the presence of HMMC can be used as proof of the use of methylone in forensic urinalysis, and its measurement should seriously be considered in cases of new onset parkinsonism.

Intravenous use of this drug can produce an extrapyramidal syndrome. It is reported with some frequency in Eastern Europe and Russia, and is associated with elevated blood manganese concentrations. Onset is very gradual, with patients reporting onset of their first neurological symptoms after a mean of 5.8 ± 4.5 years of methcathinone use. MRI scans of symptomatic patients have shown symmetric hyperintensity in the globus pallidus and in the substantia nigra and innominata. The neurologic deficits apparently did not resolve after patients discontinued methcathinone use (Stepens et al., 2008).

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4.5 Phenylalkylamines

4.5.1 Simple Tryptamines

Tryptamines are monoamine alkaloids that occur naturally in plants and animals. It is thought that small amounts are present in the human brain as well, where they act as neurotransmitters. Tryptamines contain an indole ring structure and are related to the amino acid tryptophan. 5-HT and melatonin are both classified as tryptamines. Interestingly, the acacia plant contains large amounts of tryptamine, and it has recently been suggested that Moses, when he received the Ten Commandments, was actually intoxicated on an acacia-based beverage.

α-Methyltryptamine (AMT) and 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT) are now scheduled drugs. Both of these compounds are tryptamine derivatives and share chemical and pharmacological similarities with other tryptamine hallucinogens, specifically α-ethyltryptamine (AET) and *N,N*-dimethyltryptamine (DMT). AMT and 5-MeO-DIPT are stimulant/hallucinogens. AMT can produce nervous tension, irritability, restlessness, inability to sleep, blurred vision, pupillary dilatation, hallucinations, and dextroamphetamine-like mood-elevating effects. 5-MeO-DIPT can produce talkativeness, disinhibition, pupillary dilatation, nausea, jaw clenching, muscle tension, and overt hallucinations with both auditory and visual distortions. Clinical studies of these drugs have never been performed and their safety for human consumption is not known.

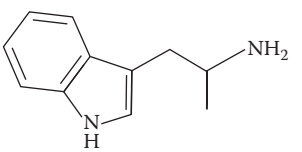

Figure 4.5.1.1 Simple tryptamines.

4.5.2 DMT

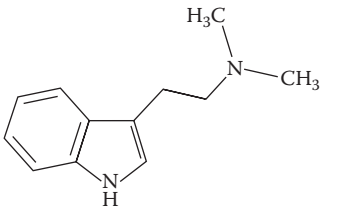

Figure 4.5.2.1 DMT molecule.

N,N-dimethyltryptamine (DMT) is a component of South American hallucinogenic snuffs. It can be isolated from both Old and New World plants, and even European mushrooms. It is almost always found to be present along with 5-OH-DMT. The Indian term *ayahuasca* is sometimes used to describe a mixture of plants containing DMT and harmaline. Harmine/harmaline is usually obtained from the *Banisteriopsis caapi* vine, and DMT (*N,N*-dimethyl-tryptamine) from the leaves of the *Psychotria viridis* bush. None of these plant substances are, by themselves, psychoactive when taken orally. Harmine/harmaline is said to cause hallucinations, but only at highly toxic levels. Smaller doses are simply tranquilizing. DMT is not orally active (hence its early use as a snuff), but it can be made active by combining it with a monoamine oxidase inhibitor (MAOI). In fact, *ayahuasca* is effective orally because the harmala alkaloids in the *Banisteriopsis caapi* vine are potent short-term MAOIs. Most tryptamines are inactivated by MAOIs. For that reason MAOIs can be used to potentiate the effects of tryptamines and to make DMT and 5-MeO-DMT (produced in toads by methylation of 5-OH-DMT to form 5-MeO-DMT) active orally (Weil and Davis, 1994).

MAOIs fall into two classes: irreversible and reversible MAOIs. Irreversible MAOIs (e.g., the hydrazides iproniazid and phenelzine) bind permanently to the enzyme and cause MAO inhibition lasting 1–2 weeks. They are used clinically to treat depression. Reversible MAOIs, such as moclobemide, which is also used as an antidepressant, and the β-carbolines harmine and harmaline, are effective for a much shorter time, perhaps up to 24 hours. Recreational drug users around the world have empirically learned to use mainly harmine and harmaline to prolong their experience.

Harmine and harmaline are indole alkaloids. Both molecules are melatonin analogs structurally related to ibogaine, an alkaloid currently under investigation as a treatment for opiate addiction (Mash et al., 2000). Harmine and harmaline are only two of many naturally occurring alkaloids found in *Peganum harmala*, also known as Syrian rue, the traditional source of the characteristic red dye used in Turkish carpets (Furst, 1985). *Peganum harmala* is a perennial herbaceous plant found not only in the Amazon basin but also in North Africa and the American Southwest (el Bahri and Chemli, 1991). *Peganum harmala* is just one of at least eight plant families, some Old World, some New, containing harmine and harmaline. They are profoundly hallucinogenic. In the New World, *Banisteriopsis*, a malpighiaceous tropical genus, is the main source of the psychoactive snuff. Terence McKenna (1982) has mentioned chocolate being a weak MAOI, which could be a reason for the popular habit of ingesting mushrooms with cocoa, and probably accounts for the very frequent seizure of psilocybin chocolate bars. Little is known about the metabolism of this drug. Autopsies of cattle that have consumed too much of the drug show little more than passive visceral congestion (Bailey, 1979).

Seeds of *Peganum harmala* (Syrian rue) contain roughly 3% harmine/harmiline. *Banisteriopsis caapi* has been found to contain from 0.18% to 1.36% β-carbolines, with the concentration of harmine being from 0.057% to 0.635% (McKenna et al., 1984).

Table 4.5.2.1 Blood Levels in an Alleged Ayahuasca Death (Values Are in Nanograms)

Substance	Heart Blood	Peripheral Blood	Urine	Liver	Brain
DMT	20	10	890	ND	570
5-MeO-DMT	1888	1200	9590	1638	150
Tetrahydroharmine	380	240	6002	13,240	430
Harmaline	70	40	6002	360	40
Harmine	170	80	1150	2310	160

Adapted from Sklerov et al., *J. Anal. Toxicol.*, 29(8), 838–41, 2005.

According to anecdotal reports, the ingestion of 1 g of *P. harmala* seeds will inhibit MAO enough to make DMT orally active.

Harmine and harmaline are hallucinogenic on their own with the effective dose starting from around 300 mg (Ott, 1999). They have few emotional or "psychedelic" effects, but produce strong visual hallucinations. Because of this the natives of the Amazon often add larger amounts (75–100 cm of stem per dose) of *B. caapi* to ayahuasca brew than is needed for MAO inhibition (Luna, 1984).

One of the characteristic features of such mixtures is that they produce nausea before inducing any psychiatric effects. DMT is usually sold on the black market as a brownish solid material that smells like mothballs. Users cut off small pieces and smoke them by placing them at the end of a cigarette, often a marijuana cigarette. DMT is sometimes referred to as the "businessman's high" because a single inhalation will produce a 5–10-minute "trip" that is entirely gone in 30 minutes (Chamakura, 1993).

Only one alleged case of ayahuasca poisoning in recreational users has ever been reported or studied. Autopsy was performed within 24 hours of death and no gross lesions were apparent. Blood levels from various sites were measured (see Table 4.5.2.1). The levels cannot be used to determine the cause of death for a number of reasons: (1) the decedent, a 25-year-old, could well have suffered from a heritable channelopathy, but no testing was done; and (2) nothing is known about blood levels in the living, or the behavior of any of these compounds after death.

Nothing is known about the toxicokinetics of smoked DMT; however, controlled double-blind studies with intravenously administered drug have been done in experienced hallucinogen users. With doses of 0.2 and 0.4 mg/kg (which are fully hallucinogenic), effects were experienced almost instantly, peaking within 2 minutes and disappearing in 20–30 minutes. Measured blood levels corresponded to the subjective effects of the drug. Peak levels varied widely from subject to subject and ranged from 32 to 204 ng after a 0.4 mg/kg dose. Hallucinogenic drugs such as DMT are serotonergic agonists, or at least partial agonists, and, in addition, have adrenergic and dopaminergic properties. DMT causes hormonal, autonomic, and cardiovascular effects. Pupils dilate, and levels of cortisol, prolactin, corticotropin, growth hormone, and β-endorphin all increase in a dose-dependent manner. Values return to near baseline within 30 minutes. Increases are

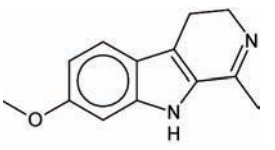

Figure 4.5.2.2 Harmaline molecule.

also observed in heart rate and blood pressure. Body temperature also rises, although that change lags slightly behind the others (Strassman and Qualls, 1994; Strassman et al., 1994). The risk of addiction is thought to be negligible (Gable, 2007).

4.5.3 Bufotenine

Bufotoxins are toxic compounds found in the parotid gland, venom, and skin of a variety of toads. They can also be found in some other amphibians, and in plants, especially mushrooms (Siperstein et al., 1957). More than 90% of the plants and animals containing bufotoxins are of New World origin (Weil and Davis, 1994). The exact composition of the venom varies greatly depending on the specific source. Toad glands can contain a mixture of toxins, including 5-MeO-DMT (see Section 4.5.4); other closely related compounds called bufagins, bufotalin, bufotenine, bufothionine, cardiac glycosides; and significant amounts of epinephrine, norepinephrine, and 5-HT may also be present.

Bufotoxin consists of three major types of endogenous glycosides, all of which are digitalis-like substances that circulate mainly in the plasma of the toad, *Bufo marinus*. One fraction is present in fresh plasma and is composed of chromatographically homogeneous polar conjugates, principally bufadienolide 3-sulfates, which range in activity from weak to very strong ATPase inhibitors. Another group, found within the parotids, is of variable and unpredictable composition.

5-Hydroxy-*N,N*-dimethyltryptamine (bufotenine) shares structural and mass spectral similarities with psilocybin and is a potent hallucinogen. The results of receptor binding studies suggest that bufotenine has approximately the same affinity for 5-HT2A and 5-HT2C receptors as LSD. It was the active ingredient in the South American hallucinogenic snuffs described by early Amazon explorers more than 400 years ago (Monardes, 1596). Under U.S. law bufotenine is a controlled substance, as are the related bufadienolides: resibufogenin, bufalin, and cinobufagin. The Chinese medication *Chan Su* and the West Indian "love stone" both contain bufadienolides, which, because they are potent cardiac glycosides, may cause potentially lethal arrhythmias. Taken in excess, these compounds can produce all the symptoms of digitalis poisoning and can be successfully treated with digoxin-specific Fab fragments (Brubacher et al., 1996).

Archaeological evidence indicates that the use of bufotenine-containing snuff goes back several thousand years. In spite of its ancient origins, the drug received little attention until a California wildlife instructor was arrested in 1994 for the possession of bufotenine, which he had collected from four pet toads. At about the same time, police from Australia began to encounter people smoking the dried skin of the Australian cane toad. Occasional samples of bufotenine began appearing at crime laboratories in the early 1990s. At the same time, "toad smoking" began to receive extensive publicity in the lay press (Ramsay et al., 1976; Gallagher, 1994).

Bufotenine is present in at least four different species of toads, and not just in their skin. The digitalis-like component of the poison can be detected in toad plasma and internal organs (Lichtstein et al., 1993). It can also be found in Asian herbal remedies prepared in China from either dried toad skins or from milked parotid secretions. One *Chan Su* is also used topically to treat skin ailments. Toad products are also added, in minute amounts, to other Asian proprietary mixtures in hopes of strengthening the heart. *Chan Su* can be legally prescribed by herbalists practicing in the U.S.

Confiscated samples of bufotenine have been described as resinous, reddish brown cubes, reminiscent of root beer barrel candies that have been sucked on. It is believed that abusers shave off some of the resin and smoke it at the end of a cigarette. The dose used is not known, and resultant blood levels have never been measured. A fairly extensive literature on the botany and chemistry of bufotenine now exists, but essentially nothing is known of its pharmacokinetics or pharmacodynamics.

In addition to the toxin, toad tissue also contains bufogenins, a group of steroid derivatives. At least one is a potent vasoconstrictor, and its effects are not entirely blocked by antidigoxin antibodies (Bagrov et al., 1993). Dogs poisoned with toad secretions develop drooling, seizure activity, cyanosis, and cardiac arrhythmias (Palumbo et al., 1975). The homodynamic effects, at least, seem to be due to the combined effects of the glycosides and catecholamines (Ojiri et al., 1991).

Human toad poisoning does occur, although death is rare. A 1986 case report described a child who developed status epilepticus after mouthing a toad (Hitt and Ettinger, 1986). Profound drooling, seizure activity, arrhythmias, and cyanosis have all been described in *Chan Su* users (Chern et al., 1991; Kwan et al., 1992; Yei and Deng, 1993; Jan et al., 1997; Chi et al., 1998). Toxicity is reported to be common in dogs (Roberts et al., 2000).

4.5.4 5-MeO-DMT (5-Methoxy-*N,N*-Dimethyltryptamine)

This is a relatively common hallucinogen and police confiscations are not infrequent. Sometimes sold as blotter acid and sometimes under its own name, it has become very popular. The toad *Bufo alvarius* does not contain 5-MeO-DMT, but it does contain the precursor 5-OH-DMT, which can be transmethylated to form 5-MeO-DMT (Weil and Davis, 1994). 5-OH-DMT can also be synthesized from standard laboratory chemicals (Shulgin and Shulgin, 1991). Of course 5-MeO-DMT also occurs naturally, mainly used in ayahuasca brews but occasionally in traditional South American shamanic snuffs. Like other naturally occurring alkaloids, it is not active when it is taken orally, so it is generally smoked. According to Shulgin the dose is 10–25 g. When smoked, it is about four times as potent as DMT. According to some of Shulgin's early experiments, effects are felt in less than 60 seconds, peak in 2–3 minutes, and disappear after 20 minutes. When it is taken orally, it is taken in combination with MAOIs (Callaway and Geyer, 1992). This has led to some controversy about the relative toxicity of the combination. A report published in the summer of 2006 described a 25-year-old white male found dead in the morning after consuming a cocktail of β-carbolines and hallucinogenic tryptamines. According to the authors, no cause of death was evident at autopsy. Blood taken from the heart was found to contain *N,N*-dimethyltryptamine (0.02 mg/L), 5-methoxy-*N,N*-dimethyltryptamine

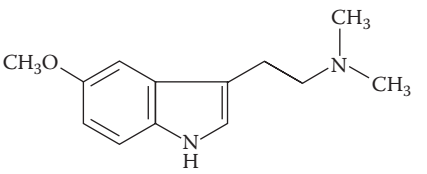

Figure 4.5.4.1 5-MeO-DMT molecule.

(1.88 mg/L), tetrahydroharmine (0.38 mg/L), harmaline (0.07 mg/L), and harmine (0.17 mg/L). The medical examiner ruled that the cause of death was hallucinogenic amine intoxication, and the manner of death was undetermined (Sklerov et al., 2005). Two years earlier the death of another young man was attributed to the same combination of drugs (Brush et al., 2004). These are the only reported cases suggesting significant toxicity.

In theory this combination of drugs could cause something very much like acute catecholamine toxicity. Unfortunately, no details of the autopsy were given in either of the report cases and whether or not there was myocardial necrosis in either is not known. One might expect that there would have been if it had been diligently sought. The other factor making assessment impossible is that no genetic screening was done of the heart, and there is no way to rule out death from heritable channelopathy or cardiomyopathy.

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4.6 Psilocybin

4.6.1 History

Psilocybin-containing mushrooms were probably used by the Aztecs, but until the 1960s they evinced little interest outside of Mexico. The name psilocybin is derived from the Greek roots *psilo*, meaning "bald," and *cybe*, meaning "head," presumably because of the shape of the mushrooms from which the active compounds are derived. The structure of the molecule was not established until 1958, when the active principle of these mushrooms was identified by Albert Hoffman at Sandoz Pharmaceuticals. Hoffman had succeeded in synthesizing LSD just a few years earlier. For some time, Sandoz marketed pure psilocybin under the brand name Indocybin®.

Psilocybin can be found in three different genera of mushrooms: *Psilocybe, Panelous*, and *Conocoybe*. All three varieties grow naturally in the northwestern and southeastern portions of the U.S. Related or identical forms grow wild in Central and South America, as

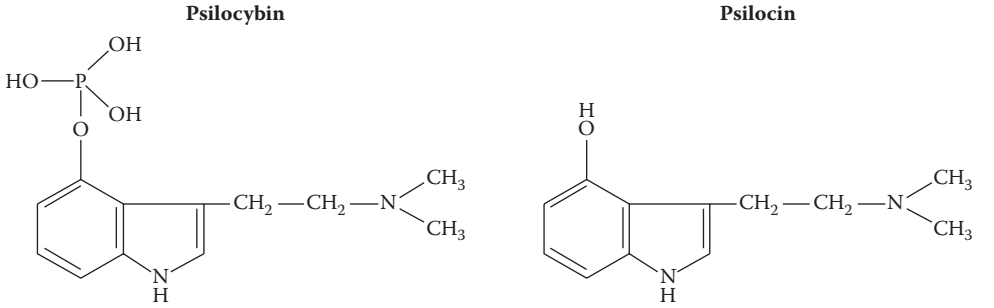

Figure 4.6.1 Psilocybin and psilocin molecules.

well as in Southeast Asia and India. Large quantities are cultivated for illegal distribution. The most common species is *Psilocybe cubensis*. It grows wild in the manure of cattle, water buffalo, and other ruminants, including deer, and possibly kangaroos. In Southeast Asia, farmers collect droppings from these animals and systematically grow the fungi in disused rice paddies (Allen and Merlin, 1992).

All three genera contain the tryptophan derivatives psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine, which, technically, is a substitute tryptophan; however, the drug itself is sufficiently unique as to command its own section) and psilocin (4-hydroxyl-*N,N*-dimethyltryptamine). *Psilocybe cubensis* is generally the preferred cultivar and on average yields 10 mg of psilocybin per gram of fresh mushroom, which is equal to an average dose. Psilocin is 1.5 times more potent than psilocybin, but, because the latter oxidizes more slowly, both contribute almost equally to the effect of the mushroom (Leikin et al., 1989). During the early 1980s, growing kits complete with spores were advertised in magazines. They are now illegal (Schwartz and Smith, 1988).

Identifying wild *Psilocybe* is difficult and dangerous. Psilocybin-containing mushrooms grow side by side with the poisonous *Galerina autumnalis*. *Galerina* species have rust-brown-colored spores, while the spores of *Psilocybe* species are gray to lilac. Some, but not all, species can be distinguished from poisonous mushrooms by their reaction to room air; when *Psilocybe* mushrooms are cut, they oxidize and turn blue within 30–60 minutes. Unfortunately, some poisonous mushrooms can do the same thing. Pathologists are much more likely to encounter cases of mushroom poisoning than they are to encounter psilocybin-associated medical problems!

4.6.2 Physiologic and Psychological Effects

After oral doses of up to 15 mg, psilocybin produces no significant alteration in pulse, blood pressure, or neuroendocrine function, although profound psychological alterations occur (Gouzoulis-Mayfrank et al., 1999). The mechanism by which these drugs exert their psychotropic effects may have recently been identified. The effects of hallucinogenic drugs, such as psilocybin and lysergic acid diethylamide, require the presence of the 2AR 5-HT receptor, and the symptoms they produce resemble many of the symptoms seen in schizophrenia. Recently published studies have shown that the metabotropic glutamate receptor #2 (abbreviated as mGluR2) interacts through specific transmembrane helix domains with the 2AR 5-HT receptor, along with a member of an unrelated G-protein-coupled

receptor family. Together, these groups form functional complexes within the brain cortex. When a hallucinogenic drug interacts with the 2AR–mGluR2 complex, a set of unique cellular responses occurs and normal behavioral responses are disrupted (González-Maeso et al., 2008).

4.6.3 Pharmaco- and Toxicokinetics

Studies in rats, which may or may not be relevant to humans, suggest that bioavailability from the stomach is only 50%, and that 65% of what is absorbed is eventually excreted in the urine, with another 20% appearing in the bile and stool. Most of the excretion occurs in the first 8 hours, but in the rat, labeled drug may appear in the urine for as long as a week (Aboul-Enein, 1974). Fatalities are rare (fewer than half a dozen case reports have ever been published), and tissue levels in humans have not been studied. One case report from more than 40 years ago described a 6-year-old child who developed hyperthermia and status epilepticus after ingesting an undetermined number of mushrooms. No toxicologic studies were performed (McCawley et al., 1962). A review of 27 patients with "magic mushroom" poisoning found that mydriasis and hyperreflexia were common, but also noted that individuals recovered uneventfully (Peden et al., 1981). A 1983 study reviewed 318 psilocybin-related cases that had been reported to poison control centers in the U.S. and found no evidence of serious toxicity (Francis and Murray, 1983). Since then, only one additional case has been reported. It involved a young man with arrhythmias and a myocardial infarction, but because the individual also had underlying congenital heart disease (Wolff–Parkinson–White syndrome), causality is impossible to determine (Borowiak et al., 1998). It seems probable that any deaths that occur in association with psilocybin use are likely to be accidental, a result of drug-induced confusion. In times of shortage, dealers may misrepresent LSD or PCP as psilocybin, producing a puzzling picture that can only be clarified with extensive toxicological testing.

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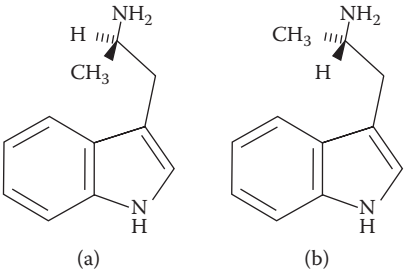

Figure 4.7.1 α-Ethyltryptamine molecule.

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4.7 α-Ethyltryptamine

Also known as Etryptamine and Monase, α-ethyltryptamine was first marketed in 1961 as an antidepressant under the brand name Monase®. It is classified as a reversible MAO-A inhibitor (Fredriksson et al., 2000), but it also causes neuronal 5-HT release (Dulawa et al., 1998). Clinically unconfirmed laboratory studies have shown that α-ethyltryptamine can produce MDMA-like effects, in spite of the very substantial differences in molecular structure (Glennon, 1993).

Although it was apparently an effective antidepressant, α-ethyltryptamine was withdrawn from the market when evidence of neurotoxicity was detected. Illicit use, or at least toxicity resulting from illicit use, is extraordinarily rare. The literature contains one case report describing a 19-year-old woman who took two tablets of what she thought was MDMA. Within a few hours, she became disoriented, vomited, and collapsed. The principal autopsy findings were pulmonary edema and terminal aspiration. Epicardial petechiae were noted but almost certainly were the result of attempted resuscitation. The only drug detected was α-ethyltryptamine. The concentration in heart blood was 5.6 mg/L, with 2.4 mg/L in the vitreous, 18.3 mg/L in the liver, 24 mg/L in the kidneys, and 22 mg/L in bile (Morano et al., 1993). A second report describes a patient with a suicidal overdose. The quantity ingested was believed to be approximately 700 mg. The cause of death was malignant hyperthermia, and the postmortem blood concentration was 1.1 mg/L (Daldrup et al., 1986).

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4.8 Ergolines

The structural skeleton of ergoline is contained in many different alkaloids including the psychedelic LSD. Ergoline derivatives, such as ergotamine, are used clinically to cause vasoconstriction by interacting with the type 1 5-HT receptor. Drugs in this group are used to treat migraine and sometimes Parkinson's disease. However, the most important ergoline is LSD. The precursors needed to produce LSD are controlled by the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. There are three main classes of ergoline derivatives; LSD belongs to the first group of water-soluble ergolines, namely the amides of lysergic acid.

4.8.1 Lysergic Acid Diethylamide

4.8.1.1 Introduction

Lysergic acid diethylamide 25 (LSD-25, or 9,10-didehydro-*N,N*-diethyl-6-methyl ergoline-8β-carboxamide) belongs to the family of alkaloids. The term *ergot* refers to a fungal disease that affects both wild and cultivated grasses. Infection with one of the *Claviceps* species leads to the formation of hard, seed-like nodules instead of the normal seeds produced by the plants. In the Middle Ages these nodules were referred to as "ergots," but they are properly referred to as sclerotia. Contained within the sclerotia is a group of indole alkaloids, collectively known as ergot alkaloids. Ergotism is a disease now rarely encountered that results from ingestion of the sclerotia or the chronic use of ergotamine-containing medications. The main symptom is intense vasospasm (Zavaleta et al., 2001). The most important of the alkaloids is *d*-lysergic acid. LSD is just one of many *d*-lysergic acid derivatives. The hallucinogenic agent lysergic acid amide, found in the morning glory (*Ipomoea violacea*), is another. All of the ergot alkaloids act, with varying degrees of specificity, at α-adrenergic, dopaminergic, and serotonergic receptor sites (Dewick, 1998).

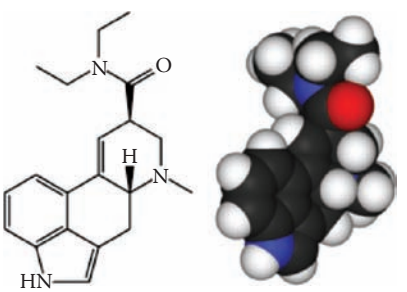

Figure 4.8.1.1.1 LSD molecule.

4.8.1.2 History

Albert Hoffman synthesized LSD in 1938. He was then working as a research chemist in the laboratory of Sandoz Pharmaceuticals in Basel, Switzerland. He was working on the chemistry of the ergot alkaloids. He had already isolated lysergic acid from ergot and was in the process of combining it with various amides via peptide linkages. Hoffman's goal was to synthesize new compounds that lacked the toxic side effects of ergot but which still might have positive effects on the circulation. He succeeded in that goal when he synthesized Methergine® (methylergonovine), which is still used today to control postpartum hemorrhage. During the course of his experiments, Hoffman had synthesized a series of compounds related to lysergic acid. The 25th compound that he produced was lysergic acid diethylamide, now known as LSD-25.

When Hoffman first tested LSD-25 on animals, the results were disappointing, and he did no further research with LSD-25 for five years. However, in April of 1943, he began working with it again. He accidentally ingested some, and that accident led to the dawn of the modern "psychedelic" age (Hoffman, 1984; Ulrich and Patten, 1991). Sandoz eventually did market LSD as a product called Delysid®. Psychiatrists were told to try it themselves, and they found out first-hand what the subjective experiences of a schizophrenic would be like!

LSD was never a commercial success, but its availability fostered research into the chemical origins of mental illness. None of the theories proposed during the 1950s and 1960s proved to be correct, but they did lead to more modern research into the neurochemistry of schizophrenia (current theory favors a disruption in dopamine metabolism with induction of a hyperdopaminergic state) (Seeman et al., 2005). The theories also led to some rather bizarre experiments by the Central Intelligence Agency (CIA), which had became interested in the field of mind control. In pursuit of this end, the CIA mounted a special operation called MK-ULTRA. Prostitutes were used to lure businessmen to brothels, where they were surreptitiously dosed with LSD and their behavior observed. Although

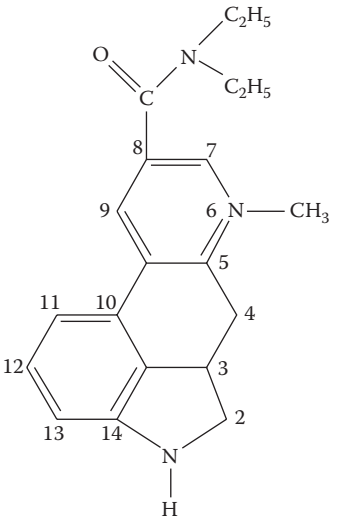

Figure 4.8.1.2.1 LSD-25. LSD-25 was produced by Albert Hoffman at Sandoz Laboratories. He had isolated lysergic acid from ergot, and was trying to make a chemical agent that would act as a circulatory stimulant. LSD-25 was the 25th compound that he produced.

all the data about this episode are yet to be disclosed, it appears that no useful new information was generated, and the experiments were abandoned.

The psychedelic age began in the early 1960s when the late Timothy Leary, then a professor at Harvard, undertook his research with psilocybin. He eventually began to experiment with LSD, and was so transformed by his experiences that he stopped experimenting with psilocybin in order to concentrate on the effects of LSD. He gave LSD to some of his students, which resulted in his being forced to leave Harvard in 1962. However, even before he was fired from Harvard, Leary's anthem — "Tune in, turn on, drop out"— had been adopted by the media, and the psychedelic age was launched.

LSD became a scheduled drug in 1965, and at nearly the same time some dubious, unconfirmed studies were published purporting to show that LSD led to chromosomal damage. Decreased availability and fears about toxicity led to a rapid decline in use (Ulrich and Patten, 1991). In the late 1990s, interest in LSD seemed to renew, although reports of toxicity continued to remain extremely rare. The Emergency Room component of the DAWN report contains 2096 LSD mentions during the first half of the year 2000. The rate of use would seem to be declining: the Emergency Room component of the DAWN report for 2004 (the most recent available) contains only 1953 LSD mentions for the whole year, roughly half the rate reported in 2000 (Ball and Albright, 2006). Estimating the true frequency of use is no easy matter. Even when large doses of LSD are taken, the drug is difficult to detect. The standard dose of LSD today is much lower than during the psychedelic era, and only very small amounts of LSD appear in the urine (concentrations rarely exceed 2–3 ng/mL). Because LSD is not included on standard immunoassay screening panels, use estimates must rely on self-reporting, a notoriously unreliable methodology.

4.8.1.3 Incidence and Epidemiology

No LSD-related deaths were listed in the Medical Examiner component of the most recent DAWN report (Kissin et al., 2000), and it appears that there have been none in the U.S. since the first report was published. The only other death to be reported was from Europe, in a polydrug abuser.

4.8.1.4 Illicit Production

Production of LSD demands considerably more skill than that required for methamphetamine, but it can be made in small, clandestine laboratories. Synthesis is possible from any one of a number of lysergic acid derivatives, including morning glory seeds or synthetic lysergic acid. Detailed instructions on how to harvest and grow ergot (*Claviceps purpurea*) can be downloaded from the Internet. The synthetic process involves potentially explosive solvents, and the investigation of possible clandestine LSD laboratories is a practice best left to individuals with specific training.

Only the *d*-isomer of LSD is psychoactive, but it undergoes isomerization at the C8 position. At equilibrium, 90% will be in the *d*- form and 10% will be present as iso-LSD (Salamone et al., 1997); iso-LSD is usually found as a contaminant in clandestinely produced LSD. Also, because *d*-LSD is almost completely metabolized, urine may contain more iso-LSD than *d*-LSD. Once synthesized, the standard practice is to add the LSD to absorbent blotter paper and then divide the paper into small squares, with each square constituting an individual dose. The average LSD content per square, in the year 2000, was between 20 and 80 mg (Nelson and Foltz, 1992). A recurring urban myth has it that

Figure 4.8.1.4.1 "Blotter acid." This means of distribution is not as popular as it was in the past. Blotter paper is soaked in an LSD-containing solution. The problem with this approach is that the LSD will migrate to the edges, so consumers who purchase tabs from the middle of the paper get too little, and those who purchase the edges get too much. (From the website of the DEA.)

children may be exposed to LSD when they apply water-soluble tattoos that are handed out at Halloween. In fact, such episodes of poisoning have never been documented.

4.8.1.5 Metabolism

Absorption is rapid and complete, and the drug is extensively metabolized in the liver (Lim et al., 1988) with only very small amounts ever appearing in the urine. Humans produce at least five different metabolites formed after initial dealkylation. These include *N*-demethyl LSD (which is sometimes referred to as nor-LSD), nor-iso-LSD, and lysergic acid ethylamide. An alternative pathway involves oxidation and hydroxylation, leading to the formation of 2-oxo-3-hydroxy-LSD, trioxylated-LSD, lysergic acid ethyl-2-hydroxyethylamine, 13- and 14-hydroxy-LSD and their glucuronide conjugates. Experiments in animals have disclosed other metabolites as well, but it appears that man does not produce them. Concentrations of the main metabolite, O-H-LSD, in urine are much higher than in plasma, and analysis for this compound can widen the window of detection (which should be on the order of 40 hours) substantially (Canezin et al., 2001).

4.8.1.6 Blood and Tissue Concentrations

In the only recent study where substantial doses of LSD were given to volunteers (4 mg/kg), plasma concentrations of LSD peaked at just under 0.8 ng/mL approximately 1 hour after administration, then fell to zero after 24 hours (Reuschel et al., 1999). In one study of 14 emergency room patients with suspected LSD intoxication, plasma LSD concentrations, measured between 2 and 11 hours after ingestion, ranged from 0.2 to 7.7 ng/mL (McCarron et al., 1990). In a more recent study of two symptomatic patients seeking emergency room treatment, 4 hours after ingestion, one patient had urine LSD and iso-LSD concentrations of 1.3 µg/L and 0.82 µg/L, respectively. In plasma they were 0.31 and 0.27 µg/L. Samples were taken 11 hours after ingestion in the second patient and the corresponding values

were 0.24 μg/L and 0.6 μg/L in, but plasma concentrations were not reported (Canezin et al., 2001). One postmortem study has been published (Favretto et al., 2006).

4.8.1.7 Testing

Because urine concentration approaches zero at 24 hours, detection was problematic in the past. Newer analytic techniques have markedly increased testing sensitivity and this problem has been largely overcome. There now exist methods, using as little as 0.5 mL of urine, that allow for the simultaneous determination of ecgonine methyl ester, benzoylecgonine, morphine, codeine, 6-acetylmorphine, amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and *d*-lysergic acid diethylamide (LSD). The technique uses liquid chromatography with tandem mass spectrometry, after solid-phase extraction in the presence of their deuterated analogs (Concheiro et al., 2007).

4.8.1.8 Clinical Syndromes

LSD and mescaline (a different class of hallucinogen) share a common mechanism of action in that their ability to cause hallucinations correlates directly with their ability to bind to 5-HT2 receptors (Aghajanian and Marek, 2000). Changes in pulse rate, respiration, and blood pressure occur, but these may just be secondary to anxiety induced by perceptual changes (Klepfisz and Racy, 1973). Panic attacks are said to be relatively common, but frank psychotic episodes are not (Blaho et al., 1997). "Acid flashbacks," though widely publicized, also appear to be uncommon. When formal neuropsychological testing is performed, few, if any, sequelae can be attributed to LSD use (or to the use of any other hallucinogen, for that matter) (Halpern and Pope, 2003).

In the past LSD was almost exclusively sold impregnated in blotter paper, but pills and tablets are more likely to be seen today. The likelihood of massive overdose is small, although adulteration with other drugs may lead to confusing symptoms. Massive LSD overdose results in vomiting and collapse along with signs of sympathetic overactivity, hyperthermia, coma, and respiratory arrest. Hyperthermia and mild generalized bleeding may also occur due to platelet dysfunction (Klock et al., 1975). Hyperthermia has been reported in other LSD users who have not taken massive doses (Bakheit et al., 1990).

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Opiates and Opioids

5

5.1 Incidence

The last complete report issued by the Drug Abuse Warning Network (DAWN) listed 8295 narcotic analgesic-related deaths as having occurred in 1999, amounting to a 49% increase from the 3403 narcotic-related deaths reported in 1990 (Kissin et al., 2000). In 2003 DAWN methodology was radically altered, so that the U.S. government no longer provides meaningful statistics on the consequences of drug abuse. Still, two trends seem to be emerging: heroin toxicity continues to account for thousands of narcotic-related deaths every year, and the illicit supply of high-quality heroin (and other synthetic narcotics) is increasing at an astonishing rate. Epidemiologic data compiled separately from DAWN demonstrate that between 1999 and 2002 the number of deaths due to poisoning from opioid analgesics, surpassed the number of deaths attributable to heroin and cocaine (Paulozzi et al., 2006). Nearly half of the opioid deaths and much of the morbidity were attributable to semisynthetic drugs such as oxycodone and hydrocodone, although mentions of heroin still remain 10 times more common than deaths from the synthetics, and these continue to rise (Anon., 2005). Approximately one third of the deaths reported in 2006 were due to methadone, and 13% from other synthetic opioids such as fentanyl (Compton and Volkow, 2006). In 1999, nearly 5000 deaths per year were being reported to the old version of DAWN. That number is unlikely to be lower now than it was in the past. Given the developments in Southwest Asia, the number is likely to rise drastically, if not in the U.S., then in Europe.

Table 5.1.1 Deaths from Narcotic Analgesics in the 1999 DAWN Report

Drug	Number of Mentions	Percentage of Mentions
Heroin/morphine	4820	41.4
Codeine	1395	12.0
Methadone	643	5.5
D-propoxyphene	466	4.0
Hydrocodone	447	3.8
Meperidine	103	0.9
Fentanyl	53	0.5
Hydromorphone	46	0.4
Oxymorphones	15	0.3

Note: A total of 17,898 drug-related deaths were reported in the DAWN survey for 1993. Of these, 3556 (19.8%) were due to cocaine and 3470 (19.3%) were due to heroin.

5.2 Epidemiology

In 2005 the U.S. National Survey on Drug Use and Health (NSDUH) estimated that 108,000 persons aged 12 or older had used heroin for the first time in the preceding 12 months. The average age at first use among recent initiates aged 12–49 was 22.2 years. There were no significant changes in the number of initiates or in the average age at first use from 2002 to 2005. Only one in seven youths aged 12–17 (14.0%) said that heroin would be "fairly" or "very" easily available. Estimates for 2005 were similar to estimates for 2003 and 2004. The average age of first use initiates was 24.4 years, unchanged since 2002 (Anon., 2006).

5.3 Classifying Narcotic and Non-Narcotic Agents

There are several ways to classify opiates. Earlier schemes grouped them according to their origins: naturally occurring opiates such as morphine or codeine; morphine-based semi-synthetic opiates (heroin or hydromorphone); thebaine-based (one of the components of opium) opiates such as oxymorphone or oxycodone; and purely synthetic opiates such as meperidine or pentazocine (Inturrisi, 1982). This type of classification offers little help in understanding mechanisms of opiate toxicity.

Alternatively, these drugs can be divided into two classes: opiates and opioids. The term *opiate* is reserved for peptide compounds derived from the morphine molecule. These drugs specifically bind to opioid receptors. The term *opioid* is used to describe any non-peptide agent that can also bind at the opiate receptor site. Members of this class include morphinans, typified by butorphanol, the benzomorphans such as pentazocine, the 3,5-diphenylamines including methadone, phenylpiperidines, and, especially, meperidine. Knowledge of receptor binding patterns allows for the most accurate predictions about how a particular drug will behave within the body.

This section is organized around the various types of harm that may occur after exposure to any opiate family member. Implicitly, opiate toxicity can occur (1) as the direct effect of the opiate or opioid drug or its metabolites (meperidine and normeperidine for example), (2) or as a direct effect of adulterants or excipients injected along with the drug (α-methyl fentanyl to street heroin or cellulose from crushed pills that are injected), and (3) from infectious, mechanical, and lifestyle complications associated with intravenous drug abuse, such as tuberculosis, endocarditis, and hepatitis C.

5.3.1 Opiate Receptors

Endogenous pain-relieving molecules with structures similar to that of morphine are called endorphins or enkephalins. Exogenous opiates such as morphine, and endogenous pain-relieving molecules called enkephalins, bind to the same types of opioid receptors located throughout the body. Depending on which type of receptor is bound, the result may be, among other things, analgesia, dysphoria, or respiratory depression.

Human opiate receptors have been cloned, expressed in tissue culture, and their behavior studied in "knockout" mice. The DNA sequences of these receptors, if not their exact mechanism of operation, are known, largely from work with mice bred to be missing (or contain exaggerated amounts of) parts or all of a given receptor. One especially important consequence of this method is that receptors can now be identified and counted, even in

postmortem material (Gabilondo et al., 1994; Wehner et al., 2000; Schmidt, 2001). These advances have yet to bring about any significant change in the way that drug-related deaths are investigated, largely because medical examiners are ill equipped to do the testing, and adoption of these methods will be slow.

It was once believed there were at least five types of opiate receptor, but now only three are recognized: μ (mu), κ (kappa), and δ (delta). The three receptors are approximately 70% homologous, meaning that their structures have in common 70% of their amino acids. Differences between receptors occur mainly at the N and C terminal ends. Morphine and all of the clinically significant opiates exert their effect at the μ receptor. Opiate receptors are connected to a long chain of amino acids folded in such a way that they loop in and out of the cell membrane. The chain connects to a receptor sitting on the outer cell surface; opiate receptors (and many others, such as adrenergic receptors) cross the cell membrane seven times and thus are described as having seven transmembrane domains (Chazot and Strange, 1992). No matter whether morphine or oxycodone or fentanyl binds with a μ receptor, the seven transmembrane unit becomes activated. Once that occurs a signaling cascade is initiated (also called second messenger pathways) and effector proteins activated, but only for as long as the opiate, or other ligand, remains connected to the receptor.

The genes that determine the shape and configuration of the different receptor subtypes are located on different chromosomes. Two μ, three δ, and two κ subtypes are currently recognized. It is assumed that these receptors arise from post-translational modifications (i.e., they arise at a late stage in protein synthesis, not in the germ cell), because their genes have not been identified. A purported fourth opiate receptor, referred to as the σ (sigma) receptor, is now recognized as a completely unrelated entity (Bodnar and Klein, 2005). The μ receptor is usually located on the presynaptic side of the synapse. These are mainly located in the periaqueductal gray region of the brain. High densities of μ receptors are also found in the superficial dorsal horn of the spinal cord. Other areas rich in μ receptors include the external plexiform layer of the olfactory bulb, the nucleus accumbens (an area deeply implicated in the process of addiction), some parts of the cerebral cortex, and some of the nuclei of the amygdala (Herz and Millan, 1990). Mu receptors avidly bind enkephalins and beta-endorphin as well as morphine.

Morphine makes pupils constrict because it excites the parasympathetic nerves supplying the pupil. Opiates cause respiratory depression because they activate μ receptors in brain stem respiratory centers. When μ receptors in the respiratory center are stimulated, they become less responsive to carbon dioxide; respiration is decreased, and may even stop. At the same time, μ stimulation also depresses respiratory centers located in the pons, further inhibiting the respiratory drive.

Suppression of respiratory drive accounts for the mechanism of death in most instances of opiate overdose. Some of morphine's other side effects, such as nausea and vomiting, are also the result of μ receptor stimulation, but these receptors are located in the chemoreceptor vomiting trigger zone of the medulla. Morphine, or compounds that bind the μ receptor, are also used to treat diarrhea. Both morphine and heroin (which is rapidly converted to morphine once within the body) are both powerful cough suppressants (Todaka et al., 2000). Indeed, heroin (Figure 5.3.1.1) was originally sold by Bayer as a cough suppressant (Karch, 1989).

Dynorphin is one of a class of peptides produced by many different types of neurons. It is classed as an endogenous opioid peptide. Dynorphin functions primarily as a κ opioid

Figure 5.3.1.1 Heroin was first marketed as a cough suppressant and recommended for the treatment of tuberculosis. Bayer began selling heroin in 1898. The name heroin derives from the German word for "great" or "heroic." (Courtesy of the National Library of Medicine.)

receptor agonist, meaning that it acts mainly at κ opioid receptors. Other opioid peptides include beta-endorphin, [met]-enkephalin, [leu]-enkephalin, and endomorphin. The dynorphins, which include dynorphin A, dynorphin B, alpha- and beta-neoendorphin, and "big dynorphin," are all the products of a single gene, "preprodynorphin" (Morley, 1997).

5.3.2 Opiates and G-Coupled Proteins

G-coupled proteins are special proteins associated with opiate receptors. It appears that their main purpose is sending signals within cells. Disruption of this signaling system can lead to disease (diabetes is a good example). GTP is the guanosine analog of ATP. When a signal (such as morphine binding to a cell wall receptor) reaches a G protein, the protein exchanges GDP for GTP causing some specific action within the cell to occur. Another type of G protein, known as "small G protein," is believed to regulate many activities within the cell (i.e., control the cell components such as the endoplasmic reticulum and Golgi apparatus). Still a third set of G proteins connects the receptors directly to ion channels. In total, the family of G proteins is believed to relay signals from more than 1000 different receptors and, indirectly, control the activity of ion channels and even enzymes.

The portions of receptors that pierce the cell membrane are referred to as helices. Different types of receptors penetrate the outer membrane different numbers of times. As a rule, most of the compounds involved in the process of addiction (and the pathologic changes that result from them) involve the seven transmembrane domains mentioned earlier. The list of compounds includes epinephrine, glucagon, 5-HT (serotonin), vasopressin, ACTH, and adenosine, among many others. In general, small ligands bind to the amino acid residues in the membrane, whereas large polypeptide and protein ligands bind to the

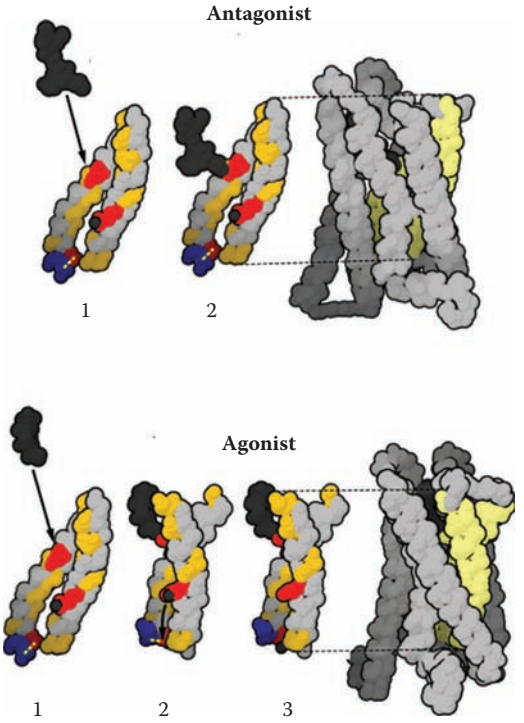

Figure 5.3.2.1 Morphine receptor and mechanism of agonist and antagonist binding. (From Wikipedia.)

extracellular domains, which are much larger in size and better able to combine with large protein molecules.

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5.4 History of Opiate Abuse

5.4.1 Origins in Antiquity

Drawings of opium poppies antedate any written mentions in the Greek literature by at least 1000 years (Kritikos and Papadaski, 1967). Homer and Hesiod discussed the medicinal merits of poppies, and writings from the classical period frequently dwell on the same subject. In Greece, the poppy was called *opion*, a term derived from the word for "juice" (*opos*). When translated into Latin, *opion* becomes opium. For the ancients, the poppy symbolized sleep, occasionally everlasting. The cup given to Socrates contained the standard solution used at the time for euthanasia and suicide: a mixture of hemlock and opium. Opium was known but used sparingly in Europe during the Middle Ages, possibly because medieval surgeons seemed to have been largely indifferent to the suffering of their patients (Kramer, 1979).

5.4.2 Introduction to Europe and Asia

Opium's popularity increased during the Renaissance. Much of the popularity had to do with the success of the efforts made by Philippus Theophrastus Aureolus Bombastus von Hohenheim, a.k.a. Paracelsus (1493–1541). Paracelsus recognized that no matter what the cause of a disease, sleep and pain relief were part of the cure. Following that precept, Paracelsus medicated his patients with formulas that contained opium. He prescribed opium in a host of different formulations, calling one of them "laudanum" (from the Latin for "something to be praised"). Laudanum was comprised of one fourth opium, to which was added henbane juice, crushed pearls, and coral, "bone of the heart of a stag, bozar stone, amber, musk, and essential oils." Paracelsus also used opium in combination with orange and lemon juice, frog sperm, cinnamon, cloves, ambergris, and saffron (Macht, 1916).

More streamlined versions of laudanum were used well into the 19th century (Lewin, 1931). In the same way that Freud later enthusiastically recommended cocaine as a wonder drug (Freud, 1884), Sydenham (1624–1689) argued that opium was the drug of choice for a range of conditions, not all of them painful (Sydenham, 1848). Thomas Dover, a ship's doctor and one of Sydenham's students, will go down in history for two different and unrelated

reasons: he rescued the real Robinson Crusoe, and he created a powdered opium formulation that became an immensely popular home remedy. Dover's Powder was still being sold in stores in the early 1900s. These developments may explain why medical writers began discussing the issue of opiate toxicity in the early 1700s.

In their groundbreaking book on addiction, Terry and Pellens (1928) quote a naïve English physician who claimed to have separated opium's "noxious Quality" from its "palliative" and "curative" actions, thus avoiding the complications associated with excessive opium use. Physicians over-relied on opium because it was one of the few drugs they could prescribe that worked; it relieved pain, calmed the stomach, and suppressed coughs. Until the 20th century, few other drugs were as effective. Because opium was widely available and widely used, it was inevitable that many people would become addicted (Haller, 1989).

In 1803 Sertürner began experimenting with opium, trying to separate its active components. In 1805, he published a report announcing that he had isolated an alkaline base in opium called *morphium*. He continued his research on *morphium* for many years, frequently using himself as a subject; at one point he nearly died of an overdose. His discovery of morphine had vital clinical importance (Weiser, 1956), but it also marked a sea change in the way researchers thought about the chemicals contained in plants and the way in which they worked. Prior to the discovery of morphine, there was universal belief that plants could only synthesize products that were acid or, at most, neutral. It was believed that only metallic compounds could be alkaline. Sertürner's discovery changed that. In relatively rapid succession, hundreds of other potent plant alkaloids, including quinine and cocaine, were isolated (Macht, 1916). Commercial morphine production began not long after morphine was first isolated. The founder of England's Royal Pharmaceutical Society, Thomas Morson, started refining and selling morphine in 1821. Shortly after, the great pharmaceutical company, Merck of Darmstad, began wholesale production (Berridge, 1987).

Addiction and abuse were major problems by the dawn of the 19th century, although there is some evidence to suggest that morphine addiction (as opposed to opium eating) may not have been all that widespread (Karmer, 1979). Patent medications such as Dover's Powder and other "cordials," "carminatives," or "soothing syrups" were nothing more than tincture of opium combined with flavorings and ample amounts of alcohol. Case reports describing "morphia" toxicity began to be published with some regularity by the late 1830s. The best-known addict of that period was De Quincy. He had first used opium to treat a toothache, but he rapidly developed a formidable habit. At one point, he was consuming more than 20 grams (not grains) per day (De Quincy, 1821). While he was only one of many addicts to be found within London's artistic community, he was the most vocal advocate for opium, having written, among other things, "happiness might now be bought for a penny, and carried in the waistcoat pocket." De Quincy's *Confessions of an English Opium Eater* was first published in 1821, and a revised, considerably expanded, second edition was published in 1856. That same year, Elizabeth Barrett Browning published her acclaimed narrative poem, *Aurora Leigh*. Although Browning was also addicted, and the poem was highly autobiographical, she never argued that much good came from the habit (Bishop, 1994). This probably explains why De Quincy's name is synonymous with drug use and Browning's is not.

Arab traders introduced opium into China during the Tang Dynasty (618–907 A.D.). At first, the Chinese used opium only for medicinal purposes. The *Pen Tsao Kang Mu*, a

materia medica published in 1590, nearly 1000 years after opium was first introduced into China, makes absolutely no mention of addiction or abuse (Way, 1982). Opium was only taken orally, and then only for treatment of pain and diarrhea. Opium smoking, which probably originated in Java, began nearly a millennium later. The first mentions of opium smoking in China are from the 16th century, occurring at just about the same time that the Portuguese were introducing tobacco to the Chinese.

Over the next two centuries, the popularity of opium smoking steadily increased. In 1880, for reasons having more to do with a balance of trade deficit than any concerns with abuse, Emperor Chin Ching banned opium importation. The East India Company ignored the ban and continued to smuggle large amounts of opium into China. In 1839, the Chinese government finally decided to take active measures against opium importation. The measures prompted England to declare a war that China quickly lost. Customs figures from 1881 show that opium imports into China were in excess of 6 million kg per year, enough to supply 1 million smokers. In spite of numerous conventions and treaties, addiction remained a major problem in China until Mao Tse-tung suppressed the habit in the early 1960s.

Striking historical parallels in the evolution of opium and cocaine abuse are apparent. Thousands of years of coca leaf chewing in South America caused few social and no detectable medical problems for the Incas. However, as soon as purified cocaine became widely available in Europe, the amount of cocaine used increased greatly. As the amount used increased, so did toxicity (Karch, 1989). Taking small amounts of opium orally was medically effective and, at worst, a benign indulgence. Much of orally administered opium is inactivated on its first pass through the liver, so this route of ingestion has some built-in safeguards. Smoking opium is another matter entirely. When smoked, much more morphine gets into the body, blood levels rise more quickly, and no "first-pass" effect occurs. The net result is that when opium is smoked, the dosage is effectively multiplied. Not surprisingly, serious toxicity and addiction result.

Chinese laborers are said to have introduced opium smoking into the U.S., but opium was already popular in America long before the Chinese immigration. In 1844, the New York City coroner held six inquests regarding opium-related deaths, and 23 inquests on deaths related to laudanum (Woodman and Tidy, 1877). According to U.S. Government figures, over 5 million tons of opium were imported into the U.S. from 1850 to 1877. This figure does not take into account opium smuggled in to avoid taxation, or any of the opium cultivated domestically. Opium was produced in California, Arizona, and the New England states (Brecher, 1972). Like their European counterparts, American physicians would have been unable to practice without opium. A survey done in Boston in 1888 disclosed that of 10,000 prescriptions dispensed by 35 pharmacies, 15% contained opium and 78% contained opiates (Brecher, 1972). Whatever the problems associated with opium abuse, they very likely would have been manageable had the hypodermic syringe not become available in the 1870s, and had heroin not been introduced at the turn of the century.

5.4.3 Invention of the Hypodermic Syringe

In 1855 a Scottish physician, Alexander Wood, published an account of his experiments injecting humans with opium (Brecher, 1972). He injected tincture of opium, and although his original intent was to achieve something akin to a nerve block, he quickly realized that injected morphine was carried throughout the body. In the course of his experiments, Wood also managed to addict his wife to intramuscular morphine. She probably was the first woman to die of an injected narcotic overdose (Terry and Pellens, 1928). Wood

may have received most of the credit, but the idea of injecting people with narcotics had been around for hundreds of years before Wood was born. Christopher Wren, the famous architect and professor of astronomy at Gresham College, Oxford, was also a physician. According to the history of the Royal Society, Wren injected dogs with intravenous opium in 1656. Using a quill attached to a small bladder, he injected lean animals with easily visible veins. No fatalities resulted. Wren was so encouraged by his preliminary studies that the following year he tried the same experiment on a man. An ambassador to the Court of St. James volunteered the services of a "delinquent servant." The volunteer was injected with an emetic, which made him faint. Other experiments were even less successful, and this area of research was ignored for nearly the next 100 years (Terry and Pellens, 1928).

Wood's publication prompted others to experiment with injecting many different drugs, but narcotics attracted the most interest, and narcotic injection soon became standard practice. Hypodermic syringes were said to have been in great demand and short supply during the U.S. Civil War (Figure 5.4.3.1) (Billings, 1905), although the shortage could not have been all that severe, as many of the veterans became addicts. Addiction was slower to evolve as a problem in America than in Europe, but by the 1870s "morphinism" was rampant in both the Old and New Worlds. The lag time may have been partially due to the fact that hypodermic injection did not catch on as quickly in the U.S. as in Europe.

Even though addiction was common, neither the mechanism of opiate action nor the process of addiction was even remotely understood. It was widely thought, for instance, that using morphine injections, as opposed to "eating opium," minimized the probability of addiction (Anstie, 1868; Howard-Jones, 1972). Treatment modalities for addiction were simplistic to the extreme. Freud's paper *Über Coca*, published in 1884, reflects the thinking of many during that period. Because the effects of cocaine seemed to be so opposite to those of morphine, Freud concluded that cocaine would be a logical treatment for "morphinism." Some prominent physicians, including Erlenmeyer (1885) disagreed, but Freud's notions were widely accepted, and a large group of patients became addicted simultaneously to cocaine and morphine. It is only quite recently, since the discovery of opiate receptors and neurotransmitters, that rational approaches to narcotics addiction have been formulated.

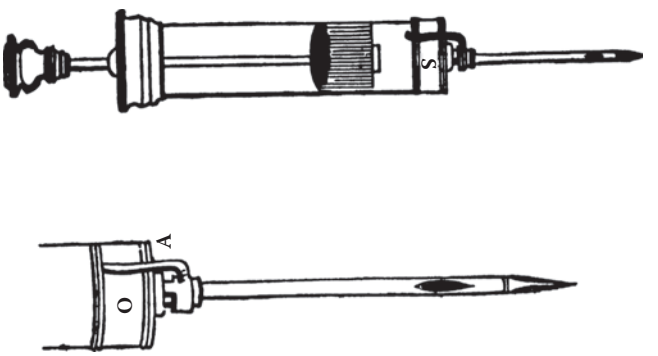

Figure 5.4.3.1 Hypodermic syringes. Commercial production of syringes began just before the Civil War. Initially, opiates were injected only subcutaneously. The intravenous injection of morphine and heroin did not become common practice until the 1920s. (Courtesy of the National Library of Medicine.)

5.4.4 Synthesis of Heroin

The other key development in the history of narcotic addiction was the synthesis of heroin. In 1874, C. R. Wright, a researcher at St. Mary's Hospital in London, boiled anhydrous morphine with acetic anhydride and produced a series of acetylated morphine derivatives (Eddy, 1953). One of the derivatives was diacetyl morphine (although the nomenclature was different at the time). He sent samples to an associate at Owens College, London, who assayed the substance for biological activity. The ability of the drug to decrease respiratory rate and blood pressure quickly became obvious. For reasons that are not clear, the discovery created very little interest. In 1898, Strube published a paper outlining his favorable results when he had used heroin to treat patients with tuberculosis. He found that the drug effectively relieved severe coughs and allowed patients to sleep. Perhaps more important, he claimed to have observed no ill effects (Strube, 1898). The Bayer Company in Eberfeld, Germany, began commercial production of heroin in 1898 (Figure 5.3.1.1).

Bayer had been in the business of making pharmaceuticals since 1889, but not exactly making great sums of money. The situation changed almost overnight when they began to supply the really profitable market for alkaloids (morphine, quinine, cocaine). Previously this market been dominated by other, larger companies such as Merck, Knoll, and Boehringer. Bayer's lead chemist, Felix Hoffman, synthesized heroin on August 21, 1897, just two weeks after he produced aspirin! Bayer pharmacologists began experimenting with both codeine and heroin, carrying out a number of tests on themselves, animals, and their employees. The Bayer chemists concluded, quite mistakenly, that heroin produced less respiratory depression than codeine (in fact, codeine only has any activity as a pain reliever because it is metabolized to morphine, a heroin breakdown product). Based mainly on Strube's observations, Bayer began production, marketing heroin as a safer, more potent, cough suppressant (Figure 5.4.4.1) (deRidder, 1994).

Figure 5.4.4.1 "Mrs. Winslows Soothing Syrup for Children Teething." This product was popular before the passage of the Food and Drug Act of 1906. Infants cutting teeth generally are irritable, but not after a dose of morphine. It was also said to be very good for treating colic. (Courtesy of Dr. Michael Bozarth.)

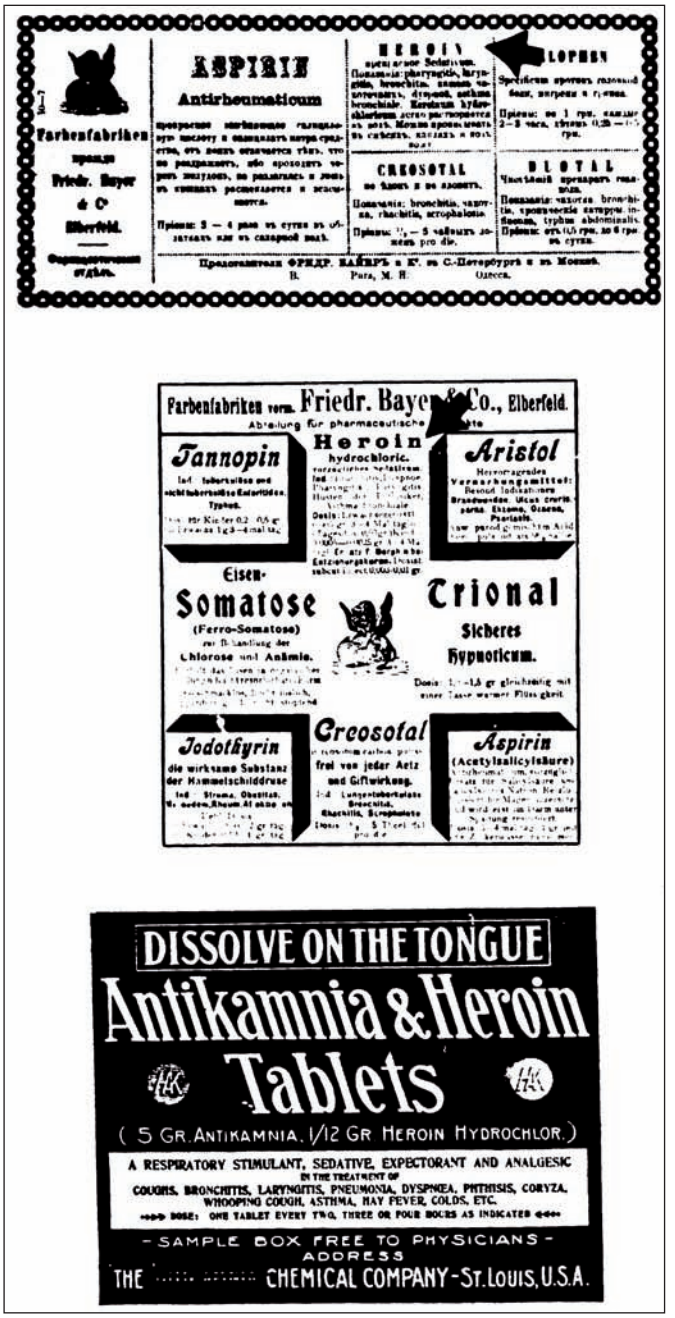

Figure 5.4.4.2 Heroin. Because of their effectiveness, heroin and heroin-containing products were not difficult to market. Many different formulations were sold in Europe and in the U.S. (From Kritikos, P. and Papadaki, S., *Bull. Narc.*, 19(4), 5–10, 1967.)

Whatever the medical profession believed about heroin, the underground warmly received it. By 1920, heroin addiction was such a problem that the American Medical Association's (AMA) House of Delegates voted to prohibit heroin importation, manufacture, and sale. Legitimate heroin production in the U.S. ceased after 1924, although low levels

of illegal imports persisted. Interestingly, it seems that no one thought to inject heroin intravenously until the early 1920s. The dating is suggested by the fact that the first report describing typical track marks was not published until 1929 (Biggam, 1929). The outlawing of production, along with international treaties and conventions, but most especially the advent of World War II, led to sharp reductions in clandestine imports. In 1950, fewer than 40 heroin seizures were reported within the U.S.

Interest in heroin resurfaced with the advent of the Vietnam War but was temporarily eclipsed by the medical community's general disinterest in sedative hypnotics and the superimposed cocaine pandemic. Heroin use, at least when judged by the amount of illicit heroin now being confiscated, is again increasing, and at a very rapid rate. In 1990, narcotic analgesics accounted for 57% of all reported drug-related deaths, with 1976 of the deaths directly attributable to heroin abuse. By 1998, the total number of deaths attributable to analgesic abuse had risen to 7259, with 4330 attributable to heroin alone (Kissin et al., 2000). One can only speculate about the situation today, but Afghanistan is now producing more heroin than at any time in the history of the world.

5.4.5 The First Pathology Studies

The first autopsy demonstrating both cerebral and pulmonary congestion (the classic hallmarks of narcotic overdose) was that of a New Yorker who died of laudanum poisoning. A Dr. Lee, first name unknown, described the case in 1852 (Woodman and Tidy, 1877). The autopsy findings in a second case of narcotic overdose were described in a later paper published in 1862. A young woman drank "gin mixed with a shilling's worth of laudanum." She quickly became comatose and intense meiosis was noted. Autopsy disclosed cerebral congestion; however, the lungs were said to be unremarkable (Slayter, 1862). A forensics text from 1877 mentions that "congestion of the lungs and of the vessels of the brain" are typically seen in opiate-related deaths but cautioned that that particular finding at autopsy was "neither certain nor characteristic" (Woodman and Tidy, 1877). Understanding of the problem advanced very little until Helpern and Rho published their paper "Deaths from Narcotism: Incidence, Circumstances, and Postmortem Findings" in 1966. In addition to carefully describing the epidemiology of the addiction, the authors systematically described all of the signs that have come to be classically associated with narcotism, including pulmonary edema, portal adenopathy, and track marks. During the years since their publication, opiate receptors have been discovered, and other disorders such as heroin-associated nephropathy (Rao et al., 1974), and leukoencephalopathy (Wolters et al., 1982) have been described. Nonetheless, our basic understanding of the pathologic changes produced by narcotic abuse has advanced very little.

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5.5 Cultivation and Manufacture

5.5.1 Botany

The Papaveraceae family is comprised of 42 genera and approximately 650 distinct species. Just how they should be divided is a matter of some dispute, and at least six different classification schemes have been proposed. *Papaver somniferum* is the most commonly cultivated "opium" poppy, but the wild growing *Papaver setigerum* also contains significant amounts of morphine. Over the years, many hybrids have been developed, but describing a generic "poppy" is difficult, if not impossible. Flowers may be single or double, with variation in both shape and color. Blossoms may be white, red, pink, purple, crimson, or one of the many shades in between. The capsules, from which the juice is extracted, also vary in shape and alkaloid content. A plant can have two, three, or more capsules. Height is also variable and may range from 30 to 150 cm or more (Kapoor, 1995).

The poppy is an annual plant, with a three- to five-month life cycle. This means that, even though the poppy can be cultivated almost anywhere, only one crop per year can be grown in areas with distinct hot and cold, or wet and dry seasons. Poppies cannot be grown in areas subject to frost. The more moderate climate to be found in many parts of Latin America permits year-round cultivation, an advantage that has not gone unnoticed by heroin producers.

When grown in humid regions, the poppy is vulnerable to infection by fungal and plant parasites. Poppies grow well in average soil, but the soil requires treatment with manure or chemical fertilizers. Plants take two to three weeks to germinate and two months to fully develop. After a field has been weeded and thinned, as many as 15 plants can be grown in a square meter. After the plant flowers and the petals have fallen off, the capsule continues to

Figure 5.5.1.1 An incised poppy bulb. A sharp razor-like knife is used to incise the bulb, allowing the latex to leak out. Once it is dried, it is scraped off the bulb.

ripen for another two weeks, at which time the opium-containing latex can be harvested. The entire cycle takes less than three months.

Traditional harvesting is a two-step process. First the capsule is incised, allowing the sap to run out and then solidify. Twelve hours after the capsule has been incised the latex is harvested. Incising the capsule is a delicate operation: if the incision is too deep, the latex will run down the inside of the plant and be lost to harvest. Farmers prefer to do the incising at sunrise or sunset. That allows the latex to exude and solidify for 8–14 hours. The caked latex can then be scraped off the capsule using a dull blade; however, by the mid-1970s, traditional harvesting techniques had been largely replaced by the use of opium "straw," where instead of collecting resin from the sides of the capsule, the entire plant is dried and processed. As the number of fields planted has increased, there seems to have been a revision to older techniques, particularly in Afghanistan, which is now the world's principal opium producer.

The opium yield per acre depends on many variables. Historically, the yield in the Mediterranean is said to be 10 kg of opium per hectare. The most recent surveys show that yields in Afghanistan are just over 39 kg of opium per hectare.

Yields in the newer fields being established in South America and in the Central Asian republics have yet to be determined, but it seems likely that they are intermediate between the high yields reported from India and the much lower yields reported from the Mediterranean countries.

Over 20 different alkaloids have been identified in opium, but only three are of any significance: morphine, codeine, and thebaine. Thebaine has almost no morphine-like activity of its own, but it can be used to manufacture other narcotic agents. Hundreds of semi-synthetic derivatives, referred to as Bentley compounds, have been synthesized from thebaine, and many of these do have narcotic effects. A few of the derivatives, such as etorphine, have 1000 times the activity of morphine. The increasingly popular heroin substitute, buprenorphine, is also synthesized directly from thebaine (Elkader and Sproule, 2005). Morphine is the principal alkaloid found in opium. It constitutes between 8 and 19% of air-dried opium. Reported ranges for codeine content are from 1.25 to 3.4% (Anon., 1963). Poppy straw, depending on the country or origin, may have a morphine content of anywhere from 0.34 to 1.3%, mainly in the mature capsules of the plant and in the upper part of the stem (INCB, 1998).

Poppy seeds sold for cooking and baking purposes may contain very substantial amounts of morphine and codeine. In one study, the morphine content was found to be anywhere from 7.3 to 60.1 mg/g of seed, while the codeine content ranged from 6.1 to 29.8 mg/g (Pelders and Ros, 1996). Even commercial poppy-seed fillings, used to make pastries, have high alkaloid contents. Concentrations in the range of 17.4–18.6 mg/g (morphine) and 2.3–2.5 mg/g (codeine) have been reported in different lots of the filling. Urinary morphine concentrations as high as 4.5 μg/L have been reported after eating these fillings, and large amounts of morphine may persist in the urine for several days after ingestion (Mule and Casella, 1988). This has posed difficulties for workplace drug testing programs where urine is screened for morphine. The initial screening cutoff of 300 ng/mL was raised to 2000 ng/mL in the 1990s; however, recent studies show that even that cutoff is too low, given that the quantity of poppy seeds contained in two bagels will cause urine to test positive for more than 24 hours (Rohrig and Moore, 2003). One way to avoid this problem is to test for acetylcodeine, which is only found in opium, not poppy seeds. The problem is that this compound has a relatively short half-life (Trafkowski et al., 2006). The same holds true for 6-monocetylmorphine, a unique heroin metabolite; however, its window of detection is only on the matter of hours.

5.5.2 Opium Production

From the end of World War II until the late 1980s, opium production was confined to two primary areas: Southeast and Southwest Asia. Since then production and output have shifted in unpredictable ways from country to country. Production in Asia's notorious Golden Triangle, once the world's center for narcotic production, is decreasing and the area could very well become opium free in the next few years. But, at the same time, production in Afghanistan continues to increase at a frightening rate. According to the United Nations, in 2006 the estimated area devoted to illicit opium production was 151,500 hectares, with significant production limited to the three main sources: Afghanistan, Myanmar, and Lao People's Democratic Republic (Lao PDR, Laos). In fact, more land is now devoted to opium production in Afghanistan than is devoted to coca cultivation in South America. The United Nations Office on Drugs and Crime (UNODC, 2007) estimates that 94% of the world's opium production occurs in Afghanistan. This amount of heroin would have a net value of more than $4 billion, most of which ends up in the hands of corrupt officials and terrorist groups.

While Andean production of opium continues, it accounts for only a small part of the whole (UNODC, 2007). Today nearly all of the world's opium supply comes from Afghanistan, where opium production rose by 50% in 2006, bringing global heroin production to a record high of nearly 600 metric tons. According to U.N. estimates, nearly half that amount was interdicted, but that still leaves more than 300 tons of heroin available on the illicit market (UNODC, 2007). Increased production in Afghanistan has gone hand-in-hand with decreased output from other producing areas. Poppy cultivation in Southeast Asia is down by more than 85% over the last decade. Between 2005 and 2006 alone, poppy cultivation in Southeast Asia declined from 35,000 hectares to 24,000 hectares.

Three distinct flows of opium/heroin trafficking can be identified: (1) from Afghanistan to neighboring countries, including the Middle East and Europe; (2) from Myanmar/

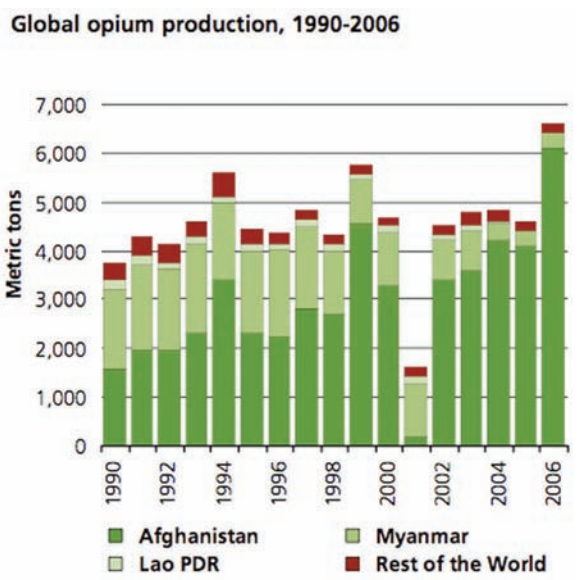

Figure 5.5.2.1 Worldwide opium production. This graph is taken from the United Nation's annual drug report. It shows trends in global opium/heroin production by country since 1990.

Laos to neighboring countries of Southeast Asia (most notably China), and to Australia and New Zealand; and (3) from Latin America (Mexico, Colombia, and Peru) to the U.S. The bulk of global opiate seizures (heroin, morphine, and opium, expressed in heroin equivalents) occur in Southwest and Central Asia, in the countries immediately surrounding Afghanistan, where more than 60% of all seizures occur. Europe accounts for another 25% of global seizures. Heroin seizures made in the U.S. account for only 4% of the global total. While there is some opiate trafficking from Southeast Asia to North America and Europe, and from Southwest Asia to Southeast Asia (notably China) and to North America, it is the feeling of the U.N. that these amounts, when compared to the total picture, are negligible (UNODC, 2006). A total of 120 tons of opium was seized around the world in 2004, amounting to roughly one quarter of the world's total production.

5.5.3 Heroin Manufacture

Heroin can be manufactured directly from opium, from semi-purified morphine, or from poppy straw. The route utilized depends mostly on the availability of the precursors. Morphine and opium are both sold on the illicit market, and the availability of one or the other depends largely on local conditions, including the availability of chemical precursors, especially acetic anhydride (1250 liters were seized in Afghanistan in 2008, while virtually none was confiscated in neighboring countries) (INCB, 2007). Until production recently exploded in Afghanistan, for many decades opium straw had been increasingly used as the starting material for opiate production. Extract derived from poppy straw has a morphine content that ranges from 40 to 80%.

The clandestine separation of morphine from crude opium involves three separate steps. A kilogram of opium is dissolved in 2 L of water along with 200 g of lime, and the resultant solution is poured through a coarse filter. Then, 250 g of ammonium chloride is added to the filtrate, causing the morphine base to slowly precipitate out. The morphine is collected on a fine cloth filter and then washed with water. The crude morphine is mixed with charcoal, and with either hydrochloric or sulfuric acid. The mixture is filtered, and ammonium hydroxide is added to the filtrate, causing purified morphine to precipitate out. The precipitate is collected by filtration and allowed to dry in room air.

In the second phase of production, the dried morphine is added to acetic anhydride. Under the terms of an International Convention signed in 1988, sales of acetic anhydride are controlled by international law, and all exports must be reported to the U.N., which operates a monitoring program known as Operation Topaz (a similar operation to monitor sales of potassium permanganate, used in the production of cocaine, is known as Operation Purple) (U.N., 2005). Afghan seizures of acetic anhydride continue to rise, even though that country has absolutely no legitimate need for that chemical. Throughout the world, multi-ton seizures of this compound are not uncommon. In one case, reported to the International Narcotics Control Board (INCB), 46 tons of acetic anhydride were smuggled across the border from China into Pakistan. Illicit heroin production can be, to some extent, gauged by demand for acetic anhydride, the key agent in conversion from morphine to heroin. Because the uses of acetic anhydride are so well known, and because sales are tracked by governmental authorities, alternative agents have been used. In the past, ethylidene diacetate was used by Southeast Asian producers. More recently, it has been reported that acetyl chloride was being substituted for acetic anhydride at clandestine laboratories in (INCB, 2006).

The dried morphine mixture is then refluxed with acidic anhydride at a constant temperature for 5 hours. After the mixture has been allowed to cool, it is neutralized with sodium carbonate. The crude heroin that precipitates out is filtered and washed with water.

In the final stage of production, heroin is purified by re-dissolving it in boiling water containing citric acid and charcoal. The mixture is filtered and purified, and heroin is precipitated by the addition of sodium carbonate. If the lab wants to produce the hydrochloride form of heroin instead of heroin base, the heroin is re-dissolved in acetone, and hydrochloric acid is added to the solution.

Depending on market demand, clandestine chemists sometimes synthesize morphine instead of opium. Production begins by dissolving 1 kg of opium in 2 L of water and adding 200 g of slaked lime, 500 mL of alcohol, and 500 mL of ether. The resultant solution is then filtered through a cloth, leaving crude morphine on the cloth. This material is further purified and decolorized by refluxing it with 2 L of dilute sulfuric acid and 250 g of charcoal for about half an hour. This solution is then filtered, and ammonium hydroxide is added to the filtrate. The off-white, semi-purified morphine that precipitates out is then air dried, and the hardened dried morphine granules are rubbed against a hard surface to produce a powder (Narayanaswami, 1985).

Until very recently, the large-scale conversion of morphine to heroin was not possible without the use of acetic anhydride or some chemical very much like it. However, a way to convert morphine to heroin at room temperature, using a mixture of trifluoroacetic anhydride (TFAA) and acetic acid, has been introduced. This method provides yields (close to 90%) that are almost comparable to those attained with acetic anhydride. Presumably a yield of nearly 90% would still be considered acceptable to illicit producers (Odell et al., 2006).

5.5.4 Sample Analysis

The ratio of heroin to acetylcodeine in illicit heroin is nearly the same as the ratio of morphine to acetylcodeine in the illicit morphine that was used to produce the heroin in the first place. The relationship is so constant that studies have shown that the ratio can be used to identify the sample's country of origin. The ratio is fairly high for samples emanating from Afghanistan (20.9:1), and quite low for specimens coming from China (6.38:1) (Narayanaswami, 1985). Traditionally, these differences, along with the detection of trace chemicals introduced during illicit process and transport, have been used to "profile" heroin samples, allowing enforcement officials to trace routes of distribution, and even laboratories (O'Neil and Pitts, 1992). However, this approach may prove less valuable if the TFAA synthetic route is widely adopted. In the final analysis, the ratio of heroin to 6-acetylmorphine and morphine is more an indicator of clandestine lab proficiency than country of origin.

Substances carried over from the original plant or from opium are referred to as adulterants. Substances added with the intent of altering the character of the heroin in some way are also called adulterants. Included in this latter group are compounds such as quinine, caffeine, and diphenhydramine, and more exotic agents such as levamisole (an antihelminthic) and a dangerous injectible anesthetic known as xylazine and most recently alpha-methyl-fentanyl. The latter is a veterinary medication used for sedation, anesthesia, muscle relaxation, and analgesia in large mammals. It is actually an analog of the antihypertensive drug clonidine, and is an agonist at the α_2 adrenergic receptors. Like all other α_2 agonists, xylazine has adverse effects, which include bradycardia, conduction disturbances, and myocardial depression (Wong et al., 2008).

Table 5.5.4.1 Adulterants Found in Heroin from Mexico, South America, Southeast Asia, and Southwest Asia

Adulterant[a]	Southeast Asia[b]	Southwest Asia[b]	Mexico[b]	South America[b]
Quinine	36	30	27	18
Diphenhydramine	17	3	20	—
Caffeine	22	8	—	8
Acetaminophen	21	8	1	6
Procaine	4	14	—	23
Cocaine	2	3	3	6
Lidocaine	1	3	4	6

[a] Other compounds are occasionally seen, but they are encountered so infrequently that no pattern is discernible.

[b] Numbers indicate the percentage of samples found to contain each adulterant.

Note: Based on data supplied by the Drug Enforcement Administration.

The term *diluent* is reserved for those substances devoid of physiologic effects that are added to increase the bulk of the final product. In the past, heroin produced in different regions could be characterized by the adulterants and diluents that had been added. However, there is very little current information on what substances are being added, and older compilations of popular adulterants and diluents (as in past issues of this book), may no longer be relevant.

Heroin purity has been relatively stable since the early 1990s. When purchased in small quantities of less than 10 g, purity ranges from 30 to 40%. The average purity of large quantities is closer to 60%, and may approach 75% at the wholesale level (>200 g). Heroin prices reached all-time lows in 2002 and stabilized at roughly those levels in 2003. Cumulatively, heroin prices have fallen roughly 85% since the DEA began tracking this data. Recent figures are not available, but prices in 2002–2003 were only about one sixth of what they were in 1981, and there is little evidence of any reversal in that trend (UNODC, 2007).

The type of material used as diluents varies from region to region and from time to time, depending on local conditions and on the preferences of the illicit manufacturer.

Table 5.5.4.2 Diluents Found in Heroin from Mexico, South America, Southeast Asia, and Southwest Asia

Diluent[a]	Southeast Asia[b]	Southwest Asia[b]	Mexico[b]	South America[b]
Lactose	46	43	39	33
Mannitol	65	73	6	67
Starch	21	19	6	27
Dextrose	5	3	—	6

[a] Other compounds are occasionally seen, but they are encountered so infrequently that no pattern is discernible.

[b] Numbers indicate the percentage of samples found to contain each adulterant.

Note: Based on data supplied by the Drug Enforcement Administration.

In the early 1990s French chemists observed drastic shifts in the composition of heroin seizures. In the late 1980s, caffeine and mannitol were the diluents most frequently encountered by French officials, but by 1991 they had been almost entirely replaced by paracetamol (Chaudron-Thozet et al., 1992). Diluents are likely to have changed in the last decade, but no current survey data are available. Lactate and mannitol are still widely used, and periodically there are reports of bizarre compounds, such as scopolamine (Dillmann, 1997), atropine (Perrone et al., 1999), and clenbuterol (Werder et al., 2006) causing outbreaks of toxicity. There is no satisfactory explanation for the use of these drugs other than, perhaps, they were available. In 2006 alpha methyl fentanyl began to appear in heroin sold in some parts of the U.S. (Wong et al., 2008).

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5.6 Morphine and Heroin

Morphine

Synonyms: morphia, morphium, dolocontin, duromorph, nepenthe, roxanol
Formula: $C_{17}H_{19}NO_3$
Molecular weight: 285.54 daltons
Bioavailability:
PO: 24 ± 12% (Hasselstrom and Sawe, 1993)
IM: 100%
IV: 100%
Subcutaneous: 100%
Transnasal: 60% (Illum et al., 2002)
Transdermal: 65–80% (Westerling et al., 1994)
Rectal: 35–90% (Lundeberg et al., 1996)
Metabolism: hepatic. (1) UGT2B7 forms M3G and M6G; UGT1A1, 1A3, 1A6, 1A9, 1A10 contribute to M3G formation only (Stone et al., 2003). (2) CYP3A4 and CYP2C8 are mainly responsible for the conversion of morphine to normorphine (Projean et al., 2003)
$T_{½β}$ (half-life): 1.9 ± 5 hours (Berkowitz, 1976)
Clearance: 21–24 hours (Berkowitz, 1976)
Excretion: primarily urine but with enterohepatic circulation (Hanks et al., 1987; Hasselstrom and Sawe, 1993)
Volume of distribution:
a. Morphine: 2.1 to a high of 4.0 L/kg (Sawe et al., 1981; Osborne et al., 1990)
b. Morphine-3-glucuronide: 0.14 to 0.33 depending on age (Hunt et al., 1999)

Morphine-6-glucuronide (adapted from Penson et al., 2002)

Synonyms: none
Formula: $C_{23}H_{27}NO_9$
Molecular weight: 497.49 daltons
Bioavailability:
PO: 11.3%
IV: 100%
Subcutaneous: 100%
Nebulized: 6 ± 2%
Metabolism: not further metabolized, excreted in urine unchanged
$T_{½β}$ (half-life):
PO: NA
IV: 1.7 ± 0.7, 2.6 ± 0.698 hours (Osborne et al., 1990)
Subcutaneous: 1.9 ± 0.4 hours
Nebulized: 3.11 hours

Clearance:
PO: NA
IV: 157 ± 46 mL/min
Subcutaneous: 154 ± 24 mL/min
Nebulized: NA

Excretion: primarily urine but with enterohepatic circulation (Hanks et al., 1987; Hasselstrom and Sawe, 1993)

Volume of distribution:
PO: NA
Nebulized: NA
Subcutaneous: 20.5 ± 3.3 liters
Intravenous: 16.2 ± 4.4 L/kg
Morphine-6-glucuronide: children, 0.42 L/kg (Hunt et al., 1999), adults 0.15 (Osborne et al., 1990)

Dosages: 2 mg IV, 2 mg SC, 4 mg nebulized, 20 mg PO

Diacetylmorphine

Synonyms: heroin, diamorphine, acetomorphine

Chemical name: (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate (ester)

Formula: $C_{21}H_{23}NO_5$

Molecular weight: 369.42 daltons

Bioavailability:
PO: negligible (Girardin et al., 2003)
IM: up to 420% (Girardin et al., 2003) (muscle lacks esterase)
IV: 100% (Girardin et al., 2003)
Subcutaneous: 100%
Inhalation: 40–75% (Girardin et al., 2003; Brenneisen et al., 2004; Rook et al., 2006a)

Metabolism: Hepatic human carboxylesterase 1 converts heroin to morphine (Kamendulis et al., 1996; Redinbo et al., 2003); once the conversion to morphine is complete UGT2B7 forms most of the M3G and M6G metabolites; UGT1A1, 1A3, 1A6, 1A9, 1A10 contribute to M3G formation only (Stone et al., 2003). CYP3A4 and CYP2C8 are mainly responsible for the conversion of morphine to normorphine (Projean et al., 2003).

$T_{½β}$ (half-life):
a. Heroin to 6MAM: 3.24–3.7 minutes (Rook et al., 2006a)
b. 6 MAM to morphine: 22–26 minutes (Rook et al., 2006a)

Clearance: 930–1939 L/h depending on route (Rook et al., 2006b)

Excretion: 10.84 minutes (Jenkins et al., 1994)

Volume of distribution:
Morphine: 2.1 to a high of 4.0 L/kg (Sawe, et al., 1981; Osborne et al., 1990)
Morphine-6-glucuronide: children, 0.42 L/kg; adults 0.15 L/kg (Hunt et al., 1999)
Morphine-3-glucuronide: not known

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5.6.1 General Considerations

Heroin is a synthetic pro-drug produced from opium by Sertürner in 1805 (Sertürner, 1806), but more than 120 years passed before its chemical structure was characterized by Sir Robert Richardson in 1927 (Schopf, 1927), and total synthesis was only accomplished in 1952 (Gates and Tschudi, 1952). The time lag between the discovery of morphine and its chemical characterization is paralleled by the slow evolution in the understanding and knowledge of its metabolism and mechanism of action. Morphine was first sold by Bayer in 1898, who produced it by acetylation of morphine's two hydroxyl groups. Heroin readily crosses the blood–brain barrier where it is converted to morphine. Heroin itself has little or no activity at the

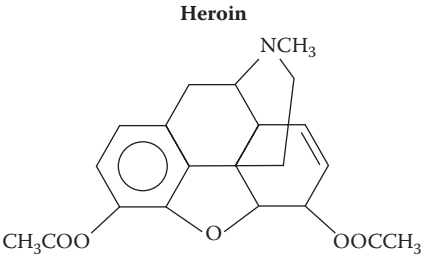

Figure 5.6.1.1 Heroin molecule.

μ receptor. It only exerts an effect after it has been converted to morphine. Injected heroin is hydrolyzed by serum and liver esterases into glucuronide-bound morphine metabolites. The first conversion, from heroin to 6-monoacetyl morphine, occurs in less than eight minutes. The second conversion, to morphine, requires on average 22 minutes. Once the conversion is complete, the fate of heroin in the body is no different than that of morphine (Hasselstrom and Sawe, 1993). Heroin does not cross the nasal mucosa as readily as cocaine, and bioavailability via this route is poor, at least when compared to cocaine.

Heroin's poor bioavailability probably explains why intravenous injection had, in the past, been the preferred route of administration by addicts in both the U.S. and Europe. Now that the purity of street heroin has increased so drastically, bioavailability is no longer a limiting factor. With the advent of harm reduction programs, the practice of injection has become increasingly stigmatized and the injection of heroin is becoming less popular (Westerling et al., 1982; Illum et al., 2002). The exact purity of the U.S. heroin supply is not known, or has at least not been stated in any published government document. But, according to the 2006 Drug Threat Assessment published by the Drug Enforcement Agency, confiscated street heroin was between 60 and 70% pure in 2001, 2002, and 2003. More recent information is not available (DEA, 2006). Heroin of this purity will readily cross the nasal

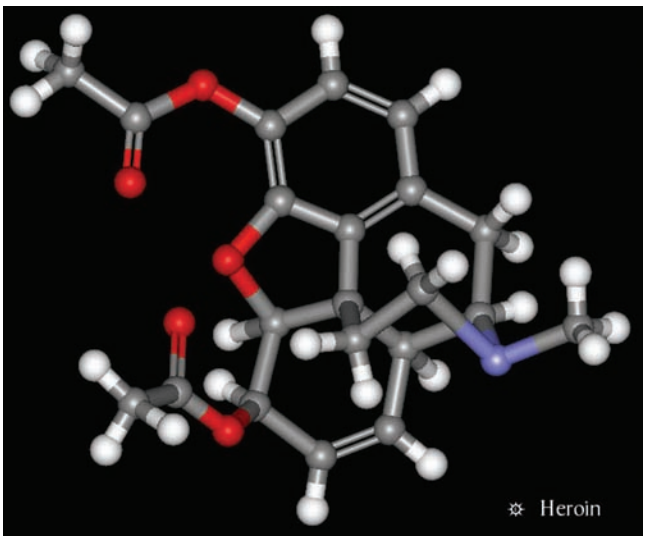

Figure 5.6.1.2 Heroin 3-D model.

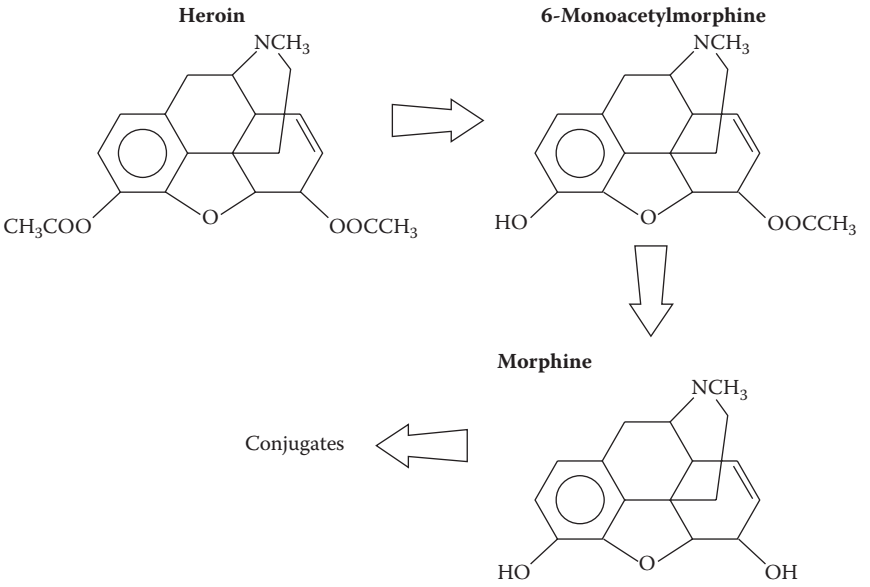

Figure 5.6.1.3 Heroin is rapidly deacylated to 6-monoacetylmorphine and then to morphine.

mucosa, and so the practice of nasal insufflation is likely to remain popular. If it does, the prevalence of some infections associated with parenteral heroin abuse may decrease.

Morphine's principal site of metabolism is the liver, but because the total body clearance of morphine is higher than hepatic flow, questions still remain about extrahepatic metabolism (Sawe et al., 1985).

The utility of measuring blood concentrations, either in the living or the dead, is debatable. Tolerance occurs, and, as is the case with cocaine, the morphine concentrations in individuals where morphine is the cause of death overlap concentrations found in other decedents where the presence of morphine is merely an incidental finding. In the

Figure 5.6.1.4 Asian refined heroin. (Photograph from the website of the DEA.)

Figure 5.6.1.5 "Black tar heroin." The same term is applied to heroin of Mexican and Iranian origin. It is black because it is semi-refined. Microscopic examination will disclose plant and animal parts that may explain why skin infection among abusers is so common. (Photograph from the website of the DEA.)

same fashion, addicts dying of overdose may have much lower blood concentrations than addicts being treated with heroin maintenance (Drummer et al., 2004). Indeed, today there are many heroin-replacement patients (Switzerland dispenses free heroin to addicts), and the plasma concentrations observed in these individuals were once presumed to be automatically fatal. Today, total concentration overlap in the living and dead is a given (Darke et al., 1997). Even in the living, relationships between impairment and pain relief on one hand, and plasma opiate concentrations on the other, have been very difficult to establish. Pharmacodynamic studies—no matter whether in normal volunteers, or cancer or trauma patients—have failed to disclose any predictable relationship between morphine plasma concentrations and analgesic effects (Hoffman et al., 1997).

5.6.2 Morphine Metabolism

Morphine's tissue distribution is biphasic; the initial phase lasts only a few minutes during which it is rapidly distributed throughout the tissues receiving the highest blood flow namely, the lung, kidney, liver, spleen, and muscle (Brunk and Delle, 1974). During a secondary phase, morphine is quickly converted to its principal metabolite, morphine-3-glucuronide (M3G), and somewhat more slowly to smaller amounts of morphine-6-glucuronide (M6G) (Figure 5.6.2.1). The transformation occurs almost entirely in the liver, takes several hours, and also leads to the production of small amounts of several other morphine metabolites. Less than 10% of a given dose of morphine is excreted in the urine as unchanged morphine.

Glucuronidation requires the production of free hydroxyl groups, catalyzed by several different enzymes, but mainly UGT2B7 (Coffman et al., 1997; Kirkwood et al., 1998). Morphine has two hydroxyl groups, one phenolic (position 3) and one hydroxyl (position 6). Depending on which hydroxyl group is involved, morphine can be glucuronidated to form morphine-3-glucuronide (M3G) or morphine-6-glucuronide (M6G). Aromatic hydroxyl groups are glucuronidated more easily than alicyclic hydroxy groups, which explains the

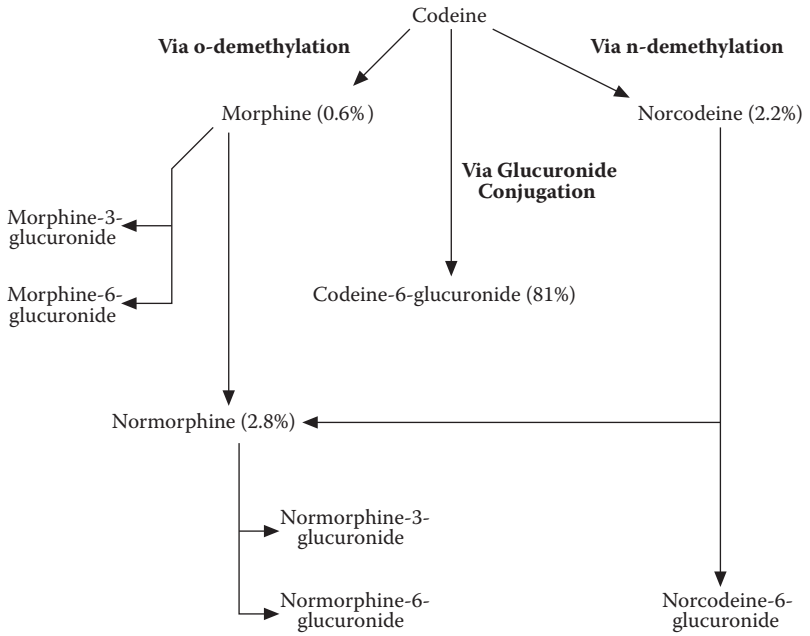

Figure 5.6.2.1 Basic elements of morphine metabolism.

pattern observed when intravenous morphine is given to healthy volunteers: the resultant M3G:morphine molar concentration ratio is roughly 6:1, whereas that of M6G:morphine is approximately 1:1. The glucuronides have a much smaller volume of distribution (less than one tenth) than that of the parent compound. This explains why near equal plasma concentrations of morphine and M6G can be observed, even though the amount of M6G in the body is only approximately 10% of that of morphine. Paying insufficient attention to the physical properties of morphine and its metabolites can lead to an interpretative muddle when postmortem samples are being analyzed.

Approximately 70% of the morphine administered is converted to one or other glucuronide (57% M3G, 10% M6G) (Hasselstrom and Sawe, 1993) and then excreted via the kidneys. Other morphine metabolites (such as morphine-3,6-diglucuronide, normorphine-3-glucuronide) are produced in very small amounts and appear to be devoid of physiologic effects (Yeh et al., 1979). Elimination of morphine is not altered by renal failure, but excretion of the morphine glucuronides is. The 6-glucuronide is psychoactive and may accumulate in those with renal failure, leading to prolonged coma. Orally administered morphine undergoes extensive first-pass metabolism. One consequence is that much more M6G is formed than if the morphine had been given intravenously.

It has been proposed that increased production of M6G after oral dosing may explain the relative increase in potency of repeated oral doses of morphine relative to repeated doses given intravenously (Hanks et al., 1987). Morphine is not, as once thought, converted to codeine (though the reverse is certainly true); the detection of codeine in urine after morphine or heroin administration is explained by the presence of codeine impurities that are present even in pharmaceutical-grade morphine (Cone et al., 1991). During life, approximately half the morphine circulating in the plasma is protein bound (Osborne et al., 1990). Abnormalities of protein binding, such as what occurs in hepatic failure and/or

malignancy, can alter the degree of protein binding. Indirectly this may lead to higher circulating levels of free morphine (Sawe, 1986). P-glycoprotein (P-gp)-mediated transport is the central mechanism responsible for the movement of morphine across the blood–brain barrier. P-gp serves as an important transport protein, located in the apical membrane of endothelial cells. Using ATP hydrolysis for energy, P-gp exports molecules attempting to pass through the cell membrane from the outside to the inside. It plays this same role with many different compounds, not just morphine (Ebinger and Uhr, 2006). For example, the common antidiarrheal medication, loperamide, binds strongly to the opiate μ receptor but produces no CNS symptoms because it is entirely bound to P-gp and cannot enter the brain.

Two types of drug transporters circulate in the bloodstream: efflux and influx. Efflux transporters like P-gp belong to a family of membrane proteins that heavily influence drug concentrations inside cells. P-gp is the best characterized, but there are many other members of this class. There is increasing evidence that genetic heterogeneity among members of this protein family may account for problems such as multi-drug resistance, not to mention the effects of individual drugs such as morphine. Table 5.6.2.1 lists some of the drugs transported by P-gp.

Since the last edition of this book was published, many distinct sequence variations in genes of this transporter family have been identified, though the clinical significance of most is still far from understood. There is, however, no question that brain concentrations of morphine depend on the amount of free morphine circulating in the plasma, and that

Table 5.6.2.1 Drugs Binding to P-gp (Adapted from Cascorbi, 2006)

Anticancer drugs	Docetaxel, doxorubicin, etoposide, imatinib, paclitaxel, teniposide, vinblastine, vincristine, doxorubicin, etoposide, dexamethasone, methylprednisolone, hormone conjugates
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus
HIV protease inhibitors	Amprenavir, indinavir, nelfinavir, saquinavir, ritonavir
Antibiotics	Erythromycin, ofloxacin, ampicillin, cefoxitime, ceftriaxone, grepafloxacin
Beta blockers	Bunitrolol, carvedilol, celiprolol, tanilolol
Ca^{2+}-channel blockers	Diltiazem, verapamil
Cardiac drugs	Digoxin, digitoxin, quinidine
HMG-CoA inhibitors	Atorvastatin, lovastatin, pravastatin
H_1-Antihistamines	Fexofenadine, terfenadine, cimetidine
Antiemetics	Ondansetron
Diverse	Amitryptiline, colchicine, itraconazole, lansoprazole, loperamide, losartan, morphine, phenytoin, rifampicin
	Glucuronide, sulfate and glutathione conjugates (e.g., leukotriene C_4)
	Bilirubin and certain drug glycosides, such as flavonoids, and saponins

the amount of free morphine circulating in the plasma is partly determined by the amount of P-gp available to bind with morphine. Because many other drugs are also P-gp bound, the potential exists for unanticipated drug reactions. For example, it has recently been suggested that up-regulation of P-gp production leads to decreased delivery of antiseizure medications to the brain, resulting in refractory seizure disorders (Robey et al., 2008). P-gp inhibitors can disrupt brain uptake and tissue disposition of morphine. Two of the best known inhibitors are verapamil and cyclosporine (Letrent et al., 1999).

P-gp proteins normally complex with morphine, but they cannot complex with either M3G or M6G because both molecules are too polar. Once the two metabolites are formed in the liver they are transported back into the circulation by complexing with another glycoprotein called MDR1 (multi-drug resistance protein 1), which is normally found in hepatic sinusoidal membranes. The gene for MDR1 is polymorphic, and individuals who have an abnormal form of the protein may not be able to effectively move the glucuronides out of the liver (Zelcer et al., 2006). This action explains the occasional case in which a very high G3P hepatic concentration is seen in the face of low plasma levels. This possible role of genetic polymorphism should always be considered in attempts at postmortem drug concentration interpretation.

Morphine also undergoes enterohepatic circulation. In seven healthy volunteers given 5-mg doses of morphine intravenously, on average 57.3% of the morphine was converted to M3G, 10.4% to M6G, and 10.9% appeared unchanged in the urine, leaving 20.8% of the original morphine unaccounted for (Hasselstrom and Sawe, 1993). These observations are in general agreement with animal studies. When rats are injected with M3G, up to 20% of the dose is recovered in bile, with the remainder (80%) being recovered unchanged in the urine (Ouellet and Pollack, 1995a). In chronic users, fecal excretion may account for between 7 and 10% of a given dose (Hanks et al., 1987).

5.6.3 Morphine Metabolites

5.6.3.1 Morphine-3-Glucuronide

The process of drug metabolism generally involves conversion of the parent compound to more highly polar compounds that are less lipophilic. The lipophilicity of heroin is much greater than that of 6-monoacetyl morphine, and both are much greater than morphine. Both M3G and M6G are highly polarized and minimally lipophilic (Gulaboski et al., 2008), and their ability to cross the blood–brain barrier is significantly less than that of the parent compound (Wu et al., 1997). M3G is morphine's major metabolite. It has almost no affinity for μ receptors and no analgesic properties. Human studies are lacking, but the results of animal experiments suggest that M3G may partly antagonize some of the effects of morphine and possibly play a role in the occurrence of side effects and also in the development of morphine tolerance (Wittwer and Kern, 2006). The terminal half-life of M3G is 3.9 ± 1.5 hours, significantly longer than that of M6G, which is only 2.6 ± 0.69 hours (Osborne et al., 1990). The apparent volume of distribution for M3G in children under the age of 11 is more than twice that observed in children over that age, and more than seven times the value observed in adults (0.76 vs. 0.33 vs. 14 L/kg) (Hunt et al., 1999). The clearance rate for M3G is also higher in young children than in adults (4.9 vs. 0.8 mL/min/kg) and is higher than that of M6G regardless of age. This observation suggests that bioavailability estimates derived from adults are not applicable to children, and that preferential metabolism to M6G or increased clearance of M3G occurs.

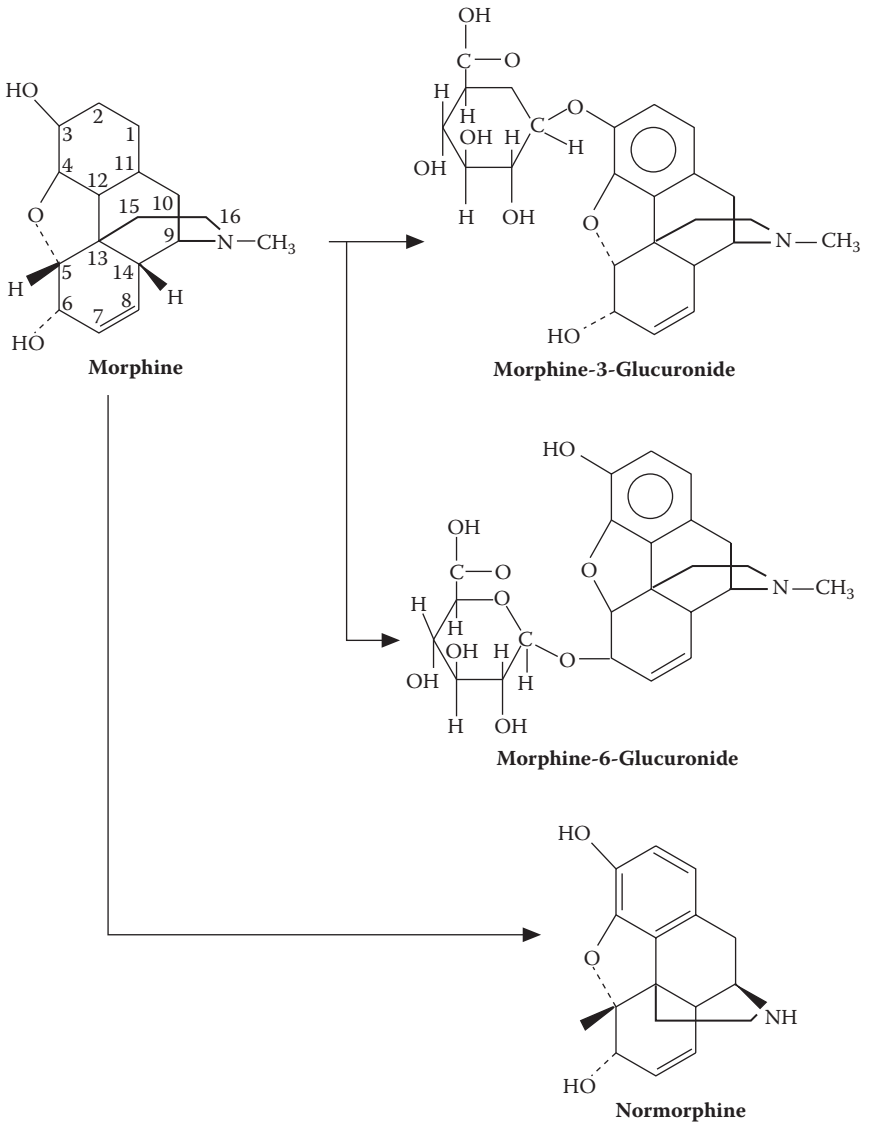

Figure 5.6.3 Human metabolism of morphine.

5.6.3.2 Morphine-6-Glucuronide

The 3-carbon position in the morphine moiety must remain accessible in order for a molecule to have opiate activity, and it remains open in the M6G molecule. Thus it is not surprising that this metabolite has analgesic effects in its own right (Osborne et al., 1990). In humans, M6G has approximately half the pain-relieving effect of morphine, but causes fewer side effects and longer lasting analgesia. At analgesic doses, M6G causes similar reduction of the ventilatory response to CO_2 but significantly less depression of the hypoxic ventilatory response. In postoperative surgical patients M6G causes 50% less nausea and 75% less vomiting (van Dorp et al., 2006). When given as a pain medication, M6G has a slower onset of action than morphine because it crosses the blood–brain barrier more

slowly; lipid solubility is 187-fold lower than that of morphine (Wu et al., 1997). M6G is not metabolized but it is excreted via the kidneys. Like morphine, M6G also undergoes enterohepatic cycling (Kilpatrick and Smith, 2005; Villesen et al., 2006). Chronic exposure to street heroin causes a relative increase in concentrations of M6G, and may contribute to some of heroin's effects (Antonilli et al., 2003).

The volume of distribution for M6G is so low (0.42 L/kg in children under the age of 11, 0.19 L/kg in older children, and 0.15 L/kg in adults) (Hunt et al., 1999) that very little M6G is found in tissues. Measurements made in fat and subcutaneous tissue, for example, disclose the presence of free morphine, but none of the glucuronides (Levisky et al., 2000). The elimination of M6G is decreased in renal failure; patients who accumulate metabolite may become toxic due to its presence (Angst et al., 2000; Penson et al., 2002).

In some animals, and very likely in humans as well, M3G is synthesized by the gut (Sloan et al. 1991; Milne et al., 1993). As a result, morphine glucuronides will continue to appear in the urine for days after heroin/morphine was last used, even in healthy individuals who have neither liver nor kidney disease. The process will continue for as long as there is morphine in the bile to be excreted. Concentrations of unchanged morphine in bile may reach extremely high concentrations. In one study of narcotic-related deaths, the average concentration of morphine in the bile was 312 mg/L (Chan et al., 1986). In Gottschalk and Cravey's series of 119 cases, the median level of morphine in the bile was 33.7 mg/L (Gottschalk and Cravey, 1980).

Morphine glucuronides excreted in the bile can be deconjugated back to morphine by bacteria in the gut, and then reabsorbed through the intestinal mucosa (Parker et al., 1980). This combination of enterohepatic circulation and bacterial deconjugation helps to make the interpretation of postmortem levels almost impossible. It is not known with any certainty just how long it takes to clear morphine from the enterohepatic circuit, but it is reasonable to suppose that patients treated with large doses of morphine, such as trauma victims maintained on respirators and former heroin abusers who have entered detoxification programs, may continue to excrete measurable quantities of morphine glucuronides in the urine for weeks after morphine was last taken. This possibility must be taken into account when interpreting drug-abuse screening tests. After death, free and conjugated morphine are stable in refrigerated blood and urine, at least for 10 days, but in the liver conjugated morphine is rapidly converted back to morphine (Moriya and Hashimoto, 1997; Alunni-Perret et al., 2003). If the postmortem interval is long, or if the tissue samples have not been frozen, inferences about the time of ingestion based on the ratio of morphine to its metabolites are almost certain to be misleading.

5.6.3.3 Normorphine

Like morphine-6-glucuronide, normorphine is also psychoactive. Though not always detectable in the plasma of morphine and heroin users, it usually can be found in the urine of cancer patients being treated with oral morphine. Normorphine is believed to be neurotoxic. More than 90% of morphine *N*-demethylation to normorphine can be accounted for via the action of two polymorphic enzymes, CYP3A4 and CYP2C8 (Projean et al., 2003). Based on published clinical profiles of renal failure patients treated with high dose oral morphine, it appears that only those individuals capable of morphine demethylation are at risk for toxicity. Glare et al. (1990) described two cancer patients being treated with morphine. One, who was experiencing myoclonus, was receiving 160 mg of morphine orally every 4 hours, had a plasma morphine of 93 ng/mL, a M3G of 19,900, a M6G of 5161, and

a normorphine of 70 ng/mL. A second patient with normal renal function received 15 mg of morphine per hour, but had no normorphine. The plasma morphine concentration was 81 ng/mL, with an M6G of 4600 and an M3G of 63 ng/mL.

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5.6.4 Absorption and Routes of Administration

Morphine is well absorbed, no matter the route of administration; the subcutaneous and intravenous routes of morphine administration are bioequivalent (Stuart-Harris et al., 2000). However, when heroin users "chase the dragon," bioavailability is much lower (on the order of 54%).

5.6.4.1 Intravenous Injection

Past studies of intravenous heroin and morphine kinetics relied upon measurements made either in healthy volunteers or in cancer patients. Neither situation is especially comparable to the situation in abusers because the doses administered are relatively small. Studies performed in the 1970s showed that a 10-mg bolus of morphine given to healthy volunteers who were undergoing elective surgery resulted in peak blood levels of 200–400 ng/mL five minutes after injection (Berkowitz, 1976). A study performed in the early 1990s compared the pharmacokinetics of smoked and intravenous heroin with measurements made in two subjects; in one subject, peak concentrations ranged from 72 ng/mL after a 10-mg intravenous dose to 401 ng/mL after a 20-mg dose. In the second subject, a 3-mg dose produced a peak level of 64 ng/mL, while a 6-mg dose gave a peak of 315 ng/mL. Levels rapidly declined thereafter and reached limits of detection within 30 minutes of injection (Jenkins et al., 1994).

In more recent studies, injecting 146 ± 48 mg of heroin into eight addicts enrolled in a heroin maintenance program produced maximal plasma concentrations of diacetylmorphine and 6-monoacetyl morphine of 3057 ng/mL and 5000 ng/mL, respectively. Heroin had a clearance rate of 11.6 L/min and a volume of distribution of 0.52 L/kg, with a terminal half-life of 3.0 minutes for both diacetyl and 6-monoacetyl morphine. A second, much larger recent study evaluated the pharmacokinetics of large doses of heroin in 74 heroin inhalers and 32 heroin injectors in a cross-over study. The terminal half-lives of both heroin and 6-monoacetyl heroin were estimated at 7.6 and 28.1 minutes, respectively. The clearance rate for morphine was estimated at 73.6 L/hr (CI 62.8, 85.4) and that of morphine-3-glucuronide and morphine-6-glucuronide at 6 and 10 L/hr, respectively. Plasma heroin and 6-monoacetyl morphine concentrations were two to four times higher after injecting than inhaling (the highest concentration recorded after intravenous use was 5042 ng/ mL). Interestingly, and inexplicably, the terminal half-life of 6-monoacetyl morphine is 13% lower in cocaine users. Another important difference highlighted by these studies was the slightly lower volume of distribution for morphine (less than 2 mL/kg) that is observed when similar studies are done with morphine, rather than heroin that has been converted to morphine. This may have to do with the size of the dose or, more likely, the pharmacokinetic model used for the study (Rook et al., 2006).

Trauma has an effect on morphine pharmacokinetics. Morphine clearance rates (2.5–10 mL/kg/min, with mean ± SD of 6 ± 2.6) and volume of distribution (0.28–3.30 L/kg, with mean ± SD of 1.4 ± 1.0) were found to be lower in trauma victims than in healthy volunteer test subjects or in cancer patients. These reductions are seen in trauma victims even when hepatic blood flow, as assessed by the rate of lidocaine clearance, is almost normal, suggesting that some other mechanism besides diminished hepatic blood flow is involved (Berkenstadt et al., 1999).

5.6.4.2 Subcutaneous Injection

Absorption via the subcutaneous route and after intramuscular injection is almost as rapid as the intravenous route; morphine plasma levels peak at 10–20 minutes, somewhat longer than after intravenous injection, but not so much longer as to have any clinical significance. The pharmacokinetic profiles for both routes are nearly the same as after intravenous injection, and plasma levels comparable to those seen after intravenous use can be achieved after subcutaneous injection. In one recent study with healthy human volunteers, a dose of 10 mg/70 kg given intravenously produced a free morphine concentration of 80 ng/mL at 5 minutes, compared to a peak concentration of 74 ng/mL at 15 minutes after the same dose was given as an intravenous bolus (Stuart-Harris et al., 2000).

These similarities may explain why, in the past, subcutaneous heroin injection (known as "skin popping") enjoyed considerable popularity among some groups of abusers. Unfortunately, this mode of administration accounts for the high prevalence of abscesses and cellulitis among some communities of injection drug users. To some extent "skin popping" may have been replaced by smoking, but the practice still occurs, as evidence by the outbreak of clostridial infections reported from the U.K. in 2000, and by continued reports of wound botulism (Brown and Ebright, 2002; Brett et al., 2004; Kimura et al., 2004; Brett et al., 2005) from both Europe and the U.S. In the U.K. and Europe, subcutaneous heroin delivered through a syringe injector is routinely used for hospice care (Oliver, 1985), and "pain pens" containing heroin are used for the treatment of cancer patients with breakthrough pain, providing an alternative to the use of oral transmucosal fentanyl (Enting et al., 2005). Continuous subcutaneous administration of heroin is the preferred treatment modality because it avoids the cycles of peak-level sedation and trough-level breakthrough pain, and nausea is lessened. In one study, an infusion of 165 mg/day of heroin at the rate of 3.45 mg/hr resulted in a stable serum concentration of 30–40 ng/mL, even though bioavailability is considerably less after subcutaneous than intravenous dosing (Mikkelsen-Lynch et al., 2000).

5.6.4.3 Oral

Parenteral administration avoids first-pass metabolism resulting in decreased production of some morphine metabolites. After oral administration, 80% of a given dose of morphine is absorbed from the gastrointestinal tract, with nearly half that amount being metabolized during the first pass through the liver. For that reason, oral bioavailability of morphine is relatively low, at just over 33% (Lotsch et al., 1999). The amount absorbed is somewhat unpredictable because the degree to which morphine is subject to gastrointestinal extraction and metabolism is altered by age, liver function, gender, the presence of food, disease states, and genetic polymorphism (Tam, 1993). Still, there is increasing interest both in the use of oral morphine (in multiple different formulations) and even in the use of

morphine-6-glucuronide. Two separate plasma concentration peaks are seen after M6G is given orally. The first is due to hydrolysis of M6G back to morphine in the small intestine and colon. The second peak, occurring several hours later, is thought to be due to the re-glucuronidation of morphine (Stain-Texier et al., 1998).

The oral route was popular among the "opium eaters" of the 17th and 18th centuries, when morphine distribution was unregulated and prices were low. Today, it is an impractical route for abusers because it costs too much. Urine measurements have been described in only one "opium eater," an addict ingesting approximately 1 g of opium per day. Morphine, codeine, normorphine, norcodeine, and noscapine were all found in the urine, but thebaine and papaverine (normal constituents of opium) were not. The concentration of unconjugated morphine (640 ng/mL) was more than twice the concentration of codeine (Cone et al., 1982).

"Brown mixture," a cough syrup used in China, contains opium powder (10.0–10.5% morphine), opium tincture (0.9–1.1% morphine), or camphorated opium tincture (0.045–0.055% morphine). In a recent study, "brown mixture" from seven different manufacturers (five tablets and two solutions) along with urine samples from alleged heroin users and volunteers with various ingestion patterns were analyzed for their morphine and codeine contents. Morphine concentrations found in urine specimens collected from volunteers ingesting brown mixture tablets (or solutions) were always < 4000 ng/mL (Liu et al., 2006).

Oral morphine has been a mainstay in the management of cancer pain for many years (Gourlay et al., 1986), but is gradually being supplanted by fentanyl and ondansetron (Llanes et al., 2006). Hospice patients may be treated with very high doses of morphine or methadone. In a study of 29 men and women (mean age 68 years), the average dose of morphine (controlled oral release) was 90 mg/day, but in some individuals the daily dose was nearly 1500 mg per day. The mean blood morphine in this group was 72 ng/mL, but in some individuals, values of as high as 700 ng/mL were recorded (Klepstad et al., 2004).

Oral overdose, intentional or accidental, can occur (Got et al., 1994). In one case involving an intentional overdose with an unspecified number of time-release morphine capsules (MS Contin®), the patient subsequently developed rhabdomyolysis and renal failure in addition to respiratory depression. Concentrations of morphine, M6G, and M3G roughly 36 hours after ingestion were 57, 154, and 798 ng/mL, respectively. In another case report involving heroin rather than morphine, concentrations of heroin, 6-monoacetylmorphine, and morphine were 109, 168, and 1140 ng/mL, respectively, in blood, and 17, 12, and 425 ng/g, respectively, in gastrointestinal contents. Only morphine was detected in the urine, at a concentration of 3650 ng/mL (Rop et al., 1997). A decade-old report describes a case of fatal intoxication in an 8-year-old child due to a medication error where oral morphine was dispensed instead of oral meperidine. Before going to bed the child took one or two teaspoons of a 20-mg/mL morphine sulfate solution and was found dead in the morning. The blood morphine concentration was 128 ng/mL, the bile 135 mg/L, and the stomach contents 16 mg/L (2.3 mg total) (Poklis et al., 1995). Case reports of infants and children with methadone overdose are much more common than reports of accidental morphine overdose The discrepancy may be explained by the observation that, while hundreds of thousands of methadone-replacement patients are young enough to have children, oral morphine solutions are more likely to be found in the homes of older individuals with cancer.

5.6.4.4 Rectal

Plasma levels after rectal morphine administration are somewhat higher than after oral morphine but are much less than after parenteral administration (Ellison and Lewis, 1984). This route does not seem to be particularly popular among abusers, at least when compared to the rectal use of cocaine, which is a fairly common practice. One reason may be that rectal administration of morphine significantly reduces first-pass exposure in the liver, resulting in decreased hepatic transformation of morphine to its pharmacologically active metabolite, M6G (Babul and Darke, 1993). When 0.6 mg/kg of morphine was given to women undergoing cancer treatment, considerable variation between individuals was observed, but peak concentrations of 31–75 ng/mL were reached at between 45 and 120 minutes (Westerling et al., 1982). Fatalities have occurred at levels that were not much higher, and seizures, particularly in neonates, have been reported at levels that were much lower. Morphine-induced seizures have occurred at blood concentrations as low as 9 ng/mL (Koren and Maurice, 1989). One report described a postoperative death from cerebral hypoxia. A child was given several 4-mg morphine suppositories over the course of 4 hours. Blood levels measured 1.5 hours after death were 94 ng/mL (Gourlay and Boas, 1992). Different studies have shown rectal bioavailability to be extremely variable, ranging from 12 to 61% (Lindahl et al., 1981; Westerling et al., 1982). Pharmacologic manipulation of the morphine medium can improve absorption and result in levels comparable to oral administration. If the carrier medium is acidified, then the percentage of unionized drug increases, resulting in better absorption. Controlled-release morphine suppositories, containing polyglycerol ester of fatty acid, are available in some areas. Plasma levels rise more slowly than after oral administration, but remain elevated for longer (Takatori et al., 2005).

5.6.4.5 Intranasal

Heroin and morphine can both be administered intranasally, but the transnasal absorption of morphine is poor, at least when compared to other agents such as cocaine. At the turn of the century, probably up to the mid-1920s, as many people took heroin by nasal insufflation as by injection. Today's abusers seem to have rediscovered this route. Government surveys report that the practice of heroin snorting has become increasingly popular on the "club" circuit, and as heroin prices continue to fall this route can be expected to become increasingly popular. The pharmacokinetics of intranasal and intramuscular heroin have been compared in at least one study. Peak heroin concentrations, after either intranasal or intramuscular administration, occur within 5 minutes. Resultant blood levels after 6-mg doses of heroin by either route are on the order of 30–40 ng/mL. The mean elimination half-life after intranasal administration was 5.4 ± 4.5 minutes vs. 4.2 ± 0.12 minutes after intramuscular administration. Concentrations of 6-acetylmorphine reach their peak at 5–10 minutes after administration by either route, with peak levels of 22.6 ng/mL occurring after a 6-mg dose. The elimination half-life was longer for 6-acetylmorphine than for heroin: 10.8 ± 8.4 minutes after intranasal compared to 11.4 ± 5.4 minutes after intramuscular dosing with 6 mg. Once the heroin had been converted to morphine, the half-life for morphine following intranasal administration ranged from 90 ± 96 minutes (6-mg dose intranasally) to 168 ± 216 (12-mg dose intranasally) (Cone et al., 1993).

Surprisingly, heroin has proven to be a well-tolerated and rapidly effective analgesic agent in the pediatric setting. The pharmacokinetic profile of intranasal heroin in adults and children has been systematically studied, and compared with intramuscular heroin.

In controlled studies intranasal and intramuscular heroin produce very similar physiological responses (including pupil diameter, respiration rate, and temperature). Changes in behavioral measures (including euphoria, sedation, and dysphoria) were also similar. In other controlled trials intranasal heroin has been compared to results with intramuscular morphine in the setting of acute orthopedic pain in children with fractures. Intranasal heroin provided the same overall degree of pain relief; pain relief was comparable, but nasal administration brought a faster onset of action (Wilson et al., 1997; Kendall et al., 2001).

The occasional abuser who dies after snorting or inhaling heroin is seen but, in general, such occurrences are uncommon. Autopsy in these individuals seldom discloses the typical pattern of liver and lung disease seen in chronic abusers and the evidence suggests the non-traditional routes of ingestion lead to lower morphine blood levels. The median blood morphine concentration in 18 decedents who were non-injectors was 0.095 μg/g (range: 0.02–0.67 μg/g), significantly lower than is usually seen in heroin injectors (Thiblin et al., 2004).

5.6.4.6 Inhalation

Heroin can also be volatilized, usually by heating it on a piece of folded tinfoil, and the fumes then inhaled. In Hong Kong, in the past, heroin used for this purpose was often dyed red, and as the fumes rose from the foil they could be imagined to have the undulating shape of a dragon's tail, explaining why the practice is called "chasing the dragon." Alternatively, the lighted end of a cigarette can be dipped in powdered heroin and then smoked. To keep the heroin from falling off the end of the cigarette, the smoker has to hold his head tilted backwards. Heroin can also be mixed into the contents of a cigarette. None of these routes is particularly effective. Studies have been done in addicts comparing urinary excretion after heroin was administered by injection, volatilization, and smoking in the form of a cigarette. The mean percentage of morphine recovered after injection was

Table 5.6.4.6.1 Tissue Levels from Five Cases of Acutely Fatal Heroin Overdose

Tissue	Range
Blood	0.06–0.90
Urine	0.21–6.60
Bile	0.09–1.25
Stomach contents	0.01–0.03
Lung	0.09–0.18
Liver	0.07–0.29
Kidney	0.01–1.18
Heart	0.09–0.10
Spleen	0.11–0.95
Brain	0.01–0.10
Vitreous humor	0.03–0.35
Testicle	0.03–0.09
Muscle	0.01–0.04

Note: Values are in mg/L or mg/kg. Urine and bile specimens were hydrolyzed to free morphine from its conjugate.

Adapted from Kintz et al. (1989).

68%, after volatilization it was 26%, and after cigarette smoking it was only 14% (Kramer et al., 1991; Strang et al., 1997). The pharmacokinetics of heroin smoking and "snorting" are reviewed in the tables at the beginning of the chapter.

Heroin treatment for otherwise resistant addicts is now being used, apparently with some success, in the U.K., Switzerland, and the Netherlands. Similar programs are actively being considered in many other European countries. One consequence of this policy shift is that controlled pharmacokinetic studies with realistic doses of heroin are possible. Inhaling, or "chasing the dragon," has always been an attractive practice among addicts, and it is also considered an attractive treatment option because it avoids disease-spreading injection practices. The pharmacokinetics of smoked heroin has been studied, both in the laboratory and clinical setting (Jenkins et al., 1994), but earlier studies were limited by the amount of heroin that could ethically be given to a volunteer. That perhaps explains why earlier studies found smoked heroin's bioavailability to be unpredictable. Jenkins et al. (1994) found that heroin could be detected in the blood within one minute of smoking. Peak levels after smoking 10.6 mg/L were 299 ng/mL in one subject, and 108 ng/mL in another, and occurred within five minutes. Blood levels then rapidly declined to limits of detection (under 1 ng/mL) within 30 minutes of smoking. Levels of 6-acetylmorphine peaked one to two minutes after smoking. Jenkins et al. (1994) estimated that the half-lives of heroin, 6-monoacetylmorphine, and morphine were 3.3, 5.4, and 18.8 minutes, respectively. In general, these results are comparable to those observed after intravenous administration, but they are somewhat at variance with more recent kinetics estimates (Rook et al., 2006).

The melting point of heroin is much higher than that of cocaine, and preparing free-base heroin is more complicated than making "crack" cocaine, which is why this practice is relatively uncommon and mostly limited to treatment centers. However, Asians still heat heroin base on aluminum foil, usually with the flame of a cigarette lighter, and use a straw to inhale the vapors. This practice is widespread, but it seems to account for relatively few deaths. A review of heroin deaths in Sydney, Australia, from 1992 to 1996 found that fewer than 1% of the heroin-related deaths were associated with smoking heroin. In the cases where smoking was responsible, the median blood morphine concentration was 0.31 mg/L (range, 0.06–0.99 mg/L), and drugs other than morphine were commonly present (Darke and Ross, 2000). In a study of incarcerated Danish heroin users, heroin smokers accounted for nearly a quarter of the cases, with intravenous users having had a longer duration of use, earlier onset of abuse, and more serious somatic complications (Andersen et al., 1996).

Heroin treatment centers in Switzerland and the Netherlands offer addicts the option of injection or "chasing the dragon," and the pharmacokinetics of both routes have been compared. Plasma concentration data were obtained from 74 heroin inhalers and 32 injectors using pharmaceutical-grade heroin in realistic doses ranging from 66 to 450 mg. The bioavailability of smoked heroin was estimated at 53% (95% CI 43.7, 62.3). The terminal half-lives of heroin and 6-acetylmorphine were 7.6 and 21.8 minutes, respectively. The clearances of morphine and its glucuronides were estimated to be 73 L/h (95% CI 62.8, 84.4) (Rook et al., 2006).

The Drug and Alcohol Services Information System (DASIS) report for April of 2007 states that the proportion of primary heroin admissions who injected the drug declined from 69% in 1995 to 63% in 2005, while the proportion of primary heroin admissions who inhaled the drug increased from 27% in 1995 to 33% in 2005 (DASIS report, 2007). Future trends in this area are impossible to predict. In a recent editorial in the *Washington Post,* the president of the United Nations agency dealing with narcotics control (Office for

Drug Control and Crime Prevention, UNODCCP) speculated why, even though the heroin supply had nearly doubled since the invasion of Afghanistan, purity had increased very little and prices not at all (Costas, 2007). He suggests that terrorist-based organizations may be hoarding heroin supplies, but there certainly are, as yet, no data to support that contention.

5.6.4.7 Skin

Morphine is not sufficiently fat soluble to be absorbed through intact skin, at least not in quantities needed to produce psychological effects, unless the epidermis has been disrupted. In the mid-1990s, attempts were made at developing a morphine patch. It worked by causing a small epidermal bleb to be formed, allowing drug access to deeper layers of the skin. The results of initial experiments suggested that clinically relevant quantities of morphine could be delivered in this manner; however, the device has not yet come to market (Svedman et al., 1996). Other opioids, particularly fentanyl and sufentanil, and also meperidine, are well absorbed via this route. Because these other agents are also much more potent than morphine or heroin, transdermal application of fentanyl and buprenorphine is practical and widely used. Both types of patches are even beginning to appear on the black market, and some deaths from the diverted patches have been reported (Tharp et al., 2004).

5.6.4.8 Maternal/Fetal Considerations

Mothers can transfer morphine across the placenta and in their breast milk (Anon., 1861), but the degree to which morphine crosses the placenta is unpredictable. Narcotic agents do passively diffuse across the placenta, but many variables and methodologic issues could affect the outcome. Given the paucity of data about all drugs in breast milk, it is customary to estimate infant exposure to maternal medications by relying upon reported milk-to-maternal plasma drug concentration ratios, maternal plasma drug levels, and the volume of milk consumed over a given time by a normal child (Wilson et al., 1980).

In fact, the only really accurate way to measure breast milk drug transmission is to collect the entire volume of milk from both breasts over 24 hours, then measure both the volume of milk and the amount of drug contained it (Begg et al., 2002). This is difficult to do, and has not been done either for morphine or heroin in humans. However, when studies have been done on other drugs, such as prednisolone, fentanyl, and propofol, the amount of drug actually transmitted has been such a small percent of the amount given to the mother that most experts see little need to discontinue breast feeding (normally, a nursing mother having elective surgery is advised to discard her milk for 24 hours) (Nitsun et al., 2006). Nonetheless, it is possible for lethal amounts of morphine to be transferred via breast milk. A recent case report described the death of a breast-fed infant who died of a morphine overdose; his mother, who was an undiagnosed hypermetabolizer (i.e., had an overly active form of CYP2D6), had been prescribed codeine. Codeine relieves pain only to the extent that it is converted to morphine. Tragically, the mother converted an inordinate amount of codeine to morphine. The concentration of morphine in the breast milk was 87 ng/mL, while postmortem blood had a concentration of 70 ng/mL (Madadi et al., 2007).

Once morphine is taken up by the fetus it is metabolized and excreted, but neonates produce morphine glucuronides at a slower rate than older children or adults (Faura et al., 1998). Morphine and its metabolites can be detected in the amniotic fluid (Rurak et al., 1991)

or in specimens of hair or meconium (Little et al., 1990; Rurak et al., 1991; ElSohly et al., 1999).

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5.7 Tissue Disposition

A very wide range of values have been reported for morphine's volume of distribution, with some groups reporting values of less than 1 L/kg (Chauvin et al., 1987; Furman et al., 1990; Lotsch et al., 1996, 1999; Berkenstadt et al., 1999a, b; Rook et al., 2006), while others have calculated values approaching 7 L/kg. The reason for the variation is unclear, but could be related to the health of the volunteers studied. In patients with congestive failure and edema, fluid content would be higher, as would the volume of distribution. Conversely, in patients with renal failure, where intravascular volume is often decreased, smaller fluid volume might yield a smaller value of distribution. Cancer patients are often cachectic with depleted fat stores, which would also tend to decrease the volume of distribution. Finally, the extreme variation could be a function of the dose; hospital patients receive doses in the tens of milligrams; addicts may inject as much as 450 milligrams at one time. In spite of these difficulties, experience suggests that a value of 2–4 L/kg can be assumed for the young and reasonably fit with a narcotic overdose. Of course, none of these considerations apply after death. Cadavers have neither "compartments," nor volumes of distribution.

One consequence of the relatively large volume of distribution of morphine is that less than 2% of a given dose is to be found circulating in the blood. After initial intravenous administration, morphine is rapidly distributed throughout the body, so that tissue concentrations generally reflect the relative blood flow. After death, the time it will take morphine to redistribute, and the final tissue concentrations achieved when redistribution is complete, can be altered by a number of factors, most especially age (Chan et al., 1975). Postmortem redistribution from tissue to blood may easily double measured blood morphine concentration (Skopp et al., 1996; Bogusz, 1997), which is why the postmortem ratio of morphine to its metabolites has little, if any, forensic value or meaning.

Another impediment to interpretation has only recently become clear. The control of UDPG production is polymorphic, as is control of P-gp. The P-gp proteins normally

complex with morphine, but cannot complex with either M3G or M6G because both of these molecules are too polar. Once the two metabolites are formed in the liver they are transported back into the circulation by complexing with another glycoprotein called MDR1 (multi-drug resistance protein), which is located in hepatic sinusoidal membranes. If the wrong form of UDPG is present, either the expected quantity of G6P may not form, or it may never make its way to the bloodstream (Zelcer et al., 2006). This is a significant problem. A meta-analysis of 57 studies examined the effects of age, renal impairment, route of administration, and method of analysis on the ratios of M3G to morphine (M3G:M) and M6G to morphine (M6G:M), and the relative concentrations of M3G and M6G in living patients The ratios of metabolites to morphine were so wide (0.001–504 for M3G:M and 0–97 for M6G:M) as to render their calculation worthless for forensic purposes in the living, let alone the dead (Faura et al., 1998).

Muscle is an important storage site for opiates simply because of its sheer bulk. Several studies have shown that postmortem muscle morphine concentrations are similar to concentrations measured in blood (Garriott, 1991; Moriya and Hashimoto 1999; Drummer, 2004). Morphine is not so highly lipophilic as some agents, such as fentanyl, but it does accumulate in fat, where it can be measured after death (Levisky et al., 2000). Morphine crosses the blood–brain barrier, but does not possess an aromatic hydroxyl group at the C3 position, so it does not enter the brain as freely as heroin. The passage of morphine across the blood–brain barrier is mediated by P-gp located in brain capillary endothelium. Drugs that interfere with P-gp (such as doxorubicin) can alter brain morphine uptake and disposition. Morphine tissue disposition does not appear to be altered by the concomitant use of sympathomimetic agents such as ephedrine and phenylpropanolamine (Dambisya et al., 1992), but whether this is also true for methamphetamine and cocaine is not known, though there is some evidence that cholecystokinin plays the same role for methamphetamine and cocaine that is played by P-gp for morphine (Loonam et al., 2003).

Morphine and its glucuronides are not degraded by formalin, and tissues that have been preserved in formalin can still be analyzed for morphine, with the caveat that morphine will diffuse from tissue into the fixative solution (actually, formalin is a very efficient agent for extracting morphine). In controlled studies, when liver samples were stored in formalin, post-storage concentrations were found to have decreased by approximately 25% and the missing morphine was accounted for by formalin extraction (Cingolani et al., 2001).

5.7.1 Blood

Postmortem redistribution occurs (Moriya and Hashimoto, 1999), and measured blood concentrations are site dependent. Concentrations measured in samples from the heart are almost higher than concentrations measured in the periphery. For most drugs of abuse, concentrations measured in left ventricular blood are likely to be higher than in samples obtained from the right ventricle. Evidence suggests that the process of redistribution is most intense within 24 hours of death. If the sampling interval is long, substantial changes may already have occurred since the time of death. In a recent study of the effects of postmortem redistribution in cases of heroin overdose, the mean ratio of total morphine in the femoral artery to the femoral vein was 1.2 (range 0–4.5), and the ratio for left heart to right heart total morphine was 1.1, but with a very wide range of 0.4–3.2 mg/L. The ratio

of total morphine in the left ventricle to femoral vein was 2.0, but, again, with a very great range of inter-individuality; reported values ranged from 0.6 to 6.9 mg/L. In other words, centrally obtained morphine concentrations are on average twice as high as in samples obtained from the periphery, and there may be greater than 3-fold difference in morphine concentration between the right and left side of the heart (Crandall et al., 2006a). However, in some cases the difference may be very small, and there simply is no way the degree of change can be determined in individual cases.

Gerostamoulos and Drummer (2000) measured concentrations of morphine and its metabolites in a group of 40 patients. The average postmortem interval was 59 hours. The results of their study are shown in Table 5.7.1.1. The median total morphine concentration was 1.07 mg/L, with corresponding values of 0.32 ± 0.23, 0.03 ± 0.07, 0.16 ± 0.13, and 0.66 ± 0.56 for free morphine, normorphine, M6G, and M3G, respectively. These values are higher than those reported by Logan and Smirnow in another moderate-size series of 48 decedents, where the median morphine concentration in femoral blood was 0.082 (range, 0.006–1.20), with a mean of 0.143 mg/L. In "ventricular blood" (side not stated), the median was 0.141 mg/L (range, 0.008–836) with a mean of 0.230 mg/L (Logan and Smirnow, 1996). Blood taken from the heart had consistently higher concentrations than blood taken from the periphery.

Body packers dying from ruptured drug packets may have heroin and morphine levels that exceed 100,000 ng/mL (Joynt and Mikhael, 1985). Blood samples in 21 heroin-related deaths had heroin levels of 0 in every case. Mean 6-acetylmorphine levels were 9.9 ng/mL (range, 0–82.9), while mean free morphine levels were 222 ng/mL (range, 11.2–1277 ng/mL). Smugglers may be found to have extraordinarily high blood morphine concentrations. In one study of 10 smugglers from Colombia, blood concentrations of morphine were < 1.0 mg/L in four victims; no morphine was detected in one (who had died of peritonitis). Two victims had blood morphine concentrations of 4.4 mg/L and 6.7 mg/L, respectively, and three had morphine concentrations of 35.8, 39.4, and 52.6 mg/L, respectively (Wetli et al., 1997).

Very high blood morphine concentrations may also be seen in individuals with patient controlled anesthesia (PCA) devices, as the machine may continue to infuse after death. One published report describes a 44-year-old male with end-stage pancreatic cancer. He was receiving morphine for pain control via a single subclavian intravenous catheter which continued to infuse for up to 45 minutes after his death. Even though death was ruled to be the result of the adenocarcinoma, analysis of free and total morphine revealed free morphine concentrations in heart blood, vitreous fluid, brain, liver, stomach contents, and

Table 5.7.1.1 Postmortem Blood, Morphine Concentrations (n = 40)

	Median Total Morphine	Median Free Morphine
Subclavian	.58	.16
Heart[a]	.76	.19
Femoral	.64	.25

[a] The original paper does not specify from which side of the heart the samples were obtained (samples from the left would be expected to contain higher concentrations than those from the right).

Adapted from Gerostamoulos and Drummer (2000).

urine that were 96 mg/L, 52 mg/L, 26 mg/kg, 88 mg/kg, 82 mg/L, and 976 mg/L, respectively. Total morphine concentrations in those same organs were 421 mg/L, 238 mg/L, 65 mg/kg, 256 mg/kg, and 325 mg/L, respectively (Kerrigan et al., 2004).

Generalizing from these results is difficult for several reasons. Most importantly, the decedents of heroin overdose usually have higher median morphine concentrations than living patients being maintained on heroin (0.35 vs. 0.09 mg/L). The blood morphine concentrations of the two groups overlap substantially, ranging from 0.08 to 1.45 mg/L. Living heroin users often have morphine concentrations higher than the median concentration recorded for fatal cases (Darke et al., 1997).

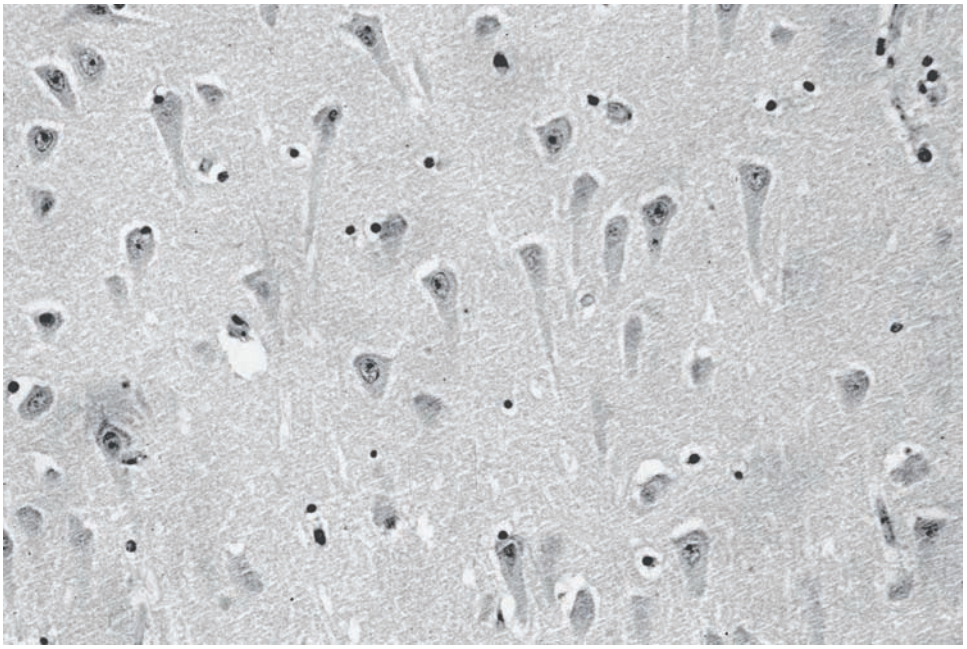
5.7.2 Brain

Immunohistochemical studies of heroin overdose show morphine localizing in the neuronal cytoplasm of the cerebral cortex, hippocampus, basal ganglia, thalamus, brain stem, and cerebellum. Binding also occurs, but to a lesser degree, in the endothelium of some brain capillaries (Liu et al., 1996). The human hippocampus is particularly rich in μ receptors (Figure 5.7.2.1), and the ganglion cells located in the hippocampus, as well as their axons and dendrites, concentrate morphine to a very significant degree, particularly in cases of heroin/morphine overdose (Wehner et al., 2000). The morphine concentrations observed in different regions of postmortem brain are at least partially dependent on the number of μ opioid receptors in that region. The number of receptors has been studied in the brains (Brodmann areas 11, 24, and 25) of dead heroin users and compared to controls (Schmidt et al., 2003). It appears there are no differences in areas 24 and 25, but the number of receptors is increased in area 11. This would suggest that the frontal lobe would be the optimal sampling site for measuring morphine concentrations.

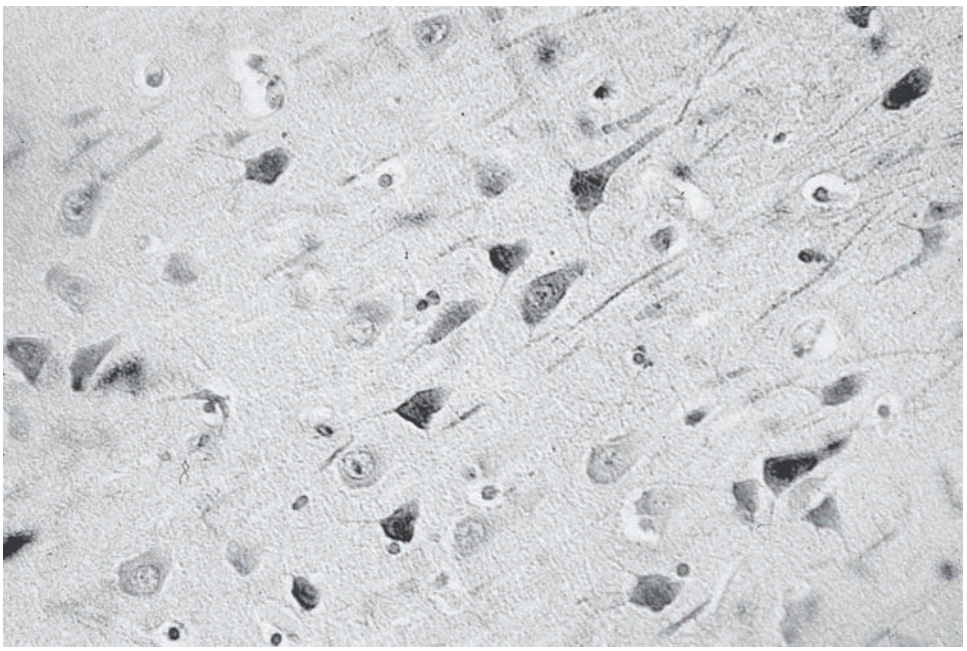
Morphine in the hippocampus exhibits a rather narrow range of concentrations. In one human postmortem study, values ranged from 134 to 298 ng/g, with good correlation between morphine concentrations in peripheral blood and hippocampus, although the concentration ranges observed in blood were much wider. For example, one victim of a lethal overdose had a total blood morphine concentration of 1.5 mg/L, but only 298 ng/mL in the hippocampus (Wehner et al., 2000). The limited concentration ranges observed in the hippocampus are presumably explained by receptor saturation. Once all of the μ receptors have bound to morphine, drug still remaining in the blood would be deposited in other tissues.

Overflow from the hippocampus is very likely the explanation for the wide range of blood/brain concentration ratios that have been reported in the literature. In the three heroin users described by Kintz et al. (1989) the blood/brain ratios were 13, 0.24, and 1.5, with tissue concentrations ranging from 0.005 to 0.089 mg/kg of wet brain. In a second small study, cerebrospinal fluid (CSF) and brain levels of 6-acetylmorphine were found to be much higher than levels in blood, liver, lung, and kidney. One individual had a blood 6-acetylmorphine level of 11.3 ng/mL, compared to levels of 58 ng/mL in the CSF and 158 ng/mL in brain. In a second case, blood levels were 16.2 ng/mL, while levels in the CSF and brain were 38.5 and 53.6, respectively (Goldberger et al., 1994). With the exception of CSF, the concentration ratio of blood morphine to the morphine concentrations in other tissues varies so widely as to make such determinations useless.

Blood/CSF ratios, however, appear to have more predictive value (2.74 ± 1.69). In 89% of reported cases, morphine levels were lower in the CSF than in the blood (Wahba et al., 1993; Moriya and Hashimoto, 1997). Some information about drug distribution has been



(a)



(b)

Figure 5.7.2.1 Histochemical demonstration of opiate receptors. The human hippocampus is particularly rich in μ receptors, and immunohistochemical studies show that the ganglion cells located in the hippocampus, as well as their axons and dendrites, concentrate morphine to a very significant degree. The micrograph on the top is from a drug-free control brain and has been stained with anti-morphine antibodies. The bottom micrograph shows intense uptake of anti-morphine antibodies in brain tissue from a heroin overdose. (Courtesy of Professor Frank Wehner, University of Tubingen.)

derived from studies of pain management. Plasma and CSF steady-state concentrations of morphine, as well as M3G and M6G, were studied in 21 cancer patients being treated with chronic subcutaneous morphine infusions. A moderate but still statistically significant correlation was found between the daily dose of morphine administered and the concentrations of morphine and its metabolites in the CSF. The mean CSF/plasma morphine concentration ratio was 0.36 ± 0.07. As is true for brain/plasma ratios, the correlation between CSF and plasma values was poor (Wolff et al., 1996). The mean M3G and M6G concentrations in CSF were less than 10% of the concentrations found in plasma.

Comparison of the morphine concentrations in the medulla oblongata and the cerebellum provides information on the interval between morphine administration and death. If the postmortem interval is relatively short, the ratio of morphine in the brain stem to the concentration in the cerebellum will be less than 1. Higher ratios suggest that a much longer time has elapsed (Vycudilik, 1988). The ratio rises above 1 if at least several hours have passed.

5.7.3 Liver

Hepatic morphine concentrations have been measured in several series. The first series, consisting of 10 cases, was reported by Felby et al. in 1974; the mean morphine concentration was 3.0 mg/kg, and the range was from 0.4 to 18 mg/kg. Two cases reported by Chan et al. in 1986 had liver concentrations of 7.0 and 2.9 mg/kg, respectively. In a series of 20 narcotic-related deaths reported by Goldberger et al. (1994), liver concentrations of free morphine ranged from 0.039 to 0.55 mg/kg, with an average value of 0.21 mg/kg. In those same individuals the average blood concentration was 0.099 mg/L (Goldberger et al., 1994). Biliary concentrations of 312 mg/L and 248 mg/L were reported in two cases by Chan et al. (1986) — these values were nearly 30 times higher than the blood levels in the same individuals. Others have reported less striking differences between liver and bile concentrations. Kintz et al. (1989) found bile levels of 0.087–0.363 mg/L, and liver morphine concentrations of 0.067–1.424 mg/kg. In the most recently reported series of 25 heroin-related deaths the mean liver concentration was 0.33 mg/g (range 0.04–1.56), while the concentration of free morphine in femoral blood was 0.135 mg/L, a 10-fold difference (Wyman and Bultman, 2004). The differences have partly to do with the amount of drug taken before death, and partly with the chronicity of use. It also appears that the rate of hepatic morphine metabolism may depend on the size of the liver itself. In controlled studies, plasma morphine concentrations are higher in patients with liver resection than they are in controls or in patients with colon resections who had been anesthetized with equivalent amounts of morphine (Rudin et al., 2007). The phenomenon is probably explained by the fact that less of the enzyme required to convert morphine to its glucuronides (UTG1A1 and UGT1A8) is available to perform the conversion (Ohno et al., 2008).

Concentrations of free morphine in the liver may be very high, but that is not the case for heroin. Even when heroin and its metabolites are measured, no heroin or 6-acetylmorphine is detected in samples from the liver, though high concentrations may be found in the brain; 158 ng/mL in one case report and 54 ng/mL in another (Goldberger et al., 1994). The same finding has been repeated in several studies (Wyman and Bultman, 2004). Quantitation of hepatic morphine levels is a particularly useful approach in the case of exhumations. Blood and urine are unlikely to be available; however, at exhumation soft tissue will

be available, and formalin embalming does not interfere with the extraction and measurement of free morphine (Levine et al., 1994). Concentrations of morphine glucuronides remain stable in liver for several days after death, but if the cadaver is not refrigerated, or if the postmortem interval is long (>3 days), free morphine will be liberated, and the ratio of free to conjugated morphine will not be a valid indicator of concentrations prior to death (Skopp et al., 1996; Bogusz, 1997; Moriya and Hashimoto, 1997). Some believe that limb skeletal muscle can be used for the same purpose (Pounder et al., 1996).

5.7.4 Lymph Nodes

Enlargement of abdominal lymph nodes occurs more often in active drug users than in normal controls. In one series, birefringent material was detected in portal lymph nodes in 42% of addicts studied, and signs of antigen stimulation, as evidenced by the number of germinal centers and plasma cells, were twice as common in heroin addicts as in controls (60% for heroin addicts vs. 30–40% in normals) (Kringsholm and Christoffersen, 1987). Enlarged hepatic lymph nodes are a very common finding in heroin addicts. Whether or not the enlargement is the result of some toxic effect exerted by morphine itself or the contaminants injected with it is not known. Human lymph nodes concentrate morphine, and in some cases nodes taken at autopsy may have higher concentrations of morphine than blood and bile. Reported levels have ranged from 0.03 to 0.87 mg per 100 g of tissue (Nakamura and Choi, 1983).

5.7.5 Other Biofluids

Most of the opiates can be detected in saliva, but results must be interpreted with some caution. The oral or intranasal use of these drugs may result in very high saliva levels due to high concentrations of drug in the oral cavity (Wang et al., 1994) and the ingestion of poppy seeds may cause unexpectedly high morphine concentrations (Rohrig and Moore, 2003). As might be expected, for the first hour after intranasal heroin administration saliva morphine concentrations far exceed those in plasma (Cone et al., 1993).

Simultaneous measurements of morphine in saliva, plasma, and urine have shown that urine concentrations of morphine may be as much as 100 times greater than concentrations measured in saliva, and 16 times higher than levels in the plasma (Cone et al., 1991). Because it is much more soluble in water than morphine, heroin appears in saliva much more quickly (Wang et al., 1994), but neither compound is likely to be detectable in saliva for much more than 12 hours. Low doses of heroin (less than 5 mg) are unlikely to be detected in saliva at all (Gorodetzky and Kullberg, 1974).

Heroin is metabolized too quickly to ever be detected in CSF levels, but 6-monoacetyl morphine may be detectable, and sometimes at very high concentrations (>0.20 mg/L), even when no heroin or 6-monoacetyl morphine is detected in the blood. However, 6MAM is more likely to be found in the vitreous than in CSF; Wyman and Bultman (2004) found it present in all 25 cases analyzed in their study. The codeine/morphine concentration ratio in vitreous humor is generally similar to that reported for blood and urine, suggesting that vitreous measurement can be used as the basis for differentiating among fatalities induced by codeine or morphine (heroin) (Lin et al., 1997). In one study of 29 heroin-related fatalities, the mean concentration of 6-monoacetyl morphine was 10 ng/mL in the CSF and 17 ng/mL in the vitreous (Pragst et al., 1999).

Morphine concentrations peak in the CSF three hours after intramuscular administration, and at equilibrium the ratio of CSF to plasma morphine is very nearly 1:1. The elimination half-life of morphine from CSF is the same as the elimination half-life of morphine from the blood (Nordberg, 1984). Measurements made in patients undergoing lumbar myelography 1.5 hours after they had been given 10 mg intramuscular doses of morphine revealed CSF levels of morphine, M6G, and M3G of 8.8 ng/mL, 35 ng/mL, and 55 ng/mL, respectively (Laizure et al., 1993). CSF morphine levels higher than 20 ng/mL are thought to be consistent with narcotic-induced fatal respiratory depression (Logan and Luthi, 1994).

5.7.6 Urine

After morphine has been converted to a glucuronide, it is excreted in the urine. In autopsy studies, urine concentrations of conjugated morphine have ranged from 100 to 120,000 ng/mL (Sawe, 1986). The concentration ultimately measured depends largely on the volume of urine that is allowed to collect between measurements (Cone, 1990). In a study of 29 victims of heroin overdose, the blood/urine ratio for morphine was 2.53 ± 5.45, but the range was so wide (0.006–25.2) that drawing any sort of inference is impossible (Wahba et al., 1993). In a study of 168 heroin-related deaths investigated by the San Francisco Medical Examiner's office in 1999, total morphine concentrations in the urine ranged from less than 10 to 85,000 ng/mL, a result strikingly similar to the results in Sawe's original study performed more than 15 years earlier (Karch et al., 2000).

Racial and inter-ethnic differences must also be considered. Chinese subjects have a higher clearance rate for morphine than Caucasians primarily because they form more glucuronide than Caucasians do, and they do so more quickly. Whether or not these differences will have a bearing on drug detection is not clear, but the differences certainly can have clinical significance; in nontolerant subjects, equal doses of morphine produce more respiratory depression and a greater drop in blood pressure in Caucasians than in Chinese (Zhou et al., 1993). The differences are, no doubt, a consequence of UDPG2 polymorphisms (see Sections 5.77 and 5.8.6.3).

5.7.7 Postmortem Tissue Measurements

In the past, the half-life of 6-acetylmorphine was believed too short to routinely quantitate. In six volunteers given single doses of heroin (3.0 and 6.0 mg), the urine half-life averaged 0.6 hours, with a total detection time of 2–8 hours. In contrast, free morphine and

Table 5.7.7.1 Postmortem Morphine Values in Swine (Concentrations Are in ng/mL)

Time	Left Ventricle	Femoral Artery	Right Ventricle	Femoral Vein	Vitreous Humor
10 minutes	424	407	394	576	880
60 minutes	1061	1346	1071	1039	439
8 hours	706	461	565	778	198

Adapted from Crandall et al. (2006b).

total morphine were detectable in the urine for up to 24 hours after heroin administration (Cone and Welch, 1991). With advances in technology, it is now possible to monitor heroin and all of its metabolites simultaneously. The measurement process is now straightforward using liquid chromatography–mass spectrometry.

Postmortem measurements of morphine and its metabolites in cases of heroin overdose have been reported. In a German study, morphine, M3G, M6G, and 6MAM were quantitated simultaneously in 21 heroin overdose victims. Blood concentrations of morphine ranged from 8 to 1539 ng/mL, M3G from 111 to 941 ng/mL, M6G from 32 to 332 ng/mL, and 6MAM from 0 to 73 ng/mL. The levels of morphine were correlated with glucuronide values and with 6MAM (Bogusz, 1997). Very similar results, at least for the glucuronides, have been reported from Australia (Gerostamoulos and Drummer, 2000) and from the U.S. (Logan and Smirnow, 1996).

Concentrations of morphine, M3G, and M6G are generally lower in blood and in vitreous humor than in CSF, but the concentrations of morphine and molar ratios of M6G to morphine in blood and CSF correlate very well. Thus, the presence of much more morphine than glucuronide is thought to be consistent with ingestion immediately prior to death. However, the ratio of morphine to its metabolites is highly dependent on (1) the time elapsed from death until tissue sampling (postmortem interval), (2) the temperature, (3) existing but unsuspected UDPG polymorphisms, and (4) the tissue being sampled, and (5) the volume of distribution of the three molecules.

Gerostamoulos and Drummer (2000) did not find significant differences between morphine and morphine metabolite concentrations in samples taken from subclavian, heart, and femoral vessels, nor did they observe any significant differences between concentrations measured on arrival at the morgue and concentrations measured, on average, 59 hours later. There are two possible explanations for this finding; either significant postmortem redistribution of morphine and its metabolites simply does not occur, which seems unlikely, or redistribution and equilibration had already occurred before the first blood samples were drawn. The latter seems more likely, given that, when others have sampled multiple sites, great concentration differences were observed (Skopp et al., 1996).

The results of recent animal studies also support the second possibility. In a study of experimental morphine overdose, 20 New Hampshire swine, each weighing between 50 and 70 kilograms, were injected with a morphine dose of 2 mg/kg. Blood concentrations were then measured and compared with concentrations in the vitreous humor, as well as in the femoral artery and vein, and left and right ventricles. Samples were obtained at regular intervals starting 30 minutes before the injection and continuing for 95 hours after the time of death.

Comparisons were then made between antemortem and postmortem values. The researchers found that concentrations of both free and total morphine varied significantly between animals, between sampling sites, and over time. Free morphine values were generally higher after death than before, but total postmortem morphine levels were similar to antemortem levels. Time had an effect, but a small one (Crandall et al., 2006b). Concentrations of free morphine had doubled within one hour of death, and then dropped by nearly three quarters in one hour.

Overreliance on morphine-to-metabolite ratios can lead to erroneous conclusions (Skopp et al., 1996). Morphine has a very large steady state volume of distribution (V_{ss} of 2–5 liters), but the volume of distribution of the metabolites is small ($V_{ss} < 1$). At equilibrium,

virtually all the free morphine is found in tissue, while all the glucuronides are found in the blood. The movement of less than 1% of free morphine from tissue back into postmortem blood would double the observed concentration and lead to the erroneous conclusion that morphine concentrations at the time of death were much higher than they actually were. Just what can be done to correct for this issue is not known, and there is no reproducible scientific method by which one could determine how much free morphine had migrated back into tissue.

Tissue levels in heroin body packers carrying balloons full of heroin in their intestines may reach astronomic levels. A woman who had swallowed a number of packets containing 25% heroin was found to have a 6-acetylmorphine level of 184,000 ng/mL. Morphine and codeine levels were equally impressive (120,000 and 1700 ng/mL, respectively) (Joynt and Mikhael, 1985; Wetli et al., 1997). A report from Thailand indicates that the average deceased body packer is carrying 30–50 g of heroin that is 50–90% pure (Sribanditmongkol et al., 2006), though this amount seems quite small compared to other reports that have described cases where more than half a kilogram of heroin was contained in the intestines (Wetli et al., 1997).

5.7.8 Excretion and Detectability

The conversion of heroin to morphine is so rapid that the probability of detecting heroin in either blood or urine is small, and the possibilities of detecting 6MAM not that much greater. However, once the conversion to morphine is complete, the limits of detection for the metabolites are the same as for morphine itself. Testing for opiates in urine is a problem. Poppy seeds are widely eaten and they contain both morphine and codeine, but not heroin. Poppy seeds from different origins contain widely variable amounts of morphine (2–251 mg/g) and codeine (0.4–57.1 mg/g) (Pettitt et al., 1987; Pelders and Ros, 1996), but under no circumstances will innocent poppyseed eaters have detectable levels of 6-acetylmorphine. Small amounts of 6MAM may also be ingested directly as contaminants produced along with heroin in the manufacturing process (O'Neil and Pitts, 1992).

German researchers recently compared concentrations of urine morphine and its metabolites in two groups of volunteers. On two separate occasions the volunteers consumed cake that had been baked with one of two different kinds of poppy seeds (10–60 g of poppy seeds): one contained high concentrations of papaverine and noscapine, two compounds considered as surrogate markers for heroin, while the other type of poppy seeds were also very high in morphine content, but contained relatively little of the marker compounds. The researchers then collected serial urine samples and tested them using liquid chromatographic–tandem mass spectrometry. Peak concentrations of morphine, codeine, and their glucuronides appeared 4–8 hours after ingestion of poppy seeds, and morphine concentrations were often in excess of 10 μg/mL. Morphine glucuronides were present in serum samples taken up to 6 hours after consumption. Free morphine was only detected in traces (1–3 ng/mL) within 2 hours of consumption. Neither noscapine nor papaverine was detectable in urine or blood samples after the consumption of poppy seeds containing up to 94 μg noscapine and up to 3.3 μg papaverine. Both of the latter were rapidly metabolized, whereas desmethylpapaverine and, especially, its glucuronide were found in urine samples even 48 hours after consumption. Thus the presence of papaverine and its metabolites should not be regarded as markers for the consumption of heroin, which can

only be inferred if a specific marker such as acetylcodeine is detected. Unfortunately, the chances of finding 6MAM are small (Trafkowski et al., 2006).

If 6MAM is not detected, distinguishing innocent poppy seed ingestion from heroin abuse can be problematic. In the past, the distinction was made by relying on the presence of confirmatory evidence such as track marks. That approach was never very effective, and now that many heroin users insufflate the drug, the presence or absence of track marks cannot be relied upon to make that distinction. Workplace testing regulations now recognize that reality and have raised the urinary opiate cutoff to 2000 ng/mL of urine. If concentrations exceed the 2000 ng/mL cutoff, 6MAM must also be detected to prove heroin use.

Thebaine, a naturally occurring compound found in poppy seeds, also offers potential as a surrogate for the diagnosis of heroin consumption. It is not present in refined heroin, but does appear in the urine of poppy seed consumers. Volunteers given an 11-g dose of poppy seeds were found to have urine thebaine concentrations ranging from 2 to 81 ng/mL (Cassella et al., 1997). Another alternative is to test hair. Both 6MAM and M6G are deposited within the hair matrix and remain stable there for many months (Rothe and Pragst, 1995). The only problem with this approach, and it is largely theoretical, is that heroin samples can also contain 6MAM. That means that the presence of 6MAM, like the presence of heroin itself, might be the result of external contamination (as in the case of a customs officer who confiscates a large quantity of heroin).

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5.8 Interpretation of Opiate Blood and Tissue Concentrations

5.8.1 Introduction

No matter which tissue is analyzed, the cause of death cannot be determined from the isolated toxicological measurements, although with some drugs very firm inferences can be drawn. It is accepted dogma that specific postmortem blood concentrations cannot be said to have caused death, morbidity, or even significant impairment, without also knowing the clinical history and autopsy findings. The problem with this concept is that nearly 10% of all autopsies are found to be "negative," a result mainly of the fact that the presence of most genetic diseases and many viral disorders cannot be detected without DNA testing. Even if gross autopsy changes are visible, the investigator still needs to observe the scene, obtain the individual's past medical and drug use history, and factor all these components together before an accurate cause of death can be determined. There is a tendency among death investigators to forget that historical information may be available from many sources, including the emergency room records and interviews, the records of physicians who attended the patient in the past, and the pharmacies that provided the drugs (Harding-Pink and Fryc, 1988). In the following sections the usefulness of each testing modality is reviewed.

5.8.2 Urine Testing

Poppy seed ingestion ensures the presence of both codeine and morphine in the urine. A prescription for codeine could explain the presence of some, but not massive, amounts of morphine detected in the urine. After oral dosing with codeine, 5–15% may be detected in the urine as free or conjugated morphine (Fell et al., 1983; Gjerde and Morland, 1991). Indeed, the conversion of codeine to morphine is believed to be the method by which codeine produces analgesia. Under current federal workplace testing rules, urine specimens are considered to be presumptively positive if an opiate concentration in excess of

2000 ng/mL is detected. For confirmation, the sample must be tested again with a different method, preferably gas chromatography and mass spectrometry. Morphine or codeine must be present in a concentration of at least 2000 ng/mL and, to specifically prove heroin ingestion, at least 10 ng/mL of 6-monoacetyl morphine must also be detected. However, the half-life of this compound is so short that these criteria often cannot be met. In the setting of a drug death investigation, the vitreous humor is the matrix most likely to yield a positive test for 6-monoacetyl morphine, as that molecule persists in the vitreous long after it has been cleared from the bloodstream (Wyman and Bultman, 2004).

Heroin use can also explain the presence of both morphine and codeine in the urine, simply because it is rapidly converted to morphine, and also because heroin is often contaminated with small amounts of codeine (Bastos et al., 1970). Humans do not metabolize morphine to codeine (Mitchell et al., 1991). Codeine-containing cough syrups (one syrup sold in Japan and Southeast Asia is responsible for a large percentage of positive tests at the U.S. Army testing lab in Hawaii) are an important cause for false positive workplace drug tests, as are poppy seed-containing pastries. Poppy seeds naturally contain morphine and codeine, and very high levels can sometimes be found in some individuals if they have consumed substantial amounts (several teaspoons) of the seeds (ElSohly et al., 1988). One must accept that if the individual being tested has a prescription for codeine, and also claims to have eaten poppy seeds, it is possible that their urine might contain more morphine than codeine in it, even if the person was not abusing drugs!

The commercial opiate assays currently in general use are unlikely to cross-react with synthetic and semi-synthetic opiates, partly because the original federal regulations regulating workplace programs are specific for morphine. However, newer assay systems are being introduced and federal rules modified so that the detection of drugs such as oxymorphine is not only possible, but also allowable. The problem looming on the horizon is that a black market in fentanyl seems to be emerging, and that compound will not be detected by traditional screening methods. Enzyme screening tests for fentanyl are now available, but their expense has, so far, prevented their widespread implementation.

5.8.3 Blood Testing

Regular opiate users rapidly become tolerant to opiate-induced respiratory depression, making the interpretation of blood/plasma concentrations (from the living or dead) extremely difficult. In acute overdose, where death is obviously due to respiratory depression and frothy pulmonary edema is present, blood concentrations have ranged anywhere from 100 to 2800 ng/mL (Felby et al., 1974; Richards et al., 1976; Reed et al., 1977; Logan et al., 1987; Sawyer and Forney, 1988; Steentoft et al., 1988; Kintz et al., 1989; Logan and Smirnow, 1996; Bogusz, 1997; Gerostamoulos and Drummer, 2000; Jung and Reidenberg, 2005; Crandall et al., 2006). Earlier reports were published before it was understood that M6G had the same psychoactive effect as morphine. The early studies were also performed when the first generation of radioimmunoassays was in use. The value of these tests is largely diminished by the fact that they had such wide cross-reactivity — they produced results that did not give an accurate picture of the free morphine in circulation. Thus the ranges reported using this technique were neither very accurate nor very meaningful. Even if these numbers did have some meaning, the same absolute morphine concentration in a naïve individual may be associated with death, while in an experienced user it

may produce minimal, if any symptoms. Morphine blood concentrations in living addicts receiving maintenance heroin may, in fact, be substantially higher than in individuals dying of heroin overdose (Darke et al., 1997). Simply put, postmortem blood morphine concentrations cannot be interpreted in isolation.

Some special considerations apply to postmortem testing that are not encountered in the clinical laboratory. Morphine and its glucuronides are extremely stable in refrigerated blood and in plasma, as is morphine in unrefrigerated blood. But the glucuronides are not stable in unrefrigerated postmortem blood (Skopp et al., 2001). Temperature, exposure to light, length of sample storage, and bacterial overgrowth all affect the final measured concentration. The longer the sample is stored and the higher the temperature, the more likely decomposition is to occur. Most of the change is a result of bacterial hydrolysis of morphine glucuronides; bacteria can be cultured from postmortem blood within 5 hours of death (Melvin et al., 1984).

Other than the fact that the respiratory drive ceases and the lungs fill with protein-rich edema, the actual cause of these deaths is not completely understood, particularly if nothing is known about the state of tolerance. At the trial of Harold Shipman, a U.K. physician who murdered hundreds of his patients with heroin injections, it was argued that the absence of heroin in the hair in the face of massive concentrations of heroin in muscle and liver proved that the decedents could not have been tolerant. Had they been taking heroin for any length of time, heroin or its metabolites would have been detected in the hair and it was not. Tagliaro et al. (1998) observed that morphine concentrations in the hair of heroin overdose victims are comparable to hair concentrations in former heroin users enrolled in rehabilitation programs, and that hair from individuals in both groups contained substantially less morphine than hair from living, active heroin users.

While it is reasonable to presume that high postmortem blood morphine concentrations in the face of low (or undetectable) hair morphine concentrations indicate a lack of opiate tolerance, there are some who dispute this contention. In a study of 60 cases, death was determined to be related to heroin intake in 28. In 18 of the 28 cases where heroin was clearly the cause of death, opioids were absent in the most recent hair segments, suggesting a reduced tolerance to opioids. But in the remaining cases, where morphine was found throughout the hair, the blood morphine levels were similar to levels in the decedents without morphine at the hair root (Druid et al., 2007). The results suggest that abstinence is not a critical factor for heroin overdose death. Clearly, more research is needed.

5.8.4 Determining the Cause of Death

5.8.4.1 Value of Scene Investigation

Examination of the death scene may reveal details that can confirm or discredit the autopsy and toxicology results. Halpern was one of the first to point out that there is sameness about heroin-related deaths (Halpern, 1972). More often than not, heroin users are found on the street or in an alley, injecting by themselves and dying in isolation. Decedents are much more likely to be male (> 70%), mostly in their mid-20s (Louria et al., 1967; Cherubin et al., 1972; Wetli et al., 1972). Since Halpern published his original observation, the percentage of male decedents has increased and now accounts for more than 90% of cases in most regions.

Drug paraphernalia is likely to be found at the victim's side. Even in the 1970s, before anyone had ever thought to add fentanyl to heroin, addicts were occasionally found dead

with needles still in their arms. Some of those cases may have been misdiagnosed homicides; at this point there is simply no way to tell. Today this finding suggests use of heroin laced with fentanyl. In the past, use of fentanyl was mainly the prerogative of medical workers; they had access. Medical workers who die of fentanyl are usually found at home or at work (often a hospital) (Henderson, 1991). Now that illicit fentanyl is being added to street heroin, the profile of decedents has changed, and the possibility of fentanyl overdose must always be considered, even in what appears to be a straightforward heroin-related death.

In spite of recent studies suggesting abstinence is not an issue, experience suggests that deaths in opiate abusers are much more likely to occur when the user has been abstinent, and it is important to establish whether the decedent had just been released from jail or a detoxification program (Harding-Pink and Fryc, 1988). It is also important to establish whether or not alcohol or other drugs have been consumed. The combination of alcohol and opiates is said to be more lethal than the consumption of either drug alone, however, this assumption remains somewhat controversial. Ruttenber et al. (1990) studied 505 heroin-related deaths and found that those who had not been drinking did have higher morphine levels in their blood and bile (500 and 7500 ng/mL, respectively) than those individuals who had been drinking (300 and 3000 ng/mL, respectively). Similar findings were reported in an Australian study (Darke et al., 1997). When blood toxicology results for deaths attributed to heroin overdose were compared with those of a sample of 100 living heroin-replacement patients who had injected within the preceding 24 hours, the fatalities had higher median concentrations of morphine than the living heroin users (0.35 vs. 0.09 mg/L), but there was massive overlap between the two groups (0.08–1.45 mg/L). Alcohol was detected in 51% of the fatalities (median = 0.10 g/100 mL) but in only 1% of the heroin-replacement patients, and there was a significant negative correlation among fatal cases between blood morphine and blood alcohol concentrations. A similar negative correlation was not found for blood benzodiazepines. These results led the authors to suggest a possible role for alcohol, and possibly benzodiazepines in some of the deaths. The suggestion is often heard in the investigation of buprenorphine-related deaths (Drummer, 2005).

The historical record is especially important when investigating deaths related to other opioids, particularly methadone, where inter-individual responses are known to vary considerably because of genetic polymorphisms (that are never measured by medical examiners), sex, weight, use of concomitant medications, duration of methadone treatment, previous exposure to other opioids, and plasma concentrations of α_1-acid glycoprotein (Garrido and Troconiz, 1999). Methadone also induces the enzymes required for its own metabolism, which means that death is more likely to occur early, rather than late in therapy. Naïve users are at much greater risk for overdose than individuals who have been taking methadone for some time (Wu and Henry, 1990; Caplehorn and Drummer, 2002). A history of liver disease (from alcoholism or hepatitis) may imply decreased production of α_1-acid glycoprotein and a sudden rise in plasma methadone levels. While it has always been assumed that death from methadone overdose was simply a function of respiratory depression, there is now evidence that the situation is much more complicated. Methadone inhibits the hERG cardiac potassium channel and that can lead to QT interval prolongation and sudden death, even when methadone is taken in relatively low doses (for a detailed discussion, see Section 5.9.7 on methadone) (Ehret et al., 2007).

5.8.4.2 Toxicology

Textbooks on forensic toxicology almost always contain the disclaimer that the cause of death can only be determined by the pathologist, who must carefully consider and integrate the findings of the scene investigation, autopsy, and toxicological analysis. However, the statement is potentially misleading, because the toxicological analysis is not an independent element of the investigation. In fact, the results of toxicological testing are a direct function of the method used to perform the autopsy and collect the specimens that are eventually tested. Several authors have dealt with this reality, referring to the problems collectively as "preanalytic issues" (Drummer and Gerostamoulos, 2002; Skopp, 2004; Flanagan and Connally, 2005; Flanagan et al., 2005). As Skopp (2004) observes, even though these issues do not involve the actual performance of an analysis, answers to these questions are nonetheless vital, because they can alter the final analytical result. A 50 mL blood sample drawn from unligated femoral vessels very likely represents hepatic, not peripheral blood. A sample from the left side of the heart or subclavian may contain a much higher morphine concentration than existed at the time of death. The longer the postmortem interval, the greater the chance that any concentration measured will not accurately reflect the concentration at the time of death. The list of "preanalytic issues" is very long, and only several of the most important will be dealt with here.

5.8.5 Provenance

Without knowing the provenance of a sample, there is no guarantee of accuracy. Every report should state how many tubes of blood were collected, and from where in the body they were obtained. The report should also note who actually did collect the specimen as they are likely to sample the same site every time. What preservative did the tubes contain? How were the tubes stored until the time of analysis? How many tubes were actually collected? What size syringe was used to draw the blood? If more than 40 mL of blood were taken from the inferior vena cava, some blood (and therefore some drug) drawn directly from the liver would be included in the sample. Since all of the abused drugs are metabolized in the liver, inclusion of hepatic blood in a peripheral specimen will yield a falsely elevated value. How long did the samples sit at room temperature until they were refrigerated (Prouty and Anderson, 1990; Drummer et al., 2004)? Not all metabolites are stable. Were the containers made of glass or plastic? Some drugs adhere to the side of plastic, but not glass tubes. If blood was drawn from the femoral vessels, were they ligated first (Pounder, 1993)? If not, how many milliliters of blood were drawn? Were other fluids and tissues collected and, if so, how were they collected and stored? Was blood drawn in the hospital prior to death collected? If it was, was it analyzed, and how did the result at autopsy compare with the results obtained antemortem? What color vacutainer was used, and what preservatives were added? Ideally, all of this information would be provided in a standardized specimen collection form. The form should include comments on any potential problems with the specimen, and on what impact these problems may have exerted on the final analytic results. If the blood sample is old, has the stability of the drug during storage ever been studied? If so, what were the results? Was the chain of custody followed? Were the samples stored in a secure area? Was a log maintained to record those with access to the specimen? These are all analytical issues, even if they do not involve analysis per se. The pathologist needs to have this information, but is unlikely to possess it, and cannot really make a valid final determination without it.

5.8.6 Postmortem Chemistry

5.8.6.1 Redistribution and Diffusion

Blood concentrations measured in postmortem material are not equivalent to measurements made in the living. "Heart blood" collected at autopsy is blood in name only. Blood is a living tissue; except to the degree bacteria can be recovered from this material, postmortem "blood" is not a living thing, it is water and tissue debris (Jones, 1998). Not one single control study, even in animals, has ever shown that postmortem drug concentrations accurately reflect drug concentrations at the time of death, but a goodly number have shown quite the opposite to be true, chiefly because of the problem of postmortem redistribution (Pounder et al., 1996; Hilberg et al., 1999; Moriya and Hashimoto, 1999; Drummer and Gerostamoulos, 2002; Flanagan et al., 2003; Ferner, 2008). "Postmortem redistribution" is defined as the movement of a drug down a concentration gradient after death. The process begins immediately and continues indefinitely, but it appears that the greatest changes occur within the first 24 hours. The greater the apparent steady state volume of distribution of a compound, the more likely the process will occur. Redistribution is one of the chief reasons why the results of quantitative postmortem blood testing can be so misleading.

Perimortem aspiration of stomach contents is just one reason why an accurately measured value may still lead to an inaccurate result (Knight, 1975; Pounder and Yonemitsu, 1991). If there is drug in the stomach, aspiration will cause high drug concentrations within the bronchial tree. Simple diffusion out of the bronchi then allows drugs to traverse thin-walled pulmonary vessels and, if aspiration occurs into the left lung, the result may be spuriously high drug concentrations if cardiac blood is the analyzate. Because of these two problems — aspiration and drug redistribution — blood samples obtained from different parts of the body are likely to contain different concentrations of the same drug. Drug measurements made in blood from the left heart blood are especially likely to be misleading.

The physical properties of the drug determine, to a large extent, the degree of postmortem redistribution. Drugs with an apparent low steady state volume of distribution, such as ketoconazole, will penetrate tissues poorly. In the living, at equilibrium, most ketoconazole will be in the plasma compartment. After death, it would still be in the plasma compartment, and not really subject to redistribution. The exact opposite is true for most drugs of abuse, which have larger apparent volumes of distribution. Their metabolites (and most glucuronides of most drugs for that matter) have a very low volume of distribution. In the living, at equilibrium, most morphine is in tissue, but most morphine metabolite is in the plasma, providing an opportunity for redistribution of free morphine to occur after death (Skopp et al., 1996, 1998; Klingmann et al., 2000). The postmortem movement of free morphine out of tissue, back into plasma, makes it impossible to estimate the time of ingestion by calculating the ratio of free to conjugated morphine.

5.8.6.2 Apparent Steady State Volume of Distribution (V_{ss})

The rate of postmortem redistribution is also a function of the V_{ss} constant of each individual drug. V_{ss} constants are not really physiologic measures, they are "fudge" factors, relating the amount of drug in the body and the concentration of drug measured in a body compartment, usually the plasma (Shargel and Yu, 1992). Most published values for V_{ss} are based upon measurements made in healthy volunteers, and their relevance to abusers,

taking massive doses of drug, remains open to question. Because V_{ss} is a physiologic measure, it may be altered by many factors (Noble, 2003). V_{ss} increases with age, as muscle mass decreases and fat content rises. For the same reason, muscle-wasting diseases also cause the apparent V_{ss} to increase. V_{ss} is altered by blood flow, and in shock states both muscle flow and renal clearance are decreased. Drug–protein binding, glycolization, liver disease, and drug interactions all can alter V_{ss}. For the reasons discussed, and no doubt for many others, there is enormous intra-individual variation of apparent V_{ss}, even in healthy volunteers, under controlled conditions. For example, the V_{ss} for methamphetamine, for healthy volunteers, given fixed doses of drug and living on a locked ward, was found to range from 2 to 11 L/kg (Schepers et al., 2003). This enormous and unpredictable degree of variability, even in the living, makes it impossible to establish any sort of relationship between postmortem drug concentrations and reported dosage, though it would seem reasonable to conclude that if low levels of drug are detected, small amounts of drug were probably taken.

5.8.6.3 Other Confounding Variables

Some of the less appreciated confounders are discussed in this section. α_1-Acid glycoprotein (AGP), which binds to methadone and other opiates, is genetically heterogeneous, with at least three different phenotypes recognized. Each type has a different affinity for methadone (Eap et al., 1990; Garrido et al., 2000). When there is liver disease, less AGP is produced, which means concentrations of free methadone are increased and so, presumably, is its narcotic effect (Israili and Dayton, 2001). Free methadone levels may also be increased in the presence of other drugs that competitively bind AGP. Conversely, AGP is increased in some inflammatory conditions, which implies that as the disease evolves, the effects of a given dose of methadone would diminish (Herve et al., 1996).

P-glycoprotein (P-gp) is a drug efflux transporter found in the liver, kidney, and gut. Many drugs (digoxin, fexofenadine, cyclosporine, and some protease inhibitors) cannot be excreted in its absence. As a practical matter, most drugs that affect CYP3A4 usually also exert an effect on P-gp (Balayssac et al., 2005). Widely used drugs such as carvedilol, cyclosporine, ketoconazole and verapamil inhibit P-gp production. Rifampin and St. John's wort, among others, induce P-gp production (Zhou et al., 2004). Could the death of a cocaine and heroin abuser, with cardiomyopathy, be related to the fact that his cardiologist had just begun treatment with carvedilol, or did the doctor at the methadone maintenance clinic administer the wrong dose of methadone? It may be impossible to say, but these complex issues exist and cannot be ignored.

Chiral variation is one reason the investigation of methadone-related deaths is so complex. Methadone is sold as a racemic mixture; even though the *l*- form does not bind opiate receptors, it does bind hERG potassium channels (responsible for the delayed rectifier current), causing QT prolongation and fatal episodes of torsades des points. Luckily, this occurs only in polymorphic individuals with an abnormal form of CYP3A4 (Eap et al., 2007). This is an irrelevant consideration for most methadone users, but not for those who are polymorphic for the needed enzyme. The apparent V_{ss} constants for the *d*- and *l*- forms are different, which almost certainly guarantees that the rate of redistribution is also different. The *d*- form also has a longer half-life than the *l*- form, which further complicates the situation (Baumann et al., 2002; Rentsch, 2002; Gerber et al., 2004). Neither chiral separation, nor CYP3A4 activity measurements are routinely performed in the postmortem

setting, so a pathologist trying to make sense of a report stating that a methadone concentration of 700 ng/mL was found in "heart blood" has no way of knowing what proportion of that 700 ng/mL is active drug, let alone what the total concentration was at the time of death, or whether the decedent was CYP3A4 deficient. In short, he is guessing.

It is not uncommon to hear an "expert" offer an opinion on how much time had elapsed between the last dose of heroin/morphine and death. Such speculation is unscientific, and not just because of the differences in V_{ss} between parent drug and metabolite, as discussed earlier. Bacteria translocate, that is, migrate through the walls of the bowel, invading the rest of the body, within a few hours of death (Kellerman et al., 1976). *E. coli* bacteria, which constitute the bulk of the bacteria in the gut, contain multiple glucuronidases. In fact, they are the main source of commercially prepared glucuronidase sold by reagent makers. Some of these enzymes are capable of both conjugating and deconjugating morphine (Moriya and Hashimoto, 1997), and the direction of the reaction is generally unpredictable. Thus, even if redistribution did not occur, the ratio of free to conjugated morphine would not provide an accurate measure of the time of last dose, since there is no way to tell which free morphine came from ingestion and which free morphine was generated by bacteria. There is also evidence that *E. coli*, clostridia species, and other bacteria may be responsible for producing some of the γ-hydroxybutyric acid found in postmortem blood (Elliott et al., 2004).

Making the situation a good deal more complex is the fact that morphine is converted to glucuronide by the action of a liver enzyme called UDPG. Multiple polymorphic forms of this enzyme exist. If an individual is a poor metabolizer, and has an ineffective form of UDPG, very little conjugated M6G will make its way back from the liver to the systemic circulation. Thus, even in the living, without knowing an individual's ability to conjugate morphine (which would require DNA resequencing), comparing the ratio of bound morphine to free morphine is a meaningless exercise.

Hydration is an issue that is rarely considered and, except for the occasional patient dying in hospital, rarely addressed. The body begins to dehydrate after death; blood clots, then liquefies, and without actually measuring the hematocrit of the sample being analyzed, there is no way to tell whether the drug present has been diluted or concentrated. Similar considerations apply to urine testing. Ingestion of very small quantities of drug can result in very high urine concentrations, depending on water intake and underlying renal function. The pathologist is unlikely to know about either.

Genetic polymorphism is responsible for some cases of drug toxicity, but the true incidence of this problem is not really known. For the present, attention is focused on P-450 isoenzymes, though it is quickly shifting to channelopathies involving multiple organs. These mutations are not visible to the naked eye, but they can cause disability and death. Some individuals may be poor metabolizers, and others rapid ones. Some individuals may have sodium and potassium channels in their hearts that do not open and close properly. The result is altered cardiac depolarization that, sometimes, leads to QT interval prolongation and sudden cardiac death. P-450 interactions explain why methadone clearance is altered when it is taken with other drugs. When alcohol and methadone are consumed at the same time, the metabolism of both is enhanced and withdrawal symptoms can occur (Kreek, 1981). Because methadone induces activity of CYP3A4, numerous interactions are possible. The problem is further compounded by the fact that drugs that inhibit CYP3A4 also inhibit P-gp, resulting in increased free blood methadone levels, perhaps to the point

of toxicity (Iribarne et al., 1997). Neither the ion channel mutations, nor the family of P-450 mutations, cause any anatomic change that can be detected at autopsy. Yet they could still be the ultimate cause of death.

5.8.6.4 What Is a Complete Autopsy?

If toxicology results cannot be considered in a vacuum, neither can autopsy findings. When a doctor "certifies" a cause of death, his certification is based upon his weighing of the evidence available to him, but it is still just his opinion and does not set a precedent for similar cases. If the decedent was a known heroin user with massive frothy pulmonary edema, a blood total morphine of 1 mg/L, and a heroin-containing needle is found at his side, the decision is not difficult. But what if the total morphine concentration had been 0.050 mg/L, there was minimal pulmonary edema, and no other apparent stigmata of drug abuse or anatomic abnormalities were observed? In the absence of identifiable anatomic changes, the pathologist would, no doubt, determine the manner of death as narcotic overdose, and an accidental death. But that would be incorrect for at least two reasons. First, the pathologist, unless he has done hair testing, would have no idea whether the decedent was a regular user, and therefore tolerant, or whether the decedent was naïve. Second, the manner of death might well be natural, since the high free morphine concentration could have been the result of genetic polymorphism. Or, then again, the high concentration could have been an artifact, due to any number of causes.

If no slides were ever taken of the myocardium, then the pathologist could never know whether the decedent was an addict suffering from an undiagnosed case of myocarditis (obscure cardiac infections are not rare in intravenous heroin users). Much of the time myocarditis will produce visible signs of infection, although there is mounting evidence that the Dallas criteria do not always work (Baughman, 2006), and that DNA analysis may be the only way to prove myocardial infection. What if the decedent, given a known history of occasional heroin use, were to catch the flu, run a mild fever, and die an arrhythmic sudden death because the fever had unmasked a previously undiagnosed case of Brugada syndrome (Sanchez and Kates, 2004)? Yes, the gross autopsy would have appeared unremarkable, but the molecular autopsy would have been remarkable and it was not performed. What, then, is the significance of a low morphine level in a case with a "normal" autopsy? The honest answer is that most "unremarkable" autopsies are actually just incomplete autopsies. As the tools of molecular biology become more potent, this conundrum can only become worse. When the tools become cheaper, and more readily available, perhaps many of these problems will be solved.

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5.9 Individual Opiates

5.9.1 Buprenorphine

Systematic name: [(5α,7α,S)]-17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphine
Formula: 1-methyl-4-phenyl-4-piperidine-carboxylic acid ethyl ester

Molecular weight: 247.34 daltons
Bioavailability:
Sublingual solution: 28–51% (Kuhlman et al., 1996; Mendelson et al., 1997)
Sublingual tablet: 49–64% (Nath et al., 1999; Schuh and Johanson, 1999)
Intramuscular: not known
C_{max}:
Buccal: 1.98 ± 0.17 (Kuhlman et al., 1996)
Solution: 3.3 ± 0.81 (Kuhlman et al., 1996)
IV: 0.001 mg/kg ×12 volunteers, 207 ng/mL (Escher et al., 2007)
$T_{½/βmax}$:
Buccal: 0.81 ± 0.17 hours (Kuhlman et al., 1996)
Solution: 3.31 ± 0.81 mg/mL (Kuhlman et al., 1996)
IV: 5.18 ± 0.55 hours (Mendelson et al., 1997); 0.001 mg/kg ×12 volunteers, 2.75 hours (Escher et al., 2007)
Metabolism: liver, CY3PA43
Plasma clearance: 1042–1280 mL/min (Kuhlman et al., 1996; Mendelson et al., 1997)
Elimination half-life:
IV: 2–3 hours (Bullingham et al., 1980); 5.2 hours (Bullingham et al., 1982), 16.2 hours (Mendelson et al., 1997)
Sublingual: 27.7 hours (Kuhlman et al., 1996)
Buccal: 19 hours (Kuhlman et al., 1996)
Excretion:
Fecal: 10–30% (Walter and Inturrisi, 1995) (almost all free)
Urine: conjugated to glucuronide, detectable 1–7 days (Bullingham et al., 1980, 1982; Cone et al., 1984; Ohtani et al., 1995; Iribarne et al., 1997; Kobayashi et al., 1998; Cowan, 2003)
Volume of distribution: 2.6–4.78 L/kg (Kuhlman et al., 1996; Mendelson et al., 1997; Nath et al., 1999; Schuh and Johanson, 1999; Zubieta et al., 2000; Greenwald et al., 2003); 0.001 mg/kg ×12 volunteers, 23 mL/kg (Escher et al., 2007)
Interactions: CYP3A4 inhibitors — antiretrovirals, antifungals, benzodiazepines (Elkader and Sproule, 2005)
Maternal fetal considerations: none
Brand names: Buprenex® Subutex®, Temgesic®

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5.9.1.1 General Considerations

Buprenorphine is a semi-synthetic opioid that, like oxycodone, is derived from thebaine. It is 25–50 times more potent than morphine. It is classified as a partial opioid agonist (Wallenstein et al., 1986). It has a slower onset of pain relief, longer duration of action, and is thought to produce less respiratory depression than morphine. The Drug Addiction Treatment Act of 2000 (DATA) allows physicians who receive specialized training to treat opiate addicts in their offices with Schedule III, IV, and V medications that have been approved by the Food and Drug Administration (FDA) specifically for addiction treatment, and this includes buprenorphine.

On October 8, 2002, the FDA approved buprenorphine for in-office treatment. Two formulations, Subutex® and Suboxone®, are now available. Subutex® (buprenorphine hydrochloride) is intended for use in the initial stages of therapy, while Suboxone® (buprenorphine hydrochloride and naloxone hydrochloride) is intended for use in the maintenance stage. As of this writing, no other medication has met the requirements of the act passed by Congress in 2000 (Buprenex® is intended for pain relief, not replacement therapy, and cannot be used in these programs). Subutex®/Suboxone® can be used to treat addiction to any opiate.

Physicians who prescribe buprenorphine therapy are required to maintain a log of all patients using Subutex® and Suboxone®, and the amount that has been prescribed to them. Their medical records are subject to periodic DEA and FDA review. More than 1700 physicians or group practices in the U.S., with nearly half located in the Northeast, are certified to prescribe buprenorphine. Initially they were not permitted to care for more than 30 patients at any one time (the limit also applied to group practices), but in January of 2007 the FDA increased the limit to 200.

French law was changed in 1996 to allow general practitioners to prescribe buprenorphine to heroin addicts. As in the U.S., French law limits methadone prescribing to special government-controlled centers. When the law was first changed, there were concerns that toxicity and lethal outcomes might be more frequent with buprenorphine than methadone. The results of recent studies indicate, however, that death rates with methadone replacement therapy are nearly three times higher than with buprenorphine (Auriacombe et al., 2001).

5.9.1.2 Pharmacology

Like morphine, but unlike most other opioids, the major metabolic pathway for buprenorphine is glucuronidation, not oxidation. Microsomal oxidation does occur (CYP3A), but only modest amounts of norbuprenorphine are produced (Cone et al., 1984). Except in the presence of end-stage liver disease, glucuronidation is generally not impaired by liver disorders, which means that buprenorphine pharmacokinetics are not affected either (Tegeder et al., 1999), and that it can be given to patients with renal failure (Boger, 2006). Free buprenorphine is not detected in urine, although the glucuronides can be detected in the urine for up to four days, and both of the glucuronides can be detected in feces, after either oral or sublingual administration, for as long as a week after ingestion. This is because of extensive enterohepatic circulation (Cone et al., 1984).

Buprenorphine can be given by any route, but because there is very great inter-individual variability in bioavailability, resultant peak plasma concentrations may vary widely as well (51.4 and 27.8% for sublingual and buccal routes, respectively) (Kuhlman et al., 1996). Studies in humans are lacking, but measurements in animals show that after nasal administration bioavailability is very high, and maximal plasma concentrations occur almost as rapidly as after parenteral administration (Lindhardt et al., 2000). This observation raises the possibility that buprenorphine could be abused by "snorting."

Plasma concentrations of 0.5 ng/mL are sufficient to produce surgical analgesia (Amani et al., 1997). In three studies, opioid naïve healthy male subjects received Subutex® tablets (buprenorphine 2 and 8 mg [n = 27] or 12 and 16 mg [n = 27]) or Suboxone® (two formulations) tablets (buprenorphine 8 mg/naloxone 2 mg [n = 36]) sublingually, under a naltrexone block for assessment of buprenorphine pharmacokinetics and tablet disintegration times. Maximum plasma values ranged from 1.6 to 6.4 ng/mL and T_{max} from 0.5 to 3 hours. Large fluctuations in plasma levels after eating were observed, strongly supporting the role of enterohepatic recirculation in buprenorphine users. The terminal half-life in these studies was approximately 26 hours (range 9–69). The results of earlier work had suggested that, during daily buprenorphine maintenance therapy, plasma concentrations needed to be greater than 0.7 ng/mL to be effective. More recent studies suggest that the number may be significantly lower.

Interaction with HIV medications is possible. *N*-dealkylation of buprenorphine is mediated by P-450 CYP3A4 (Cowan, 2003). With each year it becomes increasingly clear that interactions do occur and that antiretrovirals and buprenorphine compete for the same enzyme. In vitro buprenorphine inhibits CYP3A4 and other CYP enzymes as well. The concurrent administration of buprenorphine with some protease inhibitors can lower levels of buprenorphine (Iribarne et al., 1998a; Bruce and Altice, 2006). Indinavir can prevent > 85% of buprenorphine's dealkylation (Iribarne et al., 1998a). As a consequence, concentrations of buprenorphine may be greatly increased when it is given with an antiretroviral. Ketoconazole and other imidazole derivatives are well known

inhibitors of buprenorphine dealkylation (Iribarne et al., 1997), as are some antidepressants, especially SSRIs such as fluoxetine and fluvoxamine (Regier et al., 1990; Iribarne et al., 1998b). There have been reports of fatal interactions between buprenorphine and some benzodiazepines (Reynaud et al., 1998; Tracqui et al., 1998a; Gaulier et al., 2000), especially diazepam and flunitrazepam. It is believed that when opiate users take both together they enhance the possibility of respiratory depression, though this mechanism has never been proven.

The clinical effectiveness of any opioid maintenance regimen for heroin dependence is believed to result from a medication's ability to decrease μ-opioid receptor availability, preventing heroin (or other opioids) from binding to them, and preventing, or at least attenuating, withdrawal symptoms These findings suggest that high-dose buprenorphine maintenance produces near-maximal μ receptor occupation, and μ receptor availability correlates well with plasma levels; buprenorphine-related opioid symptoms and antagonist blockade exhibit concentration–effect relationships. Other studies have shown that buprenorphine, unlike morphine, does not depress immune responses or activate the hypothalamic–pituitary–adrenal axis (Gomez-Flores and Weber, 2000).

In animal studies, buprenorphine treatment causes a statistically significant but clinically insignificant change in pulse and blood pressure (Martinez et al., 1997). In patients undergoing open-heart procedures with cold cardioplegia, pretreatment with buprenorphine is cardioprotective; postoperatively there is improved metabolism and higher cardiac output. The protective effect is in some way related to activation of μ opiate receptors (Boachie-Ansah et al., 1989), and there is interest in the use of this drug as an adjunct during heart surgery.

5.9.1.3 Detection

Buprenorphine is quickly cleared from the urine and it is many times more potent than morphine, which means that detection could be problematic. Earlier methodologies using radioimmunoassays could not separate parent from metabolite and were unreliable. A number of reagent makers now produce ELISA kits, though these kits are expensive, and tandem mass spectrometry would seem to offer a better alternative. Buprenorphine can usually, but not always, be detected in hair samples, at concentrations ranging from 6 to 597 ng/g (mean, 137 ng/g) (Tracqui et al., 1998a). It is very stable in refrigerated blood samples, with recovery rates of more than 70% after 6 months of storage (Hadidi and Oliver, 1998).

5.9.1.4 Drug Concentrations

When measured in postmortem blood, concentrations of buprenorphine and its primary metabolite norbuprenorphine range from 1.1 to 29.0 ng/mL (mean, 8.4 ng/mL) and 0.2 to 12.6 ng/mL (mean, 2.6 ng/mL), respectively. As is true for morphine and heroin, these concentrations overlap those that have been reported in clinical settings, where there is no evidence of toxicity. Somewhat surprisingly, given the high degree of buprenorphine protein binding, extensive tissue distribution occurs. Buprenorphine accumulates in bile, where concentrations may reach values of more than 75 mg/L. Norbuprenorphine seems to have the same pattern of distribution as the parent compound, although measured concentrations are generally very much lower than those of the parent compound.

5.9.1.5 Maternal/Fetal Considerations

There is general consensus that buprenorphine produces a milder withdrawal syndrome than methadone (Johnson et al., 2003), and that exposure of infants to buprenorphine is minimal, even though milk concentrations are similar to those in plasma. The explanation appears to be that even when swallowed, bioavailability in the infant is poor (Elkader and Sproule, 2005). This may explain why there have been no reported cases of neonatal abstinence symptoms following the cessation of breast feeding (Johnson et al., 2003). Several studies relevant to buprenorphine opiate replacement patients have been published. In one study, concentrations of buprenorphine and norbuprenorphine were measured in 10 random breast milk samples collected over four successive days. Concentrations of the parent drug ranged from 1.0 to 14.7, while those of norbuprenorphine ranged from 0.6 to 6.3 ng/mL, respectively. The authors of the study concluded "drug exposure of the infant may be considered to be low" (Grimm et al., 2005). In a second study of one woman, concentrations on day three were the same in plasma and breast milk (0.52 ng/mL). On day six they were still nearly identical (0.72 and 0.64 ng/mL, respectively) (Johnson et al., 2003). A case report published in 1997 described a pregnant addict who took buprenorphine 4 mg/day for five months. Twenty hours after birth, plasma buprenorphine concentrations were higher in the infant than in the mother's serum just before birth, though the reverse was true for norbuprenorphine. Based on measurements made in breast milk at age four weeks, the authors calculated that the infant would have received a total of 3.28 μg of buprenorphine and 0.33 μg norbuprenorphine over a 24-hour period (Marquet et al., 1997).

5.9.1.6 Postmortem Considerations

Provided salinized tubes are used, buprenorphine appears to be relatively stable (> 70% recovery) after a year (Hadidi and Oliver, 1998). Several autopsy series have been published, all from France, where buprenorphine was first used for replacement therapy. Nearly 100,000 opiate addicts have been enrolled in programs to date. The first French fatalities were reported almost as soon as the drug was licensed in 1996 (Tracqui et al., 1998a, b; Kintz, 2001, 2002). Since then fewer than 60 additional reports have been published. Virtually all the decedents were polydrug abusers, and postmortem concentrations of buprenorphine and norbuprenorphine were not very different from those seen in living substitution patients. Autopsy findings in these studies have been poorly described, but it appears that the findings resemble those in any other opiate-related death.

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5.9.2 Codeine

Synonyms: none
Name: (5α,6α)-7,8-didehydro-4-5-epoxy-3-methoxy-17-methylmorphinan-6-ol
Formula: $C_{18}H_{21}NO_3$

Molecular weight: 299.37 daltons
Metabolism: converted by CYP2D6 to morphine
$T_{½β}$ (half-life): 2.9 ± 0.07 hours (Quiding et al., 1986)
C_{max}: after 30 mg orally, mean peak of 66 ng/mL (34.0–118.8) (Quiding et al., 1986)
T_{max}: 2 hours
Excretion: 86% excreted unchanged in urine
Volume of distribution: 2.6 ± 0.03 L/kg (Quiding et al., 1986)
Known interactions: no significant, but if an individual is a poor metabolizer they will not obtain pain relief
Other names: codeine anhydrous, codeine base, Codicept, *l*-codeine, methylmorphine, morphine monomethyl ether, norcodeine, *N*-methyl codeine, norcodine
Codeine-containing products: Cough Syrup (bromodiphenhydramine hydrochloride); Codimal® PH Syrup (containing codeine phosphate, phenylephrine hydrochloride, and pyrilamine maleate); Colrex® Compound (containing codeine phosphate, acetaminophen, chlorpheniramine maleate, and phenylephrine hydrochloride); Cycofed® Expectorant (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Decohistine® DH (containing codeine phosphate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); Decohistine® Expectorant (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Dihistine® DH Elixir (containing codeine phosphate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); Guaifenesin DAC® (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Guiatuss DAC® Syrup (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); HaNew Riversin® DAC (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); KG-Fed® Expectorant Syrup (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Mytussin® DAC (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Novahistine® DH (containing codeine phosphate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); Nucofed® (containing codeine phosphate and pseudoephedrine hydrochloride); Nucotuss® Expectorant (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Pediacof® Cough Syrup (containing codeine phosphate, chlorpheniramine maleate, phenylephrine hydrochloride, and potassium iodide); Phenergan® VC with Codeine Syrup (containing codeine phosphate, phenylephrine hydrochloride, and promethazine hydrochloride); Phenhist® DH with Codeine Modified Formula (containing codeine phosphate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); Prometh® VC with Codeine Phosphate Cough Syrup (containing codeine phosphate, phenylephrine hydrochloride, and promethazine hydrochloride); Robitussin®-DAC (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride); Ryna-C® (containing codeine phosphate, chlorpheniramine maleate, and pseudoephedrine hydrochloride); Triacin-C® Cough Syrup (containing codeine phosphate, pseudoephedrine hydrochloride, and triprolidine hydrochloride); Tussar® SF Syrup (containing codeine phosphate, guaifenesin, and pseudoephedrine hydrochloride)
Known drug interactions: Codeine is a pro-drug and its pain-relieving abilities derive from its conversion to morphine. Some CYP2D6 polymorphs convert too much codeine to morphine and toxicity may result.

Maternal/fetal considerations: codeine is generally considered safe for breast feeding mothers but in the light of the discovery of hypermetabolizers with high concentrations of morphine in their breast milk, use should probably be limited to a day or two

Other considerations: Chinese metabolize codeine less well than Caucasians. After a 60 mg dose of codeine, Yue et al. (1997) found a higher C_{max}, and a slightly longer half-life in Chinese, mostly because the Chinese cannot form glucuronides as readily.

Quiding, H., Anderson, P. et al. (1986). Plasma concentrations of codeine and its metabolite, morphine, after single and repeated oral administration, *Eur. J. Clin. Pharmacol., 30*(6), pp. 673–7.

Yue, Q. Y., Iselius, L. et al. (1997). Indices and graphical approaches for the detection of interindividual and interethnic variations in codeine metabolism, *Br. J. Clin. Pharmacol.,* 44(3), pp. 239–44.

5.9.2.1 General Considerations

Codeine is one of several naturally occurring alkaloids found in opium. Depending on where the poppies are grown, the codeine content of raw opium ranges from 0.7 to 2.5%. Codeine was first isolated from opium by Robiquet in 1832, 27 years after Sertürner isolated morphine. Most of the codeine consumed in cough and analgesic mixtures is of semisynthetic origin, produced by the methylation of morphine. The DAWN report for 1990 listed only 501 codeine-related deaths. The current incidence of codeine-related deaths is not known, but the Emergency Room component of the new DAWN report contains no mention of codeine, even though tons are consumed annually in prescription medications.

Codeine undergoes *O*-dealkylation to morphine. The conversion is catalyzed by polymorphic CYP2D6 (the same enzyme also converts dihydrocodeine, hydrocodone, and oxycodone) (Lotsch et al., 2004; Zanger et al., 2004; Kreek et al., 2005). Without testing there is no way to predict how much morphine an individual will form from codeine without knowing how many copies of CYP2D6 they possess. Individuals entirely lacking CYP2D6 activity are called poor metabolizers and are not likely to get much pain relief from codeine because they cannot convert enough of it into morphine. But it is also possible to have multiple duplications of CYP2D6, making the individual into an ultrametabolizer who can transform abnormally large amounts of codeine into morphine. Someone with gene duplication might experience an overdose even though only a modest dose of codeine is taken. In fact, this situation has been reported (Kirchheiner et al., 2006). Duplication might also explain the finding of very high levels of codeine in postmortem blood samples, even though the clinical history indicated that very little drug had been taken. Once the conversion to morphine has taken place, morphine is further metabolized by *N*-demethylation and glucuronidation, just as it would have been if it had been ingested primarily.

Codeine is also *N*-demethylated by CYP3A4 and then conjugated by UGT2B4 and UGT2B7 to form codeine-6-glucuronide (Caraco et al., 1996; Yue and Sawe, 1997). The latter is highly polymorphic (Court et al., 2003), but since two different enzymes are capable of making the same conversion, genetic variation in this phase of codeine metabolism seems to be irrelevant. Not all of codeine's psychoactivity is attributable to morphine formation. Very small amounts may be converted to norcodeine, which is believed to be psychoactive (Fraser et al., 1960). There is also evidence that codeine-6-glucuronide itself

may be psychoactive (Lotsch et al., 2006). All of these compounds are excreted in the urine, where somewhat less than 90% of a single dose of codeine can be recovered within 48 hours, mostly as codeine-6-glucuronide (Chen et al., 1991).

5.9.2.2 Routes of Administration

The radioimmunoassay used in early studies of codeine metabolism measured both codeine and its metabolites, and thus yielded spuriously high concentrations of codeine in the plasma and urine (Chen et al., 1991). With current technology, morphine, codeine, and each of their main metabolites are assessed simultaneously (Musshoff et al., 2006). Peak concentrations of codeine in healthy volunteers (50 mg orally) occur within 1–2 hours and the plasma half-life is on the order of 2.4–3.2 hours (Chen et al., 1991). The peak concentration of codeine in the saliva is nearly three times that measured in the blood, even though the half-life in both fluids is approximately 3.2 hours (Chen et al., 1991). After oral dosing, plasma levels of codeine glucuronide reach concentrations 5–10 times higher than those of codeine (Chen et al., 1991; Lafolie et al., 1996). Chronic administration of codeine does not appear to alter its kinetics but, as indicated earlier, the genetic polymorphism may alter clinical responses and increase the chances of toxicity.

It had been thought that small amounts of morphine were metabolically converted to codeine (Boener and Abbott, 1973), but, in fact, that is not the case (Yeh, 1974). The codeine detected in urine after giving morphine is present because it exists as a contaminant even in pharmaceutical-grade morphine preparations (Vaughan and Dennis, 1979). Thus, the presence of codeine should not be presumed to be evidence for anything but the ingestion of codeine. The presence of trace amounts of morphine, on the other hand, is accounted for by the metabolic conversion of codeine to morphine.

Codeine may be converted to hydrocodone, as can morphine. However, the latter conversion seems to occur only in individuals treated with large amounts of morphine. In one study, 10 of the 13 patients treated with morphine excreted minor amounts of hydrocodone in their urine (120–1400 ng/mL). Morphine concentrations in these patients were very high (>10,000 ng/mL), suggesting that the conversion constitutes only a minor pathway (Cone et al., 2006). Allegations of illicit hydrocodone use have been made against individuals taking physician-prescribed oral codeine who strenuously deny ever taking hydrocodone, but who nonetheless have positive urine tests for that drug. Generally, the

Table 5.9.2.2.1 Effects of Genetic Polymorphism on Codeine Metabolism

Drug	Hydroxylators	Non-Hydroxylators
Codeine	411 ± 219	239 ± 60
Codeine-6-glucuronide (C6G)	4090 ± 3380	3890 ± 949
Norcodeine (NC)	48 ± 26	48 ± 13
NCG	108 ± 44	146 ± 8
Morphine-3-glucuronide (M3G)	186 ± 121	9.1 ± 8.2
Morphine-6-glucuronide (M6G)	41 ± 23	Not detectable
Normorphine (NM)	41 ± 33	Not detectable
Morphine (M)	27 ± 23	Not detectable

Note: Values are in nmol/dL. All measurements are from healthy volunteers who had been previously screened for the ability to hydroxylate debrisoquine.

Data derived from Yue et al. (1991).

hydrocodone concentrations in these cases are quite low, on the order of 100 ng/mL or less (Oyler et al., 2000).

5.9.2.3 Codeine Tissue Disposition

Data on the tissue distribution of codeine are sparse. The results of the few studies that have been performed suggest that in cases where codeine is clearly the cause of death, total and free codeine concentrations completely overlap concentrations in cases where codeine is an incidental finding. Hair morphine concentrations measurements can be used to assess morphine tolerance after death (Tagliaro et al., 1998), but it is not clear whether hair codeine measurements can be used in the same fashion, though it is not difficult to measure (Musshoff et al., 2005).

Simultaneous measurements of blood and bile concentrations in codeine-related deaths disclosed a mean blood morphine concentration of 0.29 mg/L (range, 0.10–0.89 mg/L) with a mean concentration of 38 mg/L in bile (range, 3.3–112 mg/L). Codeine concentrations measured at the same time were 0.06–6.4 mg/L (mean, 1.5 mg/L) in blood, and 0.22–89 mg/L (mean, 24 mg/L) in bile (Crump et al., 1994). Results were not very different in a second study of 107 codeine-related deaths. In only six of the cases (8.8%) was codeine considered to be the actual cause of death. The mean concentration of total codeine in femoral blood was 4.0 ± 2.3 mg/L (range, 2.1–8.0 mg/L), while the mean concentration of free codeine was 1.3 ± 0.9 mg/L (range, 0.4–2.8 mg/L). Free and total codeine concentrations were not significantly different in cases where other drugs were present and where codeine was not deemed to be the cause of death (Gerostamoulos et al., 1996).

The importance of CYP2D6 polymorphisms cannot be over emphasized. A recent case report in the *Lancet* describes a breast-feeding mother being treated with moderate doses of codeine (which works by conversion to morphine) whose child died unexpectedly 12 days after birth. Because he was looking ill and not feeding, the mother saved all of her milk production on day 10. Analysis of the milk showed an astonishing 70 ng/mL concentration of morphine. Genotype analysis was done for cytochrome P-450 2D6 (*CYP2D6*), the enzyme catalyzing the *O*-demethylation of codeine to morphine. The mother was found to be heterozygous for a *CYP2D6*2A* allele with *CYP2D6*2°–2* gene duplication, and was classified as an ultra-rapid metabolizer (Koren et al., 2006).

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5.9.3 Fentanyl

Synonyms: china white
Chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide
Formula: $C_{22}H_{28}N_2O$
Molecular weight: 336.5 daltons

C_{max}:
IV: after 200 µg, 4.6 ± 1.87 hours (Hung et al., 1995)
IM: not known
Oral: after 15 mg, 4 hours (Darwish et al., 2006)
Sublingual: 0.24–0.91 ng/mL (Lennernas et al., 2005); 0.39–2.51 ng/mL (Mystakidou et al., 2006)
Transdermal: 2.6 ± 1.3 hours (Portenoy et al., 1993)
Effervescent: *n* = 31, 800 µg dose, 1.59 ± ng/mL (Darwish et al., 2006)

$T_{½\beta}$:
IV: 219 ± 10 minutes (McClain and Hug, 1980); 3.7 ± 0.04 (Olkkola et al., 1999)
IM: not known
Oral: after 200 µg, 200 minutes (manufacturer's package insert)
Sublingual: 5.4–6.1 hours (Lennernas et al., 2005); 3.2–6.4 hours (Mystakidou et al., 2006)
Transdermal: 21.9 ± 8.9 (Portenoy et al., 1993)
Effervescent: *n* = 31, 800 µg, 11.70 hours (Darwish et al., 2006)

T_{max}:
IV: 0.4 hours (35 ± 15 hours) (Olkkola et al, 1995)
IM: not known
Oral: 39–57 minutes (Lennernas et al., 2005)
Sublingual: after 200 µg, 40 ng/mL (range 20–120)
Transdermal: 20–40 hours (Mystakidou et al., 2006); 2.6 hours (Portenoy et al., 1993)
Buccal: *n* = 31, 800 µg, 35–45 minutes (Darwish et al., 2006)

V_{ss}: 3.99 ± 20 L/kg (McClain and Hug, 1980); 3.6 L/kg (Han et al., 2007); 2.75 L/kg (Nitsun et al., 2006)

Metabolism: piperidine *N*-dealkylation with the formation of norfentanyl, CYP3A

Interactions: volume of distribution almost doubles in patients with burns

Names: Actiq® (Abbot Laboratories), and in combination with the neuroleptic drug droperidol (Astra USA). Alfentanil hydrochloride is available as Alfenta® (Janssen Pharmaceuticals), and sufentanil is sold as Sufenta® (Janssen Pharmaceuticals). Actiq (citrate), Remifentanyl. A new effervescent buccal form has been introduced. It has higher bioavailability and more rapid onset.

Note: pharmacokinetic values are altered by age, disease, and dosage

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5.9.3.1 General

Fentanyl (Figure 5.9.3.1) is a μ agonist, a synthetic phenylpiperidine derivative with a structure closely related to meperidine (Demerol®). Fentanyl was first synthesized in 1960 by chemist Paul Janssen, who later founded the Belgian pharmaceutical firm Janssen Pharmaceutica. Janssen produced fentanyl by reacting *N*-phenethylpiperidone with aniline to create 4-anilino-*N*-phenethylpiperidine. The product was then reacted with propionyl chloride to give pure fentanyl. On a weight-for-weight basis, fentanyl is 50–100 times more potent than morphine. Two other clinically important fentanyl analogs were subsequently introduced: alfentanil (Alfenta®), an ultra-short (5–10 minutes) acting agent; and sufentanil (Sufenta®), which is 5–10 times more potent than fentanyl. The latter is used mainly in heart surgery. The Duragesic® patch is a fentanyl transdermal patch used for the management of chronic pain. Actiq® is a lozenge formulation of fentanyl citrate designed for transmucosal absorption. It is intended mainly for opiate-tolerant patients and for cancer patients with breakthrough pain. An effervescent tablet meant for the same purposes is also available. Carfentanil (Wildnil®), a fentanyl analog with an analgesic potency 10,000 times that of morphine, is used in veterinary practice to immobilize certain large animals. At least 12 different illicit fentanyl analogs have been identified (Sorkin et al., 1994), but α-methyl fentanyl is the form most frequently used to adulterate heroin, an increasingly common practice.

The illicit synthesis of fentanyl is more difficult than that of other abused drugs such as methamphetamine and phencyclidine. At least three synthetic routes, all different from Janssen's original method, are possible. The most popular route involves the use of norfentanyl or 3-methyl-norfentanyl intermediates. These are produced from 1-benzyl-4-poperidone by reductive amination with aniline then acetylation and hydrogenation to form norfentanyl. Fentanyl and its analogs are then manufactured by alkylating the piperidine with nitrogen (WHO, 1990). The *cis*-isomer of 3-methylfentanyl, illicitly manufactured by clandestine laboratories in the Russian Federation, is thought to be 5500 times more potent than morphine (Sorkin et al., 1994). Until recently, fentanyl was not detected by routine drug-screening tests, so that the prevalence of use was impossible to estimate, though the

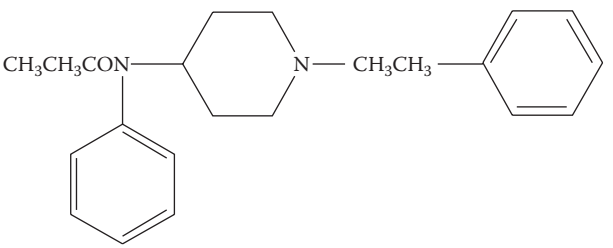

Figure 5.9.3.1 Fentanyl.

Figure 5.9.3.1.1 Duragesic® patch. Fentanyl is extremely lipophilic, more so than any other currently available opiate. The mean apparent partition coefficients of oxycodone, morphine, and fentanyl in *N*-octanol at pH 7 are 0.7, 0.5, 10.5, and 399, respectively, giving fentanyl a 570-times greater affinity for fat than morphine (Poyhia and Seppala, 1994). The patches are sold in four different strengths (2.5, 5, 7.5, and 10 mg per patch). A transmucosal form was introduced in 2003.

DEA reports that the number of prescriptions for fentanyl rose from half a million in the early 1990s to over 4 million in 2003. Antibody-based ELISA tests for urine screening are now available (Neogen Corporation, Bio Quant Inc.), but they are expensive, and routine screening is still not performed.

The high cost of testing for fentanyl may prove to be a necessary expense, given the increasing illegal market for this drug. Some time in 2006 street gangs began dealing in α-methyl fentanyl, adding it to street level heroin. It was not the first time that illicit fentanyl had appeared in the U.S., though the scale of the most recent seizures dwarfs past confiscations. The first two deaths from the use of illicit fentanyl were reported in the U.S. in 1979. Both decedents were found with their injection paraphernalia at their sides, and postmortem examination revealed typical findings associated with narcotic overdose: needle tracks and pulmonary edema. Toxicology testing of blood and tissue samples, and even of the injection paraphernalia, was negative for opiates. Six additional deaths occurred before it was finally determined that the individuals had taken α-methyl fentanyl (Kram et al., 1981).

Clustered outbreaks of fentanyl-related deaths have occurred on a regular basis ever since (Wahaba and Winek, 1989; Henderson, 1991; Hibbs et al., 1991; McGee et al., 1992;

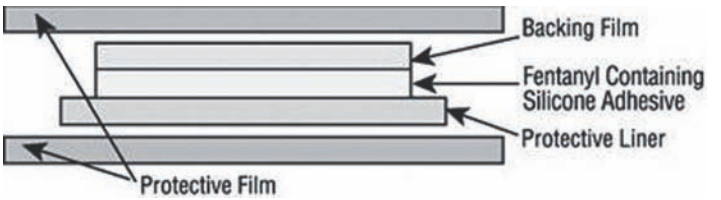

Figure 5.9.3.1.2 Schematic of Duragesic® patch. A polyester backing overlies a drug reservoir and an alcohol gel. A release membrane in direct contact with the skin controls the rate of release.

Smialek et al., 1994; Kronstrand et al., 1997; Anderson and Muto, 2000; Kuhlman et al., 2003; Lemos et al., 2004) but mostly fentanyl-related deaths are sporadic, involving either drug abusers with illegally acquired patches, or addicted medical professionals injecting themselves with intravenous fentanyl.

Until the early 1990s, it was assumed that doctors became addicted to fentanyl simply because they had easy access, which made the drug tempting (Storr et al., 2000; Trinkoff et al., 2000). However, recent studies have shown that aerosolized fentanyl is detectable within operating rooms, possibly making operating room workers more susceptible to addiction (McAuliffe et al., 2006).

The increasing number of deaths reported since the early 1990s is mainly due to a massive increase in supply. From 1990 to 1996, the amount of fentanyl prescribed in the U.S. increased by more than 1000%, from 3263 to 41,371 grams (Joranson et al., 2000). The increase was due to sales of the fentanyl patch (Duragesic®). With so much fentanyl being prescribed, it is inevitable that some of the patches will ultimately find their way onto the black market, and there now exists a black market in both new and used (removed from cadavers) patches. Abusers, unacquainted with the potency of the drug, are at great risk (Flannagan et al., 1996).

Until fairly recently, the number of illicit patches finding their way to the street has been relatively small. Accordingly it was reasonable for death scene investigators to assume that patches found on a decedent's body were present because the decedent was being treated for a medical condition. That situation no longer obtains, and with fentanyl now contaminating a portion of the U.S. heroin supply, and abusers swallowing and smoking the contents of used patches (Barrueto et al., 2004; Teske et al., 2007), pathologists are increasingly confronted with cases where fentanyl is the cause of death, and not simply an incidental finding. As with all opiates, both tolerance (Albrecht et al., 1997; Bot et al., 1998) and redistribution occur (Anderson and Muto, 2000). It follows that isolated blood fentanyl concentrations cannot be used to make the diagnosis of fentanyl overdose.

5.9.3.2 Pharmacology and Pharmacokinetics

Fentanyl acts at the μ-receptor producing the same adverse effects as any other opioid: sedation, nausea, vomiting, and constipation. In addition to the anticipated side effects, fentanyl can cause rigidity of the chest wall muscles, resulting in a condition known as "wooden chest syndrome" (Jackson, 1994). Unexpected increases in muscle tone may make ventilation difficult and pose a significant danger during endoscopic procedures, a situation where fentanyl is often given. The results of animal studies suggest that increased muscle tone is in some way related to altered serotonergic transmission (Jaros and Kolasiewicz, 1995).

Treatment with fentanyl causes modest increases in intracranial pressure and small decreases in both mean arterial blood pressure and cerebral perfusion pressure, which is much the same reaction observed after treatment with intravenous morphine. In studies of high dose anesthesia for cardiac surgery, plasma fentanyl concentrations between 34 ± 7 ng/mL and 48 ng/mL were observed (Lunn et al., 1979), but respiratory depression may be detected at levels as low as 1–5 ng/mL (Fung and Eisele, 1980; Andrews et al., 1983). The plasma level required to produce effective analgesia in general surgical patients is 1–3 ng/mL, but with considerable inter-patient variability (Gourlay et al., 1988). Values in the 1–3 ng/mL range can also be associated with severe respiratory depression.

depression is observed in human volunteers at plasma concentrations between 2 and 3 ng/mL (Cartwright et al., 1983).

When fentanyl patches are used to treat cancer patients, steady state serum concentrations of 2.6 (± 1.3 ng/mL) are approached by the time the second patch has been applied, and the kinetics of the drug remain stable for the duration of treatment.

5.9.3.3 Routes of Administration

All routes of fentanyl administration may be utilized by abusers. No matter the route, CYP3A4 genetic variability guarantees that there will be wide inter-individual variability in resultant plasma concentrations (Jin et al., 2005). Evidence also exists that some of the variability in the metabolism of alfentanil may be related to CYP3A5 polymorphisms (Klees et al., 2005).

After an oral dose of 15 μg/kg, peak plasma concentrations in healthy volunteers average 3.0 ng/mL. Peak plasma levels after administration of that same amount intravenously are nearly 10 times higher. The difference is attributable partly to first-pass effects in the liver, and partly to the fact that fentanyl is metabolized in the gut wall. However, the terminal elimination half-life is approximately 7 hours after either intravenous or oral administration (Streisand et al., 1991). This route is not used clinically.

Outside of the operating room, fentanyl is most often given by transdermal application. Duragesic® patches have four layers. A polyester backing overlies a drug reservoir composed of fentanyl and an alcoholic gel. A release membrane in direct contact with the skin controls the drug's rate of release, and the product is held in place by a final layer of adhesive. Four different sized patches are available (25, 50, 75, 100 μg/hour). All of the patches release fentanyl at the same rate, but the larger the patch, the more fentanyl there is to release. Once the patch is applied, drug is absorbed into the upper layers of the skin and none appears in the systemic circulation for at least two hours. By the time 8–12 hours have elapsed, plasma concentrations approximate those seen when fentanyl is given intravenously (Calis et al., 1992), and blood concentrations reach steady state by 24 hours. Because of the lag in absorption and delayed onset, the patches are not used for immediate or postoperative pain relief (Fiset et al., 1995). Plasma fentanyl concentrations gradually decline over the second and third day, but not enough to lose effectiveness. Because a depot has been formed in the skin, fentanyl continues to be absorbed into the systemic circulation even after a patch has been removed (Grond et al., 2000). Absorption continues for as long as 12 hours after the patch is removed.

Lozenges containing fentanyl citrate have been used to premedicate children before surgery (Fentanyl Oralet®), and they are also used in the elderly (Actiq®, Cephalon Corporation). When fentanyl is given by this route, plasma concentrations peak in 20 minutes, and may reach levels of 3–4 ng/mL (Mystakidou et al., 2006). In children the estimated fentanyl bioavailability via this route (mean ± SD) is low (36.1 ± 0.4%), as are the peak plasma concentrations (1.03 ± 0.31 ng/mL), suggesting that many children swallow a large fraction of the dose, which probably explains why peak concentrations occur a relatively long time after administration (53 ± 40 minutes) (Wheeler et al., 2002). Other workers have reported slightly lower peak levels (C_{max} 0.39–2.51 ng/mL) (Mystakidou et al., 2006). As with adults, great variation exists in the plasma concentration finally achieved, and very little relationship exists between drug concentrations and pain relief (Dsida et al., 1998). The important issue with oral and transmucosal formulations is that absorption via this

route avoids hepatic first-pass metabolism, greatly increasing bioavailability and, presumably, effect (Mystakidou et al., 2006).

Very recently effervescent fentanyl tablets have been introduced to the market (Cephalon®). The tablets come in various strengths and are meant to be inserted between the gum and lip. They are intended for use mainly in patients with cancer, particularly those undergoing chemotherapy or radiotherapy, who may develop oral mucositis. In one study of 16 patients, 8 with and 8 without oral mucositis, the median C_{max} was essentially the same no matter whether oral inflammation was present or not: 1.14 ng/mL (range 0.26–2.69 ng/mL) in patients with mucositis, and 1.21 ng/mL (range 0.21–2.34 ng/mL) in patients without mucositis. The T_{max} was the same in both groups: median T_{max} was 25.0 minutes (range 15–45 minutes) in patients with and without mucositis and so was absorption. In a well-designed phase III trial in opioid-tolerant patients with cancer, a single dose of fentanyl buccal tablets 100–800 μg provided clinically significant improvements in pain intensity from 15 to 60 minutes after the dose. Single doses of fentanyl buccal tablets of 100–800 μg are generally well tolerated, at least among those who are already tolerant. Abuse of this particular formulation seems fairly unlikely, but it still would be prudent to swab the gum area in suspect cases.

Abusers have found a surprising number of ways to obtain fentanyl from the Duragesic® patch. Suicides may attach multiple new (or used) patches to their body. Depending on the amount of fentanyl remaining in the patch, results may or may not be fatal (Flannagan et al., 1996; Tharp et al., 2004). Addicts may simply attach multiple used (often taken from cadavers) patches. Anecdotal reports describe users extracting residual fentanyl from the patches and injecting it intravenously (Lilleng et al., 2004; Tharp et al., 2004), chewing whole patches (Liappas et al., 2004) (which greatly enhances absorption), inserting new or used patches vaginally and rectally (Coon et al., 2005), and even using them for tea bags (Barrueto et al., 2004). An analysis of fentanyl patches worn by hospice patients disclosed that 0.7–1.22 mg still remained in the 2.5-mg patches, and 4.46–8.44 mg remained in the 10-mg patches (Marquardt and Tharratt, 1994; Flannagan et al., 1996; Yerasi et al., 1997; Kramer and Tawney, 1998). If respiratory depression does occur, just removing the patch will do nothing to stop further fentanyl absorption, since a depot will have already been deposited in the skin.

Heating the patches to liberate fentanyl vapor is not uncommon, and deaths from respiratory depression have been the result (Marquardt and Tharratt, 1994). Systemic absorption after inhalation is extremely fast. A 1994 case report describes an individual who collapsed after only one inhalation. The concentration was 2.6 ng/mL in femoral blood, 3.3 ng/mL in the vitreous, and 122 ng/g in the liver. The pharmacokinetics of nasal insufflation has not been studied, but clinical trials with hospice patients have shown that effective relief of breakthrough pain can be achieved via this route (Zeppetella, 2000).

5.9.3.4 Metabolism and Excretion

After initial rapid uptake by lung and fat, fentanyl is slowly released back into the circulation. Metabolism occurs mainly in the liver, but when fentanyl citrate is given orally, it is subject not only to first-pass metabolism in the liver, but also metabolism by the same P-450 3A4 microsomes located in the duodenum. Piperidine *N*-dealkylation with the formation of norfentanyl is fentanyl's predominant metabolic pathway; however, small amounts of fentanyl undergo amide hydrolysis to form despropionylfentanyl and alkyl hydroxylation to form hydroxyfentanyl. Secondary metabolites are also formed; small

amounts of hydroxynorfentanyl undergo *N*-dealkylation to yield hydroxyfentanyl (Labroo et al., 1997). Metabolism does not appear to be altered by age (Kharasch et al., 2007), but obese individuals will have lower blood levels than predicted for a given dose.

Studies of surgical patients have shown that unchanged fentanyl appears in the urine shortly after administration, and that it persists there for up to 24 hours. By 72 hours, fentanyl is undetectable. Norfentanyl appears in the urine almost as quickly as fentanyl, but in much higher concentrations. Norfentanyl is detectable in the urine of all surgical patients for 48 hours, and in half of these patients for periods as long as 96 hours. Neither fentanyl nor its metabolites are consistently detectable in saliva (Silverstein et al., 1993). Radioimmunoassay screening kits for the detection of fentanyl, sufentanil, and alfentanil are all commercially available. GC/MS can reliably be used to measure fentanyl and sufentanil with a detection limit approaching 0.5 ng/mL (Schwartz et al., 1994).

5.9.3.5 Tissue Concentrations

All of the fentanyls are highly lipid soluble and distribute widely throughout the body (Hess et al., 1972). When administered intravenously, 3–4% of the dose will be secreted into the gastric juice, where there is minimal reabsorption (Stoeckel et al., 1979). Thus, the detection of fentanyl in gastric contents does not imply oral administration. In the series of 112 fentanyl-related deaths described by Henderson (1991), fentanyl concentrations in blood ranged from 0.2 to > 50 ng/mL, and urine concentrations ranged from 0.2 to > 800 ng/mL. If the few individuals with extremely high levels are excluded, then the mean fentanyl level at autopsy was 3.0 ± 3.1 ng/mL in the blood and 3.9 ± 4.3 ng/mL in the urine. In the handful of deaths due to fentanyl citrate (the pharmaceutical-grade product used as an intravenous anesthetic), blood concentrations have ranged from 3 to 27 ng/mL (Garriott et al., 1984; Matejczyk, 1988). Blood and tissue concentrations were recently described in a series of 25 decedents wearing transdermal patches (Table 5.9.3.5.1). While the observed blood concentrations ranged from 1.8 to 139 ng/mL, the mean blood concentration in eight decedents being treated for cancer was 3.6 ng/mL (range, 2–7 ng/mL). Concentrations in abusers were generally much higher (Anderson and Muto, 2000).

McGee et al. (1992) compared blood and tissue levels in seven overdose deaths with fentanyl levels observed in anesthetized patients dying at surgery (Table 5.9.3.5.2). As is the

Table 5.9.3.5.1 Blood and Tissue Fentanyl Concentrations in 25 Decedents Wearing Transdermal Fentanyl Patches

Organ/Tissue	Concentration Range (ng/mL)
Heart blood	1.8–139
Femoral blood	3.1–43
Vitreous	< 2.0–20
Liver	5.8–613
Bile	3.5–262
Urine	2.9–895
Gastric content	0–1200
Spleen	7.8–79

From Anderson and Muto (2000).

Table 5.9.3.5.2 Comparison of Blood Levels in Fentanyl-Related "Overdose" Deaths and Levels Seen in Anesthetized Patients Dying of Surgical Complications

	Deaths from Fentanyl Overdose	Deaths at Surgery
Blood	11–233 ng/mL	5–45 ng/mL
Brain	20–194 ng/mL	18–85 ng/mL
Liver	28–1000 ng/mg	41–158 ng/mg

From McGee et al. (1992).

case with transdermal patches themselves, overdose deaths cannot be linked to a particular concentration. Though deaths in abusers tend to be associated with concentrations 5–10 times higher than those observed in anesthetic and/or surgical deaths, that is not always the case. A report from Germany describes two polydrug abusers who intravenously injected the contents of fentanyl patches. In one case the fentanyl concentration in postmortem blood was 2.7 ng/mL, while in the second it was 13.9 ng/mL (Lilleng et al., 2004).

As is true in all opiate-related deaths, other drugs are frequently detected. In nearly 40% of the deaths from fentanyl, alcohol is also present, frequently at high levels. In 20% of Henderson's case series, cocaine was also detected (Henderson, 1991). In deaths associated with the use of the transdermal patch, other drugs are almost inevitably present (Anderson and Muto, 2000). There appears to be no correlation between dosage (patch size) and urine concentration. Indeed, concentrations in specimens from legitimate chronic-pain patients are often far less than those recorded in cases of obvious overdose (Poklis and Backer, 2004).

Fentanyl can also be detected in hair. Wang et al. (1993) used radioimmunoassay to analyze fentanyl in hair from 13 patients who had received 1–6 μg of fentanyl during surgical anesthesia. Hair concentrations ranging from 13 to 48 pg/mg were identified (Wang et al., 1993). A case report published in 1995 described the findings in a criminalist suspected of stealing fentanyl patches from cadavers; his hair concentration was 20 pg/mg (Selavka et al., 1995). LeBeau et al. (2002) used tandem mass spectrometry to test hair samples from a registered nurse suspected of narcotic theft and abuse. Fentanyl concentrations ranging from 20 to 93 pg/mg were detected. More recently, Kintz et al. (2005) reported on their analytic findings in four anesthesiologists suspected of fentanyl abuse. Two were using only fentanyl and had hair concentrations of 101 and 644 pg/mg, respectively. One decedent was chronically abusing multiple drugs. Analysis of cardiac blood revealed an acute overdose of alfentanil (45 ng/mL), but ethanol (1.32 g/L), was also detected; in the hair alfentanil (2 pg/mg) and fentanyl (8 pg/mg) were also detected (Kintz et al., 2005).

5.9.3.6 Maternal/Fetal Considerations

The concentration of fentanyl in the breast milk of women undergoing surgery has been studied, and the amount of fentanyl transferred by this route is so negligible (0.0006 to 0.073% of a given dose) that women who receive fentanyl at surgery are not advised to discontinue breast feeding (Nitsun et al., 2006).

5.9.3.7 Autopsy Findings

The autopsy findings in fentanyl-related deaths are the same as in heroin overdose: pulmonary and cerebral edema. If licit transdermal patches are present, nothing prevents the continuous release of fentanyl after death. In such cases and in instances where multiple

patches have been applied, postmortem concentrations may be well over 50 ng/mL (Edinboro et al., 1997). No study has ever addressed the problem of continuing release of fentanyl from patches after death. It is quite conceivable that a patient with a painful injury, being treated with a fentanyl patch, might die from their original injury while wearing a fentanyl patch. If absorption from the patch continues after death, and there is no reason to assume that the patch will stop releasing fentanyl at the time of death, high fentanyl concentrations observed at autopsy might mistakenly be considered the cause of death.

Fentanyl's volume of distribution is large enough that redistribution is almost certain to occur and, if the patch has been placed directly over the heart, or even near to it, diffusion from the patch into the bloodstream should be anticipated. The result may be a spuriously high reading that should not be overly relied upon. In such situations, measurement of hair fentanyl concentrations can be extremely helpful, as they will reveal patterns of abuse and may allow some inferences about tolerance. Finally, the issue of P-450 heterogeneity cannot be ignored. Fentanyl is metabolized both by 3A4*1B and 3A5*3. Individuals without the normal enzyme may not be able to metabolize fentanyl at the same rate as normal individuals, and genetic deficit could be a contributory cause of death. Postmortem measurement of enzyme activity is now possible with appropriately preserved specimens and this option should be considered in appropriate cases (Jin et al., 2005).

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5.9.4 Hydrocodone

Synonyms: dihydrocodeinone
Name: 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one
Formula: $C_{28}H_{21}NO_3$
Molecular weight: 299.4 daltons
Bioavailability: high, but never quantitated in control studies
Metabolism: Hepatic: *O*-Demethylation (CYP2D6) and reduction of the 6-keto group (CYP3A4) (Hutchinson et al., 2004). Hydrocodone is a minor metabolite of codeine (Anon., 2004)
Protein binding: not known
$T_{½β}$: approximately 4 hours (Anon., 2004)
C_{max}: 18–32 ng/mL (mean 23 ng/mL) after 10 mg oral dose (Anon., 2004)
T_{max}: 1.5 hours (Barnhart and Caldwell, 1977)
Excretion: Renal, 26% in 72 hours. Only 12% excreted unchanged, but multiple metabolites exist and all are active when not conjugated.
V_{ss}: 3.3–4.7 kg/L (Holstege, 2006)
Known drug interactions: other opioids; any drug metabolized by CYP2D6
Brand names: Hycodan® tablets and syrup, Hycotuss®, Vicodin®, Vicoprofen®, Zydone®, Hycet®, Lorcet®, Lortab®, Maxidone®, Norco®, Pneumotussin®, Repexain®, Tussafed®, Tusso®

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5.9.4.1 Clinical Considerations

Hydrocodone is a semi-synthetic narcotic and a potent antitussive, very widely prescribed for the treatment of cough, especially by oncologists (Homsi et al., 2002). It is a poorly studied drug and information about human toxicity is limited mainly to the fact that, as a μ receptor agonist, it can, if taken in sufficiently large doses, produce respiratory depression. Injectable formulations are not produced, but addicts solubilize pills (and syrup) and then inject it. Hydrocodone's antitussive actions are thought to be the result of medullary depression, but the mechanism has never been addressed. Randomized controlled trials have shown that its analgesic properties are comparable to those of oxycodone (Marco et al., 2005).

5.9.4.2 Postmortem Data

In seven cases of fatal hydrocodone monointoxication, the mean and median hydrocodone concentrations were 0.53 mg/L and 0.40 mg/L, respectively. The range was 0.12–1.6 mg/L, with 11 cases (65%) less than 0.5 mg/L (Spiller, 2003). Because hydrocodone has a relatively large volume of distribution, significant redistribution should be anticipated. Hydrocodone can also be measured in hair, but no apparent correlation with blood concentrations

has ever been demonstrated. In hair specimens collected from 24 volunteers administered hydrocodone, the range of concentrations observed was extremely wide (130–15,933 pg/mg). Hair from the volunteers was also found to contain hydromorphone (range from 59 to 504 pg/mg) (Moore et al., 2006).

5.9.4.3 Maternal/Fetal Considerations

A recent case report described the findings in two breast-feeding women who were taking hydrocodone. Pumped milk was analyzed for hydrocodone. All of the milk that was present — earlier measurements of breast milk drug concentration are of limited value as the composition of milk expressed initially is very different from what follows it. The infants of these two women received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone dosages were 8.58 μg/kg per day and 3.07 μg/kg per day because of the differences in the dosages ingested by their mothers. The findings suggest that moderate dosages of hydrocodone do no harm to breast-feeding children, though the maximum safe dosage has yet to be determined (Anderson et al., 2007).

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5.9.5 Hydromorphone

Synonyms: none
Name: 4,5 α-epoxy-3-hydroxy-17-methyl morphinan-6-one
Formula: $C_{17}H_{19}NO_3$
Molecular weight: 285.338 daltons
Bioavailability:
Oral: after one dose, 50.7 ± 29.8% (Parab et al., 1988)
Rectal: 33 ± 22% (Parab et al., 1988)
Intravenous: (n = 8, 2 mg) 51.35 ± 29.3%
Metabolism: CYP3A and, to a lesser extent, CYP2C9, catalyze hydromorphone *N*-demethylation in humans (Benetton et al., 2004)
Urinary excretion: only 6% unchanged
T_{max}: 2 mg IV (n = 24) = 0.167 (range 0.083–0.25) hours (Coda et al., 2003)
C_{max}:
IV: 242 ng/mL after 2 mg bolus (Parab et al., 1988); 332 (Coda et al., 2003)
Oral: 11.8 ± 2.6 (4 mg to six subjects) 18–27 ng/mL, mean 22 (Vallner et al., 1981)
Intranasal: (1 mg, n = 24) 17 ng/mL

$T_{½β}$: 2.4 ± 0.06 (Parab et al., 1988); *n* = 24, 2 mg 5.9 hours (Coda et al., 2003)
Volume of distribution: 2.90 ± 0.6 L/kg (Moulin et al., 1991)
Interactions: troleandomycin and ketoconazole prevent breakdown to norhydromorphone
Brand names: Dilaudid®, Hydromorph®, Hydal®, Sophidone®, Hydrostat®, Hydromorfan®, Hydromorphan®, Laudicon®

Anon. (2004). Hydromorphone. In: Moffat, A., Osselton, D. et al. (eds.), *Clarke's Analysis of Drugs and Poisons*. Pharmaceutical Press, London, p. 1114.
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5.9.5.1 General Considerations

Hydromorphone is increasingly used for the management of patients with chronic pain, especially those with cancer. Like the other semi-synthetic opiates it is a powerful μ opioid agonist, and produces the same effects as any other potent μ agonist. It is 3–7.5 times more potent than morphine (Coda et al., 2003).

5.9.5.2 Clinical Considerations

Long-term treatment may produce a neuroexcitation syndrome with agitation, myoclonic activity, and even seizures. Occurrence of this complication is not gender or age related. It has been suggested that these symptoms are a result of the accumulation of hydromorphone-3-glucuronide, a metabolic product of hydromorphone (Dean, 2004). In patients with renal compromise the half-life may be greatly prolonged, possibly to 40 hours or more (Dean, 2004).

5.9.5.3 Postmortem Data

There are no diagnostic lesions and no way to differentiate hydromorphone-related deaths from those produced by any other narcotic. A handful of postmortem measurements have been reported. Deaths from hydromorphone are uncommon. In 2006 a paper was published reviewing the findings in an examination of 251 hydromorphone-positive cases that had occurred in the Canadian province of Ontario from 1985 to 2003. Thirty-three of these cases were reviewed in detail. In four cases in which hydromorphone was the sole drug detected and death was attributed to hydromorphone toxicity, concentrations ranged from 77 to 2684 ng/mL. Hydromorphone concentrations ranged from 21 to 441 ng/mL in 28 cases in which at least one other drug was detected. In five deaths attributed to natural causes, blood hydromorphone concentrations ranged from 75 to 423 ng/mL (Wallage and Palmentier, 2006).

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5.9.6 Kratom

5.9.6.1 General Considerations

Very little is known about either the human pharmacology or toxicology of this ancient herbal remedy. Nonetheless, it can be abused, and in vitro studies show rather convincingly that at least one of its components, mitragynine, is a potent opiate agonist, capable of producing analgesia comparable to that of morphine. In fact, one of the minor kratom metabolites, 7-hydroxymitragynine, is actually thought to be more potent than morphine (Babu et al., 2008).

5.9.6.2 Active Agents

Mitragynine only accounts for about 70% of the active alkaloid found in kratom leaves. Many other indole alkaloids have been identified (paynantheine, speciogynine, speciociliatine, 7-α-hydroxy-7H-mitragynine, and rhynchophylline). Clinical reports suggest that at lower doses, chewing the plant leaves produces effects reminiscent of those produced by cocaine or any other stimulant. There is no evidence that the leaves ever produce hallucinogenic effects, but the results of animal studies suggest that kratom's interactions are not confined to opiate receptors. An as yet to be identified component of the plant interacts with the serotonergic and adrenergic systems. Kratom is beginning to gain popularity in the U.S. as a recreational drug. Internet advertisements promote it as a legal psychoactive herb (which it is).

Kratom grows in Thailand, Malaysia, Myanmar, and other areas of Southeast Asia. It is in the same family as the coffee tree (*Rubiaceae*). *Mitragyna speciosa* is a leafy tree that grows from 3 to 15 meters tall, and perhaps as much as 15 feet around. It is referred to by many names both in Southeast Asia and the U.S. The most common alternate names include kratom, ketum, kakuam, ithang, and thom. In Southeast Asia the leaves have traditionally been used for brewing tea that is supposed to have medicinal value (Shellard, 1989).

Mitragynine is an indole alkaloid isolated from kratom. A 9-demethyl analog of mitragynine, 9-hydroxycorynantheidine, is synthesized from mitragynine. It is also a potent μ agonist, but not nearly as potent as mitragynine. Possible explanations for the plant's stimulant effects have never been determined, but there is ample evidence that these effects are quite real. In fact, until the recent changes in Thai law, kratom extracts were included in commercial energy drinks that were especially popular among construction workers (Pichainarong et al., 2004).

5.9.6.3 Clinical Information

Possible negative effects include dry mouth, increased urination, loss of appetite, and constipation, but none of these is likely to take a person to the emergency room. Unlike many

other indoles, mitragynine itself is unlikely to produce nausea or vomiting — usually inexperienced users just get sleepy. A United Nations report published more than a quarter of a century ago described the kratom alkaloids as addictive. When it is fed long-term to experimental animals, kratom reduces both food and water intake, and the animals do not develop tolerance to the drug's effects, but no other ill effects have been noted. Kratom is used by the Thailand military for its stimulant properties.

Information on the illicit use of kratom in the U.S. is anecdotal, and it would not be detected by any of the present immuno-screening systems used in medical examiner laboratories (mitragynine is easy enough to detect with GC/MS, but only if an effort is made to find it). Thus, it is not known whether any morbidity or mortality has ever resulted from kratom abuse. Based on information posted on the Internet, it appears that kratom is mainly being abused orally as a tea, but chewing kratom leaves is another method of consumption. Doses in the range of 2–10 g are said to produce the desired effects. In London, kratom dealers promote it as an "herbal speedball." In Malaysia, kratom (known as ketum) juice preparations are sold in stores (Jansen and Prast, 1988).

In 2005, five Thai distributors of "ketum" juice were arrested. In that same year a BBC report claimed that young Thai troops were required to drink a "4 × 100," a kratom formula designed to help them stay alert during military missions. The product "4 × 100" is a mixture of boiled kratom leaves, mosquito coils, cola, or a mixture of boiled cough syrup, and whole kratom leaves served with ice. In Thailand it is available in local coffee and tea shops. As of this writing kratom was still not a controlled substance in the U.S. However, sales are controlled in Thailand, Malaysia, and Myanmar. In 2004, mitragynine and kratom have both been placed in Schedule 9 (the most restrictive level) of the Australian National Drugs and Poisons Schedule (Assanangkornchai et al., 2008).

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5.9.7 Methadone

Synonyms: none
Name: 6-dimethylamino-4,4-diphenyl-3-heptanone
Formula: $C_{21}H_{28}ClNO$
Molecular weight: 345.91 daltons
Bioavailability: 41–95% (Meresaar et al., 1981; Nilsson et al., 1982; Rostami-Hodjegan et al., 1999)
Metabolism: hepatic CYP3A4 metabolizes methadone in vitro, but in vivo CYP2D6 and CYP2C19 perform most of the conversion

Protein binding: > 80% (Inturrisi et al., 1987) and variable degrees of binding to α-1-acid glycoprotein (Rodrigues-Rosas et al., 2005)

$T_{½β}$:

α phase: 1.9–4.2 hours

β phase: 23 hours (Inturrisi et al., 1987); 26.8 hours (Wolff et al., 2000)

β phase *l*- form: 53.0 hours (measured in hospice patients) (Auret et al., 2006)

β phase *d*- form: 33.5 hours (measured in hospice patients) (Auret et al., 2006)

C_{max}: 2.5 hours (Wolff et al., 1993); 3 hours (Meresaar et al., 1981; Nilsson et al., 1982)

Clearance:

l- form: 0.082 (0.052–0.112) L/kg/hour (measured in hospice patients) (Auret et al., 2006)

d- form: 0.117 (0.061–0.163) L/kg/hour (measured in hospice patients) (Auret et al., 2006)

Excretion: Renal

First 24 hours: 15–60%

Hours 24–96: 52%

V_{ss}:

Addicts: 4.2 –9.2 L/kg (Wolff et al., 1991)

Chronic pain: 1.71–5.34 L/kg

l- form: 3.8 L/kg (measured in hospice patients) (Auret et al., 2006)

d- form: 4.82 L/kg (measured in hospice patients) (Auret et al., 2006)

Detection time in urine: depends on pH

Known drug interactions:

CYP3A4 inducers: barbiturates, carbamazepine, dexamethasone, efavirenz, felbamate, hypericum, nelfinavir, nevirapine, oxcarbazepine, phenytoin, phosphophenytoin, rifampin, risperidone, ritonavir, topiramate (Ferrari et al., 2004)

CYP3A4 inhibitors: cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, josamycin, ketoconazole, nefazodone, norfloxacin, norfluoxetine, paroxetine, protease inhibitors, venlafaxine (Ferrari et al., 2004)

CYP2B6 inducers: glucuronyltransferase (UGT), rifampin, UFT1A6, phenobarbital, quercetin, as well as numerous agrochemicals (Hodgson, 2007; van de Kerkhof et al., 2008)

Brand names: Dolophine®, Methadose®

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5.9.7.1 General

Methadone is a derivative of diphenylpropylamine. Drugs in this class have a general formula that looks quite different from the basic morphine molecule. On closer examination it is apparent that methadone contains the same basic structures common to all morphine analgesics (Figure 5.9.7.1.1). Methadone is supplied as a racemic mixture, but almost all of the opiate activity derives from the *l*- form. Unfortunately, the *d*- form, while lacking an opiate activity, avidly binds to the hERG potassium receptor and may cause sudden death. There is good reason for supposing that many methadone deaths, previously thought to be a result of respiratory depression, were in fact the result of malignant ventricular arrhythmias induced by the useless *d*- form (see below) (Eap et al., 2007). In the 1999 DAWN survey, 643 methadone-related deaths were reported to the federal government, amounting to 5.5% of all reported narcotic deaths for that year (Kissin et al., 2000). Now that the DAWN Medical Examiner System is no longer functional, the true extent of the problem is not known, though the number of deaths is probably still quite small when compared to heroin.

In 1965 methadone was introduced as a maintenance drug for the treatment of heroin addiction. One of methadone's attractive features is its half-life, which can exceed 50 hours; this makes outpatient management feasible. Since 1965 new agents such as L-LAAM (*l*-α-acetylmethadol) and buprenorphine have been introduced to replace methadone. Both of the new agents were thought to offer advantages over methadone, however, L-LAAM turned out to be an hERG cardiac K^+ blocker with serious pro-arrhythmic effects

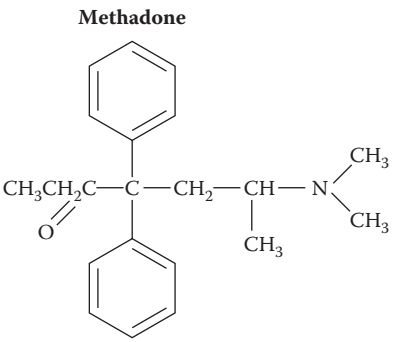

Figure 5.9.7.1 Methadone.

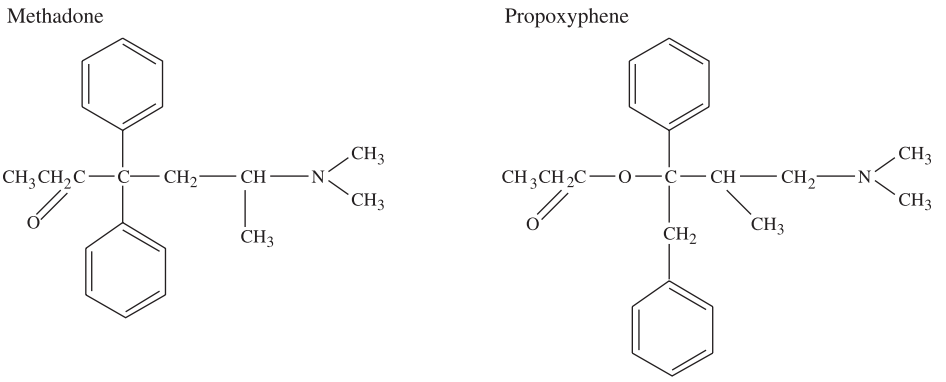

Figure 5.9.7.1.1 Methadone and propoxyphene. Even though it is not obvious, the methadone molecule contains the same basic structures as all the other morphine-related analgesics. Propoxyphene is a derivative of morphine.

(Kang et al., 2003), even greater than those of methadone (Ehret et al., 2006). As a result, L-LAAM is no longer used in clinical practice. Buprenorphine is thought to be safer than methadone, and much less likely to be abused, but it is also much more expensive than methadone, and so methadone remains the drug of choice for the treatment of heroin addiction. Methadone is now also prescribed for cancer patients and for the management of patients with intractable pain (Novick and Kreek, 1992; Nixon, 2005; Zimmermann et al., 2005).

Depressed immune function is a common problem in heroin addicts and there is a body of laboratory and clinical evidence suggesting that methadone replacement normalizes immune function (Alonzo and Bayer, 2002). If methadone does reverse long-term heroin-related immune suppression, it may have more to do with improved lifestyle and a decrease in the number of intravenous injections, rather than with any direct effect of the drug itself (McLachlan et al., 1993; Radkowski et al., 1996). Diversion of legally prescribed methadone appears to be the only source for black market methadone within the U.S. A recent Cochrane review recommended methadone replacement treatment in all countries where HIV is an emerging disease (Ferri et al., 2005), as well as in areas where HIV is already endemic and unsafe injecting practices are the rule.

5.9.7.2 Pharmacology

The *S*- form of methadone exerts little narcotic effect, but pure *R*- isomer is expensive to make. As a compromise, in most countries a racemic mixture is produced. Each isomer has a different pharmacokinetic profile (see below). However, only the *S*- form binds to the hERG (rapid delayed potassium rectifier channel) and thus has the ability to cause QT prolongation, torsade de pointes, and sudden death. Fortunately, it appears that only individuals who are slow metabolizing polymorphs for CYP2B6 are at risk (Eap et al., 2007). No one who is a CYP2B6 slow metabolizer should ever be placed on racemic methadone, because the *S*- form of methadone (the inactive form) is metabolized by CYP2B6. Slow metabolizing CYP2B6 polymorphs cannot metabolize methadone's *S*- form and it will accumulate. When enough accumulates, poisoning of the hERG channel occurs, and normal cardiac depolarization is prevented.

After oral administration, peak methadone plasma concentrations occur within 2.5–4 hours. Metabolism occurs mainly in the liver but also, to a small degree, in the intestines (Benmebarek et al., 2004; Kharasch et al., 2004). The main metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine [EDDP]) is inactive (Sullivan and Due, 1973). Methadone dosage is difficult to manage because the same dose given to different people produces very different plasma concentrations. Acceptable clinical responses are associated with (*R*)-methadone plasma concentrations of 250 ng/mL and (*R,S*)-methadone plasma concentrations of 400 ng/mL (Foster et al., 2000).

The variability in clinical response, and plasma concentrations, is mainly a result of variations in the activity of the cytochrome P-450 (CYP) system (Eap et al., 2000). CYP3A4 was thought to be the main enzyme involved in methadone metabolism (Dyer et al., 2001; Wang and DeVane, 2003), but laboratory studies increasingly suggest a role for other enzymes in the P-450 series (CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2C19, and CYP1A2). CYP2B6 is implicated in the metabolism of a range of psychoactive drugs, including MDMA (Kreth et al., 2000), and even nicotine (Inoue et al., 2000). CYP2B6 is expressed mainly in the liver, but low levels can be found almost anywhere else in the body (Ekins and Wrighton, 1999). Not all human livers express the same amount of CYP2B6, and even if they did the form expressed may be mutated and relatively ineffective (Lang et al., 2001; Klein et al., 2005).

5.9.7.3 Clinical Considerations

Tolerant individuals may take doses of methadone that would induce fatal respiratory depression in naïve users, and so plasma concentrations, taken in isolation, are poor predictors of toxicity. In several independent studies, heroin addicts treated with methadone doses ranging from 180 to 260 mg/day have experienced no ill effects (Walton et al., 1978; Crettol et al., 2005). Plasma methadone values in hospitalized patients have ranged from 20 to 1308 ng/mL with a mean concentration of 451.4 ± 306 ng/mL (Loimer and Schmid, 1992).

Deaths have been reported in addicts who were just beginning methadone maintenance, receiving a mean dose of only 57 mg/day (Drummer et al., 1992). This was thought to be a consequence of advancing the dosage of methadone too quickly so that fatal respiratory depression occurs (Wu and Henry, 1990; Coleridge et al., 1992; Caplehorn and Drummer, 1999). The relative risk of respiratory depression is nearly seven times higher in patients starting therapy than in untreated heroin addicts and 97.8 times higher than for methadone maintenance patients who have been in maintenance for more than two weeks. It now seems likely that a significant proportion of these deaths occur in individuals who are CYP2B6 polymorphs, unable to metabolize the *S*- form of methadone. Nonetheless, tolerance must also be considered when trying to evaluate these cases, and a detailed medical history must be obtained before certifying the cause of death (Foster et al., 1999, 2000).

Individual response also depends on sex, weight, use of concomitant medications, duration of methadone treatment, previous exposure to other opioids, and plasma concentrations of acid glycoprotein (AAG) (Garrido et al., 2000). If death does not occur at the initiation of therapy, and is not a consequence of illegal drug diversion, it almost certainly is the result of an underlying medical problem or of an unrecognized drug interaction. Actually, cases of torsade seem to occur mostly in individuals receiving high dose intravenous treatment (Almehmi et al., 2004).

The role of AAG methadone-related deaths is probably just as important as that of herg abnormality. Methadone is a basic molecule and nearly 90% exists bound to plasma proteins. The fact that methadone binds to acid glycoprotein raises the possibility that unexpected illness might lead to an increase in the concentrations of free methadone because of a relative AAG deficiency. The result would increase the chances for respiratory arrest (Romach et al., 1981; Inturrisi et al., 1987; Wilkins et al., 1997). Levels of AAG fluctuate depending on the underlying health of the individual. AAG levels increase when there is significant stress. As stress levels rise, as they well might during abstinence, the amount of free (and therefore active) methadone decreases (Wilkins et al., 1997). An alcoholic addicted to heroin might inadvertently overdose if less AAG were produced during a flare up of liver disease.

5.9.7.4 Metabolism and Pharmacokinetics

Information about the clinical toxicology of methadone is largely derived from studies of healthy volunteers given single doses of methadone or cancer patients injected with methadone intravenously (Inturrisi et al., 1987). Studies of drug addicts suggest that measurements made in the chronically ill falsely underestimate methadone's terminal half-life and volume of distribution (Kristensen et al., 1996; Wolff et al., 1997; Rostami-Hodjegan et al., 1999). Naïve users take much longer to clear methadone from their circulation, which is one reason why they are at greater risk for overdose. However, even long-term patients are at risk if they take another drug, illicit or prescription, that competes for CYP3A4 or other polymorphic members of this family (Foster et al., 1999, 2000).

Some clinicians rely upon measurement of the plasma methadone-to-EDDP ratio as an indicator of safe and effective dosing. Various reports have placed the normal value for the methadone-to-EDDP ratio at between 18 and 22 (de Vos et al., 1996), depending on whether pure *l*-methadone, or *dl*-methadone has been administered. The ratio seems to be much lower in postmortem blood samples (means value of 13.6:1 in 38 methadone-related fatalities) (Karch and Stephens, 2000), probably because of redistribution (methadone has a very large volume of distribution, while EDDP, though never measured, very likely does not).

At least three main phenotypes of AAG are recognized, and each of these has a different affinity for methadone (Callaghan and Riordan, 1993). In studies with human volunteers, measured fractions of free racemic, *d*-methadone, and *l*-methadone ranged from 10 to 14% (Eap et al., 1990), with the remainder of the drug bound to various other proteins. In hospitalized heroin addicts, the severity of abstinence symptoms correlates with AAG concentrations; the higher they are, the worse the withdrawal symptoms (Garrido et al., 2000).

Reported values for the terminal half-life of methadone are very wide, ranging from 13 to 58 hours (Inturrisi and Verebely, 1972; Goldstein and Herrera, 1995). In opioid addicts, methadone kinetics are best described by a single-compartment model. The volume of distribution is large (6.7 L/kg), and the clearance rate is low (3.1 mL/min/kg). The observed elimination half-life of 26.8 hours in addicts appears to be substantially lower than earlier estimates had suggested (Wolff et al., 1993).

Methadone clearance is altered in the presence of other drugs. When alcohol and methadone are taken at the same time, the metabolism of each is enhanced, and withdrawal symptoms can ensue (Tong et al., 1981). When methadone and cocaine are taken together, methadone plasma levels decrease, apparently because the cocaine accelerates methadone excretion (Tennant and Shannon, 1995). Because CYP3A4 activity is involved

with the metabolism of so many drugs, numerous interactions are possible. Drugs that inhibit CYP3A4 metabolism can be expected to increase blood methadone concentrations. Some of the better known CYP3A4 inhibitors include itraconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, ritonavir, and grapefruit juice. Many of the drugs used to treat HIV are metabolized by CYP3A4, and treatment with any of them can cause a precipitous drop in methadone blood concentration, even bringing on withdrawal symptoms (Fromm et al., 1997; Iribarne et al., 1997; Heelon and Meade, 1999).

5.9.7.5 Maternal/Fetal Considerations

There is general agreement that infants born to mothers being treated with methadone are significantly less mature and lower in weight than control infants. More than half of all such infants can be expected to develop neonatal abstinence syndrome, and most stay in the hospital longer than infants not exposed to drugs (Kelly et al., 2000). However, it is also agreed that methadone treatment during pregnancy is vastly preferable to either medical detoxification or leaving heroin-addicted women dependent on street drugs. Treatment reduces maternal and fetal morbidity and mortality (Kandall et al., 1999). During the first day of life, maternal plasma methadone levels correlate significantly with neonatal plasma methadone levels. It also has been observed that the severity of central nervous system signs of withdrawal correlates with the rate of decline in the infant's plasma methadone levels. In 21 neonates with symptoms of withdrawal, the mean maternal methadone level 16 hours after delivery was 183 ± 118 ng/mL, while the mean plasma level in samples drawn from the infants at the same time was 26 ± 8 ng/mL. Methadone levels decreased in the infants at the average rate of 0.2 ± 0.3 ng/mL/hr (Doberczak et al., 1993).

In a second study blood and milk samples were obtained from 12 breast-feeding women who were taking methadone in daily doses ranging from 20 to 80 mg per day, and blood was also obtained from eight of their infants who were also observed for withdrawal symptoms. The mean (95% CI) milk/plasma ratio was 0.44 (0.24–0.64). Exposure of the infants (calculated on the assumption that the average milk intake was 0.15 L/kg/day and that bioavailability was 100%) was 17.4 (10.8–24) μg/kg/day. The mean infant dose expressed as a percentage of the maternal dose was 2.79 (2.07–3.51)%. In seven of the infants, methadone concentrations were below the limit of detection, while one infant had a plasma methadone concentration of 6.5 μg/L (Wojnar-Horton et al., 1997). The other maternal/fetal consideration that cannot be ignored is childhood exposure, either intentional or accidental. Deaths have occurred in children given methadone to stop their crying (Kintz et al., 2005), and others have occurred in toddlers who find their parents' take-home dose of methadone (Inselman, 1971; Klupp et al., 2000).

5.9.7.6 Hospice and Pain Patients

Hospice patients and those with chronic pain syndromes are often maintained on very high doses of either morphine or methadone. A recent study of 13 terminally ill hospice patients disclosed an average steady state methadone concentration of 1970 ng/mL (980–379) for the *d*- isomer, and 2720 (550–3780) for the *l*- isomer, and only half of these individuals achieved adequate pain relief. At these very high levels, the apparent volumes of distribution for the *l*- and *d*- forms were 6.5 L/kg and 4.8 L/kg, respectively. The half-lives also differed: 53.3 hours for the *l*- form and 31.5 hours for the *d*- form. By

comparison, when this same group was treated with morphine (mean dose 178 mg/day) the mean plasma morphine concentration was 290 ng/mL (111–750 ng/mL) (Auret et al., 2006). It should be apparent from these very high concentrations that tolerance occurs on a massive scale and any attempt at relating plasma concentration to outcome would be futile.

5.9.7.7 Routes of Administration

Oral absorption of methadone is excellent, and when compliance is good, a high degree of correlation exists between the dose administered and plasma levels. Over the range of 3 to 100 mg, plasma methadone concentrations increase by 263 ng/mL for every milligram of methadone per kilogram of body weight. A similar, nearly linear, concentration increase is also observed in saliva, although the peak levels are somewhat higher and the half-life somewhat longer (Wolff et al., 1992). In cancer patients, a 10-mg intravenous injection produced a peak plasma level slightly above 500 ng/mL, falling to below 100 ng/mL at one hour (Inturrisi et al., 1987). Blood and plasma concentrations after the less common routes of administration have not been measured. High dose intravenous administration is associated with the occurrence of QT prolongation and torsade de pointes presumably because of hERG blockade by the large amounts of the l-form being injected (Almehmi et al., 2004; Krantz and Mehler, 2004; Ehret et al., 2006).

5.9.7.8 Compliance Monitoring

Lack of venous access makes monitoring replacement patients difficult. When blood is available, the ratio of methadone to its principal metabolite is considered effective; however, compliance can also be monitored by urine, sweat, and hair testing. A study of established replacement patients found that methadone and EDDP were present in very high concentrations in the urine samples, but that the methadone concentration in the hair samples was scattered in the range of 9.5–80.8 ng/mg, while EDDP was detected in the range 2–6.25 ng/mg. The methadone concentration in the sweat samples from the same group of patients ranged from 120 to 2160 ng/patch with EDDP concentrations ranging from 25 to 535 ng/patch. It is noteworthy that none of the measurements in any of the individuals' hair or sweat correlated with the dose given, but the methadone/EDDP ratio in every case fell between 0.1 and 0.3, which is the same ratio that is observed in testing the blood of living replacement patients (Fucci and De Giovanni, 2007).

5.9.7.9 Autopsy Findings

Methadone maintenance clients are likely to have some cutaneous stigmata of past intravenous heroin abuse. They are also very likely to be infected with hepatitis C virus, even if histologic changes are not evident. Table 5.9.7.9.1 lists the most frequent abnormalities detected at autopsy in a series of 38 methadone-related deaths (Karch and Stephens, 2000). Many of the autopsy findings, such as terminal aspiration and pneumonia (15.6%), are known complications of intravenous opiate abuse. QT interval prolongation in hospitalized methadone maintenance patients is not rare, even if no anatomic changes are identifiable in the heart. Whether or not an arrhythmia will occur depends not only on cardiac anatomy, but also the dose of methadone, the presence of cytochrome P-450 inhibitors, the antemortem potassium level, and liver function (Ehret et al., 2006).

Table 5.9.7.9.1 Autopsy Findings in Methadone Users

Diagnosis	Number	Percent (%)
Track marks	13	34.2
Coronary artery disease	9	21.0
Cirrhosis	7	18.4
Pneumonia	6	15.7
Hepatic fibrosis	5	13.1
Fatty liver	4	10.5
Necrotizing fasciitis	4	10.5
Birefringent crystals	4	10.5
HIV	3	7.8

Based on an analysis of 38 cases investigated by the Office of the San Francisco, CA, Medical Examiner. (Karch, S. B. and Stephens, B. G., *West. J. Med.*, 172(1), 11–14, 2000. With permission.)

5.9.7.10 Postmortem Blood Concentrations

Because methadone has a very high volume of distribution, concentrations can be expected to rise after death, with four-fold increases having been reported (Levine et al., 1995; Milroy and Forrest, 2000). Postmortem methadone concentrations are also site dependent (Levine et al., 1995) and, for unexplained reasons, the increases appear to be greater in men than women (Caplehorn and Drummer, 2002). In every series ever published methadone blood concentrations in fatal cases completely overlap those found in methadone maintenance program participants. Similarly, levels in cases of overdose are indistinguishable from those in decedents where death is due to trauma, where the presence of methadone was simply an incidental finding (Karch and Stephens, 2000; Milroy and Forrest, 2000; Gagajewski and Apple, 2003; Pirnay et al., 2004; Wolf et al., 2004). In a study of 38 decedents where methadone was detected, the mean blood methadone concentration was 975 ± 681 ng/mL, the mean blood EDDP was 253 ± 529 ng/mL, and the mean blood methadone-to-EDDP ratio was 13.6. Urine concentrations of methadone ranged from 5 to 6 mg/L, and were the same in individuals where methadone was an incidental finding and in those where it was the cause of death. The mean blood methadone-to-EDDP ratio for the entire group of 38 was 13.5 ± 17.4, but the range was so wide, from 0.572 to 60, that determination of the ratio was of no diagnostic value (Karch and Stephens, 2000).

A study from England analyzed the findings in 55 cases where methadone poisoning was listed as the sole cause of death. The mean methadone concentration in adult cases was 584 ng/mL (median, 435; range, 84–2700). The value was not significantly lower when other drugs were present (Milroy and Forrest, 2000). Given the degree of overlap of findings in cases where methadone is, and is not, related to the cause of death, it is simply impossible to distinguish between the two categories on the basis of toxicology testing alone. As with other drugs, central samples are likely to show greater increases than samples taken from the periphery.

In the most recently published autopsy case series, 139 methadone-positive cases were analyzed for the presence of other drugs besides methadone. Both prescription and illicit drugs were frequently detected (usually benzodiazepines or cocaine). Concentrations ranged from 0.114 to 1.939 mg/L (mean 0.0559 mg/L) in cases where death was attributed

to methadone toxicity; 0.050 to 1.903 mg/L (mean 0.411 mg/L) in cases of combined drug toxicity; 0.069 to 0.644 mg/L (mean 0.224 mg/L) in deaths where other drugs were thought to be the cause of death; and 0.062 to 1.090 mg/L (mean 0.344 mg/L) in cases where death was attributed to natural causes (Wolf et al., 2004).

Very little can be determined from postmortem methadone measurements when they are considered in isolation, especially if the decedent was taking the drug chronically. Redistribution of both isomers can be anticipated, as can the existence of tolerance. A plasma concentration that might seem certainly lethal may actually have been too low to relieve pain. In most cases, the situation is not nearly so clear cut, and pathologists would be well advised not to "over read" the toxicology report.

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5.9.8 Meperidine

Synonyms: pethidine
Name: 1-methyl-4-phenyl-4-piperidine-carboxylic acid ethyl ester
Formula: $C_{15}H_{21}NO_2$
Molecular weight: 247.3 daltons
Bioavailability: 41–60% (Mather et al., 1975; Pond et al., 1981)
Metabolism: hepatic (CYP2B6 and CYP3A4, a minor contribution from CYP2C19) isoenzymes (Ramirez et al., 2004)
$T_{½β}$ (half-life): 3.1–4.1 hours
Normal: 3.2 hours (Boreus et al., 1983), 4.2–8.7 (Mather et al., 1975; Mather and Tucker, 1976; Mather and Meffin, 1978)
IV: 3.93 ± 0.33 hours (Stambaugh et al., 1976)
IM: 3.25 ± 0.71 hours (Stambaugh et al., 1976)
PO: 3.49 ± 0.37 hours (Stambaugh et al., 1976)
Cirrhotic: 8.3–18.7 hours (Pond et al., 1981)
Sickle cell: (n = 4) 2.5 mg/kg IV or IM; 3.18 hours, 5.1 respectively (Yang et al., 1995)
Clearance: 1012 L/min (Boreus et al., 1983), 730–1300 mL/min (McHorse et al., 1974; Mather and Meffin, 1978)
Excretion: renal
Intravenous: V_{ss}: 2.8 (Stambaugh et al., 1976); 4.0 (Boreus et al., 1983)
Known drug interactions: Selegiline induces serotonin syndrome (Goodnick, 2007), propofolol induces antimuscarinic syndrome (Snow, 2007). Linezolid also causes serotonin syndrome (Das et al., 2008).

Maternal/fetal considerations: meperidine is transmitted in small amounts in breast milk, but the risk is considered acceptable (Spigset and Hagg, 2000); concentrations measured in lactating women have ranged from 36.2 to 314 ng/mg (Quinn et al., 1986)

Proprietary brand names: In the U.S., Demerol®. In Europe, Dispadol®, Dolantine®, Dolantin(a)®, Dolestine®, Dolosal®, Mefedina®, Pethoid® and as an ingredient in Mepergan® and Pamergran P10®.

Normeperidine

Formula: $C_{14}H_{15}D_4NO_2$

$T_{½β}$ (half-life):

Normal: 14–21 hours (Szeto et al., 1977); 24–48 (Chan et al., 1975a)

Renal failure: > 30 hours (Chan et al., 1975b; Szeto et al., 1977; Kaiko et al., 1983)

Excretion: renal, accumulates in face of renal compromise

V_{ss}: 5 L/kg (McHorse et al., 1974; Mather and Meffin, 1978), 4.25 L/kg (Hartvig et al., 1982)

Known interactions: other opiates and benzodiazepines (Lewis and Stanley, 1999)

Maternal/fetal considerations: Normeperidine is transmitted in small amounts in breast milk. Concentrations measured in nursing mothers have ranged from 0 to 333 ng/mg (Quinn et al., 1986).

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5.9.8.1 General Considerations

Meperidine is a synthetic phenylpiperidine derivative. It was first developed as an anticholinergic agent and introduced into clinical medicine during the 1930s. It was created in the hope that it might be effective in the management of patients with gallstones and pancreatitis, where cholinergic-linked spasm of the sphincter of Oddi was thought to be the primary etiology of gallstone pancreatitis. In spite of widespread use during the 1970s and 1980s, there still are no studies directly comparing the effects of meperidine and morphine on sphincter pressure, no comparative studies in patients with acute pancreatitis, and no outcome-based studies comparing the effectiveness of meperidine and morphine in patients with acute pancreatitis. Many clinicians feel that morphine may be of more benefit than meperidine because it offers longer pain relief with less risk of seizures (Thompson, 2001). These observations explain why use of this agent is falling into disfavor, not just among palliative care experts (Beckwith et al., 2002), but with others as well. Nonetheless, meperidine is still very widely used in patient-controlled anesthesia devices (Seifert and Kennedy, 2004).

In 1999, the last year when any meaningful data were reported, meperidine accounted for 0.9% of all narcotic-related deaths mentioned in the old DAWN report (103 deaths vs. 4820 for heroin). There are no mentions of meperidine in the government's most recent analysis (SAMHSA, 2006b) of common drug seizures, nor is it mentioned in the Emergency Room component of the 2004 DAWN report (SAMHSA, 2006a). Access to meperidine remains limited; episodes of abuse and toxicity usually involve medical personnel or else result from drug administration errors and/or unanticipated drug reactions.

5.9.8.2 Metabolism

Meperidine has two different metabolic routes. The primary route is conversion to an inactive metabolite called meperidinic acid. This conversion is performed by liver carboxylesterases. Meperidinic acid is then conjugated and excreted by the kidneys. The pathway of the most clinical significance is the *N*-demethylation by hepatic P-450 enzymes to form normeperidine (Eisendrath et al., 1987). Substantial racial and intra-individual variation exists due to polymorphisms of the P-450 system, and these differences may explain some variations in the clinical effects observed (Braenden et al., 1955; Houghton et al., 1992). Normeperidine has modest analgesic properties, but, more importantly, it is a potent CNS stimulant and can cause seizures. Normeperidine is subsequently metabolized to normeperidinic acid and excreted by the kidneys. P-450 microsomes also form small amounts of *N*-hydroxynormeperidine; it also undergoes renal excretion (Dahlstrom et al., 1979). The existence of these polymorphisms may, perhaps, explain why there is very little correlation between blood levels and pain relief.

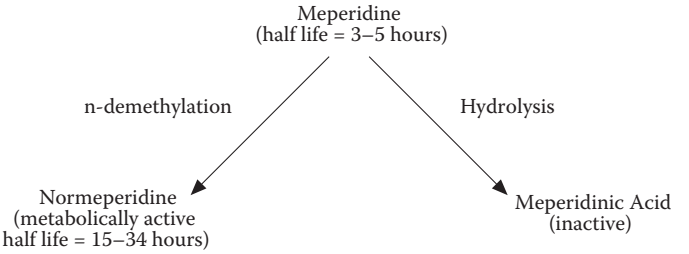

Figure 5.9.8.2.1 Meperidine metabolism. The metabolite normeperidine has about half the analgesic potency of meperidine and is also neurotoxic. The half-life of normeperidine is much longer than that of meperidine, and toxic levels may accumulate in individuals with renal impairment.

Meperidine is well absorbed by all routes of administration, but absorption is significantly slowed in the presence of cirrhosis and renal disease. There is considerable first-pass effect when meperidine is given orally. Kidney disease prevents the excretion of both meperidine and normeperidine, but the clearance of the metabolite decreases to a much greater degree than that of the parent, and toxic levels of normeperidine may accumulate. After oral administration there is extensive hepatic first-pass metabolism so that only 50–60% of a dose reaches the systemic circulation (Chan et al., 1975a; Edwards et al., 1982). Another consequence of oral administration is that more normeperidine will be generated in the liver, increasing the possibility of neurotoxicity, especially when patients are given large doses or when a patient is chronically treated with the oral form of the drug (Pond et al., 1981). Interestingly, the probability of toxicity is greater in normal individuals than in cirrhotics; cirrhotics are less able to form normeperidine (Pond et al., 1981). The amount of normeperidine excreted in the urine is the same after intramuscular and intravenous dosing, but much greater after it is taken orally, another proof of increased hepatic metabolism (Stambaugh et al., 1976).

In healthy individuals, after a single intramuscular dose of meperidine, the half-life is approximately 3.5 hours. In healthy volunteers, intravenous and subcutaneous administration produces peak concentrations within 10 minutes. However, after oral administration peak concentrations are not reached until 45 minutes later (Schmitt et al., 1994). Peak plasma concentrations vary from individual to individual and do not correlate in any predictable way with analgesic effects. Part of this variability is a consequence of intra-individual variation. Meperidine's volume of distribution increases with age (3.8 L/kg in the young, but up to 4.5 in the elderly, and over 5.0 L/kg in those with cirrhosis) and some diseases. Evidence suggests that chronic heroin users metabolize meperidine more slowly than non-drug users and, as a result, they may develop higher blood levels (Houghton et al., 1993). Because substance abuse is a frequent finding among trauma victims (McLeod et al., 1999), the potential for meperidine toxicity should not be ignored.

Meperidine's apparent volume of distribution is significantly greater than that of either heroin or morphine (4.4 vs. 3.3 L/kg), and its half-life is more than a third longer (approximately 3.2 vs. 1.9 hours) (Pond et al., 1981; Edwards et al., 1982). Its liver metabolism is mainly catalyzed by CYP2B6 and CYP3A4, with a minor contribution from CYP2C19 isoenzymes (Ramirez et al., 2004) (Figure 5.9.8.2.1). Liver carboxylesterases catalyze the conversion of meperidine to meperidinic acid and ethanol (Zhang et al., 1999). Patients with cirrhosis have decreased meperidine clearance and increased bioavailability

(Tegeder et al., 1999), raising the possibility of increased toxicity if the dosage in cirrhotics is not reduced. Age appears to have no effect on the rate with which meperidine is cleared or normeperidine formed (Holmberg et al., 1982) but, as indicated above, the steady state volume of distribution rises with age.

5.9.8.3 Toxicity

Clinical signs of toxicity are not uncommon, but reports of death are rare. Two types of toxicity may be distinguished: direct respiratory depression secondary to excessive accumulation of the parent compound, and indirect neurotoxicity, where seizures occur secondary to the accumulation of normeperidine, the principal metabolite. Normeperidine is metabolically active, with approximately half the analgesic potency of meperidine. However, it exerts different effects than the parent compound. Meperidine binds to the μ receptors and causes respiratory depression comparable to that of morphine (to a lesser degree it also binds to 5-HT, norepinephrine, and dopamine transporters). Accordingly, meperidine's respiratory effects are reversed by naloxone (Lomenzo et al., 2005).

Normeperidine does not bind to μ receptors (Reifenrath et al., 1980) and therefore it is not displaced from its receptors by naloxone. Instead, normeperidine accumulates in the central nervous system, where it causes seizures and symptoms of 5-HT excess (Jiraki, 1992). Seizure activity is especially probable in patients with underlying renal insufficiency (especially the elderly and patients with debilitating cancers, and even those with sickle cell disease; Danziger et al., 1994; Marinella, 1997; Simopoulos et al., 2002). Even in the absence of pre-existing disease, normeperidine tends to accumulate with chronic dosing (Kaiko et al., 1983).

There exist case reports suggesting that daily doses of meperidine in excess of 400–600 mg can result in the accumulation of normeperidine causing toxic reactions, especially in susceptible individuals (Szeto et al., 1977). Hypertension, hyperpyrexia, tachycardia, and seizures are the expected result (Austin et al., 1980; Chan et al., 1987; Fairlie et al., 1999) when excessive doses of meperidine are given. Morphine should not be used if an opioid analgesic is required in a patient who is also receiving an MAOI (Barlow and Lewis, 1951; Chan et al., 1975b).

Meperidine is also a negative inotrope, and intravenous administration causes a significant, but transient, decrease in blood pressure. Meperidine is rapidly taken up by the myocardium, but just what effect it exerts on the myocardium to cause decreased output is not clear (Upton et al., 1999). Like morphine, meperidine causes histamine release and exerts atropine-like effects on heart rate (Bowdle, 1998).

The postmortem toxicology of meperidine has been poorly studied. Meperidine blood concentrations measured in one analysis of six autopsies ranged from 4300 to 12,000 ng/mL (Siek, 1978). Hepatic drug concentrations were twice the blood concentrations of patients who were intravenous users, but only one-half the blood concentrations if the individuals had taken the meperidine orally. Clinical evidence of normeperidine toxicity has been reported, with concentrations ranging from 425 to 1900 ng/mL and normeperidine-to-meperidine ratios of 0.79 to 5.4 (Szeto et al., 1977). The importance of pre-existing renal disease in cases of meperidine toxicity is illustrated by one case report describing a heroin addict with end-stage renal failure; he was found to have a meperidine blood concentration of only 60 ng/mL, while at the same time the normeperidine concentration was 3000 ng/mL (Jiraki, 1992).

5.9.8.4 Drug Interactions

Serotonin syndrome can occur if meperidine is administered at the same time as a drug such as dextromethorphan, pentazocine, tramadol, any monoamine oxidase inhibitor (MAOI), or SSRIs. Symptoms include confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, and occasionally diarrhea. Serotonin syndrome occurs when excess 5-HT is available within the central nervous system and, in particular, when concentrations at the 5-HT1A-receptor sites are elevated. Serotonin syndrome is something of a rarity; symptoms are usually mild and self-limited, although the occurrence of hyperthermia signals a poor outcome and requires aggressive cooling measures (Sporer, 1995; Upton et al., 1998; Weiner, 1999). If large doses of meperidine are given, normeperidine accumulates in the plasma (Koska et al., 1981). In normal individuals the terminal half-life of normeperidine is from 15 to 34 hours, but in the presence of renal impairment, clearance may require 3 or 4 days, and toxicity, when it occurs, may be prolonged (Szeto et al., 1977). In control studies, only 5% is excreted unchanged in the urine, while more than 25% is excreted as meperidinic acid or normeperidinic acid.

5.9.8.5 Patient-Controlled Anesthesia Devices

The results of animal studies, and occasional anecdotal case reports, suggest that large doses of meperidine given via patient-controlled analgesia (PCA) devices may result in generalized seizures. McHugh (1999) described the case of a 35-year-old woman, weighing 47 kg, who underwent elective laparotomy. She requested Demerol®-PCA and 23 hours postoperatively experienced a generalized seizure but she recovered without adverse sequelae. The cumulative meperidine dose was 3000 mg and the normeperidine level was 1.8 μg/mL. The authors of the report suggest that large cumulative doses given via this route be avoided. In another case report, 23 hours after undergoing laparotomy, a woman developed seizures with myoclonic jerking; her meperidine concentration was 3000 mg/L with a normeperidine of 1.8 μg/L (McHugh, 1999). Both intrathecal and epidural patient-controlled devices are popular in obstetric care. Both routes appear effective, with plasma concentrations ranging from 450 μg/L to 700 μg/L, and, in general, the normeperidine concentrations are lower than those known to be associated with neurotoxicity (Jung and Reidenberg, 2005). In a study of 20 women treated with meperidine delivered via an epidural device, dosages ranged from 124 to 140 mg (mean 575 mg) over 48 hours with great inter-individual variation in meperidine concentrations, though in every case meperidine levels were less than 0.46 μg/mL (Ngan Kee et al., 1996). Intrathecal meperidine is also given to control intractable cancer pain. In one study of 10 cancer patients, plasma concentrations of parent drug and metabolite both increased rapidly and in some patients normeperidine concentrations actually exceeded those of meperidine. Plasma meperidine concentrations ranged from below 60 ng/mL to 1840 ng/mL. Normeperidine concentrations increased very rapidly with concentrations ranging from below 40 ng/mL to 423 ng/mL (Vranken et al., 2005).

Still another case report described a 36-year-old man admitted to the hospital for surgical treatment of a pancreatic cyst. He developed contrast-related renal failure after a CT scan but, because of a history of morphine abuse, he was placed on meperidine PCA. On days 3 through 11 he received varying doses of meperidine, ranging from a low of 319 mg/day to maximum doses of 940 mg. He had myoclonus for 4 days and then developed a respiratory arrest. Plasma concentrations of meperidine and normeperidine, drawn

during resuscitation, were 500 and 9000 ng/mL, respectively (Geller, 1993). In a controlled study of meperidine given in conjunction with intra-abdominal surgery, normeperidine concentrations never exceeded 500 ng/mL. How much higher concentrations may go before seizures occur is not known (Hartvig et al., 1982). In general, when normeperidine toxicity has been reported, plasma concentrations have averaged between 1.5 and 3.0 mg/L (Stone et al., 1993). In the most recently published survey, patients with severe pain required, on average, 16.9 mg/kg/day (14.7–19.2), and the authors recommended 10 mg/kg/day as the maximum safe meperidine dose to be given by an IV PCA device (Simopoulos et al., 2002).

5.9.8.6 Postmortem Issues

No matter the age or the underlying medical condition, meperidine has a very large volume of distribution, but the V_{ss} for normeperidine has never been measured. The greater the V_{ss}, the more likely it is that postmortem redistribution will occur. It should never be presumed that concentrations measured in postmortem plasma samples bear any meaningful relation to blood concentrations at the time of death, especially if the sample being analyzed was obtained from a central source; it is almost certain that the postmortem concentrations of both parent drug and metabolite will be higher than in life (Drummer and Gerostamoulos, 2002; Jung and Reidenberg, 2005; Yarema and Becker, 2005). There are also animal data suggesting that the distributions of parent drug and metabolite are very different, making it impossible to speculate about the situation obtained in life. Table 5.9.8.6.1 shows the tissue distribution of meperidine and normeperidine in near-term rhesus monkeys whose mothers had been injected with a 1.25 mg/kg bolus containing equal parts of meperidine and normeperidine just prior to caesarean delivery. The samples were harvested 30 minutes later. Note that normeperidine concentrations in the brain stem were 35 times higher than in the blood. Concentrations of both drugs in muscle were essentially the same, confirming the belief of many that postmortem blood concentrations in muscle are quite similar to those found in blood.

In vitro studies have shown that meperidine and normeperidine, like morphine, remain stable in stored frozen tissues. However, when tissue is stored in formalin, all three opiates leach into the storage solution; both tissue and storage fluid must be tested together (Xiang et al., 2001).

Table 5.9.8.6.1 Fetal (Rhesus) Tissue Distribution of Meperidine and Normeperidine*

Organ	Meperidine	Normeperidine
Liver	6.39 ± 2.42	40.26 ± 7.66
Gallbladder	4.90 ± 2.10	21.26 ± 6.10
Brain stem	12.15 ± 3.69	24.59 ± 4.59
Kidney	36.01 ± 5.24	39.74 ± 6.04
Muscle	26.42 ± 4.32	28.59 ± 5.43
Serum	2.23 ± 0.09	0.67 ± 0.42

* Data adapted from Morrison et al. (1988).

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5.9.9 Oxycodone

Name: (5α)-4-5epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one
Formula: $C_{18}H_{21}NO_4$
Molecular weight: 315.37 daltons
Bioavailability: oral 50–80%, rectal 61.6 ± 30%, intranasal 46% (Takala et al., 1997)
Metabolism: CYP2D6
$T_{½β}$ (half-life): 3.4 hours (± 1.1) (Leow et al., 1992), 3.4–13.9 hours depending on presence or absence of liver disease
Excretion: renal
V_{ss}, after oral administration (Lalovic et al., 2006):
10 mg = 6.15 ± 0.45 L/kg (Lalovic et al., 2006)
15 mg = 6.6 ± 2.1 L/kg (Lalovic et al., 2006)
20 mg = 6.4 ± 2.7 L/kg (Lalovic et al., 2006)
C_{max}:
10 mg = 26 ng/mL
15 mg = 36 ng/mL
20 mg = 43 ng/mL
T_{max}:
10 mg = 68 min
15 mg = 84 min
20 mg = 51 min
Clearance: 45.5 L/hour (Leow et al., 1992), 46.8 L/hour (Poyhia et al., 1991)
Rectal absorption: (30 mg) 52% (Leow et al., 1992)
Known drug interactions: sertraline, fluoxetine, norfluoxetine
Brand names: Combunox®, Dihydrohydroxycodeinone®, Dihydrone®, Dihydroxycodeinone®, Dinarkon®, Diphydrone®, Endocet®, Endonan®, Endone®, Eubine®, Eucodal®, Eutagen®, Ossicodone®, Oxanest®, Oxicodona®, Oxicoon®, Oxycet®, Oxycodeinone®, Oxycodon®, OxyContin®, Percocet®, Percodant®, Roxicet®, Supendol®, Tecodin®, Tylox®

Lalovic, B., Kharasch, E. et al. (2006). Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites, *Clin. Pharmacol. Ther.,* 79(5), pp. 461–79.
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5.9.9.1 History and Extent of Use

Oxycodone is a derivative of thebaine, a minor opium component. Thebaine itself is not a narcotic, but it is used as a precursor in the production of other useful opioids including oxycodone (Lenz et al., 1986). In 1917 oxycodone was first introduced as a pain reliever (Faulk, 1917), and it has been in use ever since. It has been administered intravenously (IV; Poyhia et al., 1991; Takala et al., 1997), intramuscularly (IM; Poyhia et al., 1992), intranasally (IN; Takala et al., 1997), subcutaneously (SC; Maddocks et al., 1996), rectally (Leow et al., 1995), epidurally (Backlund et al., 1997), and orally. Transdermal formulations have also been tested, but oxycodone is not nearly as lipophilic as fentanyl and buprenorphine and the transdermal form of oxycodone is unlikely to have any clinical importance (Plummer et al., 1990). In clinical studies of cancer patients, oral oxycodone and oral morphine appear to provide comparable pain relief. On a weight-for-weight basis, morphine administered intravenously is three times more potent than oral oxycodone (Zhukovsky et al., 1999).

OxyContin® is the brand name of a time-release formulation of oxycodone, first sold in 1996, by the Purdue Pharma LP. In 2000 reports of OxyContin® abuse began to circulate, and the extent of abuse only increased in 2004 when a generic version of OxyContin® came to market. The Purdue formulation dominates the single-entity oxycodone market. According to the DEA, 7,185,000 prescriptions of single-entity oxycodone products were sold in 2000, and approximately 5.8 million (81.4%) of them were for OxyContin® (DEA, 2006).

In the absence of what Purdue considered to be adequate federal monitoring, the company began its own large-scale surveillance program. The company's own results indicated that abuse of all oral prescription pain medications has become a problem over the last decade, with oxycodone formulations being the worst offender (followed by hydrocodone > other oxycodone > methadone > morphine > hydromorphone > fentanyl > buprenorphine) (Purdue Pharma, 2002; Cicero et al., 2005).

The true national extent of this problem is difficult to assess. The U.S. National Office of Drug Policy (2006) stated that 9% of all Americans have used pain relievers illegally in their lifetime. Just how many of those were using OxyContin® is not known, nor is the number of fatalities that have resulted. Preference for this drug appears to be regional, with most reports coming from rural Maine, Virginia, West Virginia, New Orleans, Philadelphia, parts of the Midwest, and Arizona (NODP, 2006). Many websites carry instructions on how to purify time-release formulation oxycodone that has been combined with other drugs. Cold-water extraction based on solubility differences of the ingredients in cold water seems to be the preferred route (Cone, 2006) and extremely simple to accomplish.

Two surveys of medical examiners have been undertaken — one by Purdue and one by the Drug Enforcement Administration. The DEA surveyed 775 members of the National Association of Medical Examiners (NAME). Of the 949 complete medical examiner reports received, the majority of deaths involving oxycodone were associated with polypharmacy. Benzodiazepines were detected in more than 40% of the cases, and in 40% a second opiate was present in addition to oxycodone, while cocaine or its metabolites were found in nearly 15%. Approximately 20% of cases were positive for alcohol. Less than 0.1% were intravenous users. This tendency to polypharmacy was also confirmed in the Purdue

sponsored study of 1243 cases. Of 851 (92.6%) cases meeting criteria for inclusion, 70% had abused multiple drugs. The authors of this study also reported finding lower mean oxycodone blood levels in deaths where multiple other drugs were detected. They concluded that oxycodone "in combination with other centrally active drugs is more toxic than when OxyContin was the only drug involved" (Cone et al., 2003, 2004a, b).

5.9.9.2 Pharmacology

Unlike immediate-release oxycodone, the time-release form is absorbed bi-exponentially. During the first 37 minutes, 38% of the dose is released and blood levels rise rapidly. Following the first peak, a second peak occurs at 6.2 hours, at which time the remainder of the drug is released. However, the bioavailability of both forms is the same.

The main known metabolic pathways for oxycodone are *O*-demethylation (CYP2D6) to oxymorphone and *N*-demethylation (CYP3A4 and CYP3A5 mediated) to noroxycodone (Weinstein and Gaylord, 1979; Poyhia et al., 1992), but the latter predominates, and none of the metabolites appears to exert any important central effects in humans. Because concentrations of noroxycodone are higher in plasma and urine after oral administration, it seems likely that first-pass metabolism of oxycodone plays an important role. There are two phenotypes of this enzyme in the white population, with 5–10% being poor metabolizers who have decreased CYP2D6 activity and 25% a decreased ability to metabolize oxycodone. Most oxycodone and noroxycodone is excreted unconjugated in the urine while oxymorphone is mainly excreted in the conjugated form (Poyhia et al., 1992).

Oxycodone's volume of distribution is 2–3 L/kg, comparable to that of morphine, but it is more slowly eliminated. The $T_{½}$ is about 2–3 hours after intravenous administration (Takala et al., 1997), 3 hours after immediate-release formulation, and about 8 hours after OxyContin® administration (Mandema et al., 1996). Maximum plasma concentrations of oxycodone are reached within 25 minutes after intravenous administration, but not until 1.3 hours after administration of immediate oral release formulations, and not until 2.6 hours after giving the continuous-release formulation. Maximum plasma concentrations of oxycodone after immediate-release oxycodone are twice as high as those observed following an equivalent dose of continuous-release oxycodone (Mandema et al., 1996). There are important age and sex differences in metabolism: absorption is greatest in elderly women and lowest in young men, and it takes women 25% longer to clear the drug (Kaiko et al., 1996).

5.9.9.3 Drug Interactions

The conversion of fluoxetine, its nor-metabolite, and the conversion of most of the other selective serotonin (5-HT) re-uptake inhibitors (SSRIs), though not some of the newer antidepressants (Brosen, 1998; Fu et al., 2000), involves the P-450 enzyme CYP2D6. All of the SSRIs seem to share the ability to both inhibit and induce 2D6 activity, often with unpredictable results (Daniel et al., 2006). It is not uncommon for cancer patients to also be taking antidepressants, which means that, deprived of the benefit of active metabolite formation, they may not achieve the same pain relief as those not taking SSRIs. Higher doses of oxycodone (with resultant higher blood concentrations of the parent compound) will be required. Conversely, SSRI–oxycodone interaction might explain an unanticipated episode of serotonin syndrome, which can be observed of the use of oxycodone (Karunatilake and Buckley, 2006).

The ability to metabolize oxycodone is reduced in patients with liver and/or kidney disease. Oxycodone pharmacokinetics has been studied in volunteers with end-stage

liver disease, both before and after transplantation. Prior to transplantation, the median elimination half-life of oxycodone was 13.9 hours (range, 4.6–24.4 hours) (Tallgren et al., 1997). In patients with diminished renal function, the mean elimination half-life is prolonged because the volume of distribution is increased and clearance reduced (Kirvela et al., 1996). Measured postmortem blood oxycodone concentrations in patients with renal or hepatic compromise are, therefore, likely to be altered by the process of postmortem redistribution.

Detection of oxycodone abuse is problematic for a number of reasons. Even under normal circumstances, it is cleared from the urine rapidly, and the window for detection (when using the popular TDx and EMIT screening systems) is certainly less than 24 hours. Genetic metabolizer status can also lead to surprising results. A recent case report described a man thought to be diverting his prescription oxycodone because his urine tests were consistently negative for the drug. Further investigation disclosed that the individual was a hypermetabolizer whose enzymes had been further induced by a concurrent prescription of rifampin; he was taking his medications, but appeared not to be (Lee et al., 2006). No doubt, without the investigation's further work the patient would have been accused of criminal diversion.

5.9.9.4 Maternal/Fetal Considerations

Available data suggest that breast feeding by oxycodone-using mothers is safe. In an older study, six postpartum women were administered either one or two capsules of oxycodone/acetaminophen every 4–7 hours; maternal plasma oxycodone concentrations of 0.014–0.035 mg/L were associated with milk concentrations of < 0.005–0.226 mg/L. The average milk to plasma concentration ratio was 3.4, but there were large variations in the ratio, and peak milk concentrations occurred 1.5–2 hours after the initial dose (Marx et al., 1986). A case report describing the death of a 10-month-old child who experienced a cardiac arrest while at a local store, published in 2004, is of particular interest, because it was written before the polymorphic nature of the P-450 enzymes was truly appreciated (Levine et al., 2004). The infant's autopsy was said to be unremarkable (though there is no mention of channelopathy testing or even microscopic examination of the heart, which can only mean that the autopsy was incomplete). The only remarkable finding was said to be the detection of oxycodone in the postmortem specimens; the blood and liver oxycodone concentrations were 0.6 mg/L and 1.6 mg/kg, respectively. Presence of the drug was arbitrarily attributed to breast feeding and the Medical Examiner ruled homicide as the cause of death. The authors of the case report used the information provided in the earlier case study and concluded that total exposure could not have been nearly so great. Even if the original report had understated oxycodone excretion by an order of magnitude, the child's maximal exposure would have been on the order of one milligram per feeding, an unlikely cause of death.

Most recently, researchers studied 50 breast-feeding mothers who were taking oxycodone. They collected blood and breast milk samples and measured oxycodone levels at 24-hour intervals afterwards. Forty-one neonates had additional blood samples taken at 48 hours. Oxycodone was noted to be present in the milk of all mothers who had taken any dose in a 24-hour period, and there was significant correlation between maternal plasma and milk levels ($R(2) = 0.81$). The median milk:plasma (M:P) ratio for the same period was 3.2:1. Over the subsequent 48 hours, the relationship between plasma and milk levels weakened considerable ($R(2) = 0.59$) and there was a larger range of M:P levels with evidence

of persistence of oxycodone in the breast milk of some mothers. Oxycodone levels up to 168 ng/mL were detected in breast milk (20% > 100 ng/mL), but oxycodone was detected in the plasma of only one infant. The measurements suggest that breast-fed infants may receive >10% of a therapeutic infant dose, but are at minimal risk because the intake of breast milk during the study period would have been quite small (Seaton et al., 2008).

5.9.9.5 Postmortem Issues

Little is known about the postmortem toxicology or pathology of oxycodone-related deaths, but it is clear that the drug undergoes extensive redistribution. In Anderson's study of 36 medical examiner cases, some individuals displayed large concentration differences between central and peripheral blood while others did not. The tissue distribution ranges of oxycodone in the 36 case examples were heart blood 0.12–46 mg/L (36), femoral blood 0.10–13 mg/L (35), liver 0.11–6.1 mg/kg (16), urine 2.5–122 mg/L (22), bile 0.19–49 mg/L (15), vitreous 0.24–0.82 mg/L (6), and gastric 0.06–119 mg total (21) (Anderson et al., 2002). No unique pathologic findings are recognized, but "ghost" pills (the matrix containing time-release oxycodone) can occasionally be identified in the gastric contents. If, as is rarely the case, oxycodone is pulverized and injected, the possibility for angiothrombotic arteriopathy exists, and birefringent crystals may be detected in the lungs, retina, or kidney.

The literature contains at least one case report describing a schizophrenic woman with a massive oxycodone overdose (4000 mg based upon pill count) whose blood level was 2600 ng/mL after arrival in the emergency room. She was resistant to naloxone treatment and required three days of ventilator support before making a complete recovery (Schneir et al., 2002). In a study of nine other oxycodone-related deaths, most of them polydrug abusers, femoral blood concentrations were between 600 and 1400 ng/mL, with a mean of 900 ng/mL. The differences between blood concentrations in cases where oxycodone was the cause of death and cases where it was an incidental finding were sufficiently wide to suggest that, concerns about postmortem redistribution aside, postmortem blood concentrations of less than 600 ng/mL are an unlikely cause of death (Drummer et al., 1994). This assumption seems to have been borne out by the results of the Purdue Pharma studies of oxycodone-related deaths. In cases where multiple drug use was identified, the mean oxycodone concentration was 0.93 μg/mL (n = 167), but when oxycodone was the only drug identified, the mean concentration was between 1.55 and 1.70 μg/mL.

There have been at least two large, and more recent, case series. None makes any mention of specific pathological alteration. Spiller (2003) analyzed postmortem blood in 24 cases where oxycodone was considered the sole cause of death. Mean and median postmortem oxycodone blood concentrations were 1.23 mg/L and 0.43 mg/L, respectively. The range was 0.12–8.0 mg/L, with more than half of the cases having blood concentrations of ≤ 0.5 mg/L (Spiller, 2003). Two years later another study of 172 consecutive oxycodone deaths was published. It included 18 where death was attributed solely to oxycodone toxicity, 117 where death was attributed to combined drug toxicity, another 23 to trauma, 9 to natural causes, and 5 to another drug or drugs. The postmortem blood concentrations of oxycodone overlapped among the groups. The mean blood oxycodone concentration among the cases of oxycodone toxicity was 0.69 mg/L, combined drug toxicity 0.72 mg/L, and trauma 0.62 mg/L. Concentrations were lower in cases of death attributed to natural causes and in those attributed to another drug or drugs (mean each 0.087 mg/L). Benzodiazepines were

detected in 96 of the cases, and cocaine in 41. The most frequently encountered benzodiazepine was alprazolam (Wolf et al., 2005). This overlap in drug concentrations has been confirmed in other recently published studies (Baker and Jenkins, 2008).

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5.9.10 Oxymorphone

Bioavailability: oral bioavailability is less than 10%, but radically increases in the presence of food or alcohol

Metabolism: Other than tramadol, oxymorphone is the only other opiate not metabolized by the P-450 system. It undergoes either reduction to form active metabolites, or glucuronidation to form inactive metabolites.

$T_{½\beta}$ (half-life):

Intravenous: 1.3 ± 1.07 hours (Anon., 2007)

Oral: (Adams et al., 2005)

5 mg = 11.30 ± 10.81 hours
10 mg = 9.83 ± 5.68 hours
20 mg = 9.89 ± 3.21 hours

C_{max}: (Adams et al., 2005)

5 mg = 1.1 ng/mL
10 mg = 1.9 ng/mL
20 mg = 4.4 ng/mL

T_{max}: 0.5 hours for all doses (Anon., 2007)
V_{ss}: 3.03 ± 1.14 L/kg (Anon., 2007)
Excretion: Less than 1% is excreted unchanged in urine, one-third is excreted as oxymorphone-3-glucuronide. In animals 90% is recovered within 5 days.
Known drug interactions: alcohol
Brand names: Numorphan® (injectable, suppository), Opana® oral tablets

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5.9.10.1 Pharmacology

Oxymorphone is an oxycodone metabolite. It has a greater affinity for the μ receptors and is nearly 9 times as potent as morphine (Kalso, 2005). For many years it was sold in the U.S. (Numorphan®) for parenteral injection or use as a rectal suppository. It recently became available as an immediate- and extended-release oral formulation. Unlike most other opiate agonists (except tramadol), oxymorphone is not metabolized by the P-450 system, though it is metabolized in the liver either by glucuronidation to form inactive metabolites, or reduction to form active metabolites.

Oxymorphone has very poor bioavailability, probably less than 10%. After oral administration it reaches peak concentrations in 30 minutes, but even more quickly if liver or kidney disease is present, or if there is food in the stomach. Alcohol ingestion causes increased absorption. If the time-release formulation is taken with alcohol, C_{max} can increase by as much as 100%. When there is food in the stomach, bioavailability is closer to 50%. The half-life is 7–10 hours. Excretion and detectability studies have not been performed in humans. Much higher peak levels occur in the elderly, but the mechanism is not understood, and the drug should be given to the elderly only with great caution (Anon., 2007).

5.9.10.2 Pharmacokinetics

A recent randomized, three-way crossover study analyzed the effect of the immediate-release (IR) tablet following single- and multiple-dose administration in healthy volunteers (Adams et al., 2005). Following a single dose of 5, 10, or 20 mg, the immediate-release oxymorphone maximum plasma concentration (C_{max}) was 1.1, 1.9, and 4.4 ng/mL, respectively. Steady state was achieved within 3 days of 6-hourly administration. The median T_{max} was 0.5 hours for all single doses of oxymorphone and, at steady state, the terminal elimination half-life ($T_{½}$) was approximately 7.3–9.4 hours.

At autopsy medical examiners must seriously consider the causal role of this opiate when significant amounts of alcohol are detected in the blood or vitreous, particularly in the opiate naïve. When oxymorphone was only given by injection, there was little danger that the patient would take the drug with alcohol. Now that danger exists and it makes the possibility of unintentional overdose much more likely.

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5.9.11 Propoxyphene

Name: [S-(R,S)]-α-[2-(dimethylamino)-1-methylethyl]-α-phenylbenzenethanol propanoate ester
Formula: $C_{22}H_{29}NO_2$
Molecular weight: 339.48 daltons
Bioavailability: poor, undergoes extensive first-pass metabolism (Anon., 2004)
Metabolism: hepatic, CYP3A4 (Somogyi et al., 2004)
C_{max}: 17–37 ng/mL (mean 23) after 130 mg orally (Verebely and Inturrisi, 1973)
T_{max}: 1–2 hours (Verebely and Inturrisi, 1973)
$T_{½}$: 5–12 hours (Hardman, 2001)
Excretion: renal (35% in 24 hours)
Volume of distribution: 16 L/kg (Anon., 2004)
Known drug interactions: CYP3A4 competitors: carbamazepine, acetazolamide, macrolide antibiotics, isoniazid, metronidazole, verapamil, diltiazem, cimetidine, and some antidepressants (Barkin et al., 2006)
Brand names: Algafan®, Antalvic®, D-Propoxyphene®, Darvocet®, Darvon®, Darvon-N®, Deprancol®, Depromic®, Dextropropoxyphene®, Dextropropoxyphene-M®, Dextroproxifeno®, Dolene®, Dolocap®, Doloxen®, Doloxene®, Erantin®, Femadol®, Harmar®, Kesso-Gesic®, Propacet®, Prophene 65®, Propoxychel®, Propoxyphene HCl®, Proxagesic®

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5.9.11.1 General Considerations

Propoxyphene is a methadone derivative but, unlike methadone, propoxyphene is a relatively weak μ agonist and has only mild analgesic properties. In the past, propoxyphene overdose was much more common than it is now, and it was associated with large numbers of fatalities (Soumerai et al., 1987). Propoxyphene is particularly toxic because, in addition to exerting the usual respiratory depressant effects common to all μ-agonist narcotics, its principal metabolites are local anesthetics with potent membrane-stabilizing activity.

In the U.S., deaths attributable to propoxyphene have been gradually decreasing. In 1999 the DAWN survey reported 466 propoxyphene-related deaths, accounting for 4% of all reported drug-related fatalities occurring that year (Kissin et al., 2000). The current situation is harder to access, as the medical component of the "new" DAWN report only contains data from six geographical areas. The emergency room component, however, does provide some data. The report contains a total of 495,732 mentions of drug-related

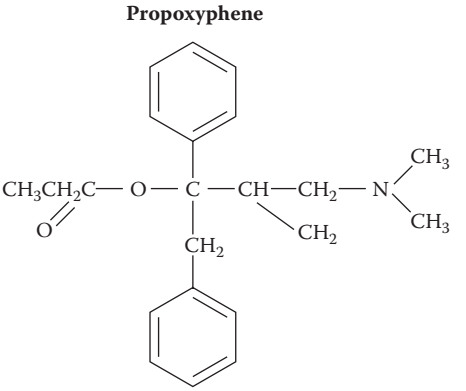

Figure 5.9.11.1 Propoxyphene molecule.

emergency room visits, of which 6448 were propoxyphene related, accounting for 0.013% of all drug visits (SAMHSA, 2006).

The decline in use is partially explained by the introduction of more effective, safer agents, and partly by the way that propoxyphene is now formulated. Early formulations contained a pellet of propoxyphene inserted at the end of a capsule containing aspirin or acetaminophen, and it was a simple matter to remove the pellet and dissolve it in water for injection. That formulation has not been produced for many years, and propoxyphene is now compounded in such a way as to make the separation of propoxyphene all but impossible. In the U.S. nearly all episodes of propoxyphene toxicity are now due to oral ingestion, though on occasion local injury from injection is reported. Propoxyphene-related deaths are more common in Europe, particularly in Scandinavia, though there seems to be wide variation from country to country and city to city (Steentoft et al., 2001). The most recent papers on drug use in Scandinavia no longer even mention propoxyphene as a problem drug (Steentoft et al., 2005). Sporadic reports suggest that some propoxyphene formulations are still injected in America.

5.9.11.2 Metabolism and Pharmacokinetics

Propoxyphene is absorbed rapidly from the gastrointestinal tract (Giacomini et al., 1980; Young, 1983; Flanagan et al., 1989). Peak plasma concentrations occur within one to two hours after a single oral dose. Propoxyphene undergoes extensive first-pass metabolism in the liver. Nonetheless, peak propoxyphene levels after a single 65-mg dose, in healthy young volunteers, range from 260 to 900 ng/mL, with a mean of 590 ng/mL (Flanagan et al., 1989). In this same group of volunteers, the drug's half-life ranged from 6.4 to 26.4 hours, with a mean of 13 hours. Simultaneous measurements of nordextropropoxyphene showed peak levels that were much higher, ranging from 510 to 2140 ng/mL, with a mean of 1950 ng/mL. This may explain some of propoxyphene's toxicity, since it is the metabolite that is cardiotoxic. The metabolite also has a longer half-life, with a mean value of 22.2 hours.

Propoxyphene is oxidized by CYP3A4 microsome to norpropoxyphene (Somogyi et al., 2004). At the same time, it appears that propoxyphene may be a CYP2D6 inhibitor, setting the stage for even more possible drug interactions. A recent case report described the occurrence of severe bradycardia in a 48-year-old man taking propoxyphene and metoprolol (which is metabolized by CYP2D6) (Marraffa et al., 2006). If propoxyphene is

co-administered with other drugs that compete for CYP3A4, such as carbamazepine, acetazolamide, macrolide antibiotics, isoniazid, metronidazole, verapamil, diltiazem, cimetidine, and some antidepressants, then potentially dangerous plasma elevations of other drugs could result (Spina et al., 1996).

No metabolic differences between the sexes are detectable, but age has definite effects on propoxyphene metabolism. The half-life of dextropropoxyphene in the young is only 13 hours, but it rises to over 35 hours in the elderly. Similarly, the half-life for norpropoxyphene in young adults is approximately 22 hours, rising to over 40 hours in the elderly (Flanagan et al., 1989). Age-related changes in metabolism are not unique to propoxyphene. They can occur with almost any drug that undergoes hepatic oxidation followed by renal excretion. Excretion can be prolonged in individuals with liver impairment, because first-pass oxidation is reduced, and concentrations of propoxyphene in the circulation are increased.

Propoxyphene-induced respiratory depression is readily reversed by narcotic antagonists but myocardial depression, which is a much more likely cause of death, is not reversed, because it is not mediated by μ receptors. Rather, it is the result of norpropoxyphene, which has a longer half-life than propoxyphene. Norpropoxyphene accumulates in cardiac tissue, where it blocks not only the inward sodium current but also the potassium currents (Ulens et al., 1999). The situation has not been investigated in detail, perhaps because the drug is no longer widely used, but low drug concentrations (5 μmol/L) facilitate hERG currents, while higher drug concentrations block hERG currents leading to an uncertain effect on cardiac depolarization (Ulens et al., 1999). Whatever the role of hERG channel activation, norpropoxyphene disrupts the orderly sequence of myocardial depolarization, conduction is delayed, and the QT interval is dispersed (Hantson et al., 1995; Karunakara et al., 2003). Myocardial contractility is also decreased, causing cardiac output and blood pressure both to drop. Neither treatment with β-adrenergic agents nor pacing has proven very effective (Whitcomb et al., 1989; Wu et al., 1997; Ulens et al., 1999).

It is believed that when propoxyphene is co-administered with ethanol, first-pass hepatic transformation is decreased, and higher blood concentrations of propoxyphene result (Oguma and Levy, 1981). The importance of an ethanol–propoxyphene interaction is difficult to assess, but ethanol is a frequent finding in cases of propoxyphene-related deaths. In the case series reported from Sweden, where propoxyphene was detected in 7.5% of forensic autopsies ($n = 1782$), ethanol was simultaneously detected in less than one-quarter of all cases (Jonasson et al., 1998). Clearly, co-ingestion of ethanol is not required to cause fatalities (Koski et al., 2003).

5.9.11.3 Tissue Distribution

Propoxyphene is highly lipid soluble, and large amounts are sequestered in fat tissue. Fatalities were frequent during the mid-1970s, and concentrations at autopsy have been reported in hundreds of cases (Worm, 1971; Adjutantis et al., 1974; McBay, 1976; Finkle et al., 1976; Christensen, 1977; Finkle et al., 1981; Caplan et al., 1985; Jonasson et al., 1998). In the past, it was believed that serious toxicity was associated with levels greater than 1 mg/L, and that fatalities were associated with levels of over 2 mg/L. But, as with all opiates, tremendous overlap exists, and fatalities have occurred at much lower levels, and higher values have been observed as incidental findings.

Postmortem measurements are unreliable. Measured concentrations depend entirely on the area in the body from which the blood samples are drawn. This variability was dramatically illustrated by a study completed in the early 1990s (Yonemitsu and Pounder,

1992). Multiple blood and tissue samples were obtained from four decedents who had died of propoxyphene poisoning. A second and third set of samples was obtained after 24 and 48 hours had elapsed. In every case, the lowest blood concentrations were observed in peripheral blood samples. When the levels in the peripheral blood measured 3.5 mg/L, the concentration in the aorta was 1.9 g/L, nearly 55 times higher! When blood was drawn from the pulmonary artery, the propoxyphene concentration increased twofold at 24 hours and threefold at 48 hours.

Given the enormous variations that have been shown to occur in the same cadaver's blood, drawing any conclusions from quantitative propoxyphene levels is unwise and unjustified. The same caveat applies to measurements made with muscle and other tissues. Analysis of these tissues is certainly a valid way to demonstrate the presence of propoxyphene, but results cannot be assumed to reflect plasma values at the time of death (Langford et al., 1998). Since death is more likely to be from metabolite cardiotoxicity than propoxyphene-induced respiratory depression, it hardly makes sense to measure propoxyphene without, at the same time, measuring concentrations of norpropoxyphene, but even that approach is unlikely to prove useful, because norpropoxyphene is a more polar molecule than propoxyphene and, therefore, would be expected to have a lower volume of distribution (it has never been measured) and different pattern of postmortem redistribution.

For forensic purposes, it may be more useful to look at the individual's electrocardiogram. Truly toxic propoxyphene concentrations will produce distinctive EKG changes (Whitcomb et al., 1989) including QRS prolongation, bundle branch block, and, in extreme cases, asystole. The antemortem demonstration of these abnormalities, particularly QRS prolongation (Afshari et al., 2005), is likely to be more probative than postmortem blood concentration measurements. As with all opiates, cause of death should never be determined by reference to blood and tissue concentration reported from earlier postmortem studies, or by comparison with "therapeutic" concentrations reported in the living.

5.9.11.4 Excretion and Detectability

Propoxyphene is not a National Institute on Drug Abuse (NIDA) drug, so it would not be detected on limited workplace screening tests that are based on immuno-technology. However, propoxyphene is included in widely used 10 drug-screening panels (Online KIMS assay [Roche] and EMIT II assays) (Lu and Taylor, 2006). With a half-life of 22 hours, propoxyphene remains detectable in the urine for at least four days and should be easily detectable. In the past, the changes of putrefaction were known to cause false positive EMIT screening tests for propoxyphene, though there have been no recent studies of the subject (Sloop et al., 1995). In any case, the issue would be easily resolved with confirmatory testing.

5.9.11.5 Maternal/Fetal Considerations

Propoxyphene is excreted in mothers' milk, but not in quantities likely to produce any effect on their infants. Propoxyphene and norpropoxyphene excretion in breast milk was studied in six healthy nursing mothers. Breast milk concentrations generally followed plasma levels, with approximately the same ratio of norpropoxyphene to propoxyphene (2.6) observed both in plasma and milk. The ratio of drug in the milk and plasma was 0.417 for propoxyphene and 0.382 for norpropoxyphene. Both parent drug and metabolites

are cleared from the milk at the rate of 4 mL/hr, with a mean half-life of 3.68 hours for propoxyphene and 5.49 hours for norpropoxyphene (Kunka et al., 1984). Nursing infants are unlikely to ingest amounts that will cause any detrimental effects during short-term treatment (Bar-Oz et al., 2003). The possibility of norpropoxyphene toxicity occurring after long-term exposure cannot be ruled out (Spigset and Hagg, 2000), although actual examples of such toxicity have never been reported.

5.9.11.6 Histologic Abnormalities and Autopsy Findings

With the exception of cases of suicidal overdose, propoxyphene-related deaths are likely to occur in chronic drug abusers, and the usual stigmata of injection drug abuse are to be expected. In some countries, titanium dioxide (TiO_2) is used as an excipient along with talc. When abusers crush these tablets and inject them, titanium deposits are visible in many organs as chalk streaks, which are actually composed of granule-laden macrophages. The titanium appears a green-tan color with routine H&E stains. These granules appear pink under polarized light (de Lima et al., 2004). Other case reports have described an acute generalized exanthematous pustulosis, but it is rarely seen. During the 1990s there were reports of liver disease characterized by centrilobular cholestasis, portal tract inflammation, and bile duct abnormalities (Bassendine et al., 1986; Rosenberg et al., 1993), however, it has been 15 years since additional cases have been reported.

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5.9.12 Tramadol

Synonyms: Anadol®, Dolol®, Dromadol®, Ralivia®, Tramacet®, Ultram®, Upziva®, Zamadol®, Zydol®
Name: 2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexan-1-ol
Formula: $C_{16}H_{24}NO_2$
Molecular weight: 263.38 daltons
Bioavailability: 87–95% (Grond and Sablotzki., 2004)
C_{max}: 11.4 ng/mL after 100 mg PO (Curry et al., 2007)
T_{max}: 1 hour (Curry et al., 2007; García-Quetglas et al., 2007)
$T_{½\beta}$ (half-life): 8.15 ± 1.28 hours
Metabolism:
O-demethylation by P-450 (CYP) 2D6
N-demethylation by CYP2B6 and CYP3A4
V_{ss}: 0.862 (García-Quetglas et al., 2007)
Known drug interactions: CYP3A4 inducers, CYP3A4 inhibitors
Dosage forms: Drops, capsules, and sustained-release formulations for oral use; suppositories for rectal use; and solution for intramuscular, intravenous, and subcutaneous injection. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours, and have a bioavailability of 87–95% compared with capsules.
Contraindications: known seizure disorder, past history of opiate addiction or abuse

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5.9.12.1 General Considerations

Tramadol is a centrally acting analgesic but with only about 10% of morphine's potency when it is administered parenterally. It is structurally related to both codeine and morphine. Tramadol has two enantiomers, but unlike methadone, each enantiomer has analgesic activity, even though different mechanisms are involved. (+)Tramadol and the metabolite (+)-*O*-desmethyltramadol (M1) are agonists of the μ opioid receptor, and they inhibit 5-HT re-uptake, but (–)-tramadol inhibits norepinephrine re-uptake. As a consequence, the (–) form enhances the inhibitory effects on pain transmission in the spinal cord.

5.9.12.2 Metabolism

The major metabolites present in plasma are *O*-desmethyltramadol and *N*-desmethyltramadol, and to a minor extent *N,N*-didesmethyltramadol, *N,N,O*-tridesmethyltramadol (M4), and *N,O*-desmethyltramadol. All of these metabolites are potent μ agonists. The *O*-desmethylated metabolite is formed by cytochrome P-450 2D6 (CYP2D6), but CYP2B6 and CYP3A4 form *N*-desmethyltramadol. The role played by CYP2D6 is very important, partly because 10% of U.S. Caucasians are deficient, and partly because 2D6 is highly polymorphic. Individuals may be ultrametabolizers, normal, intermediate, or poor metabolizers, and metabolizer status determines how a particular individual will respond to the drug. For reasons that remain unclear, when poor metabolizers are given tramadol, they have higher epinephrine plasma concentrations than normal metabolizers. It is thought by some that, in addition to binding to the μ receptor, its ability to prevent the re-uptake of both norepinephrine and serotonin both contribute to its significant analgesic properties (Barkin, 2008).

Tramadol is rapidly distributed in the body and is approximately 20% protein bound. Tramadol is mainly metabolized by *O*- and *N*-demethylation and then by conjugation reactions to form glucuronides and sulfates that are all mainly excreted by the kidneys. The mean elimination half-life is about 6 hours.

5.9.12.3 Clinical Issues

Pharmacokinetic–pharmacodynamic characterization of tramadol is difficult because of differences between tramadol concentrations in plasma and concentrations at the site of action, not to mention pharmacodynamic interactions between the two enantiomers of tramadol and their active metabolites. Tramadol provides postoperative pain relief comparable with that of meperidine. The analgesic efficacy of tramadol can further be improved by combination with non-opioid analgesics.

Tramadol is thought to be particularly useful in patients with poor cardiopulmonary function, especially after surgery of the thorax or upper abdomen. Tramadol is reported to be an effective, well-tolerated agent, useful in the treatment of pain secondary to trauma, renal or biliary colic, labor, and neuropathic pain. Tramadol appears to produce less constipation and dependence than equianalgesic doses of strong opioids (Grond and Sablotzki, 2004).

There are reports of tramadol diversion to the illicit market (Cicero et al., 2005; Inciardi et al., 2006). Tramadol is neurotoxic and can cause generalized seizures, usually within the first 24 hours of use (Jovanovic-Cupic et al., 2006). Studies in human users are lacking, but when rats were exposed to tramadol for up to 10 days (doses of 20–80 mg/kg) they exhibited raised liver enzymes. Light microscopy revealed severe centrolobular congestion and focal necrosis in the liver, as well as vacuolization in tubular cell groups (Atici et al., 2004).

5.9.12.4 Postmortem Considerations

Very few tramadol deaths have been reported or studied. There are only nine case reports in the literature, and all of those have occurred in individuals taking multiple other drugs. Peripheral blood concentrations of tramadol in these polydrug users have ranged from 1.6 to 15 ng/mL. Whether or not the drug produces any recognizable lesions is not known. A recent case report describes a case of pure tramadol poisoning (DeDecker et al., 2008); a 28-year-old hospitalized man, taking only tramadol, was found apneic. He was

asystolic and acidotic when the paramedics arrived and could not be resuscitated. Routine toxicology screening of blood and urine, performed on samples obtained during resuscitation, was negative. Other tests disclosed liver failure. He died after two days. Autopsy disclosed pulmonary edema with alveolar hemorrhage, diffusely hemorrhagic gastric mucosa, "shock" liver, and acute tubular necrosis. Toxicological analysis of serum and gastric lavage specimens, obtained on admission at the ICU, revealed a tramadol concentration of 8 and 400 mg/L, respectively. Analysis of postmortem blood (site of origin not specified) disclosed tramadol and the metabolite *N*-desmethyltramadol in the blood, liver, and kidney; tramadol concentrations were 5.2 mg/L, 6.5 µg/g tissue, and 4.5 µg/g tissue, respectively.

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5.10 Medical Consequences of Opiate Abuse

As patterns and practices of drug abuse change, so does the clinical profile of the drug users. More than 45 years have passed since Wetli published the first systematic analysis of autopsy findings in narcotic abusers (Wetli et al., 1972). Since Wetli's paper was published, others have followed; however, most are epidemiologic studies, containing either no specific details of particular types of lesions that might be encountered, or even which drug was abused.

For purposes of comparison, unpublished data from the office of the San Francisco Medical Examiner in the late 1990s are provided. That similar patterns occur elsewhere is confirmed by the findings of at least one very large autopsy study (nearly 900 drug abusers) (Passarino et al., 2005). Although the authors did not relate specific drugs to specific lesions, all of the decedents were known drug users. The overall picture that emerged from this European study was very similar to the pattern observed in San Francisco

Table 5.10.1 Most Common Anatomic Diagnoses in Heroin Abusers (n = 154)

Diagnosis	Percent (%)
1. Pulmonary edema	46
2. Track marks	44
3. Birefringent crystals in lung or liver	27
4. Pneumonia	18
5. Hepatic steatosis	16
6. Severe coronary artery disease	12
7. Hepatitis	12
8. Myocardial fibrosis	11
9. Extensive aortic atherosclerosis	9
10. Cerebral edema	9

Source: Unpublished data, office of the San Francisco Medical Examiner.

during roughly the same time frame. Skin infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is now the principal disorder that brings addicts to inner-city hospitals, and the problem seems to be becoming worse. The proportion of skin infections caused by MRSA has increased from 29% in 2001–2002 to 64% in 2003–2004 (Morgan et al., 2006). No clinical or historical features reliably predict MRSA etiology, but many of these cases are presumed to be secondary to injection drug use. The 10 most frequent anatomic diagnoses encountered by the San Francisco Medical Examiner in 1999 are listed in Table 5.10.1.

5.10.1 Dermatologic Sequelae

Skin lesions are associated with all types of intravenous drug abuse, but they are more common among opiate abusers. The difference has to do with the properties of the drugs themselves. Stimulants and hallucinogens do not cause histamine release, so their use is not associated with pruritus or excoriations. Cutaneous complications in injecting users are often related to the adulterants and excipients injected along with the drugs. Occasionally the consequences can be dire. In Europe, more so than in America, spore-forming bacteria are often present in the drugs injected by abusers. In the U.K., in the year 2000, *Clostridium novyi* caused 63 cases of severe illness, and seven additional cases were reported in 2001. For the first time since World War I, cases of wound botulism are now being reported in England. The first cases occurred in 2000 (6 cases) with 51 further cases through March of 2004. Infections with tetanus, *C. histolyticum*, *C. sordellii*, and *Bacillus cereus* have also been reported (Brett et al., 2005). Other clusters of wound botulism have also been reported from Germany (Galldiks et al., 2007).

5.10.1.1 Fresh Needle Punctures

Finding recent injection sites is usually a simple matter, but sophisticated abusers often take great pains to conceal evidence of injection, and these lesions may be hard to find. The presence of dried blood on the surface of the skin surrounding a puncture is confirmatory evidence that death occurred almost immediately following injection (Hirsch, 1972). The antecubital fossa

is the preferred site for self-injection, but punctures may be found at the wrist, under a watchband, or between the toes. The path of the needle may be confirmed by making a skin incision immediately adjacent to the suspected site. This will reveal the presence of small subcutaneous hemorrhages that occur after venipuncture (Hirsch, 1972). Alternatively, a single longitudinal incision can be made on the flexor surface of the arm from mid-biceps to distal forearm, and the subcutaneous tissues exposed by either blunt or sharp dissection.

Subcutaneous hemorrhage may not be evident in every case, but chemical analysis of tissue around the needle track often yields evidence of the drug injected.

Demonstration of drug in skin taken from a suspected injection site does not, by itself, prove that the drug was injected at that site. If the decedent survives for even a few minutes, the circulation will have distributed drug throughout the body, including the skin! The only way to prove that drug was introduced into the body at a particular site is to sample skin from both sides of the body; the concentration on the side in question should be significantly higher than on the other. The purity of street heroin is now so high that heroin "snorting" is a common practice. In cases where no track marks are evident, but narcotic overdose is strongly suspected, the nasal cavity should be examined and then swabbed with saline for toxicology testing. Of course, the same considerations apply to nasal mucosa (or mucosa at any other site) swabs as for skin tests. The detection of drug on the mucosa does not prove that it was applied there, only that the drug was circulating throughout the body.

5.10.1.2 Atrophic Scarring

Subcutaneous injection is a fairly common practice, especially among novice users, or chronic users with difficult venous access. The flexor aspect of the arm is the preferred site for injection, followed by the anterior thigh. Absorption of heroin is good by this route, but the deposition of excipients in the subcutaneous tissue eventually leads to the development of oval or irregularly shaped lesions measuring 1–3 cm. Lesions are slightly depressed and often hyperpigmented. Most lesions are found at the sites of healed abscesses, but they may occur without abscess formation. Alternatively, they may become confluent (see Figure 5.10.1.2.1).

This type of lesion has been recognized for more than half a century, but the dermatopathology remains poorly characterized and the etiology unclear. Early workers suggested

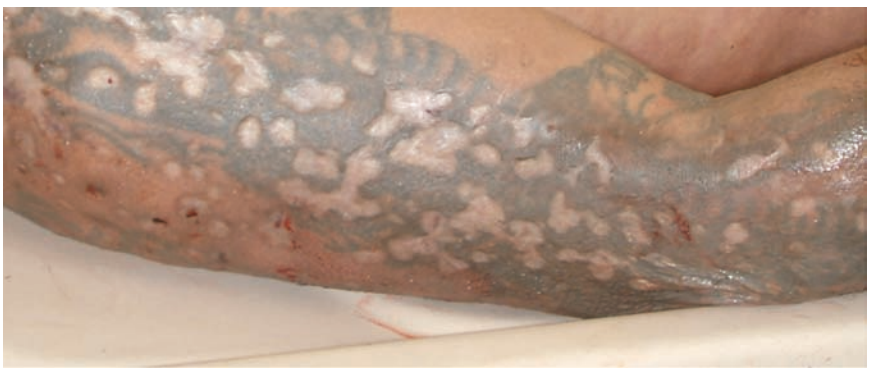


Figure 5.10.1.2.1 "Skin popping." When an addict has thrombosed all accessible veins they often resort to injecting under the skin. This may introduce infectious agents and form an indolent ulcer.

that the lesions were a direct result of the effect of heroin on the skin (Light and Torrance, 1929), but adulterants or infectious agents are just as likely to be the cause. Evidence indicates that the pH of the solution injected rather than the drug itself may be what determines whether tissue injury occurs (Pollard, 1973; Thomas et al., 1995). Microscopic examination of healed atrophic lesions usually reveals subcutaneous fibrosis. Foreign body granulomas may or may not be present, but birefringent material, such as talc or starch crystals, is likely to be seen with the aid of nothing more complex than a polarizing filter (Hirsch, 1972).

5.10.1.3 Abscesses and Ulceration

Abscesses are common in heroin abusers who inject subcutaneously. The practice, frequently involves the site of injection, is known as "skin popping" (Webb and Thadepalli, 1979; Orangio et al., 1984). Lesions occur primarily on the extensor surfaces and lateral aspects of the arms and hands but can be seen almost anywhere on the body. Injection into the subclavian area and the femoral triangle may cause life-threatening infections (Pace et al., 1984; Schondorf et al., 2000; Rhodes et al., 2007), as can injection into the intercostal vessels (Gyrtrup, 1989). The ulcers have a punched-out appearance, with indurated borders surrounding a central core of granulation tissue. Nothing distinguishes the appearance of injection site abscesses from any other sort of soft tissue abscess. Reports from the older literature suggested that the responsible organisms are usually *Staphylococcus* and *Streptococcus* (Sapira, 1968) and today that is even more likely, but many different Gram-negative organisms have also been cultured, and polymicrobial infections are not uncommon (Webb and Thadepalli, 1979).

In May 2000 health authorities in Dublin, Ireland, identified a cluster of unexplained severe illness among injecting drug users (IDUs). All had injection-site inflammation severe enough to require hospitalization, and nearly a third of those infected died. Cardiogenic shock was common, as were leukemoid reactions. Almost as soon as the first cases were identified in Dublin, similar cases were reported throughout the U.K. Nearly 80% of the patients reported injecting heroin intramuscularly in the two weeks before illness. Of 11 patients with adequate specimens available for testing, two (18%) were positive by 16S rDNA PCR for *Clostridium novyi*. Clinical and laboratory findings suggested that histotoxic *Clostridia* caused the infections (Finn et al., 2003; Murray-Lillibridge et al., 2006). Only heroin users who injected subcutaneously were affected. The responsible organism was the same organism responsible for thousands of deaths from wound infection during World War I. Today, *Clostridium novyi* type A infection most often involves domestic animals (Seifert et al., 1996), and infection in humans is extremely rare.

Public health officials suspect that the outbreak in the U.K. occurred because spores of the bacteria were present in the heroin that was being injected. *Clostridia* spores can lie dormant in soil for months or years and only become active when they are placed in an oxygen-free environment, which probably explains why the outbreak involved only drug users who injected directly into skin and muscle. Similar outbreaks due to different strains of *Clostridia* have occurred in California, but evidence of cardiotoxicity in the California cases has been conspicuously lacking (Maselli et al., 1997). There is speculation that the outbreak occurred because some heroin dealers had added diatomaceous earth to their product as a diluent. This form of powdered earth looks very much like heroin, at least to the naked eye, and it might prove a tempting substitute for some of the more traditional materials used to dilute heroin. Unfortunately, diatomaceous earth contains spores of bacteria that can germinate if injected under the skin.

5.10.1.4 "Track" Marks

This lesion was first described in 1929. It occurred in a heroin addict who had contracted malaria from intravenous injections (Biggam, 1929). Lesions were said to resemble railroad tracks because they were linear, indurated, and hyperpigmented. What the lesions actually look like, and how rapidly they form depends on the substances being injected. The excipients found in illicit cocaine and methamphetamine are usually water soluble, so "track" marks are a less common finding in this group of abusers (Wetli et al., 1972). Paregoric, which is also injected by desperate heroin users, causes an intense sclerotic reaction. When paregoric injecting was popular in the 1960s, addicts quickly ran out of peripheral veins and were forced to inject themselves in the neck and groin (Lerner and Oerther, 1966). Heroin, even in its adulterated form, is less toxic to veins than paregoric, but prolonged use will eventually cause thickening and sclerosis of the subcutaneous veins, if only because impure heroin is being injected.

The skin overlying the sclerotic veins becomes hyperpigmented, probably as a result of the underlying chronic inflammatory process (Vollum, 1970), but the degree of hyperpigmentation depends largely on the individual's coloration, not necessarily on how long the addict has been injecting himself. Discoloration of the surrounding skin can also be the result of inadvertent tattooing. Addicts may try to sterilize their needles with a match flame, causing small amounts of soot to be deposited on the outside of the needle. The soot is then carried into the skin at the time of injection. Injection drug users have traditionally tried to conceal these marks by tattooing or even by burning themselves in the hopes of scarring the entire area (Wetli, 1984; Martinez and Wetli, 1989; Sperry, 1992).

The histology of sclerotic veins is variable (Schoster and Lewis, 1968). Only fibrous thickening of the vein wall may be evident, suggesting a low-grade, chronic inflammatory process. In other instances, thrombophlebitis, sterile or septic, may occur. The results are difficult to predict, and Halpern even commented that on occasion the veins repeatedly used by addicts "show less evidence of closure by thrombosis than the veins of patients subjected to repeated punctures by physicians for medical purposes" (Halpern, 1972).

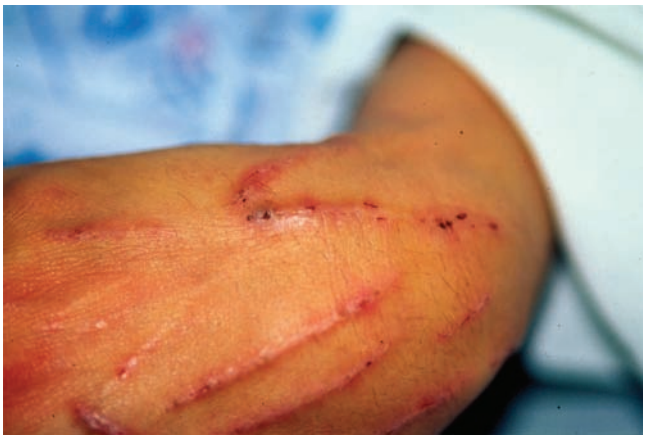


Figure 5.10.1.4.1 "Track" marks are the result of repeated injection with heroin that is contaminated with substances that irritate the veins. Microscopic examination will show birefringent crystals of the diluent and localized inflammation.

5.10.1.5 Tattoos

The practice derives its name from the Tahitian word *tatau*, which means "the results of tapping," the way in which Tahitian tattoos were applied. Tattooing dates back to antiquity. Tattoos have been found on Egyptian mummies from the Eleventh Dynasty, making the practice at least 4000 years old (Sperry, 1991). In prison, tattoos are applied by using the "melted-toothbrush" technique. Any pointed object, such as a bedspring or matchbook staple, can be used as a needle. The end of a plastic toothbrush is then melted in a flame and the smoky residue collected. The residue is mixed with soap and water to form an ink (Sperry 1991). A great deal of significance was once attributed to the design and location of these tattoos. Symbols on the thumb webbing were said to indicate criminal specialties. The results of more recent studies suggest that hand-web tattoos probably have significance only in the prison where they are applied (Martinez and Wetli, 1989). In some specific subpopulations, such as the Marielitos, tattoos may represent religious symbols or themes, but these interpretations cannot be generalized to other subgroups, nor does the presence of tattoos seem to correlate with any particular personality traits or beliefs (Koch et al., 2004). This type of skin ornamentation is thought to explain the extraordinarily high incidence of hepatitis C among addicts (greater than 90% in most urban areas) (Hellard et al., 2007).

5.10.1.6 "Puffy Hands" Syndrome

Lymphedema sometimes occurs in chronic opiate injectors. The condition was first described in the 1960s as a complication of heroin abuse (Abeles, 1965; Ritland and Butterfield, 1973), but it is also seen with buprenorphine and pentazocine abuse (Andresz et al., 2006). This abnormality is generally thought to be an indicator of long-term abuse, and usually does not appear until three to five years after the initiation of drug use (Simonnet et al., 2004). It is difficult to say with certainty, because the incidence of this disease is not recorded, but puffy hands are more likely to suggest the use of buprenorphine or other synthetic narcotics than heroin. Drugs like buprenorphine are very insoluble and injection of ground tablets into the hand is thought to destroy the lymphatic system. The same considerations apply to pentazocine. The hands become smooth and slightly edematous with obliteration of the normal anatomic landmarks, but pitting edema is absent. In contrast to the changes seen in the hands of myxedematous patients, the skin in addicts with "puffy" hands is thin and smooth. The skin on the volar aspect of the forearm is also normal, even though evidence of repeated injections can be seen in both antecubital fossae (Prasad et al., 2005).

5.10.1.7 Necrotizing Fasciitis

Necrotizing fasciitis was first described over 120 years ago. The term describes a severe infection of the superficial fascia and subcutaneous tissue. Initially, the infection does not involve the overlying skin (Wojno and Spitz, 1989). In the absence of drug abuse, necrotizing fasciitis usually occurs in diabetics or in patients with severe atherosclerosis, where the infectious process is initiated by surgery or even by minor trauma to relatively ischemic tissue.

Reports and studies suggesting a link between necrotizing fasciitis and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) continue to appear (Zerr and Rubens, 1999; Chikkamuniyappa, 2004; Souyri et al., 2008). When these cases occur, they are often related to virulent strains of exotoxin-producing *Streptococcus*, almost always group A organisms

such as *Streptococcus pyogenes*. NSAID users with surgical wounds, burns, diabetes, the elderly, neonates, the immunocompromised, and even those who have just delivered are all at risk. Unfortunately, a clinical trial has never been conducted, and these reports must remain what they are — anecdotal observations about a common disease occurring in people taking common medications. If a link does exist, and the issue is still debated, the most likely explanation is that NSAIDs mask the signs and symptoms of an existing infection, leading to a delay in diagnosis, although others have suggested that NSAIDs may somehow decrease the immune response. Of course, narcotic abuse would have exactly the same effects, masking pain and leading to delayed diagnosis (Holder et al., 1997; Baghai et al., 2001; Aronoff and Bloch, 2003).

Another cause for this condition is the process of drug injection itself. In one recent study, it was discovered that nearly half of the cases of necrotizing fasciitis investigated by the medical examiner could be related to the injection of black tar heroin (Mexican origin). Of those infections contracted from heroin, nearly half were due to clostridial species, and nearly one-third of those were *C. sordellii,* an obscure species of clostridia recently linked to the occurrence of spontaneous abortion (Zane and Berg, 2006). Clostridia were found in only three of the cases not associated with intravenous drug abuse. Roughly half of all the cases in the study were found to be polymicrobial infections (Dunbar and Harruff, 2006).

Once the infection is established, necrosis spreads rapidly through fascia and subcutaneous tissues. The overlying skin looks normal until very late in the course of the disease, and the underlying muscle is usually not involved (Tehrani and Ledingham, 1977). Hematogenous seeding may occur with spread to organs throughout the body. Even purulent myocarditis has been reported as a complication. The fact that the overlying skin looks normal may delay the diagnosis and lead to a fatal outcome (Wojno and Spitz, 1989). At one time it was thought that Gram-positive aerobes were the causative agents, but in more recent studies the etiology has been polymicrobial. In a review of 182 patients with documented necrotizing soft-tissue infections, wound cultures grew an average of 4.4 different microbes. Infection was due to a single pathogen in only 28 instances (15%). Nearly half the patients had combined aerobic and anaerobic growth. The most common organisms, listed in declining order, were *Bacteroides* species, aerobic *Streptococcus, Staphylococcus, Enterococcus, Escherichia coli*, and other Gram-negative rods (Elliott et al., 2000). Whether this same hierarchy applies today is not known.

5.10.1.8 Histamine-Related Urticaria

Skin excoriations are common, but it is not always clear if they are the result of narcotic-induced pruritus or psychological disorder (Young and Rosenberg, 1971). Histamine release in narcotic abusers is not a true IgE-mediated allergic response (Hermens et al., 1985). Opiates act directly on mast cells to produce histamine release. The process is thought to be G-protein mediated (Barke and Hough, 1993). The amount of histamine released depends on the type and amount of opiate administered. For example, there is some evidence that equipotent doses of heroin cause less pruritus than morphine (Haemmig and Tschacher, 2001). In one series, more than 20% of the patients receiving postoperative opiates developed urticaria (Withington et al., 1993). In some instances, the amount of histamine liberated can be large enough to cause hypotension, in addition to erythema and tachycardia. Not all narcotics cause histamine release. Elevations in plasma histamine occur after

dosing with intravenous morphine, meperidine, and diacetylmorphine (heroin) but not after treatment with fentanyl or sufentanil (Flacke et al., 1987).

5.10.1.9 Acute Generalized Exanthematous Pustulosis

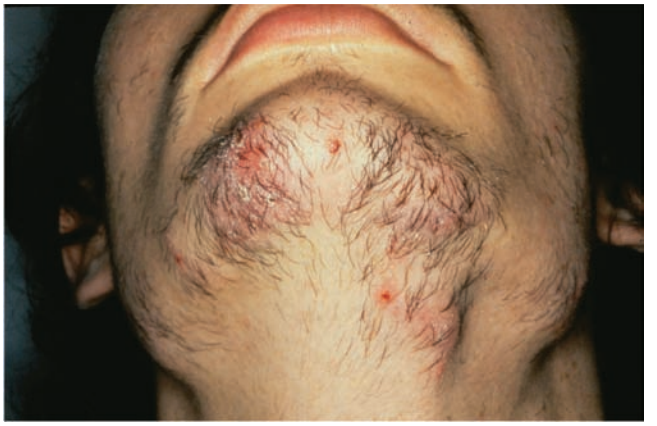
A serious drug-induced eruption, acute generalized exanthematous pustulosis (AGEP), usually accompanied by fever and neutrophilia with elevated total white blood cell count, has been reported occasionally in heroin abusers (Lee et al., 1995). Many small follicular pustules can be seen superimposed on areas of bright erythema. This disorder has been reported in association with the use of many different drugs, including morphine, though most of the time the offending agent is an antimicrobial or acetaminophen. This disorder overwhelmingly involves women. Some studies implicate T cells, while others suggest the induction of an antigen–antibody complex by the culprit drug or infection, with subsequent activation of the complement system followed by neutrophil chemotaxis (Girardi et al., 2005; Tamir et al., 2006).

5.10.1.10 Fungal Lesions

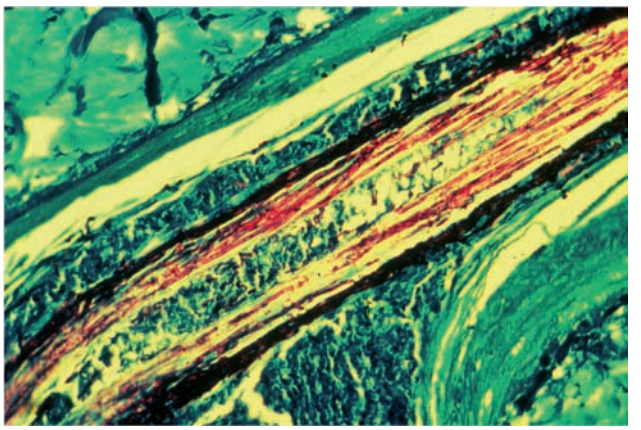
Oral candidiasis is the most common opportunistic infection seen in HIV patients. When the HIV pandemic first began, the prevalence of oral thrush in AIDS patients was 40–90%, but with the introduction of HAART the pattern of HIV-related oral disease has changed, and in industrialized countries the prevalence of this disorder is estimated to range between 10 and 50% of those infected (Hodgson et al., 2006). The prevalence of esophageal involvement is much lower, but fully 75% of those who develop oral candidiasis will at some time develop esophageal involvement (de Repentigny et al., 2004). As a rule, *C. albicans* infections in AIDS patients are limited to the mucosa. Disseminated disease does not occur unless the infected individual is also a heroin user or has some other similar risk factor (steroid therapy, indwelling catheter, severe granulocytopenia) (Dupont and Drouhet, 1985).

Candida-related febrile septicemia with cutaneous involvement is a disorder confined to heroin addicts. The syndrome was first described in 1981 when a cluster of cases occurred in Paris (Vinceneux et al., 1981). Subsequently, hundreds of additional cases were reported across Europe and Australia, but only sporadic cases have been reported in the U.S. (Collignon and Sorrell, 1983; Martinez-Vazquez et al., 1998). Epidemiologists eventually linked the outbreak to the use of poorly soluble heroin that had been exported from Iran ("brown" heroin). In order to dissolve the heroin for injection, users added lemon juice or some other acidifying agent (Mellinger et al., 1982). It was found that even bottled lemon juice could become contaminated with the *C. albicans* found on an addict's skin (Berger et al., 1988). A significant majority of the cases have been due to a single strain of *Candida*, serotype A, biotype 153/7 (Shankland and Richardson, 1989). Subcutaneous lesions are seen in 75–100% of the cases, ocular involvement in approximately 60%, and osteoarticular involvement in 20–50% (Dupont and Drouhet, 1985).

In a typical case, symptoms occur within 2–24 hours after the last heroin injection. Chills, fever, headache, and profuse diaphoresis quickly follow one after another. Within one to three days, patients develop disseminated folliculitis and scalp nodules. Any hair-bearing area may be involved, but the scalp is the most common site (Dupont and Drouhet, 1985). Painful cutaneous nodules, usually measuring less than 1 cm, erupt quite suddenly.



(a)



(b)

Figure 5.10.1.10 (a) Facial appearance of a heroin addict with Candida septicemia. (b) Yeast filaments in the hair of the same individual.

As many as 100 of these nodules may be present, and it is said that the scalp of such an individual feels like "a sack of marbles." Smaller pustules may be seen adjacent to the nodules. The pustules strongly resemble lesions produced by staphylococcal or streptococcal infection, but microscopic examination discloses yeast and filaments of *C. albicans*. Biopsy of the follicular nodules is more likely to be diagnostic than blood cultures. Gomori methenamine–silver staining will reveal bifurcated filaments of *C. albicans* admixed with an intense, mixed inflammatory infiltrate (Dupont and Drouhet, 1985). Since the initial reports were first published, others have appeared describing the same syndrome after injection of methadone-containing syrup diluted with orange juice (Scheidegger et al., 1993; Moller et al., 1997), after injection of buprenorphine tablets diluted in lemon juice (Scheidegger and Frei, 1989), and even after intravenous methamphetamine use (Mohri et al., 1991) and cocaine (Le Thien et al., 1998).

Nonetheless, this disorder seems to be becoming increasingly rare, at least within the U.S., and there is no apparent explanation.

5.10.1.11 Miscellaneous Cutaneous Abnormalities

Other skin disorders are occasionally seen, but none with sufficient frequency to be of any diagnostic value. After self-injecting with opiates, abusers may fall asleep with cigarettes in their mouths, resulting in burns of the anterior chest when the head falls forward (Sapira, 1968). Sometimes the burns occur in a circular pattern. Other lesions reflect usage patterns that were unique to a specific time and place and are mainly of interest as historical curiosities. In the late 1800s, when opium smoking was still popular, the presence of cauliflower ears (swelling of the auricles) was considered almost pathognomonic for opium use. They were the result of lying for long periods on opium beds with hard wooden pillows (Owens and Humphries, 1988).

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5.10.2 Cardiovascular Disorders

5.10.2.1 Introduction

The definition of heart disease in opiate abusers has changed over the years. While it is still true that the hearts of heroin abusers are more susceptible to endocarditis, and to the various complications associated with HIV infection, it is not even clear that these forms of heart disease are any more frequent among opiate abusers than they are in controls (Kringsholm and Christoffersen, 1987). In Siegel and Halpern's classic 1966 paper on the "Diagnosis of death from intravenous narcotism," heart disease was not even mentioned, nor were any significant cardiac abnormalities noted in the study by Wetli et al. (1972) of 100 consecutively autopsied narcotic abusers. When Louria et al. (1967) analyzed the discharge diagnosis of addicts admitted to Bellevue Hospital's general medicine service, the incidence of endocarditis was under 10% and no other cardiac disorders were noted. The difficulty faced by researchers today is that most drug abusers are polydrug abusers. The combined use of heroin and cocaine is especially common, making it virtually impossible to determine, in any particular individual, whether the cause of their heart disease is a consequence of stimulant or opiate abuse.

Making sense of the older studies and even some of the newer ones is difficult, if not impossible. The phrase "narcotic addict" has never been applied consistently. Early workers used the term to apply to any sort of intravenous drug abuse, even though the effects of sympathomimetic (cocaine, methamphetamine) drugs are manifestly different from those of opiates. In early studies, chemical confirmation of the diagnosis of drug abuse was impossible except by observing associated clinical signs. Such inferences can be very useful at the bedside, and sometimes even in court, but the only reason these early observations ever made their way into the peer-reviewed medical literature was the inability, at the time, to accurately detect drugs in postmortem material.

Even after routine toxicological screening became available, the limits of detection were far higher than they are today. Worse, almost all of the studies of drug abusers, old and new, were uncontrolled. This led to some very strange conclusions, which should have been suspect. Dressler and Roberts (1989b) reported finding lesions in the heart of every abuser they examined, but their study lacked controls, and nearly all of the 168 cases examined had been referred to a tertiary center because the original prosecutors suspected that cardiopulmonary abnormalities were present. The abnormalities reported by Dressler and Roberts are utterly at odds with the experience of most medical examiners. Unfortunately, very few controlled studies have compared the cardiopulmonary pathology in opiate-related deaths with age-matched controls, but in general, the hearts of the opiate addicts appear to differ in no significant way from those of the controls.

Another problem is the nonspecific nature of the histologic alterations. Cardiac fibrosis may be the result of ischemia, infarction, cardiomyopathy (which would include toxic cardiomyopathy) and myocarditis. Whatever the cause, it is the result of injury to individual cardiomyocytes, the excessive deposition of extracellular matrix materials, and myocardial remodeling. No matter the initiating cause, the process is mediated by fibroblasts, which probably have migrated from the marrow and are unrelated to the fibroblasts normally resident in the heart. The process of fibrous replacement is induced by transforming growth factors (transforming growth factor β) and other bone marrow proteins, no matter what the initiating factors were. Just how any opiate could initiate, or participate in this process is not known. Fortunately, the process can be halted, and possibly even reversed, by medical interventions, such as treatment with angiotensin-converting enzyme inhibitors (Towbin, 2007).

Another issue that makes the early data impossible to interpret is that, until very recently, it was simply not possible to measure what effects the drugs were exerting at the molecular level. For example, it is now obvious that opiate users, particularly those taking very large doses of synthetic opiates, are at risk for QT interval prolongation and a potentially lethal arrhythmia known as torsade de pointes (Almehmi et al., 2004; Krantz and Mehler, 2004; Ehret et al., 2006; Sticherling et al., 2005; Wedam et al., 2007). In some cases, large doses may not even be required. Certain polymorphs for CYP2D6 cannot metabolize the S- form of methadone, and it is the S- form that binds to the hERG potassium channel, thereby causing the QT prolongation and dispersion leading to torsade de pointes (Eap, et al., 2007). But a decade ago no forensic pathologist had ever heard of QT dispersion or hERG potassium channels, nor was it any clearer to early researchers that heroin/morphine is, in fact, cardioprotective (Peart and Gross, 2004, 2005, 2006).

The relative scarcity of heart diseases (excluding endocarditis in intravenous drug users) may be due to the cardioprotective effects of heroin/morphine. The mechanism involves a process known as "preconditioning." If the heart is exposed to sublethal myocardial ischemia, it is actually protected from later, severe ischemic insults for up to 72 hours. The protected period can be divided into two phases, acute and chronic. During the first 24 hours myocardial protection is conferred by the increased production of inducible nitric oxide. During the second, longer phase, protection is the result of increased cyclooxygenase-2 (COX2) production. Treatment with opioids produces exactly the same results and the same degree of cardioprotection as ischemic preconditioning (Peart and Gross, 2004, 2005, 2006).

The frequency with which any particular cardiac lesion is observed is a function of the pattern of drug abuse within the population being studied. When Rajs reviewed the cardiac pathology in a group of 25 intravenous drug users he found contraction band necrosis, fibrosis, and inflammatory infiltrates (Rajs and Falconer, 1979), but amphetamine, not opiate, abuse was common in the population being studied, and the changes observed by Rajs are consistent with that fact. In some areas, especially in parts of Europe, the injection of pills meant for oral use is still a very common practice (and anecdotal evidence suggests that popularity is increasing in the U.S. as well). Where this practice is popular, granulomatous lung disease and pulmonary hypertension are common, and the spectrum of cardiac lesions seen at autopsy is likely to reflect that fact (Crouch and Churg, 1983). As drug abuse is now a universal phenomenon, the picture has become far less clear, and it has become harder and harder to generalize about what pathological changes are to be expected.

The frequency of incidental cardiac lesions in addicts dying of trauma has never been tabulated. Because of the HIV pandemic, heart disease in intravenous opiate users has come to be almost synonymous with HIV infection, though the picture of involvement has changed as treatment has improved (Morgello et al., 2002). HIV/AIDS tends to have a greater impact on people of working age, whereas heart disease and malignant neoplasms have a greater impact on people over 65 years of age, no matter whether or not they are drug abusers, and no matter whether they are HIV infected. Since 1995, largely as a result of treatment advances, there has been a rapid reduction in the effect of HIV/AIDS on life expectancy, at least in the U.S. population. This is especially true for black males of working age (Sudano et al., 2006).

5.10.2.2 HIV-Associated Cardiovascular Pathology

In the HIV infected, cardiovascular disease can be the result of the virus itself, opportunistic infections or neoplasias, antiretroviral drugs, or the secondary result of treating opportunistic complications. These disorders include both pericarditis and myocarditis. Pericarditis may lead to pericardial effusion but rarely to tamponade (Moreno et al., 1997; Chen et al., 1999). Cardiomyopathy in the HIV infected is often clinically silent, with asymptomatic left ventricular systolic dysfunction. Endocarditis is mainly seen in the HIV infected who also happen to be intravenous drug abusers. Pulmonary hypertension, potentially leading to right-heart failure, is another recognized HIV complication. The incidence of cardiomyopathy and pericarditis in the HIV infected has been reduced by highly effective antiretroviral therapy. However, antiretroviral therapy can lead to premature coronary atherosclerosis, and this complication is now a growing problem. Treatment with antiretrovirals can also have serious metabolic consequences, not all that different from what is seen in the non-infected who suffer from metabolic syndrome. The prolonged use of protease inhibitors can cause lipodystrophy, a clinical syndrome of peripheral fat wasting, central adiposity, dyslipidemia, and insulin resistance. Underlying these symptoms may be all the other elements of metabolic syndrome, including hyperlipidemia, hyperglycemia, and hypertension, which is why these individuals may be good candidates for lipid-lowering therapies. Metabolic syndrome only complicates the issue of HIV treatment because it is very likely that the patient will be treated with lipid-lowering drugs that interact with the P-450 system, leading to inactivation of some antiretroviral agents (Sudano et al., 2006).

Pericardial effusion is the cardiac lesion most commonly seen in AIDS patients (Table 5.10.2.2.1), but effusions large enough to cause tamponade are very uncommon. In developing countries the effusion may be the result of tuberculosis, but in the industrialized world it is more likely to be a consequence of myocarditis (Moreno et al., 1997). Rarely,

Table 5.10.2.2.1 Cardiac Findings in AIDS Patients at Autopsy, in Probable Order of Frequency

1. Pericardial effusion
2. Myocardial disease (cardiomyopathy, myocarditis, lymphoma, drug toxicity)
3. Pulmonary hypertension
4. Cardiac tumors
5. Endocardial disease

an effusion may represent underlying Kaposi's sarcoma or lymphoma. Patients with effusions appear to have a much worse prognosis than those without them (Chen et al., 1999).

Cardiomyopathy is probably the most common clinical manifestation of myocardial disease in these patients, the result of an inflammatory response to the virus itself. The most common outcome is clinically silent left ventricular systolic dysfunction. A case report published in 2002 described an association between cardiomyopathy and severe mitochondrial damage in an HIV-infected patient treated with nucleoside reverse transcriptase inhibitors (Frerichs et al., 2002). How often this problem occurs is not known. Myocarditis occurs, but is an increasingly uncommon complication of HIV infection, and the offending agent is usually never determined, though opportunistic infection must be considered.

Primary pulmonary hypertension is seen in approximately 0.5% of patients with HIV infection, versus the general population where the yearly incidence is only approximately 1 to 2 per million people (Sudano et al., 2006). While it is certainly true that repeated opportunistic pulmonary infections can cause right ventricular dysfunction and cor pulmonale, there does not appear to be a connection between opportunistic infection and pulmonary hypertension in these patients (Mesa et al., 1998). Histologically, plexogenic arteriopathy is usually apparent, appearing no different from the findings in the seronegative suffering from the same disease. The prognosis is dismal.

Myxoma, fibroelastoma, sarcoma, and lymphoma all occur in the hearts of the HIV infected. Kaposi's sarcoma generally occurs in the setting of widespread mucocutaneous disease (Stotka et al., 1989). It is very rare for the heart to be the only organ infected, and the lesions are likely to be asymptomatic. The pericardium, epicardium, and myocardium and can all be involved and there may also be a pericardial effusion. Primary cardiac lymphomas, especially B-cell lymphomas of the right atrium, have a very poor prognosis.

Coronary artery disease is a relatively frequent finding in heroin-related deaths, but so are reports of myocardial infarctions in HIV-infected young people, especially those receiving protease inhibitor therapy. Even without the underlying history of drug abuse, the combination of protease inhibitors taken with reverse transcriptase inhibitors (HAART) is known to be associated with lipodystrophy and the metabolic syndrome, making coronary artery disease all the more likely (Passalaris et al., 2000). Indeed, recent studies have shown that an increased risk of myocardial infarction exists in patients exposed to abacavir and didanosine within the preceding 6 months. The excess risk does not seem to be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after drug cessation, and it is not known whether this increased risk is associated with any specific morphological changes (D:A:D Study Group, 2008). On the other hand, coronary artery disease in these individuals could also be a consequence of concurrent stimulant abuse, a practice known to be associated with accelerated coronary artery disease (Karch et al., 1995).

Coronary artery lesions in the HIV infected have features intermediate between the lesions observed in common coronary atherosclerosis and the type of disease associated with chronic rejection of cardiac transplants. Thickening of the media and increased production of elastic fibers have both been demonstrated (Tabib et al., 2000). The etiology of these changes remains obscure, but increasingly appears to be a complication of treatment with protease inhibitors (Meng et al., 2002b). There is also emerging evidence that this group of drugs may even promote ventricular remodeling and left ventricular hypertrophy (Meng et al., 2002a).

5.10.2.3 Endocarditis

After HIV infection, endocarditis is the only other cardiovascular disease with an incidence that is clearly higher among intravenous drug abusers than in the general population. Among intravenous drug users, most infections are still due to *S. aureus*, and the tricuspid valve is still the most commonly involved valve. However, infection with multiple Gram-negative organisms is increasingly common (Reisberg, 1979). Surprisingly little effort has been expended in investigating the issues that place intravenous drug users at greater risk for valve infection. Autopsy studies indicate that most (> 80%) vegetations occur on previously normal valves (Dressler and Roberts, 1989a). The results of echocardiographic studies suggest that the valves of intravenous heroin users, even those with no clinical evidence of endocarditis, are abnormal; small areas of thickening on both the mitral and tricuspid valves are often present (Pons-Llado et al., 1992). Similar changes have been observed in intravenous cocaine users, where nearly half of the patients studied showed, at a minimum, valve thickening (Willoughby et al., 1993). The findings suggest that some type of endothelial trauma must occur to allow deposition of the microscopic thrombi, which, in turn, constitute the first stage of infection. Some studies have found that those with antiphospholipid syndrome, which results in valvular thickening, may be more at risk (Blank et al., 2005; Tincani et al., 2005).

The literature has always emphasized that addicts are prone to right-sided infection, and there is no question that the tricuspid and pulmonic valves are involved more often in addicts than in the general population. But it is also true that in some series left-sided involvement occurs more often than right (Hubbell et al., 1981; Dressler and Roberts, 1989a). The origin of the infectious agent is also a matter of dispute. Because addicts seldom practice sterile techniques, the needles they use may be contaminated and the injected material likely to be unsterile. The injection site, especially if the groin is being injected, may be colonized with pathogenic organisms. Thus, a number of possible sources for infection exist. With the exception of *Candida* infection (Dupont and Drouhet, 1985), studies have failed to link the heroin itself, or the paraphernalia used, to any particular infectious organism (Tuazon et al., 1974). More often than not, the infectious organism is derived from either the addict's normal surface flora (Hubbell et al., 1981) or from a pre-existing infection such as cellulitis or suppurative thrombophlebitis.

Platelet deposition, no matter what the cause, damages valvular epithelium, exposing the matrix of subendothelial connective tissue below, and allowing the further deposition of fibrin and platelet thrombi. Vegetations are friable, white or tan, and most likely to be found along the line of valve closure. Bacterial vegetations tend to arise on the atrial aspect of the atrioventricular valves and on the ventricular surfaces of the aortic and pulmonary valves. With time, they may proliferate and involve the opposite side of the valve or spread to the chordae tendineae or onto the parietal pericardium. The lesions ulcerate, and the ulcerations seen in acute endocarditis tend to be larger and deeper than those associated with subacute disease (Silber, 1987). To some degree, the size, color, and appearance of the vegetations depend on the type of infectious agent responsible. Fungal lesions tend to be larger and bulkier than bacterial vegetations and are more likely to cause valvular insufficiency and embolization. Streptococcal vegetations grow more slowly than staphylococcal vegetations, but they may eventually be much larger (Ciliberto et al., 1999; Ellis et al., 2001).

Vegetations much smaller than those seen with bacterial or fungal infection are seen at autopsy in approximately 2% of severely cachectic patients. The lesions are sterile, and the process of their formation is generally referred to as nonbacterial thrombotic endocarditis

(NBTE; also marantic endocarditis) (Angrist and Oka, 1963). The same process also occurs in association with autoimmune disorders, but here, too, diagnosis during life is rare unless the verrucae embolize and cause a thromboembolic event (Reisner et al., 2000). NBTE associated with systemic embolism usually occurs as a complication of advanced or terminal malignancies, and it appears to be associated more with some malignancies than others (Eftychiou et al., 2005).

The verrucae of NBTE are composed of bacteria-free, amorphous material. Depending on how much fibrin has been deposited, the color of the vegetations can range from white to tan or gray. On microscopic examination, the lesions of marantic endocarditis are easily distinguished from those of infectious endocarditis; masses of fibrin, platelets, and polymorphonuclear leukocytes can be seen surrounding colonies of bacteria located directly on the surface of the valve. Necrotic areas of valve become surrounded with a mixed cellular infiltrate that often includes giant cells. In older lesions, capillary proliferation occurs, along with the formation of granulation tissue (Saphir et al., 1950). Fibrous tissue eventually proliferates over the vegetations, and the necrotic material becomes organized and eventually endothelialized. Healed lesions are often calcified.

The pattern of valvular involvement is different in drug abusers than in the population at large, and so are the symptoms. In Dressler and Robert's series of 80 autopsied addicts with infectious endocarditis (Dressler and Roberts, 1989a), the tricuspid valve was involved almost half the time. However, in the general population tricuspid valve involvement occurs less than 5% of the time in subacute cases, and less than 15% of the time in acute endocarditis (Lerner and Weinstein, 1966; El-Khatib et al., 1976). Table 5.10.2.3.1 compares the frequency of involvement in addicts with the frequency seen in the general population. It seems that the likelihood of infection depends upon the pressure to which the valve is subjected (Lepeschkin, 1952) so the high incidence of low-pressure valve disease in addicts remains puzzling and unexplained. Equally difficult to explain is the fact that a significant incidence of right-sided involvement has been reported in some non-drug-using populations (Grover et al., 1991).

There is no satisfactory explanation for why the spectrum of organisms attacking the right heart should be so different from, and so much more virulent than, the group of agents that infect the mitral and aortic valves. *Staphylococcus aureus* is the predominant organism infecting right-sided valves, while 60–80% of the time the causative organism on the left is a *Streptococcus viridans* sp. (Weinberger et al., 1990). The predominant organisms in

Table 5.10.2.3.1 Frequency of Valve Involvement in Addicts vs. General Population

Site	Addicts (%)	General (%)
Left side	41	85
Aortic	23	15–25
Mitral	19	30–45
Right side	30	5–20
Tricuspid	29	1–15
Pulmonic	1	< 1
Right and left sides	16	5–10

Source: Data for addict population derived from Dressler and Roberts (1989a); data for the general population derived from published clinical studies.

Table 5.10.2.3.2 Pathogens Reported in Addicts with Infectious Endocarditis, Compared with Pathogens Observed in the Non-Addicted Population

Pathogen	Addicts (%)	Non-Addicts (%)
Streptococcus	15	65
Viridans (β-hemolytic)	< 5	35
Group D	< 5	25
Staphylococcus aureus	50–80	25
Pseudomonas aeruginosa	10–40	< 5
Polymicrobial	10–20	< 1

Source: Summary of data from published studies.

addicts and the general population are compared in Table 5.10.2.3.2. Sporadic case reports suggest that 8–9% of addicts have polymicrobial infections.

Infection with multiple organisms is uncommon on the left side, but polymicrobial involvement of the tricuspid valve is prevalent, especially among intravenous drug abusers. Until recently, polymicrobial infection was a distinctly rare entity. In one retrospective study of nearly 1000 patients seen from 1951 to 1966, only one case was found (Weinstein and Rubin, 1973). In more recent reports, the incidence has been closer to 8% (Crane et al., 1986). As many as seven or eight different organisms may be involved at one time, and because many of these organisms are quite fastidious, all may not be diagnosed by routine laboratory methods (Mah and Shafran, 1990; Adler et al., 1991).

Right-sided cardiac involvement results in symptoms that are more pulmonary than cardiac in nature. Dislodged vegetations frequently embolize to the lung, producing multiple segmental infiltrates, especially in the lower lobes (Chan et al., 1989). Tricuspid vegetations can, on occasion, grow quite large, and may even interfere with valve function. Papillary rupture, on the other hand, produces relatively few symptoms on the right because of the low intracavity pressure (Conway, 1969). Aneurysm of the sinus of Valsalva may result when infection dissects into the valve ring. This process is most often seen in cases of staphylococcal infection. Staphylococcal infections may also extend outward from the ring and, in addition to resulting in ring abscess, the infection may also spread to involve the interventricular septum (Conde et al., 1975). Lethal arrhythmia can result. Extension of the infection outward may result in purulent pericarditis or even cardiac rupture. In fact, purulent pericarditis occurs in nearly 20% of all cases of endocarditis, even without the rupture of any large abscess (Silber, 1987). Smaller abscesses may be scattered throughout the myocardium, and even though abscess formation is more common in cases of acute endocarditis, it may be seen in subacute cases as well. Abscesses may be subendocardial or subpericardial but are most likely to be found in the left ventricle (Arnett et al., 1976). A spectrum of other myocardial alterations short of frank abscess formation can also be seen. In acute cases, there may be cloudy swelling of the myocytes, hemorrhage, or even tiny areas of infarction. Small infarcts occur in subacute cases where small emboli obstruct distal branches of the coronary arteries (Saphir et al., 1950).

The peripheral sequelae of valve infection have changed little since Osler described them in the Gulstonian Lectures in 1885 (Osler, 1886). The most frequent complications associated with endocarditis in addicts are the same as those in the general population with endocarditis. Many of the extracardiac manifestations are the result of arterial embolization of the friable vegetations. Mycotic aneurysm is the result of septic emboli, most of which

occur at the bifurcation of medium-sized arteries. This process is especially common in the brain but can also occur elsewhere. In the kidneys, septic emboli can cause infarction, especially when *Staphylococcus* is the etiology. Glomerulonephritis is seen in more than half of the patients and is the result of immune complex deposition (Bell, 1932). In addition to the classic focal embolic changes seen in the kidneys of patients with endocarditis, diffuse proliferative glomerulonephritis may also be seen. In these latter cases, there is strong evidence for an immune-related etiology. It may well be that other peripheral lesions, such as Roth's spots and even Osler's nodes, have an immune etiology (Bayer and Theofilopoulos, 1990).

If there is any suspicion that the decedent was suffering from infectious endocarditis, aseptic techniques should be used at autopsy to ensure the collection of uncontaminated material. The major vessels should be clamped before removing the heart from the body. An area on the surface of the heart adjacent to the affected valve (e.g., entrance through the posterior right atrial wall would give access to the tricuspid valve) should then be seared and the center of the area incised with a sterile scalpel, allowing direct access to the valve, which can be sampled and cultured. If such an approach is not followed, the samples obtained may well be contaminated. In addition to routine Gram stains, slides should also be stained for fungi (Gomori stain) and for acid-fast organisms.

5.10.2.4 Myocardial Fibrosis

Interstitial fibrosis is also a frequent finding in the hearts of drug abusers. Certain patterns of fibrosis play a role in the generation of malignant rhythm disorders and sudden cardiac death (Strain et al., 1983). Microfocal fibrosis is most typically seen in stimulant abusers (Rajs and Falconer, 1979; Tazelaar et al., 1987) where it is the result of healing contraction band necrosis, secondary to catecholamine excess (Szakacs and Cannon, 1958), and myocardial remodeling caused by cocaine's ability to activate calmodulin kinase II (Henning et al., 2006), but is also seen in roughly 2% of young adults with sudden death and no other obvious risk factor (Lecomte et al., 1993). Given the increasing rate at which drug users combine narcotic and stimulant drugs, the occurrence of myocardial fibrosis in opiate abusers probably is just a function of stimulant cardiotoxicity. On the other hand, healed endocarditis and healed myocarditis also cause fibrosis, as do poorly controlled hypertension with ventricular remodeling. The mechanism in non-catecholamine fibrosis involves increased expression of the proteinases (urokinase-type plasminogen activator [uPA] and matrix metalloproteinases [MMPs]) (Heymans et al., 2006). The mechanisms responsible for other forms of interstitial myocardial fibrosis are not so clear, but seem to involve increased production of tissue growth factor-β (John et al., 2004).

Larger zones of fibrosis are likely to represent healed areas of ischemic infarction. Large zones of fibrosis could also be related to healed endocarditis, as emboli may cause infarction in some of the smaller coronary artery branches (Silber, 1987), but this is a relatively uncommon occurrence. The detection of fibrosis is not simply an incidental finding; it may very well be the cause of death. Viable muscle tissue trapped within scar tissue can give rise to re-entrant circuits, leading to fatal arrhythmias. When identified in life these areas are increasingly treated with ablation.

5.10.2.5 Myocardial Hypertrophy

There is little evidence that myocardial hypertrophy is a complication of chronic heroin abuse (Willoughby et al., 1993). Right-sided cardiac enlargement in intravenous abusers

with lung disease is to be expected as the injection of contaminated heroin and crushed pills will diminish the size of the pulmonary bed. However, the finding of hypertrophic myocardium in a pure heroin abuser is most likely to reflect either untreated hypertension or concurrent cocaine use. As more and more heroin users also abuse cocaine, and some methamphetamine, the latter explanation becomes more likely. Unlike cocaine, which activates calmodulin kinase and, therefore, causes myocyte enlargement, hypertrophy in methamphetamine abusers is likely to be related to chronic catecholamine excess and/or HIV disease.

5.10.2.6 Coronary Artery Disease

Intravenous heroin abusers have abnormal, atherogenic lipid profiles (Maccari et al., 1991; Sztajzel et al., 1994). Whether the incidence of coronary artery disease in heroin addicts is any different from that in age-matched controls is not known. There are case reports describing coronary spasm and acute myocardial infarction in heroin abusers, where acute myocardial infarction occurred after the injection of heroin, but there is no way to tell whether the episodes were due to the heroin, an adulterant, concurrent myocarditis, or some direct effect of heroin on coronary arteries (Yu et al., 2004). However, it is known that nearly all heroin users smoke cigarettes, if not marijuana as well (Patkar et al., 2002). Dressler and Roberts (1989b) found significant coronary artery disease (> 75% narrowing) in 8% of their referral cases, but this observation has not been confirmed. In fact, no mention of coronary artery disease is made in any published autopsy series of heroin abusers (Halpern and Rho, 1966; Siegel and Halpern, 1966; Louria et al., 1967; Froede and Stahl, 1971;

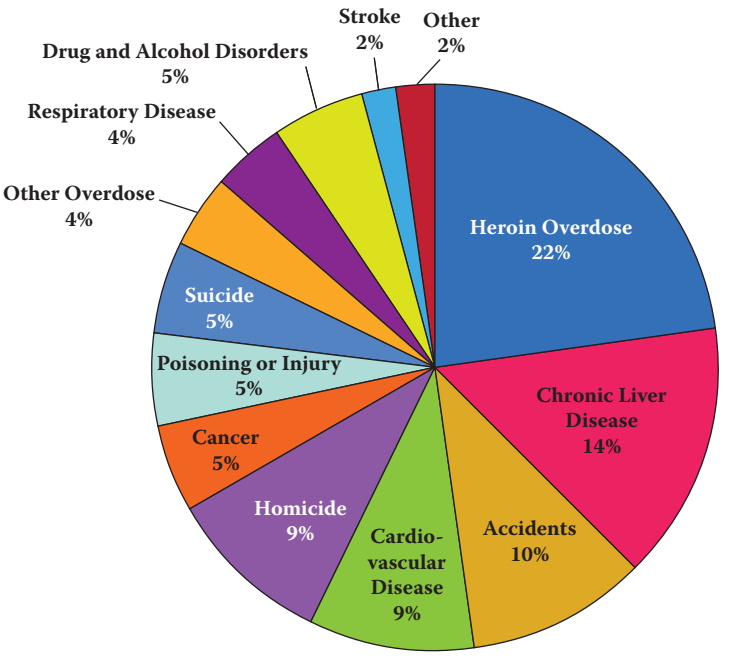

Figure 5.10.2.6.1 The life span and cause of death in heroin users, from 1962–1967. (From *NiDA Notes*, 21(c) 19, 2008.)

Wetli et al., 1972). As discussed in the introduction, morphine protects the heart from ischemic damage and it may well be that heroin addicts are in some way protected, being at less, rather than more, risk for coronary artery disease. The results of a recent study support this idea. Investigators compared the coronary arteries in 98 decedents with methadone or opiates in their blood at autopsy with 97 frequency-matched decedents without opiates. Multiple logistic regression analysis showed that the heroin users had benefited from a protective effect, and that they had much less coronary artery disease than was evident in the controls (Marmor et al., 2004).

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5.10.3 Pulmonary Complications

5.10.3.1 Pulmonary Edema

As illustrated by the rising number of deaths due to the ingestion of fentanyl-containing heroin, illicit heroin users have no way of knowing how much heroin they are injecting, or even being sure it is heroin. If the material injected is less adulterated than normal, or

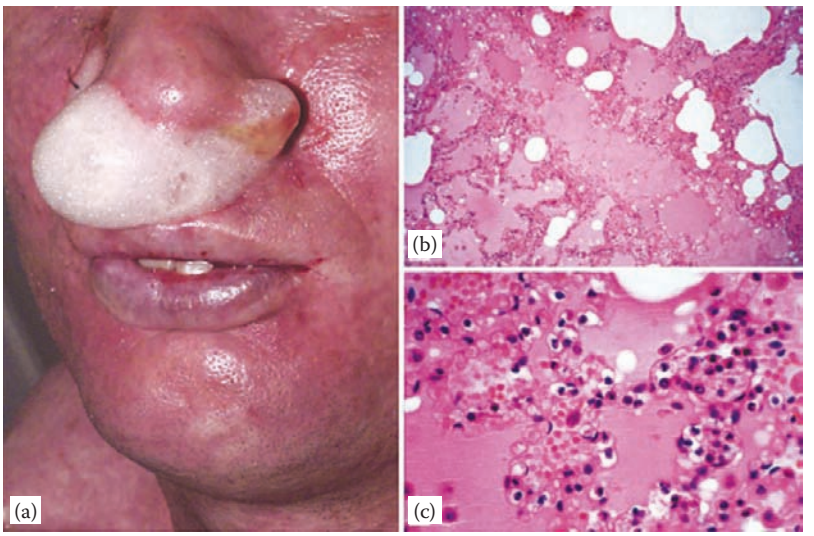

Figure 5.10.3.1.1 Pulmonary edema; the pink staining material that fills the alveoli is highly proteinaceous and typical of narcotics overdose. Because of the high protein content of the edema fluid it will form froth that may exude from the upper airway and even out of the mouth of the cadaver. (With permission from *Current Diagnostic Pathology* [Elsevier] and Dr. F. Tomashfeski, 2007.)

if it contains another respiratory depressant such as fentanyl, fatal respiratory depression may ensue.

A physician named Lee, in New York in the 1850s, first noted the existence of narcotic-related pulmonary edema. Lee described the simultaneous occurrence of cerebral edema and pulmonary congestion in a man dying from a laudanum overdose (Woodman and Tidy, 1877). Nearly 150 years later, the mechanism of narcotic-induced pulmonary edema still remains unknown. It is generally presumed that pulmonary edema in heroin abusers is in some way related to respiratory depression and respiratory failure, although there are those who still adhere to the notion that narcotic-induced pulmonary edema is the result of some sort of allergic or anaphylactic reaction (Edston and van Hage-Hamsten, 1997; Dettmeyer et al., 2000) or histamine release. All opiates decrease the responsiveness of the respiratory centers to increased levels of PCO_2, and if enough narcotic is given, the respiratory drive disappears. In practice, postmortem examination will reveal pulmonary congestion of varying degrees, but not always florid pulmonary edema.

The edema fluid associated with narcotic overdose is rich in protein. Agonal respiratory efforts will cause the fluid to froth, much like beaten egg white. In extreme cases, congealed froth is seen in the mouth and nares. In one large autopsy series, the average weights of the right and left lungs were 830 and 790 g, respectively (Levine and Grimes, 1973). In the case series described by Siegel et al. (1966), the average total was slightly lower (1400 g). Almost the identical result (1419 g) was found in 154 heroin-related deaths investigated by the San Francisco Medical Examiner's office in 1999 (Karch et al., 2000).

Fluid accumulation occurs in a lobular distribution, with areas of congestion and edema alternating with other areas of air trapping and acute emphysematous change. The posterior lower lobes are most severely affected, especially if gastric aspiration has also occurred. Histologic examination may reveal a spectrum of changes. In less severe cases, the only abnormality found will be widening of the interstitial spaces, especially around the bronchi and extra-alveolar vessels (Pietra, 1991). In more extreme cases, the alveolar spaces are flooded with protein-rich fluid.

If there is enough time for hypoxic heart failure to occur, blood vessels in the nose and pharynx rupture, giving a pink tinge to the edema fluid. After 24 hours, hyaline membranes will be visible in the alveoli. They are composed of necrotic alveolar cell debris, mixed with the protein-rich edema fluid, deposited on the alveolar walls. This phase is followed by a recovery phase. During this final phase, the cut surface of the lung will be firm and brownish, suggesting the diagnosis of pneumonia. Type II alveolar cells and fibroblasts proliferate, and the fibrinous exudate in the alveoli is replaced by granulation tissue (Kringsholm and Christoffersen, 1987).

Studies of heroin users published in the older literature describe thickening of the alveolar septa, fibrosis, and hypercellularity, with hemosiderin-laden macrophages often present in the alveolar walls and even in the lamina of the alveoli and respiratory passages (Rajs et al., 1984). More recent studies point to the frequent finding of hyperplastic pulmonary perivascular lymphatic tissue. At one time, it was thought that the presence of hemosiderin-containing macrophages was nearly diagnostic for chronic heroin use, but because so many heroin abusers also smoke "crack" cocaine, such conclusions are no longer warranted.

Sputum from "crack" smokers is usually turbid, gray, or even black, and considerably darker than sputum seen in heavy tobacco smokers dwelling in the same urban environment. "Crack" smokers tend to have carbonaceous sputum and, not infrequently,

emphysematous changes in their lungs (Klinger et al., 1992). Carbon-laden macrophages can also be found in the pleural fluid of "crack" smokers who develop malignancy or HIV-related pulmonary disease (Singh et al., 1995) and small intrapulmonary hemorrhages are also common in this subgroup. The pattern is obvious in microscopic sections, even before they are placed under the microscope; it is highly reminiscent of the pattern seen in "coal miner's lung." When the pattern of injury produced by cocaine smoking is superimposed on the pattern of injury produced by intravenous heroin abuse, the resultant picture is difficult to predict (Forrester et al., 1990; Bailey et al., 1994; Gallouj et al., 1999).

One of the more puzzling features of this syndrome is why some individuals with opiate-induced respiratory failure should develop florid pulmonary edema and others not. In a retrospective review of 1278 cases of heroin overdose treated in a large urban emergency room over a 53-month period, only of 27 patients met the criteria for the diagnosis of noncardiogenic pulmonary edema (Sporer and Dorn, 2001). It has been suggested that heroin has direct toxic effects on pulmonary capillaries or even the heart, leading to hypoxic-induced heart failure (Menon, 1965). A role for altered capillary permeability is suggested by the fact that the protein content of the edema fluid is almost twice that of serum (Katz et al., 1972), but immunochemical studies of IgE, collagen IV, and laminin have failed to disclose any abnormalities in the capillary membranes (Dettmeyer et al., 2000). Other theories that have been proposed include acute allergic reactions to heroin, the presence of contaminants in the heroin, causing histamine release, a centrally mediated effect, or locally induced cardiovascular disruption (Katz et al., 1972). The latter possibility seems unlikely, given that whenever hemodynamic measurements have been made in these patients, the only abnormality detected is moderately elevated pulmonary artery (PA) pressure.

Alveoli normally stain negatively for laminin and type IV collagen, but in disease states, when membrane destruction is present, both compounds leach out. When stained with IgE antibodies, lung specimens from opiate overdose victims do not appear significantly different from controls, just the contrary to what would be expected if the edema was due to anaphylaxis (Dettmeyer et al., 2000). For the present, the most plausible explanation would appear to be one that was first proposed more than 30 years ago: respiratory depression leading to hypoxia, which in turn causes increased capillary permeability and fluid extravasation into the alveoli (Duberstein and Kaufman, 1971).

5.10.3.2 Needle and Mercury Emboli

Attempts at central vein injection may sometimes result in needle fragments embolizing to the lung. These events are usually not fatal, and the needle fragments may only be detected incidentally at autopsy. For example, one recent report described a cocaine-related death where a needle fragment was found protruding into the cavity of the right ventricle. Death was a consequence of cocaine toxicity, and the needle fragment was only an incidental finding (Thorne and Collins, 1998). Nonetheless, the x-ray appearance can be quite frightening (Lewis and Henry, 1985; Angelos et al., 1986). These episodes must be quite rare, since no new cases have been reported in more than a decade.

5.10.3.3 Foreign Body Granulomas

Foreign particle embolization is frequent in intravenous drug abusers, but clinical symptoms are not. Granuloma formation is an inconsistent but relatively frequent finding at

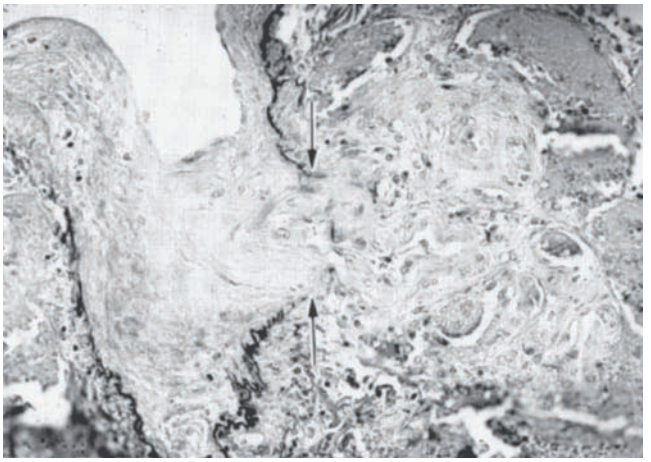

Figure 5.10.3.3.1 Thromboembolic arteriopathy. Repeated injection of particulate material can lead to pulmonary hypertension. Organizing and recanalizing thrombi in drug abusers can look very much like the plexiform lesions of primary pulmonary hypertension. The plexiform lesions of primary pulmonary hypertension, such as those shown here, are typically seen only at the branch points of stenotic small arteries. Lesions are composed of a complex network of small blood vessels and proliferating myofibroblasts. (Courtesy of Giuseppe Pietra, Director, Division of Anatomic Pathology, Hospital of the University of Pennsylvania.)

autopsy (Halpern and Rho, 1966; Sapira, 1968; Gottlieb and Boylen, 1974; Glassroth et al., 1987; Wolff and O'Donnell, 2004). Granulomas form when drug users repeatedly inject themselves with aqueous suspensions of pharmaceutical preparations designed for oral administration (Figure 5.10.3.3.1). Heroin has been available since the turn of the century, and morphine for nearly 200 years, but pulmonary granulomatosis in drug users was only first described in 1950 (Spain, 1950). The time lapse suggests that the injection of oral medications is a relatively recent innovation.

In some cases, the granulomas are caused by cotton fibers. The cotton is introduced when addicts load their syringes by drawing up the liquid through a cotton ball; small fibers of cotton are drawn up at the same time. Most granulomas, however, are due to magnesium trisilicate (talc), because talc is widely used in the pharmaceutical industry as a filler. The amount of active ingredient in most pills can be quite small, so talc is added to create a pill of manageable proportions. When injected, talc particles become trapped in the pulmonary arterioles and capillaries, producing acute focal inflammation and thrombosis. The reported incidence of talc-containing granulomas ranges from 15% (Hopkins, 1972) to 90% in some series. The tissue reaction to cotton resembles the response to talc. In areas where the injection of crushed pills is common, the frequency of foreign body granulomas is increased (Tomashefski and Hirsch, 1980; Kringsholm and Christoffersen, 1987). Fungal spores are an extremely rare cause of granulomatous disease. The soil saprophyte *Scopulariopsis brumptii* was found to be the cause of hypersensitivity pneumonitis in at least one addict (Grieble et al., 1975), and analysis of confiscated heroin samples has shown the presence of many different fungal varieties. Following the epidemic of clostridia poisoning in Scottish heroin abusers, an analysis of the then available street heroin disclosed the presence of multiple bacterial, but no fungal spores (Jones et al., 2002; McLauchlin et al., 2002).

Table 5.10.3.3.1 Characteristics of Birefringent Materials Found in the Lungs of Intravenous Drug Users

Substance	Shape	Size (μm)	PAS Staining
Talc	Needle-shaped	5–15	Negative
Potato starch	Maltese cross, eccentric center	20–200	Positive
Maize starch	Maltese cross, concentric	10–30	Positive
Microcrystalline cellulose	Elongated rod	25–200	Positive
Cotton fibers	Irregular	Variable	Negative

Note: Talc and cellulose are frequently seen in conjunction with granulomatous reactions, but other agents are not.

Source: Adapted from Kringsholm and Christoffersen (1987).

Whether the offending agent is talc, cotton, cornstarch, or cellulose (Table 5.10.3.3.1), the clinical course and pathologic findings are much the same. Trapped particles cause microthrombosis and granuloma formation. Some of the trapped material may migrate into the perivascular space, where more granulomas form. If the process is ongoing, a reduction in the size of the pulmonary bed occurs, and pulmonary hypertension can result. Associated anatomic changes include medial hypertrophy and eccentric/concentric intimal fibrosis. The tissue diagnosis can be confusing, because organizing and recanalizing thrombi seen in intravenous drug users can appear very much like the plexiform

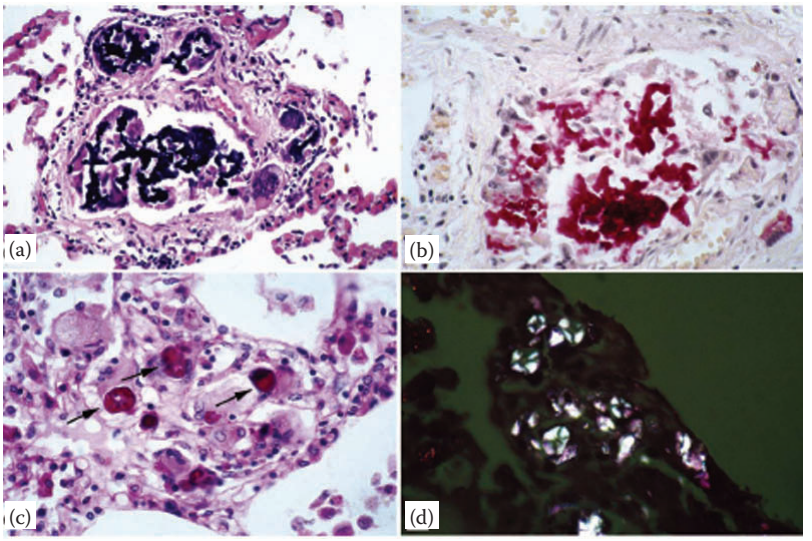

Figure 5.10.3.3.2 Birefringent crystals are especially easy to detect in the liver, kidney, and lungs. A mixture of different tablet filler crystals is represented here. (a) Intravascular and perivascular deposits of crospovidone with foreign body giant cell reaction (H&E stain). (b) Intense staining of crospovidone with mucicarmine. (c) Small interstitial foreign body granuloma with cornstarch particles (arrows) (PAS stain). (d) Central Maltese cross birefringence of cornstarch. Note also small spicules of microcrystalline cellulose (polarized light). (From Tomaschefski and Hirsch, 1980, with permission.)

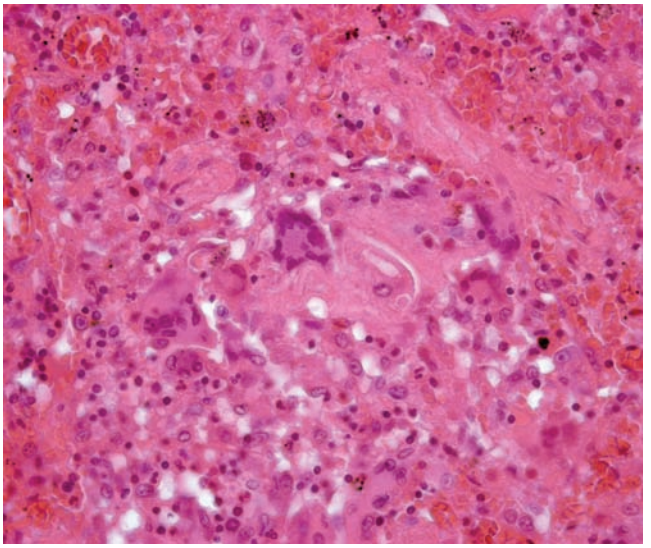

Figure 5.10.3.3.3 Foreign body granuloma in the lung of a chronic intravenous heroin abuser. (Courtesy of Vittorio Finescni, University of Foggia, Italy.)

lesions of primary pulmonary hypertension. The two conditions can be distinguished by the fact that plexiform lesions are typically seen only at the branching points of stenosed small arteries (Pietra, 1991).

Microcrystalline cellulose, a depolymerized form of cellulose, is also used as a filler and binder in the manufacture of oral medications. Cellulose crystals are anywhere from 20 to 90 μm across, and are a good deal larger than talc or cornstarch crystals. The larger size of these crystals explains granuloma formation in the larger elastic pulmonary arteries and even the right ventricle. Cellulose granulomas can be identified by their distinctive Maltese cross pattern (visible with a polarizing microscope), and by the fact that they stain as carbohydrates (Tomashefski and Hirsch, 1980). The presence of foreign bodies in the interstitium is consistent with a longstanding process. The presence of foreign material only in the media of vessels is consistent with more recent use.

5.10.3.4 Injuries of the Great Vessels

Adulterants and excipients mixed with illicit heroin can provoke an inflammatory reaction; peripheral veins become sclerotic, and abusers must use central veins for access. The two most popular sites are the vessels of the groin and neck (the "groin hit" and the "pocket shot") (Lewis et al., 1980; Pace et al., 1984; Hillstrom et al., 1990; Roszler et al., 1989; Mackenzie et al., 2000). The neck vessels are especially difficult for the abuser to inject into and, for a fee, other addicts will do the injecting for them. The results are predictable. Pneumothorax is a frequent occurrence, as is hemothorax from laceration to one of the great vessels (Lewis et al., 1980; Douglass and Levison, 1986; Jackson et al., 1995). Pyohemothorax and pseudoaneurysm (Johnson et al., 1984; Navarro et al., 1984; Zorc et al., 1988; Zhao et al., 1998) are also seen. In Europe, the use of intercostal vessels is an occasional alternative to neck injections. Reported complications include both pneumothorax and infection (Gyrtrup, 1989). Vocal cord paralysis secondary to repeated neck injection has also been

described (Hillstrom et al., 1990). None of these complications is reported with any great frequency, quite possibly because the purity of street heroin has increased and more people either "snort" or "chase the dragon." Injury to the great vessels seems to be increasingly common in addicts, especially when heroin is injected with cocaine. An epidemiology study of heroin/cocaine users, undertaken in London in 2006, found that individuals who simultaneously inject heroin/crack not only do not see anything particularly dangerous about the process but also may actually prefer this route, partly because of cocaine's local anesthetic effect (Rhodes et al., 2007).

5.10.3.5 Aspiration Pneumonia

The combination of depressed cough reflex and decreased level of consciousness, in conjunction with a general tendency to retain secretions, favors aspiration (Cherubin et al., 1972). If aspirated stomach contents are of very low pH, acute chemical pneumonitis will result. If there is much particulate matter present, then acute airway obstruction is possible. Pneumonitis is usually a result of infection with Gram-negative and anaerobic organisms (Warnock et al., 1972). Aspiration pneumonia in narcotics abusers is not any different from aspiration pneumonia in alcoholics or in patients debilitated by chronic disease. This complication of heroin abuse appears to have been completely ignored in the modern literature.

5.10.3.6 Community-Acquired Pneumonia

Even before the HIV epidemic, intravenous drug abusers were at increased risk for pneumonia and for infections in general (Cherubin et al., 1972; Harris and Garret, 1972; Moustoukas et al., 1983; Scheidegger and Zimmerli, 1996), and even if opiate users had normal immune function, which they do not (Novick et al., 1989), the injection of unsterilized material through contaminated syringes would still cause a transient septicemia. HIV-positive intravenous drug users are much more prone to develop community-acquired pneumonia and tuberculosis than are their HIV-negative counterparts, and when they do, their clinical courses are said to be more severe (Scheidegger and Zimmerli, 1996). Among HIV-infected patients, including those without AIDS, the increased rate of infection can be striking. In one study, the annual attack rate for *Streptococcus pneumoniae* was only 0.7–2.6/1000 in the general population, compared to 21/1000 in asymptomatic HIV-infected intravenous abusers (Selwyn et al., 1988). HIV-infected heroin abusers are more likely to develop empyema, and empyema may even be the first evidence of infection in those infected (Hernandez Borge et al., 1998). The rate of opportunistic lung infections among HIV-positive intravenous drug abusers is similar in frequency to that of other HIV-positive subgroups (Niedt and Schinella, 1985; Ambros et al., 1987). Eosinophilic pneumonia appears to be less common in heroin addicts than in cocaine users and "crack" smokers, but can occur. Diffuse pulmonary infiltrates composed of eosinophilic bronchoalveolar fluid have been described, and appear to be the result of an IgE-mediated hypersensitivity reaction (Brander and Tukiainen, 1993), but no new reports of this syndrome have appeared for nearly a decade.

Bronchiolitis obliterans has been described in heroin abusers. One case report describes a patient who presented with rapidly deteriorating pulmonary function after injecting heroin. When no etiology could be determined, open-lung biopsy was performed. It revealed patchy, temporally homogeneous, interstitial pneumonia with lymphocytic infiltration

and intraluminal fibroblastic proliferation consistent with organizing pneumonia. Scattered non-necrotizing granulomas with rare giant cells were also present and they were seen to contain polarizable foreign bodies (Bishay et al., 2008). Just how frequently this syndrome occurs is not known, but it may be that many possible cases are not diagnosed for lack of proper tissue sampling.

5.10.3.7 Fungal Pneumonia

Pulmonary fungal infections occur even in HIV-negative intravenous drug users (Rosenbaum et al., 1974; Mellinger et al., 1982; Collignon and Sorrell, 1983). Street heroin is often contaminated with fungal species, and precipitins to *Aspergillus, Saccharopolyspora rectivirgula*, and *Thermoactinomyces vulgaris* can, if sought, be found in the blood of many intravenous drug abusers (Smith et al., 1975). The preponderance of evidence suggests that most of the fungi found in illicit drug samples are there largely because of airborne contamination, introduced when the users prepared their drugs for injection. The presence of specific fungi cannot be used to identify the origin of a sample, although some types of heroin seem to contain more contaminants than others.

Analysis of several outbreaks of fungal pneumonia among addicts suggested that the cause of infection was contaminated paraphernalia, including preserved lemon juice used to prepare the heroin injection (Clemons et al., 1991). Some types of heroin (Mexican brown) are poorly soluble in water and can only be dissolved after they have been acidified. The two most popular agents for acidifying are lemon juice and vinegar. *Candida* species are present as contaminants of the lemon rind. Infected patients most often present with lobar pneumonia. In a high percentage of cases, peripheral nodules, with or without cavitation, may be seen. Lung abscess and empyema may also develop (Mellinger et al., 1982). Hilar and mediastinal adenopathy can be a prominent finding that resolves over the course of weeks or months. Pleural effusions are seen in about 20% of cases, and pleural thickening may result (Lazzarin et al., 1985). DNA analysis has shown that all strains of *Candida* appear to be equally infective, and no particular genotype is linked with disease in the addict population (McCullough et al., 1998).

Disseminated *Candida* infections have a rapid onset, only a few hours after injecting. The infection may be manifest as a self-limiting lobar pneumonia, or as a generalized infection with endocarditis, chorioretinitis, and hepatitis, with or without soft tissue abscesses. Occasionally the septicemia is manifested only as an isolated endophthalmitis (Dupont and Drouhet, 1985; Shankland and Richardson, 1989). Repeated showers of emboli cause mycotic aneurysms of the pulmonary arteries, but these are usually asymptomatic and are only incidentally found at autopsy. Histologic diagnosis can sometimes be made by examination of scalp biopsy specimens, which will show infiltration of the hair follicles with chronic inflammatory cells and *Candida albicans*.

5.10.3.8 Tuberculosis and Melioidosis

The incidence of tuberculosis in both HIV-positive and -negative opiate abusers has increased, and the disease seems to be much worse in patients who also use heroin. A recent retrospective case-control study of pulmonary tuberculosis in heroin-abusing patients was performed in China. It was found that patients with tuberculosis and heroin addiction suffered from much worse tuberculosis than those in the non-heroin-addicted group. More lesions were found in their chest x-rays, higher sputum tuberculosis-positive

rates were recorded, and the results of medical treatment were poorer (Wang et al., 2006). Evidence persists that the connection between heroin and tuberculosis has more to do with lifestyle than with any biological determinants; in a study of heroin users with tuberculosis treated in Barcelona, a history of prior imprisonment was found to be a much better predictor for infection than either concurrent HIV infection or number of years of heroin use (Manzanera et al., 2000). Pulmonary melioidosis (due to *Burkholderia pseudomallei*), which can resemble tuberculosis on x-ray, also occurs rarely in narcotic addicts (Cooper et al., 2000).

5.10.3.9 Septic Pulmonary Emboli

Septic pulmonary emboli, occasionally associated with pneumothorax, are not an infrequent finding in intravenous abusers. Recurrent emboli of infected material may arise from infected bone or soft tissue at the injection site, leading to septic thrombophlebitis, or even endocarditis. In the past, the most probable source for these emboli was vegetations on the tricuspid valve. Recurrent septic pulmonary emboli should raise the possibility of tricuspid vegetations (Reiner et al., 1976). However, Asian addicts have developed a new way of administering parenteral heroin, and this new pattern of injection could also be the source of emboli and infection.

Heroin injectors in Southeast Asia, particularly Vietnam, use a novel injection process known as *cay ma*, a Vietnamese idiom meaning "injection sac." The "sac" is formed by repeatedly inserting a hypodermic needle into the same area on the skin surface. The area chosen always overlies a large vein. Repeated injection leads to sclerosing of the injection site, in turn leading to the increased formation of fibrocytes and fibroblasts, leading to the production of type I collagen, giving the "sac" an elastic quality. An addict wanting to inject drugs simply inserts the needle through the sac directly into the vein, decreasing the chances for extravasation and increasing bioavailability (Clatts et al., 2007). Although never measured in a controlled study, it seems likely that use of this method would be particularly likely to lead to infection.

5.10.3.10 Emphysema

Emphysematous changes are occasionally seen in the subset of intravenous abusers who inject medications meant for oral use. The process may involve both the upper (Pare et al., 1989) and lower lobes (Smeenk et al., 1990). Rarely, disease is panacinar (Groth et al., 1972). Typically, the upper lobes show the most damage. Intravenous drug abusers with emphysema are in their late 30s, which distinguishes them from those with emphysema due to smoking or α_1-antitrypsin deficiency; victims of the latter tend to be much older. Emphysematous changes have always been more common in stimulant abusers than in individuals taking opiates (Schmidt et al., 1991), but now that simultaneous abuse of both stimulants and narcotics is common practice it may be impossible to determine the etiology of the changes.

5.10.3.11 Cotton Fever

"Cotton fever" is a benign syndrome occasionally seen in intravenous narcotic abusers. Those who filter their "fix" through a wad of cotton may be injecting themselves with limited amounts of endotoxin (Shragg, 1978; Ferguson et al., 1993). Cotton plants are heavily colonized with Gram-negative bacteria, especially *Enterobacter agglomerans* (Rylander and Lundholm, 1978). Endotoxin released by *E. agglomerans* may activate pulmonary

macrophages and neutrophils, and activation of those cells promotes the release of other chemicals, causing fever and leukocytosis. The same symptoms occur in cotton workers who inhale the endotoxin, which floats freely in the air of cotton mills. There is no effective way to immediately differentiate patients who have injected themselves with limited amounts of preformed endotoxin and those who have actually inoculated themselves with *E. agglomerans* or other bacterial agents. Because the latter group is at risk for sepsis or endocarditis, prudence dictates that patients presenting with "cotton fever" should have blood cultures drawn and then be treated, at least initially, with empiric antibiotic therapy.

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5.10.4 Gastrointestinal Disorders

5.10.4.1 Introduction

Liver disease has always been a common finding in intravenous heroin abusers (Edland, 1972; Passarino et al., 2005). Infiltration of the portal triads, though nondiagnostic, is easily demonstrated in the livers of most chronic abusers, as is hepatic steatosis and limited portal fibrosis. In many instances these infiltrates are, in fact, evidence of previously undiagnosed hepatitis. The incidence and prevalence of hepatitis C seems to be declining (Des Jarlais et al., 2005), but hepatitis C remains endemic among drug users (Hagan et al., 2005). Most intravenous drug users with hepatitis C remain asymptomatic, but in a small percentage infection leads to cirrhosis and, even less often, to hepatocellular carcinoma.

5.10.4.2 Bowel Disorders

Opiates that bind the μ receptor decrease gut motility and cause severe constipation or obstipation. The diagnosis of narcotism is easily made from the appearance of the colon at autopsy; it will be distended with hard feces. The other bowel disease associated with opiate abuse is the "body packer" syndrome. Suarez et al. first noted this disorder in a cocaine courier in 1977. The majority of reported cases have involved cocaine rather than heroin (Greenberg et al., 2000), but the incidence of the latter seems to be increasing (Wetli and Mittlemann, 1981). Smugglers, known as "mules," ingest anywhere from 20 to 100 rubberized packets containing multiple-gram quantities of drug. At first, the packets were made from condoms, balloons, or the fingers of surgical gloves. Today more care is devoted to the packaging process than the past, not only because the packets occasionally rupture and kill the courier, but also because the earlier versions of these packets were too easy to see on x-ray (Krishnan and Brown, 1999). Fifteen years have elapsed since the first reports of this syndrome, but methods for detection remain imperfect. Even with contrast enhancement, helical CT scanning may not divulge all of the packets present in a "mule's"

abdomen (Hahn et al., 2004). Smugglers attempt to avoid detection by minimizing the contrast difference between the packets and the surrounding feces. To this end, sophisticated smugglers may drink mineral oil to minimize the contrast differences. Even if the packets are difficult to see with plain films, the presence of packets, if not their actual number, can easily be demonstrated using CT scanning. Urine testing, at least in the case of cocaine smugglers, is often positive even if none of the packets rupture; the rubber wrapping acts as a semi-permeable membrane through which small amounts of the contents of the packet gradually diffuse and enter the bloodstream (Gherardi et al., 1988).

5.10.4.3 Liver Disease

The first paper suggesting heroin-related direct hepatotoxicity was published in 1935 (Gherardi et al., 1988), but substantial confirmatory evidence has not been forthcoming. It is true that when death results from acute narcotic overdose, more often than not the liver is enlarged and congested (often weighing over 2000 g). However, the other abdominal organs are also likely to be congested because congestion is the result of acute cardiac decompensation. Experimental models for heroin and opiate toxicity are virtually nonexistent; however, one study did review histologic and ultrastructural changes in liver sinusoids of otherwise healthy heroin users and found a significant increase in sinusoidal wall surface (Trigueiro de Araujo et al., 1993). The increase is due to hypertrophy of the sinusoidal cells and results in fibrosis within the space of Disse. It is not clear whether these changes represent damage or possibly some protective adaptation. There is, however, some evidence, both clinical and experimental, that buprenorphine is directly hepatotoxic. Buprenorphine is mainly metabolized in the liver by the cytochrome CYP3A4 system, with only 10% excreted by the kidneys. This particular cytochrome is highly polymorphic, leading to great inter-individual variation in how buprenorphine is metabolized. If too much of this drug accumulates, whether because of overdose or poor metabolizer status, mitochondrial damage may occur (Berson et al., 2001; Zuin et al., 2008).

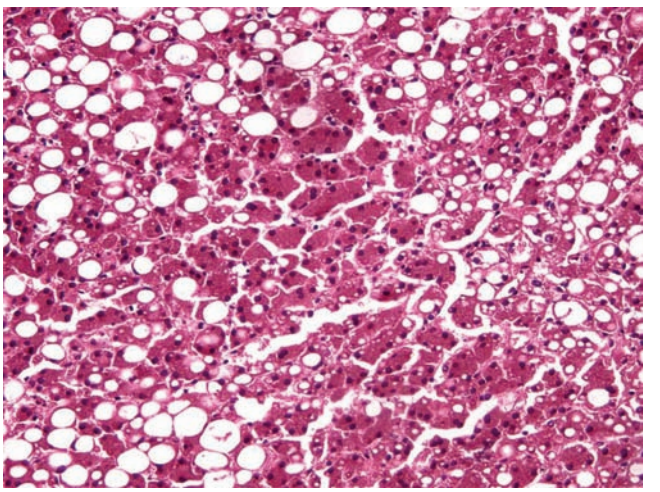


Figure 5.10.4.3.1 Hepatic steatosis. Fatty infiltration of the liver is seen in a high percentage of stimulant and opiate abusers.

5.10.4.4 Porta Hepatis Adenopathy

Enlargement of lymph nodes located in direct proximity to the liver is common and nearly diagnostic for chronic intravenous heroin abuse. The exact incidence of this lesion has never been tabulated, but some have placed it at over 75% (Edland, 1972; Kringsholm and Christoffersen, 1987). The porta hepatis, subpyloric and peripancreatic lymph nodes, the cystic node at the neck of the gallbladder, and other nodes located along the common duct may all be involved. Not infrequently, the gastroduodenal and pancreatoduodenal nodes will also be enlarged. These nodes are gray, firm, and sharply demarcated. The degree of enlargement may be striking. Nodes measuring as much as 2 cm across are not uncommon. Microscopic examination of these nodes shows only a nonspecific pattern of reticuloendothelial hyperplasia.

There are at least three possible explanations for this type of adenopathy, all unproven. Node enlargement could be a reaction to the injection of particulate material. In one series, birefringent material was found in 39% of nodes from confirmed addicts (Table 5.10.3.3.1) (Kringsholm and Christoffersen, 1987). Another possible explanation is recurrent infection. Long before the existence of hepatitis C virus was even recognized, histologic changes consistent with nonspecific reactive hepatitis were observed in more than half the known drug users coming to autopsy (Paties et al., 1987). Deep abdominal lymphadenopathy can also be seen in HIV infection, though usually only in individuals with overt AIDS and secondary malignancy (Subramanyam et al., 1985; Cassani et al., 1993). Finally, there is the possibility that morphine itself might exert some direct effect on lymph nodes, causing them to enlarge. Morphine is easily detectable in nodes draining the portal areas, and in most cases the concentration of morphine is greater in the nodes than it is in the blood. Lymph node morphine concentrations measuring anywhere from 300 to over 8000 ng/mL have been recorded (Nakamura and Choi, 1983).

5.10.4.5 Inflammatory Disease

Inflammation of the portal tracts is a nearly constant autopsy finding in long-term intravenous drug abusers. The incidence was over 92% in one series (Table 5.10.4.5.1) (Paties et al., 1987). The pattern of inflammation seen in addicts is commonly referred to as "triaditis," referring to a predominantly lymphocytic infiltrate frequently admixed with plasma cells. On occasion, neutrophils may also be present, but these infiltrates are usually devoid of eosinophils (Kaplan, 1963; Siegel et al., 1966; Paties et al., 1987).

Lobular inflammation is almost as common as "triaditis" (85%), but necrosis is less common (46%) and, when it occurs, it tends to be widely scattered. The changes in addicts should be distinguishable from those seen in alcoholics, as there is no centrolobular necrosis, no Mallory's hyaline, and only rarely are neutrophils present. True bridging necrosis is also uncommon. Infiltrates in areas of necrosis are composed mainly of monocytes. Steatosis, which was once believed uncommon, can be found over 70% of the time. Fatty accumulations may be microvesicular, macrovesicular, or mixed, but these distinctions are of little diagnostic value. Given the reality of polydrug abuse, multiple abnormalities may be detected on the same slide. There is, for example, some evidence that methamphetamine is associated with steatosis (Karch et al., 1999; Kahraman et al., 2006). Even in the case of an obvious heroin overdose, unless hair testing is performed at autopsy, there is no method by which one can establish the decedent's prior drug history or anticipate what sort of lesions might be encountered.

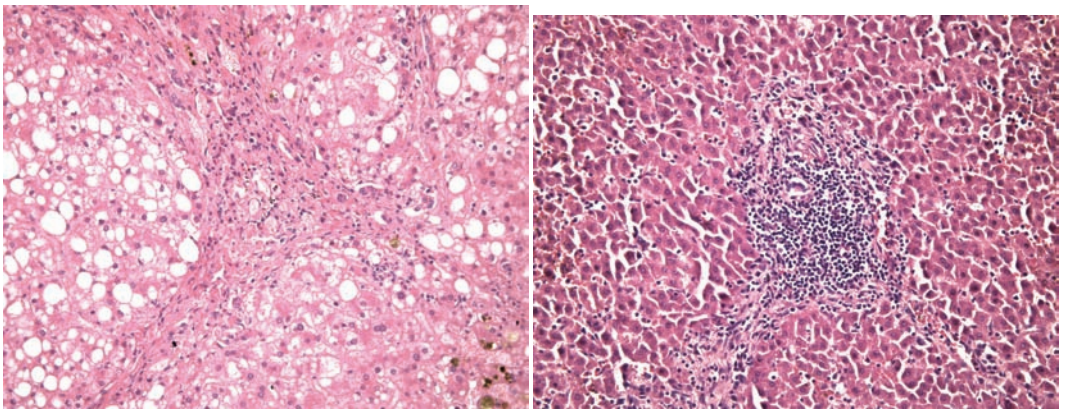
Table 5.10.4.5.1 Frequency of Hepatic Lesions in 150 Randomly Selected Drug Addicts

Lesion	Incidence (%)
Steatosis	70
Portal fibrosis	47
Portal phlogosis	93
Piecemeal necrosis	46
Lymphoid follicles	40
Plasma cells	34
Acidophil bodies	23
Viral antigens	16
Bile duct proliferation	6
Bridging necrosis	5
Granulomas	2
Birefringent material	< 1
Mallory's hyaline	Absent

Note: Patients had a mean age of 23.3 years and were predominantly male (86%).

Source: Adapted from Paties et al. (1987).

Hepatic foreign body granulomas are uncommon, as most injected contaminants are trapped in the pulmonary vascular bed and never enter the systemic circulation. Whether or not birefringent material will be found in the liver or within hepatic nodes depends, in large part, on the population being studied. If the population of addicts consists of crushed pill injectors, then the probability of finding birefringent material is greater. Foreign bodies can become widely disseminated if a septal defect and shunt are present, and users with widespread systemic granulomas have been reported occasionally (Riddick, 1987).



(a) (b)

Figure 5.10.4.5.1 "Triaditis." Infiltration of the portal triads is a common finding in both stimulant and opiate abusers. For many years the etiology of this finding was unclear, but now it is generally accepted that it is hepatitis related. Virtually all heroin users in California are hepatitis C infected. The rate is not much lower in the rest of the country or in Europe. The infiltrate on the left is superimposed on existing cirrhosis and fatty infiltrate. (Photographs courtesy of Vittorio Finneschi, Sienna.)

5.10.4.6 Hepatitis

In Paties et al.'s (1987) autopsy study of 150 addicts, changes consistent with chronic active hepatitis were found in 24% and acute hepatitis was diagnosed in 12%. Most of these individuals had immunohistochemical evidence of one or more viral antigens. In acute cases, scattered foci of parenchymal cell loss with acidophilic necrosis and swelling, along with proliferating reticuloendothelial cells and mononuclear infiltrates, was seen. During the last 10 years, the prevalence in intravenous drug abusers of both hepatitis B and C virus (HBV and HCV, respectively), as well as HIV, increased but the changes being reported are regional and, to some degree, unpredictable. In a study that examined health conditions among an aging cohort of 108 male narcotics addicts in California, half of the sample had abnormal liver function, 94.2% tested positive for hepatitis C, 85.6% for hepatitis B, 3.8% for syphilis, and 27.3% for tuberculosis (Hser et al., 2004). But when seroprevalence was measured in Italian prison inmates, 12.5% of inmates were HIV positive, 8.1% HBV positive, and 31.1% HCV positive, and 25 subjects were found to be positive for both HIV and HCV (Sabbatani et al., 2004). In Germany, blood screening of chronic intravenous drug abusers showed even lower rates for HBV and HCV.

5.10.4.7 Hepatitis A Virus

Ancient Chinese, Greek, and Roman physicians recognized hepatitis A infection, but the first documented report was not published until the 18th century. The prevalence of hepatitis A virus (HAV) is much lower than that of hepatitis B virus (HBV) or hepatitis C virus (HCV), largely because the introduction of a hepatitis A vaccine in 1995 led to a drop in the number of reported cases of hepatitis A in all age groups. In the year 2000, there were 125,000 to 200,000 new cases reported annually. According to the Centers for Disease Control (2006), only 56,000 new cases were reported in 2004 (the most recent year for which data are available). Transmission is primarily fecal–oral, although there have been rare instances of transmission through blood products, including contaminated and reused needles.

The various viruses that cause hepatitis belong to the Picornaviridae family and carry a single strand of RNA. There are seven genotypes. Antibodies of the IgM and IgA classes appear in the serum early in the disease, at about the time of symptom onset. The diagnosis of hepatitis A infection is confirmed by the finding of IgM anti-HAV antibodies, routinely performed using an ELISA test. Treatment is supportive. Intramuscular anti-A gamma globulin is used for passive immune prophylaxis, and there is an efficient vaccine for active immune prophylaxis. Ten to twenty percent of symptomatic patients experience a prolonged or relapsing course of illness and, occasionally, chronic infection has been reported. Fulminant infection, with fatal outcome, occurs in less than 1% of those infected (Pereira and Goncalves, 2003).

5.10.4.8 Hepatitis B Virus

In the U.S. the number of new HBV infections per year has declined from an average of 260,000 in the 1980s to about 60,000 in 2004. The highest rate of disease occurs in 20–49-year-olds, but with the advent of an effective vaccine, the greatest decline has happened among children and adolescents. It is estimated that 1.25 million Americans are chronically infected, and that 20–30% of them acquired their infection in childhood (CDC, 2006).

Estimates suggest that more than 350 million people worldwide (Wright, 2006) are infected, and over 1 million die annually of HBV-related chronic liver disease. Many, perhaps most, of those infected eventually become noninfective. However, if a prolonged immunologic response persists, it may lead to cirrhosis, liver failure, or hepatocellular carcinoma in up to 40% of patients. In endemic areas, where carrier rates are over 5%, most become infected in early childhood or even at birth. Prevalence is low in the U.S., except in particular areas and populations such as immigrants and some native Indians. Sexual contact in childhood is another important means of transmission. Gender, ethnicity, and immune status also influence the risk of chronic infection. Perinatal transmission, which is the most common mode of infection transmission worldwide, can be reduced by appropriate prophylaxis. Five drugs (interferon, lamivudine, adefovir, entecavir, and peginterferon alfa-2a) are now FDA approved for the treatment of HBV (Wright, 2006).

In the U.S., the main routes for transmission are high-risk sexual activity and intravenous drug abuse. In San Francisco, nearly one third of intravenous drug users under the age of 30 report sharing needles, and nearly two thirds report having had more than two sexual partners in the previous month; only 10% reported having received vaccinations for hepatitis B infection (Seal et al., 2000).

Approximately 2.1% of patients with chronic HBV develop cirrhosis each year. The annual incidence of hepatocellular carcinoma is only 0.1% in asymptomatic patients, rising to 1% in patients with chronic HBV, and increasing still further to 3–10%, when cirrhosis is present. Many otherwise healthy HBV-infected patients first come to medical attention only after they have become infected with a different virus, such as hepatitis C, or even A. The combined infection places them at greatly increased risk of fulminant hepatic failure. For reasons that are not clear, HCV superinfection may lead to negative HBV tests (HBsAg positivity) (Chu, 2000).

There are no histopathologic differences between patients with HBV and HCV — not in the severity of inflammatory activity, degree of architectural damage, or appearance of the bile ducts (Thorne et al., 1982). Nor is it possible to distinguish, at least not with any certainty, patients with a hepatotropic virus from those with nonalcoholic hepatic steatosis. More than a third of the viral cases will have steatosis, and 80% have some evidence of necrosis (Goldstein et al., 1995). Some recent reports have suggested that high viral load is associated with poorer patient outcomes (e.g., more rapid progression to cirrhosis and a higher incidence of hepatocellular carcinoma) (Gish and Locarnini, 2006).

5.10.4.9 Hepatitis C Virus

Over 4.1 million Americans (1.6%) have been infected with HCV, and 3.2 million of them remain chronically infected. Most infections with this virus are due to the injection of illicit drugs. The number of new infections per year has now declined from an average of 240,000 in the 1980s to about 26,000 in 2004. Part of the decline is attributable to improved screening of blood for transfusion. In fact, transfusion-related cases now rarely occur (CDC, 2006).

HCV is also caused by a single-stranded RNA virus. In 60–80% of patients, infection with the virus leads to chronic hepatitis. Strong multispecific T-lymphocyte reaction against HCV proteins is associated with viral clearance. Both CD4+ and CD8+ lymphocyte functions are required to clear the virus. In chronic infection, genetic and environmental factors determine the progression of inflammation and fibrosis in individual patients. Of the individual factors that can alter outcome, age, gender, race and alcohol use seem to be

the most important. The development of hepatocellular carcinoma is mainly restricted to patients who already have cirrhosis (Kohla and Bonacini, 2006).

The early stages of HCV infection do not produce any unique histologic features, and the picture may even resemble unrelated disorders, such as nonalcoholic steatohepatitis. Besides fatty change, a mixed cellular inflammatory infiltrate may be seen extending across the lobule, with evidence of hepatocyte injury and fibrosis (Neuschwander-Tetri, 2000). Similar alterations were first noted in intravenous heroin abusers more than 25 years ago and recognized in stimulant abusers a decade later. Depending upon the stage of the disease, biopsies of HCV-infected patients usually provide a variegated picture. The disease may take an acute course, in which case the morphologic features will be those of classical acute hepatitis, usually without bridging necrosis. In particular, features of HCV infections include prominent portal inflammation with lymphoid follicles, hepatic bile duct lesions, and the lobular changes of eosinophilic hepatocytes, eosinophilic bodies, and steatosis (see Section 5.10.4.10) (Dienes et al., 1999).

Occasionally prominent sinusoidal reactions occur. They may have an inflammatory pattern simulating the pattern seen in infectious mononucleosis. Cholestasis, if present, is usually mild, but cholestatic hepatitis can occur. It is rare to encounter submassive or massive hepatocyte necrosis. Within portal areas, lymphoid infiltrates are nearly always present with lymphoid aggregates or follicles; germinal centers are present in 50–78% of cases. The picture becomes even more confusing when there is HIV coinfection (Bach et al., 1992; Scheuer et al., 1992). Often these lymphoid follicles are located close to bile ducts, which manifest various degrees of bile duct damage. Still, it may be hard or even impossible to distinguish these features from those of chronic hepatitis.

5.10.4.10 Steatosis

Steatosis (fatty liver) is a frequent finding in the livers of chronic drug abusers. It is usually attributed to co-ingestion of alcohol, and possibly to the abuse of stimulant drugs. In alcoholics, steatosis may be the only finding in otherwise unexplained cases of sudden death (Chejfec, 2001). Sudden death in patients with steatosis due to chronic alcoholism is the result of an abnormality in the cardiac conduction system that is manifested as a prolonged QT interval. The triggering event in these cases of sudden death is not known, but hypoglycemia, hypophosphatemia, and hypomagnesemia are all considered good candidates.

Fatty liver may also be a marker for the presence of nonalcoholic steatohepatitis (NASH). NASH is a histologic diagnosis applied to a picture that looks very much like alcoholic liver disease, except that it occurs in the absence of alcohol abuse. Liver enzymes, especially aminotransferases, will be elevated, which often establishes the diagnosis. Obesity is a major risk factor and weight loss is usually sufficient to cure the condition. Fifteen to 40 percent of NASH patients will go on to develop hepatic fibrosis, with 1–2% developing cirrhosis (Harrison and Neuschwander-Tetri, 2004). Susceptibility to NASH is greatest in patients carrying the C(-159)T polymorphism in the CD14 gene promoter region (Brun et al., 2006). Insulin resistance may also play a role.

Drugs such as amiodarone, tamoxifen and some antiretroviral drugs can induce both steatosis and NASH. Stavudine and zidovudine are often implicated. NASH occurs because of two different types of mitochondrial dysfunction: (1) the mitochondrial respiratory chain function is disrupted and (2) mitochondrial beta-oxidation of fatty acids is increased, leading to the generation of reactive oxygen species (ROS). Increased ROS leads to lipid peroxidation, and the release of highly reactive aldehydic derivatives,

such as malondialdehyde. Damage to the mitochondrial genome also occurs, and hepatic mitochondrial dysfunction can also induce apoptosis or necrosis, explaining why either or both changes may be detected. If enough products of lipid peroxidation accumulate, several different cytokines (TNF-α, TGF-β, Fas ligand) are produced, causing inflammation, fibrosis, and cell death (Begriche et al., 2006).

5.10.4.11 HIV Infection

The gastrointestinal tract is a less common target for HIV involvement than either the brain or respiratory tract (Jellinger et al., 2000). Nonetheless, liver disease is common in the HIV infected, especially in intravenous drug users, who are likely to be already infected with HCV. The viruses themselves, as well as treatment with dideoxynucleoside analogs (didanosine and stavudine), make the occurrence of steatosis and hepatic fibrosis even more likely (Bani-Sadr et al., 2006; McGovern et al., 2006). HAART has changed the clinical features of HIV infection, and while the number of HIV deaths is decreasing, the proportion involving liver and heart disease is increasing (Palella et al., 2006). In a review of HIV deaths occurring after HAART's introduction, the leading causes of AIDS deaths were (1) AIDS multiple causes (31%), (2) *Mycobacterium avium* complex (18%), (3) *Pneumocystis* pneumonia (10%), and (4) non-Hodgkin's lymphoma (7%). Hepatic disease accounted for 19% of the deaths in this series (Krentz et al., 2005). Data from the U.S. are not available, but in Spain, where there are an estimated 60,000 to 80,000 individuals coinfected with HIV and HCV and 5000 to 10,000 coinfected with HIV and HBV, 10–15% have liver cirrhosis (Miró et al., 2004).

Hepatic disease in HIV patients may be a consequence of alcoholism, or previously existing viral hepatitis, or a manifestation of opportunistic infections or opportunistic tumors, drug therapy, or any combination of the above (Zeremski and Talal, 2006). Some of the opportunistic liver infections include *Mycobacterium avium-intracellulare*, which causes multiple granulomas obstructing the terminal branches of the biliary tree (Glasgow et al., 1988), cytomegalovirus, *Cryptococcus neoformans*, and type 2 herpes simplex virus, to name but a few (Schneiderman, 1988; Ainsworth et al., 2000; Limaye et al., 2000; Sheikh et al., 2000; Small et al., 2000). As HIV infection spreads more widely around the world, infection with even more new organisms, such as leishmaniasis (Singh, 2006), should be anticipated.

HIV-infected patients, like anabolic steroid abusers, may develop peliosis, a condition characterized by the presence of many small, cystic, blood-filled areas, usually in the liver but occasionally in the lungs or other organs. Blood-filled lesions are randomly scattered throughout the liver, often in association with foci of hepatocellular necrosis. The condition was first recognized in conjunction with tuberculosis, but the connection with anabolic steroid abuse has been obvious for some time (Bagheri and Boyer, 1974; Taxy, 1978). Peliosis is the result of infection with *Bartonella quintana*.

Bartonellae are Gram-negative bacteria that grow slowly on culture media enriched with hemin or bovine serum. There are at least 15 species in the genus *Bartonella*, and they can be found anywhere in the world. Bartonellae live, without producing symptoms in animals and insects, by producing a permanent intraerythrocytic bacteremia (Pitassi et al., 2007). Cat scratch disease (CSD) is caused by *Bartonella henselae*. Other *Bartonella* sp. (i.e., *B. quintana*) can cause opportunistic infections (Chomel, 2000; Medkova, 2004). These include bacillary angiomatosis, vasculitis of the liver and spleen (peliosis hepatis, splenis), endocarditis, and others. The frequency of these infections seems to be increasing,

particularly in the HIV infected. Bacteria may or may not be visualized, but the causative organism can be identified by PCR. At autopsy, cut sections of the liver display a "swiss cheese" appearance. Microscopically, two different patterns are recognizable: "parenchymal," consisting of unlined irregular cavities, or "phlebectatic," which is characterized by regular, spherical cavities lined by endothelium and/or fibrosis. Peliosis can cause spontaneous rupture of the liver (or any other affected organ) and at autopsy the appearance could easily be confused with a traumatic injury (Tsokos and Erbersdobler, 2005).

Bartonella infection is easily eradicated by treatment with erythromycin (Santos et al., 2000). Peliosis is closely related to bacillary angiomatosis, but unlike peliosis, bacillary angiomatosis is only seen in individuals with HIV infection (Leong et al., 1992). *Bartonella henselae* is responsible for bacillary angiomatosis, and this disorder is also responsive to treatment with erythromycin, as well as a host of other drugs, including rifampin, ciprofloxacin, gentamicin, trimethoprim and sulfamethoxazole, clarithromycin, and azithromycin (Conrad, 2001).

5.10.4.12 Amyloidosis

Intravenous drug abusers with hepatic amyloid often are HIV infected, and may well also have HCV. Nonetheless, when hepatic amyloid deposition occurs in heroin and cocaine abusers, it is almost invariably a consequence of the chronic suppurative skin lesions, a result of poor hygiene and repeated subcutaneous heroin injection. In heroin addicts, the type of amyloid deposited is unpredictable and of no diagnostic value, nor is the pattern of deposition (Osick et al., 1993).

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5.10.5 Renal Disease

5.10.5.1 Introduction

Chronic use of intravenous narcotics can lead to renal disease. The factors determining individual susceptibility remain vaguely understood, and it is not always clear whether the type of drug injected, or some other factor, is responsible for the disease that occurs. In the U.S., focal segmental glomerulosclerosis in urban black heroin abusers was once the most frequent cause of nephrotic syndrome in heroin addicts, but this disease has never been seen outside of the U.S. (Dettmeyer et al., 1998), and its incidence in the U.S., which began to decline in the early 1990s (Friedman and Tao, 1995), continues to decline (Vupputuri et al., 2004). The type of renal disorder encountered seems to depend on the pattern of drug abuse in any specific area. In some populations of drug users, renal amyloidosis is the predominant histopathologic lesion. In Europe, chronic glomerulonephritis is more likely to be encountered (Dettmeyer et al., 1998). It is also becoming clear that HVC infection, present in most American addicts, may make the picture worse, as may the use of certain therapeutic drugs. Table 5.10.5.1.1 lists the more common renal disorders that have been identified in narcotic abusers.

5.10.5.2 Focal Segmental Glomerulosclerosis

"Focal segmental glomerulosclerosis" (FSGS) is the term used to describe a common lesion seen in a disparate group of progressive renal diseases. Clinicians, however, use the term to describe the clinical syndrome associated with this lesion. Different patterns of focal segmental sclerosis exist, and each is associated with a different disease. Once the diagnosis of FSGS has been made, the pattern present must be distinguished from other possible types of disease, and this is done by looking for the presence of five different patterns that can be seen with the light microscope.

Table 5.10.5.1.1 Renal Disorders in Opiate Abusers

Focal glomerulosclerosis
Membranoproliferative glomerulonephritis
Renal amyloidosis
Necrotizing angiitis with renal involvement
Interstitial nephritis
Acute tubular necrosis due to rhabdomyolysis

FSGS is common in chronic drug abusers. It can also occur in conjunction with many different disorders: immune-complex mediated injury, hypertension, obesity, diabetes, reflux nephropathy, chronic interstitial nephritis (CIN), and human immunodeficiency virus (HIV) infection (Rossini and Fogo, 2004). Nonetheless, if one of the five light microscopic patterns can be identified, rational treatment is possible.

In the early 1970s, reports began to appear describing a relentlessly progressive variety of nephrotic syndrome. It was unresponsive to therapy and terminated in renal failure within a few months to a few years (Rao et al., 1974; Cunningham et al., 1983; Dubrow et al., 1985). The syndrome occurred only in heroin abusers, primarily in blacks, and only in the U.S. The predominant histologic alteration in these individuals was focal segmental glomerulosclerosis (Grishman et al., 1976). By the mid-1990s, however, new cases stopped appearing (Friedman and Tao, 1995). Although it has never been proven, many believe that kidney failure in these individuals was an immune-mediated process. However, many different conditions can lead to a picture that is histologically indistinguishable. Infection with HIV, parvovirus B19, simian virus 40 (D'Agati et al., 1989; Moudgil et al., 1997; Li et al., 2002), and using heroin all lead to the same morphologic picture, although some distinctions may be possible with special staining and/or electronmicroscopy (Rossini and Fogo, 2004).

There are, however, some other histologic features that may be helpful to the nonspecialist: the kidneys of heroin abusers usually show evidence of marked interstitial fibrosis with interstitial infiltrates of lymphocytes and plasma cells. In addition, Bowman's capsule may be markedly thickened. By contrast, the focal segmental glomerulosclerosis that occurs in HIV patients is usually devoid of cellular infiltrates, and HIV patients generally do not have interstitial fibrosis. The results of animal studies suggest that the glomerular and renal epithelial cells are the primary targets of HIV-1 pathogenesis in the kidney, and that the essential pathologic process involves dysregulation of the epithelial cell cycle, with increased proliferation, apoptosis, cellular dedifferentiation, and altered cellular polarity (Genderini et al., 1990; Barisoni et al., 2000).

Even though cases of heroin-associated nephropathy (HAN) have never been reported from Europe, that does not mean that renal disease is rare among European heroin users. A retrospective study of 179 forensic autopsies disclosed that slightly less than two-thirds of the decedents had nonlymphocytic membranoproliferative glomerulonephritis, and half of the specimens contained deposits of IgM antibody, but none showed any evidence of focal glomerulosclerosis. In any individual case it is impossible to say whether IgM antibody deposits are a response to infection with HCV, or HBV, or to some toxic adulterant mixed with street heroin (Dettmeyer et al., 1998). Whatever the cause, progression of the lesions ultimately leads to glomerular destruction and symptomatic renal disease. Advanced lesions consist primarily of intracapillary deposits of eosinophilic, PAS-positive material involving isolated or multiple segments of the glomerulus.

Table 5.10.5.2.1 Histological Differentiation of HAN from HIV

Heroin-Associated Nephropathy (HAN)	Human Immunodeficiency Virus (HIV)
Mesangial hypercellularity	Mesangial hypocellularity
Interstitial infiltrates present	Interstitial infiltrates absent
Interstitial fibrosis prominent	Interstitial fibrosis absent

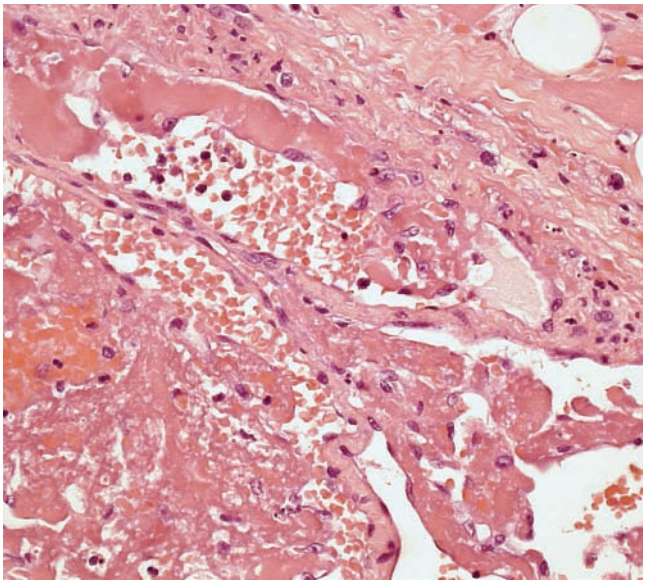
Other infectious diseases can also involve the glomerulus, either directly or indirectly. Many heroin injectors with endocarditis will have focal or diffuse glomerulonephritis as a result of the deposition of circulating antigen–antibody complexes (Rao et al., 1974). The deposition of immune complexes causes diffuse proliferative changes and even classic crescent formation. Most reported cases are in the older literature and occurred in individuals with staphylococcal endocarditis (Louria et al., 1967; Gutman et al., 1972). The true incidence of glomerulonephritis in addicts has never been established, but reports are uncommon. In Sapira's (1968) autopsy study, the incidence of chronic glomerulonephritis in known addicts was 8%. That value may no longer apply today. More recent experience suggests that the incidence of acute renal disease may be much lower. In most cases of endocarditis, renal embolization with infarction is more likely than immune complex deposition. In either case, these lesions rarely cause significant disease. Finally, membranous nephropathy associated with chronic hepatitis B surface antigenemia is a recognized entity (Cunningham et al., 1983), and chronic HCV infection may be associated with mixed cryoglobulinemia which may in turn result in glomerulonephritis (Ramos et al., 1994; Bakir and Dunea, 2001). Like focal glomerulosclerosis in addicts, reports of cryoglobulinemia in addicts have simply disappeared.

5.10.5.3 Necrotizing Angiitis

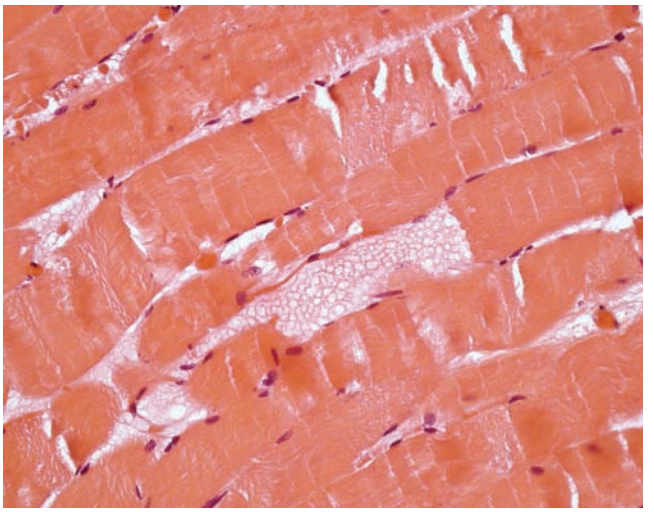
In 1970, Citron et al. described a polyarteritis-like syndrome occurring in intravenous drug abusers who were living in New York City; medium-sized and small arteries in most organs, as well as the arterioles in the brain, were involved. The elastic arteries, capillaries, and veins were all spared. Acute fibrinoid necrosis of the media and intima was observed, along with prominent infiltrates of eosinophils and lymphocytes. Occlusive thrombi were also present. The subacute process was marked by intimal proliferation and luminal narrowing, with saccular aneurysms, especially at vessel bifurcations. Very little evidence suggests that such a disorder ever occurs in opiate abusers, or even that it occurs among today's amphetamine abusers. Most of the patients described by Citron were intravenous amphetamine abusers, or polydrug abusers taking combinations of amphetamine and other drugs. Of the patients Citron studied, none who used only heroin developed the syndrome. Sporadic reports have been appearing ever since (Samuels et al., 1996; Niehaus and Meyer, 1998). Unfortunately, this entity remains in the literature and is frequently invoked to explain otherwise puzzling symptoms or outcomes.

5.10.5.4 Acute Renal Failure and Nontraumatic Rhabdomyolysis

Rhabdomyolysis accounts for a significant proportion of morbidity and mortality among intravenous drug users. The connection was first noted nearly 40 years ago (Richter et al., 1971), and cases have been reported regularly since then, with literally hundreds of case reports in the literature. There have been no reports of this disease in any of the European centers dispensing pharmaceutical-grade heroin and clean needles, suggesting very strongly that the problem is due to toxic agents mixed with the heroin, or to sanitary practices in general (Gschwend et al., 2004). Rhabdomyolysis is caused by a confluence of events, including hypotension, fluid imbalance, and pressure necrosis. The result is muscle destruction and liberation of myoglobin into the bloodstream. However, as Richter et al. (1971) observed, the syndrome can occur in patients who are neither comatose nor subject to muscle compression (Richter et al., 1971); in those cases, it seems likely that mycotoxic adulterants play a role (de Ganc and Stam, 1985; Melandri et al., 1996). Case series have



(a)



(b)

Figure 5.10.5.4.1 Acute rhabdomyolysis in an intravenous heroin abuser. Both slides are from the same patient. (Courtesy of Dr. U. Oehler, Institut für Pathologie, Singen, Akademisches Lehrkrankenhaus der Universitat Freiburg.)

been published suggesting that heroin itself may be directly toxic to muscle, particularly heart muscle, but this conclusion has never been demonstrated by a controlled experiment in animals (Scherrer et al., 1985). Whatever the etiology, the clinical course is always the same with rapid onset of oliguria is followed by azotemia, acidosis, hypophosphatemia, hyperuricemia, and all the other electrolyte and chemical disorders associated with renal failure. Once it is recognized, the condition is rarely fatal, so these patients rarely come to autopsy or even biopsy. There is no reason to suppose that the histologic changes are in any way different from those encountered in cases due to traumatic rhabdomyolysis.

5.10.5.5 Secondary Amyloidosis

The occurrence of renal amyloidosis in a heroin abuser was first described in a paper published in 1978 (Jacob et al., 1978). Since then it has become apparent that the incidence of renal amyloid in heroin addicts is significantly higher than the incidence of amyloid in the general population (Dubrow et al., 1985). There is very little evidence that the incidence of this disorder has increased over the last decade. Amyloid deposits are more commonly found in the kidneys of older, long-term abusers. Amyloid deposition results in massive proteinuria, with or without azotemia. Unlike autosomal dominant hereditary amyloidosis (Granel et al., 2006), amyloid in addicts is an acquired disease. Over 90% of addicts with renal amyloid will have clinical evidence of repeated skin infections with suppurative cutaneous lesions (Meador et al., 1979; Dubrow et al., 1985; Neugarten et al., 1986). Most of the reported cases of renal amyloid in heroin abusers have been from New York City, raising the possibility that some local practice has a role. Evidence suggests that subcutaneous injecting, and the inevitable chronic skin infections that result, are the cause (Campistol et al., 1988). Renal amyloid is hardly unique to heroin users, and a proven mechanism in these other patients is still wanting (Maury and Teppo, 1982). Routine light microscopy with hematoxylin–eosin or PAS staining shows large amounts of eosinophilic material within the glomerulus. Confirmation that the material is in fact amyloid can be obtained by Congo red staining or by using polarizing microscopy. Amyloid has a typical apple-green birefringence. Electron microscopy shows amyloid fibrils.

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5.10.6 Neuropathology

5.10.6.1 Introduction

When the first reports of heroin toxicity were published at the turn of the 20th century, it was thought that opiates were neurotoxic (Nissil, 1897; Creutzfeldt, 1926). Fatty degeneration, particularly of neurons in the deeper layers of the frontal cortex and Ammon's horn, was thought to be diagnostic for morphinism. Subsequent studies have shown that the changes observed were either nonspecific or artifactual. Decades later, it was argued that heroin abusers were uniquely prone to infarction of the basal ganglia (Jervis and Joyce,

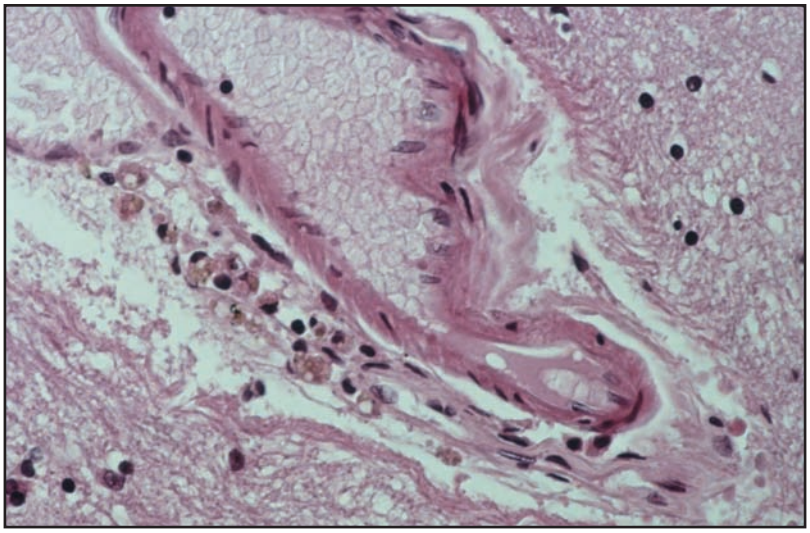

Figure 5.10.6.1.1 Hemosiderin-laden macrophages. Micrograph from the brain of an HIV-negative heroin addict. Similar cells are often seen in the lungs. In both locations, they appear to be the result of repeated intravenous injections of particulate matter. (Courtesy of Professor Francoise Gray, Départment de Pathologie, Hôpital Henri Mondor, Gretiel, France.)

Table 5.10.6.1.1 Neuropathologic Complications of Narcotic Abuse

1. Hypercapnic hypoxia
   a. Cerebral edema
   b. Venous congestion
   c. Focal hemorrhage
2. Infectious
   a. Complications of endocarditis
   b. Complications of HIV infection
      i. Encephalopathy
      ii. Opportunistic infections
      iii. Opportunistic tumors
   c. Phycomycosis
3. Spongiform encephalopathy
4. Transverse myelopathy
5. Peripheral neuropathy
6. Rhabdomyolysis
7. Stroke
8. Necrotizing angiitis
9. Parkinsonism

1948; Strassmann et al., 1969; Hall and Karp, 1973). The nonspecific nature of this finding is also now appreciated. With the exception of perivascular pigment deposition within macrophages, which probably is the result of repeated intravenous injection of foreign material (Figure 5.10.6.1.1) (Gray et al., 1992), no one lesion is diagnostic for narcotic abuse, at least not at the light microscopic level. Noninvasive imaging techniques have disclosed a host of abnormalities, but none of these are grossly evident with the light microscope. Even when morphologic changes are evident, they are almost always a consequence of some infectious process acquired during the process of heroin injection. The better-known neuropathologic complications of narcotic abuse are listed in Table 5.10.6.1.1.

5.10.6.2 Hypoxic Encephalopathy

Deaths from acute opiate toxicity are usually associated with cerebral edema, meningeal congestion, and flattening of the gyri (Adelman and Aronson, 1969; Strassmann et al., 1969; Pearson et al., 1972; Levine and Grimes, 1973; Metter, 1978). As a rule, these deaths occur so rapidly that morphologic evidence of cellular injury is not apparent with the use of immunohistochemical staining. With longer periods of survival, characteristic patterns of tissue necrosis emerge. The explanation is that hypoxic deaths are very quick, and there simply is not time for the characteristic injury patterns to become visible. The injuries seen are not so much a result of hypoxia but rather a result of the arterial hypotension that ensues because of the hypoxia (Brierley et al., 1971). In any event, the earliest visible change is neuronal microvacuolation that can be seen 2–4 hours after death. Neurons maintain their shape, but vacuoles may form within the cytoplasm, then the neurons themselves become distorted and the cell body shrunken and the cytoplasm becomes intensely eosinophilic. This change persists for at least six hours (Brierley et al., 1971; Graham and Adams, 1971). Should the victim survive an episode of acute hypoxia, the changes become progressively

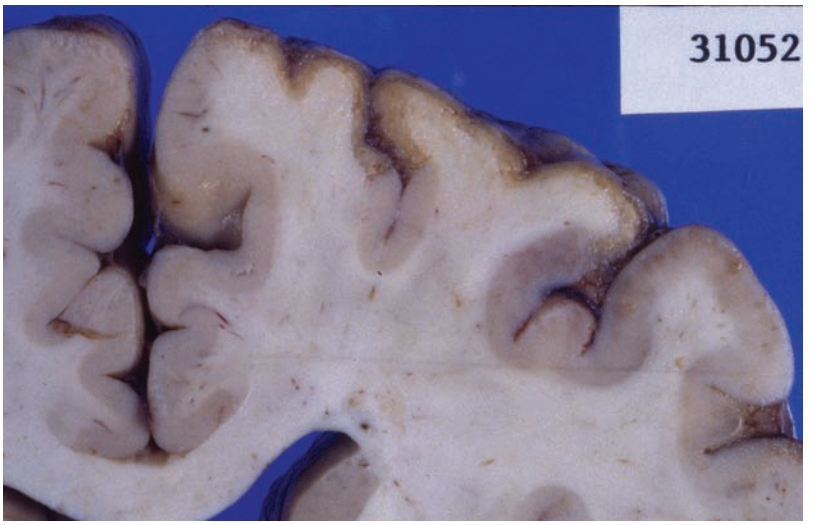

Figure 5.10.6.1.1 Laminar necrosis. When a drop in blood pressure is partial and sustained, laminar necrosis may be prominent.

worse. Acute swelling of glial cells may occur very rapidly, but several days must elapse before there is any noticeable proliferation of astrocytes.

The three recognizable phases of neuronal death can each be related to a different molecular event occurring in the dying cell. Excess activation of ionotropic glutamate receptors causes the influx and accumulation of Ca^{2+} and Na^{+} ions (Annunziato et al., 2007). That process leads to rapid swelling and subsequent neuronal death. Oxidative stress occurs due to the accumulation of reactive oxygen and nitrogen species. Finally, apoptosis or programmed cell death comes into play, but is not, at first, apparent microscopically (Won et al., 2002).

Under certain circumstances, the pattern of injury may reveal a great deal about the clinical events that preceded death. A major abrupt decrease in systemic blood pressure typically produces necrosis in the arterial boundary zones between the major arteries. The area most frequently involved is the parieto-occipital region (Figure 5.10.6.2.1). If the drop in blood pressure is more gradual and longer in duration, then laminar necrosis of the calcarine cortex may be seen. This lesion is also prominent in the deeper layers of the cerebellum (Greenfield et al., 2002).

A pattern of continuous necrosis, often accentuated in arterial border zones, may also be encountered. The Purkinje cells of the cerebellum are particularly vulnerable to injury, as are the cells of Sommer's sector, located in the hippocampus (Adams et al., 1966). Some time must elapse before these patterns become apparent. If death occurs within 3–6 hours, the probability of detecting anything but chronic changes is small. With the passage of more time, typical eosinophilic degenerative changes become apparent in scattered neurons. The cells of the caudate and putamen may or may not be involved. If changes are to be detected in those nuclei, then sampling from multiple sites will be required.

These gross findings are consistent with single photon emission computed tomography (SPECT) studies of opiate addicts, where baseline perfusion reductions are apparent in the frontal and parietal cortices, while at the same time flow to the thalamus is increased. When these same individuals are given naloxone, cerebral perfusion to these areas decreases (Krystal et al., 1995). Chronic hypoxic episodes from repeated drug overdoses predictably result in necrosis and scarring of the hippocampus. However, the diagnostic value of this observation is limited by the fact that most heroin abusers today are in fact polydrug abusers. For example, hippocampal atrophy is common in alcoholics, particularly women (Agartz et al., 1999), as is reduced cross sectional area of the corpus callosum (Pfefferbaum et al., 1996). These acute lesions may be superimposed on pre-existing chronic or subacute changes. Thus, zones of parietal-occipital necrosis may be seen along with areas of laminar necrosis, suggesting an initial acute hypotensive episode followed by prolonged hypotension and decreased cerebral flow. This type of pattern is not uncommon in heroin addicts.

5.10.6.3 Neurologic Complications of Endocarditis

Narcotics abusers develop infectious diseases because of their unhealthy lifestyles, because their injection techniques are not sterile, because chronic opiate use causes immunosuppression, and occasionally because the heroin they are injecting is contaminated (Hagmann, 2000). Some very bizarre infections, such as aspergillosis (Morrow et al., 1983), nocardiosis (Hershewe et al., 1988), phycomycosis (Adelman and Aronson, 1969), chromoblastosis (Kasantikul et al., 1988), and mucormycosis (Masucci et al., 1982) have been reported. Generally, these exotic infections are not major causes of morbidity. On the other hand, septicemia, endocarditis, and even necrotizing fasciitis are increasingly common,

and all three disorders may have neurologic sequelae. In fact, the incidence of neurologic complications resulting from subacute endocarditis has changed hardly at all since the introduction of antibiotics (Ziment, 1969).

Vegetations on the aortic and tricuspid valves can shed, producing disseminated microabscesses throughout the central nervous system, with smaller lesions centering around septic emboli that lodge in terminal vessels, producing cerebral infarction (Louria et al., 1967; Dreyer and Fields, 1973; Grindal et al., 1978). In more severe cases, foci of metastatic suppuration may be seen throughout the leptomeninges. Intracranial hemorrhage secondary to the rupture of mycotic aneurysms can occur, but even today such events remain relatively uncommon (Jones et al., 1969; Chu et al., 2005). The main sites of bacterial infection of the brain are in the capillaries and small venules. They are usually surrounded by perivascular collections of polymorphonuclear leukocytes. As a rule, microabscesses do not produce severe or focal symptoms, and their presence may often be camouflaged by other more obvious disease processes (Biller et al., 1986).

5.10.6.4 Complications of HIV Infection

In addition to the obvious detrimental systemic effects on the immune system, HIV-1 enters the brain almost as soon as the infection begins. Once established in the brain, the virus can induce a variety of severe and debilitating neurological disorders and opportunistic infections, many of which lead ultimately to dementation. Infected peripheral macrophages (and other cell types, though macrophages predominate) infiltrate the brain and provoke a series of deleterious responses that may be very widespread. Viral and host factors, such as the viral strain and the way that the host's immune system responds, have a huge influence on how disease will progress.

In addition, HIV-1-dependent diseases in the periphery may have a substantial effect on central nervous system (CNS) pathology. In the CNS, HIV-1 initiates activation of chemokine receptors, inflammatory mediators, extracellular matrix-degrading enzymes, and glutamate receptor-mediated excitotoxicity. These agents, in turn, activate numerous downstream signaling pathways that disrupt neuronal and glial function. Although treatment has improved remarkably in the last 5 years, thanks largely to the introduction of HAART, most of the advances have been in the treatment of peripheral disease. There still is no cure for HIV dementation (Kaul and Lipton, 2006).

HIV-1 is a neurotrophic lentivirus. When it enters the CNS of adults and children, a family of different clinical syndromes emerge. In adults the result is AIDS–dementia complex, while in children the most common effect is HIV-1-associated progressive encephalopathy. The neuropathologic findings seen in the pediatric patients include impaired brain growth, reactive gliosis, myelin pallor, calcifications of the basal ganglia, cortical and cerebral atrophy with neuronal loss and ventricular enlargement, and abnormalities of the cerebral vasculature. In adults the picture is quite different. Disease is frequently more advanced and complicated by opportunistic infections (Schwartz and Major, 2006). Thus, even with HAART, HIV-infected intravenous drug abusers still can be expected to have CNS abnormalities detectable at autopsy. The lung is the organ most frequently involved by complications of HIV, though the actual incidence of brain involvement is not much lower than in the lung (Masliah et al., 2000). It is hard to say how much lower, as there has been no large autopsy series published since the introduction of HAART. AIDS-associated neurological disorders can be divided into four groups: (1) AIDS encephalopathy, due to the direct effects of the virus itself; (2) opportunistic viral, fungal, parasitic, and bacterial

infections; (3) opportunistic neoplastic processes, particularly primary brain lymphoma; and (4) HIV-related lymphocytic meningitis. The most frequently seen abnormality in the brains of AIDS patients is atrophy with diffuse or focal lesions in the white matter (Mossakowski and Zelman, 1997). Necrosis and pallor of the myelin is usually obvious with necrosis likely to be especially obvious in the centrum semiovale. Diffuse or focal neuronal loss in the caudate and putamen may also occur (Navia et al., 1986). In cases where diffuse white matter damage is present, multifocal microgranulomatous lesions and multinucleated giant cells can be seen.

5.10.6.5 Primary Phycomycosis

Fungal brain infection is usually associated with poorly controlled diabetes or the presence of some disorder, such as leukemia, that depresses immunity (Song et al., 2006). A handful of reports have linked phycomycosis to intravenous drug abuse, usually in heroin users (Adelman and Aronson, 1969; Hameroff et al., 1970; Chmel and Grieco, 1973; Masucci et al., 1982; Kasantikul et al., 1988; Micozzi and Wetli 1985; Carpenter et al., 2007). Rarely it occurs in those who are immunosuppressed, and there are scattered reports of this infection involving the HIV infected (Samanta et al., 2001; Perez-Uribe et al., 2005). Infection begins in the nasal cavities, then invades the turbinates and the veins that drain them, extends into the paranasal sinuses, and eventually reaches the orbit. In other instances, the infection reaches the brain by a hematogenous route. It may be that the brain supplies a particularly conducive environment in which the fungus can grow. Whatever the route of infection, the result is edema, proptosis, and ultimately destruction of the trigeminal and facial nerves. At least in drug addicts, the disease follows a fulminant course. Most patients die within two weeks of onset. Diagnosis in life may require brain biopsy, because fungi are not detected in the cerebrospinal fluid. Both CT and MRI scanning may be invaluable for early diagnosis (Moll et al., 1994). Lesions are usually multiple and symmetric, and involve the basal ganglia. Material removed at surgery or autopsy is composed of aggregates of macrophages, lymphocytes, and multinucleated giant cells. Even routine H&E staining will show the broad, branching, nonseparate fungal mycelia (Schwartz et al., 1982).

5.10.6.6 Spongiform Leukoencephalopathy

In 1982, an epidemic outbreak of spongiform leukoencephalopathy occurred in the Netherlands (Wolters et al., 1982; Haan et al., 1983). Nearly 50 patients were involved, and the only factor common to all those affected was that they were addicts who smoked heroin. In most cases, the disorder ran a 2–3-month course. In the initial stages, motor restlessness and apathy, with obvious cerebellar signs, rapidly gave way to hypertonic hemiplegia or even quadriplegia. In some cases, patients developed myoclonic jerks or choreoathetoid movements. Onset of hemiplegia seemed to mark a turning point in the progression of the disease. Half of the patients stabilized or improved while the other half progressed to a final, fatal stage with central pyrexia, spastic paresis, and akinetic mutism. These individuals died of respiratory failure. Magnetic resonance imaging typically disclosed symmetrical lesions in the white matter of the cerebrum, cerebellum, and midbrain. Selective involvement of the corticospinal tract, the solitary tract, and the lemniscus medialis also has been found. In 1997, the first cases were reported in the U.S., and additional cases have been reported from around the world since then (Kriegstein et al., 1999).

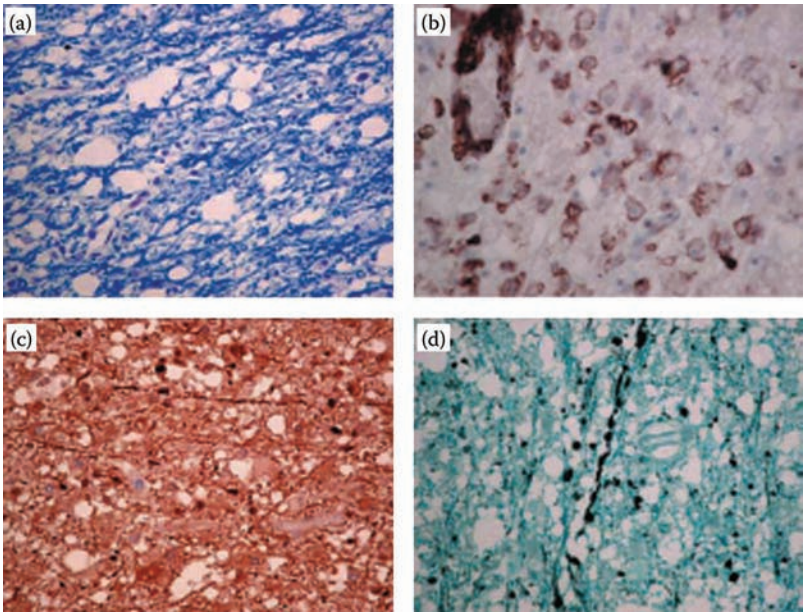

Figure 5.10.6.6.1 Spongiform leukoencephalopathy. Vacuolar change in the deep frontal white matter (a) (Luxol–Fast Blue) associated with variable macrophage infiltrate (b) (common leukocyte immunostain); axonal loss (c) (neurofilament) and degenerating axons with spheroid formation (d) (amyloid precursor protein). (Reproduced from Ryan et al., *J. Neurol. Neurosurg. Psychiatry*, 2005, 76(7):1014–6, with permission.)

All of the patients in the original series reported from the Netherlands had obvious cerebral edema with flattening of the convolutions and brain weights of 1380–2560 g. In all cases, microscopic examination showed damaged white matter filled with vacuoles. In some areas, the vacuoles had coalesced to form larger cavities. Around the cavities could be seen a fine network of attenuated myelin. The number of oligodendroglia was reduced, but no myelin breakdown products were evident. Inflammatory cells were also absent. Electron microscopy done in several cases showed multivacuolar degeneration of the oligodendroglia, with swollen mitochondria and distended endoplasmic reticulum. Although not visible with light microscopy, electron micrographs also showed abnormalities of the myelin lamellae and axoplasm, which also contained swollen, abnormal mitochondria. Magnetic resonance studies have demonstrated the presence of elevated lactate concentrations in white matter, raising the possibility that the underlying abnormality in these individuals may be mitochondrial dysfunction.

Evidence continues to accumulate that the defect is, indeed, mitochondrial. In addition to a direct toxic effect on myelin and mitochondrial dysfunction, it is possible that hypoxic injury may also contribute to the axonal damage and spongiform white matter change (Vella et al., 2003). It is currently believed that a latent period exists between toxin exposure and the development of symptoms and signs. The Dutch even have a name for this phenomenon and refer to it as "coasting" — similar time delays have been observed with other toxins (Berger et al., 1992).

The "coasting" phenomenon may account for the negative toxicology results that are inevitably found in each of the cases reported. The suggestion is that the toxic compounds

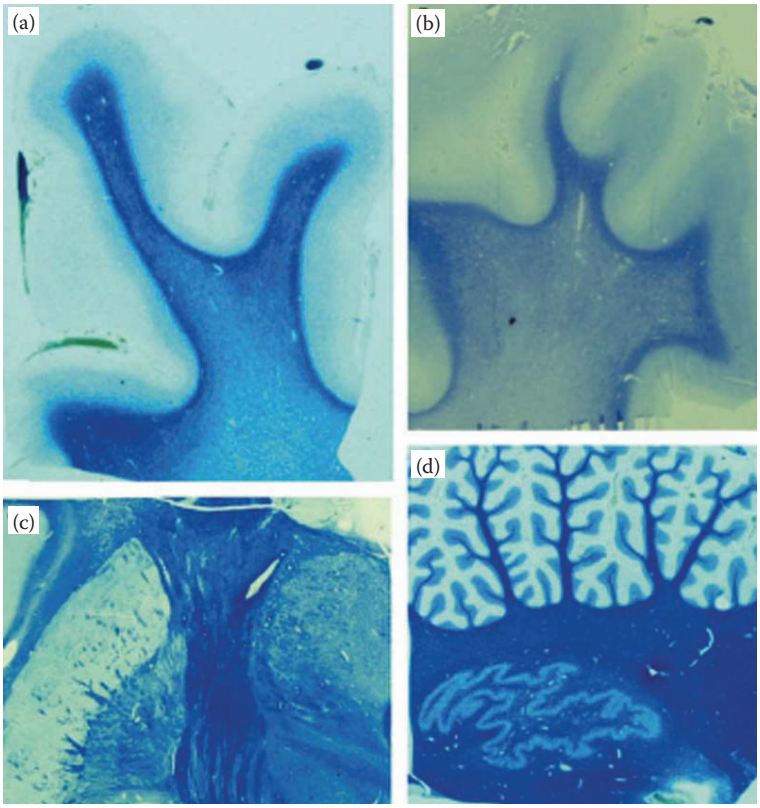

Figure 5.10.6.6.2 Spongiform leukoencephalopathy. Myelin pallor in frontal (a) and parietal (b) white matter, contrasted with normal myelin staining intensity in internal capsule (c) and cerebellum (d). Note preservation of subcortical U fibers in the frontal and parietal white matter. (All stained with Luxol–Fast Blue.) (Reproduced from Ryan et al., *J. Neurol. Neurosurg. Psychiatry*, 2005, 76(7):1014–6,with permission.)

may be deposited and stored in lipid-rich myelin and then slowly released, resulting in ongoing tissue destruction and symptom progression. It has also been suggested that the toxin, whatever it is, may induce a metabolic change that persists long after the toxin itself is gone. Under this scenario, patients would only become symptomatic after the toxin is gone, and there is nothing to detect over and above the clinical symptoms themselves.

Chemical analyses of samples of local heroin used by the addicts affected by this disorder have shown only the usual adulterants: caffeine, lidocaine, procaine, phenobarbital, and methaqualone. None of these agents has ever been shown to be neurotoxic, and no one seriously believes that a toxic adulterant is responsible for these cases.

The changes in these individuals are easily distinguishable from those seen in AIDS-associated progressive multifocal leukoencephalopathy (PML), a disorder that may be present in 10% or more of autopsied patients with AIDS (Aksamit et al., 1990). Before the AIDS epidemic, PML was rare, usually seen only in association with leukemia and lymphoma. PML is due to infection with JC virus, a papovavirus that most people are exposed to in childhood (Sweeney et al., 1994). In spongiform leukoencephalopathy demyelination with oligodendroglial and astrocytic pathology is always evident. Changes tend to be widespread with predominant oligodendroglial abnormalities (Mossakowski and

Zelman, 2000). Changes in the cerebellum can be very striking, and some have suggested that it represents a different form of disease (Gullotta et al., 1991). Changes also occur in the microvasculature, including mural thickening, pleomorphism of the endothelial cells, and prominent perivascular collections of HIV-positive monocytes and multinucleated cells. Even with treatment, survival in patients with AIDS-associated progressive multifocal leukoencephalopathy is poor, with a 6-month survival rate of less than 10%.

5.10.6.7 Transverse Myelitis

This rare entity was first described in 1926. Its etiology also remains undetermined, but its occurrence has been noted in conjunction with a heterogeneous group of disorders, including viral infections, AIDS, systemic lupus erythematosus, smallpox vaccination, trauma, extreme physical exertion, and heroin abuse. The association with heroin abuse was first noted in 1968 (Richter and Rosenberg, 1968). Since the index report, transverse myelitis has been reported on a number of occasions, but the incidence of this disorder is really not very high and, in spite of the increased availability of heroin, the incidence of this disorder does not seem to be increasing; only eight new case reports have been published since 1995 (Yang et al., 1995; Bernasconi et al., 1996; Sverzut et al., 1998; Derkinderen et al., 2000; McCreary et al., 2000; Nyffeler et al., 2003; Sahni et al., 2008).

The patients first described by Richter had all stopped taking heroin, many for a period of months, and they developed neurologic symptoms only after they began injecting heroin again. In all of the cases reported, onset of symptoms was quite rapid, ranging anywhere from a few hours to a few days. Victims developed flaccid paralysis and complete sensory loss ascending from the lower extremities to thoracic or even cervical levels. In the addict subpopulation, at least, fairly rapid improvement seems to be the norm, though residual deficits usually are seen. Myelography in acute cases is unremarkable (Arlazoroff et al., 1989). The few cases that have been studied with modern imaging techniques have all shown infection to be the cause (spinal cord abscess, spondylodiscitis, and epidural abscess), but in the few cases where autopsy has been performed the only findings have been extensive but nonspecific necrosis. Cerebrospinal fluid analysis has also been unremarkable.

Transverse myelitis was initially thought to be the result of anterior spinal artery occlusion, but when more cases were studied it became evident that the circulation in other territories could also be involved. Even ventral pontine disease has been observed which, when it occurs, is usually the result of an isolated vascular accident within the spinal cord (Hall and Karp, 1973). In the case of narcotic abusers, it is not clear whether that accident is the result of thromboembolic phenomena, some sort of inflammatory vascular disease, or a toxic manifestation due to some contaminant injected along with the heroin. It is clear that heroin administration decreases blood flow to specific areas of the brain (Wang et al., 1997), a condition that would favor both ischemic damage as well as making the area more vulnerable to infection.

5.10.6.8 Peripheral Neuropathy

Unsterile injections may lead to local infection with nerve involvement, as can the injection of toxic adulterants. Neuropathy associated with rhabdomyolysis is a well-recognized entity, but nerve injury in heroin abusers is a fairly frequent occurrence anyway; in one series peripheral neuropathy accounted for nearly 50% of heroin-related admissions. Nerve injury may be an indirect result of elevated compartment pressure or a direct result

of ischemia that can occur if compartment pressures rise high enough. Unperceived pressure or traction can also cause plexus or peripheral nerve injuries, even without muscle swelling (Kaku and So, 1990). Evidence suggests that at one time or another, all of these mechanisms come into play.

In addition, HIV-positive patients are subject to peripheral and autonomic neuropathies, probably due to direct invasion by the virus, though it has also been suggested that an autoimmune etiology might be possible. Distal sensory polyneuropathy (DSP) is thought to be the most common neurologic complication of HIV infection, though the risk factors for its occurrence remain poorly defined, particularly since the advent of HAART. Established risk factors, including CD4 cell count, plasma HIV RNA, and use of dideoxynucleoside antiretrovirals, seem to be unrelated to the progression of distal sensory polyneuropathy and treatment remains unsatisfactory (Simpson et al., 2006). Nerve injuries in addicts have never been studied in an autopsy series.

5.10.6.9 Rhabdomyolysis

Heroin had been available for nearly 70 years before anyone observed that its intravenous injection occasionally gave rise to acute myoglobinuria (Richter et al., 1971). Since then additional cases have also been reported (Koffler et al., 1976; Gibb and Shaw, 1985; Yang et al., 1995; Abdullah et al., 2006), but controlled studies have never been done. Nor is the incidence of rhabdomyolysis in heroin users known with any precision, but the number of cases does not seem to be increasing.

In some instances, the cause of muscle injury is obvious: pressure necrosis from the weight of the patient's own body while the individual is lying comatose (Schreiber et al., 1972), but few of the reported cases can be explained in this fashion (Chan et al., 1995). Cases with unequivocal evidence of concurrent cardiac necrosis, where the etiology could hardly have been pressure necrosis, have been reported (Schwartzfarb et al., 1977; Wynne et al., 1977; Scherrer et al., 1985; Larpin et al., 1990; Melandri et al., 1996). A direct effect of heroin or of an adulterant seems to be responsible.

There is animal evidence suggesting that heroin is directly myotoxic (Pena et al., 1993). Lesions produced in this model include hypercontraction of muscle fibers and disruption of the sarcoplasmic reticulum. In the experimental model, eosinophils are frequently observed around the degenerating fibers, suggesting that muscle destruction might be the result of a hypersensitivity reaction. Rhabdomyolysis has also been reported after rapid opioid detoxification with subcutaneous naltrexone maintenance therapy, although the possible mechanisms in that case are not known (Chanmugam et al., 2000).

Patients usually complain of muscle weakness, pain, and swelling that begins several hours to several days after using heroin. The muscles of the lower limbs are involved more often than those of the upper limbs. Associated neurologic complaints and neuropathies occur in conjunction with heroin-induced rhabdomyolysis although it should be noted that not all neuropathies in heroin users are a consequence of rhabdomyolysis. The presence of symmetric brachial neuropathy should raise the suspicion of lead poisoning, a rare consequence of using contaminated heroin (Antonini et al., 1989a, b).

The diagnosis of rhabdomyolysis is clearly suggested by the presence of muscle swelling and elevated creatinine phosphokinase. However, muscle swelling need not always be evident, and the presence of myoglobin in the serum is an unreliable indicator at best, because myoglobin is rapidly cleared from the plasma. Early in the course of the disease,

laboratory tests will disclose marked elevations of creatinine phosphokinase and aldolase. Some individuals may complain of dark urine, and about half will eventually develop full-blown renal failure, with typical laboratory findings.

Since the introduction of HAART, muscular complications of HIV infection have become more common, and should not be dismissed as diagnostic possibilities (Bakir and Dunea, 2001). These complications can roughly be divided into four groups: (1) HIV-associated myopathies and related conditions including polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis syndrome, HIV-wasting syndrome, vasculitis, myasthenic syndromes, and chronic fatigue; (2) iatrogenic conditions including mitochondrial myopathies, HIV-associated lipodystrophy syndrome, and immune restoration syndrome; (3) opportunistic infections and tumor infiltrations of skeletal muscle; and (4) rhabdomyolysis (Authier et al., 2005).

5.10.6.10 Stroke

Stroke occurs in heroin users, but in spite of very substantial increases in the number of heroin abusers, the reported number of case reports has not increased proportionally. In most instances, the etiology is obscure. It was once thought that the re-exposure of addicts to heroin after a period of abstinence might lead to vascular hypersensitivity reactions (Rumbaugh et al., 1971) but the theory has never been substantiated.

Necrotizing angiitis (see Section 5.10.5.3) can certainly cause cerebral infarction (Citron et al., 1970), but there is rarely evidence for this disorder, and the few cases that have been reported have been almost exclusively in methamphetamine abusers (Toffol et al., 1987). The decline in reported new cases of necrotizing angiitis, even among methamphetamine abusers, suggests that when cases did occur they may have been the result of some toxic contaminants mixed with the heroin (Citron et al., 1970). As often as not, angiographic studies in heroin-abusing stroke victims will be normal (Herskowitz and Gross, 1973). If any change is in evidence it all, it is likely to be spasm (Niehaus and Meyer, 1998).

Table 5.10.6.10.1 lists additional mechanisms that can cause stroke in opiate abusers. The same mechanisms that cause stroke in stimulant abusers could also cause stroke in opiate abusers but, barring vasoactive contaminants, vasospasm seems unlikely in opiate users, as opiates share no common pharmacologic mechanisms with stimulants and do not (except for pentazocine) cause elevations in circulating catecholamines. A likely mechanism in many cases of stroke is positional vascular compression. One report describes a 35-year-old addict with dense hemiparesis. Regional flow studies demonstrated severe hyperemia of the entire carotid territory on the affected side, but normal vessels on angiography.

Table 5.10.6.10.1 Possible Etiologies for Stroke in Opiate Abusers

Thromboembolism
Thrombocytopenia
Vasculitis
Septic emboli
Hypotension
Secondary to arrhythmia
Secondary to decreased cardiac output
Secondary to peripheral vasodilation
Positional vascular compression

Such localized hyperemia is often seen following restoration of flow in stroke patients and after cerebral spasm (Caplan et al., 1982). Generalized hyperemia is more likely to be observed after global ischemia. Stroke in these patients may be the result of an unfortunate set of circumstances. Large doses of narcotic lead to hypotension, decreased respiration, and generalized cerebral ischemia. If the carotid artery is then compressed by lying in the wrong position, perfusion may be lowered beneath some critical level, and stroke could occur in an already ischemic brain (Olson and Winther, 1990). In the absence of experimental evidence, such an explanation is speculative, but it could well account for an occasional infarct.

Hemorrhagic stroke in heroin abusers is the result of a deranged clotting mechanism, as might be encountered in cases of fulminant hepatitis or in individuals with AIDS-associated thrombocytopenia (Brust and Richter, 1976; Chevalier et al., 1995). Rupture of a mycotic aneurysm or underlying AV malformation is also possible but still uncommon enough to be reportable (Dreyer and Fields, 1973; Brust and Richter, 1976; Jensen et al., 1990; Bartolomei et al., 1992; Niehaus and Meyer, 1998). This is in contrast to hemorrhagic stroke in cocaine users, where victims commonly bleed from a pre-existing malformation or aneurysm.

5.10.6.11 Parkinsonism

MPPP is a potent meperidine analog. When it is synthesized by clandestine chemists, inattention to detail occasionally results in the production of a byproduct known as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Figure 5.10.6.11.1). MPTP is itself nontoxic, but astrocytes oxidize MPTP to a pyridinium metabolite (MPP+) that can damage neuronal cells. Dopaminergic neurons are particularly vulnerable to MPTP toxicity because they accumulate MPP+ and retain it for prolonged periods. Two pathways of astrocytic MPP+ formation have been identified, one utilizing monoamine oxidase (MAO) and the other requiring the presence of transition metals, though experimental studies suggest MAO plays a minor role in human MPTP toxicity (DiMonte et al., 1996; Przedborski and Jackson-Lewis, 1998). Whatever the metabolic route of MPTP production, it results in selective destruction of dopaminergic neurons in the substantia nigra and the globus pallidus (Jenner et al., 1992).

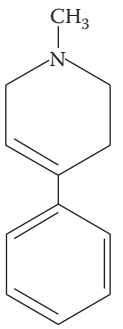

Figure 5.10.6.11.1 MPTP. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) molecule.

There is new evidence that genetic predisposition plays a role in the etiology of this disease. Exposure to MPTP selectively kills dopamine neurons in the substantia nigra, and genetic models incorporating mutations in the α-synuclein gene that cause disease in human patients appear to operate in the same fashion. Novel gene expression changes may well underlie both conditions. There is evidence that the MPTP model and the disease share a gene expression profile. Although hundreds of differentially expressed genes have been identified in experimental models and human disease, only a few overlap human and animal changes in the substantia nigra: dopamine phenotype, synaptic function, and mitochondrial metabolism. The presynaptic end of the neuron has been identified as a primary site of injury (Miller and Federoff, 2005).

If taken in sufficient quantity, MPTP can produce all the classic symptoms of parkinsonism including resting tremor, rigidity, bradykinesia, and postural instability. At least three isolated outbreaks of recognized MPTP toxicity have been reported. The first reported case occurred in 1979 (Davis et al., 1979). A graduate student who had been synthesizing and intravenously injecting MPPP for six months made a mistake in synthesis. Shortly after he injected the new batch of what he believed to be MPPP he developed symptomatic Parkinson's disease. Later analysis by authorities disclosed that the student had in fact produced a mixture of MPPP and MPTP. His symptoms responded well to treatment, but he died of an unrelated drug overdose some two years later. Detailed neuropathologic examination of his brain disclosed degenerative changes within the substantia nigra that were confined to zona compacta. A marked astrocytic response and focal glial scarring were present along with abundant collections of extraneuronal melanin pigment.

A second cluster of patients was reported in 1983. Four patients bought what they thought was "synthetic heroin" and within a matter of days developed striking features of parkinsonism. Analysis of material injected by these individuals showed they had been using mixtures of MPTP and MPPP (2.5–3.2% MPTP, 0.3–27% MPPP) (Langston et al., 1983). Since the original report, 22 additional cases with less florid symptoms have been identified, all stemming from exposure to product from the same clandestine lab that had been operating in Northern California (Tetrud et al., 1989). The results of follow-up epidemiological studies indicate that during the three-year period from 1982 to 1985, over 500 individuals were exposed to MPTP, probably all from the same clandestine lab (Ruttenber, 1991).

Additional cases stemming from exposure to products from other sources were reported in 1983 and 1984, and continue to be reported episodically (Kramer et al., 1998). The first of these was in a non-drug-abusing chemist exposed to MPTP at work. He developed classic symptoms of parkinsonism that responded to treatment. The most recent reported case was in a polydrug-abusing chemist who responded to initial treatment but died of unrelated causes two years later. This individual preferred to snort his drug, but his parkinsonian symptoms were no less severe than those of the intravenous users. When he accidentally drowned, examination of his brain was perfunctory, and the substantia nigra was never even examined (Wright et al., 1984).

Other than the fact that different age groups are involved (average age in the 30s vs. average age in the 60s), there is little to distinguish parkinsonism occurring after MPTP exposure from parkinsonism in the general population. Initial symptoms may be mild or quite severe, though some evidence suggests that tremor is somewhat less common in the drug abusers. It is an open question whether additional new cases are likely to be encountered. Only sporadic seizures of samples containing MPTP have been reported. The most recent was in 1985, the same year that production of MPTP was made illegal. A closely related analog of MPTP called PEPTP (1,2-phenylethyl-1,2,5,6-tetrahydropyridine) can be generated as a byproduct of PCP production and may well possess the same neurotoxicity as MPTP, but no cases of parkinsonism attributable to PCP contamination have been reported.

5.10.6.12 Seizures

Seizures have been attributed to a long list of different opioids: meperidine (Szeto et al., 1977; Goetting and Thirman, 1985), fentanyl (Fujimoto et al., 2003), alfentanil (Katz et al., 1988), sufentanil (Brian and Seifen, 1987), tramadol (Koussa et al., 2003), pentazocine (Jackson et al., 1971), normeperidine in those without renal failure (Gordon et al.,

2000), and even high dose morphine (Hagen and Swanson, 1997), as well as extradural morphine (Borgeat et al., 1988), the latter occurring only in known epileptics. A single case report described a seizure in a 7-year-old with sickle cell disease after the administration of codeine (Borgeat et al., 1988). Another case report describes seizures after oxycodone administration in individuals known to be seizure-prone (Klein et al., 2005). The mechanism by which opiates can produce seizures is not known. One proposed theory is that the opiates may inhibit activity within the locus ceruleus (Tempelhoff et al., 1990). As DNA screening for CYP26 polymorphisms becomes more readily available, it seems probable that more cases of untoward reactions will be recognized in users of these drugs, and that they are the result of the individual's metabolizer status. Perhaps as much as 10% of the population may not be able to metabolize drugs such as oxycodone in an efficient manner, resulting in high levels, and possibly seizures.

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5.10.7 Hormonal and Immune Alterations

The idea that opioids modulate the immune system is not new. In the late 19th century, Joan Cantacuzene used morphine to suppress cellular immunity and lower the resistance of guinea pigs to bacterial infection. While exogenous opioids mediate immunosuppression, endogenous opiates exert opposite actions. Acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity.

Opiates behave like cytokines, modulating the immune response by interaction with their receptors in the central nervous system and in the periphery. Potential mechanisms

Table 5.10.7.1 Immune Abnormalities in Opiate Abusers

Depressed E-rosette formation (in vitro)
Depressed cutaneous sensitivity
Depressed mitogenic response
Elevated CD4 cells
Elevated CD4/CD8 ratio
Elevated levels of CD4 receptor
Elevated neopterin levels
Elevated soluble interleukin-2 receptors
Elevated γ-interferon levels

Source: Adapted from Pillai et al. (1991).

by which central opiates modulate peripheral immune functions may involve both the hypothalamic–pituitary–adrenal axis and the autonomic nervous system. The presence of opioid receptors outside the central nervous system is increasingly recognized. These receptors have been identified not only in peripheral nerves but also in immune inflammatory cells. The immunosuppression mediated by opiates may explain the increased incidence of infection in heroin addicts. Opiates may also promote immunodeficiency virus infection by decreasing the secretion of α and β chemokines (important inhibitory cytokines for the expression of HIV) and at the same time increasing the expression of chemoreceptors CCR5 and CCR3, coreceptors for the virus. The fact that peripheral immunosuppression is mediated at least in part by opioid receptors located in the central nervous system and that intrathecally administered opioids do not exert the same immunosuppressive effects may have important clinical implications for those patients receiving long-term opioid therapy for malignant and nonmalignant pain.

Heroin abusers are subject to a number of hormonal alterations, mostly involving sexual and reproductive functions. Studies have demonstrated decreased levels of both testosterone and luteinizing hormone, with testicular atrophy and impotence (Mirin et al., 1980; Mendelson and Mello, 1982). Opiates induce hyperprolactinemia in both experimental animals and in chronic opiate abusers (Tolis et al., 1978). Compared to non-drug-using controls, long-term heroin users have decreased levels of parathyroid hormone and decreased levels of testosterone. As a consequence, they have abnormal bone and mineral metabolism, with decreased vertebral bone density (Pedrazzoni et al., 1993). The etiology of these changes is unknown, but there is some evidence that opiates may act directly on the pituitary. When compared to controls, the response of β-endorphin and adrenocorticotropic hormone (ACTH) to metyrapone administration in addicts is significantly blunted, suggesting that the chronic stimulation of opiate receptors in some way impairs the function of the anterior pituitary gland (Vescovi et al., 1990). This notion is also supported by the observation that pituitary volume in healthy men addicted to heroin and cocaine, when assessed by MRI, is nearly twice as great as the volume observed in healthy controls (Teoh et al., 1993).

Long before the advent of HIV, it was generally agreed that heroin addicts had higher rates of both opportunistic infection and cancer than the population at large (Sapira, 1968). Studies done in the early 1900s proved that morphine acts directly on lymphocytes (Atchard et al., 1909; Terry and Pellens, 1928) but, of course, no one had any idea why, let alone how endogenous opioids act to decrease immunity! During the early years of the

20th century, following the advent of intravenous narcotic abuse, other abnormalities of the immune system were also recognized. These included generalized lymphadenopathy (Halpern and Rho, 1966), elevated serum immunoglobulins (Kreek et al., 1972), lymphocytosis (Sapira, 1968), and abnormal T-cell rosette formation (McDonough et al., 1980).

It has become increasingly evident that morphine alters the immune response of most of the major cell types involved. Its actions include depressing the activity of natural killer (NK) cells, depressing T-cell function (manifested by either inhibition or induction of delayed-type hypersensitivity reactions), altering cytotoxic T-cell activity, and causing abnormal expression of T-cell antigen (Eisenstein and Hilburger, 1998). Both acute and chronic administration of opioids inhibit humoral and cellular immune responses, including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity. Opiates behave like cytokines, modulating the immune response by interaction with their receptors in the central nervous system and in the periphery.

Morphine downregulates phagocytic cell function in both human peripheral blood mononuclear cells (PBMCs) and human polymorphonucleocytes. Not only does exposure to morphine inhibit phagocytosis, but it also disrupts chemotactic responses and interleukin production, and at the same time it inhibits the generation of activated oxygen intermediates and activation of the arachidonic acid cascade. How all these actions are accomplished is not known, but the existence of an in vivo neural–immune control mechanism seems to be increasingly likely (Weber and Pert, 1989; Eisenstein and Hilburger, 1998).

Opioids suppress immune function by acting within the central nervous system to increase the activity of the hypothalamic–pituitary–adrenal axis, and activate the sympathetic nervous system. Catecholamine and adrenocorticoid production are responsible for many of the observed immunomodulatory effects that occur following opioid administration. In general, the sympathetic nervous system has been shown to play a role in regulating lymphocyte proliferation and natural killer cell activity as well as several other parameters of immune function (Hall et al., 1998).

The lifestyles of addicts are partially responsible for some of their immune abnormalities. Chronic infection with HIV and other viruses contributes. Hepatitis C is now the most common chronic bloodborne infection (from 35 to 95% of all injection drug users in any given area), and infection with this virus is associated with many nonspecific immune changes (Dalekos et al., 1993; Garfein et al., 1998). In addition to indirectly controlling mast cell function via cytokine release, opiates can also bind directly to specific receptor sites on the mast cell membranes (Fjellner and Hagermark, 1984). One result is that histamine release can lead to bronchospasm, hives, and flushing.

Opiate-induced histamine release is IgG antibody related, and it has occasionally been referred to as "pseudoallergy" (Biagini et al., 1992). However, it is now clear that opioids bind to G-coupled proteins on mast cell walls, and that their stimulation leads to histamine release (Ramkissoon et al., 2006). Urticaria seen in heroin users is simply histamine-induced dermal edema occurring secondary to vasodilatation. Histamine produces a prototypic, short-lived urticaria, but other molecules, including prostaglandins, leukotrienes, cytokines, and chemokines are also produced by activated mast cells and also play a role. Urticaria in addicts occurs after binding of IgG autoantibodies to IgE and/or to the receptor for IgE molecules on mast cells. Mast cell activation can also result from type III hypersensitivity reactions via binding of circulating immune complexes to mast cells expressing Fc receptors for IgG and IgM. Under some circumstances, even

T-cells cause histamine release. When that occurs, the process is referred to as a type IV hypersensitivity reaction. Nonimmunological urticarias due to mast cell activation are also possible; these mechanisms, however, play no role in the narcotic user (Hennino et al., 2006).

IgM antibodies specific for morphine and codeine have also been demonstrated. In two studies, IgM antibodies were detected in 50–60% of addicts tested (Gamaleya et al., 1993). Most addicts have elevated serum immunoglobulins, especially IgM. The immunoglobulin elevations are thought to be a consequence of the repeated injections of antigenic material (Cherubin and Millian, 1968). This abnormal state reverts when heroin use is discontinued, unless, of course, chronic HCV infection has supervened. The immunosuppression mediated by opiates may explain the increased incidence of infection in heroin addicts. Opiates may also promote immunodeficiency virus infection by decreasing the secretion of α and β chemokines (important inhibitory cytokines for the expression of HIV) and at the same time increasing the expression of chemoreceptors CCR5 and CCR3, co-receptors for the virus (Vallejo et al., 2004).

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5.10.8 Bone and Soft Tissue Disorders

5.10.8.1 Introduction

Fibrous myopathy is a recognized complication of both chronic pentazocine abuse and meperidine abuse (Levin and Engel, 1975; Rousseau et al., 1979). Evidence suggests fibrosis may also be an undesirable consequence of repeated heroin injections (Mastaglia, 1982). Controlled studies of heroin users in methadone replacement programs have also shown osteopenia, which does not improve within the first year of abstinence. At the same time, concentrations of osteoresorption marker (type I collagen cross-linked telopeptide) and osteoformation markers (osteocalcin and propeptide of type I collagen) are increased in comparison to normal controls and methadone users after one year of treatment (averages 814 ng/L, 43.1 μg/L, 76.4 μg/L, respectively). Serum testosterone levels in heroin-addicted men are significantly decreased (3.3 nmol/L). After one year of treatment, osteoresorption measures return to normal, but testosterone levels do not (Wilczek and Stepan, 2003). The explanation has to do with the presence of μ receptors on human osteoblasts. In tissue culture, human osteoblast-like cells express the three main types of opioid receptors. Osteocalcin synthesis is significantly inhibited by high concentrations of the μ agonists such as morphine, but it is restored to normal when osteoblastic cells are incubated simultaneously with naloxone, the narcotics antagonist. So far as is known, no opioid agonist has any effect on alkaline phosphatase secretion (Perez-Castrillon et al., 2000).

Female heroin users infected with the HIV virus develop significantly worse osteoporosis than HIV-infected women who are not heroin users (Teichmann et al., 2000). Osteopenia is, in any event, common in HIV infection, and it just becomes worse in those treated with protease inhibitors. Serum levels of parathyroid hormone and 1,25-dihydroxyvitamin D (1,25(OH2)D) are significantly lower in HIV-infected women, even prior to therapy, as is

serum osteocalcin (Teichmann et al., 2003). However, most bone and soft tissue disorders seen in opiate abusers are infectious in origin and are, in fact, the main reason that drug abusers are hospitalized (Cherubin et al., 1972; White, 1973). This situation has changed very little in the last half century (Harris and Young, 2002; Warner and Srinivasan, 2004; Lucas, 2005). It is the mundane conditions such as cellulitis, soft tissue abscess, and septic thrombophlebitis that most often bring the abusers to medical attention.

5.10.8.2 Bone and Joint Infections

In most instances, the source of bone and soft tissue infections is either the solution used to dissolve the drug or the abuser's own skin flora (Tuazon et al., 1974). Once a contaminated needle is introduced into the body, infection may spread locally or hematogenously. With repeated injection, insoluble substances may accumulate or disseminate. Typically, this leads to injection site related abscesses, cellulitis, necrotizing fasciitis, and chronic ulceration (Harris and Young, 2002; Warner and Srinivasan, 2004). The pattern of sites most frequently infected, and the organism responsible for the infection depend on the injection sites.

In the past, the skeletal sites most frequently infected were the vertebral column and sternoarticular joints (Goldin et al., 1973; Gifford et al., 1975; Bayer et al., 1977) but reports of these complications seem to be diminishing. This may be a direct consequence of needle exchange programs. In more recent studies the extremities, especially the left knee (Chandrasekar and Molinari, 1987), were found to be involved much more than the sternoarticular joint. The shift seems to be due to the fact that more addicts are injecting themselves in the groin and the fact that infection is most likely to occur in the structures closest to the injection site. Because most individuals are right handed, the left side is most frequently injected.

In early studies, *Pseudomonas aeruginosa* was responsible for most (more than 80%) of the joint and bone infections in intravenous drug abusers (Waldvogel and Papageorgiou, 1980), but any number of organisms may be responsible. More recently, *Clostridium* species have been responsible for widespread illness, particularly in subcutaneous and intramuscular injectors. Infectious discitis caused by *Enterobacter cloacae* has been described in both HIV-positive and -negative intravenous drug users (Marce et al., 1993), as have infections with *Candida*, however, the number of reported cases seems to have declined markedly, possibly because of public health measures (Lafont et al., 1994; Jensenius et al., 1999; Derkinderen et al., 2000).

Heroin users occasionally develop osteomyelitis of the cervical spine (Silvani et al. 1987), an infection that almost never occurs in non-drug abusers. More often than not, the infectious agent is *Staphylococcus*, introduced when addicts inject into the great veins of the neck (Endress et al., 1990). In life, CT scanning will show an inflammatory reaction about the carotid sheath, with prevertebral soft-tissue masses adjacent to the areas of bone destruction. *Candida* bone infections, on the other hand, almost never involve the cervical spine. While such infections may occur in intravenous abusers, they are more commonly seen in immunosuppressed patients in general, and those with indwelling catheters in particular (Eisen et al., 2000). Just why the blood supply should favor the lower lumbar spine is not obvious, but almost all cases of *Candida* osteomyelitis have involved the lower lumbar area. The reason appears to be that infection spreads into the endplate of the vertebral body, which is supplied by ventral branches of the spinal arteries. *C. albicans* is usually the responsible agent (Almekinders and Greene, 1991), but the more exotic infections also must be considered (Owen et al., 1992).

The prevalence of tuberculosis is increased in heroin users, especially those who are HIV seropositive. Extrapulmonary involvement, with or without obvious lung lesions, is seen in 15% of cases (Alvarez and McCabe, 1984), and in many of those the extrapulmonary site involved is osteoarticular, usually the vertebral bodies and their intervertebral discs. Involvement of the bony arch usually produces a compression syndrome. Fortunately, involvement of the vertebral arch is rare, but it has been reported in intravenous heroin users (Martos et al., 1989). Pott's disease is also a rarity, but it does occur. Clinically, tuberculous osteomyelitis of the spine can be distinguished from pyogenic or fungal infection by its less indolent onset. Patients with Pott's disease can be expected to present with fever, back pain, weight loss, and night sweats.

5.10.8.3 Soft Tissue Infections

Skin and soft tissue infections are common among intravenous abusers, but there is nothing to distinguish their appearance from similar lesions in non-drug users. The bacteriology of these infections is controversial, with conflicting results being reported from different centers. In one series, most infections were polymicrobial, and only 19% had isolates of *S. aureus*, the remainder being anaerobes, including *Clostridium* and *Bacteroides* spp. (Webb and Thadepalli, 1979). Other series have also described polymicrobial infections, with *S. aureus* present in almost every case, along with enteric Gram-negative aerobes and oropharyngeal organisms (Orangio et al., 1984). In more recently published series, *Streptococcus* seems to be as common as any of the more unusual agents (Hoeger et al., 1996; Mackenzie et al., 2000). *E. corrodens*, a Gram-negative anaerobe, part of the normal flora in the mouth, is occasionally seen when addicts use their saliva to dilute or dissolve their drug for injection (Brooks et al., 1974; Zumwalt and Franz, 1983). Femoral drug injection is associated not only with infection and bacteremia, but also with iliofemoral thrombosis (Mackenzie et al., 2000).

5.10.8.4 Fibrous Myopathy

This condition occurs primarily with pentazocine abuse and is the result of a foreign body reaction with crystallization of the drug within the muscle (Levin and Engel, 1975), but since that drug has decreased in popularity, so has the incidence of fibrosis. There have been no new reports of this disorder in more than a decade. When it occurs, woody infiltration, cutaneous ulcers, and abnormal pigmentation can be seen surrounding areas of repeated pentazocine injection. Clinically, the syndrome is marked by limitation of motion, neuropathic symptoms, and even muscle and joint contractures (Kim and Song, 1996). The contractures and neuropathic symptoms are secondary to nerve damage and reflex sympathetic dystrophy. Microscopically, birefringent crystals may be found in the areas of most intense induration (Adams et al., 1983). Myocytes are destroyed and replaced with dense, fibrotic tissue. Inflammatory infiltrates may or may not be present. Dystrophic calcification may be sufficiently pronounced to detect with x-ray or sonography.

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Dissociative Anesthetics

6

6.1 Introduction

The drugs described in this chapter — phencyclidine (PCP), ketamine, γ-hydroxybutyrate (GHB), dextromethorphan, and *Salvia divinorum* — are hallucinogens. The first four appear to operate through the same mechanism: these drugs are all NMDA channel blockers (Jordan et al., 2006), and, at least in vitro, none of them binds to the D_2 dopamine receptor. Though their psychological effects appear to be grossly similar, Salvia is a pure κ blocker and it operates via completely different mechanisms than the other group members. The first three drugs are legitimately used as dissociative anesthetics, while dextromethorphan is a cough remedy that shares many of the same properties as the first three agents. Salvia is a pure hallucinogen. It has no known anesthetic effects (nor would any be expected given its known method of action). Patients who are given PCP or ketamine remain conscious but exhibit no apparent response to surgical pain. The same is also true of GHB. None of these anesthetic agents causes muscle relaxation. As a consequence, when any of these drugs is used at surgery (either human or animal) other agents must be administered to produce muscle relaxation. Salvia induces neither anesthesia nor muscle relaxation.

Compared to heroin and cocaine, none of these drugs is widely used or abused. Perhaps more importantly, Salvia is a legal drug and it enjoys brisk sales over the Internet. No Salvia-related fatalities have ever been reported, but occasional episodes of death and morbidity have been attributed to the other dissociative drugs. Except for dextromethorphan, there are no relevant data, either on the number of deaths or even the number of people abusing these drugs. In 1999 only 98 PCP-related deaths were reported in the Drug Abuse Warning Network (DAWN) survey, and even fewer were attributed to ketamine (21). Neither Salvia nor GHB were even mentioned. Clearly, deaths from GHB overdose do occur, but how often is anyone's guess. According to the "new" DAWN report (SAMHSA, 2007), dextromethorphan abuse accounted for 12,584 emergency room visits in 2004, which amounts to 0.7% of all drug-related ER visits.

Interest in all of these drugs, especially the legal ones, is increasing. The Emergency Room component of the 1999 DAWN report lists 2973 GHB-related visits, compared to only 55 in 1994. Ketamine-related visits increased from 19 in 1995 to 396 in 1999 (SAMHSA, 2007). Massive doses of PCP can cause rhabdomyolysis and death, while large doses of GHB can induce transient (but potentially fatal) respiratory paralysis. However, the principal toxic effects exerted by these drugs are psychiatric. Considerable attention has been devoted to the use of GHB in drug-facilitated sexual assault, but the magnitude of the problem is not known. The few studies that have been done suggest that the incidence is very low (ElSohly and Salamone, 1999).

Methamphetamine and PCP both induce psychotic states that closely resemble schizophrenia, as can ketamine (Krystal et al., 1994). NMDA glutamate receptor antagonists, including PCP, ketamine, GHB and dextromethorphan, produce a dose-dependent loss of inhibition in which NMDA antagonists abolish GABAergic inhibition. The result is the simultaneous excessive release of acetylcholine and glutamate, and the NMDA receptor becomes less functional. Progressive increases in the severity of NMDA receptor hypofunction within the brain result in abnormal brain function. Under-excitation of NMDA receptors, induced by even relatively low doses of NMDA antagonist drugs, can lead to specific forms of memory dysfunction, with or without clinical psychosis. However, if NMDA function is severely reduced, the result can be a clinical syndrome very similar to a psychotic exacerbation of schizophrenia. Large doses, administered over a long time, can lead to histopathologic changes (Farber, 2003).

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6.2 Phencyclidine (PCP)

Synonyms: PCP, angel dust, supergrass, killer weed, embalming fluid, rocket fuel, wack, ozone

Chemical name: 1-(1-phenylcyclohexyl) piperidine

Formula: $C_{17}H_{25}N$

Molecular weight: 243.39 daltons

Metabolism: Hepatic inactivation by hydroxylation and glucuronidation. Approximately 75% is excreted in the urine within 10 days, the remainder in the feces. Phencyclidine inactivates CYP2B6.

Bioavailability:
Smoking: 100% (Cook et al., 1982b)
Oral: 72%

C_{max}: 2.7–2.9 ng/mL (Cook et al., 1982a, b)

T_{max}: 2.5 hours after 1 mg oral dose (Cook et al., 1982b)

$T_{½}$: 24 ± 7 hours (Cook et al., 1982a, b), 17.5–48 hours (Cook et al., 1983)

V_{ss}: 6 L/kg

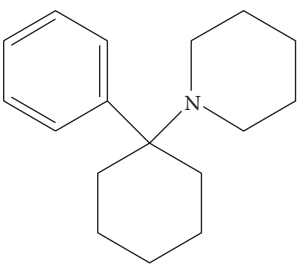

Figure 6.2.1 Phencyclidine molecule.

Interactions: any drug metabolized by CYP2B6, particularly chemotherapeutic agents such as cyclophosphamide (Tran et al., 2008)

Cook, C. E., Brine, D. R. et al. (1982a). Phencyclidine disposition after intravenous and oral doses, *Clin. Pharmacol. Ther.,* 31(5), pp. 625–34.
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Cook, C. E., Perez-Reyes, M. et al. (1983). Phencyclidine disposition in humans after small doses of radiolabeled drug, *Fed. Proc.,* 42(9), pp. 2566–9.
Tran, A., Bournerias, F. et al. (2008). Serious haematological toxicity of cyclophosphamide in relation to CYP2B6, GSTA1 and GSTP1 polymorphisms, *Br. J. Clin. Pharmacol.,* 65(2), pp. 279–80.

6.2.1 Incidence

Phencyclidine (PCP), or PCP in combination with another drug, was the 34th most frequent cause of drug-related deaths reported in both the 1998 and 1999 DAWN surveys. In 1999, 98 deaths were reported, amounting to 0.84% of the drug-related deaths reported to the government that year. PCP use is, in fact, not very frequent. In the first half of 1999 there were 2154 emergency room visits for treatment of PCP-related illness, 10,447 for methamphetamine, and 84,320 for cocaine-related illness (a ratio of nearly 40:1). Mentions of PCP and PCP in combination with other drugs began to decline in 1996 and have been stable since then, with no change in 1997 or in the first half of 1998 (Kissin et al., 2000). The 2006 "new" DAWN report lists 8928 PCP-related emergency room visits out of a total 1,997,993 for all drugs, amounting to less than 0.06% of visits (SAMHSA, 2006). The fact that the Drug Enforcement Administration (DEA) does not even tabulate PCP seizures in any of its publications (see, for example, the DEA *Briefing Book* prepared for the Office of Congressional and Public Affairs in October 1999), suggests that, in the U.S. at least, production of and interest in this drug continues, but at a very low level.

6.2.2 History

Phencyclidine (1-(1)-phenylcyclohexyl piperidine, or PCP) was discovered by pharmacologists at Parke-Davis in 1956 (Greifenstein et al., 1958). It was first sold as an intravenous anesthetic called Sernyl® (Collins et al., 1960). In recommended doses, PCP produces neither respiratory nor cardiovascular depression and, at least in animals, is devoid of cellular toxicity (Chen and Weston, 1960). Use in humans had to be discontinued when it was discovered that 10–20% of patients given PCP became delirious and/or unmanageable for many hours after surgery (Greifenstein et al., 1958). In 1978, PCP was transferred to Schedule III under the Controlled Substance Act. In the United Kingdom legal production was discontinued entirely, and ketamine was labeled as a class c drug in January 2006. In Canada and Hong Kong it is classified as a schedule I drug.

The first reports of recreational abuse came from California during the late 1960s; however, the drug rapidly developed a reputation for causing antisocial, violent behavior (Fauman et al., 1976). Abuse was still prevalent during the 1970s and early 1980s. But, if the "new" DAWN report is to be believed, interest in this drug is no longer very great, although availability is increasing. Criminal groups produce most of the PCP available throughout the U.S., especially in California, primarily in the Los Angeles area, though labs have also been raided in Northern California. Massive labs were confiscated in Southern California

in 2005 and 2006. Still, the number of laboratories seized amounts to less than a dozen each year.

6.2.3 Clandestine Laboratories

The synthetic route preferred by clandestine chemists begins with the condensation of 1-phenylcyclopentylamine with pentamethylene dibromide (Kalir et al., 1969). It is also possible to make PCP from piperidine, though acquiring this compound is becoming more difficult since it now falls under international controls. The direct conversion of piperidine to PCP is also possible (the piperidine ring is the central core of the PCP molecule). The synthesis is simple, and the economics attractive. Given an average street dose of 1–10 mg, 1 kg of piperidine can be converted to anywhere from 100,000 to 1,000,000 doses (INCB, 1999).

Many different PCP derivatives have been produced, some psychoactive and some not. The resultant psychological effects are at least partly related to how well the synthetic derivatives bind the σ receptor (Loustau-Then et al., 1997). Some of these derivatives are used in positron emission scanning in order to help localize σ receptors and to study the effects of prolonged drug use.

Bulk phencyclidine is sold either in liquid or powder form. Street drug may be anywhere from 50 to 100% pure. The ethyl ether and other volatile solvents used in the production process give off a distinctive odor that often gives away the location of the laboratory. The fumes are also quite explosive, making illicit PCP production a risky affair. PCC (1-piperidinocyclohexanecarbonitrile) appears in poorly synthesized batches as a by-product of the manufacturing process. When present in significant amounts (10–25%) it may induce abdominal cramps, bloody emesis, diarrhea, or even coma. PCC is an unstable compound; it is degraded fairly quickly to piperidine. As a result, contaminated batches of PCP can sometimes be recognized by the strong fishy odor of piperidine. On heating (smoking), PCC liberates hydrogen cyanide, so the possibility of cyanide poisoning in PCP smokers must also be considered.

6.2.4 Routes of Administration

Phencyclidine can be smoked, snorted, injected, or swallowed. Results of animal studies indicate that the effects produced are essentially the same whether the drug is smoked or taken intravenously (Meng et al., 1996). That observation probably explains why smoking PCP has become the preferred route of administration. Cigarettes soaked in PCP were very popular during the 1980s. In some parts of the country, PCP-laced cigarettes were called "Sherms," because the cigarette preferred for soaking purposes was produced by the Nat Sherman Tobacco Company. The term may still be in use, but there are many other synonyms.

Parsley leaves soaked in PCP are occasionally substituted for marijuana leaves, with little apparent difference in result. Studies on human volunteers who smoked 100 mg of (^{3}H)-phencyclidine indicate that most smoked PCP is absorbed. Peak blood levels occur 15–20 minutes after smoking, but a second peak occurs slightly later, suggesting delayed release from the lungs. The maximum concentration achieved in this particular smoking study was 1.5 ng/mL. The mean half-life of the smoked PCP was 24 hours ± 7 hours (Cook et al., 1982b). Oral absorption is nearly as good as intravenous administration. Volunteers given 1 mg orally had average PCP concentrations of 2.7 ng/mL. Plasma concentrations after 1 mg given intravenously were 2.9 ng/mL (Cook et al., 1982a).

Peak plasma levels after oral dosing occur at 2.5 hours, although levels are near maximal at 1.5 hours. After both oral and intravenous administration, a 1–2-hour plateau period follows, during which plasma levels remain relatively stable (Cook et al., 1983). Skin absorption does occur and can result in positive urine tests, possibly at levels exceeding National Institute on Drug Abuse (NIDA) cutoffs. In one study, a crime lab chemist was found to have a PCP level of 28 ng/mL (Pitts et al., 1981). Just how relevant all of these measurements are to the problems of clinical intoxication is not entirely clear. The amount used for the volunteer studies was probably very small when compared to the amounts taken by abusers. When PCP was first introduced as a legal anesthetic, sophisticated techniques for measuring blood levels were not available. Now that such techniques exist, ethical considerations prevent the administration of PCP in quantities that accurately reflect street practices.

6.2.5 Metabolism

PCP is a noncompetitive antagonist of glutamate-type NMDA receptors (Su, 1991). In low doses it binds to a specific receptor in the NMDA channel. This may explain why low doses produce only mild inebriation. At higher doses, PCP acts as an indirect agonist at σ sites, and can produce long-lasting psychotic episodes.

In many ways, PCP's effects resemble those of methamphetamine. The resemblance is explained by the fact that both PCP and methamphetamine block dopamine uptake. On a weight-per-weight basis, PCP is nearly as potent a re-uptake blocker as methamphetamine. And, like methamphetamine, PCP also causes the release of stored catecholamines, though in this respect, at least, it is much less potent than methamphetamine (McMahon and Cunningham, 2003; Takamatsu et al., 2006). In the rat model, PCP has a biphasic course of action. High doses lead to an initial increase in brain glucose metabolism at 3 hours, followed by decreased glucose utilization at 24 hours, and a return to normal at 48 hours. Low doses of PCP cause no initial changes in glucose metabolism, but at 24 hours glucose uptake is depressed and remains so for some time (Gao et al., 1993). PCP also inhibits ATP-sensitive K^+ channels in both heart and brain, increasing the inward Ca^{2+} current and blocking the outward K^+ current (Kokoz et al., 1994). This is an important effect because there is evidence that σ-1 receptors in the heart are directly coupled to K^+ channels in intracardiac neurons, and that activation of σ-1 receptors depresses the excitability of intracardiac neurons, thereby blocking parasympathetic input to the heart (Zhang and Cuevas, 2005).

PCP causes selective neurotoxicity in the cortex of animals following subchronic administration (Wang et al., 2005), but it also plays a central role in the processes of neuroprotection and cognition. PCP is also implicated in the pathophysiology of multiple neurological and neuropsychiatric disorders including Parkinson's disease, Huntington's chorea, schizophrenia, alcoholism, and stroke (Waterhouse, 2003). In animals, treatment with PCP induces apoptosis of striatal neurons, particularly neurons that project to the globus pallidus. The mechanism by which cell death is induced in these neurons is not clear, but animals that display this sort of neural damage also show evidence of early gene activation (*c-fos*), a process that has come to be associated with apoptosis (Griffiths et al., 1999). On the other hand, the mechanism by which PCP protects neurons against ischemia has never been established. Clinical trials in humans with PCP-like drugs have been universally disappointing, in spite of clear protective effects exerted by PCP and by PCP-derivatives such as MK-101 in experimental animals.

PCP attaches to σ receptors throughout the body, not just those found in the central nervous system but also on membranes from endocrine, immune, and peripheral tissues. Sigma stimulation is thought to be responsible for many of the unpleasant side effects associated with opiate use and could possibly explain why in vitro studies have shown that lymphocyte function is depressed after exposure to relatively low doses of PCP (Thomas et al., 1993). In addition to PCP, cocaine, pentazocine, dextromethorphan, and even anabolic steroids all bind σ receptors, which may explain certain similarities in the behavioral effects of these drugs.

In cases of PCP overdose, death appears to be a consequence of respiratory and cardiac depression. In the dog model of extreme PCP intoxication, respiratory failure is followed by a combination of hypoxia, hyperpyrexia, and acidosis. If the animals are paralyzed, convulsions and hyperthermia are prevented but respiratory and cardiac depression still occurs. At the highest doses, death seems to be entirely due to myocardial depression (Davis et al., 1991). These results can be extrapolated to humans only with great caution, because reports of massive overdose (blood concentration > 1800 ng/mL) in humans do not mention myocardial compromise (Jackson, 1989).

Because PCP is so lipid soluble, the volume of distribution is quite high, though not nearly so high as marijuana (> 15 L/kg). PCP circulating in the blood is highly protein bound (60–70%), although just which proteins are involved is not known; less than one quarter of PCP is bound to albumin (Busto et al., 1989). Recovery of PCP and its metabolites in urine and feces is incomplete. Hydroxylated derivatives, accounting for less than 50% of a total dose, can be recovered from the urine. At the same time, unchanged PCP can be found in saliva and sweat, suggesting that some elimination may occur by these routes (Cook et al., 1983).

PCP is metabolized by hydroxylation on position 4 of the cyclohexane ring and/or on the piperidine moiety. Both of the resulting metabolites are pharmacologically inactive. The metabolites then undergo glucuronidation and are excreted in the urine. Because PCP is a weak base, acidification of the urine enhances its excretion. In the past, individuals with PCP overdoses were given ammonium chloride or ascorbic acid in hopes of increasing excretion and minimizing toxicity. This approach was eventually found to be ineffective. On the other hand, continuous gastric suction has proved a useful treatment because PCP is excreted into the stomach, setting up a pathway for gastroenteric recirculation (Aniline and Pitts, 1982).

The window for detection of PCP in the urine is variable. In experimental animals the half-life for PCP is only 3–5 hours (Woodworth et al., 1985), but in humans it is much longer. After oral administration, PCP's terminal half-life may approach 24 hours, which means that PCP should still be detectable in the blood for 5 days, and for at least as long in the urine. NIDA cutoffs require a urine concentration of at least 25 ng/mL before a measurement may be reported as positive.

6.2.6 Tissue Concentrations

Concentrations of PCP measured during clinically apparent intoxication and also at autopsy have been extensively reported. Intoxication in humans is not apparent when blood levels are less than 3 ng/mL, and clinical correlations between blood levels and physical findings, except for systolic blood pressure, are generally poor (Bailey, 1978). In 70 cases where PCP was deemed a factor in the death, blood concentrations in 90% of the decedents ranged

Table 6.2.6.1 Blood and Tissue Levels in 70 Fatal Cases of PCP Intoxication

Blood (ng/mL)	Urine (ng/mL)	Liver (ng/mL)	Bile (ng/mL)	Brain (ng/mL)	Kidney (ng/mL)
100–2400	100–7600	100–7820	100–1690	30–710	400–900

Source: Adapted from Budd and Liu (1982).

from 10 to 300 ng/mL (Table 6.2.6.1) (Budd and Liu, 1982). In a smaller series including five PCP-related deaths, concentrations at autopsy ranged from 8 to 2100 ng/mL. Plasma concentrations in ten individuals with clinical evidence of intoxication were lower, ranging from less than 10 up to 812 ng/mL (Bailey, 1978). A case report from 1989 described a man who swallowed two balloons full of PCP and promptly lapsed into a coma. The particulars of the case were unknown until day 11 when the man passed the two PCP-filled balloons, one ruptured, while he was still comatose. The maximum blood level on the third hospital day was 1879 ng/mL. His blood level at the time he passed the two balloons was not recorded, but the level in his cerebrospinal fluid was 245 ng/mL, and the plasma level the day before was nearly 1000 ng/mL (Jackson, 1989).

PCP plasma concentrations may be affected when other drugs are taken at the same time. In a dog model of PCP intoxication, concurrent administration of PCP with marijuana resulted in higher blood and brain PCP concentrations than when PCP was given alone. Alcohol, on the other hand, does not exert this effect (Godley et al., 1991). This synergy may explain why PCP and marijuana are frequently detected in the same urine specimens. PCP appears in saliva, and saliva concentrations appear to correlate well with blood levels (McCarron et al., 1984; Kidwell et al., 1998).

6.2.7 Interpreting Blood and Tissue Concentrations

Blood and urine measurements of PCP are of historical interest only. They prove that the individual in question did, at one time, take PCP. The clinical and forensic importance of isolated blood and urine levels is impossible to determine. PCP is rapidly extracted from the blood by brain and fatty tissues and then slowly released back into the circulation. In one animal study, PCP levels in adipose tissue were 13 times higher than brain concentrations and 20 times higher than plasma levels (James and Schnoll, 1976). Continued slow release from fat depots can occur over an extended period of time. PCP also makes its way back into the circulation after being reabsorbed from the gastric contents and entering the small bowel. Measurable levels may persist for months (Aniline and Pitts, 1982). NIDA guidelines calling for screening and confirmation tests with a 25-ng/mL cutoff have significantly reduced the time frame for detectability. If the cutoff were reduced by one half, the period during which PCP could be detected might be lengthened by a period of weeks!

Controlled studies on the limits of detection have not been published, but in one case report a police chemist who had daily contact with PCP still had a plasma level of 70 ng/mL six months after leaving the laboratory (Aniline and Pitts, 1982). PCP remains stable in stored urine specimens for long periods of time with almost no change in PCP concentration after three months of cold storage; one half of the initial concentration of PCP is still present after six months (Hughes et al., 1991). Because PCP is no longer sold either as a human or veterinary anesthetic, its presence can only be explained by illicit use.

Phencyclidine can be detected in vitreous fluid. On average, the blood phencyclidine concentrations are greater than the vitreous humor phencyclidine concentrations, with average blood/vitreous ratios of 2.85 for heart blood and 2.51 for subclavian blood. However, there is an enormous degree of inter-individual variation, and interpretation of isolated concentration measurements is not possible (Cox et al., 2007). Similar considerations also apply to measurements of phencyclidine in fingernails; the values can be quantitated, but not really interpreted (Jenkins and Engelhart, 2006).

Episodes of fatal PCP intoxication, as opposed to homicides and trauma deaths where PCP is an incidental finding, are uncommon (Noguchi and Nakamura, 1978; Budd and Lindstrom, 1982; Poklis et al., 1990; Li and Smialek, 1996). Tolerance to PCP is seen in animals, and almost certainly occurs in humans. It has been argued that tolerance in humans is proven by the fact that blood levels in patients dying directly from the effects of PCP overlap with the blood levels seen in victims of accidental deaths (Poklis et al., 1990). This same phenomenon can be seen in cocaine-related deaths and probably in all other stimulant-related fatalities. A further problem in PCP-related fatalities is the very great volume of distribution of the drug. At any given instant, almost all of the PCP in the body is found in tissues, not circulating in the blood. If, after death, even a small percentage of the PCP found in tissues was to redistribute into the blood (which it almost certainly would do), then the blood level measured in a postmortem sample might be many times higher than the actual plasma concentration in the immediate antemortem period. Maternal–fetal relationships have not been studied in depth, but the few papers that have been published have shown not only that PCP crosses the placenta with ease, but also that the fetus concentrates the drug and usually has higher levels than the mother (Aniline and Pitts, 1982).

6.2.8 Toxicity by Organ System

6.2.8.1 Neurologic Disorders

Autopsy studies make no mention of unique neuropathologic changes. It is not clear whether this reflects a lack of toxicity or just a limited number of observations. Most PCP-related deaths occurred before it was known that PCP induced cell apoptosis. Indeed, most of the deaths occurred before the process of cell apoptosis was even recognized (neurons programmed to self-destruct can be recognized by condensed and fragmented cell chromatin contained within an intact cellular membrane) (Raff et al., 1993).

All of the arylhexylalkylamines similar to PCP have been tested, including MK-801, ketamine, and tiletamine, and they all produce acute changes in rat brains. Vacuolization of neurons in the posterior cingulate and retrosplenial cortices can be seen within four hours of subcutaneously injecting 1 mg/kg of PCP. Some evidence suggests that the changes resolve and tolerance to the effects develops with repeated usage (Olney et al., 1989; Gao et al., 1993). Evidence also indicates that PCP, but not MK-801, can cause damage to Purkinje cells of the cerebellar vermis (Nakki et al., 1995). It is conceivable that these transient changes could account for behavioral disorders that are seen in human PCP users. Fatal status epilepticus has been reported (Kessler et al., 1974; McCarron et al., 1984), which is puzzling, because PCP and related compounds such as MK-801 have anticonvulsant properties (Balster, 1987). One contributing factor may be the ability of phencyclidine to block the action of calcium ATPase in both the heart and the brain (Pande et al., 1999).

6.2.8.2 Cardiovascular Disease

Most of the studies on the cardiovascular actions of PCP were done more than 30 years ago, using experimental animals given very large doses by continuous infusions. Under those conditions PCP increases heart rate, cardiac output, blood pressure, and temperature (Hackett et al., 1981). More recent in vitro and animal studies have shown that, even in low doses, PCP inhibits the calcium-dependent ATPase located in cardiac sarcoplasmic reticulum. That action effectively disrupts intracytosolic calcium homeostasis and decreases cardiac output (Pande et al., 1998). The differences between the old and new studies are probably just a reflection of the dose used; massive infusions of PCP activate sympathetic mechanisms that would more than make up for any calcium-mediated decrease in cardiac output. Altered myocyte calcium concentrations should result in recognizable lesions (contraction band necrosis), but such lesions have not been reported in either human PCP users or experimental animals.

6.2.8.3 Renal Disorders

In one series of 1000 PCP-intoxicated patients, 2.2% had rhabdomyolysis, and three of these patients had renal failure that required dialysis (McCarron et al., 1981a, b). Renal failure usually occurs in deeply comatose patients with convulsions (Cogen et al., 1978; Hoogwerf et al., 1979; Fallis et al., 1982).

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6.3 Ketamine

Street names: jet, super acid, special "K," green, K, cat valium
Chemical name: α(±)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone
Formula: $C_{13}H_{16}ClNO$
Molecular weight: 237.73 daltons
C_{max}: > 400 ng/mL produces analgesia; concentrations > 1000 ng/mL produce anesthesia
T_{max}: 30–50 minutes after oral ingestion
$T_{½}$: 2.5 hours (Wieber et al., 1975), undetectable after 6 hours (Yanagihara et al., 2003)

Bioavailability: (Malinovsky et al., 1996)
IV: 100%
Nasal: 50%
Rectal: 50%
Oral: 17%

V_{ss}: 3–5 L/kg (Wieber et al., 1975), 1 L/kg (Yanagihara et al., 2003)

Interactions: there is a potential for interaction with antiretrovirals

Detection times: up to 10 days in primates, probably less in humans

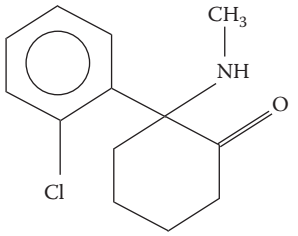

Figure 6.3.1 Ketamine molecule.

Brand names: (–)-Ketamine®, (S)-(–)-Ketamine®, (S)-Ketamine®, CI 581 base®, CLSTA 20®, Esketamine®, Ketaject®, Ketalar®, Ketalar base®, Ketanest®, Ketolar®

Malinovsky, J. M., Servin, F. et al. (1996). Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children, *Br. J. Anaesth.,* 77(2), pp. 203–7.

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6.3.1 Incidence

Ketamine abuse occurs, but not very often. The Medical Examiner component of the 1999 DAWN report contained 21 ketamine mentions. An insignificant increase from 3 to 16 deaths was reported in 1997, placing ketamine in the number 71 position on the DAWN list and accounting for 0.18% of all drug-related deaths reported to the federal government that year (Kissin et al., 2000). According to the Drug Abuse Warning Network's 2005 report there were only 275 ketamine-related emergency room visits in the proceeding year, none fatal (SAMHSA, 2005).

6.3.2 Epidemiology

No mentions of ketamine appeared in the Emergency Room component of the 1993 DAWN survey, and only 19 episodes were mentioned in 1994. The report for 1999, however, contains 396 mentions, compared to 5126 LSD mentions and 2850 emergency room visits related to use of MDMA (Kissin et al., 2000). Even on the club scene, ketamine is not a widely abused drug.

6.3.3 History

Ketamine was first introduced as an anesthetic agent in 1965 (Domino et al., 1982). It is classified as a dissociative anesthetic with a structure and actions closely related to those of PCP. Even though it was used for many years as an anesthesia adjunct (Ketalar®, Parke-Davis), in 1999 the DEA placed ketamine, including all of its salts, isomers, and salts of isomers, into Schedule III of the Controlled Substances Act (21 U.S.C. 801 et seq.). It continues to be sold in the U.S. as a veterinary anesthetic under the names Ketajet®, Ketaset®, and Vetalar®. Although it appears that Ketalar® is no longer sold in the U.S., it is widely sold in Europe and even offered

for sale in the U.S. by Internet pharmacies. Ketamine has a chiral center at the C-2 carbon of the cyclohexanone ring, allowing the existence of both (+) and (–) isomers. Veterinary ketamine preparations are supplied as mixtures containing equal amounts of both isomers.

6.3.4 Clandestine Laboratories

Ketamine used in the recreational drug market is illegally diverted from legitimate suppliers. Commercial anesthetic products are allowed to evaporate and the crystals are scraped into a fine powder, then packaged. No clandestine ketamine laboratory has ever been discovered in the U.S.

6.3.5 Routes of Administration

Ketamine can be administered by almost any route, with the route chosen depending on the intent. In addition to intramuscular and intravenous routes, epidural and intrathecal administration has been employed, but with somewhat ambiguous results. In one study, 50 mg of ketamine given intrathecally provided adequate anesthesia, but it was of short duration (Bion, 1984). Other studies have shown that epidural morphine was more effective and longer lasting than ketamine (Kawana et al., 1987). Oral administration is also possible and, because of first-pass effects and the formation of norketamine, anesthetic effects are observable at lower blood concentrations. Rectal administration has a more rapid onset, and ketamine has been used as an induction agent in children (Idvall et al., 1983). When used as a recreational drug, ketamine is usually insufflated. Bioavailability and blood concentrations in this setting have not been determined. In children undergoing surgery, mean plasma concentrations of ketamine and norketamine after intranasal and rectal administration were measured after a 3 mg/kg dose given nasally or a 9 mg/kg dose given rectally. In the intranasal group, mean plasma concentrations of ketamine peaked 20 minutes later at a concentration of 496 ng/mL. After rectal administration concentrations peaked within 21 minutes at a mean concentration of 2104 ng/mL. Plasma concentrations of norketamine peaked at approximately 120 minutes after nasal ketamine, more rapidly than after rectal administration of ketamine, and were always higher than ketamine concentrations (Malinovsky et al., 1996).

6.3.6 Metabolism

Ketamine's mode of action is still not known, probably because so many different mechanisms are involved. Even at subanesthetic doses ketamine is a potent analgesic, and the analgesic effects can be explained by the ability of ketamine to bind opiate receptors. But, like PCP, ketamine blocks the NMDA receptor as well, a receptor classified by some as a subtype of the σ opiate receptor. Still, other research points to possible effects on muscarinic receptors, not to mention voltage-dependent ion channels, particularly L-type calcium channels (Wong and Martin, 1993).

The situation is complicated by the fact that, until recently, ketamine was produced as a racemic mixture. The (S) form has a four times greater affinity for the MDMA receptor than the (R) form, but the opposite applies with the sigma receptor. The pharmacokinetic differences between the two have never been studied. The pure (R) form is now sold under the name of Esketamine and is increasingly used in Europe.

Bioavailability is high after either intravenous or intramuscular injections, one of the reasons this agent is so attractive for use in the battlefield setting. Taken orally, first-pass

effects result in lower blood concentrations but, somewhat surprisingly, more rapid onset. The explanation has to do with hepatic formation of norketamine, an active metabolite with approximately one third the activity of the parent compound. Ketamine is metabolized in the liver by the P-450 system, mainly to norketamine. Norketamine is then hydroxylated, conjugated, and excreted in the urine. The cyclohexanone ring undergoes oxidative metabolism (Adams et al., 1981; Reich and Silvay, 1989).

6.3.7 Pharmacokinetics

Ketamine has a very high degree of lipid solubility so it is hardly surprising that it also has a very large volume of distribution (between 3 and 5 L/kg) (Moffat et al., 2004). The elimination half-life is 2.17 hours (Domino et al., 1984). The pharmacokinetics in children is not very different than in adults, although children do form more norketamine (Grant et al., 1983). The pharmacokinetic behavior of ketamine after intravenous injection may be described in terms of an open two-compartment model. The alpha phase of ketamine's serum half-life is about 11 minutes and the beta phase 2.5 hours. The half-life of ketamine and its metabolites in urine is comparable to that in serum. The duration of anesthesia correlates with its rapid metabolic breakdown and elimination, but is also, to a degree, a reflection of its very wide tissue distribution (Wieber et al., 1975).

6.3.8 Tissue Concentrations

When given orally, a 5-mg/kg dose of ketamine resulted in analgesia and plasma concentration of 400 ng/mL 30 minutes afterward (Grant et al., 1983). However, when ketamine is given intravenously, doses only half as great as those given orally result in plasma concentrations more than twice as high as oral administration (Wieber et al., 1975). Even in modest doses, ketamine plasma concentrations in recovering alcoholics induce symptoms very similar to those seen after giving ethanol. Chronic alcohol consumption is thought to increase NMDA receptor function and to partially account for the seizures and other evidence of neurotoxicity seen in chronic alcoholics (Fidecka and Langwinski, 1989). In 20 detoxified alcoholics, an intravenous dose of 0.1 mg/kg produced peak ketamine concentrations of approximately 75 ng/mL after 80 minutes. When the dose was increased to 0.5 mg/kg, peak concentrations occurred at the same time but were much higher (400 ng/mL) (Krystal et al., 1998).

6.3.9 Interpreting Blood Concentrations

In general, plasma concentrations of 400 ng/mL or more are associated with analgesia, and concentrations of greater than 1000 ng/mL with anesthesia. Compared to other anesthetic agents, ketamine appears to possess little intrinsic toxicity. In a recently published review of 87 ketamine-positive deaths occurring over a two-year period, almost all of the positive test results were found in hospitalized patients following surgical procedures or burn treatment, and no single case of death could be attributed to intoxication with ketamine (Gill and Stajic, 2000). A 1994 report may or may not be relevant. It describes a homicide committed by injecting a man with a massive amount of ketamine (Licata et al., 1994). The resultant blood concentration was 27.4 mg/mL; urine, 8.51 mg/mL; bile, 15.2 mg/mL; brain, 3.24 mg/mL; liver, 6.6 mg/mL; and kidney, 3.38 mg/mL. Given the extreme lipophilicity of this drug, the relatively low brain concentration (at least when compared to the other

tissues) suggests that death must have been very rapid. Norketamine was detected in all samples, proving that the decedent had lived long enough to metabolize at least some of the drug.

Another bizarre case was reported in 1995: homicide caused by chronic ketamine poisoning. The victim was a 34-year-old married woman with no previous medical history who died in her own home. Investigation revealed that her husband had chronically poisoned her with ketamine over a period of about one year. The ketamine concentration was 21 μg/mL in gastric contents, 3.8 μg/mL in blood, and 1.2 μg/mL in urine (Tao et al., 2005).

6.3.10 Toxicity by Organ System

Ketamine is classified as a "dangerous drug," but it has quite an extraordinary safety profile. A 1996 study on the use of ketamine as an anesthetic in the developing world surveyed 122 physicians, operating in less-than-ideal circumstances, about their experience with ketamine in more than 12,000 patients. Pulse oximetry was used in fewer than 10% of the cases, and intermittent vital signs were taken in less than half. One unexplained pediatric death occurred during an unmonitored, unobserved ward recovery, and an adult suffered cardiac arrest after a failed intubation attempt. Apnea, possibly related to ketamine, was reported in ten patients, and laryngospasm in six. Similar experiences were reported by the Red Cross in its field hospitals (Lenz and Stehle, 1984). Even in the case of a substantial overdose, the main effect seems to be prolonged sedation. Green et al. (1999) described nine cases of inadvertent ketamine overdose in children. Three of the children received 5 times the recommended dose, five received 10 times the ordered dose, and one child was given a dose 100 times greater than ordered (all by intravenous or intramuscular route). All nine experienced prolonged sedation (3–24 hours). Except for prolonged sedation, no adverse outcomes were noted (Green et al., 1999).

6.3.10.1 Neurological Disorders

Ketamine dependence has been reported, particularly among hospital workers with ready access to the drug (Ahmed and Petchkovsky, 1980; Jansen and Darracot-Cankovic, 2001). Ketamine has the advantage, at least so far as hospital workers are concerned, of a short half-life and relatively rapid renal clearance, making detection less likely. Intrathecal and epidural ketamine is sometimes used in the management of chronic pain, generally without significant side effects (e.g., no respiratory depression or urinary retention) (Yaksh, 1996). Small doses, on the order of 50 mg, produce complete pain relief for at least one hour. Large doses result in longer pain-free periods. However, there is at least one report of isolated lymphocytic vasculitis of the spinal cord, presumably related to ketamine administration (Stotz et al., 1999). Intrathecal ketamine therapy is usually reserved for patients with terminal illness, so the true incidence of this complication remains unknown.

Preliminary evidence suggests ketamine may have some use as an antidepressant. In a recent blinded controlled trial, 17 individuals with depression were studied. All suffered from moderate to severe depression and all had failed to respond to at least two types of conventional drug treatments. Depression improved within one day for 12 of the 17 who received ketamine. These patients showed a 50% reduction in their symptoms, according to the Hamilton Depression Rating Scale. Overall, while 9 of the 17 patients had a 50% reduction in their depression within the first two hours of ketamine treatment, only one person receiving the placebo experienced the same effect in this period of time.

The antidepressant effects of ketamine lasted for a week in four people and at least two weeks in another two subjects. The striking results are thought to be a consequence of NMDA antagonism (Zarate et al., 2006; Maeng et al., 2008).

6.3.10.2 Cardiovascular Disease

Ketamine is used for anesthesia induction in trauma victims because, unlike other anesthetic agents, ketamine causes an increase in blood pressure, and the increase may be of considerable magnitude (Tanaka and Nishikawa, 1994). The mechanism has always been presumed to involve activation of the sympathetic nervous system and release of catecholamines. Experimental proof for this theory has recently been provided. Hearts taken from rabbits that had been repeatedly anesthetized with a mixture of ketamine and xylazine (an agent without effects on the sympathetic nervous system) displayed histologic evidence of the type of microfocal interstitial fibrosis that is classically associated with catecholamine excess (Marini et al., 1999).

In the homicide described earlier, where death was due to chronic ketamine poisoning, there was also striking fibrosis of the cardiac myofibers and hyaline degeneration of small arteries in the heart (Tao et al., 2005). No similar case has ever been reported.

6.3.10.3 Hematologic Disorders

In small doses, ketamine attenuates the cytokine response to cardiac surgery. As blood circulates through the bypass pump, there is activation of the inflammatory pathways. One recent study measured blood concentrations of interleukin-6 (IL-6) after giving 0.25 mg/kg of ketamine along with a general anesthetic. Normally, IL-6 concentrations begin to rise immediately after surgery, returning to baseline after eight days, but this rise never occurred in the ketamine-treated patients (Roytblat et al., 1998).

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6.4 γ-Hydroxybutyrate (GHB)

Synonyms: liquid ecstasy, scoop, easy lay, Georgia home boy, grievous bodily harm, liquid X, goop

Chemical name: 4-hydroxybutanoic acid (or hydroxybutyric acid or 4-hydroxybutyrate)

Formula: $C_4H_8O_3$
Molecular weight: 104.11 daltons
Metabolism: hepatic oxidation; substantial amounts may be converted to γ-butyrolactone
$T_{½}$: 30.4 ± 2.45 minutes (Brenneisen et al., 2004), 20 minutes (Palatini et al., 1993). Excretion: 1.2 ± 0.2 unchanged.
V_{ss}: 0.752 ± 0.22 L/kg (Brenneisen et al., 2004), 0.4 L/kg (Palatini et al., 1993)
T_{max}: 20–45 minutes, 20–40 minutes 20 mg = 6.4
C_{max}: 550 mg/L after 250–500 mg dose
Clearance: 1228 ± 233 μL/min, 1400 μL/min (Brenneisen et al., 2004)
Detection time in urine: 12 hours (Hoes et al., 1981)
Known drug interactions: ethanol
Brand names: Xyrem®

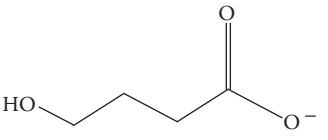

Figure 6.4.1 GHB molecule.

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6.4.1 Incidence

Emergency department visits related to GHB increased significantly from 1994 to 1999, but deaths attributable to GHB remain a very rare occurrence. The "new" DAWN report lists a total of 170 reported deaths occurring from 1994 to 1999 (SAMHSA, 2002). No more current data are available. GHB is not detected by any of the standard urine screening tests performed at hospital emergency rooms, and is not part of standard postmortem toxicology screens. Even when GHB is detected in postmortem blood specimens its significance is impossible to interpret, because GHB forms spontaneously after death. The mere presence of GHB is not proof that death was a consequence of GHB ingestion, or even that it was consumed. This state of affairs is still not generally appreciated by many coroners and medical examiners, so it may well be that the incidence of GHB deaths (as opposed to emergency room visits by living patients) has been, and continues to be, higher than it appears. On the other hand, GHB is stable in urine (Stephens et al., 1999), and reasonable criteria have been established for separating natural GHB production (which occurs in all living people), and GHB ingestion (Fieler et al., 1998; LeBeau et al., 2006).

6.4.2 Epidemiology

GHB is approved for the treatment of narcolepsy in the U.S. and it is sold under the brand name Xyrem® (Tunnicliff and Raess, 2002), nonetheless, the majority of GHB users report that they take GHB for "recreational" purposes. Nearly two thirds of GHB-related emergency room visits are due to "overdose," and one third to "unexpected" reactions. Nearly 60% of emergency room visits involved the use of multiple other drugs, usually GHB in combination with ethanol (76%), cocaine (6%), marijuana (5%), and MDMA (4%) (Woodworth, 1999). The DEA webpage merely indicates that use is increasing, but no actual values are provided.

6.4.3 History

γ-Hydroxybutyrate was first synthesized by French researchers attempting to create a GABA analog that could freely cross the blood–brain barrier (Tunnicliff, 1997). It turned out that GHB was not a true GABA agonist, but it is a naturally occurring inhibitory neurotransmitter (Bessman and Fishbein, 1963). GHB rapidly crosses the blood–brain barrier and produces sedation that is almost immediate. European surgeons began using GHB as an anesthetic adjunct in the early 1960s, but GHB does not produce analgesia, so opiate administration is also required for effective surgical anesthesia (Kleinschmidt et al., 1997).

Since the use of additional analgesic drugs is required, and because large doses of GHB cause seizure-like activity (Dyer, 1991), GHB anesthesia never really became popular in the medical community, even though some European neurosurgeons still resort to it on occasion. In spite of the fact that large doses induce seizures, smaller doses may actually inhibit them. GABA modulates most of synaptic brain inhibition. And, in fact, the idea of increasing GABAergic transmission by giving GHB is being investigated as a treatment for epilepsy, muscle spasticity, stiff-person syndrome, and even some psychiatric disorders (Wong et al., 2003).

Abuse of γ-hydroxybutyrate first began in 1977 when Japanese researchers observed that GHB could stimulate the release of human growth hormone (Takahara et al., 1977). The observation was of mild interest to the medical community but of very great importance to weight lifters and body builders who were convinced, quite correctly, that treatment with growth hormone could increase strength and endurance (Neely and Rosenfeld, 1994). During most of the 1990s GHB and γ-butyrolactone, which is readily converted to GHB once in the body, were easily obtained at health food stores and gyms, and they continue to remain readily available over the Internet. GHB is a Schedule III drug, meaning that suppliers can be prosecuted under federal law, but the lactone is a widely used solvent, found in such diverse products as engine degreasers and nail polish, making attempts at regulation somewhat futile. During the early 1990s GHB made the transition from gyms and health clubs to bars and dance clubs, where it became popular as a mild intoxicant (Williams et al., 1998).

GHB has increasingly been implicated as an agent in drug-facilitated sexual assault (Slaughter, 2000; Kintz et al., 2004; Varela et al., 2004; Anderson et al., 2006), in spite of the fact that poison control centers across the U.S. report decreasing use (Anderson et al., 2006). Estimating incidence of such assaults is difficult to gauge for two important reasons: GHB has a very short half-life, and it produces amnesia. A large industry-sponsored surveillance program analyzed more than 3000 urine specimens collected from alleged rape victims. All of the specimens were examined within 72 hours of the incident. Specimens were collected at the time of rape examination, then frozen and shipped to a central laboratory for analysis. Approximately half of the specimens analyzed in the survey tested negative for all drugs. Of those that did contain drugs, 4% were positive for GHB compared to over 40% positive for alcohol (ElSohly and Salamone, 1999). If the study were to be repeated today it is not clear whether the results would be higher or lower.

6.4.4 Clandestine Synthesis

GHB is usually synthesized as sodium or potassium salt. It is said to have a salty or soapy taste. GHB is thermally unstable and reverts to the lactone when it is heated. Analysis and

identification are complicated by the fact that GHB has no distinctive chromatographic properties, no distinguishable ultraviolet characteristics, and it is easily produced by the hydrolysis of γ-butyrolactone. In theory, GHB can be produced either by acid or base cleavage, but most of the formulas circulated on the Internet and most of the recipes disseminated in "underground" magazines use base cleavage for the primary reaction (Suner et al., 1997). The difficulty with this approach is that too much sodium hydroxide may be used, leading to a corrosive mixture that can produce burns and erosion of the lips, mouth, and esophagus. One of the most widely used formulas instructs would-be producers to heat one quart of γ-butyrolactone to its boiling point and then add one pound of sodium hydroxide crystals. The instructions say that the resultant solution should then be neutralized to a pH of between 6 and 7. If the instructions are actually followed, a 50% GHB solution is produced, which, in turn, is diluted to give a 20% solution. One teaspoon of this 20% solution will contain 1 g of GHB (Sanguineti et al., 1997).

6.4.5 Routes of Administration

According to anecdotal police reports, when GHB is used to facilitate sexual assault it is often placed in a used Visine® container or some other small squeeze bottle. Predators can then quickly and surreptitiously introduce GHB into an intended victim's drink. Investigators should look for such containers at the scene. GHB ingestion by anything but the oral route has not been studied in any detail. It is completely absorbed when taken orally.

6.4.6 Metabolism

Endogenous GHB is produced from GABA, which is first converted by GABA aminotransferase to succinic semialdehyde (Figure 6.4.6.1) (Roth and Giarman, 1969). The semialdehyde is then converted to GHB by $NADP^+$-dependent reductase (Anderson et al., 1977).

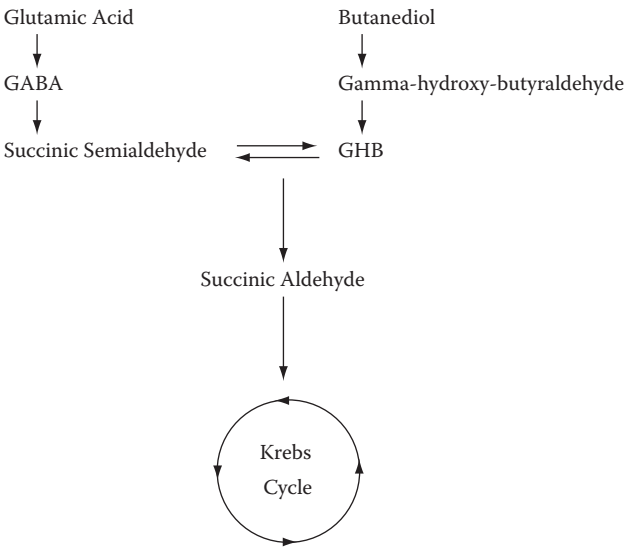

Figure 6.4.6.1 Production of GHB.

Metabolic breakdown is accomplished by oxidation back to succinic semialdehyde, which is then shunted into the Krebs cycle (Doherty and Roth, 1978). In the fetus, GHB dehydrogenase converts succinic semialdehyde to succinic acid (Kaufman et al., 1979). In adults, it appears that GHB-ketotranshydrogenase is responsible for the conversion (Nelson and Kaufman, 1994). There is no evidence for in vivo conversion of GHB to γ-butyrolactone (Ferrara et al., 1993). A rare genetic disease is recognized in which GHB accumulates because of a deficiency of brain succinic semialdehyde dehydrogenase (Jakobs et al., 1984; Rating et al., 1984).

6.4.7 Pharmacokinetics

Absorption and disposition kinetics have been studied in eight healthy male volunteers following oral administration of single doses of 125, 250, and 500 mg/kg, and, in a separate study, at lower doses of 20 and 40 mg (Palatini et al., 1993; Brenneisen et al., 2004). GHB does not bind to plasma proteins to any significant degree. Both the oral absorption and elimination of GHB are capacity-limited processes: the greater the dose, the slower the absorption and the longer the elimination period.

Peak plasma GHB concentrations occur 20–40 minutes after oral administration. Plasma samples collected from volunteers being given either 250 or 500 mg/day of GHB had mean peak concentrations of 550 mg/mL (range, 240–880 mg/mL) and 900 mg/mL (range, 510–1580 mg/mL). Multiple dose regimens do not lead to GHB accumulation. Peak urine concentrations occur within 3–4 hours of ingestion (Ferrara et al., 1993).

Pharmacokinetic parameters in healthy volunteers are essentially the same as those in alcohol-dependent patients with compensated alcoholic liver disease (Palatini et al., 1993). Based on the findings of several different studies, the half-life of GHB in humans is known to be approximately 20 minutes, with a clearance rate of 14.0 mL/min/kg (Palatini et al., 1993). No exogenous GHB is detectable in the blood of the living after 8 hours, and none in the urine after 12 hours (Hoes et al., 1981). Case reports are few, but it appears that most GHB users often imbibe ethanol at the same time. That practice may be dangerous, because in animal studies, high concentrations of either drug affect the metabolism of the other. When large doses of GHB are given, ethanol elimination is reduced (Hoes et al., 1981), an effect that would almost certainly lead to higher ethanol concentrations and probably to increased GHB toxicity. The picture becomes even more complicated when other drugs are used in addition to alcohol, as is often the case (Liechti et al., 2006).

6.4.8 Tissue Concentrations

γ-Hydroxybutyrate appears almost immediately in the plasma and saliva of healthy volunteers given 100-mg/kg doses of drug, but no correlation between plasma and saliva concentrations has been observed. In urine specimens collected from living non-GHB-using donors, the detection of anything more than negligible GHB concentrations is distinctly uncommon (Fieler et al., 1998). GHB is not likely to be found in the blood of the living unless it has been ingested. Fieler et al. (1998) found no GHB in blood or urine samples taken from 20 living non-GHB users, and no GHB was demonstrated in urine samples obtained at autopsy from 25 non-GHB users. However, blood from these same 25 postmortem cases had GHB concentrations ranging from 0 to 168 mg/L.

In fact, GHB is a postmortem artifact, and tissue concentrations at autopsy have no meaning.

Depending on the time elapsed after ingestion, blood concentrations of GHB measured during life may be very high. Couper and Logan (2000) found concentrations of 3.2 mg/L in the blood of a sexual assault victim, concentrations of 33 and 34 mg/L in two DUI cases, and levels of 130 and 221 mg/L in two overdose victims who were successfully resuscitated. In a second study from the same group, GHB was identified in the blood of 13 subjects arrested for impaired driving, and the blood concentrations ranged from 26 to 155 mg/L (mean 87 mg/L, median 95 mg/L) (Couper and Logan, 2001). These values are comparable to those seen when GHB is used as an anesthesia adjunct; plasma concentrations of 260 mg/L are associated with deep but reversible coma (Helrich et al., 1964).

Several studies have addressed the issue of endogenous urinary GHB levels in the living. In one study GHB was measured in urine collected over 24 hours from 16 adults who had been given single doses of 50 mg/kg GHB (Xyrem®) alone, and combined with 0.6 g/kg ethanol. Peak GHB urine concentrations averaged 150–200 mg/L and occurred in the 0–3-hour urine collection. There was, however, great variability in the urine levels found in different volunteer individuals. It appears that Caucasians have lower urine concentrations than other races/ethnic groups, and men have slightly lower GHB levels than women, at least within the first 3 hours after dosing. Ethanol does not significantly alter renal clearance of GHB (Haller et al., 2006).

A recently published study would seem to have finally put to an end the debate over how much endogenous GHB is found in the urine. Endogenous GHB production was measured in 207 urine samples from individuals who reported they did not use GHB. Urine concentrations ranged from 0.00 to 2.70 μg/mL in all specimens, with a median concentration of 0.24 μg/mL. Males ($n = 130$) had an average endogenous GHB concentration of 0.27 μg/mL (0.00–2.70 μg/mL), whereas females ($n = 77$) averaged 0.29 μg/mL (0.00–0.98 μg/mL) (LeBeau et al., 2006). Based on these findings, a cutoff of 10 mg/L is generally used to distinguish endogenous from exogenous GHB levels (LeBeau et al., 2002).

6.4.9 Interpreting Tissue Concentrations

γ-Hydroxybutyrate blood concentrations depend on the postmortem interval, the type of preservative, length of storage, storage temperature, and possibly even the analytical method used. Furthermore, the evidence is quite overwhelming that GHB forms in blood as a postmortem artifact. The evidence for postmortem formation in urine is somewhat less clear, but if it does occur the amounts formed are generally much less than in postmortem blood. Without a history of witnessed ingestion, the detection of GHB in postmortem blood is without significance. The diagnosis of GHB-related death, or even the use of GHB during life, should not be made on the basis of a single isolated blood measurement. High postmortem blood concentrations do not prove that the drug was taken, though low urine levels may mean just that. Similarly, the absence of GHB in the urine of a sexual assault victim 24 hours after the event does not mean that GHB was not administered. Conversely, if seizures and respiratory arrest occur after the witnessed ingestion of GHB and no other anatomic cause is apparent, then the absolute amount of GHB detected would seem to matter very little to the final diagnosis.

6.4.10 Clinical Considerations

The dose–response curves in humans and animals are quite similar and demonstrate a very narrow therapeutic index. Low doses, on the order of 50–100 mg/kg, produce mild agitation and excitement. Doses of 100–200 mg/kg induce euphoria and probably hallucinations. At doses much above 200 mg/kg, users become unresponsive. Seizures occur in the 400–800-mg/kg range, as does respiratory arrest. The most unique aspect of GHB intoxication is its very brief duration. A number of case reports describe deeply comatose patients, requiring ventilator support, who wake after only a few hours, extubate themselves, and simply walk out of the emergency room (Dyer, 1991; Lu et al., 1996; Louagie et al. 1997; Chin et al., 1998; Li et al., 1998).

Recreational GHB users who overdose usually present at emergency rooms with obtundation, mild hypothermia, and asymptomatic bradycardia. Emesis is very common, but, when large series of such patients are reviewed, clinical aspiration is uncommon (Chin et al., 1998). If enough GHB has been ingested (> 500 mg/kg), victims may require temporary respiratory support.

When GHB first became a popular club drug, reports were published suggesting that chronic use of GHB might lead to addiction and result in withdrawal syndrome (Woolverton et al., 1999). However, the suggestion has not proved correct. Except for death from respiratory depression, few medical complications of GHB use are recognized. The little data available has mostly come from abstracts presented at toxicology meetings, with almost nothing in the peer-reviewed literature; and most of these reports describe death in polydrug users. It is quite possible that some other drug or drug interaction may have been the cause of death. Similar considerations apply to the solitary case of Wernicke–Korsakoff psychosis that was reported in a GHB user (Friedman et al., 1996).

6.4.11 Organ Toxicity

γ-Hydroxybutyrate is not known to produce any specific pathologic lesions. But because GHB-related deaths invariably occur in polydrug users, postmortem examination is likely to reveal the typical anatomic changes associated with polydrug abuse. Ethanol is frequently detected, and it may in fact contribute to toxicity. Hepatic steatosis is common in drug users, but the etiology is multifactorial.

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6.5 Salvia Divinorum

6.5.1 History

Salvia divinorum (Lamiaceae) is a psychotropic mint plant. The leaves are used for medicinal and religious purposes by Mazatec shamans in the Mexican state of Oaxaca. The Mazatecs call the plant *ska pastora* or *ska Maria pastora*, meaning "leaves of the shepherdess." It is traditionally ingested as a water infusion or by eating the fresh leaves (González et al., 2006). Ethnologists report that, among native peoples, it is a second class drug, used only when psilocybin is in short supply. Interest in Salvia has greatly increased in recent years among recreational users. The use of Salvia has spread to Europe and North America and occupies a similar niche to other natural hallucinogenic drugs, just as ayahuasca (DMT)

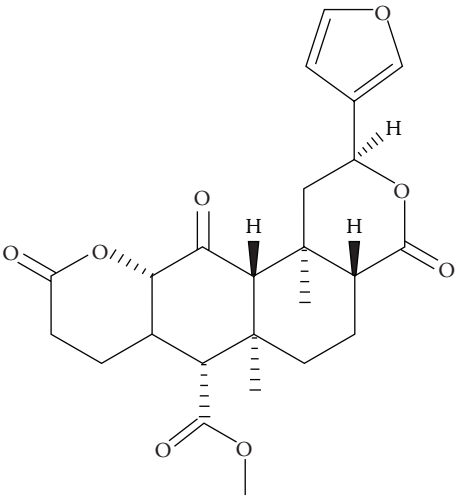

Figure 6.5.1 *Salvia divinorum* molecular structure.

Figure 6.5.1.1 *Salvia divinorum* — a psychotropic mint whose leaves were originally used for medicinal and religious purposes by Mazatec shamans in the Mexican state of Oaxaca. It is now used as a hallucinogen. (From Wikipedia, with permission.)

did a decade ago, though the actual extent of use in the U.S. and Europe remains completely unknown (Halpern, 2003, 2004).

6.5.2 Epidemiology

Several studies of Salvia users have been reported. In the most recent, a total of 32 Salvia users were studied, of whom 18 (56%) were male. The mean age of the sample was 25 years (SD: 4.32; range: 18–40 years), with three quarters of the users having graduated high school, but only one quarter having graduated college. At the time of the survey, 22 (69%) were attending college. The most commonly cited positive effects were the "trip" the drug elicits (41%), followed by its euphoric (28%) and dissociative effects (19%). Among the worst aspects, its short duration (38%) was the problem most frequently cited (González et al., 2006).

Much the same findings were reported in a novel Internet survey of 500 users. Users were predominantly male (93%) with a mean age of 23.4 ± 8.7, range 13–68 years. They reported that, on average, they had used Salvia 13.3 ± 22.9 times (range 1–250), usually to explore altered consciousness or to have a spiritual/mystical experience. The plant was smoked by 92.6%, 61.4% used a concentrated extract, and 37.3% reported using dried leaf; effects were estimated to last 14.1 ± 12.8 minutes (Baggott et al., 2004).

6.5.3 Pharmacology

The psychoactive properties of Salvia are produced by salvinorin A, a diterpene that is the plant's main psychoactive principle. Salvinorin A is a highly selective full agonist of the κ opioid receptor (Roth et al., 2002; Chavkin et al., 2004). Unlike all other hallucinogens, salvinorin A does not interact with the 5-HT-2A receptor. Nonetheless, it is a very powerful drug. Inhaling as little as 200 μg of the vaporized active principle will produce thinking disorders and feelings comparable to those observed after using LSD (Siebert, 1994). The route of administration appears to determine the intensity of the experience, which may be in the same range as LSD. Chewing the leaves and retaining the juices in the mouth allows absorption through the oral mucosa, and extracts can be administered either sublingually or rubbed on the insides of the cheeks. The plant can also be smoked (Siebert, 1994).

Diverse subjective effects have been described in self-experiments and the rsults described in case reports range widely. Based upon the literature at least, results are somewhat unpredictable, from relaxation to laughter (Siebert, 1994; Dennehy et al., 2005). In systematic psychometric testing, the subjective effects reported by users were similar to the feelings reported after high doses of classical psychedelics with 5-HT-2A receptor agonist activity; however, the intense derealization and impairment that most users reported seem to be a unique characteristic of Salvia.

6.5.4 Pharmacokinetics

No systematic studies of Salvia's pharmacology or toxicology in humans have been published. It is not even clear how Salvia is metabolized. When salvinorin A (0.032 mg/kg) was injected as an IV bolus in rhesus monkeys ($n = 4$, 2 male, 2 female) the elimination $T_{½}$ was rapid (56.6 ± 24.8 minutes) for all subjects. Pharmacokinetic differences (distribution $T_{½}$,

elimination $T_{½}$, and AUC) were observed between males and females, suggesting potential sex differences in its pharmacologic effects. Salvinorin B, the presumed major metabolite, is observed to accumulate in vivo; however, in this study it never reached the limit of detection (Prisinzano, 2005; Schmidt et al., 2005).

Analytical methods have been developed to study the routes of metabolism of salvinorin A in vitro or in vivo. The method (LC-MS/AP) has been validated in rhesus monkey plasma, rhesus monkey cerebrospinal fluid, and human urine (Schmidt et al., 2005). Results of these studies confirm that salvinorin B is the principal metabolite of salvinorin A, but it is not found in significant amounts in plasma of nonhuman primates.

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6.6 Dextromethorphan (DXM)

Synonyms: Robo, skittles, triple C's, rojo, dex, tussin, vitamin D. Dextromethorphan abuse is called "robotripping" or "tussing." Users might be called "syrup heads" or "robotards." The compound is contained in at least 140 different OTC products, and many prescription products as well.

Chemical name: ((+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan)

Formula: $C_{18}H_{25}NO$

Molecular weight: 370.33 daltons

Bioavailability:

C_{max}:

IV: 79.9 ng/mL (0.5 mg/mL) (Duedahl et al., 2005)

Oral: 3 ng/L (30 mg PO) (Carlton et al., 1997)

T_{max}:

Oral: 2 hours (Ramachander et al., 1977)

$T_{½}$:

IV: 3.1 ± 3.5 hours (Duedahl et al., 2005)

Oral: 3.1–7.9 hours ($n = 13$, 15 mL of Vicks Cough Syrup 0.5 mg/kg) (Eichold et al., 2007); 3.2–3.6 hours ($n = 10$, oral dose of 60 mg) (Silvasti et al., 1987); 3.1 (30 mg oral dose) 0.6 hours ($n = 22$, dose either 30 or 60 mg) (Moghadamnia et al., 2003)

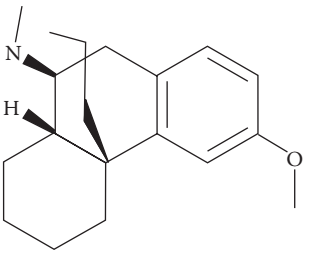

Figure 6.6.1 Dextromethorphan molecular structure.

V_{ss}: 3.4–4.5 L/kg (Moffat et al., 2004)

Metabolism: hepatic CYP26 (*O*-demethylation), conjugation, renal excretion

Interactions: some antiretroviral drugs (AM070) will increase the V_{ss} of dextromethorphan (Nyunt et al., 2008), but dextromethorphan is important mainly because it interferes with certain P-450 enzymes

Brand names: Robitussin DM®, Tylenol®, NyQuil® and Vicks brands are the best known, but there are literally hundreds of formulations containing dextromethorphan

Carlton, S. M., Rees, H. et al. (1997). Dextrorphan attenuates responses of spinothalamic tract cells in normal and nerve-injured monkeys, *Neurosci. Lett.*, 229(3), pp. 169–72.

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6.6.1 General Considerations

Dextromethorphan (DXM), the *d*-isomer of the opiate agonist levorphanol, is a codeine derivative, an effective cough suppressant and, along with guaifenesin, the principal ingredient found in over-the-counter (OTC) cough and cold remedies. It is not a controlled drug. The FDA approved dextromethorphan as an OTC drug in 1958, as it was thought

to have less abuse potential than codeine but still possessed a potent cough suppressant effect. In fact, the Controlled Substances Act (CSA) specifically excluded DXM from any of the schedules in 1970 because there was simply no evidence of opiate-like abuse potential, with the proviso that DXM could be added to the CSA through the traditional scheduling process if warranted. During the 1960s and 1970s, DXM was sold under the brand name of Romilar®, but in 1973 Romilar® was taken off the shelves; young people had discovered it could be used as a recreational drug. Rarely, DXM is mixed with MDMA tablets, but it is primarily abused as an OTC cough remedy, either in liquid or solid form. The *l*- form of DXM also has narcotic properties but it is not commercially available. Differentiation between the *d*- and *l*- forms is a forensic issue because DXM is not a controlled substance, but its isomer, levomethorphan, is a Schedule II controlled substance. Statistics are difficult to come by, but abuse of DXM seems to be increasing.

6.6.2 Incidence, Epidemiology, and History

The U.S. government reports that in 2006, approximately 3.1 million persons aged 12 to 25 had, at some time, used an OTC cough syrup containing DXM, and done so with the specific intent of getting "high." In the younger age groups females are more likely than males to have misused OTC cough syrups in the preceding year, but among older age groups, male abusers predominate. Among persons aged 12 to 35 years who had abused an OTC cough remedy, 30.5% had misused a NyQuil® product, 18.1% had misused a Coricidin® product, and 17.9% had misused a Robitussin® product. There is no ready explanation for the relative popularity of these drugs (NSDUH, 2008)

Interest in DXM seems to be increasing. In a 2006 survey of high school students in Dayton, Ohio, it was found that, among 12th-grade students ($n = 2437$), 4.9% reported lifetime use of dextromethorphan (usually Coricidin® or Robitussin®), and 3.7% reported abuse in the past 12 months. Among 12th graders who reported use, 55% had used it three times; among 11th graders, 33.9% had used it three times. In fact, the lifetime prevalence of dextromethorphan abuse among these students exceeded that associated with anabolic steroids (2.2%), MDMA (4.0%), heroin (4.1%), crack cocaine (4.4%), and Ritalin® (4.8%), and rivals that of methamphetamine (5.5%) (Falck et al., 2006).

According to the Drug Abuse Warning Network (DAWN) report for 2004, there had been an estimated 12,584 emergency department (ED) visits involving pharmaceuticals containing dextromethorphan (DXM), amounting to 0.7% of all drug-related ED visits. The rate of ED visits resulting from nonmedical use of DXM for individuals aged 12 to 20 years was 7.1 per 100,000 population versus only 2.6 or fewer per 100,000 for other age groups. The rate of ED visits resulting from any type of use of DXM among those aged 12 to 20 was 10.3 per 100,000 population compared with 4.3 visits per 100,000 for the population overall. Perhaps not surprisingly, given the age group, alcohol was implicated in about a third (36%) of ED visits involving nonmedical use of DXM for those aged 18 to 20 and in 13% of visits for those aged 12 to 17 (Ball and Albright, 2006).

6.6.3 Synthesis

There is no clandestine production of this drug and there are no clandestine laboratories. All DXM abusers take the various OTC products containing DXM. This may occasionally lead to the ingestion of multiple other agents such as diphenhydramine and

chlorpheniramine. However, methods for extracting DXM from cold medications are readily available on the Internet and from other sources. The process is referred to as the "Agent Lemon" technique. The cold medication is mixed with equal amounts of ammonia and naphthalene (cigarette lighter fluid). The aqueous layer is discarded and the process repeated. Lemon juice is used to acidify the mixture, the oily layer discarded, and the aqueous layer allowed to crystallize and is then taken orally (Hendrickson and Cloutier, 2007). Abusers of DXM have also developed a simple acid–base extraction technique to "free-base," or extract, the DXM from the unwanted guaifenesin, coloring agents, sweeteners, and alcohol that are typically included in combination cold preparations (Hendrickson and Cloutier, 2007).

6.6.4 Routes of Administration

There is no evidence that this drug is ever taken parenterally. All use and abuse is oral. There have been experiments where dextromethorphan has been given intravenously to human volunteers, both to determine pharmacokinetic behavior and to evaluate DXM's anti-hyperalgesic effect. A dosage of 0.5 mg/kg caused no ill effects and only minor side effects.

6.6.5 Pharmacology

There is extensive first-pass metabolism of DXM leading to low plasma levels on the order of 1–5 ng (Barnhart and Massad, 1979; Silvasti et al., 1987). Metabolism is dependent on the P-450 enzyme CYP2D6. Approximately 10% of the U.S. population is deficient in this enzyme and, therefore, metabolize DXM much more slowly than others. In these individuals, blood levels after typical therapeutic doses (20 mg) are in the 10–20-ng/mL range (Hou et al., 1996). The 2D6 enzyme catalyzes *O*-demethylation to form dextrorphan (DXR), which is then conjugated and excreted in the urine (Lutz et al., 2004). DXM is a noncompetitive NMDA receptor agonist.

6.6.6 Pharmacokinetics

The 10% of the population classified as "slow metabolizers" requires 17–22 hours in order to metabolize the same amount of DXM that can be metabolized by "extensive" metabolizers in 1–4 hours (Eichhold et al., 2007). DXM has specific serotonergic and σ-1 opioidergic properties. The active metabolite, dextrorphan, has similar properties to DXM, but it is a weaker σ opioid receptor agonist and a stronger NMDA receptor antagonist (Miller, 2005). Intoxication with dextrorphan produces symptoms that are hard to distinguish from any other NMDA blocker or dissociative anesthetic. A normal dose of DXM is 15–30 mg. It is claimed that hallucinatory effects may be experienced with doses as low as 100 mg, and frank psychosis at higher levels (Roberge et al., 1999; Miller, 2005). Ingestion of hundreds of milligrams has been reported, but with few or no side effects.

6.6.7 Tissue Levels

Both DXM and DXR are concentrated in brain tissue with a very high ratio of brain to plasma concentration (Carlton et al., 1997). There are a handful of case reports in the

medical literature, but in most the metabolizer status of the individual was not known. Postmortem measurements are impossible to interpret.

6.6.8 Toxicology by Organ System

Agitation is the most common presentation of DXM intoxication, leading eventually to ataxia, tremors, hyperreflexia, nystagmus, and hypertension. Pupillary size is variable (Roberge et al., 1999; Hendrickson and Cloutier, 2007). None of the standard antidotes appears to be effective. Serotonin syndrome has been reported in DXM abusers, and sometimes during anesthesia (Otton et al., 1993; Bowdle, 1998; Karunatilake and Buckley, 2006).

Because deaths involving DXM are so rare, it is not known whether or not any specific lesions are associated with acute or chronic use. Certainly, none has been identified. Clinical syndromes, however, should be recognizable, though the presentation can be confusing if anticholinergic symptoms predominate. One recent case report describes two individuals who had overdosed on Coricidin®, both of whom were taking antidepressants. Initially the patients were somnolent, confused, normothermic, tachycardiac, and hypertensive (Kirages et al., 2003).

The presentation of DXM intoxication may change in the near future as the practice of extracting DXM from OTC cold remedies becomes more widespread. A recent report describes a 20-year-old who had ingested 1 g of "crystal dex," and came to the emergency room after becoming obtunded. Initially he was hypotensive and tachycardiac and failed to respond to flumazenil and naloxone. These symptoms improved over the course of 5 hours but, as his vital signs normalized, he became more agitated and psychotic. He eventually improved with supportive care (Hendrickson and Cloutier, 2007).

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Anabolic Steroids

7

Athletes abuse steroids because they know that they improve performance. In healthy young people, steroid abuse increases lean body mass, strength, and aggressiveness, and shortens the recovery time between workouts (Plymate and Friedl, 1992; Foster and Housner, 2004). Rational scientific exploration into the mechanism of these effects, and possible medical complications, is limited because abusers routinely take doses of anabolic steroids well in excess of those that any physician could ethically administer.

7.1 Testosterone

Name: testosterone
Proprietary names: Androderm®, Androgel®, Andropatch®, Striant®, Testim®
Chemical name: 17-betahydroxyamndrost-4-en-3-one
Formula: $C_{19}H_{28}O_2$
Molecular weight: 288.43 daltons
C_{max}:
Intramuscular testosterone enanthate (200 mg): 1600 ng/mL
Testosterone patch (1 patch): 500 ng/mL
Testosterone skin gel (100 mg): 500 ng/mL
Intravenous (300 μL); still rising at 10 minutes after injection (White et al., 1998)
$T_{½}$: 10–100 minutes intravenously (White et al., 1998)
Intramuscular: approximately 2 hours (Schürmeyer and Nieschlag, 1984)
Testosterone patch: approximately 2 hours (Yu et al., 1997)
Testosterone gel: approximately 2 hours (Wang et al., 2000)
V_{ss}: (n =11, elderly men) 1.18 L/kg (White et al., 1998)
Metabolism: hepatic, metabolized to estradiol and dihydrotestosterone
Interactions: Multiple interactions are theoretically possible. Injected testosterone causes (1) increased clearance of propanolol, (2) decreased blood sugar with increased glucose requirements, and (3) possibly artifactual depression of total T_4

Schürmeyer, T., and Nieschlag, E. (1984). Comparative pharmacokinetics of testosterone enanthate and testosterone cyclohexanecarboxylate as assessed by serum and salivary testosterone levels in normal men, *Int. J. Androl.,* 7(3), pp. 181–7.
Snyder, P. J. and Lawrence, D. A. (1980). Treatment of male hypogonadism with testosterone enanthate, *J. Clin. Endocrinol. Metab.,* 51(6), pp. 1335–9.

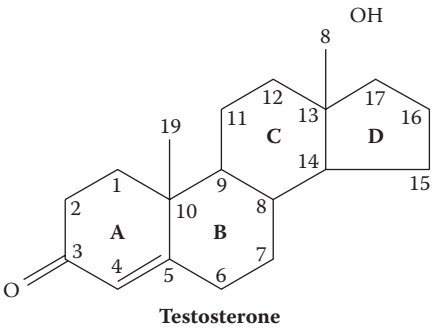

Figure 7.1.1 Testosterone. Testosterone is rapidly degraded by the liver when it is given orally. Modifications at position 17, such as esterification of the β-hydroxyl group, prevent hepatic breakdown and allow the drug to be given orally.

Wang, C., Berman, N. et al. (2000). Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study, *J. Clin. Endocrinol. Metab.,* 85(3), pp. 964–9.

White C. M., Ferraro-Borgida, M. J. et al. (1998). The pharmacokinetics of intravenous testosterone in elderly men with coronary artery disease, *J. Clin. Pharmacol.,* 38(9), pp. 792–7.

Yu, Z., Gupta, S. K. et al. (1997). Testosterone pharmacokinetics after application of an investigational transdermal system in hypogonadal men, *J. Clin. Pharmacol.,* 37, pp. 1139–45.

7.1.1 Prevalence and Epidemiology

Anabolic steroid use is increasing and, somewhat surprisingly, the rate of increase is said to be even greater among women. The 1999 Monitoring the Future (MTF) study, an ongoing NIDA-funded study that surveys the extent of drug abuse among middle school and high school students across the U.S., found that 2.7% of 8th graders, 2.7% of 10th graders, and 2.9% of 12th graders had taken anabolic steroids at least once in their lives (NIDA, 2007a). If true, these figures represent an increase of nearly 50% from previous surveys among 8th and 10th graders, with an increase of 38% among 12th graders.

Most of the young people experimenting with these drugs do not mention their usage to official authorities because steroid abuse is classified as a crime comparable to any other sort of drug abuse. Nonetheless, as any newspaper reader knows, athletes at all levels of competition abuse steroids, not only to improve performance but, especially among adolescents, also to improve their cosmetic appearance (NIDA, 2007b).

Other evidence, from different government sources, indicates that there is a tendency for steroid abuse to decline as adolescents age. A 5-year study of children in Minnesota found that adolescent steroid abuse certainly occurred, but that the practice was so uncommon as to be of no concern. According to another study, there was no change in the prevalence of steroid use by middle school adolescents between the years 1999 and 2004, in spite of extensive media coverage and government attention (vandenBerg et al., 2007).

Results of the MTF survey tends to confirm the results of other studies. The rate of steroid use among high school students was unchanged from 2005 to 2006, for both boys and girls. At the same time, the survey found that there had been significant reductions in

lifetime use a trend that first began in 2001. Past year use was reported by 0.9% of 8th graders, 1.2% of 10th graders, and 1.8% of 12th graders in 2006 (NIDA, 2007a).

7.1.2 History

Anabolic steroids are synthetic compounds structurally related to testosterone, the male sex hormone. Testosterone has two different effects on the body: it promotes the development of secondary male sexual characteristics (androgenic effects), and it accelerates muscle growth (anabolic effects). The final result depends on which androgenic receptors are activated and which are not (Saudan et al., 2006). The hormonal basis for male sexual characteristics was first determined in 1849, when it was observed that the male characteristics of roosters disappeared after they were castrated. These characteristics reappeared when the testes were implanted into the rooster's abdomen. It was correctly deduced that the testes were secreting something into the blood that controlled the development of male sexual characteristics.

In 1930, a scientist who worked at the same medical school in Göttingen where the original discovery had been made succeeded in isolating 15 mg of an anabolic compound from 25,000 L of policemen's urine. The compound was named androsterone for three reasons: it was virilizing (thus *andro*, the Greek word for male), the nucleus of its molecule was like that of cholesterol ("ster"), and it contained a ketone group ("one"). A few years later testosterone was crystallized from bull testes, and its chemical structure was characterized (Kochakian, 1990).

In the 1940s, once testosterone had finally been synthesized, it was discovered that the positive effects of testosterone on nitrogen balance and muscle growth could partially be separated from testosterone's androgenic effects. In the process of trying to separate the androgenic from the anabolic effects, it was found that substitutions at the 17 position of the testosterone molecule produced compounds that could be taken orally, and that these compounds had anabolic effects like testosterone, but with only a fraction of the androgenic effects. Further manipulations of the testosterone molecule at the 17 position have led to the production of a series of "anabolic" steroids that are active when taken orally (Figure 7.1.2.1).

When commercially prepared anabolic steroids became available just prior to World War II, they were used to promote healing and speed recovery. An effect on mood quickly became apparent and these same steroids were also used to treat depression (Ehrenreich et al., 1999). It is alleged that steroids were given to German storm troopers to increase both strength and hostility.

Nandrolone remains the most popular of the oral anabolic agents, both among athletes and cattlemen attempting to grow larger animals. Small amounts of nandrolone are produced naturally in the human body, but concentrations of more than 2 ng/mL are considered as evidence of sports doping; the urine concentration in non-steroid abusers never exceeds 0.6 ng/mL. A loophole in the regulations of most international sporting organizations allows athletes to exceed these ingestion limits and not be disqualified. Nandrolone is most commonly sold as its decanoate ester (Deca-Durabolin®) and less commonly as a phenylpropionate ester (Durabolin®). The sale of both is limited in the U.S. by the Controlled Substances Act.

In the early 1990s competitive athletes stopped using nandrolone, not because it was ineffective, but because it remained in the body for weeks and was too easily detected. Nandrolone precursors, 19-norandrostenedione and 19-norandrostenediol, both legally sold in

Figure 7.1.2.1 Anabolic steroids. When these agents first became available, they were often used for indications that are no longer considered acceptable today. This advertisement is from a 1961 issue of *JAMA*.

health food stores, took their place. Once in the body, these compounds are rapidly converted into nandrolone (Lee et al., 1991), although under the World Anti-Doping Agency's (WADA) doctrine of absolute liability, any athlete testing positive would still be disbarred, even if he or she claimed to be only using legal precursors.

However, the final chapters in the war between regulators and athletes have yet to be written. There is evidence that an endogenous nandrolone metabolite can also be detected in urine in concentrations above acceptable IOC limits. This is thought to be the result of an athlete combining a high protein diet and a nutritional supplement such as creatinine. It has also been suggested, but not proven, that false positives might result from eating beef that was hormone supplemented (Anon., 2000).

While seemingly farfetched, innocent ingestion from dietary sources is possible. Meat from uncastrated male pigs normally contains 19-norandrosterone, and consumption of boar meat can cause positive urine tests in humans (De Wasch et al., 2001). Similar findings have been demonstrated after consumption of lamb (de Brabander et al., 1994). It appears that the worst offender in this regard is pig offal, which, if ingested in the hours

before testing, will produce a strongly positive test result. A much more likely scenario involves female athletes. Norsteroid metabolites are formed during pregnancy and excreted as minor metabolites of norethisterone with small amounts appearing in the urine (Ayotte, 2006). Trace contamination of the androstenedione sold in health food stores seems to be the most likely explanation for many of the positive tests. Contamination of androstenedione with 19-norandrostenedione is sufficient to cause positive urine test results for 19-norandrosterone, the standard marker for nandrolone use.

7.1.3 Steroid Abuse

No agent is purely anabolic. All so-called anabolic steroids exert androgenic effects; the only difference between agents is the ratio of anabolic to androgenic effects that are produced.

There is a thriving black market for anabolic agents, and it is supplied by two different sources. Since the dissolution of the former Soviet Union, laboratories in the former component republics have started producing steroids (along with other drugs) intended specifically for European and U.S. black markets. When sold in the U.S. they often still carry their Cyrillic markings. Analyses of confiscated samples have shown wide variations in steroid content. Many products are falsely labeled.

The other source is clandestine laboratories operating in the U.S. and Canada. The custom laboratories design steroids with the specific intent of avoiding detection. The drug tetrahydrogestrinone ("the clear" or THG), widely abused by professional athletes, is perhaps the best known. This designer drug binds to the androgen receptor and the progesterone receptor, but not to the estrogen receptor (Friedel et al., 2006), and has roughly 10 times the androgenic potency of nandrolone or trenbolone. For a time it was considered the anabolic of choice because it was so difficult to detect, though that is no longer the case.

The various approaches to taking steroids are referred to as stacking, cycling, and pyramiding. Stacking is the practice of using several different steroid preparations at once in the hope that maximal anabolic effects will be achieved while, at the same time, androgenic effects are minimized. Cycling describes a pattern of use where combinations of drugs are taken in alternating 6- to 12-week cycles; the rationale here is that the practice will prevent tolerance from occurring. "Pyramiders" start with low doses of the drug and gradually increase the amount of drug taken over several weeks, tapering off entirely before a competition. Not uncommonly, serious steroid abusers combine all three approaches.

Even though ethical considerations prevent physicians from participating in "megadose" steroid studies, that was not always the case. During the Cold War, within the sporting community, steroid abuse by East German athletes was considered a given. No one had any idea how widespread the practice actually was until Werner Franke, a cell biologist at the German Cancer Research Center in Heidelberg, obtained copies of Stasi (state secret police) files and brought them to the West. He was assisted in this venture by his wife, who was a former Olympic competitor (Franke and Berendonk, 1997).

According to the documentation supplied by Franke and Berendonk, the extent of the problem was far greater than anyone had ever believed. The records show that hundreds of doctors, scientists, and coaches were involved in the business of sports doping, acting on behalf of the East German government and participating in a classified, state-sponsored program known as State Plan 14-25. Under this program, from 1974 to 1989 athletes were treated with steroids, often without their knowledge, while the participating doctors measured responses to the treatments. Much of the testing was carried out in East Germany's

State Anti-Doping Laboratories, one of only a handful of such laboratories approved by the IOC. In fact, the laboratory functioned as a "doping" laboratory, literally in charge of administering drugs that was supposedly prohibited. Drug excretion times were plotted for each athlete so that their coaches would know how long before a competition they would have to stop administering steroids. Since the original discovery, German athletes have successfully brought suits against the state and the trainers.

7.1.4 Pharmacology

7.1.4.1 Synthesis and Metabolism

Dihydrotestosterone is the primary active metabolite of testosterone. It is produced by the enzyme 5α-reductase. Activity of this enzyme is concentrated mainly in the testicles, skin, prostate, intestines, brain, bones, and adipose tissues, which explains why the androgenic effects of anabolic–androgenic steroids predominate in these organs. Testosterone's anabolic effects are seen mainly in muscles, bones, heart, and kidney. Since these organs do not have significant 5α-reductase activity, testosterone's anabolic activity predominates, leading to protein synthesis, muscle fiber development, and erythropoiesis. As a group, anabolic steroids displace glucocorticoids from their receptors. The result is that muscle catabolism is inhibited and muscle building is promoted (Saudan et al., 2006).

Testosterone is synthesized both by the testes and the adrenal glands, but adrenal synthesis only accounts for about 5% of the body's total production. Testosterone is a 19-carbon molecule synthesized from cholesterol that is produced from acetate stored in the testes, not from the cholesterol that circulates in the bloodstream bound to low-density lipoprotein. Conversion from cholesterol to pregnenolone occurs in the mitochondria. Pregnenolone is then transported from the mitochondria to the endoplasmic reticulum where it is converted to testosterone in a three-step process and immediately released into the circulation (Miller, 1988).

Once it has been produced in the cytoplasm of the Leydig cells and is released into the circulation, testosterone enters cells located throughout the body, then easily crosses the cell nuclear membrane. Once in the cell, testosterone binds to protein receptors located in cell nuclei, either as testosterone or dihydrotestosterone. The latter is actually the compound responsible for testosterone's androgenic effects — it has a much greater affinity for androgenic receptors than testosterone. Once the testosterone–protein complex is formed it exerts effects on gene expression, resulting in the formation of the readily recognized male characteristics. When testosterone circulates in the bloodstream, about 50% is tightly bound to a protein produced in the liver called sex hormone binding globulin (SHBG) (Harman et al., 2001). The other half is only loosely bound to albumin, leaving only 2% unbound or "free." It had been believed that all of testosterone's effects were exerted by the unbound 2%, but now it is widely accepted that the fraction bound to albumin is available for tissue uptake and can exert testosterone's traditional effects. Nomenclature regarding testosterone has accordingly been changed: "free" testosterone and testosterone complexed with albumin are now both referred to as "bioavailable" (Muller et al., 2005). However, testosterone that is tightly bound to globulin (SHBG) is not active, because the bond is so very strong. When measuring total testosterone concentration, the SHBG concentration must also be considered since its concentration may have a drastic effect on the amount of testosterone that is actually available to tissues (Kumar et al., 1997).

Orally administered testosterone is rapidly metabolized by the liver and there is an extensive first-pass effect. But testosterone derivatives that have been substituted at carbon #17 (see Figure 7.1.1), such as methyltestosterone, are not metabolized as extensively and can be taken orally. Once testosterone reaches the liver it is transformed into a series of 17-ketosteroids and then excreted in the urine along with much larger amounts of 17-ketosteroids that have been produced by the adrenal cortex. More than 90% of testosterone is excreted either as the glucuronic or sulfuric acid conjugate, with approximately 6% excreted in the feces unchanged. In a normal, healthy male, less than 250 μg/day appear unchanged in the urine (VanEenoo and Delbeke, 2006).

7.1.4.2 The Andropause

Longitudinal and cross-sectional studies have shown that testosterone concentrations decrease as men age. The decrease is often greater than it appears because at the same time that testosterone concentrations are decreasing, concentrations of SHBG are increasing. The net effect is that during the aging process, less and less free testosterone is available. The rate of decline appears to be variable and difficult to estimate because there is no accepted definition of what constitutes a "normal" testosterone concentration. For the purposes of replacement therapy, which is becoming a subject of increasing interest, most investigators define a "normal" testosterone in an aging man as being equivalent to whatever is considered the lower level of normal for a healthy young man (Tenover, 1998; Bhasin and Wu, 2006).

A prospective cohort study of health and endocrine function, performed in a randomly selected cohort, disclosed substantial declines in total serum testosterone and free testosterone concentrations as aging progresses. But, because many health and lifestyle changes are associated with an accelerated decline in testosterone concentrations, the results of this study are not so easy to interpret as they might appear. A 4- to 5-kg/m^2 increase in body mass index (defined as the weight in kilograms divided by the height in meters squared), or loss of spouse, were both found to be associated with declines in total serum testosterone comparable to that associated with approximately 10 years of aging. Results were similar for free testosterone, but fewer factors were associated with SHBG after age was taken into account. It is apparent that both chronological aging, and changes in health and lifestyle, are associated with declines in serum testosterone. The evidence suggests that lifestyle influences may be as strongly associated with declining testosterone levels as age itself, at least over the short term (Travison et al., 2007).

Table 7.1.4.2.1 Signs of Andropause

Loss of libido
Erectile dysfunction
Depression
Lethargy
Inability to concentrate
Sleep disorders
Irritability
Osteoporosis
Loss of muscle mass with fatty replacement

There is general agreement that, in selected hypogonadal men, androgen replacement can improve symptoms of erectile dysfunction but, because most cases of erectile dysfunction are of vascular or neurogenic origin, treatment with testosterone supplements is unlikely to provide any benefit (Myers and Meacham, 2003). Testosterone can increase manic tendencies, aggression, and sexual interest, and induce feelings of euphoria in normal (nonhypogonadal) men, but only after administration in nonpharmacologic doses. Because aging is associated with decreases in lean body mass that can, to a measurable degree, be reversed with testosterone, there is great interest in the use of testosterone supplementation, but there is also concern about the ability of testosterone supplements to induce prostate cancer, even though the most recent data suggest that this is not a valid concern (Hoffman et al., 2000; Bain, 2007; Morgentaler, 2007).

7.1.4.3 Legitimate Clinical Indications

As far as the Food and Drug Administration (FDA) is concerned, the only legitimate indication for testosterone treatment in males is replacement therapy when, for whatever reason (trauma, congenital), there is testicular failure and hypogonadism. Multiple percutaneous delivery systems are available and these are often prescribed off label as anti-aging indications. The Drug Enforcement Administration (DEA) classifies all of the testosterone-containing products as Category III restricted drugs (Handelsman, 2006).

Androgens are occasionally used to treat women who have metastatic breast cancer involving bone. Higher blood concentrations of testosterone are associated with higher breast density and decreased apoptosis, but androgen use has largely given way to the prescribing of tibolone; it has both androgenic and estrogenic effects (Hofling et al., 2005).

Steroids classified as anabolic agents include drugs such as a testosterone derivative known as Danazol®. Danazol® (17-pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol) is a synthetic analog of 17-ethinyl testosterone. Binding studies using endometrial tissue have shown that Danazol® binds with varying affinities to multiple different steroid hormone receptors (SHR), including glucocorticoid, progesterone (PR), estrogen (ER), androgen receptors, and can even displace other steroids from their receptors (Tamaya et al., 1984). Sometimes Danazol® is used to treat hereditary angioedema. Danazol® increases levels of C4 complement and thereby reduces attacks of angioedema. In patients with hereditary angioedema, Danazol® also increases the level of deficient C1 esterase inhibitor. Danazol® is also used on occasion to treat patients with idiopathic thrombocytopenic purpura.

Compounds that exert both androgenic and anabolic effects are also indicated for the treatment of deficient red blood cell production (acquired aplastic anemia and myelofibrosis), although this indication has largely been abandoned because erythropoietin (EPO) is so much more effective. Methyltestosterone is also sold in combination with estrogens (Premarin®) for the relief of symptoms associated with menopause.

Regular treatment with exogenous testosterone can reverse some of the alterations normally associated with aging, such as central fat deposition (Forbes et al., 1992; Katznelson et al., 1996; Elbers et al., 1999), decreased bone mass and muscle mass, and loss of lean body mass (Lexell, 1995). Not only does muscle mass decrease with age, but so does the number of muscle fibers. The amount of creatinine excreted in the urine is a good indirect indicator of muscle mass and muscle creatinine content. Between the ages of 20 and 90 years, urinary creatinine excretion decreases by nearly two-thirds (Tzankoff and Norris, 1977).

That observation alone may explain the increasing number of older runners, with very impressive competition times, who are subsequently found to have been using steroids.

7.1.5 Steroid-Related Disorders

7.1.5.1 Liver Disease

The incidence of liver disease in patients taking androgenic hormones is said to be higher than for the general population. There are reports of hepatic adenomas, cholestasis, peliosis, nodular regenerative hyperplasia, and hepatocellular carcinoma. However, causation has been very difficult to establish. Elevated amino transferase activity has also been observed in steroid-abusing athletes, but because exercise itself can be associated with some enzyme changes (depending on when the sample is drawn in relation to exercise), it is difficult to be sure if any connection exists at all. Similar doubts exist about other disorders (hepatic adenoma, peliosis hepatis) said to be related to anabolic steroid abuse.

7.1.5.1.1 Peliosis Hepatis This obscure disorder has been recognized for well over 100 years. It is characterized by the presence of scattered small, cystic blood-filled lakes found throughout the liver. Some of the cysts may be lined with epithelium, while others are not (Kalra et al., 1977). These collections of blood are often located adjacent to zones of hepatocellular necrosis. The lungs may also be involved in the same process, as may the entire reticuloendothelial system. Lesions have been described in the spleen, lymph nodes, and bone marrow (Taxy, 1978).

Peliosis is seen as a complication of numerous, apparently unrelated disorders, including debilitating illnesses such as tuberculosis, hematological malignancies, the acquired immunodeficiency syndrome, and post-transplant immunosuppression, as well as intravenous drug abuse, chronic alcoholism, and in conjunction with the intake of oral contraceptives or steroids (Tsokos and Erbersdobler, 2005).

Peliosis only develops in organs that form part of the mononuclear phagocytic system (liver, spleen, bone marrow, and lymph nodes) (Tsokos and Puschel, 2004), though the occasional rare report implicates other organs, including the lungs and kidneys. It has been suggested that the disorder is really a congenital malformation of vessels, but the cause is still debated. At autopsy the lesions have a "Swiss cheese" appearance. Microscopically, two forms of disease are recognized: parenchymal and phlebectatic. In the former there are irregular cysts with no apparent cellular lining. In the latter there are regularly shaped, spherical cavities lined by endothelium and/or fibrosis. When the spleen is involved the peliotic lesions may be sporadic or widely disseminated, but all of the cavities have well-demarcated margins and some of the cavities may be lined by sinusoidal endothelium (Tsokos and Erbersdobler, 2005).

Peliosis is easily diagnosed by ultrasonography as well as by conventional x-ray, CT scans, and magnetic resonance imaging (Parmar et al., 2000; Iannaccone et al., 2006). However, because most individuals with peliosis are asymptomatic, the probability that they will be scanned is very small. Patients with peliosis occasionally bleed to death from these lesions (Nadell and Kosek, 1977) or die of hepatic coma. Because most deceased patients with peliosis studied were gravely ill with other disorders, it is difficult to determine what caused the fatal event. In recent years peliosis has been described in AIDS patients, where the lesions may be confused with Kaposi's sarcoma (Hnatuk et al., 1994).

Early researchers thought that peliosis was a congenital disease (Zak, 1950), but cows with peliosis (known as St. George's disease) can be cured simply by a change of pasture (Graham and Kennedy, 1990). In fact, a heterogeneous group of agents have been implicated. Many cases, particularly those occurring in the immunosuppressed, are infectious in origin. Bacillary angiomatosis and bacillary peliosis, opportunistic infections caused by *Bartonella henselae* and *B. quintana*, involve skin and bone as often as the liver. *B. quintana* and related organisms such as *B. henselae* (the same organism responsible for cat scratch disease) can be identified with polymerase chain reaction (PCR) techniques, using DNA obtained from either skin or liver biopsy specimens (Piemont and Heller, 1996). If the diagnosis can be made, infections do respond to long-term antibiotic treatment (Santos et al., 2000). Whether chemically induced cases without underlying infection ever occur is unclear.

7.1.5.1.2 Cholestasis The 17-α-alkyl-substituted steroids can cause cholestatic jaundice. Bile accumulates in the canaliculi but without evidence of inflammation or necrosis (Foss and Simpson, 1959; Westaby et al., 1983). The frequency of cholestasis in testosterone abusers is unknown. Different estimates place the incidence at anywhere from less than 1% to at least 17% (Plymate and Friedl, 1992). Several deaths from cholestatic jaundice have been attributed to steroids, but they occurred in elderly, debilitated patients, and the evidence of causality is far from convincing.

Tissue culture studies show that 17-α-alkylated steroids such as methyltestosterone, oxymetholone, and stanozolol are directly toxic to hepatocytes, but nonalkylated steroids such as testosterone cypionate, 19-nortestosterone, testosterone, and estradiol are not (Welder et al., 1995). At the same time, the results of animal studies suggest that CYP3A polymorphisms, leading to under-expression of the enzyme, may play a role in toxicity (Paolini et al., 2000). Many drugs can affect the composition of bile, and it may be that the expression of specific human cytochromes is the final common pathway leading to cholestasis. A solitary case report, published in 1994, described severe cholestasis and jaundice in a user of non-C17-alkylated steroid (testosterone propionate), raising the possibility that cholestasis may not be confined to users of oral agents (Yoshida et al., 1994).

7.1.5.1.3 Hepatic Tumors A clear association exists between the use of C17-alkylated androgens and the occurrence of hepatic tumors. Hepatocellular adenomas, similar in many ways to the adenomas that arise in the livers of women taking birth control pills, are not uncommon even in men who are not steroid abusers. Judging from the number of reports, the incidence is 1–3% among users of 17-alkylated androgens (Friedl, 1990). Like peliosis, hepatocellular adenomas are usually silent; patients with adenomas only come to medical attention when the adenomas rupture and cause hemoperitoneum, or as incidental findings at autopsy (Lesna et al., 1976; Creagh et al., 1988). Liver function tests may be normal in asymptomatic cases (Westaby et al., 1983) and the distribution of the lesions is such that even if their existence is suspected, percutaneous biopsy may miss them, though with CT assisted biopsy this possibility becomes less and less likely.

Adenomas have the same appearance in men treated with androgens and women taking birth control pills. In either case, the adenoma is composed of sheets of cells that look like normal hepatocytes. There are, however, some differences. One important difference is that androgen-related adenomas tend to be larger. Adenomas in steroid users range in size from a few millimeters to several centimeters in diameter (Socas et al., 2005).

Androgen-related adenomas often form bile-containing acini, which is somewhat disturbing because without a history of androgen abuse, acini formation is usually considered to be histological evidence of malignancy.

Adenomas in steroid users may also display other features that are suspect for malignancy, such as bizarre nuclei and even rare mitoses (Creagh et al., 1988). The benign nature of most of these lesions is confirmed by their sharply demarcated margins, their failure to metastasize, the absence of demonstrable alpha-fetoprotein, and the absence of associated cirrhosis (the most frequent setting for hepatocellular carcinoma). The fact that adenomas regress when androgens are discontinued also argues against their malignant nature (Friedl, 1990). Nonetheless, hepatocellular carcinoma has been diagnosed in individuals taking C17-substituted androgens (Overly et al., 1984; Goldman, 1985; Garoyski et al., 2008), so the possibility for conversion from adenoma to carcinoma cannot be entirely ruled out (Boyd and Mark, 1977). Rarely, nodular hyperplasia may result in portal hypertension, even in the face of a normal biopsy (Stromeyer et al., 1979). As a consequence, bleeding esophageal varices may occur (Winwood et al., 1990).

7.1.5.2 Cardiovascular Disease

Continuously mounting evidence supports the theory that steroid abuse causes heart and vascular disease. The evidence is derived from animal experimentation, some observational studies, and a handful of case reports. Nonetheless, there appears to be sufficient evidence to conclude that steroid abuse, by the right person and under the right circumstances, can induce myocardial hypertrophy and interstitial fibrosis, leading to sudden cardiac death (Luke et al., 1990). Anabolic androgens directly affect myocyte growth, metabolism, and programmed cell death. Myocardial hypertrophy is easily produced in the rat model of steroid toxicity (Tseng et al., 1994) and has been documented in controlled trials of steroid-abusing weight lifters (Dickerman et al., 1998; Stevens et al., 2002). Myocardial hypertrophy, from whatever cause, is accompanied by remodeling and fibrosis; either or both can provide the required substrate to cause sudden cardiac death (Haider et al., 1998).

In animal models, new capillary formation does not keep pace with steroid-induced myocyte hypertrophy (Tagarakis et al., 2000a, b). Thus, at the cellular level, even in the absence of significant disease of the epicardial vessels, and even in the absence of extreme exertion, the myocardium of steroid abusers may be relatively ischemic, and ischemia could account for many of the reported episodes of sudden death in steroid abusers.

There are four hypothetical models that can explain how anabolic steroid abuse might cause heart disease (atherogenesis, thrombosis, coronary artery vasospasm, and direct injury models) (Melchert and Welder, 1995). Most recent evidence seems to favor the direct injury model, consistent with the observation that cardiomyocytes express androgen receptors. This theory gains added strength from the observation that myocardial necrosis can be demonstrated in the hearts of steroid abusers who die suddenly (Fineschi et al., 2001, 2007; Di Paolo et al., 2007), as can areas of myocardial fiber disarray and other anatomic abnormalities. The pattern of necrosis described by Fineschi et al. is almost identical to that seen in stimulant abusers (Urhausen et al., 1994; Baroldi et al., 2001).

Reports describing myocardial infarction in steroid abusers (Winwood et al., 1990; Ferenchick and Adelman, 1992; Fineschi et al., 2001, 2007; Wysoczanski et al., 2008) are not uncommon. Heart disease has been reproduced in an animal model. When hypercholesterolemic New Zealand rabbits are treated for 16 weeks with testosterone (25 mg/kg/week)

and nandrolone (50 mg/kg/week) both testosterone and nandrolone significantly reduced HDL cholesterol levels and, at the same time (a) potentiated vasoconstriction responses to epinephrine, 5-HT, and endothelin-1, and (b) attenuated vasorelaxant responses to sodium nitroprusside. In addition nandrolone, but not testosterone, also caused a significant increase in LDL cholesterol levels. The results suggest both that steroid abusers run the risk of accelerated atherogenesis, and that they are prone to vasospasm (Ammar et al., 2004).

Chronic abuse of anabolic steroid results in pathologic alterations that are probably dose-related. It has been established that androgens can directly mediate a significant hypertrophic response in cardiac myocytes (Marsh et al., 1998). Vascular endothelial cells may also be altered in such a way as to favor the occurrence of vasospasm (Melchert and Welder, 1995). The difficulty in establishing a firm relationship between testosterone and heart disease is the fact that abusers take a very large number of different steroid products and they take them in very large doses (Hausmann et al., 1998).

In all but one of the reported steroid-related infarcts (Lyndberg, 1991), the coronary arteries were free of atheroma, and there was no evidence of thrombi (Fineschi et al., 2001). It has recently been proposed that steroid-taking body builders experience sustained increases in heart rate and blood pressure, and that these increases may, in turn, result in compensatory hypertrophy of the left ventricular wall (Urhausen et al., 2004). If that were proven to be the case, it would be consistent with the clinical and autopsy findings reported to date. However, when steroid abuse is combined with intense exercise training, the pattern of hypertrophy is not the eccentric variety associated with athletes' hearts but, rather, concentric hypertrophy of the left ventricular wall, indistinguishable from the pattern seen in untreated hypertensives whose impaired diastolic function, increasing the risk for sudden cardiac death (Urhausen et al., 2004). How this observation is to be interpreted remains unclear, because concentric hypertrophy is also seen in drug-free weight lifters (Dickerman et al., 1998), and the change may have nothing at all to do with steroid abuse.

The limited results of research that have been published also suggest that not all anabolic steroids are atherogenic; it is only use of 17-α-alkylated anabolic steroids that is associated with this disorder. There is no evidence that 17-β-esterified agents such as nandrolone produce atherogenic changes (Glazer and Suchman, 1994). How these different molecules act to make steroid abusers more susceptible to coronary artery disease is not known (Kabakci et al., 1999).

Another potential mechanism for testosterone cardiotoxicity is drug-induced apoptosis. Apoptosis is a term used to describe "cell suicide." Apoptosis is a form of cell death in which a programmed sequence of events leads to the destruction of cells without causing the release of harmful substances into the surrounding area. Apoptosis is absolutely required for normal growth and tissue differentiation. For example, the differentiation of fingers and toes in a developing human embryo requires cells between the fingers to initiate apoptosis so that the digits can separate. Not only is apoptosis a necessary part of growth and development, it also plays a role in disease. Excessive apoptosis can result in hypotrophy and ischemic damage, whereas insufficient apoptosis may lead to situations where there is uncontrolled cell proliferation, such as cancer.

When it was first discovered that animals treated with methandrostenolone develop myocyte necrosis, cellular edema, and mitochondrial swelling, there were no plausible explanations for the process (Behrendt and Boffin, 1977; Appell et al., 1983). It is now known, mainly from the results of more recent histochemical studies, that myocyte damage in

experimental animals is secondary to anabolic androgen-induced apoptosis (Abu-Shakra and Nachtman, 1995; Abu-Shakra et al., 1997). Of concern to weight lifters and other steroid abusers, the damage seems to be dose related. When rat ventricular myocytes were exposed to stanozolol, testosterone enanthate, and testosterone (0.1 μmol/L, 1 μmol/L, 10 μmol/L, and 100 μmol/L) in vitro for 20 hours, the percentage of myocytes undergoing apoptosis was markedly increased when compared to controls (Zaugg et al., 2001).

The histological appearance of apoptosis consists of myocyte swelling, plasma membrane bleb formation, and rapid disappearance of the nucleolus, but without hemorrhage. This pattern is easily distinguished from the pattern seen in myocardial ischemia. To the untrained eye the changes may be very difficult to recognize, and special staining ("TUNL") is usually required. Even though the presence of apoptosis may not be apparent, it can still lead to a fatal outcome. Apoptotic myocytes are eventually replaced by fibrous scar tissue, providing another possible substrate for the occurrence of re-entrant arrhythmias.

Finally, cardiomyopathic changes have been described in the hearts of steroid abusers, but there have been no systematic studies so it is impossible to say whether the change is due to anabolic steroids or some previously undiagnosed underlying disease.

7.1.5.3 Neurological Disorders

Episodes of cerebral, coronary artery, intracardiac, and peripheral thrombosis have been linked to steroid abuse (Frankle and Borrelli, 1990; Akhter et al., 1994; Fisher et al., 1996; Hartgens and Kuipers, 2004; Kindermann and Urhausen, 2004; Urhausen et al., 2004; Kindermann, 2006) but reports are still rare. Psychiatric disturbances are, on the other hand, relatively common. There is some evidence that in susceptible individuals, particularly the aging (Lunenfeld, 2006), suicidal behavior is more common in steroid abusers (Thiblin et al., 1999). One of the more interesting new discoveries about anabolic steroid abusers is that both hematocrit and homocysteine plasma concentrations are higher than in controls, suggesting users are at increased risk of thrombotic episodes (Graham et al., 2006).

Anabolic androgenic steroid use among teenagers is increasing and there is evidence that increased steroid use is associated with increased risk for violent behavior. Studies in rodents tend to confirm that exposure to testosterone and nandrolone, but not stanozolol, increases aggression. Pubertal rats receiving anabolic androgenic steroids respond appropriately to social cues as they are more aggressive toward intact males than they are toward castrates. On the other hand, there is no evidence that steroid abuse leads to indiscriminate acts of aggression. Experimental studies suggest that these drugs sensitize animals to their surroundings and lower their threshold to respond to provocation with aggression. If the same holds true in humans, steroids may well be the cause of inappropriately aggressive behavior (McGinnis, 2004).

The problem with trying to attribute individual aggressive acts to steroid abuse is that many users of anabolic androgenic steroids also abuse alcohol and/or various illegal substances. One study of 500 steroid abusers in California found that 95% were found to be taking other drugs (Parkinson and Evans, 2006). Substance abuse is a well-known risk factor for violent behavior, so when violent behavior is observed in a steroid abuser, it might just as likely be due to some other drug and not the steroid (Klotz et al., 2007).

Until now claims of steroid-related psychosis ("roid rage") have not been successful in court and the occurrence of clinically proven effects on behavior remains controversial, largely because confirmatory animal studies are not convincing. For example, in a double-blinded controlled clinical trial where supraphysiological doses of testosterone

(600 mg/week) were administered to volunteers, aggressive behavior was not increased (Tricker et al., 1996). Still, as more solid animal data are produced, it seems likely that, at some point, the "roid rage" defense will prevail.

7.1.5.4 Musculoskeletal Disease

Compared to controls, tendons from mice chronically treated with anabolic steroids are stiffer, absorb less energy, and rupture with lesser degrees of elongation, although maximal tendon strength is unaffected (Inhofe et al., 1995). Recent experimental studies have shown that anabolic androgenic steroid treatment can impair tissue remodeling in the tendons of animals undergoing physical exercise. Anabolic steroid treatment down-regulates matrix metallopeptidase activity, and the result is increased potential for tendon injury (Marqueti et al., 2006). Initial suggestions that these mechanical changes described above are accompanied by recognizable histological abnormalities have not been confirmed (Evans et al., 1998). Still, the observed physiological changes may explain the occasional report of steroid-related tendon rupture (Hill et al., 1983; Kramhoft and Solgaard, 1986; Laseter and Russell, 1991; Freeman and Rooker, 1995; Liow and Tavares, 1995). It may also be that microscopic alteration in tendons is not necessary for rupture to occur. Anabolic steroid abuse causes muscle hypertrophy and the resultant muscle mass may simply overpower tendon strength.

Avascular necrosis of the femoral heads similar to that seen with long-term glucocorticoid therapy has also been reported (Frankle, 1992), but it is not clear that the phenomenon is due to anabolic steroid abuse. It could just as easily represent an idiosyncratic reaction (Frankle et al., 1984; Pettine, 1991). When exercise-conditioned animals are given anabolic steroids the normal number of capillaries is reduced, not just in the heart, but

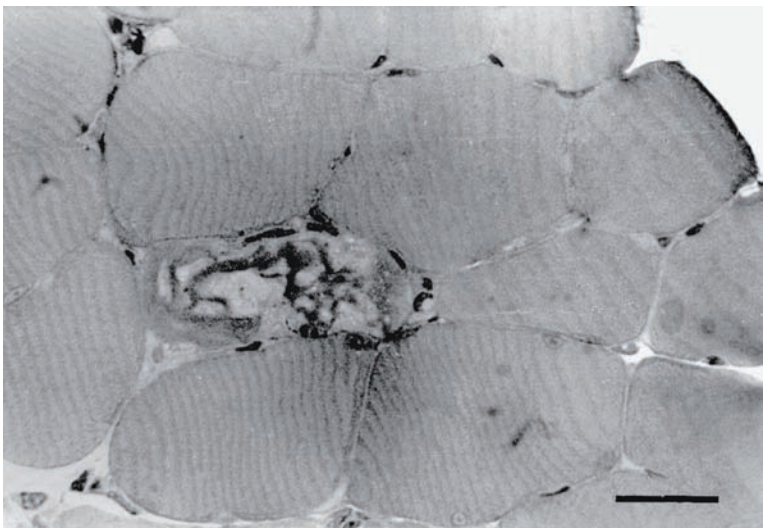

Figure 7.1.5.4.1 Degenerating muscle in steroid-treated rat. The peripheral muscle of rat treated with nandrolone decanoate and forced to exercise. Focal necrosis occurs, with degenerating fibers intermingled with normal-appearing fibers (scale bar = 50 μm). Morphometric analysis of these same fibers shows decreased numbers of capillaries when compared to controls. (Courtesy of Dr. J. M. Soares, Faculty of Sport Sciences, University of Porto, Porto, Portugal.)

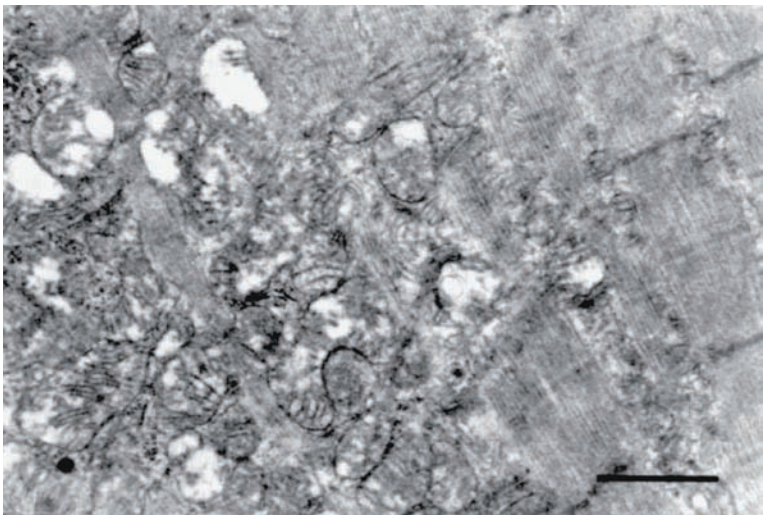

Figure 7.1.5.4.2 Steroid-induced mitochondrial damage in rat. Electron micrographs of rats chronically treated with nandrolone show mitochondrial swelling and disruption very similar to what is seen in the hearts of animals exposed to high levels of catecholamines (scale bar = 2 µm). (Courtesy of Dr. J. M. Soares, Faculty of Sport Sciences, University of Porto, Porto, Portugal.)

also in skeletal muscle fibers. At the same time, the amount of fatty and connective tissue in their muscles increases (Soares and Duarte, 1991). The relative decrease in the number of capillaries per fiber suggests an inefficient exchange of respiratory gases and nutrients in the hypertrophied muscles. The typical histological picture in these animals is patchy fiber necrosis. Degenerating fibers are surrounded by fibers that have normal morphology (Figures 7.1.5.4.1 and 7.1.5.4.2). Control studies in humans are lacking.

7.1.6 Detecting Steroid Abuse

Anabolic steroid abusers fit a clinical profile, and reference to it is often helpful, especially if the history is unclear. Typical findings are shown in Table 7.1.6.1. Testosterone blood concentrations vary too widely to be used for detection purposes. Testosterone has been measured in conditioned athletes both before and after exercising; observed concentrations have been between 16 and 17 nmol/dL. In one study, it was found that after an intense period of strength training, testosterone levels increased by 27%. Testosterone levels increased even more after endurance training (37%) but after both types of training, levels returned to normal within a few hours of the exercise cessation (Jensen et al., 1991). In addition to being affected by exercise, testosterone blood concentrations also depend on time of day, age, and body mass index (BMI). Aging affects both testosterone and the free T index (testosterone divided by concentrations of SHBG), and so does the use of other drugs, including prescription medications such as beta-blockers (Harman et al., 2001). Postmortem blood testosterone concentrations in the forensic setting have still not been studied, though a number of studies have been published on postmortem testosterone concentrations observed in obscure endocrine disorders.

Because blood measurement is an unpredictable indicator for testosterone administration, it cannot be used for doping control. As an alternative, the IOC has chosen to base

Table 7.1.6.1 Profile of a Steroid Abuser

Social
Recent changes in friends, acquaintances
Obsession with health, exercise, weight lifting
Spends most of time in gyms or health clubs
Takes large amounts of vitamins and food supplements
Very high calorie intake
Does not abuse other drugs because of concern with leading a "healthy lifestyle"
Physical
Rapid weight gain and muscle development
Increased body hair, deepening of voice
Acne (both sexes)
Hair loss (both sexes)
Breast enlargement (males)
Testicular atrophy
Difficulty urinating
Elevated blood pressure
Complaints of stomach upset
Jaundice
Edema of extremities
Mental Changes
Increased aggression
Hyperactivity, irritability
Auditory hallucinations
Paranoid delusions
Manic episodes
Depression and anxiety
Panic disorders
Suicidal thoughts
Laboratory Findings
Decreased HDL cholesterol
Decreased luteinizing hormone
Decreased follicle stimulating hormone
Decreased thyroid stimulating hormone
Decreased thyroid hormones
Elevated liver enzymes
Increased hematocrit
Increased LDL cholesterol
Increased triglycerides
Increased glucose

Source: Adapted from Narducci, W. A. et al., *J. Toxicol. Clin. Toxicol.,* 28(3), 287–310, 1990.

its testing protocols on the urinary ratio of testosterone to epitestosterone (T/E). Epitestosterone is a natural component of human biological fluids. It had been believed to be a weak antiandrogen (Havlikova et al., 2002), but the biosynthetic pathway and site of its formation in man have not been unequivocally determined. Its production apparently parallels the formation of testosterone (T), but its concentration is not influenced by exogenous administration of testosterone, which is why the T/E ratio was originally selected as a screening tool for sports doping (Starka, 2003).

In 1984 the IOC declared that a urine T/E ratio greater than 6 was proof that supplemental testosterone was being used. However, in 2005, WADA (the agency charged with IOC testing) dropped the acceptable T/E ratio to 4. While this is a much more realistic approach than the old one, it still allows careful athletes to cheat because, in reality, most of the population have a T/E ratio much closer to 2, even lower among Asians. It is possible to take supplemental testosterone and still not exceed the 2:1 ratio.

Athletes may excrete a decreased amount of epitestosterone because they are polymorphic for the promoter gene (CYP17 and UGT2B) enzymes required to synthesize epitestosterone. If less epitestosterone is produced, less will be excreted and the resultant ratio of testosterone to epitestosterone will be elevated above the 4:1 accepted by WADA (Schulze et al., 2008).

Measurement of the carbon isotope ratio now appears to offer the most effective approach to testosterone doping detection. Both ^{12}C and ^{13}C are stable carbon isotopes, making it possible to separate exogenous from endogenous testosterone by the ratio of $^{13}C/^{12}C$. This is possible because exogenous (manmade) testosterone contains less ^{13}C than testosterone made by the body. If a urine testosterone is tested and the ratio of ^{13}C to ^{12}C is very low, it is evidence for the use of exogenous testosterone.

The problem with isotope ratios is that the body produces testosterone from sterols. Sterols are a normal component of the human diet. Plants make sterols by several different synthetic paths. Some of these synthetic pathways cause large shifts, relative to the atmosphere, in the $^{13}C/^{12}C$ ratio of the materials being metabolized, but other routes do not. For example, the sterols that are found in wheat, rice, potatoes, and barley have different isotope ratios than sterols found in maize, sugar cane, and pineapple. The metabolic quirks of these plants create major problems for drug testers, because diets are not the same around the world, which means that the types of testosterone and testosterone/epitestosterone ratios are different in different parts of the world. It is known, for example, that samples collected in Kenya have a higher content of ^{13}C steroids than those collected in other parts of the world (Saudan et al., 2006).

Testosterone and nandrolone-like drugs can reliably be detected in hair, and the evidence suggests that this approach is much more likely to detect abusers than urine testing. In one study, the effectiveness of urine and hair testing was compared in samples obtained simultaneously from a group of professional bicyclists; 12% of the hair tests, but none of the urine tests, disclosed the presence of anabolic agents (Gaillard et al., 2000). Even though hair drug concentrations are low (in the picogram range), currently available analytic techniques allow for reliable detection, particularly now that LC/MS/MS testing has become widely available (Bresson et al., 2006; Kintz et al., 2006). Most sports regulatory bodies still do not yet accept hair testing for anabolic steroids.

Until the late 1990s, athletes rarely tested positive for oral anabolic agents. Oral anabolic steroids such as nandrolone may remain detectable in the blood and urine for many weeks after ingestion, and so cannot be taken by those who know they are subject to "in-competition" testing. But in 1999, a loophole in IOC regulations allowed a number of prominent athletes to self-administer nandrolone in the form of the precursors 19-norandrostenedione and 19-norandrostenenediol. Even though these precursors were turned into testosterone, their use did not lead to disqualification. At the time, the rules of the IOC and the International Amateur Athletic Foundation (IAAF) specified that nandrolone and "related substances" were prohibited, but precursor-containing compounds sold as dietary supplements were not. That loophole has now been closed. WADA enforces a policy of

strict liability, so that even if an individual innocently ingested a precursor compound as a contaminant of a legal supplement, the individual would still be disqualified.

Many approaches besides the T/E ratio have been suggested for separating abusers from biological false positives. The ketoconazole test is often used for this purpose. This antifungal drug inhibits testosterone production by inhibiting 17-α-hydroxylase and 17,20-lyase activity. If testosterone concentrations are high because testosterone has been injected, ketoconazole will not cause concentrations to drop. On the other hand, if an innocent athlete with a testosterone-to-epitestosterone ratio greater than 6 were given ketoconazole, one would expect a steep drop in testosterone production and a concomitant decrease in the ratio. This has proven to be the case when ketoconazole is given to athletes with high ratios (Kicman et al., 1993).

The British 800-meter runner Diane Modahl, who was banned for four years after testing positive for testosterone in 1994, was later cleared after it was revealed that her urine sample had been left unrefrigerated in the official IOC testing laboratory for at least two days before it was analyzed (Bilton, 1995). Modahl's attorneys successfully argued that the resulting bacterial growth caused the positive result. Laboratory studies have partly confirmed these claims. While bacterial contamination does not result in production of testosterone or epitestosterone, a few organisms can synthesize 5-α-androstanedione, 5-β-androstanedione, and androstenedione using endogenous steroids as a substrate. Other organisms are capable of cleaving steroid glucuronides and sulfate conjugates, converting them to measurable free testosterone (de la Torre et al., 2001).

In 2003 the Food and Drug Administration obtained evidence that an unapproved new drug called tetrahydrogestrinone (THG, known by athletes as "the clear") was being used to enhance performance. THG was not detectable by the drug tests then in use. THG has a chemical structure similar to gestrinone and trenbolone (18α-homo-pregna-4,9,11-trien-17-ol-3-one). THG binds both androgen and progestin receptors. When it was first discovered, there were no controlled in vivo human excretion studies that would have helped to identify urinary markers of this compound. In vitro studies done with human hepatocytes suggested there was a metabolic pathway for THG, which included the addition of a hydroxyl group and a β-glucuronic acid at C-18 (Catlin et al., 2004; Death et al., 2004; Lévesque et al., 2005).

THG is not detectable in the urine by any of the standard doping-control techniques used to screen for anabolic steroids (pertrimethylsilyl derivatization with GC/MS), but the underivatized form of the drug is easily detected with LC/MS/MS (Catlin et al., 2004). Based upon this knowledge, new analytical chromatographic methodologies have been developed aimed at detecting THG-related substances. The latest advance has been the introduction of novel yeast reporter gene androgen bioassays and high-throughput immuno-screening technologies (Salvador et al., 2007). One can only speculate when the next generation of illicit androgens will be discovered.

7.1.7 Postmortem Considerations

Very little has been written on the subject. An interesting study of SIDS victims, published in 2005, found that male SIDS infants had higher testosterone concentrations than controls (4.8 ± 0.4 vs. 2.2 ± 0.4 nmol, respectively; $p < .005$) and females (2.4 ± 0.2 vs. 1.6 ± 0.2 nmol, respectively; $p < .03$), leading the authors to suggest that high testosterone concentrations might be causal in SIDS (Emery et al., 2005). This suggestion has never

really been confirmed. There are reports of sudden death in steroid abusers/body builders, and most have had evidence of myocardial hypertrophy and interstitial fibrosis (see Section 7.1.5.2). In the final analysis it may be possible to identify a pattern (e.g., classic physical characteristics combined with hepatic adenomas and myocardial fibrosis), but that hardly would be sufficient to prove causation. Today, the generally accepted theory is that for sudden death to occur, there must first be a substrate and then an appropriate environmental interaction. Interstitial myocardial fibrosis could well supply the substrate, and steroid abuse the environmental trigger, but so could many other factors. For example, recent evidence suggests that the incidence of heritable channelopathy is much higher than had previously been thought (Chugh et al., 2004), and there is equally compelling evidence that individuals may die of myocarditis even though the histologic evidence of infection is scanty or entirely absent (Kühl et al., 2003). Neither of the last two conditions could be diagnosed without DNA testing, a modality conspicuously absent from most medical examiners' offices.

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Solvents

8

8.1 Introduction

Volatile solvents, liquids that vaporize at room temperature, are commonly abused. The practice of solvent inhalation is referred to as "huffing." The abuse of inorganic volatile solvents is confined largely to less affluent teenagers and young adults, but it is also popular among disadvantaged adults. The particular agent abused seems to be largely a function of availability.

Inhalants can be conveniently divided into five categories: (1) volatile (industrial and household solvents such as pain thinners, degreasers, dry-cleaning fluid, and gasoline), (2) art or office supply solvents (correction fluids, felt-tip marker fluid, and electronic contact cleaners), (3) aerosols (household aerosol propellants found in spray paints, hair spray, deodorants, and fabric protector sprays), (4) gases (including butane lighters and propane tanks), and (5) whipping cream aerosols or dispensers and refrigerant gases. More exotic agents, such as gases used for medical anesthesia, are much less commonly encountered. The nitrites should probably be considered as a unique category; volatile organic nitrites such as cyclohexyl, butyl, and amyl nitrite, commonly known as "poppers," are closely linked with sexual practices and not drug abuse per se. These agents are often sold, both in the U.S. and in Europe, in small brown bottles labeled as "video head cleaner," "room odorizer," "leather cleaner," or "liquid aroma."

Toluene is the major active component in many of the agents listed above, and the agent most likely to be responsible in cases of fatal intoxication, though it seems likely that much "abuse" occurs accidentally, with intoxication resulting from occupational exposure (Bowen et al., 2006). Because toluene, the main offender, is a lipophilic compound, it binds strongly to myelin and other lipid-containing organs, which is why it tends to concentrate in the brain (Chen et al., 2004).

Acute intoxication causes bizarre behavior. Nearly all of these agents produce short-term effects just like any other anesthetic agent, but generally they are shorter acting. The most common symptoms are euphoria, headache, and ataxia (Weiss, 1983; Evans and Balster, 1991), however, these changes are usually transient. MRI scan shows that toluene preferentially affects white matter structures and periventricular/subcortical (relative to cortical) regions (Yücel et al., 2008), so histological examination should focus on these areas. Neuropile vacuolization without inflammatory changes is another notable feature. At autopsy the presence of paint around the nares should suggest the diagnosis (Byard et al., 2006). Chronic abuse leads to irreversible brain damage.

White matter damage usually precedes any clinical evidence of cerebellar dysfunction or psychiatric disease. Occasional episodes of parkinsonism, including spasticity and cognitive changes, may also be reported. Children born to mothers who use toluene during pregnancy develop a distinctive fetal solvent syndrome, including growth retardation, craniofacial dysmorphism, hearing loss, cleft palate, developmental delay, cerebellar dysfunction, and hyperactivity (Hougaard et al., 2005; Bowen and Hannigan, 2006; Grandjean and Landrigan, 2006).

8.2 Incidence

The practice of "huffing" is more widespread than was originally supposed. According to the National Survey on Drug Use and Health performed by the U.S. National Institute on Drug Abuse, more 8th graders have tried inhalants in their lifetime than any other illicit drug. Combined data for 2002 to 2006 indicate that an annual average of 593,000 adolescents aged 12 to 17 had used inhalants for the first time in the year before their survey interview. Among past year inhalant initiates aged 12 to 15, the three most commonly used types of inhalants were (1) glue, shoe polish, or toluene; (2) spray paints; and (3) gasoline or lighter fluid; in comparison, nitrous oxide or whippets (nitrous oxide packaged in small cartridges, then enclosed in a container of cream, to produce whipped cream) were the most common type of inhalant used among initiates aged 16 or 17 (NSDUH, 2008).

8.3 Epidemiology

The percentage of young adults reporting regular use of inhalants decreased by nearly 50% from 1997 to 1998 (2.0 to 1.1%), but the reported rate of first use among youths aged 12–17 years rose significantly during that same period. From 1988 to 1996, the number of young adults aged 18–25 who abused solvents for the first time increased threefold (from 3.7 to 10.7 per 1000 potential new users). The Medical Examiner component of the 1998 Drug Abuse Warning Network (DAWN) report lists a total of 105 deaths related to "solvents/aerosols." Most decedents (70%) were male. Deaths from solvent abuse accounted for 1% of all reported drug-related deaths in the year 2000 (Kissin et al., 2000).

Significant data are no longer available from DAWN, but among students surveyed as part of the 2005 Monitoring the Future study, 17.1% of 8th graders, 13.1% of 10th graders, and 11.4% of 12th graders reported lifetime use of inhalants. Approximately 37.5% of 8th graders and 45.7% of 10th graders surveyed in 2005 reported trying inhalants once or twice, suggesting that use is becoming more popular, at least within the U.S. (Johnston et al., 2005).

The Centers for Disease Control and Prevention (CDC) also conducts a survey of high school students throughout the U.S. called the Youth Risk Behavior Surveillance System (YRBSS). Among students surveyed for the 2005 YRBSS, 12.4% reported using inhalants at least one time during their lifetime (Eaton et al., 2006).

8.4 General Considerations

Hundreds, perhaps thousands, of commercial and household products contain solvents that can be abused. The medical complications of acute solvent toxicity still remain poorly characterized, but much more is now known about the consequences of chronic exposure.

Solvent abuse is not a new problem. Recreational solvent abuse was recognized before World War I, and the abuse of ether was popular in England during the 1890s. Deaths from recreational chloroform abuse were first reported at an even earlier date, but never has so much of the population been exposed — unintentionally or intentionally.

Solvent abusers are most likely to be males between the ages of 13 and 15, but the prevalence of abuse and the age of the abusers vary from location to location. Some adults, especially those living in rural communities and in locations where there is ready access to the appropriate chemicals, are also abusers (Flanagan and Ives, 1994). While solvent abuse was once much more common in the U.K. than in the U.S., the number of reports in the literature suggests that the rates in both countries are converging, and rising in the rest of the world. In several different areas of the world, inhalant abuse is "ubiquitous and epidemic," most notably among street children living in Brazil, Cambodia, India, Mexico, Peru, and Russia (Carlini-Marlatt et al., 2003; NIDA, 2005).

Solvents are highly soluble in lipids and they rapidly enter the central nervous system, where they act as depressants. Animal studies have disclosed a host of different molecular targets. Many of the solvents appear to share a common mechanism: they inhibit NMDA receptors. Prolonged exposure can modulate the expression of these glutamatergic receptor subtypes, but the final outcome depends on which animal model is being studied. Many other receptors appear to be involved. $GABA_A$, glycine, and type 3 5-HT receptors are all disrupted by solvent exposure (Bowen et al., 2006). In addition, toluene reversibly and noncompetitively inhibits neuronal acetylcholine receptors, at least in animals (Bale et al., 2002). Some toluene deaths may be attributed to toluene's ability to reversibly inhibit cardiac voltage-activated sodium channels. Whether or not inhibition occurs depends on the toluene concentration. Because sodium channels are required for the initial phase of the cardiac action potential, it has been suggested that this effect might explain the phenomenon of sudden cardiac death in "huffers" (Cruz et al., 2003). It has recently been demonstrated that toluene abuse is associated with QT prolongation and QT dispersion, an alteration that may account for some cases of sudden death in toluene abusers (see Section 8.6.4) (Alper et al., 2008).

Solvents share some characteristics with other depressants such as barbiturates, benzodiazepines, and alcohol (Evans and Balster, 1991). Chemicals such as toluene, 1,1,1-trichloroethane (TCE), and trichloroethylene (TCY) affect ligand-gated ion channel activity. In vitro studies have shown that solvents may cause reversible enhancement of γ-aminobutyric acid A ($GABA_A$) receptor-mediated synaptic currents in hippocampal brain slices, and increase expression of α-1-glycine receptors (Beckstead et al., 2000). These are essentially the same effects produced by sedative hypnotic drugs such as barbiturates and benzodiazepines. The ability of solvents to produce a state of true dependence remains a matter of some dispute (Miller and Gold, 1991) but the results of animal studies certainly suggest that solvent abusers can become physically dependent (Evans and Balster, 1991), as do other animal studies clearly demonstrating that exposure to toluene and related compounds at concentrations of 2000–6000 ppm results in anxiolytic-like effects (Paez-Martinez et al., 2003).

Psychiatric, neurological, renal, and hepatic disorders have been reported as complications of solvent abuse, as has teratogenesis, but the primary risk has always been sudden death. A U.K. study (Flanagan et al., 1990) analyzed the patterns and mechanisms of death in a series of 1237 solvent abusers over a 20-year period. Deaths were divided into four different groups according to the type of solvent involved: (1) aerosol propellants, (2) gas fuels,

(3) chlorinated and other types of solvents, and (4) solvents from adhesives. The proportion of deaths due to direct toxicity, aspiration, and asphyxia was remarkably similar in all the groups except for adhesive solvents (containing mostly toluene). Among individuals abusing adhesives, trauma was the most frequent cause of death, suggesting that impairment of judgment is somewhat more likely with the use of adhesives than with the use of other types of solvents.

8.5 Absorption and Tissue Disposition

Not all solvents are abused. In order to have abuse potential, a compound must be sufficiently volatile to be inhaled. This explains the generally low abuse potential of petroleum distillates, such as kerosene and ethylene glycol. Industrial workers exposed to ethylene glycol fumes can develop an assortment of chronic disorders, including testicular degeneration (Lee and Kennedy, 1991), but reports of toxicity in chronic abusers are rare. Toluene, the solvent most often used in contact adhesives, is highly volatile and frequently abused. Table 8.5.1 lists some of the more commonly abused agents.

Table 8.5.1 Partial List of Agents That May Be Responsible for Inhalant Abuse Toxicity, Grouped by Pattern of Toxicity*

A. *Aerosol propellants (air fresheners, deodorant spray, hair spray)*
Dimethyl ether
Butane
Halogenated fluorocarbons
Bromochlorodifluoromethane (from fire extinguishers)
Carbon tetrachloride
Ethyl chloride
Perchloroethylene
Trichloroethylene
B. *Gas fuels (disposable cigarette lighters)*
Propane
Butane
Liquid petroleum gas
C. *Chlorinated solvents (commercial dry cleaning/degreasing agents)*
Carbon tetrachloride
Dichloremethane
Methanol
Tetrachloroethylene
Toluene
D. *Solvents from adhesives (also paints, nail polish, varnish remover)*
Acetone
Butane
Cyclohexanone
Toluene
Xylene

* Agents from group A are more likely to be associated with traumatic injuries and death. Agents from the other three groups are more likely to manifest direct toxicity.

The popularity of individual solvents depends on their boiling range. The range for toluene is quite low, allowing abusers to pour the solvent into a plastic bag, gather the ends of the bag together, hold the top of the bag over the mouth and nose, and inhale the vapors. Plastic bags can also be used to collect propellants from aerosol cans. Volatile agents such as gasoline are simply sniffed from soaked rags (Flanagan and Ives, 1994). When toluene is inhaled, it is rapidly taken up by the brain and by fat stores elsewhere in the body, then slowly released over the course of many hours. Once released back into the circulation, hepatic conjugation is followed by renal excretion as hippuric acid. The co-ingestion of ethanol increases plasma concentrations of most solvents (Baelum, 1999); resultant concentrations of toluene may be nearly double those seen when the solvent is inhaled by itself.

Toluene toxicity can be explained mostly by its very low solubility in water, so low that it cannot effectively be excreted in the urine. The methyl group of toluene is more easily oxidized by cytochrome P-450 2E1 (James et al., 2008) than is the benzene ring. With chronic exposure toluene induces the production of more CYP2E1, and 95% of the toluene is oxidized to become benzyl alcohol and then excreted (Nakajima et al., 1997). The remaining 5% is oxidized to form benzaldehyde and various cresols (Chapman et al., 1990). Most of the reactive products are detoxified by conjugation to glutathione but the remainder cause cell damage.

8.6 Clinical Syndromes

8.6.1 Neurologic Disorders

An acute syndrome of toluene-induced nausea, abdominal pain, impaired judgment, altered consciousness, and seizures is well recognized (Watson, 1982). Transient neurologic symptoms can also occur after the use of amyl nitrite and related compounds, but neurologic sequelae have not been associated with the practice.

The first reports describing a toluene-related neurologic disorder were published more than 40 years ago (Grabski, 1961; King et al., 1981). Cerebellar signs predominate, and patients present with ataxia, tremor, and nystagmus (Rosenberg et al., 1988a). A variety of other neurologic disorders may occur, ranging from relatively minor degrees of cognitive dysfunction and poor performance in school (Fornazzari et al., 1983; Hormes et al., 1986) to much more serious disorders, even some with evidence of pyramidal tract damage. Cerebral and cerebellar atrophy have been described (Hormes et al., 1986). Cranial nerve injury has also been reported. Some users, particularly adults, may present with a disorder mimicking Guillain–Barré syndrome (Streicher et al., 1981), and even central pontine myelinolysis (Hong et al., 1996).

Most of the time symptoms disappear, or at least improve, when exposure to solvent ceases. In some cases, however, symptoms persist. Seizure disorders and evidence of cognitive impairment may be permanent (Byrne and Kirby, 1989). Chronic toluene abuse also causes paranoid psychosis with schizophrenic symptoms that may be atypical, including visual (rather than auditory) hallucinations. Only a limited number of neuropathologic studies have been published (Escobar and Aruffo, 1980; Rosenberg et al., 1988b) but the available evidence suggests that when symptoms persist, it is usually because widespread demyelination has occurred.

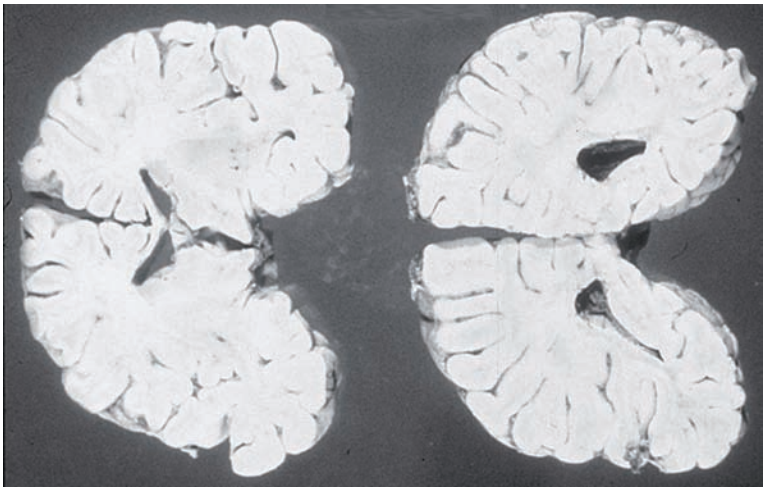

Figure 8.6.1.1 Discoloration of white matter and atrophy of corpus callosum. Lesions are confined almost entirely to the white matter, helping to distinguish solvent-related myelinopathy from the pattern seen in hypoxic injury. (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

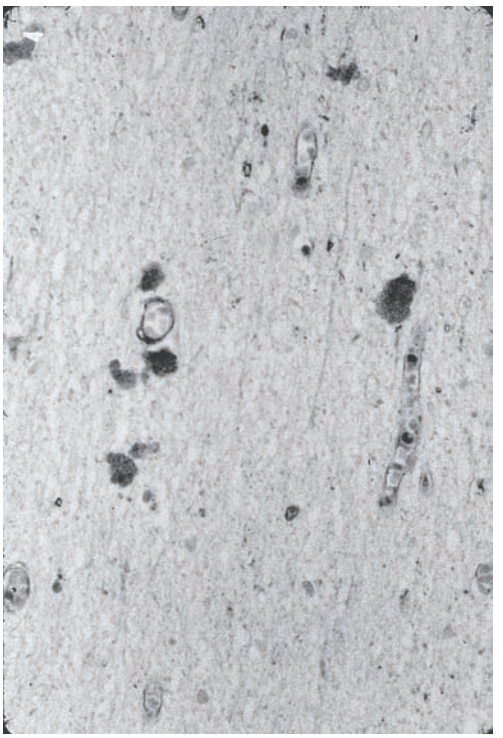

Figure 8.6.1.2 Macrophages filled with PAS-positive granules, most often with a perivascular distribution, are almost always identified in the brains of solvent abusers. The histologic appearance is not that different from the picture seen in adrenoleukodystrophy. (Luxor fast blue, PAS stain.) (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

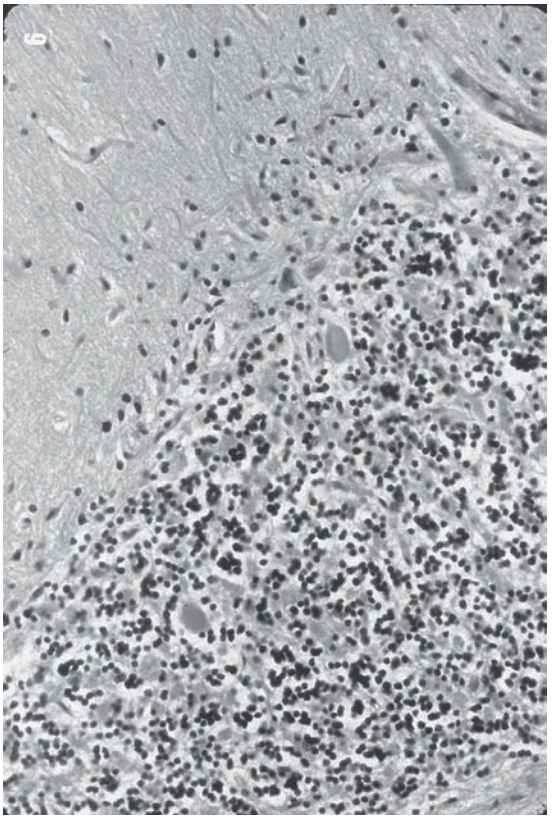

Figure 8.6.1.3 Cerebellar injury. Solvent abusers often have prominent cerebellar symptoms. As illustrated by this H&E section, loss of Purkinje cells is accompanied by Bergmann gliosis. (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

In the three cases described by Kornfeld et al. (1994) the essential features of the disorder were severe but spotty loss of myelin with only relatively mild axonal loss and gliosis. Macrophages filled with PAS-positive granules are a constant feature (Figure 8.6.1.1, Figure 8.6.1.2, and Figure 8.6.1.3). The histologic appearance is not that different from the picture seen in adrenoleukodystrophy. Biochemically, the lesions are characterized by an increase of very long chain fatty acids in the white matter (Kornfeld et al., 1994). Magnetic resonance imaging (MRI) scanning confirms the loss of white matter, with cerebral atrophy most evident in the corpus callosum and cerebellar vermis (Kamran and Bakshi, 1998). Bilateral abnormalities of the basal ganglia, red nucleus, and thalamus have also been described (Yamanouchi et al., 1995; Caldemeyer et al., 1996; Miyagi et al., 1999). MRI studies of relatively naïve users are likely to appear normal, even though decreased perfusion of the thalamus and basal ganglia can be demonstrated with single photon emission computed tomography (SPECT) scanning (Ryu et al., 1998).

More recently data have been published suggesting that chronic solvent abuse can produce central hypothyroidism, even when MRI of the pituitary shows no significant changes. Because of toluene's extreme lipophilicity it easily enters the brain and, like other organic solvents, alters dopaminergic and adrenergic transmission within various parts of the brain. The result may well be abnormal secretion of pituitary hormones

resulting in transient central hypothyroidism and abnormal gonadotropin levels (Chen et al., 2003).

8.6.2 Renal Disease

Toluene inhalation can result in multiple electrolyte and acid–base abnormalities, and should be considered in the diagnosis of any young patient who presents with unexplained hypokalemia and normal anion gap metabolic acidosis (Tang et al., 2005). Occasionally acute respiratory failure with hypokalemia can occur with secondary rhabdomyolysis with acute renal failure (Kao et al., 2000). Hematuria is common (Crowe et al., 2000) and glomerulonephritis has been documented (Streicher et al., 1981), but the actual incidence of these complications is low. Disorders of the renal tubules are more frequent than disease of the glomerulus (Taher et al., 1974; Fischman and Oster, 1979; Moss et al., 1980; Voigts and Kaufman, 1983). In animal experiments, when rats were chronically exposed to toluene vapors there was histological evidence of interstitial cell infiltration and interstitial nephritis, and the greater the exposure, the greater the degree of damage (Cobanoglu et al., 2008). The mechanism by which toluene damages the renal parenchyma is not known.

8.6.3 Gastrointestinal Disease

Histological evidence of gastrointestinal disease is uncommon, but symptoms are frequent. Solvent-related centrolobular necrosis was first reported more than 40 years ago (Baerg and Kimberg, 1970), but only one case of fulminant hepatic failure has been linked to solvent abuse (McIntyre and Long, 1992). Surveillance studies of workers with long-term solvent exposure have not found evidence for subclinical alterations in liver or kidney function (Brogren et al., 1986). In animal experiments, the simultaneous administration of methamphetamine enhances carbon tetrachloride hepatotoxicity (Roberts et al., 1994). In theory, a solvent abuser taking amphetamines might be at increased risk. In practice, except for ethanol, solvent abusers hardly ever abuse other drugs at the same time.

8.6.4 Cardiovascular Disease

Sudden cardiac death is the most common cause of death in solvent abusers, although the mechanism remains debated. Some toluene deaths may be attributed to toluene's ability to reversibly inhibit cardiac voltage-activated sodium channels, especially in the heart. Whether or not inhibition occurs depends on the toluene concentration. Because sodium channels are required for the initial phase of the cardiac action potential, it has been suggested that this effect might explain the phenomenon of sudden cardiac death in "huffers" (Cruz et al., 2003). Earlier theories simply postulated that exposure to toluene and other organic solvents, via some unknown mechanism, sensitized the myocardium to the effects of catecholamines (Cunningham et al., 1987). However, current thinking is that toluene inhalation results in QT interval prolongation and QT dispersion, favoring the occurrence of torsade de pointes (Alper et al., 2008).

Another possible mechanism for toluene-induced arrhythmias may involve decreased intracytosolic calcium concentrations. Trichloroethylene (and probably other halogenated solvents as well) reduces calcium levels within cardiomyocytes (Hoffmann et al., 1992). The force of myocyte contraction depends on intracytosolic calcium. In order to initiate a

contraction, intracytosolic calcium must increase to a certain critical setpoint. Decreased availability of calcium within the cardiac myocytes translates into decreased force of contraction. Whether or not solvent abuse results in myocardial depression sufficient to decrease coronary artery perfusion, causing ischemia and sudden death, has never been established. At the time this mechanism was first suggested, the importance of the ryanodyne receptor had not been recognized. We now know that mast cell derived pro-inflammatory mediator leukotriene D(4) (LTD(4)) induces an increase in intracellular free Ca^{2+} in at least some human muscles, and that the increase is ryanodyne mediated (Bouchelouche et al., 2003).

Studies with isolated membrane fractions have shown that calmodulin (CaM) inhibits the ability of cardiac muscle cells to release Ca^{2+} from the ryanodine receptor channel 2 (RyR2). Taken together, the data suggest that impaired CaM inhibition of RyR2, associated with defective sarcoplasmic reticulum Ca^{2+} release and altered gene expression, can lead to cardiac hypertrophy and early death (Yamaguchi et al., 2007). When it is sought, mutation of the *RyR2* gene can be detected in nearly a third of young sudden-death victims. It may be that toluene-related deaths only occur in individuals who are polymorphic for *RyR2*, but this hypothesis has never been tested (Tester et al., 2005).

Amyl nitrite inhalation causes methemoglobin formation, and fatal amounts of methemoglobin may be produced if too much amyl nitrite is consumed (Guss et al., 1985; Hoffmann et al., 1992; Sarvesvaran et al., 1992). Alternatively, amyl nitrite-induced vasodilation and intense vagal stimulation could also lead to arrhythmias and sudden death. Still another possibility is fatal respiratory depression; if solvent concentrations in the brain reach sufficiently high levels, fatal respiratory depression could occur. Asphyxial death from vomiting with aspiration is common. Flanagan and Ives (1994) reported that aspiration was the cause of death in 20–30% of all solvent-related sudden deaths. Nonetheless, respiratory depression seems to be a real possibility because of the high brain toluene concentrations that are often detected at autopsy (Yajima et al., 2005).

8.6.5 Maternal/Fetal Considerations

Clinical cases of toluene-related embryopathy and malformations have been reported after toluene abuse by pregnant women (Bowen and Hannigan, 2006). Very high levels of maternal solvent exposure typical of abuse can lead to perinatal death and there are reports that surviving neonates show evidence of teratogenicity. At birth, the affected infants are typically premature with growth retardation and microcephaly with severe facial dysmorphology (e.g., deep-set eyes, small face, low-set ears, micrognathia), and spatulate fingertips and small fingernails. The term "fetal solvent syndrome" has been adopted to describe this constellation of morphological and behavioral effects, following the model of fetal alcohol spectrum disorders (FASD) and comparing the phenotype of toluene embryopathy to the effects of prenatal alcohol exposure (Jones and Balster, 1998).

8.6.6 Clinical Toxicology

In 51 individuals admitted to the hospital for suspected toluene toxicity, 34 males and 17 females, the average age of the males was 21.4 years and of the females 16.2 years. The toluene concentrations in the blood collected on admission ranged enormously, from 0.3 to 22.8 μg/g. Blood concentration measurements were poor predictors of toxicity. Nine of

the patients with concentrations of more than 3.0 μg/g were quite ill, but twice as many of the subjects (18) with blood toluene concentration greater than 3.0 μg/g had no physical signs whatsoever. In three semicomatose individuals the blood toluene concentrations were found to exceed 10.0 μg/g. Still, in the majority of cases (24), concentrations were below 3.0 μg/g, and there were no physical signs (Miyazaki et al, 1990).

8.6.7 Postmortem Considerations

Only a few reports have described postmortem toluene concentrations. One case disclosed toxicological findings in a known solvent abuser who died suddenly. Using gas chromatography, peaks of toluene, xylene, and ethylbenzene were detected in the blood and gastric contents. The brain is especially useful for purposes of postmortem analysis, though it cannot necessarily be used to determine the cause of death because no specific level has ever been shown to absolutely cause toxicity. In one reported case, the concentration of toluene in the brain was 20.0 μmol/g, but the value was considered nonlethal because the decedent had obviously died of head trauma (Yajima et al., 2005).

8.6.7.1 Storage and Sample Handling

In the analytical investigation of volatile substances, the chemical properties and volatile nature of the compounds make proper sample collection, storage, and handling especially important. However, useful qualitative results can still be obtained, even if the conditions for sample storage and handling are less than ideal. In fact, the greatest forensic difficulties posed by these cases arise from establishing the presence of any solvent at all.

Loss of the volatile substances by evaporation makes quantitative toxicology in these cases very difficult. Therefore analysis of the sample should start as soon as possible. Volatile substances diffuse from the sample into the atmosphere until equilibrium is reached. Every time the sample container is opened, losses of solvents occur due to their displacement by air. Every time fresh air enters the container, diffusion of the solvent will create a new equilibrium. Samples should therefore be stored in gas-tight, well-sealed containers with minimal headspace. Addition of an internal standard to the sample immediately after autopsy will minimize experimental errors due to evaporation during storage or tissue homogenization.

It is also a good idea to seal the sample against contamination from environmental and laboratory sources of volatiles. Storage, transport, and handling of the sample should always occur at approximately −5 to 4°C. Lower temperatures should be avoided for long-term blood sample storage because they will lead to the formation of *n*-hexanol from degradation of fatty acids. The presence of *n*-hexanol often leads to interference in the analysis of low toluene concentrations; however, in true cases of solvent intoxication the contribution from *n*-hexanol remains limited. Samples should only come in contact with inert materials such as glass, Teflon®, or aluminum foil. Soft rubber stoppers should be avoided due to their high affinity and permeability for toluene.

For non-postmortem blood sample analysis an anticoagulant (lithium heparin) will be required. Tubes containing EDTA and gel separators should not be used to collect blood at autopsy because they may very well yield false positive results for xylene, ethylbenzene, toluene and 1-butanol — all of these compounds have been reported in the separator gel and, if present, will contaminate the sample. Other agents, such as 1-butanol and 2-methyl-2-propanol, have also been detected in tubes coated with EDTA (Streete et al., 1992).

Addition of sulfuric acid or sodium fluoride (Flanagan et al., 1990; Streete et al., 1992) is advised when esters such as ethyl acetate are present in the sample; adding sulfuric acid abolishes esterase activity, allowing preservation of the sample. Sodium azide should also be added to prevent growth of microorganisms (Flanagan et al., 1990).

When the goal is to monitor for occupational and environmental exposure, urinalysis is probably the method of choice. Analysis of metabolites in urine allows an extended window for detection and these volatile gases are easy to detect. In postmortem cases, metabolites seem to be of less importance, although trichloroethanol and trichloroacetic acid are routinely analyzed in cases of chloral hydrate and trichloroethylene.

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Marijuana

9

Common names: bhang, dagga, ganja, hashish, marijuana, kif, spliff, dope, blunts
Chemical name: (–)-*trans*-δ-9-tetrahydrocannabinol
Formula: $C_{21}H_{30}O_2$
Molecular weight: 314.5 daltons
C_{max}: 3–8 minutes, depending on route
$T_{½}$: Depends on the compartment. The terminal elimination half-life is approximately 1 day but it has been reported to be as long as 3–13 days in frequent users (Huestis et al., 1992a, b)
V_{ss}: 4–14 L/kg
Metabolism: CYP2C9
Drug interactions: Tetrahydrocannabinol (THC), but no other metabolite, increases the rate of phenytoin metabolism in humans. Phenytoin levels would be lower in the face of THC ingestion, making seizures more likely.
Detection times: On average, when a drug-free individual smokes one standard NIDA cigarette (containing 3.5% THC), the urine will test positive for 4 days after cessation. In chronic living smokers, depending upon the cutoff selected, it may be substantially longer. When abstinent chronic marijuana smokers were monitored in a closed ward, plasma THC concentrations in many exceeded 2 ng/mL after 1 week (Karshner et al., 2008).

Huestis, M. A., Henningfield, J. E. et al. (1992a). Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana, *J. Anal. Toxicol.,* 16(5), pp. 276–82.
Huestis, M. A., Henningfield, J. E. et al. (1992b). Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma concentrations of delta 9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THCCOOH), *J. Anal. Toxicol.,* 16(5), pp. 283–90.

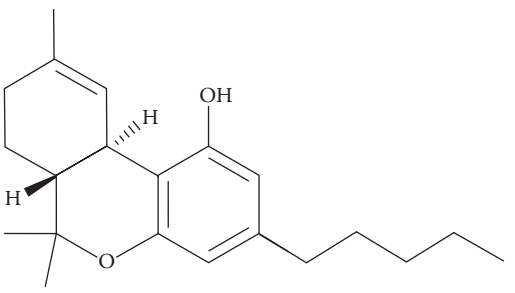

Figure 9.1 Marijuana molecule.

9.1 Botany

The term "marijuana" refers to most parts of the plant *Cannabis sativa* L., whether growing or not: the seeds; the resin extracted from any part of the plant; and every compound, salt, derivative, or mixture, but it does not include the mature stalks, fiber produced from the stalks, or oil or cake prepared from the seeds (Farnsworth, 1969). *Cannabis sativa* L. is an annual plant that grows in all parts of the world, generally reaching a height of 16–18 ft. It is widely accepted that *Cannabis sativa* L. belongs to a family (Cannabaceae) that has only one genus (*Cannabis*) with only one species (sativa) (ElSohly and Slade, 2005).

Not only is *Cannabis* an abused drug, it is cultivated commercially to produce hemp. The bulk of the commercial plant consists of stalks with very little foliage, except at the apex. In contrast, the wild plant and those cultivated illegally possess numerous branches, as the psychoactive ingredient is concentrated in the leaves and flowering tops. There may be significant differences in the gross appearance of marijuana plants due to climatic and soil conditions, the closeness of other plants during growth, and the origin of the seed. Marijuana is simply the crude drug derived from the plant.

In 1980 the total number of natural compounds identified in *C. sativa L.* was 423 (Turner, 1980). By 1995 the number had risen to 483, and recently six new compounds, four cannabinoids and two flavonoids, have been described (Ross et al., 2005).

The major psychoactive constituent of marijuana is δ-9-tetrahydrocannabinol, commonly referred to as THC. Different parts of the plant contain varying concentrations of THC: leaves contain < 1% to 10% THC by weight, while hashish resin prepared from the flowering tops of the plant contains approximately 15% THC. THC may be synthesized using citral and olivetol in boron trifluoride and methylene chloride (Lander et al., 1976). Although no reports have appeared within the published peer-reviewed literature, there are persistent reports from within the enforcement community suggesting that intensive cross-breeding has led to the production of plants that have a THC content well over 20%. These "super" plants appear to be grown mainly along the Canadian–American border, primarily by Asian gangs.

9.2 Epidemiology

The prevalence of marijuana smoking among adults in the U.S. has remained stable, at approximately 4%, for the last decade (Compton et al., 2004). Even that low rate (four times as many Americans smoke cigarettes) still translates into more than 6 million active users. In 2002, an estimated 19.5 million Americans aged 12 or older admitted to having used illicit drugs during the month prior to the survey interview. That number translates into 8.3% of the population over age 12. Seventy-five percent of these individuals reported using marijuana, and 72 million individuals report having smoked marijuana at least once in their life (SAMHSA, 2005).

9.3 Origins

In spite of the fact that most marijuana consumed in the U.S. comes from Mexico and Canada (where it is largely produced by Vietnamese gangs), enormous amounts are grown within the U.S. Figure 9.3.1 shows total marijuana seizures (in kilograms) in the northern

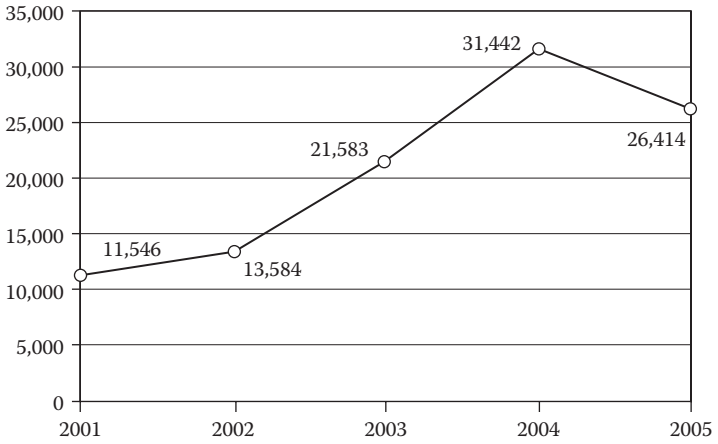

Figure 9.3.1 Marijuana seizures (kilograms) made along the Northern American Border, 2001–2005. It is not known if the downward trend continues. (*Source:* Federal-Wide Drug Seizure system.)

border states made by the U.S. government. Slight declines were recorded in 2005, but the decline seems to have ended. Figure 9.3.2 shows that the purity of confiscated marijuana samples has more than doubled since 1985. Hashish (Figure 9.3.3) is prepared only from the flowering tops of the female cannabis plant; it can be smoked or chewed. Figure 9.3.4 shows sinsemilla, the flowering tops of the marijuana, which are free of seeds because it is grown in a pollen-free environment. Generally, any adulterants added to marijuana are benign in nature — oregano or other plant products — but early in the winter of 2007 English drug researchers started reporting the appearance of "grit weed" on the market. This consisted of normal marijuana plants that had been adulterated with tiny glass beads. Figure 9.3.5 is a scanning micrograph of the glass beads that had been deposited on the leaves. An analysis carried out by the French Observatory of Drugs and Drug Addiction found that the glass particles were between 0.02 and 0.3 mm across, which suggests that the particles posed little health hazard because they were too large to pass into the lungs.

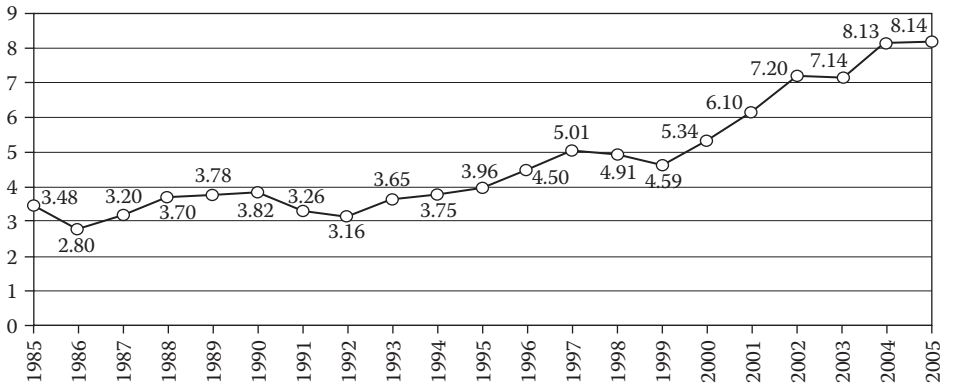

Figure 9.3.2 As the graph indicates, the THC content of marijuana has more than doubled since 1986. (*Source:* The University of Mississippi Potency Monitoring Project.)

Figure 9.3.3 Hashish. (Photograph from the website of the Drug Enforcement Administration.)

Figure 9.3.4 Sinsemilla. (Photograph from the website of the Drug Enforcement Administration.)

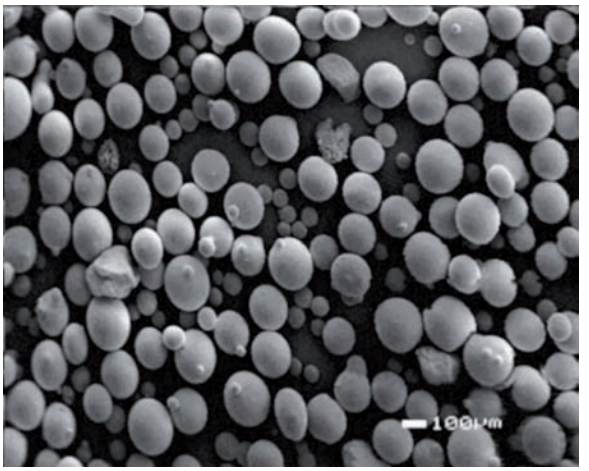

Figure 9.3.5 Glass beads sprayed onto marijuana plants. Published anonymously on the Internet. Police believe that the glass beads were sprayed on to increase the weight of the product.

Evidence suggests that it was the growers' intent to increase the weight of their product by spraying plants with the reflective element from the paint used on road lines. The tiny reflective glass beads became imbedded in the leaves and increased the total weight.

9.4 Pharmacology

Marijuana is typically smoked or taken orally in doses of 5–20 mg (Kiplinger and Manno, 1971). It may produce a variety of pharmacological effects including sedation, euphoria, hallucinations, and temporal distortion. In addition, THC possesses activity at benzodiazepine, opioid, and cannabinoid receptors and also exerts effects on the synthesis of prostaglandins, DNA, RNA, and even alters protein metabolism (Bhattacharya et al., 1980; Cabral and Staab, 2005).

Early workers thought that the effects of THC were nonspecific, but in the late 1980s a cannabinoid receptor was finally identified in the brains of rats. There are two types of cannabinoid receptor: CB1 and CB2. These receptors are the primary targets for endogenous cannabinoids (endocannabinoids). THC binds to both of the cannabinoid receptors. The CB1 receptor is mostly found in the brain, while the CB2 receptors are found in immune tissues such as the spleen, thymus, and tonsils, but not in the brain (Pertwee, 1999). Specific antagonists exist for each of the CB1 and CB2 receptors.

Cannabinoid receptors are coupled to G proteins. They are involved in the control of many processes, including metabolic regulation, food craving, pain, anxiety, bone growth, and immune function. The exogenous cannabinoids found in marijuana plants can also exert effects via G proteins that negatively modulate cyclic AMP levels, and activate the inward rectifying K^+ channels (Demuth and Molleman, 2006). Manipulation at either receptor site may have important clinical consequences, and therapies based upon cannabinoid–receptor interactions are under development.

Cannabinoids mediate a decrease in blood pressure and can suppress cardiac contractility in hypertension. Conversely, if the CB1-mediated cardiodepressor and vasodilator effects of anandamide are enhanced (by blocking its hydrolysis), blood pressure tends to normalize (Batkai et al., 2004). Many clinical developments taking advantage of these properties are likely to occur. Though yet to be approved for sale in the U.S., rimonabant (Acomplia®), a C_1 blocking agent, is already dispensed by European doctors to promote weight loss (Engeli and Jordan, 2006).

9.4.1 Alternative Testing Matrices

It is possible to detect marijuana and its metabolites in other tissues besides blood. At present there is great interest in hair and saliva analysis. However, because of the drug's very great steady state volume of distribution, it can be recovered from many tissues. One study, published nearly 20 years ago, analyzed THC concentrations in fat samples obtained from heavy marijuana users one week before and four weeks after smoking. The concentration of δ-THC in these samples ranged between 0.4 and 193 ng/g wet tissue (Johannson et al., 1989). While fat biopsies are unlikely to become routine forensic tests, there is very active interest in the use of saliva and urine. To date, methods for the detection of THC in hair have been somewhat problematic, but there seems to be progress in this area.

9.4.2 Hair and Saliva Testing for Marijuana

The relationship between blood and saliva concentrations has been poorly studied. Only two systematically controlled studies have addressed the relationship (Huestis and Cone, 1999; Kauert et al., 2007). Although great effort has gone into developing methods for the detection of THC in saliva (toxicologists tend to refer to saliva as "oral fluid," acknowledging that saliva contains many cellular components), and a number of devices have come to market, the results are not particularly encouraging; the oral kinetics of THC are not understood well enough to use for forensic purposes. Results with hair testing are much more encouraging, and it may even be possible to quantitate, not just detect, long-term use. In one recent study of 22 healthy men, hair samples from 12 chronic marijuana users (average age 22 ± 2 years) were compared to those obtained from 10 non-users, and detailed histories of their drug-use pattern were obtained; average cannabis usage ranged from 0.25 to 2.5 g/day (mean ± SD: 0.74 ± 0.60 g/day). Most of the subjects had smoked at least every 2 days for the past year.

Concentrations of δ-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) were measured in the hair of each subject. In every one of the users, concentrations of all three metabolites were detected in the hair and there was an increase in the concentration of all major cannabinoids in hair proportionate to the amount consumed — the more marijuana smoked, the higher the concentration of marijuana and its metabolites found in the hair. Hair color and hair treatments had no effect on the outcome. Both the reported cumulative cannabis dose during the last 3 months and the cannabis use during the last 3 months — estimated from the daily dose and the frequency per year — were more closely related to the sum of THC, CBN, and CBD concentrations rather than to the THC content alone (Skopp et al., 2007).

9.5 Absorption

Marijuana is usually self-administered by smoking dried marijuana leaves rolled into a cigarette. Smoking results in rapid drug delivery from the lungs to the brain. However, loss of drug occurs during the smoking process due to pyrolysis and the production of sidestream smoke. In an in vitro experiment specifically designed to minimize loss due to sidestream smoke, Perez-Reyes et al. (1983) found that a 30% loss of THC due to pyrolysis alone had occurred. Once THC reaches the lungs, it is rapidly absorbed. Peak plasma THC concentrations of 100–200 ng/mL occur after 3–8 minutes. THC is present in blood after the first puff from a marijuana cigarette. Mean ± SD THC concentrations of 7.0 ± 8.1 ng/mL and 18.1 ± 12.0 ng/mL were observed after the first inhalation of low or high dose marijuana cigarettes (1.75%, 3.55%), respectively. In a separate study, peak concentrations occurred 9 minutes after the first puff (Lemberger et al., 1970). Cone and Huestis (1993) demonstrated that physiological and subjective measures of drug effect occurred simultaneously with the rise in blood THC concentrations.

After oral administration, THC is 90–95% absorbed. However, the oral route produces lower peak plasma concentrations and it takes longer to achieve. Perez-Reyes et al. (1983) reported a mean peak plasma THC concentration of 6 ng/mL after oral ingestion of 20 mg. Wall and Perez-Reyes (1981) noted that peak plasma THC concentrations occurred 30 minutes after intravenous administration. Reported values for the bioavailability of THC after smoking have ranged from 18 to 50%. This wide range reflects the large inter- and

intra-subject variability that occurs in smoking dynamics (McGilveray, 2005). Altering the number, duration, and spacing of puffs, the length of time the inhalation is held, and the inhalation volume or depth of puff may vary the amount of drug delivered (Grotenhermen, 2003).

Measures can be taken to minimize the loss due to side- and mainstream smoke, as well as optimizing the temperature for drug volatilization. Such measures would, in turn, increase the amount of drug available for delivery to the lungs. One facet of smoking that cannot be controlled by the smoker is drug deposition on non- or poorly absorbing surfaces within the body. Deposition outside of the lungs is usually a function of drug particle or vapor size. Drug may be deposited in the nasopharyngeal region or the upper bronchial tree. This reduces the amount of drug reaching the lung alveoli where rapid absorption into the blood and subsequent transport to the brain occurs.

Ohlsson et al. (1980) compared the bioavailability of THC after intravenous, smoked, and oral administration. Eleven healthy subjects were administered 5 mg intravenously, 19 mg smoked, and 20 mg orally. Plasma concentrations rose very quickly after intravenous administration, reaching 161–316 ng/mL at 3 minutes and declining rapidly thereafter. Peak plasma concentrations also occurred at 3 minutes after smoking, with lower concentrations of THC ranging from 33 to 118 ng/mL. The plasma concentration time curve after smoking was similar to that obtained after intravenous administration but at lower concentrations. In contrast, low THC concentrations were found after oral administration, with much higher inter-subject variability. The authors determined the bioavailability of THC to be 8–24% after smoking compared with 4–12% after oral ingestion.

9.6 Detection Times

In one reported study researchers collected urine from seven healthy volunteers (ages 20–35 years, four male), all chronic cannabis users, during enforced abstinence on a locked ward, for up to 29 days. All of the subjects were regular marijuana smokers who reported smoking one to five "blunts" (marijuana rolled into a tobacco leaf which results in the appearance of a cigar) per day. Every urine specimen collected during their confinement was analyzed, using a method that had a 2.5 ng/mL limit of quantification. The minimum time until the urine was cleared of 11-OH-THC ranged from 7.56 to 29.8 days, with concentrations ranging from 25 to 133 ng/mL. Maximum urinary concentrations of the other metabolite, THCCOOH, fell into the same time range as 11-OH-THC. In federally regulated workplace testing, a 15 ng/mL cutoff is mandated for workplace drug testing, and the volunteers studied above would have been considered active marijuana smokers even though they had not smoked for more than one week (Abraham et al., 2008).

Similar results have been observed with plasma measurement. Twenty-eight self-reported daily marijuana smokers (ages 19 to 36 years, roughly equal numbers of men and women, 84% African American) underwent enforced abstinence in a locked ward. Plasma specimens were collected when the volunteers arrived on the locked ward and then daily. After not smoking marijuana for 16 hours, 93% of the participants were still positive for the drug (THC > 0.25 ng/mL — the minimum level of detection). On the seventh day of observed abstinence, half of the participants continued to test positive for THC, and four of these individuals had levels > 2.0 ng/mL, the value that is usually considered proof of recent use by the European Union and some U.S. states. The median THCCOOH concentration in this group was 11.5 ng/mL after one week's abstinence. In other words, the

detection of THC in plasma is a dubious forensic value because it does not reliably differentiate between acute and chronic use. This observation is almost certainly explained by the accumulation of THC in deep tissue compartments with gradual release of THC from tissue stores into the bloodstream; in the living, the detection of low THC concentrations does not reliably identify recent use (Karschner et al., 2008).

9.7 Distribution

THC is 97–99% bound to plasma protein with very little present in red blood cells. Due to its lipophilicity, THC rapidly distributes into tissues. Highly perfused organs, such as the brain, accumulate THC rapidly after administration, whereas THC distributes more slowly into and is released more slowly from poorly perfused tissues such as fat. Harvey (1999) reported finding maximum THC concentrations in the brains of mice 30 minutes after a single intravenous dose. The distribution of THC into various tissues and organs, such as brain, liver, heart, kidney, salivary glands, breast milk, fat, and lung, is a result of its extremely large volume of distribution (4–14 L/kg) (Ohlsson et al., 1980; Johansson and Halldin, 1989). Hunt and Jones (1980) proposed a four-compartment model to describe four tissue composites into which THC distributes after intravenous injection. They observed average half-lives of 1 minute, 4 minutes, 1 hour, and 19 hours to distribute in each of the compartments. They concluded that a "pseudoequilibrium" is achieved between plasma and tissues 6 hours after an intravenous dose. Thereafter, THC is slowly eliminated as it diffuses from tissue to the blood. The terminal elimination half-life is approximately 1 day but has been reported to be as long as 3–13 days in frequent users (Huestis et al., 1992a, b).

9.8 Blood Levels

THC levels increase very quickly after smoking and, in fact, blood levels peak before the smoker has finished the cigarette; concentrations then rapidly decline. At any given time mean peak blood concentrations of HO-THC levels are always much lower than those of THC, with peak levels occurring just as smoking is complete. Levels of the inactive THCOOH rise very gradually, plateau, and then persist for some hours. Peak THCOOH levels occur approximately 2 hours after the end of smoking. Blood concentrations of the conjugated THCOOH-glucuronide are always higher than concentrations of THC. The fact that THCOOH glucuronides tend to spontaneously decompose makes it very difficult to devise a formula that accurately estimates time of ingestion, often confounding results.

Daily smokers accumulate cannabinoids in their blood. When clearance time was measured in 28 daily marijuana smokers. At the time of admission, 15 had no cannabinoids detectable in whole blood samples. In the remainder, the mean concentrations of THC, 11-OH-THC, and THCCOOH were 1.1 ± 1.7 (range 0.03–7.0), 1.1 ± 1.7 (range 0.3–6.3), and 19.2 ± 20.4 ng/mL, respectively. After 7 days of witnessed abstinence, the values were 1.3 ± 1.0 (range 0.4–4.0), 0.6 ± 0.3 (range 0.3–0.9), and 6.0 ± 8.4 (range 0.4–36.5) ng/mL, respectively. After one week, a few of the participants actually had a modest increase in whole blood THC concentration (Schwilke et al., 2007). This confirms that THC remains in deep fat stores with slow release back into the blood occurring over an as yet undefined interval.

9.9 Metabolism and Excretion

Hepatic metabolism is the major route by which THC is eliminated from the body. Hepatic metabolism consists primarily of hydroxylation by CYP2C9 to form 11-hydroxy-THC (abbreviated as HO-THC), which is also a psychoactive compound. Hydroxylation is followed by oxidization, probably by alcohol dehydrogenase or, possibly, a microsomal enzyme known as aldehyde oxygenase, another member of the CYP2 subfamily. This compound is eventually excreted as THC-COOH in the urine after first forming a glucuronide at the carboxyl group.

In humans, over 20 metabolites have been identified in urine and feces of marijuana users (Widman et al., 1975). Metabolism in humans involves allylic oxidation, epoxidation, aliphatic oxidation, decarboxylation, and conjugation. The two monohydroxy metabolites, 11-hydroxy (OH)-THC and 8-β-hydroxy THC, are active, with the former exhibiting similar activity and disposition to THC, while the latter is less potent. Plasma concentrations of 11-OH-THC are typically < 10% of the THC concentration after marijuana smoking. Two additional hydroxy compounds have been identified, namely, 8-α-hydroxy-THC and 8,11-dihydroxy-THC, but they are believed to be devoid of THC-like activity. Oxidation of 11-OH-THC produces the inactive metabolite, 11-nor-9-carboxy-THC, or THC-COOH. This metabolite may be conjugated with glucuronic acid and is excreted in substantial amounts in the urine.

The average plasma clearance for THC is 600–980 mL/min with a blood clearance of 1.0–1.6 L/min, which is very close to hepatic blood flow. This indicates that the rate of metabolism of THC is dependent on hepatic blood flow. Approximately 70% of a dose of THC is excreted in the urine (30%) and feces (40%) within 72 hours (Widman et al., 1975). Because significant quantities of the metabolites are excreted in the feces, enterohepatic recirculation of THC metabolites may occur. This would also contribute to the slow elimination and hence long plasma half-life of THC. Unchanged THC is present in low amounts in the urine along with 11-OH-THC, but accounts for only 2% of a dose.

The other urinary metabolites consist of conjugates of THC-COOH and unidentified acidic products. Following a single smoked 10-mg dose of THC, urinary THC-COOH concentrations peaked within 16 hours of smoking, at levels of 6–129 ng/mL (n = 10) (McBurney et al., 1986). Huestis and Cone (1998) reported a mean (± SEM) urinary excretion half-life for THC-COOH of 31.5 ± 1 hour and 28.6 ± 1.5 hour for six healthy volunteers after administration of a single marijuana cigarette containing 1.75% or 3.55% THC, respectively. Passive exposure to marijuana smoke may also produce detectable urinary metabolite concentrations. Cone et al. (1987) exposed five volunteers to the smoke of 16 marijuana cigarettes (2.8% THC content) for 1 hour each day for 6 consecutive days. After the first session, THC-COOH concentrations in urine ranged from 0 to 39 ng/mL. A maximum THC-COOH concentration of 87 ng/mL was detected in one subject on Day 4 of the study (Cone et al., 1987).

THC may be ingested orally by consuming food products containing the seeds or oil of the hemp plant. Ingestion of 0.6 mg/day (equivalent to 125 mL hemp oil containing 5 μg/g of THC or 300 g hulled seeds at 2 μg/g) for 10 days resulted in urine THC-COOH concentrations of < 6 ng/mL (Leson et al., 2001). In another study the maximum urinary concentration of THC-COOH after ingestion of hemp oil containing 0.39–0.47 mg THC/day for 5 days was 5.4–38.2 ng/mL (n = 7). After oral administration of a higher dose (7.5 and 14.8 mg THC/day), peak urinary concentrations of THC-COOH ranged from 19.0 to

436 ng/mL. Controlled studies have shown that at the federally mandated cannabinoid cutoffs, it is possible, but unlikely, for a urine specimen to test positive after ingestion of manufacturer-recommended doses of low-THC hemp oils (Gustafson et al., 2003). On the other hand, a patient taking Marinol®, the synthetic form of THC approved by the U.S. Food and Drug Administration for the control of nausea and vomiting in cancer patients, will almost certainly test positive. Dronabinol or synthetic THC is present in Marinol® capsules. ElSohly et al. (2001) found that within 24 hours of administering a single 15 mg dose of dronabinol to four subjects, peak urine THC-COOH concentrations were between 189 and 362 ng/mL (Huestis et al., 2006).

Synthetic THC (dronabinol, Marinol®) is used as an antiemetic in cancer patients. But, since synthetic and naturally occurring THC are completely identical, it is impossible to determine the source of the urinary THC metabolites — their presence could represent either use of the antiemetic or signify that the person being tested was a marijuana smoker. One way to make the distinction is to test for the C3 homolog of THC, known as δ-9-tetrahydrocannabivarin or THCV. THCV is a natural component of most cannabis products and is found, along with THC, in marijuana plant. However, Marinol® is a synthetic product and contains no THCV. THCV is metabolized by human hepatocytes to 11-nor-δ9-tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH), and if its presence is detected in a urine sample it should be considered as proof of marijuana smoking. This theory has been confirmed in a controlled study with human volunteers (ElSohly et al., 2001).

9.10 Cardiovascular Effects

Activation of peripheral CB1 receptors causes profound coronary and cerebral vasodilatation and hypotension (Wagner and Anthony, 2002). In humans the vascular response to THC is a largely dose-dependent increase in heart rate, usually accompanied by a mild increase in systolic pressure. Orthostatic hypotension is a recognized complication in occasional users, but is generally not an issue because near complete tolerance develops to the tachycardiac and hypotensive effects. Electrocardiographic alterations produced by marijuana smoking are said to be minimal (Benowitz and Jones, 1975).

The results of animal studies suggest there is a triphasic response to endocannabinoids. Rats injected with anandamine first experience a transient increase in blood pressure, then a transient decrease followed by a prolonged decrease. This first drop in blood pressure is abolished by atropine or cervical sympathectomy, suggesting that it is mediated by the vagus nerve. The prolonged decrease in pressure appears to be mediated by stimulation of cannabinoid receptors (Siqueira et al., 1979).

Smoking marijuana may trigger myocardial infarction in individuals who have preexisting coronary artery disease. When nearly 4000 patients (1258 women) hospitalized with acute myocardial infarction were interviewed, 124 (3.2%) reported smoking marijuana in the prior year, 37 within 24 hours, and 9 within 1 hour of the onset of symptoms. Typical patients were more likely to be men (94% vs. 67%, $p < .001$), more likely to be current cigarette smokers (68% vs. 32%, $p < .001$), and more likely to be obese (43% vs. 32%, $p = 0.008$). The risk of myocardial infarction onset in the marijuana smokers was elevated 4.8 times over baseline (95% confidence interval, 2.4–9.5) in the 60 minutes after marijuana use, dropping to a relative risk of 1.7 in the second hour, after which no increased risk was

apparent (Mittleman et al., 1999). The increased relative risk associated with sexual activity was comparable to the risk associated with marijuana smoking, which was roughly double the relative risk of acute myocardial infarction in healthy individuals, or even in patients with a prior history of angina, or those with prior infarction. Clearly, the relative risk for infarction is definitely increased, but the absolute risk of marijuana-triggered infarction is extremely low and extremely transient.

The role of marijuana smoking in myocardial ischemia has become further complicated with the realization that marijuana may actually accelerate coronary artery disease. There is evidence that cannabinoid signaling plays a fundamental role in the development of atherosclerosis. The net effect of CB2 receptor activation is to protect against myocardial ischemia/reperfusion injury, and even prevent atherosclerosis from occurring in the first place. Expression of both CB1 and CB2 receptors has been reported on platelets. Whether this plays any role in thrombus formation is not known (Mendizabal and Adler-Graschinsky, 2007; Mach et al., 2008). It is far too early to determine whether any of these effects are of any clinical benefit or detriment.

9.11 Pulmonary Complications

Chronic marijuana smokers generally manifest nondiagnostic lung damage (Barsky et al., 1998). Changes consistent with acute and chronic bronchitis may be apparent, but there is no way to distinguish the changes produced by marijuana smoking from the changes induced by cigarette smoking, or any other environmental pollutant. Nonetheless, more particulate matter is generated by marijuana smoking, making damage to the respiratory tract more likely. The effects of cannabis and tobacco smoking are additive and independent. In the only published autopsy series, the lungs were examined in 13 cases of sudden death where the decedents were known marijuana smokers (age 15–40 years). Accumulations of pigmented monocytes were apparent within the alveoli, and variable, spotty, infiltrates of monocytes and lymphocytes were seen within the interstitium (Morris, 1985). Whether or not the changes are dose related is not known.

More recent studies have shown that alveolar macrophages recovered from the lungs of marijuana smokers have a decreased ability to release pro-inflammatory cytokines and produce nitric oxide (NO). They are also less effective at killing bacteria. THC alters human immune responses. Lymphocytes of marijuana smokers contain increased amounts of mRNA encoding for both types 1 and 2 cannabinoid receptors. THC suppresses T-cell proliferation, inhibits the release of interferon-γ, and alters the production of T-helper cytokines (Roth et al., 2002).

9.12 Postmortem Measurements

THC has the largest volume of distribution of any abused drug. Various estimates have placed this value at between 4 and 14 L/kg (Lemberger et al., 1970; Drummer, 2004). This physical property all but guarantees postmortem redistribution and ensures that it occurs very quickly. Indeed, the process may occur so quickly that it is completed by the time of autopsy. Accordingly, postmortem blood concentrations defy interpretation. Large amounts accumulate in fatty tissues, including the brain. In life, when a regular

marijuana user stops smoking, THC will be slowly released from deep body stores, so it is not uncommon to find substantial amounts of THC in the plasma of living users weeks after use has been discontinued. After death, THC continues to be released from tissues, but at an accelerated rate because the body is decomposing. The result is a phenomenon known as postmortem redistribution; all drugs diffuse down a concentration gradient from areas of higher to areas of lower concentration. Measurements of THC in the fat of chronic users have shown concentrations of well over 100 ng/mL, many times higher than concentrations in blood just a few minutes after smoking. It follows that the concentration of THC measured in blood obtained at autopsy bears no predictable relationship to concentration just before the time of death.

Another reason why postmortem concentrations are impossible to interpret is that whole blood is analyzed, and all formulas for predicting time of use are based upon measurements made in plasma (Huestis et al., 1992a, b). Even in the living, relating measurements made in whole blood to measurements made in plasma is problematic. When δ(9)-THC, 11-OH-δ(9)-THC, and δ(9)-THCCOOH concentrations were measured in the plasma and whole blood taken from eight chronic marijuana smokers, the values of the plasma to whole blood distribution ratios were very similar, and the individual coefficient of variation relatively low. These results suggest that plasma levels can be calculated from whole blood concentrations by taking into account a "multiplying factor" of 1.6. Unfortunately, similar attempts with postmortem "blood" results in a distribution of cannabinoids between whole blood and "serum" that is scattered over too wide a range to be of any forensic value; the Huestis models cannot be applied to postmortem specimens (Giroud et al., 2001).

When nonspecific populations have been screened for the presence of marijuana metabolites at autopsy, the results have generally mirrored the patterns of drug abuse within the rest of the population. Of 500 sequential specimens screened by the Medical Examiner's Office in Maryland, 63 (13%) were initially positive by EMIT assay, and 58 of those (12%) were confirmed positive (Isenschmid and Caplan, 1988).

Sample preservation is an important issue in forensic cases, and marijuana is a particular problem. THC in blood and plasma is stable at room temperature for 2 months, but 90% will have disappeared within 6 months. Even if the sample is frozen, the levels decline notably after 17 weeks. Repeated freezing and thawing has little effect, but THC is an extremely lipophilic molecule that will bind to a hydrophobic surfaces, leading to false reductions in concentration measurements. Some have reported that THC binds to rubber stoppers and others that THC is stable in unsilanized glass, but not in polystyrene tubes to which the THC adheres (Levine and Smith, 1995). For all of these reasons, little weight should be given to reanalysis of samples that have been in storage for months, particularly if they have been stored in plastic or with a rubber stopper.

The biggest problem with interpreting postmortem marijuana concentrations is that medical examiners invariably analyze whole "blood" (technically the term "blood" should not even be used since blood is a living tissue and the material collected at autopsy is not). Clinical laboratories, on the other hand, analyze serum or plasma. The distribution between plasma and red blood cells may lead to very large errors in actual concentration measurements, depending on whether the drug in question is found mainly in plasma (like digoxin) or in blood cells. In the case of THC, the blood to plasma ratio is only 0.5, meaning that most of the drug is in plasma — yet the analyte used for autopsy studies contains both plasma and blood cells.

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Appendix 1: Conversion Formulas

Toxicology reports are not standardized. Depending on the units of measure used, what looks like a very large number may in fact be a very small one. Forensic toxicology laboratories report results in µg/mL.

Converting Units of Measure

A blood cocaine concentration of 1200 ng/mL (approximately the plasma concentration after smoking one rock of cocaine), might be reported as:

1200 ng/mL = 1.2 µg/mL = 1200 µg/L = 1.2 mg/L

The concentrations of hormones such as epinephrine are much lower than the concentrations of exogenous drugs and are usually expressed in picograms (pg). If the concentration of cocaine in the above example were expressed in picograms (which, as a practical matter, it never is), 1200 ng/mL would be equal to 1,200,000 pg/mL.

Converting Moles into Grams

Clinical laboratories express results in millimoles (mmol) or Standard International Units (SI). To convert to standard concentration measurements, divide 1000 by the molecular weight and then divide that number into the concentration value expressed as µmol/L.

Example: In a research study of morphine pharmacokinetics, the maximum blood concentration after giving a 10-mg subcutaneous injection of morphine to a 70-kg man was reported as 262 ± 49 nmol/L. To convert that concentration into ng/mL:

1. Divide 1000 by the molecular weight of morphine:
   1000/285.34 (the molecular weight of morphine) = 3.50
2. Convert nanomoles (nmol) into micromoles (µmol):
   262 nmol/L = 0.262 µmol/L
3. Divide the number of mmol/L by 3.50:
   0.262/3.50 = 0.0748 µg/mL = 74.8 ng/mL

Appendix 2:
Blood Alcohol Concentrations

Individuals who take abused drugs often ingest alcohol at the same time. Widmark's formula is the standard method used by forensic toxicologists to calculate blood alcohol concentrations, and is universally recognized by the legal system. However, an approach first suggested by Charles Winek, from Duquesene University, works equally well and is easier to remember (*Forensic Sciences,* C. W. Wecht, Ed., Matthew Binder Press, New York, chap. 31B, 1984). Winek's formula is based on the observation that a 150-lb man will have a blood alcohol concentration of 0.025% after drinking one ounce of 100-proof (50%) alcohol. Given that assumption (which is accurate under almost all circumstances), then the formula for calculating the blood alcohol concentration (BAC) is

$$\text{BAC} = (150/\text{body weight})(\%\ \text{ethanol}/50)(\text{ounces consumed})(0.025)$$

Example: A 200-lb man drinks five 12-ounce cans of beer. The beer contained 4% ethanol. The BAC would be given by the equation:

$$\text{BAC} = (150/200)(4/50)(60)(0.025)$$

$$\text{BAC} = (.75)(.08)(60)(0.025)$$

$$\text{BAC} = 0.090\%$$

Remember when using this calculation that it assumes all the ethanol was ingested at one time.

Appendix 3: Volume of Distribution Calculations

Some drugs, such as morphine, rapidly leave the blood and distribute widely throughout the body. Other drugs, such as morphine metabolites, stay mostly in the blood. The tendency for a molecule to remain in the blood or distribute into tissue can only be determined by actual measurement. The volume of distribution is the apparent volume needed to contain all of the drug injected in the body at the same concentration as observed in the blood. If, for example, 10 g of food coloring were dissolved in a 10-L aquarium, the resultant concentration would be 1 g/L, and the volume of distribution, abbreviated as V_{ss}, would be 10 L. The V_{ss} for drugs that remain mostly in the bloodstream, such as the morphine glucuronides, will be much less than 1. The V_{ss} for drugs that penetrate widely into tissue, such as cocaine (V_{ss} = approximately 3), will be much greater than 1. V_{ss} calculations can be used to estimate the amount of drug administered:

Dose = (body weight [kg]) × (volume of distribution [L/kg]) × (blood concentration [mg/L])

V_{ss} calculations apply *only to the living*. Postmortem redistribution and other postmortem changes make V_{ss} calculations in the deceased extremely unreliable. An example taken from an actual court case appears below. An individual was charged with accidentally administering a lethal dose of diphenhydramine (Benadryl®). Witnesses observed that the accused administered one injection with a 10-cc syringe. The decedent weighed 72.6 kg and at autopsy had a blood diphenhydramine concentration of 5.1 mg/L. Thus, the accused would have to have injected:

$$\text{Dose} = 72.6 \text{ kg} \times 4.5 \ V_{ss} \times 5.1 \text{ mg/L} = 1666.2 \text{ mg}$$

The average 30-mL multidose vial of diphenhydramine contains only 500 mg. The accused had only a 10-cc syringe. If the V_{ss} calculation is to believed, the accused would have to have injected the victim with more than three vials of diphenhydramine, a process that would have required at least 10 separate injections!

The main utility of V_{ss} calculations in postmortem investigations is as a quality assurance check of reported blood concentrations. If the V_{ss} calculation suggests that an implausible amount of drug has been ingested, an error in laboratory or sampling methods may be indicated (the blood analyzed may, for example, have been scooped from the chest cavity).

Appendix 4: Normal Heart Weights

Predicted Normal Heart Weight (g) as a Function of Body Height in 392 Women and 373 Men

Body Height		Women[a]			Men[a]		
(cm)	(in)	L95	P	U95	L95	P	U95
130	51	133	204	314	164	232	327
132	52	135	207	319	167	236	333
134	53	137	210	324	170	240	338
136	54	139	214	329	173	243	344
138	54	141	217	334	175	247	349
140	55	143	220	338	178	251	355
142	56	145	223	343	181	255	361
144	57	147	226	348	184	259	366
146	57	149	229	353	187	263	372
148	58	151	232	358	189	267	378
150	59	153	236	363	192	271	383
152	60	155	239	368	195	275	389
154	61	157	242	372	198	280	395
156	61	159	245	377	201	284	400
158	62	161	248	382	204	288	406
160	63	163	251	387	207	292	412
162	64	165	254	392	209	296	417
164	65	167	258	397	212	300	423
166	65	169	261	401	215	304	429
168	66	171	264	406	218	308	435
170	67	173	267	411	221	312	440
172	68	176	270	416	224	316	446
174	69	178	273	421	227	320	452
176	69	180	277	426	230	324	458
178	70	182	280	431	233	328	463
180	71	184	283	435	235	332	469
182	72	186	286	440	238	336	475
184	72	188	289	445	241	341	481
186	73	190	292	450	244	345	487
188	74	192	295	455	247	349	492
190	75	194	299	460	250	353	498
192	76	196	302	465	253	357	504
194	76	198	305	469	256	361	510
196	77	200	308	474	259	365	516
198	78	202	311	479	262	369	522
200	79	204	314	484	265	374	527
202	80	206	318	489	268	378	533
204	80	208	321	494	271	382	539
206	81	210	324	499	274	386	545
208	82	212	327	508	276	394	557
210	83	214	330	508	279	394	557

[a] L95 = lower 95% confidence limit; P = predicted normal heart weight; U95 = upper 95% confidence limit.

Note: Observed heart weight should be compared to predicted heart weight in all cases, not just those where drug abuse is suspected. Variations of more than 10% are very likely to be clinically significant but not apparent if only wall thickness is determined. Percentage-based formulas (e.g., 0.4% of body weight for men and 0.45% for women) are approximations only and not nearly so accurate or reliable.

Source: From Kitzman, D. et al., Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity). A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old, *Mayo Clin. Proc.,* 63, 1237–1246, 1988. With permission.

Predicted Normal Heart Weight (g) as a Function of Body Weight in 392 Women and 373 Men

Body Weight		Women[a]			Men[a]		
(kg)	(lb)	L95	P	U95	L95	P	U95
30	66	133	196	287	162	213	282
32	71	137	201	295	167	220	291
34	75	141	206	302	172	227	300
36	79	144	211	310	177	234	309
38	84	148	216	317	182	240	317
40	88	151	221	324	187	247	325
42	93	154	226	331	191	253	334
44	97	157	230	337	196	259	341
46	101	160	234	344	200	265	349
48	106	163	239	350	205	270	357
50	110	166	243	356	209	276	364
52	115	169	247	362	213	281	371
54	119	171	251	368	217	287	379
56	123	174	255	374	221	292	386
58	128	177	259	379	225	297	392
60	132	179	262	385	229	302	399
62	137	182	266	390	233	307	406
64	141	184	270	395	237	312	412
66	146	187	273	401	240	317	419
68	150	189	277	406	244	322	425
70	154	191	280	411	248	327	431
72	159	194	284	416	251	331	437
74	163	196	287	420	255	336	444
76	168	198	290	425	258	341	450
78	172	200	293	430	261	345	455
80	176	202	297	435	265	349	461
82	181	205	300	439	268	354	467
84	185	207	303	444	271	358	473
86	190	209	306	448	275	362	478
88	194	211	309	453	278	367	484
90	198	213	312	457	281	371	489
92	203	215	315	461	284	375	495
94	207	217	318	465	287	379	500
96	212	219	320	470	290	383	506
98	216	221	323	474	293	387	511
100	220	222	326	478	296	391	516
102	225	224	329	482	299	395	521
104	229	226	331	486	302	399	526
106	234	228	334	490	305	403	531
108	238	230	337	494	308	406	536
110	243	232	339	497	311	410	541
112	247	233	342	501	314	414	546
114	251	235	345	505	316	418	551
116	256	237	347	509	319	421	556
118	260	239	350	513	322	425	561
120	265	240	352	516	325	429	566
122	269	242	355	520	327	432	570
124	273	244	357	523	330	436	575

Cont.

Predicted Normal Heart Weight (g) as a Function of Body Weight in 392 Women and 373 Men (Cont.)

Body Weight		Women[a]			Men[a]		
(kg)	(lb)	L95	P	U95	L95	P	U95
126	278	245	360	527	333	439	580
128	282	247	362	531	335	443	584
130	287	249	364	534	338	446	589
132	291	250	367	537	341	450	593
134	295	252	369	541	343	453	598
136	300	253	371	544	346	456	602
138	304	255	374	548	348	460	607
140	309	257	376	551	351	463	611
142	313	258	378	554	353	466	616
144	317	260	381	558	356	470	620
146	322	261	383	561	358	473	624
148	326	263	385	564	361	476	629
150	331	264	387	567	363	479	633

[a] L95 = lower 95% confidence limit; P = predicted normal heart weight; U95 = upper 95% confidence limit.

Source: From Kitzman, D. et al., Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity). A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old, *Mayo Clin. Proc.*, 63, 1237–1246, 1988. With permission.

Index

Page references in *italics* refer to figures.
Page reference in **bold** refer to tables

A

abacavir, 512
abscesses
  from injection of ground tablets, 306, 307, 308
  injection site, 117–118, 498, 500, 571
absinthe
  abuse, *212*
  cocaine and, 213
  epidemiology, 210
  ethanol content, 214, 216
  history of, 209, 211–214
  incidence, 210
  manufacture of, 214–215
  pharmacology, 215–216
  properties, 210
  tissue concentrations, 216
  toxicity, 216
acacia plant, 351
acetaminophen
  as heroin adulterant, **385**
  poisoning, 197
  propoxyphene and, 490
acetic anhydride, 383–384
acetone, 27
acetyl chloride, 383
acetylcholine receptors, toluene binding, 637
acetylcodeine, 381, 419
N-acetyl compounds, cocaine use and, 144–145
6-acetylmorphine
  blood levels, 412
  half-life, 403, 405
acid flashbacks, 365
acid glycoprotein (AAG)
  in methadone-related deaths, 465–466
  phenotypes, 465
α1-acid glycoprotein (AGP), 428
Acomplia®, 653
acquired immunodeficiency syndrome (AIDS), *See also* human immunodeficiency virus
  cardiovascular pathology associated with, 127–128, 511–512
  dementia, 553
  and glomerulosclerosis, 182
  liver disease and, 540–541
  muscular complications, 559
  neurological complications, 553–554, 558
  opportunistic infections, 540–541, 553–554
  peliosis in, 617
  progressive multifocal leukoencephalopathy, 556
  thrush and, 504
ACTH, *See* adrenocorticotropic hormone
Actiq®, 446, 449
acute angle glaucoma, 240
acute generalized exanthematous pustulosis, 504
acute myocardial infarction
  cocaine-related, 119–122, 123
  khat chewing and, 258
Adderall®, 261, 262
  FDA recommendations, 292–294
addiction
  arcuate nucleus and, 188
  nucleus accumbens and, 143–144, 173, 230
  and seven transmembrane domains, 370
  striatum and, 162
addiction treatment
  L-LAAM, 462–463
  buprenorphine, 435–436, 462–463
  methadone, 436, 462–463
adenomas
  birth control pills and, 618–619
  hepatocellular, 618–619
adenosine, 229
adenosine receptors, 225, 230
  caffeine binding, 225–226, 227–228, 229–230, 232
ADHD, *See* attention deficit/hyperactivity disorder
adhesive solvents, 638, **638**
adipose tissue, drug binding, 74–76; *See also* fat depots
adrenal glands
  cocaine and, 188, 189
  opiates and, 188
adrenergic receptors, 97; *See also* α-adrenoreceptors; β-adrenoreceptors
adrenocorticotropic hormone (ACTH), 188, 334
  heroin use and, 567
adrenoleukodystrophy, 641
adulterants, skin abscesses from, 117–118
aerosols, 635, **638**
Afghanistan, opium production, 382–383
Africa, khat production, 254
"Agent lemon" technique, 605
aggression, anabolic steroid-associated, 621–622
agitation, 606
albumin
  cocaine binding, 76
  testosterone binding, 614

alcohol, 637
addiction, use of cocaine for, 11
blood concentrations, 667
in breast milk, 77
cocaine and, 2, 10–11, 48, 52–54, 125
fentanyl and, 452
GHB and, 591, 592, 595, 597
hepatic steatosis and, 539
-induced hallucinations, 16
methadone and, 429, 465
and NMDA receptor function, 588
opiates and, 425
oxycodone and, 482
oxymorphone and, 488
and solvent abuse, 639
in vitreous humor, 81
aldehyde oxygenase, 657
Alfenta®, 446
alfentanil, 446, 449, 561
alkaloids
coca leaf, 22–23, 24, 25, 30
ephedra-containing plants, 232
ergoline, 361–365
harmala, 352
in kratom, 459–460
monoamine, 351–356
in opium, 381
plants containing, 209
17-α-alkyl-substituted steroids, 618–619, 620
allergic disease, 192
allergic granulomatous angiitis, 130
Alles, Gordon, 267
allococaine, 28
allylbenzene, 275
α-adrenoreceptors, 96, 343
BZP and, 326
xylazine and, 384
α-ethyltryptamine (AET), 351
alpha-fetoprotein, 619
α-methyl fentanyl, 36
as heroin adulterant, 446, 447
α-methyltryptamine (AMT), 351
alprazolam, 486
alveoli
"crack"-associated damage, 153–156, 192
marijuana smoking and, 659
narcotics abuse and, 521–523
Alzheimer's disease, 222, 226, 230
2-amino-5-(*p*-hydroxyphenyl)-4-methyl-2-oxazoline, 345
aminophylline, potentiation of caffeine toxicity,228
aminorex, 344–345
aminotransferases, 539
amiodarone, 66, 539
amitriptyline, 5
amniotic fluid
benzoylecgonine in, 76
cocaine in, 41, 42, 76, 77
ecgonine methyl ester in, 76
morphine in, 406
norcocaine in, 76
amphetamines
ADHD and, 292–294
analogs, 286
blood levels, 274
catecholamine-mediated toxicity, 278
central nervous system effects, 288–290
"designer," 290, *317*, 322
gastrointestinal effects, 292
half-life, 274
history, 241, 267–271
impairment, 281–282
infant postmortem blood levels, 277–278
interactions, 263
introduction of, 17
manufacture of, 271–273
medicinal uses, 267, *268*, 269
metabolism, 274–276
oral effects, 291
postmortem redistribution, 279–281
properties, 262–263
-related deaths, 269
renal disease, 290–291
routes of administration, 273–274
and serotonin levels, 286–288
structure, *240*, *257*
synonyms, 262
tissue disposition, 276–281
toxicity, 282–292
trafficking, 270–271
worldwide production, 264
amyl nitrite, 635, 639, 643
amyloidosis, 541
hepatic, 197
renal, 548
anabolic steroids, *See* steroids, anabolic
analgesia, ketamine, 585–590
anandamide, 653, 658
anatoxin, 54
Andean Counterdrug Initiative, 21
Andes
cocaine production, 21, 22–23, 27
opium production, 382
androgen receptors, 613, 614, 616, 626
androgen replacement therapy, 615–616
androgens, cardiac potassium channels and, 66
andropause, 615–616
signs of, **615**
androstenedione, 613
androsterone, 611
anesthetics
dissociative, 575–576, 599–606
γ-hydroxybutyrate (GHB), 591–597
ketamine, 585–590
phencyclidine, 576–583
anethol, 223
aneurysms
aortic, 128–130
berry, 169, 206
hypertension and, 170
methamphetamine-related,286, 287
mycotic, 515–516
saccular, 169–170
sinus of Valsalva, 515

angelica, 215
angioedema, hereditary, 616
angiotensin II, 63
angiotensin-converting enzyme inhibitors, 510
Anhalonium lewinii, 315
anhydroecgonidine, 49
anhydroecgonine, in nails, 74
anhydroecgonine methyl ester (AEME), metabolism of, 54
anise, 214, 215
antecubital fossa, 498–499
anthracosis, pulmonary, *153*
antidepressants
  ketamine as, 589–590
  serotonin re-uptake inhibitors, 156, 162
antidiuretic hormone, 334
anti-drug efforts, U.S funding for, 21
antiemetics, THC as, 658
antifungal drugs, buprenorphine and, 434
antiglomerular basement membrane (anti-GBM) antibodies, 182
antihelminthics, 325
antihistamines, 325
antimuscarinic syndrome, 472
antioxidants, 334
  in coffee, 230–231
antiretroviral drugs
  buprenorphine and, 434, 436
  cocaine and, 65
  dextromethorphan and, 603
  HAART, 512, 540, 553, 559
  interactions, 436
  ketamine and, 586
  liver disease and, 539
  MDMA and, 330
aortic dissection, 128–130
  MDMA-related, 340
  methamphetamine-related, 286
aortic medial disease, 129–130
aortic valve, 553
apical ballooning, 284
Apiquel®, 344
apnea, 589
apoptosis, 87
  anabolic steroid-induced, 620–621
  androgen-induced, 621
  cocaine-induced, 62, 206
  early gene activation, 579
  PCP-induced, 582
appetite suppression, 288
aquaporin-4 (AQP-4), 173
arabica beans, 223
arcuate nucleus, addiction and, 188
arecoline, 54
arrhythmias
  amyl nitrite, 643
  bufadienolides, 354–355
  cocaine, 14, 34, 63, 87–105
  drug-induced, 66
  in endocarditis, 515
  methadone, 467
  methamphetamine, 283
  phenylpropanolamine, 247
  re-entrant, 97, 206, 340
  toluene, 642
  ventricular, 99
Artemisia absinthum, 211
Artemisia pontica, 2111
arteriosclerosis, renal artery, 179–180
arthritis, ma huang for, 345
arylhexylalkylamines, 582
α-asarone, 215
β-asarone, 215
Asia/Asians
  drug trafficking by gangs, 331
  hair cocaine levels, 71–72
  opium production, 382–383
Aspergillus, 528, 552
aspiration pneumonia, 528
aspirin, propoxyphene and, 490
asthma, 241
asystole
  cocaine-associated, 206
  in excited delirium, 138, 142
ataxia, solvent-induced, 635
atherogenesis
  cocaine abuse and, 167
  steroid abuse and, 620
atherosclerosis, *129*
athletes
  caffeine use, 232
  steroid abuse, 609, 610, 611–613
athletic supplements, 222
ATPase inhibitors, 354
atrial natriuretic factor, 87, 226
atrioventricular valves, 513–516
atrophic scarring, subcutaneous injection, 499–500
atropine, 386
attention deficit/hyperactivity disorder (ADHD), 240, 261, 292–294, 303
Aurora Leigh, 373
autoimmune disease, 192
autopsy
  complete, 60–61, 430
  negative, 422
ayahuasca, 352, **353,** 355

B

bacillary angiomatosis, 541, 618
bacillary peliosis, 618
Bacillus cereus, 498
Bacteroides, 572
Banisteriopsis caapi, 352
barbiturates, 461, 637
barotrauma, 151–153
Bartonella henselae, 540–541, 618
Bartonella quintana, 540, 618
basal ganglia
  adenosine receptors, 230
  hypertensive hemorrhage, 170
baton choke hold, 139
batu, 270

Baudelaire, 213
Bazett correction, 246
B-cell lymphoma, 512
Bell, Lewis, 137
Benadryl®, volume of distribution calculations, 669
Bentley compounds, 381
Benzedrex®, 269
Benzedrine®, 267, *268*, 269
benzocaine, in cocaine, 186
benzodiazepams, 637
benzodiazepine receptors, THC binding, 653
benzodiazepines
  buprenorphine and, 434, 437
  and heroin overdose, 425
  oxycodone and, 482, 485–486
benzoic acid, 25
benzomorphans, 368
benzoylecgonine (BZE), 2, 3, 25, *26*, 30, 48–49
  in amniotic fluid, 42, 76
  blood-brain barrier and, 51, 70, 205
  blood levels, *47*, 195
    postmortem, 62
  brain levels, 71
  in coca-based teas, 40–41
  cutoff values, 65
  excretion time, 79
  fetal levels, 50, 59, 80
  half-life, 50, 80
  hepatic levels, 73
  immunoassay kits, 48
  metabolism of, 49–51
  postmortem changes, 50
  in saliva, 78
  in skin, 74
  in sweat, 82
  urinary concentrations, 48, 78–80
  in vitreous humor, 81
  volume of distribution, 63, 205
benzoylnorecgonine (BNE), 49, 79
1-benzyl-3-methylnaphthalene, 273
N-benzylpiperazine (BZP), 325–327
berry aneurysms, 169, 206
β-adrenoreceptors, 88, 96–97, 201
  down-regulation, 98
  ephedrine and, 243–245
β-endorphins, 369, 370, 567
beverages, caffeine content, 218, **219–220**
bicarbonate, in "crack" cocaine, 36
big dynorphin, 370
bile, 397
  codeine levels, 443
  morphine levels, 414
birefringent crystals, 286, 307
  fibrous myopathy, 572
  liver, 536
  lymph nodes, 415, 535
  opiate use and, *525*
  oxycodone use and, 485
  in track marks, *501*
birth control pills, adenomas and, 618–619
birth weight
  caffeine exposure and, 228
  cigarette smoking and, 201
  cocaine use and, 202
Black Bolivian, 21
blacks, cocaine-related deaths, 8
black tar heroin, 117, *392*, 503
black tea, 223
blood, postmortem drug redistribution, 62, 69–70, 427
blood alcohol concentration (BAC), 667
blood-brain barrier
  benzoylecgonine and, 51, 63, 70, 205
  caffeine and, 233
  cocaethylene and, 70
  cocaine and, 51, 63–64, 70, 174–175, 192, 205
  GHB and, 593
  heroin and, 389–390, *391*
  HIV-1 infection, 173–174, 192
  morphine and, 394, 410
  theobromine and, 233
blood pressure
  cocaine and, 206
  ketamine and, 590
blood sample collection, 410–411, 426
blotter acid
  DOB, 321–322
  LSD, 363, *364*
  5-MeO-DMT, 355–356
body mass index (BMI), 623
body packer syndrome, 17
  bowel obstruction, 38
  cocaine, 34, 36, 37–40, 193
  and excited delirium, 138
  fatalities, 36, 39–40
  genital application, 34
  heroin tissue levels, 418
  marks/mutilations, 115
  opiates, 533–534
  postmortem heroin/morphine levels, 411
body stuffing, cocaine, 36
Boerhave, Hermann, 9
Bolivia, cocaine production, 23, 24
bone infections, 571–572
bowel obstruction, 38, 194
Bowman's capsule, *180*, 545
brain
  bacterial infections, 553
  benzoylecgonine levels, 71, 205
  caffeine concentrations, 227, 229–230
  cocaine, 60, 61, 70–71, 163
    in excited delirium, 145
    -induced calcium overload, 162
    postmortem, 63–64
  cocaine/BZE ratios, 205
  dextromethorphan in, 605–606
  dopamine receptors, 163
  fungal infections, 554
  glucose metabolism, 164
  hallucinogen binding, 317
  HIV infection, 553–554
  lymphoma, 554

MDMA-induced hyperthermia, 335
methylphenidate and, 304
morphine levels, 412, *413*, 414
opiate-induce hypoxia, 551–552
opiate receptors, 369
response to chronic drug abuse, 280
reward center, 173
solvent abuse, 639–642
succinic semialdehyde dehydrogenase, 595
theophylline concentrations, 227
toluene and, 635, 644
brain/blood ratio, cocaine, 51
Brazil
anti-drug efforts, 21
cocaine production, 24
Brazilian sassafras, 333
breast cancer, androgen treatment of, 616
breast-feeding, recommendations for cocaine users, 42
breast milk
alcohol in, 77
amphetamines in, 276
caffeine in, 233
cocaethylene in, 76
cocaine in, 40, 41–43, 76–77
fentanyl in, 452
khat chewing and, 258
methadone in, 466
methylphenidate in, 305–306
morphine in, 406
nicotine in, 77
norbuprenorphine in, 438
norpropoxyphene in, 492–493
oxycodone in, 484–485
propoxyphene in, 492–493
broken heart syndrome, 284
bromo, 323
4-bromo-2,5-dimethoxyphenethylene (2-C-B), 323
bromo-DMA, 321–323
bronchiolitis obliterans, 527
bronchodilatation, ephedrine, 242, 245
brown fat, 76, 278
brown heroin, 504
Browning, Elizabeth Barrett, 373
brown mixture, 402
Brugada syndrome, 53, 202, 430
buccal mucosal leukoderma, 150
bufagins, 354
bufalin, 354
bufogenin, 355
bufotalin, 354
bufotenine, 354
bufothionine, 354
bufotoxins, 354–355
Buprenex®, 435
buprenorphine, 381
addiction treatment, 435–436, 462–463
autopsy findings, 438
blood levels, 437
detection, 437
drug interactions, 436–437
metabolism, 534
pharmacology, 436–437
properties, 433–434
routes of administration, 436
skin patch, 406
withdrawal syndrome, 438
bupropion, 307
Burnett's Dandruff Shampoo, *13*
buscaline, 318
"businessman's high," 353
2-butanamine-2 homolog, MDMA, 345
1-butanol, 644
butorphanol, 368
butyl nitrite, 635

C

caffeine
autopsy studies, 233–234
blood levels, 223, 226
newborns, 41, 59, 228
cardiovascular effects, 230–232
cocaine and, 11, 130
in cord blood, 59
dependence, 229–230
ephedra/ephedrine and, 222, 225–226, 242
epidemiology, 219, **219–220**
ergogenic effects, 232
half-life, 222, 226–227, **227**
hematological effects, 232
heroin and, 224, 384, **385**, 386, 556
history of, 221–222
incidence, 218–219
inhaled, 224
interactions, 223
intravenous, 224
mechanism of action, 225–226
metabolism, 224–225
neurological effects, 229–230
pharmacokinetics, 224, 226–227
plants containing, 218
pregnancy and, 228, 233
properties, 222
psychological effects, 229
sources of, 223
tissue concentrations, 227–229
tolerance development, 231
toxicity, 229–233
caffeine/ephedra, 243, *244*
calamus, 215
calcium
cardiac levels, 87–88, 96–98, 642–643
cocaine-induced myocardial overload, 99–104, 125, 145, 162
calcium channels, 96
ketamine and, 587
calcium-dependent ATPase, PCP and, 582, 583
calcium signaling dysfunctions, 89
calmodulin, 88–89, 643
calmodulin kinase II, 97
cocaine-induced activation, 62, 87, 89, 145, 516
ephedrine and, 247
methamphetamine-induced activation, 89, 145

Camellia sinensis, 223
camphor, 215, *215*, 216
cancer
  pain relief
    fentanyl for, 450
    heroin for, 401–402
    hydromorphone for, 458
    methadone for, 463
  tea and, 221
Candida spp.
  bone/joint infections, 571
  disseminated infections, 528
  oral infections, 504
Candida albicans, in lemon juice, 504
cannabidiol, 654
cannabinoid receptors, 653, 659
  CB1, 216
cannabinoids
  endogenous, 653, 658
  fetal exposure to, 42, 58
cannabinol, 654
Cannabis sativa, 650
Cantacuzene, Joan, 566
carbamazepine, 461
carbon isotope ratio, 625
carboxylesterase, 52
cardiac glycosides, 354
cardiovascular system
  anabolic steroids and, 619–621
  caffeine and, 230–232
  cardiac fibrosis, 510
  catecholamine toxicity, 283, 285–286
  cocaine and, 282–286
    aortic dissection, 128–130
    catecholamines, 96–98
    conduction abnormalities, 53–54
    contraction band necrosis, 16, 96, *98*, *100*, 101–104, **101**, 516
    coronary artery disease, *120*, 121–122, *121*, 123–124
    coronary artery dissection, *128*, 130, 131–132
    coronary artery spasm, 119, 121, 124–125
    eosinophilic myocarditis, 36, 130–131
    flow reserve, 91, 92, 125–126
    heart uptake, 72
    HIV-related myocardial disease, 127–128, 511, 512
    ion channel remodeling, 93–95
    left ventricular hypertrophy, 89–93
    mechanisms of cardiotoxicity, *95*
    microvascular disease, 91, *91*, 122–123, 207
    multiple hits theory, 94–95
    myocardial apoptosis, 55, 87
    myocardial hypertrophy, 89–93, 167, 206
    myocardial infarction, 32, 87–105, 119–122, 123–124
    myocardial remodeling, 61, 62–63, 87–89, 206, 510
    nonatheromatous coronary artery disease, 132
    QT dispersion, 93
    valvular heart disease, 128
    vascular disease, 126
  ephedrine and, 246–247
  inhalants and, 637
  ketamine and, 590
  khat chewing and, 258
  marijuana and, 658–659
  MDMA and, 338–340
  meperidine and, 476
  methamphetamine and, 282–286
  methylphenidate and, 307
  nordextropropoxyphene toxicity, 490, 491
  opiates and, 509–511; *See also* opiates, cardiovascular disorders
  PCP and, 583
  solvents and, 642–643
  stress-induced cardiomyopathy, 284
  transplacental toxicity, *200*
Carfentanil®, 446
CARTs, 76, 188
carvedilol, 428
Cat, 345
catecholamines
  amphetamines and, 283
  blocking re-uptake of, 162
  cardiotoxicity, 283, 285–286
  cocaine and, 98, 185
  and ephedrine use, **247**
  excess, 98, 185, 516
  free radicals from, 124
  MDMA and, 337–338
  -mediated gastrointestinal lesions, 194
  myocardial necrosis, 101, **102**
  role of, 96–98
  toxicity, 307
    histopathology of, 99–104
    mechanisms, 98–99
catechol-*O*-methyl transferase (COMT), 289
cathine, 248, 257
cathinone, 256, *257*
cat scratch disease, 540, 618
Caucasians
  cocaine-related deaths, 8
  codeine metabolism, 441
  CYP2D6 deficiencies, 483, 496
  hair cocaine levels, 71–72
cauliflower ears, opium smoking, 506
cause of death
  certifying, 430
  cocaine as, 204–207
  determining, 424–430
cay ma, 529
CD14 gene promoter region, 539
CEDIA DAU cocaine assay, 81
cellulose granulomas, 157, 525, 526
Central Asia, poppy cultivation, 381
Central Intelligence Agency (CIA), LSD experiments, 362–363
central nervous system
  amphetamines and, 288–290
  ephedrine and, 242
  HIV infection, 553–554
cerebral blood flow
  caffeine and, 229
  cocaine and, 172–173

cerebral edema
fentanyl-related, 452–453
laudanum overdose, 522
opiate toxicity, 551–552
cerebral hemorrhage, 169–171
cerebral hypoperfusion, 163, 164
cerebral sinus thrombosis, 335
cerebral vasculitis, 118, 167–169
cerebrospinal fluid
6-monacetyl morphine in, 415
morphine in, 412, 414, 416
c-fos, 163
chalk streaks, 493
channelopathies
cocaine-related, 93–95
and drug toxicity, 429
hereditary, 104–105, 202
chaparral tea, 241
"chasing the dragon," 227, 400, 404, 405
chemokines, 567, 569
chemoreceptors
CCR3, 567, 569
CCR5, 567, 569
children
caffeine in, 219, 222, 226–227, **227**
cocaine in, 37, 64, 76
intranasal heroin for pain relief, 403–404
methadone overdose in, 402
China/Chinese
ephedrine production, 241, 242, 245
codeine metabolism, 441
opium use, 373–374
tea production, 218
china white, 444
chloral hydrate, 645
chloride channels, GABA-gated, 215, 216
chloride transport, cAMP-regulated, 229
4-chloro-2-5-dimethoxyamphetamine, 325
chloroform abuse, 637
1-(3-chlorophenyl)piperazine (mCPP), 326
chlorpheneramine, 271–272
chlorphenhydramine, 604
chocolate, 223
psilocybin-containing, 352
cholecystokinin, 410
cholestasis, 618
cholinesterase
and cocaine metabolites, 51
placental, 58
chronic interstitial nephritis (CIN), 545
Churg-Strauss syndrome, 130
cigarettes
burns, 506
PCP-laced, 578
cigarette smoking
cocaine and, vasoconstriction, 125
low birth weight and, 201
and marijuana, 659
usage patterns, 8
cimetidine, 197, 461
cinnamoylcocaine, 25, *26*
in coca-based teas, 40
cinobufagin, 354
ciprofloxacin, 461
cirrhosis, 226
hepatitis B virus and, 538
hepatocellular carcinoma and, 539
and meperidine metabolism, 475–476
methamphetamine-associated, 291
clarithromycin, 65, 461, 466
Claviceps purpurea, 363
clenbuterol, 386
Clostridium, 401, 571
injection site infections, 498
soft tissue infections, 572
Clostridium histolyticum, 498
Clostridium novyi, 498, 500
Clostridium sordellii, 498, 503
in black tar heroin, 117
clotting mechanisms, cocaine and, 185–186
clozapine, 223
"coasting," 555–556
coca
hybridized, 21
soft drinks, 40
teas, 40–41
wines, 10, *11*, *14*, 18
Coca-Cola, 11, 23
cocaethylene, 2, 10–11
blood-brain barrier and, 70
blood levels, *47*
in breast milk, 76
drug interactions, 2
effects of, 53
formation of, *52*
half-life, 53
hepatotoxicity, 73, 193, 197
metabolism of, 52–54
placental binding sites, 42, 59
properties, 2
in saliva, 78
in vitreous humor, 81
cocaine
absinthe and, 213
absorption
body packer syndrome, 34, 36, 37–40
from breast milk, 40, 41–43, 76–77
dermal, 32–33, 34–35
fetal, 40, 41–43, 58–59
gastrointestinal, 37–41
mucous membranes, 31–32, 34
passive, 64–65
abuse
cycles of, 17
employment and, 8
external markers, 109–115, 150
gender differences, 6–8
incidence of, 3–6
poverty and, 8
activation of calmodulin kinase II, 87, 89, 145
adulterants, **66**, 117, 130, 326–327

airborne levels, 35
alcohol and, 2, 10–11, 48, 52–54, 125
in amniotic fluid, 41, 42, 76, 77
antiretrovirals and, 65
availability, 21
benzocaine in, 186
"binging," 9
blood-brain barrier and, 70, 205
blood levels, 30
  body packer syndrome, 39–40
  and cause of death, 205–206
  coca leaf chewing, 30–31, *31*, 37
  compared to saliva levels, 78
  compared to vitreous humor levels, 81
  "crack," *31*, 36–37
  in excited delirium, 145
  intravenous use and, *31*, 33–34
  metabolites, *47*
  newborns, 41
  postmortem, 60–61, 69–70
  and route of ingestion, *31*
  snorting and, 31–32, *31*
  surgical applications, 32–33
body stuffing, 36
brain/blood ratio, 51
brain levels, 70–71
  in excited delirium, 145
in breast milk, 40, 41–43, 76–77
caffeine and, 11
calmodulin kinase II activation, 516
cardiovascular effects, 282–286; *See also* cardiovascular system, cocaine and
as cause of death, 204–207
coca leaf chewing, 30–31, *31*, 37
in cord blood, 76
"crack," 18
  acute aortic dissection, 128–130
  anhydroecgonine methyl ester, 54
  bicarbonate in, 36
  black sputum, 151, 153, 522–523
  blood levels, *31*, 36–37
  contaminants, 36
  "crack dancing," 173
  "crack hands," 114–115
  "crack keratitis," 113, *114*
  "crack lips," 111, *112*
  "crack thumb," 111, *112*
  dermal absorption, 34–35
  effect on alveolar macrophages, 192
  inhalation, *31*, 35–37
  intravenous, 34
  metabolism, 48
  origins of, 35–36
  prices, 28
  pulmonary disease associated with, 150–157
  smoking, 28
  urinary levels, 79–80
cutoff values, 65
"cutting," 28
deaths
  body packer syndrome, *See* Body packer syndrome
  causes of, 60–61
  DAWN report, 18
  electrophysiology of, 87–105
  excited delirium, *See* excited delirium
  first reports of, 13–14
  first autopsy findings, 16
  incidence of, 5, 7, 8
  misconceptions, 204
  multiple hits theory, 94–95
  myocardial remodeling, 62–63
  temperature and, 138
dental erosions, 114
dependence, 7
detection, 16, 17, 33, 48
  sweat-collection patches, 35
diastomers, 28
disulfiram and, 65
dopamine receptors and, 142
drug interactions, 2, 65–66
excited delirium, 16; *See also* excited delirium
elixirs, 11
epinephrine and, 32
ER visits, 265
erythrocytosis, 186
estimating time of ingestion, 63–64
excretion times, 78–80
exposure
  environmental, 37, 64–65, 204
  occupational, 33, 35
facial necrosis and, 110
in fat stores, 204
fentanyl and, 36
fetal gastric aspirates, 77
fetal metabolism, 40, 41–43, 58–59
first illustration of, *22*
free base
  dermal absorption, 34
  and ischemic strokes, 165
  smoking, 35–37
gastrointestinal disorders, 193–198
  hepatic disease, 195–198
  ischemic colitis, 193–195
  stomach injuries, 194
gender differences in response, 6–8, 188
genital application, 34, 194
GHB and, 592
gonads and, 189–190
in hair, 47, 64, 71–72
half-life, 1, 30, 32, 47, 50, 205
  newborns, 80
  in saliva, 78
hallucinations from, 16
hematological abnormalities, 185–186
hepatic receptors, 73
hERG channel and, 53, 63, 65–66, 94
as heroin adulterant, **385**
history, 9–18
and HIV infection, 192
hormones and, 188–190
immune system and, 191–192
inhalation, 14, 31–32, *31*, 35–37

interferon and, 191–192
intravenous use, *31*, 33–34
ketamine and, 197
as local anesthetic, 11, *12*, 32–33 155–156
low-affinity receptors, 69
maternal-to-fetal ratio, 71
melting point of, 405
metabolism, 1, 2, 3, 47–49, 69, 195; *See also individual metabolites*
methadone and, 465
methemoglobinemia, 186
in nails, 73–76
nasolacrimal duct obstruction, 110
neurological disorders, 162–174
  blood-brain barrier alterations, 174–175
  cerebral hemorrhage, 169–171
  cerebral vasculitis, 167–169
  ischemic stroke, 165–167
  movement disorders, 173
  neurotoxicity, 163
  psychiatric symptoms, 164–165
  seizures, 171–173
in ophthalmic surgery, 11, *12*, 13, 32–33
oral lesions, 114
organ transplantation and, 183
"parrot beak" nails, 110–111
performance enhancement, 164–165
pharmacokinetics, 1–2, 30
placental binding sites, 42, 50, 58, 200–202
plant sources, 9
postmortem redistribution, 62, 65, 69–70
pregnancy and, 50, 58, 172, 200–202
pressor effects, 126
production, 14
  Bolivia, 23, 24
  Brazil, 24
  coca leaf cultivation, 22–23
  coca paste, 24–28
  Columbia, 23
  Europe, 23, *24*
  global, 20
  Peru, 23, 24
  prices, 20, 21, 23, *24*, 28
  purity, 20, 21, 28
  South East Asia, 23
  United States, 23, *24*
prolactin and, 188–189
properties, 1–2
protease inhibitors and, 65
psychological disorders, 16
pulmonary disease associated with, 150–157
purification, 10
rectal use, 403
refining process, 24–258
renal disease and, 179–183
renal uptake, 72
rhabdomyolysis, 179–181
routes of ingestion, 30–43
in saliva, 77–78
scleroderma and, 118
seizures, 115
in semen, 82
septal perforation, 109–110, 150
sequestered, 64
serotonin deficit, 144
serotonin re-uptake inhibition, 144, 156
in sewerage effluent, 3–4
sex hormones and, 189
skeletal muscle toxicity, 180
in skin, 73–76
skin infections, 117–118
snorting, 14, 31–32, *31*, 35–37
  septal perforation from, 109–110, 150
speedballing, 34, 131
in spinal fluid, 78
strokes and, 206
structure, *2*
subcutaneous injections, *75*, 113, *114*, 117–118, 306
surgical applications, 32–33
in sweat, 74, 82
synonyms, 1
teratogenicity studies, 182
test interpretation, 60–66
testosterone and, 185, 190
thrombocytopenic purpura, 185–186
thrombosis, 185–186
tissue disposition, 16–17, 69–82
tolerance development, 61–62, 164–165, 206
  snorting and, 31–32
toxicity, 18
  first histological studies, 14
  first reports of, 13–14
  long-term use, 51
  ruptured "packets," 38–40
  urinary concentrations, 48
track marks, 111–113, *113*
trafficking, Colombia, 20–21
transesterification to cocaethylene, *52*, 197
as treatment for morphinism, 375
in urine, 3–4, 16–17, 33, 78–80
  postmortem changes, 50
usage patterns, 7–8
U.S market, entry points, 20
vasoconstriction, 98, 109, 110
  and ischemic stroke, 163, 165–167
vasospasm and, 165, 167
in vitreous humor, 80–81
volume of distribution, 1, 35, 63, 65, 205
cocaine- and amphetamine-regulated transcripts (CARTs), 76, 188
cocaine hydrochloride, 27
  dermal absorption, 34
  gastrointestinal absorption, 37
  in patent medicines, 14
cocaine-*N*-oxide, 48
cocaine paste (mud), 32
coca leaf, 9
  alkaloid content, 22–23, 24, 25, 30
  chewing, 30–31, *31*, 37
    pulmonary disease associated with, 150–151

cultivation, 20, 22–23
Andes, 27
first illustration of, *22*
refining, 23
South American production, 20, 22–23, 27
coca paste, 24–28
impurities, 28
smoking, 27
Coca Sek™, 40
cocoa, 218, 223
codeine, 381
in bile, 443
blood levels, 443
conversion to morphine, 422, 441
drug interactions, 440
half-life, 442
immunoglobulins to, 569
metabolism, *396*, 441
genetic polymorphisms, **442**
as morphine contaminant, 442
in opium, 441
products containing, 440
properties, 439–441
routes of administration, 442–443
in saliva, 442
tissue disposition, 443
in urine, 422–423
codeine-6-glucuronide, 441–442
coffee
antioxidants in, 230–231
caffeine in, 218, 219, 223
origins of, 221
coffee enemas, 233
coffee houses, 221
cognitive impairment, solvent-related, 639
cola drinks, 219
cold remedies
caffeine in, 218, **219–220**
dextromethorphan in, 602–604
methylephedrine in, 243
colitis, cocaine-associated, 193–195
Colombia
cocaine production, 20–21, 23
cocaine trafficking, 20–21
community-acquired pneumonia, 527–528
compartment syndrome, 335
compliance monitoring, methadone, 467
COMT, 334
Concerta®, 293
Confessions of an English Opium Eater, 373
Conocoybe, 357–358
constipation, 258, 533
contraction band necrosis (CBN)
cocaine and, 16, 96, *98*, *100*, 101–104, **101**, 516
cocaine-associated rhabdomyolysis, 181
conditions associated with, **101**
and sudden death, 104
Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, UN, 273
cor bovinum, *90*
cord blood
caffeine levels, 59, 228
cocaine levels, 59, 76
cotinine levels, 59
nicotine levels, 59
Coricidin®, 604
corneas, "crack" smokers, 113
cornstarch granulomas, 525, 526
coronary artery disease
in AIDS patients, 512
atheromatous, *120*, 121–122, *121*, 123–124
caffeine and, 231
cocaine and, *120*, 121–122, 123–124
marijuana smoking and, 659
methamphetamine and, 283
nonatheromatous, 132
opiates and, 517–518
in stimulant abusers, 283
coronary artery dissection, *128*, 130, 131–132
coronary artery spasm, 119, 121, 124–125
coronary flow reserve (CFR), 91, 92, 125–126
coronary vasospasm, and adrenergic function, 126
corticosterone, 188
cortisol, 188, 334
khat chewing and, 258
cotinine
blood levels, newborns, 41
in cord blood, 59
cotton fever, 529–530
cotton fiber granulomas, 524–525
cough suppressant formulas
brown mixture, 402
codeine, 423
dextromethorphan, 602–604
heroin, 376
hydrocodone, 456–457
methylephedrine, 243
opiates, 369, *370*
"crack" cocaine, *See* cocaine, "crack"
"crack dancing," 173
"crack eye," 113, *114*
"crack hands," 114–115
"crack keratitis," 113, *114*
"crack lips," 111, *112*
"crack thumb," 111, *112*
creatine kinase, 180
creatine phosphokinase, amphetamine use and, 291
creatinine
normalizing BZE to, 80
in nutritional supplements, 612
in urine, 616
creatinine phosphokinase, elevated, 558–559
crime technicians, cocaine exposure, 35
cryoglobulinemia, 546
Cryptococcus, 127
Cryptococcus neoformans, 540
"crystal dex," 606
crystal labs, 25, 27
2C-T-7, 319
currency, cocaine-contaminated, 64
cuscohygrine, 25

cyanide poisoning, 578
cyanogen bromide, 344
cyanosis, 142
cyclic AMP, 97
cycling, 613
cyclohexyl nitrite, 635
cyclooxygenase-2 (COX-2), 510
cyclophosphamide, 577
cyclosporine, 210, 395
cystic fibrosis transmembrane regulator (CFTR), 229
cytochrome P-450 system
  CVP3A, methamphetamine metabolism, 274
  CYP1A2
    caffeine metabolism, 224, 226, 227
    growth retardation and, 228
    inhibitors, 225
    smoking and, 226
  CYP2B6
    inducers, 461
    slow metabolizers, 463
  CYP2C6, inducers, 262
  CYP2C8, morphine metabolism, 397
  CYP2D, methamphetamine metabolism, 274
  CYP2D6
    codeine metabolism, 441, 443
    deficiencies, 483, 496
    dextromethorphan metabolism, 605
    MDMA-induced inhibition, 333
    oxycodone metabolism, 483
    SSRIs and, 483
  CYP3A4
    buprenorphine metabolism, 534
    cocaine metabolism, 48, 65
    codeine metabolism, 441–442
    inducers, 461
    inhibitors, 461, 466
    methadone and, 428–429
    morphine metabolism, 397
    propoxyphene metabolism, 490–491
  CYP3A5, fentanyl metabolism, 449, 453
  in liver, 197
  methadone metabolism, 461, 463–464
  polymorphisms
    and drug toxicity, 429
    and meperidine metabolism, 474, 475
  tramadol metabolism, 496
cytokines, 540
  cocaine and, 191–192
  ketamine and, 590
  opiates and, 568
cytomegalovirus, 127, 540
Czech Republic, 213

D

Dallas criteria, 430
Danazol®, 616
deaths, drug-related, **4**, *5*; *See also under individual drugs*
death scene, investigation, 424–425
Deca-Durabolin®, 611
Degas, Edgar, 212–213
dehydroepiandrosterone, 334
dehydrothujone, 215
delayed-type hypersensitivity granulomas, 191
δ-opiate receptor, 369
delusional parasitosis, 164
delusions, amphetamine-related, 289
Delysid®, 362
dementia, AIDS-related, 553
Demerol®, 446
N-demethyl LSD, 364
demyelination
  solvent-related, 639, *640*, 641
  spongiform leukoencephalopathy, 554–557
Department of Defense (DOD), cocaine cutoff levels, 33
depolarization cycle, 88
Deprenyl®, 279
depressants, 637
De Quincy, 373
dermis, drug binding, 74
α-desmethyl DOB, 323
desmethylpapaverine, 418
despropionylfentanyl, 450
dexamethasone, 461
Dexedrine®, 292
dextroamphetamine, 261
  mood-altering properties, 267
  synthesis of, 267
dextrofenfluramine, 287
dextromethorphan, 271–272, 575, 602–603
  agitation from, 606
  incidence, 604
  meperidine and, 477
  methamphetamine and, 262
  pharmacokinetics, 605
  pharmacology, 605
  synthesis, 604–605
  tissue levels, 605–606
dextrorphan, 605
diabetes mellitus, type 2, 226, 243–244
diacetylmorphine, 376, 400
  histamine release and, 504
  properties, 388
diarrhea, morphine for, 369
diastolic runoff, 243
diatomaceous earth, as a diluent, 500
diazepam, 437
didanosine, 512
diethyl ether, 27
digit symbol substitution test (DSST), 269
dihydrotestosterone, 614
diltiazem, 117, 130–131, 461
diluents, 385, **385**, 500
2,5-dimethoxy-4-n-propylthiophenethylamine (2C-T-7), 319
methyl-2,5-dimethoxyamphetamine (DOM), 319
3,6-dimethyl-2,5-diphenylpyrazine, 256
1,3-dimethyl-2-phenylnaphthalene, 273
dimethyl-amphetamine, 275
N,*N*-dimethyltryptamine (DMT), 351, 352–354
dimethylxanthines, 224
diphenhydramine, 604
  as heroin adulterant, 384, **385**

in methamphetamine synthesis, 271–272
volume of distribution calculations, 669
3,5,-diphenylamiones, 368
diphenylmethane, 273
diphenylpropylamine, 462
discitis, infectious, 571
disseminated intravascular coagulation, 138
distal sensory polyneuropathy (DSP), 558
disulfiram, cocaine and, 65
diuresis, 226
dobutamine, 338
dopamine receptors
cocaine and, 10–11, 163
excited delirium and, 142
MDEA and, 343
dopamine re-uptake inhibition, 162
methamphetamine, 579
PCP, 579
dopaminergic reward system, 225
dopamine transporter, 172
cocaine inhibition of, 162
methylphenidate inhibition of, 304
platelet receptors, 185
striatal, 164
doping testing
carbon isotope ratio, 625
ketaconazole test, 626
testosterone/epitestosterone ratio, 624–626
Dover's Powder, 373
Dover, Thomas, 372–373
doxylamine, 271–272
Dronabinol, 658
Dr. Tucker's Asthma Specific, 14
drug abuse
cycles of, 17
and female sex hormones, 189
gender differences, 6–8
intravenous, and HIV infections, 127
and lifestyle diseases, 60
and poverty, 8
Drug Abuse Warning Network (DAWN) report, 4–6
cocaine abuse, 3, 4
cocaine-related deaths, 5, 7, 8, 18, 441
dextromethorphan abuse, 575
drug deaths, **4**, *5*
ketamine abuse, 586
methadone-related deaths, 462
methamphetamine use, 264, 266
narcotic deaths, **367**
PCP use, 577
solvent abuse deaths, 636
website, 4
drug addiction, *See* addiction
Drug Addiction Treatment Act (DATA) of, 435, 2000
Drug and Alcohol Services Information System (DASIS), heroin use, 405
drug control, international, 273
drug couriers, 34, 36; *See also* body packer syndrome
marks/mutilations, 115
"Drug Czar," 20
Drug Enforcement Agency, STRIDE report, 28
drug paraphernalia, 424
contaminated, 528
drug-protein binding, 428
drugs, postmortem redistribution, 62, 69–70, 427
drug smuggling, 115, 117–118; *See also* body packer syndrome
drug testing
fentanyl, 423, 447
hair, 71–72
marijuana, 653–656
morphine, 381
nail analysis, 73–76
opiates, 418–419, 422–423
propoxyphene, 492
drug trafficking, 271
Asian gangs, 331
Columbia, 20–21
South America, 20–21
drug transporters, 394
Dublin, monitoring wastewater for cocaine, 3–4
Durabolin®, 611
Duragesic® patch, 446, *447*, 449, 450
postmortem findings, 450, **451**, 452–453
Dutch Colonial Development Board, 14, *15*
dynorphins, 369–370
dyslipidemia, 511
dystonia, 173

E

early genes, 189
activation and apoptosis, 579
Eastern Europe, absinthe production, 213
East Germany, steroid abuse by athletes, 613–614
East India Company, 374
ecgonine, 25, *26*, 50
ecgonine methyl ester (EME), 48
in amniotic fluid, 76
blood levels, *47*
in coca-based teas, 40–41
half-life, 50
metabolism of, 49–51
postmortem changes, 50
in saliva, 78
in sweat, 82
in urine, 79
Ecstasy, 265, 291; *See also* MDMA
initiation of use, 313
PMA-contaminated, 320–321
Ecuador, anti-drug efforts, 21
efavirenz, 65, 461
efflux drug transporters, 394
Eikenella corrodens, 572
Eldepryl®, 279
elemicin, 323–325
elixirs, cocaine in, 11
Ellis, Havelock, 316
emboli, 529
foreign body, 523–526
vegetative, 515

embryopathy, toluene-related, 643
EMIT screening tests, 492
empathogen, 331
emphysema, 286, 529
encephalopathy, HIV-associated, 553
endocardial cells, 93
endocarditis
  heroin abusers, 509
  HIV infection and, 511
  neurological complications, 552–553
  opiates and, 513–516
  staphylococcal, 546
endomorphin, 370
endorphins, 368
endothelial dysfunction, 125
endothelin-1 (ET-1), 153, 155
  sex hormones and, 190
endurance training, 623
enkephalins, 368, 369, 370
entactogen, 331
Enterobacter agglomerans, 529–530
Enterobacter cloacae, 571
enterocolitis, cocaine-associated, 193
eosinophilic coronary arteritis, 130
eosinophilic myocarditis, 36, 130–131
eosinophilic pneumonia, 527
ephedra
  blood levels, 243
  routes of administration, 242–243
Ephedraceae, 242
ephedrine, 209, 267, *272*
  blood levels, *244*, 245
  β-receptor binding, 97
  caffeine and, 225–226, 242
  cardiovascular effects, 246–247
  control of, 265
  deaths, 5
  dermatological effects, 248
  drug testing, 248
  gastrointestinal effects, 248
  half-life, 245
  history, 241–242
  interactions, 230
  metabolism, 243–245
  in methamphetamine production, *240*, 241, 242
  N-methylcathinone production from, 345–346
  neurological effects, 246
  pharmacology, 243–245
  postmortem blood levels, 248–249
  prescription use of, 240–241
  properties, 229–230
  renal effects, 245, 246
  structure, *240*
  synthetic production, 242
  toxicity, 245–248
  uses, 242
epicardial cells, 93
epilepsy, 593
epinephrine
  in bufo toad glands, 354–355
  cocaine and, 32
  and malignant ventricular arrhythmias, 99
  -mediated gastrointestinal lesions, 194
epistaxis, 32
epitestosterone, 624–626
erectile dysfunction, 616
ergolines, 361–365
ergot, 363
ergotamine, 361
ergotism, 361
Erox, 323
erythrocytosis, cocaine and, 186
erythromycin, 65, 461, 466, 541
erythropoietin, 616
Erythroxylum coca, 22
Erythroxylum coca var. *ipadu,* 22
Erythroxylum novogranatense, 22
Erythroxylum novogranatense var. *truxillense,* 22
escaline, 318
Escherichia coli, 429
essential oils, 210, 215
esterases, in cocaine metabolism, 48–49
estradiol, 189, 619
estragole, 223
estrogen receptors, 616
estrogens, cardiac potassium channels and, 66
estrous cycle, 189
ethanol, *See* alcohol
17-ethinyl testosterone, 616
ethyl acetate, 24
ethylbenzene, 644
ethylene glycol, 638
α-ethyltryptamine, 360
etorphine, 381
Etryptamine, 360
eucalyptus, 210
euphoria, solvent-induced, 635
Europe
  β-thujone limits, 210, 214
  caffeine intake, 219
  cocaine abuse, 3, 7–8
  cocaine production, 23, *24*
  coffee drinking, 221
  MDMA-related deaths, 331–332
  methamphetamine market, 270–271
  opium use, 372–373
excited delirium, 139, 140, 141–142
  amphetamine use and, 289
  autopsy findings, 145
  cause of death determination, 146–148
  cocaine binging, 71
  deaths from, 138
  determining, 204
  gender differences, 138, 144–145
  history, 137
  investigation protocol, **147**
  neurochemistry, 142–145
  restraint asphyxia, 140–142
  rhabdomyolysis in, 179–181
  stages of, 138–139
  toxicology, 145

exercise physiology, of positional asphyxia, 140–142
extrapyramidal syndrome, 346

F

facial necrosis, 110
fast-twitch muscle, 180
fat depots
  cocaine storage, 204
  morphine in, 410
  PCP in, 581
  THC storage, 74, 659–660
fatty liver, *See* hepatic steatosis
felbamate, 461
femoral heads, avascular necrosis, 622
femoral triangle injections, 151, *152*, 500
femoral vein, 70
fenchone, *215*
fennel, 210, 214
fentanyl
  alcohol and, 52
  analogs, 446
  blood levels, 448, 449–450, 451–452
  brand names, 445
  in breast milk, 452
  for cancer pain relief, 402, 450
  cocaine and, 36, 130–131
  deaths, 367, 447–448, **451**, **452**
  in hair, 452
  heroin and, 425
  illicit synthesis of, 446–447
  metabolism, 450–451
  μ-receptor binding, 369
  oral, 449–450
  overdose, 425
  pharmacokinetics, 448–449
  postmortem tissue redistribution, 453
  properties, 444–445
  respiratory depression, 522
  routes of administration, 449–450
  screening tests, 423
  seizures, 561
  structure, *446*
  tablets, 450
  tissue concentrations, 451–452
  transdermal patch, 406, 446, *447*, 449, 450
    postmortem findings, 450, **451**, 452–453
  in urine, 447, 451
  volume of distribution, 453
fentanyl citrate, 449, 450, 451
Fentanyl Oralet®, 449
fetal alcohol spectrum disorders (FASD), 643
fetal gastric aspirates, cocaine in, 77
fetal solvent syndrome, 643
fetus
  brain cocaine levels, 71
  BZE levels, 50
  cocaine exposure, 40, 41–43, 64–65, 200–202
  cocaine metabolism, 58–59
  morphine exposure, 406
  PCP exposure, 582
fibrinogen, 186
fibroelastoma, 512
fibrous myopathy, 572
  opiates, 570, 572
fingernails, *See* nails
flow reserve, 125–126
fluconazole, 461
flunitrazepam, 437
fluoxetine, 437, 461, 483
fluspirilene, 66
fluvoxamine, 437, 461
focal segmental glomerulosclerosis (FSGS), 544–546
Food and Drug Administration (FDA), 435
foreign body granulomas, 156, 523–526
formalin embalming, and morphine levels, 415
N-formyl cocaine, 27
Forskal, Peter, 255
fractional flow reserve (FFR), 126
Franke, Werner, 613
freebasers, 34, 35–37
free radicals, from catecholamines, 124
French Wine Cola, 11
Freon®, 269
Freud, Sigmund, 11, 13, 213, 375

G

GABA, See γ-aminobutyric acid
Galerina autumnalis, 358
gallstone pancreatitis, 474
γ-aminobutyric acid (GABA), 594
  and cocaine-induced seizures, 172
  -gated chloride channels, 215, 216
  receptors, solvents and, 637
γ-butyrolactone, 593, 594
γ-hydroxybutyric acid, in postmortem blood, 429
γ-hydroxybutyrate (GHB), 575, 593, 594
  alcohol and, 591, 595, 597
  blood levels, 595
  endogenous, 594, 596
  history, 593
  incidence, 592
  metabolism, 594–596
  for narcolepsy, 592
  overdose, 597
  pharmacokinetics, 595
  as postmortem artifact, 596
  properties, 591–592
  routes of administration, 594
  in saliva, 595
  synthesis, 593–594
  tissue concentrations, 595–596
  in urine, 596
gases, 635
gasoline, 636, **638**
gastrointestinal disorders
  cocaine, 193–198
    absorption, 37–41
    hepatic disease, 195–198
    ischemic colitis, 193–195
    stomach injuries, 194

khat chewing and, 258
methylphenidate and, 307–308
opiates
bowel disease, 533–534
hepatitis, 537–541
inflammatory disease, 535–536
liver disease, 533, 534
porta hepatis adenopathy, 535
steatosis, *534*, 539–540
solvents and, 642
gating, 93
G-coupled proteins
cannabinoid receptors and, 653
opiate binding, 370–371, 568
Germany
amphetamine abuse, 290
methamphetamine abuse, 271
gestrinone, 626
"ghost" pills, 485
glass beads, in marijuana, 651, *652*
glomerulonephritis, 516
cocaine and, 182
opiates and, 544, 546
solvents and, 642
glomerulosclerosis
cocaine and, 182
heroin and, 182
glomerulus, cocaine-induced lesions, *180*
glossitis, 150
glucocorticoid receptors, 616
glucuronidases, bacterial, 429
glucuronidation, morphine, 392–393
glucuronyltransferase, 461
glue, 636
glutamate receptors, 552
glutathione, 195
glycine receptors, solvents and, 637
glycosides, in bufo toad glands, 354–355
gonads
cocaine and, 188, 189–190
opiates and, 188
graft-versus-host disease, 191, 192
grain alcohol, 211
grand mal seizures, 171, 322
granulomas
cellulose, 525, 526
cornstarch, 525, 526
cotton fiber, 524–525
talc, 524–525
granulomatosis, pulmonary, 524
grapefruit juice, CYP3A4 inhibition, 461, 466
"green faire," 212–213
green tea, 223
grit weed, 651
groin shot, 151, *152*, 157, 526
growth restriction, intrauterine, 228
GTP, 370
guaifenesin, 603
guarana, 218–219, 223
guaranine, 218, 222
Guillain-Barré syndrome, 639
Guillain, Georges, 16
Gulstonian Lectures, 515
gunpowder tea, 223
gut motility, and μ-opioid receptor, 533

H

HAART, 512, 540, 553, 559
hair
amphetamines in, 276
cocaine in, 47, 64, 71–72
fentanyl in, 452
heroin in, 72, 424
khat testing, 259
marijuana in, 654
methamphetamine in, 276
morphine in, 280, 407, 419, 424, 443
testosterone in, 625
Haiti, cocaine trafficking, 20
hallucinations
alcohol-induced, 16
amphetamine-induced, 289
cocaine-induced, 16, 163
LSD-like, 323
hallucinogens
4-MAX, 344–345
amphetamines, 329–346
4-bromo-2,5-dimethoxyphenethylene (2-C-B), 323
bufotenine, 354–355
calamus, 215–216
dextromethorphan, 602–603
2,5-dimethoxy-4-iodophenethylamine, 325
DMT, 351, 352–354
DOB, 321–323
DOC, 325
DOM, 319
ergolines, 361–365
α-ethyltryptamine, 360
γ-hydroxybutyrate (GHB), 591–597
incidence, 313–314
ketamine, 586–590
4-MAX, 344–345
MDA, 340–342
MDEA, 343–344
MDMA, 329–340
MDMA homologs, 345
5-MeO-DMT, 355–356
mescaline, 315–318
N-methylcathinone, 345–346
nutmeg, 323–325
phencyclidine, 576–583
phenylalkylamines, 351–356
piperazines, 325–327
PMA, 320–321
psilocybin, 352, 357–359
Salvia divinorum, 599–606
substituted amphetamines, 318–325
TMA, 318–319
tryptamines, 351
types of, **314**
urine testing, 365

haloperidol, 66
Hamilton Depression Rating Scale, 589
hands, "crack hands," 114–115
hanyak, 270
harmaline, 352–354
harmine, 352–354
Harrison Narcotic Act, 213
hashish, 37, 651
headache, solvent-induced, 635
head shop, 214
Health Canada, 293
heart
  AIDS-related infections, 127
  α-receptors, 96
  β-receptors, 88, 96
  blood samples from, 62, 69–70
  cocaine and, 60, 61, 72, 206
  enlarged, 97
    amphetamine use and, 285
    cocaine use and, 206
    in excited delirium, 145
    MDMA-related deaths, 339
    opiates and, 516–517
  Kaposi's sarcoma, 127
  norepinephrine, *96*, 97
  normal weight, 92, **671–673**
  postmortem drug redistribution, 62, 69–70
heart rate, cocaine and, 52–53
heat-shock proteins, myocardial, 283
helices, 370
hematocrit, 186
hematology, cocaine abuse, 185–186
hematuria, 6442
hemlock, and opium, 372
hemoglobin, 186
hemolytic uremic syndrome (HUS), cocaine-related, 179, 181, 182
hemoptysis, 155
hemorrhage
  amphetamine-related, 288
  cerebral, 169–171
  intracerebral, 170, 288, 335
  intracranial, 246
  intraventricular, 169–171
  subarachnoid, 169–171, 288, 335
hemothorax, 151, 526
hemp, 650
hemp oils, 658
hepatic steatosis
  alcohol and, 539
  ephedrine and, 248, 249
  methamphetamines and, 276, 291
  opiates and, *534*, 539–540
hepatitis
  and intravenous drug abuse, 60
  transmission, 538
hepatitis A virus, opiate abuse and, 537
hepatitis B virus, 128
  opiate abuse and, 537–538
hepatitis C virus, 128, 276, 291, 568
  in methadone users, 467
  opiate abuse and, 538–539
  tattooing and, 502
hepatocellular carcinoma, 226
  cirrhosis and, 539
hepatotoxicity
  cocaethylene, 193, 197
  norcocaine, 193
  reactive oxygen species, 195
hERG cardiac potassium channel, 88
  cocaine and, 53, 63, 65–66, 94
  dysfunction, 60, 63, 95
  methadone and, 425, 462, 463, 510
  propoxyphene and, 491
heroin
  acute generalized exanthematous pustulosis, 504
  addiction, 377–378
  adulterants, 117, 384, **385**, 526, 556
  autopsy findings, **498**
  bioavailability, 390
  black tar, 117, *392*, 503
  blood-brain barrier and, 389–390, *391*
  body packer syndrome, 37
  bone/joint infections, 571–572
  brown, 504
  caffeine and, 224
  cardioprotective effects, 510
  cause of death in abusers, *517*
  central vein injections, 151, *152*
  "chasing the dragon," 227, 400, 404, 405
  cough suppression, 369, *370*, 376
  deaths, 5, 367, 378, 424
  diluents, 385
  endocarditis, 509
  epidemiology, 368
  ER visits, 265
  fentanyl and, 425
  fibrous myopathy, 570, 572
  focal segmental glomerulosclerosis (FSGS), 544–546
  foreign body granulomas, *526*
  fungal contaminants, 528
  global production, 382
  in hair, 72, 424
  half-life, 405
  hemorrhagic stroke and, 560
  histamine release and, 504
  hormone alterations and, 567
  immunosuppression, 463, 567
  injection sac, 529
  injection sites, 526
  intramuscular, 403–404
  intranasal, 403
  intravenous, 390, 400–401
  life span of abusers, *517*
  lipid profiles, effect on, 517
  lipophilicity, 395
  liver disease, 533, 534
  manufacture, 383
  melting point of, 405
  and meperidine metabolism, 475
  α-methyl fentanyl in, 446, 447
  necrotizing fasciitis, 503

nephrotic syndrome, 182
overdose, 402, **404**
blood levels, 411–412
brain levels, 412, *413*, 414
postmortem tissue levels, **404**, 410, 416–418
postmortem redistribution, 410
prices, 385
primary phycomycosis, 554
pulmonary disease associated with, 156, 521–523
refined, *391*
rhabdomyolysis and, 546–547, *547*, 558–559
in saliva, 415
sample analysis, 384
skin popping, 117–118, 306, 401, *499*, 500
smoking, 400, 404–406
snorting, 391, 403–404
speedballing, 34
spongiform leukoencephalopathy and, 554–557
street, 390–391, 528
structure, *390*
subcutaneous injection, 117–118, 306, *499*, 500
synthesis of, 376–378
testosterone and, 570
track marks, 499, 501
trafficking, 382–383
transverse myelitis, 557
for treating tuberculosis, 375, 528–529, 572
treatment centers, 405
urticaria in, 568
heroin-associated nephropathy (HAN), 544, **545**
Herpes simplex virus, 540
Hesiod, 372
heure verte, 212
n-hexanol, 644
HI hypophosphorus acid, 273
hippocampus
morphine in, 412
opiate receptors, 412, *413*
hippuric acid, 639
hiropon, 242, 270
Hispanics, cocaine-related deaths, 8
histamine
mast cells, 123–124
opiate-induced release, 568
-related urticaria, 503–504
Histoplasma, 127
Hoffman, Albert, 357, 362
Hoffman, Felix, 376
hog tying, 139, 147, 148
Homer, 372
Homer protein family, 280
Hooker, Sir William, 9
hormones
cocaine and, 188–190
heroin use and, 567
hospice care, methadone and, 466–467
HO-THC, 657
huffing, 635, 636, 637–638, 642–643
human growth hormone, GHB stimulation of, 593
human immunodeficiency virus (HIV), *See also* acquired immunodeficiency syndrome
cocaine and, 127–128, 192
differentiating from HAN, **545**
and female sex hormones, 189
and intravenous drug use, 34, 60
neurological complications, 553–554
and organ transplants, 127
human immunodeficiency virus (HIV) medications, *See* antiretroviral drugs
Hyde, Henry, 20–21
hydrochloric acid, 290
hydrocodone, 442–443, 456–457
deaths from, 367
hydrofentanyl, 450
hydromorphone, 457–458
hydromorphone-3-glucuronide, 458
hydroxybenzoylecgonine, 54
m-hydroxybenzoylecgonine, 49, 76, 79
p-hydroxybenzoylecgonine, 49, 79
m-hydroxy-COC, 49
p-hydroxy-COC, 49
m-hydroxycocaine, 79
p-hydroxycocaine, 79
9-hydroxycorynantheidine, 459
5-hydroxyindoleacetic acid, 287
4-hydroxymethamphetamine, 275
7-hydroxymitragynine, 459
5-hydroxy-*N*,*N*-dimethyltryptamine, 354
N-hydroxynorcocaine, 73, 195
4-hydroxynorephedrine, 275
N-hydroxynormeperidine, 474
hydroxythujones, 215
5-hydroxytryptamine, *See* Serotonin
hydroxyzine, 117
hygrine, 25
hypericum, 461
hyperkalemia, 320
hypersensitivity myocarditis, 130
hypersensitivity reactions, opiate-induced, 568
hypertension, 129–130
and aneurysm formation, 170
PMA-induced, 320
hyperthermia
amphetamines and, 291
in excited delirium, 138, 142
MDEA-induced, 343
MDMA-induced, 334, 335
PMA-induced, 320
rhabdomyolysis and, 180–181
serotonin syndrome, 477
hypodermic syringe, invention of, 374–375
hypoglycemia, 320
hypokalemia, 642
hypotension, anesthetic-related, 209, 242
hypothalamic-pituitary-adrenal (HPA) axis, 567
cocaine and, 188
opiates and, 568
hypothyroidism, 641–642
hypovolemia, 181
hypoxic encephalopathy, 551–552
hyssop, 210

I

ibogaine, 352
ICDM classification system, 204
"ice," 269–270
idiopathic thrombocytopenic purpurea, 616
Ik channel, 88
Ikr, 94
imidazoles, buprenorphine and, 436
immune system
  cocaine and, 191–192
  heroin and, 463
  opiates and, 552, 566–569
immunoglobulins, 568
  codeine-specific, 569
  morphine-specific, 569
inactivation gating, 93
indinavir, 65, 436
indole alkaloids, in kratom, 459–460
Indonesia, cocaine production, 14, *15*
infants, *See* newborns
influx drug transporters, 394
inhalants, *See also* solvents
  alcohol and, 639
  cardiovascular effects, 637
  categories, 635
  epidemiology, 636
  gastrointestinal disease, 642
  incidence, 636–637
  neurological disorders, 639–642
  renal disease, 642
  storage/handling, 644–645
  toxicity, **638**
inhalers, nasal, 267, *268*, 269
injection sac, heroin, 529
injection site
  abscesses, 498, 500, 571
  infections, 498
insomnia, 229
insulin resistance, 511
interferon, cocaine and, 191–192
interleukin-6 (IL-6), 245, 590
interleukin-10 (IL-10), 191
internal cardiac defibrillator (ICD), 146
International Amateur Athletic Foundation (IAAF), 625
International Narcotics Control Board (INCB), 383
International Olympic Committee (IOC)
  anabolic steroid testing, 625–626
  caffeine limits, 225, 232
  ephedrine testing, 248
  sports doping, 614
intracerebral hemorrhage, 170, *170*
intraventricular hemorrhage, 169–171
ion channels
  cocaine-induced remodeling, 93–95
  defects, and long QT syndrome, 93–94, *94*
  genes for, 88
  G proteins and, 370
ion gates, 93
ischemic colitis, cocaine abuse and, 193–195
ischemic heart disease, HIV infection and, 127
ischemic necrosis, myocardial, 101, **102**
ischemic preconditioning, 510
ischemic stroke, cocaine-induced, 163, 165–167
Israel, drug trafficking, 331
ithang, 459
itraconazole, CYP3A4 inhibition, 466
Iwo Jima, cocaine production, 14

J

Janssen, Paul, 446
Japan
  ephedrine production, 242
  "ice" laboratories, 270
  methamphetamine use, 283, 289
  methylephedrine use, 243
jaundice, cholestatic, 618
JC virus, 556
Jeff, 345
joint infections, 571–572
joint pain, 241
josamycin, 461

K

kahweh, 221
kaksonjae, 270
kakuam, 459
Kamikaze pilots, ephedrine use, 209, 242
Kaposi's sarcoma, 512
  heart dissemination, 127
κ-opioid receptor, 144, 369
  salvinorin A and, 575, 601
Kat, 345
KCNE1, 88
KCNQ1, 88
keratin, 74
kerosene, 638
Ketajet®, 586
Ketalar®, 586
ketamine, 575
  antidepressant effects, 589–590
  blood levels, 588–589
  cardiovascular effects, 590
  cocaine and, 197
  cytokines and, 590
  dependence, 589
  epidemiology, 586
  half-life, 588, 589
  history, 586–587
  incidence, 586
  interleukin-6 (IL-6) and, 590
  isomers, 587
  lipophilicity, 588
  metabolism, 587–588
  neurotoxicity, 582
  properties, 585–586
  routes of administration, 587
  tissue concentrations, 588
Ketaset®, 586

ketoconazole, 427, 428
buprenorphine and, 436
cocaine and, 65
CYP3A4 inhibition, 466
hydromorphone and, 458
methadone and, 461
ketoconazole test, anabolic steroids, 626
ketum, 459
ketum juice, 460
khat, 209
blood levels, 257
clinical effects, 257–258
detection, 259
epidemiology, 254
half-life, 254
history, 255–256
incidence, 254
pharmacology, 256–257
production, 255
properties, 253–254
urine levels, 257
khoka, 9
kidneys
amphetamines and, 276, 290–291
cocaine abuse and, 72, 179–183
differentiating HAN from HIV, **545**
kindling, cocaine-induced, 172
kola nut, 218
Korea, "ice" production, 270
kratom, 459–460

L

labor, cocaine stimulation of, 201
lacrimal duct surgery, 32–33
lactate, 386
laminar necrosis, *551*
Lao People's Democratic Republic, opium production, 382
late genes, 189
Latin America, poppy cultivation, 380
laudanum, 372–373, 378, 522
learning disabilities, and prenatal cocaine exposure, 201
Leary, Timothy, 362
left ventricular dysfunction, 511, 512
cocaine and, 89–93
methamphetamines and, 284–285
lemon juice, *Candida*-contaminated, 504, 528
leptin, 76, 188
leukotrienes, calcium levels and, 643
levamisole, 117, 384
levorphanol, 603
Lewin, Louis, 315, 316
lidocaine
as cocaine adulterant, 130
as heroin adulterant, **385**, 556
lifestyle diseases, and drug abuse, 60
lighter fluid, 636
limbic system, 172–173
linezolid, 472
lipid profiles, heroin abusers, 517
lipodystrophy, protease inhibitors, 511, 512
liqueurs, herb-based, 211
liver
amphetamines in, 276
anabolic steroids and, 617–619
birefringent material, 536
cocaine and, 73, 195–198
coffee and, 226
cytochrome P-450 activity, 197
drug-associated lesions, **536**
HIV infection and, 540–541
khat chewing and, 258
MDMA-related disorders, 340
methamphetamine and, 291
methylphenidate and, 307–308
morphine levels, 414–415
opiates and, 533, 534
inflammatory disease, 535–536
porta hepatis adenopathy, 535
steatosis, *534*, 539–540
L-LAAM, 462–463
locus ceruleus, 317, 562
long QT syndrome, 88, 105; *See also* QT interval prolongation
ion channel defects, 93–94, *94*
loperamide, 394
Lophophora williamsii, 315
Los Angeles, drug deaths, 5
"love drug," 340
lozenges, fentanyl citrate, 449, 450
LSD, *See* lysergic acid diethylamide
lungs
and "crack" smoking, 153–156, 192
foreign body granulomas, 523–526
local anesthetic effect of cocaine, 155–156
marijuana smoking and, 659
narcotic-related pulmonary edema, 521–523
lupus erythematosus, 192
luteinizing hormone
drug use and, 189
heroin use and, 567
khat chewing and, 258
lymphadenopathy, opiates and, 568
lymph nodes
birefringent material in, 535
morphine in, 415, 535
lymphoma, 127, 512
brain, 554
lysergic acid diethylamide (LSD), 313, 358, 361
blood levels, 364–365
history, 362–363
isomers, 363
metabolism, 364
production, 363–364
structure, *362*
testing, 365
tissue concentration, 364–365

M

macroangiopathy, 181
macrophages, alveolar, 153–155; *See also* alveoli

carbon-laden, 523
"crack" smoking and, 192
hemosiderin-laden, 522, *550*
PAS-positive granules, *640*, *641*
"magic mushroom" poisoning, 359
Magnan's syndrome, 16, 164
Magnan, Valentine, 16, 213
ma huang, 243, 245
Malaysia, cocaine production, 14
Maltine, 14
mammary glands, amphetamines in, 276
Manet, Edouard, 212–213
manganese, in cocoa paste, 28
manganese poisoning, 345–346
manner of death, 430
mannitol, 386
marantic endocarditis, 514
Marfan's syndrome, 129
Mariani, Angelo, 10, *11*, 212
Marielitos, 502
marijuana, 656
absorption, 654–655
adulterants, 651, *652*
blood levels, 656, 660
cardiovascular effects, 658–659
cultivation, 650
detection times, 655–656
DMT and, 353
epidemiology, 650
ER visits, 265
GHB and, 592
glass beads in, 651, *652*
hair testing, 654
interactions, 649
metabolism, 657–658
origins, 650–653
PCP and, 581
pharmacology, 653
postmortem redistribution, 659–660
properties, 649
saliva testing, 654
sample preservation, 660
structure, *649*
testing, 653–656
tissue concentrations, 653
and tobacco smoking, 659
U.S seizures, *651*
volume of distribution, 653
Marinol®, 658
marjoram, 215
Marzine®, 325
mast cells, 568
adventitial, *120*, 123–124
histamine-rich, 123–124
mate de coca, 40–41
mateine, 218, 222
matrix metalloproteinases, 516
Mayo Clinic, normal heart weight table, **671–673**
Mazatec shamans, 599, *600*
M cells, 93
McKenna, Terence, 352
MDA (3,4-methylenedioxyamphetamine), 263, 264, 290, *317*
blood levels, 342
enantiomers, 341
half-life, 341
history, 341
from MDMA degradation, 336
postmortem distribution, **342**
properties, 340–341
MDEA, 343–344
MDMA (Ecstasy)
blood levels, 336
cardiovascular effects, 338–340
deaths, 6
enantiomers, 336–337
epidemiology, 331–332
GHB and, 592
hepatotoxicity, 340
history, 330–331
homologs, 345
incidence, 331–332
initiation of use, 313
interactions, 330
mechanism of action, 331
metabolism, 333–334
neurotoxicity, 334, 337–338, 343
PMA-contaminated, 320–321
postmortem redistribution, **336**
production, 332–333
properties, 329–330
serotonin syndrome, 334–335, 337–338
tablet logo, *332*, 333
tissue distribution, 336–337, **337**, **342**
trafficking, 331, 333
3,4-MDP-2-P, 265, 332
measurements, converting units of, 665
meconium
cocaine in, 200
morphine in, 407
medications, caffeine content, 218, **219–220**
melanin, 71, 74
melatonin, 351, 352
melioidosis, 529
memory dysfunction, 576
men
drug abuse in, 6
excited delirium in, 138, 144–145
normal heart weight, 92, **671–673**
response to cocaine, 188
meningitis, lymphocytic, 554
Menocil®, 344
menopause, 616
menstrual cycle, 189
meperidine, 368, 446
blood levels, 475, 477–478
cardiovascular effects, 476
drug interactions, 472, 477
fibrous myopathy, 570, 572
first-pass effect, 475
half-life, 472
in heroin users, 475

histamine release and, 504
intrathecal, 477
metabolism, 474–476
in patient-controlled anesthesia (PCA) devices, 474, 477–478
postmortem blood levels, 476
postmortem redistribution, 478
properties, 472–473
routes of administration, 475–476
seizures, 561
skin patch, 406
volume of distribution, 475, 478
meperidinic acid, 474
mescaline
accidental deaths, 318
analogs, 318
blood levels, 317–318
clinical syndromes, 318
history, 315–316
mechanism of action, 317
metabolism, 317–318
production, 316–317
serotonin receptor binding, 365
structure, *317*
tissue disposition, 317–318
metabolic syndrome, 511, 512
metabotropic glutamate receptor #2 (mGluR2), 358–359
Metadate®, 293
metaescaline, 318
metaproscaline, 318
methadone, 368
for addiction treatment, 436, 462–463
alcohol and, 429, 465
autopsy findings, 467–469
blood levels, 464, 468–469
in breast milk, 466
chirality, 428–429
cocaine and, 465
compliance monitoring, 467
deaths, 367, 425, 428–429, 462, 464
drug interactions, 461
fetal effects, 466
half-life, 465
hERG cardiac potassium channel and, 425, 462, 463, 510
intravenous, 467
isomers, 462, 463
metabolism, 463–464, 465–466
methadone:EDDP ratio, 465, 467, 468
oral, 467
overdose, 402
pharmacokinetics, 465
pharmacology, 463–464
postmortem blood levels, 468–469
postmortem tissue redistribution, 469
properties, 460–461
in saliva, 467
structure, *462*, *463*
tolerance development, 464, 467
volume of distribution, 468
methamphetamine, 210
abnormalities associated with abuse, **282**
activation of calmodulin kinase II, 89, 145
blood levels, 273–274, 277–278
cardiovascular effects, *90*, 282–286
central nervous system effects, 288–290
deaths, 6, 264
decomposition products, 375
dopamine re-uptake inhibition, 579
epidemiology, 265–267
false positives, 279
gastrointestinal effects, 292
history, 267–271
impairment, 281–282
infant postmortem blood levels, 277–278
manufacture of, 271–273
metabolism, 274–276
and microvascular disease, 91
morphine and, 279
myocardial hypertrophy, *90*
oral effects, 291
postmortem redistribution, 279–281
pregnancy and, 267
properties, 261–262
psychosis, 289
renal disease, 290–291
routes of administration, 273–274
in saliva, 274, 276
screening tests, 281
and serotonin levels, 286–288
snorting, 286
structure, *317*
synonyms, 2561
synthesis
ephedrine in, *240*, 241, 242
from phenyl-2-propanone (P2P), 271–272
phenylacetone route, 273
"red phosphorus" route, 272–273, *272*
tissue disposition, 276–281
tolerance development, 279–280
toxicity, 269–270, 282–292
in urine, 275, *275*
worldwide production, 264
methaqualone, 556
methcathinone, 345
Methedrine®, 267
methemoglobin, 643
methemoglobinemia, cocaine and, 186
Methergine®, 362
methicillin-resistant *Staphylococcus aureus* (MRSA), 498
"meth mouth," 291
2-methoxy-5-hydroxy-4-bromoamphetamine (2M5H4BA), 322
5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), 351
5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), 355–356
2-methyl-2-propanol, 644
4-methylaminorex (4-MAX), 344–345
N-methylcathinone, 345–346
methylecgonine, 25, *26*, 59
3,4-methylenedioxymethamphetamine, *See* MDMA

3,4-methylenedioxyphenylacetone (MDP2P), 265, 332
methylenedioycathinone, 346
methylephedrine, 210, 243
methylergonovine, 362
methyl fentanyl, 384, 386, 446
Methylin®, 293
methyl isobutyl ketone (MBK), 24
methylphenidate, 292
  alcohol and, 305
  blood levels, 305
  in breast milk, 305–306
  cardiovascular effects, 307
  enantiomers, 304
  hepatotoxicity, 307–308
  injection of ground tablets, 306, 307, 308
  mode of action, 304
  nervous system disorders, 308
  pharmacokinetics, 305
  postmortem measurements, 306
  properties, 302–303
  routes of administration, 304
  snorting, 307
  tissue disposition, 306
  toxicity, 306–308
  transdermal, 304
  in urine, 306
methylsafrylamin, 331
methyltestosterone, 618
methyltheobromine, 222
methylxanthines, 231
Mexico, methamphetamine trafficking, 271
mexiletine, 223
microangiopathy, 181
microvascular disease
  cocaine and, 91, *91*, 122–123, 207
  methamphetamines and, 91
Middle East, coffee drinking, 221
migraine, 361
millimoles, 665
Mitragyna speciosa, 459
mitragynine, 459
MK-101, 579
MK-801, 582
Mobitz type-I atrioventricular block, 216
Modahl, Diane, 626
moles, converting into grams, 665
Monase®, 360
Monitoring the Future (MTF) study
  drug abuse in schools, 610
  solvent abuse, 636
6-monoacetyl morphine, 72, 381, 390, *391*, 400
  in CSF, 415
  in urine, 418
  in vitreous humor, 415, 423
monoamine oxidase inhibitors (MAOIs), 188
  amphetamines, 283
  irreversible, 352
  MDMA and, 335
  5-MeO-DMT and, 355
  meperidine and, 477
  reversible, 352
monoamine oxidase type A (MOA) inhibition, 320
mood alteration, 257
Mormon tea, 241
morning glory, 361
"morphia" toxicity, 373
morphinans, 368
morphine, 381, 387
  acute generalized exanthematous pustulosis, 504
  addiction, 269
    use of cocaine for, 11, 13
  in bile, 414
  blood-brain barrier and, 394, 410
  blood levels, 391, 423–424
  brain levels, 412–414
  in breast milk, 406
  cardioprotective effects, 510, 518
  codeine and, 441, 442
  in CSF, 412, 414, 416
  discovery of, 373
  excretion, 418–419
  first-pass effect, 403
  in fixed tissues, 410
  and formalin embalming, 415
  in hair, 280, 407, 424, 443
  histamine release and, 504
  immunoglobulins to, 569
  immunosuppression, 568
  intravenous, 374, 393, 400–401
  liver levels, 414–415
  in lymph nodes, 415, 535
  manufacture, 382–384
  in meconium, 407
  metabolism, 391, 392–395
  methamphetamine and, 279
  multi-drug resistance protein (MDR1)-binding, 395, 410
  μ-receptor binding, 369
  nasal insufflation, 403–404
  oral, 393, 401–402
  overdose, 402
  and P-glycoprotein (P-gp)-mediated transport, 394–395, **394**, 409–410
  pharmacokinetics, 400–407
  postmortem blood/tissue levels, 392, 397, 409–419
  postmortem redistribution, 409–410
  production, 389
  properties, 387
  protein binding, 394–396, 409–410
  pupillary constriction, 369
  receptor, *371*
  rectal use, 403
  routes of administration, 400–407
  seizures, 562
  skin patch, 406
  subcutaneous injection, 401
  tissue distribution, 392, 409–419
  tolerance development, 395
  transplacental transfer, 406
  trauma and, 401
  urine concentrations, 397, 415, 416
  in vitreous humor, 81
  volume of distribution, 63, 409, 417–418

morphine-3-glucuronide (M3G), 392–395, 396–397, 410
  blood/CSF ratios, 414
  clearance, 400
  postmortem tissue levels, 416–418
  stability in blood samples, 424
  tissue distribution, 409–419
morphine-6-glucuronide (M6G), 392–393, 410
  blood-CSF ratios, 414
  clearance, 400
  oral, 402
  postmortem tissue levels, 416–418
  properties, 387–388
  stability in blood samples, 424
  tissue distribution, 409–419
"morphinism," 375
morphium, 373
Morson, Thomas, 373
mothers
  brain cocaine levels, 71
  environmental cocaine exposure, 64–65
movement disorders, 173
MPTP, neurotoxicity, 560
MRSA, 498
Mrs. Winslow's Soothing Syrup, *376*
mucormycosis, 552
muffrai, 256
mules, 39
multi-drug resistance protein (MDR1), morphine binding, 395, 410
multiple hits theory, cocaine-related deaths, 94–95
μ-opioid receptor, 369, *413*
  buprenorphine and, 437
  fentanyl and, 446–453
  and gut motility, 533
  hydrocodone and, 456
  hydromorphone and, 458
  kratom and, 459–460
  meperidine and, 476
  oxymorphone and, 488
  propoxyphene and, 489
  tramadol and, 495, 496
muscarinic neurons, 172
muscarinic receptors
  ketamine and, 587
  placental, 58
muscle building, 614
muscle spasticity, 593
mushrooms, psilocybin-containing, 352, 357–359
Musto, David, 17
Myanmar Republic
  methamphetamine production, 270–271
  opium production, 382
mycobacteria, 127
Mycobacterium avium-intracellulare, 540
mycotic infections, opiate-associated, 528
myelin, spongiform leukoencephalopathy, *556*
myelinopathy, solvent-related, 639, *640*, 641
myocardial hypertrophy
  cocaine and, 89–93, 206
  MDMA and, 335–336
  methamphetamines and, *90*
  opiates and, 516–517
myocardial infarction
  amphetamines and, 286
  cocaine and, 32, 87–105, 119–122, 123–124
  marijuana smoking and, 658–659
  in steroid abusers, 619–620
myocarditis, 430
  in AIDS patients, 512
  eosinophilic, 130–131
  hypersensitivity, 130
  from skin infections, 503
  toxic, 130
myocardium
  calcium overload, 99–104
  catecholamine-induced changes, 99–104
  cocaine-induced apoptosis in, 55, 87
  cocaine-induced remodeling, 61, 62–63, 87–89, 206
  eosinophilic myocarditis, 130–131
  flow reserve, 91, 92, 125–126
  HIV-related disease, 127–128
  necrosis of, 247
  norcocaine-induced fibrosis, 55
  oxygen demand, 125
  postmortem cocaine levels, 72
  repolarization, 94
myocytes
  anabolic steroid-induced apoptosis, 620–621
  catecholamine toxicity, 99–104
  depolarization, 88
  types of, 93
myofilaments
  contraction band necrosis (CBN), 16, 96, *98*, *100*, 101–104, **101**, 181
  ischemic vs. catecholamine necrosis, 101, **102**
myoglobinemia, 181
myoglobinuria, 558
myoinositol, 145
myopathies, HIV-associated, 559
myosin, 87
Myristica fragrans, 323
myristicin, 323–325
myxoma, 512

N

nails
  anhydroecgonine in, 74
  cocaine in, 73–76
  methamphetamine in, 276
  "parrot beak," 110–111
naloxone, 476
naltrexone maintenance therapy, 558
nandrolone, 611, 613, 620, 625
narcolepsy, 240
  GHB for, 592
narcotic abuse
  deaths from, **367**
  histamine release, 503–504
  history of, 372–378

intravenous, 33, 374–375
neuropathology, **550**
overdose hallmarks, 378
postmortem findings, 447, 497, **498**
pulmonary edema, 521–523
renal disease, 544–548
transplacental transfer, 406
nasal decongestants, 248
l-methamphetamine, 273
nasal insufflation
cocaine, 31–32, *31*
heroin, 391
morphine, 403–404
nasal mucosa, sample collection, 499
nasal septum, perforated, 109–110, 150
nasolacrimal duct obstruction, 110
National Collegiate Athletic Association, 232
National Drug Threat Assessment, 20, 21
National Household Survey of Drug Abuse (NHSDA)
cocaine abuse, 3
methamphetamine use, 265–266
National Institute on Drug Abuse (NIDA), cocaine testing, 33
National Survey on Drug Use and Health (NSDUH)
cocaine use, 3
hallucinogen use, 313
heroin use, 368
Native American Church, 315–316
natural killer (NK) cells, 568
neck, injection site injuries, 526
necrotizing angiitis, 169, 546, 559
necrotizing enterocolitis, 194
necrotizing fasciitis, 117, 502–503
necrotizing vasculitis, 169
Nederlandsche Cocaine Fabriek, 14, *15*
needle punctures, 498–499
nefazodone, 65, 461, 466
nelfinavir, 461
neoendorphins, 370
neonatal abstinence syndrome, 466
neothujol, 215
nephrosclerosis, 249
nephrotoxicity, cocaine, 179–183
Netherlands, Ecstasy production, 265
neurodegenerative disease, 228, 289
neuroexcitation syndrome, 458
neuroleptic drugs, 173
neurons, opiate-induced apoptosis, 552, 582
neuropathology
cocaine and, 162–163
blood-brain barrier alterations, 174–175
cerebral hemorrhage, 169–171
cerebral vasculitis, 167–169
ischemic stroke, 165–167
movement disorders, 173
neurotoxicity, 163
psychiatric symptoms, 164–165
seizures, 171–173
α-ethyltryptamine, 360
ketamine, 582
MDEA, 343
MDMA, 334, 337–338, 343
methamphetamine, 288–290
MPTP, 560
normorphine, 397–398
opiates, 549–551, 552, 582
complications of endocarditis, 552–553
complications of HIV infection, 553–554
hypoxic encephalopathy, 551–552
MPTP-induced parkinsonism, 560–561
peripheral neuropathy, 557–558
primary phycomycosis, 554
rhabdomyolysis and, 558–559
seizures, 561–562
spongiform leukoencephalopathy, 554–557
strokes, 559–560
PCP, 579, 582
tiletamine, 582
tramadol, 496
neuropathy, peripheral, 557–558
neuropile vacuolization, 635
neuroprotection, PCP, 579
neurotransmitters, cocaine-induced seizures, 172
nevirapine, 461
newborns
amphetamines levels, 277–278
buprenorphine exposure, 438
BZE half-life, 50, 80
caffeine metabolism, 222, 226–227, **227**, 228
cocaine exposure, 40, 41–43, 47, 58–59, 76, 80
drug withdrawal, 200
methadone exposure, 466
morphine exposure, 406
oxycodone exposure, 484–485
toluene abuse and, 643
New World plants, 9
New York, drug deaths, 5
Nexus, 323
nicotine
blood levels, newborns, 41
in breast milk, 77
in cord blood, 59
placenta and, 58
plant sources, 9
Niemann, Albert, 10
Nigeria, cocaine production, 14
nitric oxide, 125
inducible nitric oxide (iNO), 510
inducible nitric oxide synthase (iNOS), 285
nitrites, volatile organic, 635
nitrous oxide, inhaling, 636
NMDA receptor
alcoholism and, 588
cocaine kindling and, 172
NMDA receptor antagonists, 575, 576
dextromethorphan, 602–603
γ-hydroxybutyrate (GHB), 591–597
ketamine, 586–590
phencyclidine, 576–583
N-methyl-D-aspartate, *See* NMDA
nocardiosis, 552
nonalcoholic steatohepatitis (NASH), 539–540

nonbacterial thrombotic endocarditis, 513–514
nonpigmented fixed drug eruptions, 248
non-steroidal anti-inflammatory drugs (NSAIDs), necrotizing fasciitis, 502–503
19-norandrostenediol, 611, 625
19-norandrostenedione, 611, 613, 625
norbuprenorphine
  blood levels, 437
  in breast milk, 438
norcocaine, *26*, 27–28, 48, 58, 65
  in amniotic fluid, 76
  blood levels, 195
  hepatotoxicity, 73, 193
  metabolism of, 54–55
  placental binding sites, 42
  properties, 53
  in urine, 49, 79
norcocaine nitrosodium ion, 195
norcocaine nitroxide, 54, 73, 195
norcodeine, 441
nordextropropoxyphene, cardiotoxicity, 490, 491
norephedrine, 256–257, 275, 344
norepinephrine, 126
  in bufo toad glands, 354–355
  cocaine and, 72
  down-regulation by local anesthetics, 172
  heart, *96*, 97
  and malignant ventricular arrhythmias, 99
  methylphenidate and, 304
norepinephrine re-uptake inhibitors, 162
  BZP, 326
  tramadol, 495, 496
norepinephrine transporters
  placental, 201
  up-regulation by cocaine, 171
norfentanyl, 446–447, 450, 451
norfloxacin, 461
norfluoxetine, 461
nor-iso-LSD, 364
norketamine, 587, 588, 589
nor-LSD, 364
normeperidine, 474, 475
  activity, 476
  blood levels, 477–478
  half-life, 477
  properties, 473
  seizures, 474, 476, 561
  volume of distribution, 478
normeperidinic acid, 474
normorphine, 397–398, 411
noroxycodone, 483
norpropoxyphene, 490, 492–493
norpseudoephedrine, 256–257
19-nortestosterone, 618
North America Free Trade Act (NAFTA), 271
noscapine, 418
NSAIDs, 502–503
nucleoside reverse transcriptase inhibitors, 512
nucleus accumbens
  addiction and, 143–144, 173, 230
  opiate receptors, 369
Numorphan®, 488
nutritional supplements, creatinine in, 612
NyQuil®, 604

O

obesity, 243–244
  amphetamines for, 268
  and myocardial hypertrophy, 91–92
  nonalcoholic steatohepatitis (NASH) and, 539
obstipation, 533
Ocotea cymbarum, 333
Office of National Drug Control Policy (ONDCP), 19
Oil of Ocotea, 333
olfactory bulb, 369
ondansetron, 402
Ondocybin®, 357
Operation Purple, 383
Operation Topaz, 383
ophthalmologic surgery, cocaine in, *12*, 13, 32–33
opiate receptors, 368–370, *413*
  buprenorphine and, 437
  chronic stimulation of, 567
  ketamine and, 587
opiates, *See also* individual opiates
  addiction patterns, 8
  alcohol and, 425
  blood testing, 423–424
  bone/joint infections, 571–572
  cardiovascular disorders, 509–511
    coronary artery disease, 517–518
    endocarditis, 513–516
    HIV-associated, 511–512
    myocardial fibrosis, 516, 570, 572
    myocardial hypertrophy, 516–517
    QT interval prolongation, 510
    torsade de pointes (TdP), 510
  cause of death, 424–426
  classification of, 368
  deaths, 378
  epidemiology, 368
  gastrointestinal disorders
    bowel disorders, 533–534
    hepatitis, 537–541
    inflammatory disease, 535–536
    liver disease, 533, 534
    porta hepatis adenopathy, 535
    steatosis, *534*, 539–540
  G-coupled proteins binding, 370–371, 568
  global production, 382–383
  histamine release, 568
  history of abuse, 372–378
  hypothalamic-pituitary-adrenal (HPA) axis suppression, 188
  immune system and, 552, 566–569
  incidence, 367
  injection site, 571
  interpretation of blood/tissue levels, 422–430
  muscle storage, 410
  neuropathology, 549–551

complications of endocarditis, 552–553
complications of HIV infection, 553–554
hypoxic encephalopathy, 551–552
MPTP-induced parkinsonism, 560–561
peripheral neuropathy, 557–558
primary phycomycosis, 554
rhabdomyolysis and, 558–559
seizures, 561–562
spongiform leukoencephalopathy, 554–557
strokes, 559–560
oxycodone and, 482
postmortem chemistry, 428–429
pulmonary disorders
aspiration pneumonia, 528
community-acquired pneumonia, 527–528
cotton fever, 529–530
cotton fiber granulomas, 524–525
emboli, 523
emphysema, 529
foreign body granulomas, 523–526
fungal pneumonia, 528
melioidosis, 529
pulmonary edema, 521–523
septic pulmonary emboli, 529
talc granulomas, 524–525
tuberculosis, 528–529
vessel injuries, 526–527
renal disorders, 544–548
rhabdomyolysis, 546–547
respiratory depression, 369, 423, 522
in saliva, 415
skin disorders, 498–506
acute generalized exanthematous pustulosis, 504
atrophic scarring, 499–500
cigarette burns, 506
fungal, 504–505
histamine-related urticaria, 503–504
infections, 498, 500, 503, 572
necrotizing fasciitis, 502–503
needle punctures, 498–499
puffy hands syndrome, 502
track marks, 499, 501
skin popping, *499*
testing for, 418–419
tolerance development, 423
toxicity, 368
trafficking, 382–383
in urine, 422–423
withdrawal syndrome in newborns, 200
opioid receptors, *See also individual receptors*
salvinorin A and, 575, 601
THC binding, 653
opioids
adverse effects of, 448
cardioprotective effects, 510
deaths, **367**, 425
defined, 368
detoxification and rhabdomyolysis, 558
in hair, 424
immune modulation, 566–569
skin patch, 406
toxicity, 368
opion, 372
opium
alkaloids in, 381
codeine in, 441
cultivation of, 380–381
eaters, 373, 402
first-pass effect, 374
global production, 382–383
and hemlock, 372
heroin from, 383
history of, 372–378
intravenous, 374–375
oral, 374
oxycodone in, 482
smoking, 374
cauliflower ears, 506
"straw," 381
oral cancer, 258
oral contraceptives, 130
organophosphates, 52
organ transplantation
cocaine use and, 183
HIV infection and, 127
oropharyngeal ulcers, 150–151
Osler's nodes, 516
osteoblasts, 570
osteocalcin, 571
osteomyelitis, 571, 572
osteopenia, 570
osteoporosis, 570
osteoresorption, 570
oxcarbazepine, 461
oxidative stress
and apoptosis, 552
and coronary artery spasm, 125
oxycodone
alcohol and, 482
benzodiazepines and, 482, 485–486
blood levels, 485
brand names, 481
in breast milk, 484–485
deaths, 5, 367, 482–483, 485
detection, 484
drug interactions, 483–484
half-life, 483
metabolism, 483
μ-receptor binding, 369
opiates and, 482
pharmacokinetics, 483–484
pharmacology, 483
postmortem redistribution, 485
properties, 481
routes of administration, 482
seizures, 562
volume of distribution, 483
OxyContin®, 482
oxymetholone, 618
oxymorphone, 483, 487–488
alcohol and, 488

P

pain relief, 218, **219–220**
  fentanyl for, 402, 450
  hydromorphone for, 458
  intranasal heroin for, 403
  methadone for, 463, 466–467
  oral morphine for, 401–402
Panama, anti-drug efforts, 21
pancreatitis, 291, 474
Panelous, 357–358
papain, in cocaine, 130
papaverine, 418
Papaver setogerum, 380
Papaver somniferum, 380
Paracelsus, 372
paracetamol, 386
paramethoxyamphetamine (PMA), 291, 320–321
para-methoxymethamphetamine, 321
paranoia
  amphetamine-related, 245
  cocaine-induced, 163, 164–165
  in excited delirium, 138
  MDMA-induced, 3338
  solvent-related, 639
parathyroid hormone, 567, 570
paraxanthine, 224, *225*, 227, 228
paregoric, 501
parenchymal disease, cocaine-associated, 153–156
Parisian Exposition Universelle, 212
Parkinson's disease, 222, 226, 230, 560–561
  ergolines and, 361
  manganese poisoning and, 345–346
  symptoms of, 561
paroxetine, 461
parvovirus, 545
paste labs, 24–28
pastries, poppy seed-containing, 423
patent medicines, cocaine in, 11, 14
patient-controlled anesthesia (PCA) devices
  meperidine in, 474, 477–478
  morphine in, 411
Patriot Act, 272
Paullinia cupana, 218
PCP, *See* phencyclidine
Peganum harmala, 352
pekoe, 223
peliosis, 540–541
  bacillary, 618
  hepatis, 617–618
Pemberton, John Styth, 11
pennyroyal, 210
pentamethylene dibromide, 578
pentazocine, 368
  meperidine and, 477
  seizures, 561
Pen Tsao Kang Mu, 373–374
pepper spray, 146
"p.e.p. pills," 325–326
PEPTP, 561
performance enhancement
  d-amphetamine, 269
  caffeine and, 229, 232
  caffeine/ephedra, 243
  cocaine and, 164–165
  khat, 255
periarteritis nodosa, 169
pericardial infusion, in AIDS patients, 511–512
pericarditis
  HIV infection and, 511
  purulent, 515
perniosis, 110–111
Pernod, Henri-Louis, 211–212, 213
personal breathing zones (PBZ), 35
Peru
  anti-drug efforts, 21
  cocaine production, 23, 24
petechiae, 145, 185
peyote buttons, 315, *316*
P-glycoprotein (P-gp)-mediated transport, 394–395, **394**, 409–410, 428
phencyclidine (PCP), 314, 575
  blood levels, 578–579, 580–582
  cardiovascular effects, 583
  deaths, 580
  half-life, 580, 581–582
  history, 577–578
  incidence, 577
  interactions, 577
  marijuana and, 581
  metabolism, 579
  neurotoxicity, 579, 582
  properties, 576–577
  rhabdomyolysis, 582
  routes of administration, 578
  in saliva, 581
  synthetic, 578
  tissue concentrations, 580–582
  tolerance development, 582
  transplacental transfer, 582
  in vitreous humor, 582
  volume of distribution, 580, 582
phenethylamines, synthetic, 318–325
phenobarbital, 461
  as heroin adulterant, 556
phentermine, 288
1-phenyl-1,2-propanedione, 256
phenyl-2-propane, 265
phenyl-2-propanone (P2P), 271–272
5-phenyl-4-methyl-2-oxazolidinone, 344
phenylacetone, 275
phenylisopropylamines, 267, 317
  catecholamine-mediated cardiotoxicity, 283, 285–286
phenylpiperazines, 326
6-α-phenylpiperidine-2-acetic acid, 306
phenylpiperidines, 368
phenylpropanolamines, 242, 243, 344
  caffeine and, 223
  cardiovascular effects, 247
  metabolism, 245
trans-phenylpropene, 275

phenytoin, 461, 649
pheochromocytoma, 99, 101, 102, 169, 194
Philippines
  ephedra smoking, 242
  "ice" production, 270
phosphodiesterase inhibitors, caffeine, 225
phospholipase, 317
phosphophenytoin, 461
phycomycosis, 552, 554
physicians, occupational cocaine exposure, 33, 35
picograms, 665
Picornaviruses, 537–539
pimozide, 66
pinenes, 215
pinocamphone, *215*
piperazines
  deaths, 6
  medical uses, 325
  side effects, 326
piperidine, PCP from, 578
1-piperidinocyclohexanecarbonitrile (PCC), 578
pisacocas, 25
pituitary hormones, cocaine and, 188–189
Pizzi, Enrique, 9
placenta
  amino acid transport, 58
  cannabinoids and, 58
  cholinesterase activity, 58
  cocaethylene and, 59
  cocaine interactions with, 42, 50, 58, 200–202
  morphine and, 406
  nicotine and, 58
  PCP and, 582
placental abruption, 201
placenta previa, 201
plants
  alkaloid-containing, 209
  ephedra-containing, 242
plasma cholinesterase (PCE), and cocaine toxicity, 51
plasminogen activator inhibitor antigen, 186
platelets
  aggregation, 231
  cocaine abuse and, 165–166, 185–186
  dopamine transporter receptor, 185
  serotonin-depleted, 163
  serotonin re-uptake, 156
pledglets, cocaine-soaked, 32, 33
plexiform lesions, 526
Pneumocystis, 127, 540
pneumomediastinum, cocaine-associated, 152
pneumonia
  amphetamine-related, 286
  aspiration, 528
  community-acquired, 527–528
  fungal, 528
  Pneumocystis, 540
pneumothorax, 526
pocket shot, 151, 157, 526
police restraint, 139
polyarteritis nodosa, 130, 290
"poppers," 635
poppies, 372, 380–381
poppy seeds, 381, 418–419, 422–423
poppy straw, 383
Po River, cocaine metabolites in, 3
porphyria, 213, 215
porta hepatis adenopathy, 535
portal adenopathy, in narcotism, 378
portal tracts, inflammation of, 535, *536*
ports of entry (POEs), 271
positional asphyxia
  cause of death in, 146–148
  exercise physiology of, 140–142
  redefinition of, 139–140
postage stamps, DOB, 322
postmortem drug redistribution, 62, 69–70, 427
potassium channels, *See also* hERG cardiac potassium channels
  cocaine abuse and, 88, 95
  Ikr, 94
  PCP and, 579
potassium permanganate, 25–27, 73, 383
Pott's disease, 572
Pott's puffy tumor, 151
poverty, and drug use, 8
pregnancy
  amphetamines and, 277
  aortic aneurysms and, 130
  caffeine and, 233
  cocaine use and, 172, 200–202
  methamphetamine use and, 267
  toluene use and, 636, 643
pregnenolone, 614
Premarin®, 616
premixed speedball, 131
pressor effects, 126
priapism, 34
procaine, **385**, 556
progesterone
  and aortic aneurysms, 130
  cocaine use and, 189
  receptors, 613, 616
progestin receptors, 626
progressive multifocal leukoencephalopathy, AIDS-associated, 556
prolactin, 334
  cocaine and, 188–189
  heroin use and, 567
propafenone, 223
propanolol, 609
propellants, 635, **638**
propofolol, 472
propoxyphene, *463*
  acetaminophen and, 490
  blood levels, 491–492
  brand names, 489
  in breast milk, 492–493
  cardiovascular effects, 491, 492
  deaths, 489, 493
  detection, 492
  drug interactions, 491
  hERG channels and, 491

metabolism, 490–491
pharmacokinetics, 490–491
properties, 489
respiratory depression, 490, 492
structure, *490*
tissue distribution, 491–492
toxicity, 489
n-propyl acetate, 24
propylhexedrine, 286
proscaline, 318
prostacyclin, 202
protease inhibitors, 436
cocaine and, 65
lipodystrophy, 511, 512
methadone and, 461
proteinases, 516
provenance, specimen collection, 426
Prozac®, 223
pseudoallergy, 568
pseudoaneurysm, 526
pseudococaine, 28
pseudoephedrine, 209–210, 242, *272*, 286
control of, 265
metabolism, 245
structure, *240*
pseudomembranous colitis, 194
Pseudomonas aeruginosa, 571
Psilocybe, 357–358
psilocybin, 352, 357–359, 363
chocolate bars, 352
psilocyin, *358*
psoralens, 223
psychedelic age, 362–363
psychosis
amphetamine, 246, 267
anabolic steroids, 621–622
cocaine and, 164–165, 289
ephedrine, 246
in excited delirium, 138
MDMA, 338
mescaline, 318
methamphetamine, 289
methylphenidate, 308
solvent-related, 639
Wernicke-Korsakoff, 597
Psychtria viridis, 352
puffy hands syndrome, 502
pulmonary artery, hypertrophy of, 156
pulmonary disease
cocaine and, 155–156
barotrauma, 151–153
coca leaf chewing, 150
parenchymal disease, 153–156
vascular adaptations, 156–157
pulmonary edema
cocaine-associated, 155–156
fentanyl-related, 452–453
heroin and, 521–523
in narcotism, 378
opiates and, 521–523
pulmonary emboli, opiates and, 523
pulmonary fibrosis
amphetamine-related, 286
methylphenidate abuse and, 307
pulmonary hypertension, 344
HIV infection and, 511, 512
pulmonic valve, 513, **514**
pupil constriction, morphine, 369
Purkinje cells, 552
pyknosis, nuclear, 102
pyohemothorax, 526
pyramiding, 613

Q

QRS complex, caffeine and, 231
QT dispersion, cocaine-related, 93
QT interval prolongation, *See also* long QT syndrome
cocaine, 126
ephedrine, 246–247
in huffers, 637
methadone, 425, 463, 467
opiates, 510
toluene, 642
quercitin, 461
quinine, 66, 384, **385**

R

reactive oxygen species, 539
hepatotoxicity, 195
myocardial damage from, 63, 97
red blood cell counts, 186
Red Nucleus, 148
"red phosphorus," 272–273, *272*
5α-reductase, 614
refrigerants, 635
relapse behavior, 188
renal amyloidosis, 548
renal artery, arteriosclerosis, 179–180
renal disease
cocaine and, 72, 179–183
heroin and, 182
renal failure
in cocaine users, 181
in excited delirium, 138
renal tubular acidosis, 245, 246
renin-angiotensin system, 87
reserpine, 215
resibufogenin, 354
respiratory depression
fentanyl, 522
methadone, 464
opiates, 369, 423
propoxyphene, 490, 492
solvents, 643
restraint asphyxia, 140
resuscitative attempts, documenting, 140
retina, talc emboli, 308
rhabdomyolysis
cocaine and, 179–181

in excited delirium, 138, 179–181
and hyperthermia, 180–181
MDMA and, 334
methamphetamine and, 291
opiates and, 546–547, 558–559
PCP and, 583
Richardson, Sir Robert, 389
rifampin, 461
rimonabant, 653
risperidone, 461
Ritalin®, 293; *See also* methylphenidate
incidence, 303
properties, 302–303
ritalinic acid, 305, 306
ritonavir, 65, 461, 466
Robitussin®, 604
robotripping, 602
robusta beans, 223
"roid rage," 621–622
Romilar®, 604
Rosee, Pasqua, 221
rosemary, 210
Roth's spots, 516
ryanodyne (RyR2) receptors, 231, 643

S

Saccharopolyspora rectivirgula, 528
safrole, 323–325, 332
sage, 211, 214
saliva
cocaine in, 77–78
codeine in, 442
GHB in, 595
heroin in, 415
marijuana in, 654
methadone in, 467
opiates in, 415
PCP in, 581
salivation, amphetamine use and, 291
Salvia divinorum, 575
epidemiology, 601
history, 599, 601
psychoactive properties, 601–602
structure, *600*
Salvia officinalis, 211
salvinorin A, 601–602
salvinorin B, 602
sample collection
blood, 410–411, 426
nasal mucosa, 499
skin, 499
San Francisco, drug deaths, 6
sarcoma, 512
sarin, 52
savin, 210
schizophrenia, 358, 362
scleroderma, cocaine-related, 118
SCN5A, 105
Scopulariopsis brumptii, 524
sebum, drug-containing, 74
sedation, GHB, 593
seizures
absinthe, 216
caffeine, 229
cocaine, 115, 171–173
DOB, 322
MDMA, 338
meperidine, 477
normeperidine, 474, 476
opiate, 561–562
solvents, 639
thujones, 210
selective serotonin re-uptake inhibitors (SSRIs), *See also* serotonin re-uptake inhibitors
MDMA and, 330
oxycodone and, 483
selegiline, 279, 472
semen, cocaine in, 82
septicemia, *Candida*-related, 504–505
Sernyl®, 577
serotonin (5-HT), 351
in bufo toad glands, 354–355
cocaine use and, 144, 156, 185
-depleted platelets, 163
α-ethyltryptamine and, 360
excited delirium and, 144
methamphetamine and, 286–288
serotonin (5-HT) receptors, 317, 323, 325
2AR receptor, 358
LSD and, 365
mescaline and, 365
piperazines and, 326
solvents and, 637
substituted amphetamines and, 323, 325
serotonin re-uptake inhibitors
antidepressants, 156, 162
buprenorphine and, 437
caffeine and, 223
cocaine and, 144, 156, 185
MDMA and, 320, 331, 335, 337
meperidine and, 477
PMA and, 320
tramadol, 495, 496
serotonin syndrome, 334
dextromethorphan abusers, 606
MDMA and, 330, 334–335, 337–338
meperidine and, 472, 477
oxycodone and, 483
serotonin transporter
cocaine and, 172
methylphenidate and, 304
placental, 201
Sertürner, 373, 389, 441
seven-transmembrane domains, 96, 369
addiction and, 370
sewerage effluent, monitoring for cocaine, 3–4
sex hormone binding globulin (SHBG), 614
sex hormones
cocaine and, 189
khat chewing and, 258

sexual assault, GHB-facilitated, 575, 593, 594
shabu, 242, 270
Sherman, Nat, 578
"Sherms," 578
Shipman, Harold, 424
shoe polish, 636
σ-receptors, 172, 369
  methamphetamine and, 289
  in neuronal tissues, 191–192
  PCP binding, 578, 579, 580
sinsemilla, 651, *652*
sinus of Valsalva, 515
ska Maria pastora, 599
ska pastora, 599
skeletal muscle, cocaine toxicity, 180
skin
  amphetamines in, 276–277
  cocaine storage, 73–76, 204
  sample collection, 499
skin disorders
  abscesses, 117–118, 572
  infections, 117–118, 498, 572
  methicillin-resistant *Staphylococcus aureus,* 498
  opiates, 498–506
skin popping
  cocaine, *75*, 117–118, 306
  heroin, 306, 401, *499*, 500
slow-twitch muscle, 180
small G protein, 370
smuggling, cocaine, 34; *See also* body packer syndrome
snuff
  bufotenine-containing, 354
  hallucinogenic, 351, 352–354
Socrates, 372
sodium azide, 645
sodium channels
  cocaethylene and, 53
  cocaine and, 53–54, 95
  hereditary defects, 105
  inhibition of, 172
  toluene and, 637, 642
sodium fluoride, 645
soft drinks
  caffeine in, 218, **219**–**220**
  coca-based, 40
soft tissue infections, 572
Sokolow Lyon voltage criteria, 91
solvents, *See also* inhalants
  alcohol and, 639
  cardiovascular effects, 642–643
  demyelination, 639, *640*, 641
  dependency, 637
  epidemiology, 636
  gastrointestinal disease, 642
  hypothyroidism and, 641–642
  incidence of abuse, 636–637
  lipophilicity, 637
  mechanism of action, 637
  neurological disorders, 639–642
  renal disease, 642
  respiratory depression, 643
  storage/handling, 644–645
  toxicity, **638**
  in urine, 645
soman, 52
Sommer's sector, 552
South America
  anti-drug efforts, 21
  coca production, 9, 23
  drug trafficking, 20–21
  hallucinogenic snuff, 351, 352–354
  poppy cultivation, 381
Southeast Asia
  cocaine production, 14, 23
  MDMA production, 332
space of Disse, 534
specimen collection, provenance, 426
speedballing, 131
sperm, cocaine receptors, 190
sphincter of Oddi, 474
spinal cord, 369
spinal fluid, cocaine in, 78
"Spiritual Highs," 326
spongiform leukoencephalopathy, 554–557
sports doping, 611, 613–614; *See also* steroids, anabolic
spray paint, 636
sputum, black, 151, 153, 522–523
Sri Lanka, cocaine production, 14
stacking, 613
Standard International Units, 665
stanozolol, 618
Staphylococcus, 500
  endocarditis, 514–516, 546
  osteomyelitis, 571
Staphylococcus aureus
  endocarditis, 514–516
  soft tissue infections, 572
Staphylococcus viridans, endocarditis, 514
statins, 210
status epilepticus, 172, 210, 582
steroid receptors, 616
steroids, anabolic
  abuse, 609, 613–614, **624**
  androgenic effects, 613, 614
  atherogenic effects, 620
  athletes and, 609, 610, 611–613
  carbon isotope ratio, 625
  cardiovascular disease, 619–621
  commercial, 611
  detecting, 623–626
  history, 611–613
  ketaconazole test, 626
  liver disease and, 617–619
  musculoskeletal disease, 622–623
  neurological disorders, 621–622
  postmortem levels, 626–627
  sudden death, 627
  testosterone/epitestosterone ratio, 624–625
sterols, 626
St. George's disease, 618
stiff-person syndrome, 593
stimulants

natural, 209–210
absinthe, 211–216
caffeine, 218–234
ephedrine, 239–249
khat, 253–259
rhabdomyolysis and, 179–181
synthetic
amphetamines, 261–294
methylphenidate, 302–308
stomach contents, aspirated, 427, 527
stomatitis, 150
stone heart syndrome, 101
stratum corneum, drug binding, 73–74
strength training, 623
Streptococcus, 500
group A, 502–503
soft tissue infections, 572
Streptococcus pyogenes, 503
striatum, 162
STRIDE report, Drug Enforcement Agency, 28
stroke
cocaine-induced, 152–153, 167, 206
ischemic, 163, 165–167
methylphenidate-induced, 308
opiate-induced, 559–560
perinatal, 58
styptic hydrastinine, 331
subarachnoid hemorrhage, 169–171, 288, 335
subclavian injections, 500
subcutaneous injection, atrophic scarring, 499–500
Suboxone®, 435
Substance Abuse and Mental Health Services Administration (SAMHSA), 3, 265
substantia nigra, 144
Subutex®, 434, 435
succinic semialdehyde, 594–595
sudden death
Adderall®, 293
amyl nitrite, 643
cocaine and, 16, 60, 96, *98*, *100*, 101–104, **101**, 206
coronary artery disease, *120*, 121–122, *121*, 123–124
electrophysiology of, 87–105
multiple hits theory, 94–95
coronary artery dissection, *128*, 131–132
and hereditary channelopathies, 104–105
in huffers, 637–638, 642–643
MDMA, 338–340
methadone, 425, 463, 467
methylphenidate, 293, 303
sudden death, *See also* excited delirium
steroid abuse and, 619–621, 627
sudden infant death syndrome (SIDS), 64, 278
congenital long QT syndrome, 105
testosterone levels, 626
Sufenta®, 446
sufentanil, 406, 446
-induced seizures, 561
suicide
anabolic steroids and, 621
caffeine and, 233–234
fentanyl products, 450
sulfuric acid, 645
super-labs, 265, 271
superoxide radicals, from norcocaine nitroxide, 54
suppositories, morphine, 403
supraclavicular fossa, injecting into, 151, *152*
surgeons, occupational cocaine exposure, 33, 35
sweat
cocaine in, 74, 82
methamphetamine in, 276
sweat collection devices, 35, 82
α-synucleins, *143*
Syrian rue, 352–354
syrup heads, 602

T

tabun, 52
Tahiti, tattooing, 502
Taiwan
cocaine production, 14
"ice" production, 270
talc granulomas, 157, 307, 308, 524–525
tamoxifen, 539
tannins, 223
tansy, 210
Taser®
cocaine-associated rhabdomyolysis from, 181
deaths associated with, 146–147
tatau, 502
tattoos, 502
T-cells, opiates and, 568
tea
anticarcinogenic effects, 221
caffeine in, 218
coca-based, 40
ephedra, 241
herbal, 223
kratom, 459
worldwide production, 218
teamster's tea, 241
tenamfetamine, 340
teratogenicity, toluene, 643
terbinafine, 76
terpenoids, 215
testosterone
anabolic effects, 611, 614
androgenic effects, 611, 614
andropause, 615–616
blood levels, 623
cardiac potassium channels and, 66
cardiovascular effects, 66, 620
clinical uses, 616–617
cocaine and, 185, 190
detecting, 624–626
endothelin and, 190
in hair, 625
heroin use and, 567, 570
interactions, 609
khat chewing and, 258
metabolism, 614, 615

properties, 609
replacement therapy, 616
structure, *610*
synthesis, 614
testosterone cypionate, 618
tetanus, 498
δ-9-tetrahydrocannabinol, *See* THC
tetrahydrogestrinone (THG), 613, 626
THC, 650
absorption, 654–655
activity of, 653
blood levels, 656, 660
cardiovascular effects, 658–659
detection times, 655–656
in fat, 74, 659–660
metabolites, 657–658
phenytoin and, 649
postmortem redistribution, 659–660
in saliva, 654
sample preservation, 660
similarity to thujone, 216
in skin, 74
synthetic, 658
testing, 653–656
tissue distribution, 653, 656
volume of distribution, 659
THCCOOH, 655, 656
thebaine, 381, 419
buprenorphine precursor, 435
oxycodone precursor, 482
"the clear," 613, 626
theine, 218, 222
T helper cells, cocaine and, 192
theobromine, 223, 224
theophylline, 218, 223, 224, *225*, 227
blood levels, 228
metabolism of, 227
Therapeutic Use Exceptions (TUEs), 248
Thermoactinomyces vulgaris, 528
thermoregulation, 291
dopamine receptor-mediated, 142
MDMA and, 320
PMA and, 319
thiomescaline analogs, 318
thom, 459
thrombocytopenia, 182
thrombocytopenic purpura, 185–186
thromboembolic arteriopathy, 286, *524*
thrombogenesis, 232
thrombophlebitis, 501, 529
thrombosis
anabolic steroid-induced, 621
cocaine and, 185–186
thrombotic macroangiopathy, 181
thromboxane, 185, 202
thuja, 210
thujol, 215
thujones, 209, *215*
in absinthe, 215
E.U. limits, 210, 214
in sage, 214
similarity to tetrahydrocannabinol, 216
tissue concentrations, 216
U.S. limits, 214
tibolone, 616
tiletamine, neurotoxicity, 582
tissue factor, 123
tissue factor pathway inhibitor (TFPI), 123
tissue growth factor- , 516
tissue plasminogen activator inhibitor, 166
tissue-type plasminogen activator antigen, 186
titanium dioxide, 493
"toad smoking," 354
tobacco, 9; *See also* cigarette smoking
toenails, *See* nails
tolbutamide, 262
toluene, 635
boiling range, 639
lipophilicity, 641
mechanism of action, 637
neurological disorders, 635, 639–642
postmortem levels, 644
pregnancy and, 636, 643
sudden deaths, 642
teratogenicity, 643
toxicity, 639, 643–644
toonies, 323
topiramate, 461
torsade de pointes (TdP)
cocaine-induced, 93, 126
drug-induced, 66
methadone-induced, 463, 467
opiate-induced, 510
toluene-induced, 642
Toulouse-Lautrec, 213
Tourette's syndrome, 173
Toxoplasma, 127
track marks
birefringent crystals in, *501*
cocaine, 111–113, *113*
heroin, 499, 501
in narcotism, 378
opiate injection, 499, 501
tramadol, 495–497
-induced seizures, 561
meperidine and, 477
transforming growth factor (TGF), 191–192
transverse myelitis, 557
Travels in Peru (Tschudi), 9
trazodone, 326
Treatment Episode Data Set (TEDS), 265
trenbolone, 613, 626
triaditis, 535, *536*
trichloroacetic acid, 645
trichloroethanol, 645
trichloroethylene, 642, 645
tricuspid valve, 513, **514**, 553
trifluoroacetic anhydride (TFAA), 384
3-trifluoromethylphenylpiperazine (TFMPP), 325–327
2,4,5-trimethoxyamphetamine (TMA), 318–319
3,4,5-trimethoxy-β-phenethylamine, 316
trimethylxanthine, 222

troleandomycin, 458
tropacocaine, 25
tropine, 25
truxillines, 25
tryptamine derivatives
  mescaline, 315–318
  piperazine, 325–327
  substituted amphetamines, 318–325
tryptophan hydroxylase, 163
tuberculosis
  disseminated, 572
  heroin abuse and, 528–529, 572
  and intravenous drug abuse, 60
  treating with heroin, 375
tubular necrosis, cocaine-associated, 181
tumor necrosis factor, 245
tussing, 602
tyrosine hydroxylase, 163, 288

U

Über Coca, 11, 13, 213, 375
UDPG
  morphine and, 40–410
  polymorphic forms, 429
UFT1A6, 461
UGT2B4, 441
UGT2B7, 392, 441
umbilical cord blood, *See* cord blood
United Kingdom
  cocaine abuse, 3, 8
  khat chewing, 254
United Nations
  Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 273
  Drug Control and Crime Prevention (UNODCCP), heroin supply, 406
  Office on Drugs and Crime (UNODC), 264, 265
United States
  anti-drug funding, 21
  β-thujone limits, 214
  caffeine intake, 219
  cocaine
    abuse, 3, 7–8
    market, 20
    production, 23, *24*
  drug deaths, **4**
  Ecstasy use, 265
  khat use, 254
urine
  benzoylecgonine in, 48, 49–51, 78–80
  caffeine in, 227
  cocaine levels, 3–4, 16–17, 33, 78–80
    postmortem changes, 50
  codeine in, 422–423
  creatinine in, 616
  ecgonine methyl ester in, 49–51
  fentanyl in, 447, 451
  GHB in, 596
  khat in, 257
  morphine in, 415, 416, 422–423
  morphine metabolites in, 397
  norcocaine in, 49
  sample spiking, 51
  sample storage, 50
  solvent metabolites in, 645
  testosterone/epitestosterone ratio, 624–626
urine testing, hallucinogens, 365
urticaria, histamine-induced, 568

V

Valsalva maneuver, 151, 152
valvular heart disease, 128
van Gogh, Vincent, 213
vascular disease, centrally-mediated, 126
vasculitis
  amphetamine-related, 290
  cocaine-associated, 118
  methylphenidate and, 308
vasoconstriction
  bufogenins, 355
  cocaine-induced, 98, 109, 110
    coronary artery spasm, 119, 121, 124–125
    and ischemic stroke, 163, 165–167
    and vascular disease, 126
  ergolines, 361
  placental, 58
vasodilatation, 125, 243
vasospasm
  cocaine-induced, 152, 165, 167, 179–180, 181
  ergotism, 361
  steroid abuse and, 620
Vaughn, James, 255–256
veins, sclerosed, 151–153
Venezuela, anti-drug efforts, 21
venlafaxine, 461
ventricular ectopy, 231
Venus, 323
verapamil, 395, 428
vermifuge, 211
Vetalar®, 586
Viagra®, 325
Vicks®, 273, 281
Vicks VapoRub®, 215
Vietnam, heroin injection sac, 529
vinegar, *Candida*-contaminated, 528
Vin Mariani, 10, *11*, 18
violence, anabolic steroid-associated, 621
vitamin D, 570
vitreous humor
  alcohol in, 81
  BZE in, 81
  cocaethylene in, 81
  cocaine in, 80–81
  6-monoacetyl morphine in, 415, 423
  morphine in, 81
  PCP in, 582
volume of distribution, 427–428
von Scherzer, Carl, 10

von Tschudi, Johan, 9–10
von Willebrand factor, 166, 186

W

Walters, John, 19–20
wastewater treatment plants, monitoring for cocaine, 3–4
waxes, plant, 25
Wegener's granuloma, 150
Wegener's syndrome, 110
weight loss, ephedrine in, 244
Wernicke-Korsakoff psychosis, 597
whippets, 636
White Bolivian, 21
white fat, 76
white matter, solvent abuse and, 639, *640*, 641
Widmark's BAC formula, 667
Wildnil®, 446
Winek, Charles, 667
wines, coca-containing, 10, *11*, *14*, 18, 212, 213
withdrawal syndrome, acid glycoprotein and, 465
Wöhler, Carl, 10
Wolff-Parkinson-White syndrome, 339, 359
women
  drug abuse and sex hormones, 189
  drug abuse in, 6
  normal heart weight, 92, **671–673**
  "parrot beak" nails, 110–111
  response to cocaine, 188
  scleroderma in, 118
Wood, Alexander, 374–375
wooden chest syndrome, 448
World Anti-Doping Agency, 248, 612
wormwood, 211, 214, 215, 216
wound botulism, 401, 498
Wren, Christopher, 375
Wright, C.R., 376

X

xanthine derivatives, 209
xerostomia, 291
XTC, 323
xylazine
  adverse effects of, 384
  as heroin adulterant, 384
xylene, 644
Xyrem®, 592

Y

yakuza gangs, 242
Yemen, khat use, 254, 255, 256
yerba mate, 218–219
yohimbine, 326
Youth Risk Behavior Surveillance System, 636

Z

Zanchevski, Vasili, 14, 16
Z-band remnants, 102
zidovudine, 539

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