

Index

- Analgesics, opioid, 37–51
- agents, 37–51, 95–132, 141–162
 - codeine, 37–38, 50
 - diacetylmorphine (heroin), 37, 48
 - etorphine (Immobilon), 38
 - fentanyl (Sublimaze), 132
 - hydromorphone (Dilaudid), 37–38
 - levorphanol (Levo-Dromoran), 37
 - meperidine (Demerol), 37, 49–50
 - methadone (Dolophine), 37–38, 48–49
 - morphine. *see* Morphine actions;
Tolerance and physical dependence, opioid
 - oxycodone (Percodan), 37–38
 - oxymorphone (Numorphan), 37–38
 - pentazocine (Talwin), 38, 51
 - phenazocine (Prinadol), 37–38
 - d-propoxyphene (Darvon), 37–38, 50–51
- receptor interactions, 70–75
- agonists (at μ and/or κ and/or σ and/or δ receptors), 70–75
 - benzomorphans, 72–73
 - β -endorphin, 73
 - cyclazocine, 70–72, 75
 - ^3H -dihydromorphine, 74–75
 - etorphine, 73
 - ketocyclazocine, 71
 - leucine-enkephalin, 73–74
 - methionine-enkephalin, 73–74
 - morphine, 71–73
- Analgesics, opioid (*cont.*)
- receptor interactions (*cont.*)
 - agonists (*cont.*)
 - N-allylnormetazocine (N-allylnorphenazocine, SKF 10,047), 71
 - normorphine, 73–74
 - pentazocine, 72
 - partial agonists (at μ and/or κ and/or σ receptors), 70–72
 - buprenorphine, 72
 - diprenorphine, 72
 - nalorphine, 70, 72
 - oxilorphan, 72
 - propiram, 72
- Antagonists, opioid, 51–61
- agents, 53–61
 - cyclazocine, 57–59
 - attenuation of physical dependence on morphine, 59
 - effects of single and repeated doses, 57–59
 - opioid-antagonistic actions, 58–59
 - tolerance and physical dependence, 58
 - nalorphine (N-allylnormorphine), 53–57
 - attenuation of physical dependence on opioids, 56–57
 - effects of single doses in the drug-free state, 53–54
 - opioid-antagonistic actions in the non-tolerant state, 55

- Antagonists, opioid (*cont.*)
- agents (*cont.*)
 - nalorphine (*cont.*)
 - opioid-antagonistic actions in the tolerant state, 55-56
 - tolerance and physical dependence, 54-55
 - naloxone (Narcan), 59-60
 - opioid-antagonistic actions, 59-60
 - naltrexone, 60-61
 - attenuation of physical dependence on morphine, 61
 - opioid-antagonistic actions, 60-61
 - physical dependence, absence of, 61
 - competitive antagonism at μ receptor, 71-72
 - buprenorphine, 72
 - cyclazocine, 71-72
 - diprenorphine, 72
 - nalorphine, 72
 - naloxone, 72
 - naltrexone, 72
 - oxilorphan, 72
 - pentazocine, 72
 - propiram, 72
 - history of, 51-53
- Brain stem, 114-131
- and morphine analgesia, 114-123
 - anterior thalamic nuclei, 123
 - decerebrate preparations, 120-121
 - floor of fourth ventricle, 115-116
 - mesencephalic reticular formation, 123
 - monoamine systems, 116-120
 - nucleus gigantocellularis, 114, 119-120
 - nucleus paragigantocellularis, 114, 119-120
 - nucleus raphé magnus, 114, 116, 117-119
 - periaqueductal gray matter (PAG), 114, 121-123
 - periventricular gray matter (PVG), 115, 121-123
 - and effects of electrical stimulation, 123-131
 - flight-fear reactions, 123-124
- Brain stem (*cont.*)
- and effects of electrical stimulation (*cont.*)
 - stimulation-produced analgesia (SPA), 124-131
 - contrasts between SPA and morphine, 130-131
 - cross-tolerance to morphine analgesia, 127
 - due to activation of nucleus paragigantocellularis, 119-120
 - due to activation of nucleus raphé dorsalis, 129
 - due to activation of nucleus raphé magnus, 129
 - due to activation of periaqueductal gray matter (PAG), 121-123, 127, 129-131
 - due to activation of periventricular gray matter (PVG), 127
 - due to activation of PVG-PAG region, 127
 - monoamines in SPA and morphine analgesia, similarities, 127-128
 - similarities between SPA and morphine analgesia, 127-128
- Cerebral cortex, 131-132
- orbitofrontal, 131
 - opioid receptor binding in frontal pole, 131
 - pain relief by prefrontal lobotomy, 131
 - pain relief by rostral cingulumotomy, 131
 - sensorimotor, 131-132
 - effects of morphine on, 132
- Conditioning processes, 28-30, 159-162, 167-215
- classical conditioning, 29-30, 160-162, 168, 178-213
 - of atropine salivation and mydriasis, 179
 - of insulin hyperglycemia, 179
 - of insulin hypoglycemia, 179
 - of morphine salivation, 178-179
 - of morphine sleep, 178-179
 - of saccharine hypoglycemia, 179
 - of the opioid agonist-abstinence cycle, 178-198

- Conditioning processes (*cont.*)
 classical conditioning (*cont.*)
 of the opioid antagonist-precipitated
 abstinence syndrome, 207-211
 in monkeys, with nalorphine,
 208-210
 in man, with nalorphine, 207-208
 in man (methadone maintenance
 patients), with naloxone, 210-
 211
 conditioned abstinence, 30, 171, 180-
 182, 186-198, 207-215
 a disease, *sui generis*, 30, 213. *See also*
 Preface
 cognitive relabeling, 208, 214, 229
 extinction of, 211-214, 227-229
 implications for relapse and treat-
 ment, 213-215
 in postaddicts, 171, 180-182
 in street-addicts, under naltrexone
 blockade, 211-213
 conditioned reinforcers and relapse, 29,
 171-178, 180-182, 200-207
 in dogs, 172
 in man, 29, 171-172, 180-182
 in monkeys, 175-176
 in rats, 174-178, 200-207
 conditioning theory of relapse, 180-181
 interoceptive conditioning, 177, 200-
 207
 extinction of, 177, 214-215
 operant conditioning, 28-29, 168-169,
 172-178
 in chimpanzees, 172-173
 in dogs, 172
 in man, 28-29, 168-169, 172
 in monkeys, 172, 175-176
 in rats, 172-178
 relation to classical conditioning, 178
- Diagnosis. *See* Opioid dependence, diag-
 nosis
- Endorphins. *See* Enkephalins and endor-
 phins
- Enkephalins and endorphins, 76-90
 agents, 73-89
 adrenocorticotrophin (ACTH, pre-
 cursor of β -lipotropin and
 Enkephalins and endorphins (*cont.*)
 agents (*cont.*)
 β -endorphin, 77-79, 84-85,
 88-89
 α -endorphin, 78-79, 86
 β -endorphin, 73-74, 78-79, 84-89
 γ -endorphin, 78, 86-87
 δ -endorphin, 73-74
 enkephalins, 73-74, 77, 85-86
 leucine-enkephalin, 73-74, 77
 β -lipotropin (precursor of
 β -endorphin), 75
 methionine-enkephalin, 73-74, 77, 86
 morphine-like factors, 76-77
 in analgesia, 79-84
 acupuncture, 81-83
 animals, 79-83
 cats, 82
 mice, 81-83
 rats, 79-80, 83
 man, 82-84
 absence of role in ischemic pain, 83
 absence of role in hypnotic
 analgesia, 83-84
 in mental disorders, 86-90
 catatonia in rats, 86-88
 produced by β -endorphin, revers-
 ible by naloxone, 86-87
 produced by β -endorphin, com-
 pared with haloperidol, 87-88
 effects of DT7E on schizophrenic pa-
 tients, 89-90
 effects of β -endorphin on depressed
 and schizophrenic patients, 89
 effects of hemodialysis on schizo-
 phrenic patients, 90
 effects of naloxone on schizophrenic
 hallucinations, 88-89
 effects of naloxone in depressions, 89
 β_{11} -Leu⁵-endorphin in dialysates of
 schizophrenic patients, 90
 in physical dependence, 84-86
 dual action of morphine on ACTH
 and β -endorphin receptors,
 84-85
 increase in intraneural cyclic AMP by
 chronic morphine, 86
 inhibition of enkephalin release by
 chronic morphine, 85

- Enkephalins and endorphins (*cont.*)
 in physical dependence (*cont.*)
 naloxone-precipitated abstinence
 after β -endorphin intracerebrally, 84
- Etiology of opioid dependence, 25–34
 definitions and dynamics, 25–30
 a disease, *sui generis*, 30, 213. *See also*
 Preface
 conditioning processes in, 28–30,
 159–162, 167–215
 classical conditioning, 29–30, 160–
 162, 168, 178–213
 operant conditioning, 28–29, 168–
 169, 172–178
 reinforcement, 26, 171–172
 and arousal, 26
 direct and indirect sources of, 26
 history of schedules of, 28–29
 dependence, psychic and physical,
 25–26
 euphoria, dysphoria, 27–28, 104–106
 tolerance, 26, 45–48, 141–162
 WHO (World Health Organization)
 definitions, 25
 mode of spread, 23–33
 personality studies, 30–31
 increased needs, 31
 psychopathy, 30–31
 prognosis, 33–34
 maturation hypothesis, 33
 Vietnam War veterans, 33–34
- Etonitazene, effects on normal and
 morphine-dependent rats, 184–
 187
- Euphoria and dysphoria, 27–28, 104–106
 after barbiturates, 105–106
 after morphine, 27–28, 104–105
- Hypothalamus and pituitary gland, 40–42
- Locus ceruleus, 86, 116
 tolerance to inhibitory effects of opioids
 on, 86
 no cross-tolerance to inhibitory effect
 of clonidine on, 86
- Morphine actions, 38–45, 95–132
 analgesic, 95–132
- Morphine actions (*cont.*)
 analgesic, conditioned emotional re-
 sponse, 100–102
 analgesic, pain and alarm thresholds,
 96–97
 analgesic, pain-anticipatory anxiety,
 97–100, 102–103
 analgesic, sites of. *See* Brain stem;
 Cerebral cortex; Spinal cord
 other, 38–45, 102–104
 electroencephalographic, 39, 43–44
 emetic, 44
 endocrine, 40–42
 performance under varying incen-
 tives, 103–104
 pupillary, 42–43
 respiratory and vasomotor, 43–44
 spinal reflexes, 44–45, 107–114
 temperature regulation, 41–42
- Morphine tolerance and physical depen-
 dence. *See* Tolerance and physi-
 cal dependence, opioids
- Non-opioid drug dependence syn-
 dromes, 5/20
 alcohol, 9–11
 amphetamines, 11–12
 cannabis (marihuana, hashish, Δ^9 -
 THC), 16–18
 cocaine, 12–14
 hallucinogens, 14–16
 sedatives, 5–9
 tobacco, 18–20
- Opioid dependence, 1–4, 25–61; 76–80,
 141–162, 167–215, 219–244
 complications, 4
 crime, 4
 deaths, 4
 marital instability, 4
 medical problems, 4
 psychiatric problems, 4
 unemployment, 4
 diagnosis, 219–222
 of opioid use, by clinical criteria,
 221
 of opioid use, by urinary drug-
 detection methods, 221–222

- Opioid dependence (*cont.*)
diagnosis (*cont.*)
 of physical dependence, by abrupt opioid withdrawal, 219
 of physical dependence, by use of narcotic antagonists, 219–221
etiology. *See* Etiology of opioid dependence
prevalence, 1–4
relation to use of marihuana and other drugs, 2–3
treatment. *See* Treatment of opioid dependence
- Pain
 effects of barbiturates on, 105
 effects of morphine on. *See* Morphine, actions, analgesic
 nature of, 95–107
 neurophysiological models of, 106–107
Physical dependence. *See* Tolerance and physical dependence, opioids
Pituitary gland and hypothalamus, 40–42
- Receptors, 69–76
 molecular pharmacology, 69–70
 definitions and measurements, 69–70
 affinity, 70
 agonists, 69
 antagonists, 70
 competitive dualism, 70
 intrinsic activity, 70
 partial agonists, 70
 receptor dualism, 70
opioid, drugs acting on, 59–61, 70–75
 benzomorphans, 72–73
 β -endorphin, 73
 buprenorphine, 72
 cyclazocine, 70–72, 75
 ^3H -dihydromorphine, 74–75
 diprenorphine, 72, 75
 etorphine, 73
 ketocyclazocine, 71
 leucine-enkephalin, 73–74
 ^3H -leucine-enkephalin binding, 73–74
 methionine-enkephalin, 73–74
 morphine, 71–73
- Receptors (*cont.*)
opioid, drugs acting on (*cont.*)
 N-allylnormetazocine (N-allylnorphenazocine, SKF 10,047), 71
 nalorphine, 70, 72
 naloxone, 59–60
 ^3H -naloxone binding, 74–75
 naltrexone, 60–61
 normorphine, 73–74
 oxilorphan, 72
 propiram, 72
stereospecific binding to, 74–76
 distribution in nervous system and intestine, 74–75
 effect of sodium ion on, 75
types of, 70–74
 in chronic spinal dog, 71–72
 in guinea pig ileum and mouse vas deferens, 72–74
 δ -receptors, 73–74
 κ -receptors, 73
 μ -receptors, 73–74
- Reinforcement, 19, 26, 171–172
 and arousal, 19, 26
 appetitive, aversive, 171–172
 positive, negative, 171–172
 sources of, direct and indirect, 26
- Relapse, 33–34, 168–210
 conditioning theory of, 180–182
 in postaddicts, 33–34, 226–227
 in rats (etonitazene drinking), 188–207
 role of conditioned reinforcers, 29, 171–178, 180–182, 200–207
 in dogs, 172
 in man, 29, 171–172, 180–182
 in monkeys, 175–176
 in rats, 174–178, 200–207
- Self regulated readdiction to morphine in man, 168–171
- Spinal cord, 107–132
 analgesic test responses, 107–108, 114
 effects of decortication, spinal transection and morphine on, 107–108
 effects of lumbar intrathecal opioids on, 114, 121
 skin-twitch, 107
 tail-flick, 107

Spinal cord (*cont.*)

- reflexes, effects of opioids on, 107-114
 - in spinal cats, 108-113
 - in spinal cats, inhibitory processes, 110-111
 - role of acetylcholine, 111
 - in spinal cats, monosynaptic arcs, 109-110
 - in spinal cats, polysynaptic arcs, 108-109
 - post- δ and C fiber arcs, 111
 - in spinal cats, supraspinal inhibitory and facilitatory mechanisms, 107-109, 113
 - in spinal cats, unit responding in dorsal gray laminae, 111-113
 - in spinal dogs, 107-108
 - in spinal man, 108
 - in spinal man (paraplegic patients), 108
- transmission of pain, 113

Tolerance and physical dependence,

- opioids, 45-51, 141-162, 183-184. *See also* Non-opioid drug dependence syndromes; Opioid dependence, diagnosis, treatment
- phenomena, 28-30, 45-48, 141-142, 159-162, 167-215, 219-220
 - abstinence syndromes, early and protracted, 46-48
 - abstinence syndromes, effects of prefrontal lobotomy on, 48
 - abstinence syndromes, precipitated by narcotic antagonists, 47, 219-220
- conditioning processes. *See* Conditioning processes
- in chronic decorticated dogs, 168
- in chronic spinal dogs, 141-142, 167
- in chronic spinal man, 142
- in man, 45-48, 141
- in rats, 183-184
- residual tolerance, 45
- reversal of abstinence hypothermia
 - by conditioned stimuli, 184
 - blockade by naloxone, 184
- theories of, 141-162
 - cellular counteradaptation, 143

Tolerance and physical dependence (*cont.*)

- theories of (*cont.*)
 - disuse supersensitivity, 145-147
 - disuse supersensitivity, to catecholamines, 146
 - disuse supersensitivity, to pentylenetetrazol, 146
 - disuse supersensitivity, to pilocarpine, 146-147
- dual action, 143-145
 - stimulant actions of opioids, 143-145
- enzyme expansion, 157-158
 - protein synthesis in, 157-158
 - protein synthesis, inhibition by actinomycin, 158
 - protein synthesis, inhibition by 8-azaguanine, 158
 - protein synthesis, inhibition by cycloheximide, 158
- homeostatic counteradaptation, 142
- immune mechanisms, 158-159
 - morphine dose-intervals and tolerance, 158
- learning factors, 159-162
 - associative (Pavlovian), 160-162
 - nonassociative, 159
- new receptors, 150-157
 - silent and pharmacological receptors, 151
 - tolerance without physical dependence, 151-152
 - increase in number of silent receptors, 152
 - decrease in number of pharmacological receptors, 152
 - tolerance with physical dependence, 152-157
 - increase in number of pharmacological receptors, 152-153, 156-157
 - decrease in number of pharmacological receptors, 153-156
- pharmacological redundancy, 147-150
 - evidence for, in chronic spinal dogs, 149
 - evidence for, in man, 148
 - evidence for, in rats, 149-150
 - neural model of, 147-148

- Tolerance and physical dependence (*cont.*)
theories of (*cont.*)
 pharmacological redundancy (*cont.*)
 effects of chronic morphine and morphine-withdrawal, 147–148
 persistence of morphine effect on respiratory center during tolerance, 148
transmitters involved in, 152–157
 acetylcholine, 152–153
 catecholamines, 153–155
 synthesis of ¹⁴C-catecholamines, 154
 turnover of ³H-dopamine, 155
 turnover of ³H-dopamine, conditionability of, 155
 serotonin, 155–157
 turnover of, 156
 blockade by morphine, 155–156
- Treatment of opioid dependence, 222–244
detoxification, 224–227
 methadone substitution and withdrawal, 225
 rapid withdrawal, 225–226
 relapse after, 226–227
 therapeutic communities, 227
- levomethadyl (LAAM) maintenance, 241–244
 comparisons with methadone maintenance, 241–243
 human pharmacology of, 241–243
- Treatment of opioid dependence (*cont.*)
methadone maintenance, 234–241
 criticisms of, 237–238
 FDA regulations governing, 238–239
 induction of, 238
 maintenance dosage in, 239
 medical complications of, 236–237
 rationale, 234–235
 results of, 239–241
 eventual methadone detoxification, 240–241
 tolerance to methadone, 235–236
- narcotic antagonist maintenance after detoxification, 227–234
 depot preparations, 234
 rationale, 227–228
 cognitive labeling, 208, 214, 229
 extinction of conditioned abstinence, 211–214, 227–229
 with cyclazocine, 227, 230–231
 with naltrexone, 228–230, 231–234
 drop-out rate in, 231–234
 results of, 231–234
- of opioid poisoning, 222–224
 differential diagnosis, 222–224
 general supportive measures, 222–223
 with naloxone, 223–224
 signs of opioid-antagonism, 223
 signs of precipitated opioid-abstinence, 223