List of Tables and Figures

Chapter 1 Introduction, Evaluation of Evidence on Mechanisms of Disease Production, and Summary		Table 4.2	Questions, answers, and scoring for Fagerström Test for Nicotine Dependence and Fagerström Tolerance Questionnaire 107
Table 1.1	Four-level hierarchy for classifying the strength	Table 4.3	Measures of nicotine addiction 109
Table 1.2	of causal inferences from available evidence 3 Causal criteria 7	Table 4.4	Bioavailability and amount of nicotine absorbed per unit dose and time to maximum venous blood concentration of nicotine by product 113
Figure 1.1	The health consequences causally linked to smoking and exposure to secondhand smoke 4	Table 4.5	Genetic linkage studies of smoking behavior phenotypes 139
Figure 1.2	General schema for the causation of disease by to bacco smoke $\ 5$	Table 4.6	Studies of candidate genes for nicotine metabolism and smoking behavior 142
Figure 1.3	Potential pathways and mechanisms for cardiovascular dysfunction mediated by cigarette smoking 6	Table 4.7	Studies of candidate genes for neuronal nicotine receptors and smoking behavior 144
Chapter 3	Shlowing 0	Table 4.8	Studies of candidate genes for dopamine and smoking behavior 146
Chapter 3 Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm		Table 4.9	Studies of candidate genes for serotonin and smoking behavior 150
Table 3.1	Selected chronic carcinogenicity studies in mice and rats with inhalation exposure to cigarette smoke <i>64</i>	Table 4.10	Other studies of candidate genes for smoking behavior 152
Figure 3.1	Tobacco alkaloids 32	Table 4.11	Lifetime and current prevalence of nicotine dependence in population studies in the United States <i>163</i>
Figure 3.2	Structures of nicotine and minor alkaloid $S(-)$ - N -methylanabasine in tobacco leaf 33	Table 4.12	Prevalence of selected symptoms of nicotine
Figure 3.3	Three forms of nicotine 33		dependence reported in selected studies 166
Figure 3.4	Tobacco-specific nitrosamines 35	Figure 4.1	Venous blood concentrations of nicotine over time for various nicotine delivery systems 114
Figure 3.5	Priority environmental polycyclic aromatic hydrocarbons 38	Figure 4.2	Mean plasma nicotine concentrations after administration of each of four smokeless tobacco
Figure 3.6	Commonly studied aromatic amines in tobacco smoke 42	Figure 4.3	products or mint snuff 115 Associative learning processes in nicotine addic-
Figure 3.7	Primary heterocyclic amines in tobacco smoke 43	Figure 4.4	tion 121 Neural pathways for γ -aminobutyric acid, glutamate, dopamine, and excitatory neurotransmitters 127
Chapter 4 Nicotine Addiction: Past and Present		Figure 4.5	Cumulative incidence curves of daily smoking
Table 4.1	Criteria for substance (nicotine) dependence	8-40	and nicotine dependence in the National Comorbidity Survey 165

Figure 4.6	Individual estimated slopes in craving ratings over three weeks prequit, from just before to just	Table 5.12	Carcinogens and tobacco-induced cancers 299
	after midnight on the quit date, and over three weeks postquit 175	Figure 5.1	Link between cigarette smoking and cancer through carcinogens in tobacco smoke 226
Figure 4.7	Reactions for the three-week period before the quit date and the three-week period after the quit date 176	Figure 5.2	Chemical structures of biomarkers of carcinogen exposure 231
Figure 4.8	Withdrawal severity and lapse behavior among smokers who abstained for the first five days of a quit attempt 177	Figure 5.3	Metabolism of six carcinogens in tobacco smoke that produce DNA adducts identified in the lungs of smokers 236
Figure 4.9	Negative affect in the days and hours preceding	Figure 5.4	Mechanism of base excision repair 255
rigure 4.5	the first lapse for smokers who attributed their first lapse to a stressor or bad mood (stress trigger) or to some other type of event (other trigger) 178	Figure 5.5	Mechanism of nucleotide excision repair: (A) global genomic repair; (B) transcription-coupled repair 256
	ger, 110	Figure 5.6	Mechanism of mismatch repair 258
Chapter 5 Cancer		Figure 5.7	Proposed mechanism of homologous recombination 260
Table 5.1	IARC evaluations of carcinogens in mainstream cigarette smoke 228	Figure 5.8	Proposed mechanism of nonhomologous end- joining 261
Table 5.2	DNA adducts in human lung tissue 243	Figure 5.9	Model of mechanism for mammalian translesion synthesis 270
Table 5.3	Selected gene polymorphisms evaluated by molecular epidemiology investigations for relationship to lung cancer through variation in susceptibility to carcinogens in tobacco smoke 246	Figure 5.10	Patterns of $TP53$ gene mutations and percentage of $G\rightarrow T$ transversion mutations in human lung cancers 278
Table 5.4	Human DNA glycosylases 253	Figure 5.11	Patterns of <i>TP53</i> gene mutations and percentage of G→T transversion mutations in different histo-
Table 5.5	Factors involved in nucleotide excision repair activity in humans 257		logic types of lung cancer 280
Table 5.6	Select candidate genes and polymorphisms implicated in repair of tobacco-induced DNA damage 262	Figure 5.12	Concordance between codon distribution of G→T transversions along <i>TP53</i> gene in lung cancers (top) and distribution of adducts of benzo[<i>a</i>]pyrene-7,8-diol-9,10-epoxide (BPDE)—DNA adducts in bronchial epithelial cells (bot-
Table 5.7	Translesion-specialized DNA polymerases (pol) and activities on various DNA lesions 270	TI - 10	tom) 281
Table 5.8	Mutational specificity of selected DNA adducts derived from tobacco smoke 271	Figure 5.13	Patterns of <i>TP53</i> gene mutations and percentage of G→T transversions in smoking-associated cancers other than lung cancer 282
Table 5.9	Frequency of mutation or deletion of tumor-sup- pressor genes in lung cancer 274	Figure 5.14	Tobacco-associated suppression of proapoptotic proteins and tumor-suppressor proteins 285
Table 5.10	Frequency of gene amplification and increased expression of genes in lung cancer 276	Figure 5.15	Protein-signaling pathways deregulated in lung cancer 286
Table 5.11	Pathways altered through gene silencing by promoter methylation 293		

Chapter 6 Cardiovascular Diseases		Chapter 7 Pulmonary Diseases	
Table 6.1	Rate ratios for coronary heart disease among White men, by age and duration of cigarette smoking <i>359</i>	Table 7.1	Causal conclusions on smoking and diseases of the respiratory tract other than lung cancer: the 2004 and 2006 reports of the Surgeon General 438
Table 6.2	Death rates and rate ratios for death from coronary heart disease among men, by age and duration of smoking by number of cigarettes smoked per day 360	Table 7.2	Definitions for principal nonmalignant respiratory diseases caused by cigarette smoking 439
Table 6.3	Biomarkers of risk for cardiovascular disease from exposure to cigarette smoke 392	Table 7.3	Selected components of cigarette smoke and potential mechanisms of injury 439
m.11. a.		Table 7.4	Measurements of oxidative stress 463
Table 6.4	Randomized controlled trials of counseling for smokers hospitalized with cardiovascular disease 396	Table 7.5	Studies of oxidative stress in smokers 464
Table 6.5	Randomized controlled trials of pharmacologic interventions for smoking cessation in patients	Table 7.6	Studies of oxidative stress in animals exposed to smoke 466
	with cardiovascular disease 397	Table 7.7	In vitro studies of oxidative stress 468
Table 6.6	Smoking reduction and cardiovascular disease endpoints: biomarkers and clinical outcomes 404	Table 7.8	Genomewide linkage analysis studies in general- population samples and in families with chronic obstructive pulmonary disease (COPD) 478
Figure 6.1	Relative and excess death rate for coronary heart disease among men, by age group 356	Table 7.9	Replicated candidate gene associations in chronic obstructive pulmonary disease (COPD) 480
Figure 6.2	Age-specific excess death rates among male smokers for coronary heart disease, lung cancer,	Table 7.10	Matrix metalloproteinases in emphysema 489
	chronic obstructive pulmonary disease (COPD), and cerebrovascular disease 357	Table 7.11	Mouse models of overexpression of a protein leading to emphysema 492
Figure 6.3	Dose-response relationship between number of cigarettes smoked per day and relative risk of ischemic heart disease 358	Table 7.12	Effects of protease inhibitors in experimental smoke-induced emphysema 493
		Figure 7.1	Lung defenses 440
Figure 6.4	Plasma nicotine and carboxyhemoglobin concentrations throughout a day of cigarette smoking 364	Figure 7.2	Fractional deposition of inhaled particles in the human respiratory tract 441
Figure 6.5	Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event 366	Figure 7.3	Comparison of normal bronchial gland (A) with enlarged bronchial glands (B and C) from a patient with chronic bronchitis 442
Figure 6.6	Potential sites of actions and mechanisms of effects of smoking on platelets 376	Figure 7.4	Natural history of decline in forced expiratory vol- ume with aging measured in a group of working
Figure 6.7	Potential sites of effects of smoking on thrombosis through oxidative stress and other mechanisms 378		men in West London over about six years 444
		Figure 7.5	Nature of an obstruction in the small conducting airways (<2 millimeters in diameter) 445

Figure 7.6	Dose-response relationship between level of smoking and the percentage of 408 patients in the St. Paul's Lung Study with morphologic evidence of significant emphysema in their lungs 446	Table 8.4	Association between maternal smoking and cardiovascular malformations, by phenotype, $1999-2008$ 546
Figure 7.7	Postmortem bronchogram performed on the lungs of a person with centrilobular emphysema 447	Table 8.5	Association between maternal smoking and non-cardiovascular congenital malformations, by type of malformation, 1998–2008 548
Figure 7.8	Details of centrilobular emphysema lesions 448	Table 8.6	Association between smoking and reproductive hormones in women 558
Figure 7.9	Cut surface of lungs removed from two patients with different forms of emphysema before receiving a lung transplant 449	Table 8.7	Association between smoking and reproductive hormones in healthy men 562
Figure 7.10	Innate and adaptive immune system of the lung,	Table 8.8	Basal maternal and fetal cardiovascular effects of smoking 569
S	including the mucous production and clearance apparatus, the epithelial barrier, and the inflammatory immune response 450	Table 8.9	Maternal and fetal cardiovascular effects: radio- isotope studies of placental intervillous blood flow (IBF) conducted before and after smoking 570
Figure 7.11 Figure 7.12	Lymphoid collections within lung tissue 452 Persistent innate and adaptive immune inflam-	Table 8.10	Acute maternal and fetal cardiovascular effects of smoking 571
rigure 7.12	matory response in alveolar tissue 454	Table 8.11	Animal and in vitro studies on association
Figure 7.13	Remodeling process after a single clean surgical wound 455	Table 6.11	between maternal smoking and congenital abnomalities with relevant genetic and/or molecular hypotheses 578
Figure 7.14	Diagram based on three-dimensional reconstructions of serial electron micrographs illustrating how inflammatory immune cells navigate through interstitial space of alveolar wall 456	Table 8.12	Reproductive and developmental effects of polycyclic aromatic hydrocarbons (PAHs), by endpoint 590
Figure 7.15	Formation of reactive oxygen species 458	Table 8.13	Studies of interactions between genotype and exposure to tobacco related to oral clefting 602
Figure 7.16	Synthesis of nitric oxide (NO) and related products 459	Table 8.14	Decreased birth weight, preterm delivery, intra- uterine growth retardation, and neonatal oxida-
Figure 7.17	Oxidant and antioxidant systems in the lungs 460		tive damage: interactions between host genotype and exposure to tobacco smoke 604
Figure 7.18	Pathogenesis of smoking-induced pulmonary emphysema 488	Chapter 9 A Vision fo	r the Future
Chapter 8 Reproducti	ve and Developmental Effects	Table 9.1	Behavioral indicators of addiction potential of a drug or addiction to a drug 656
Table 8.1	Association of adult cigarette smoking and in utero exposure to cigarette smoke with semen parameters and fertility in adults 528	Figure 9.1	Effects on survival of stopping smoking cigarettes at ages 25–34 years (effect from age 35), ages 35–44 years (effect from age 40), ages 45–54 years (effect from age 50), and ages 55–64 years (effect
Table 8.2	Association between maternal smoking and spontaneous abortion (SAB), $1998-2006$ 532	Figure 0.9	from age 60) 649
Table 8.3	Association between maternal smoking and orofacial clefts (OFCs), 1999–2009 542	Figure 9.2	Molecular-profiling approaches to the development of personalized therapy 650