Chapter 1
Introduction, Evaluation of Evidence on Mechanisms of Disease Production, and Summary

Introduction

Since the first of the series in 1964, reports of the Surgeon General have provided definitive syntheses of the evidence on smoking and health. The topics have ranged widely, including comprehensive coverage of the health effects of active and passive smoking (U.S. Department of Health, Education, and Welfare [USDHEW] 1979; U.S. Department of Health and Human Services [USDHHS] 1986, 2004, 2006), the impact of tobacco control policies (USDHHS 2000), and addiction (USDHHS 1988). A goal of these reports has been to synthesize available evidence for reaching conclusions on causality that have public health implications. In reaching conclusions on causation, the reports have followed a model that originated with the 1964 report: compilation of all relevant lines of scientific evidence, critical assessment of the evidence, evaluation of the strength of evidence by using guidelines for evidence evaluation, and a summary conclusion on causation (USDHEW 1964; USDHHS 2004). The 2004 Surgeon General's report provides a review of this approach and gives a set of ordered categories for classifying the strength of evidence for causality that was used in the 2004 and 2006 reports on active and involuntary smoking, respectively (Table 1.1). The Surgeon General's reports have established a long list of health consequences and diseases caused by tobacco use and exposure to tobacco smoke (Figure 1.1).

This report considers the biologic and behavioral mechanisms that may underlie the pathogenicity of tobacco smoke. Many Surgeon General's reports have considered research findings on mechanisms in assessing the biologic plausibility of associations observed in epidemiologic studies. Mechanisms of disease are important because they may provide plausibility, which is one of the guideline criteria for assessing evidence on causation. The 1964 report, for example, gave extensive consideration to the presence of carcinogens in tobacco smoke and the findings of animal models (USDHEW 1964). This new report, however, specifically reviews the evidence on the potential mechanisms by which smoking causes diseases and considers whether a mechanism is likely to be operative in the production of human disease by tobacco smoke. This evidence is important to understand how smoking causes disease, to identify those who may be particularly susceptible, and to assess the potential risks of tobacco products. In addition, this evidence is relevant to achieving the tobacco-related goals and objectives in the Healthy People initiative—the nation's disease prevention and health promotion agenda—and to developing the interventions for our nation's tobacco cessation targets for the year 2020 (USDHHS 2009).

In the planning of this report, the diseases and other adverse outcomes causally linked to smoking served to define the scope of issues considered in each of the chapters. Because sufficient biologic plausibility had been established in prior reports for all causal conclusions, the evidence on biologic and behavioral mechanisms reviewed in this report complements and supports the causal conclusions established earlier. The report is *not* focused on whether the evidence supports the plausibility of a causal association of smoking with a particular disease. In fact, most of the diseases and other adverse outcomes considered in this report have long been causally linked to smoking. This report focuses on the health consequences caused by exposure to tobacco smoke and does not review the evidence on the mechanisms of how smokeless tobacco causes disease.

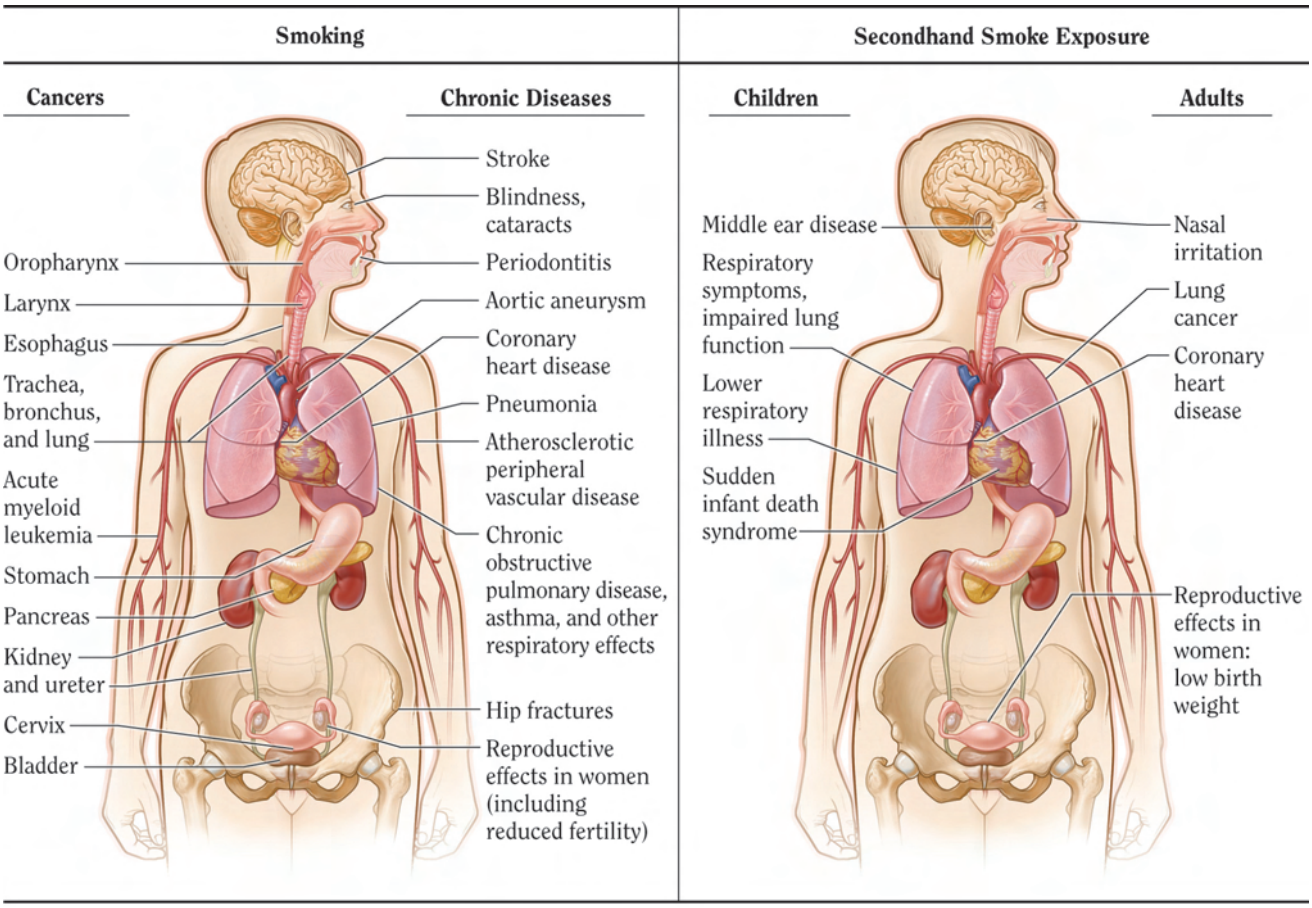
The determination of whether a particular mechanism figures in the causation of disease by tobacco smoke has potential implications for prevention, diagnosis, and treatment. A general schema for the causation of disease by tobacco smoke is provided in Figure 1.2. The assumption is that disease may be a consequence of one or more pathways, each possibly having one or more component mechanisms. The figure shows multiple pathways, each comprised potentially of multiple mechanisms. Moreover, the same mechanism might figure into several different pathways. For example, mutations of genes are likely to

Table 1.1 Four-level hierarchy for classifying the strength of causal inferences from available evidence

Level 1	Evidence is **sufficient** to infer a causal relationship
Level 2	Evidence is **suggestive but not sufficient** to infer a causal relationship
Level 3	Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting)
Level 4	Evidence is **suggestive of no causal relationship**

Source: U.S. Department of Health and Human Services 2004, 2006.

Figure 1.1 The health consequences causally linked to smoking and exposure to secondhand smoke



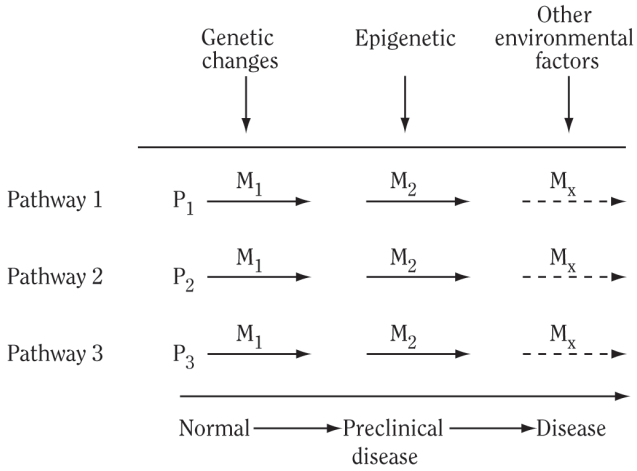
Source: USDHHS 2004, 2006.

figure into several different pathways for the causation of cancer. As a complex mixture with many different toxic components, tobacco smoke is likely to act through multiple pathways in causing disease, and multiple genes may be involved. Genes may modulate the activity of these pathways, and there may also be connections between the pathways. Other environmental factors may act through the same pathways as tobacco smoke or through different pathways and, thereby, augment the contribution of smoking to disease incidence. For example, the combined effects of smoking and radon may contribute to causing lung cancer (National Research Council 1998).

Pathways and mechanisms by which active and passive smoking contribute to causation of cardiovascular disease are illustrated in Figure 1.3 (Ambrose and Barua 2004). This depiction of cigarette components in the "tar phase" and "gas phase" shows their action through several interacting pathways, indicating a role for genetic as well as other factors.

The characterization of mechanisms by which smoking causes disease could lead to applications of this knowledge to public health by (1) assessing tobacco products for their potential to cause injury through a particular mechanism, (2) developing biomarkers of injury to identify smokers at early stages of disease development, (3) identifying persons at risk on a genetic basis through the operation of a particular mechanism, (4) providing a basis for preventive therapies that block or reverse the underlying process of injury, and (5) identifying the contribution of smoking to causation of diseases with multiple etiologic factors. Consequently, research continues on the mechanisms by which smoking causes disease, even though the evidence has long been sufficient to infer that active smoking and exposure to secondhand smoke cause numerous diseases (USDHHS 2004, 2006). In addition, the resulting understanding of mechanisms is likely to prove applicable to diseases caused not only by

Figure 1.2 General schema for the causation of disease by tobacco smoke



Note: **M** = disease mechanisms; **P** = disease pathways.

smoking but by other agents that may act through some of the same mechanisms.

This report is written at a time when new research methods have facilitated exploration of the mechanisms by which smoking causes disease at a depth not previously possible. With the powerful methods of molecular and cellular research, disease pathogenesis can now be studied at the molecular level, and animal models can be developed to explore specific pathways of injury. Consequently, the range of evidence considered in this report is broad, coming from clinical studies, animal models, and in vitro systems. The coverage extends from research at the molecular level to population-level biomarker studies.

Evaluation of Evidence on Mechanisms of Disease Production

Approaches for evaluation and synthesis of evidence on mechanisms have not been previously proposed in Surgeon General's reports, although substantial emphasis has been placed on biologic mechanisms. The 1964 report indicated that three lines of evidence would be reviewed: animal experiments, clinical and autopsy studies, and population studies. It further commented on the essential nature of all three lines of evidence in reaching conclusions on causality. That report and subsequent reports of the Surgeon General, however, have given only general guidance on assessing biologic plausibility (USDHEW 1964; USDHHS 2004). The 1964 report used the term "coherence of the association" as one of the criteria for causality (Table 1.2). In addressing lung cancer, the report stated: "A final criterion for the appraisal of causal significance of an association is its coherence with known facts in the natural history and biology of the disease" (USDHEW 1964, p. 185).

The 1982 report of the Surgeon General noted:

> Coherence is clearly established when the actual mechanism of disease production is defined. Coherence exists, nonetheless, although of a lesser magnitude, when there is enough evidence to support a plausible mechanism, but not a detailed understanding of each step in the chain of events by which a given etiologic agent produces disease (USDHHS 1982, p. 20).

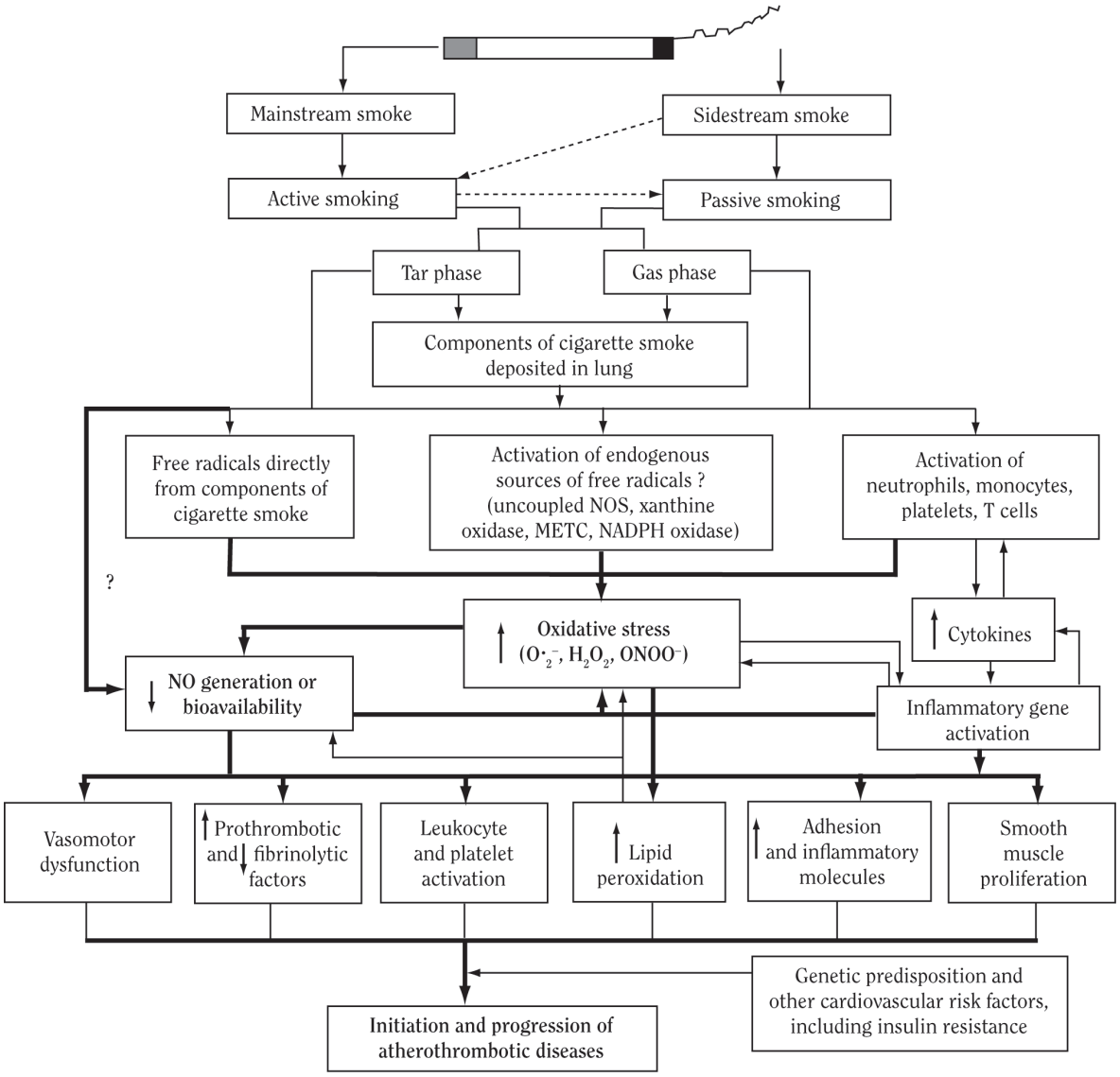
The 2004 report discussed coherence, plausibility, and analogy together, commenting:

> Although the original definitions of these criteria were subtly different, in practice they have been treated essentially as one idea: that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data, such as ecologic patterns of disease…. In addition, if biologic understanding can be used to set aside explanations other than a causal association, it offers further support for causality. Together, these criteria can serve both to support a causal claim (by supporting the proposed mechanism) or refute it (by showing that the proposed mechanism is unlikely) (USDHHS 2004, p. 22).

Hill (1965) listed both plausibility and coherence among his nine criteria but did not offer a sharp distinction between the two. He commented on the linkage of the concept of plausibility to the contemporary state of knowledge, and his views of coherence were largely consistent with statements in the 1964 Surgeon General's report.

Current evidence on mechanisms of disease causation raises issues that could not have been anticipated at the time of the 1964 report. With advances in laboratory research over the last several decades, researchers are challenged to interpret molecular and cellular evidence on mechanisms and causation. The need for new approaches to interpret such evidence has been recognized in several research areas including infectious diseases and cancer. Approaches have been proposed by agencies and researchers that assess carcinogens.

Figure 1.3 Potential pathways and mechanisms for cardiovascular dysfunction mediated by cigarette smoking



Source: Ambrose and Barua 2004. Reprinted with permission from Elsevier, © 2004.
Note: The bold boxes and arrows in the flow diagram represent the probable central mechanisms in the complex pathophysiology of atherothrombotic disease mediated by cigarette smoking. **H_2O_2** = hydrogen peroxide; **METC** = mitochondrial electron transport chain; **NADPH** = reduced nicotinamide adenine dinucleotide phosphate; **NO** = nitric oxide; **NOS** = nitric oxide synthase; **$O^{\bullet}_2^-$** = superoxide anion; **$ONOO^-$** = peroxynitrite.

In infectious disease research, the arrival of molecular techniques for studying microbes led to a recognition that extensions of Koch's postulates were needed to accommodate this new type of information (Falkow 1988; Fredericks and Relman 1996). Falkow (1988) proposed "molecular Koch's postulates" for considering the role of specific microbial genes in pathogenicity. Fredericks and Relman (1996) listed seven criteria for evaluating whether a disease could be attributed to a putatively identified pathogen, found by sequence-based methods. They emphasized that "coherence and plausibility are important" (p. 30). Pagano and colleagues (2004) also acknowledged the complexities of causally linking cancer to infectious agents.

Research has broadened and increased the literature on mechanisms of carcinogenesis and has contributed to a similar rationale for developing approaches to review information on mechanisms. Approaches have been proposed by the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (EPA).

In the preamble to its monographs on carcinogenicity, IARC describes its approach for characterizing the strength of evidence regarding mechanisms relevant to the agent being evaluated (IARC 2006). For animal experiments, IARC offers a four-level classification of the strength of evidence, which parallels the categories of the 2004 Surgeon General's report: *sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity,* and *evidence suggesting lack of carcinogenicity*. The strength of evidence on mechanisms is described with terms such as "weak," "moderate," or "strong." The IARC working group preparing the monographs is also charged with assessing whether the mechanism is operative in humans. Guidance is given for evaluating the role of a mechanism in experimental animals. Emphasis is placed on consistency across experimental systems and on biologic plausibility and coherence.

EPA covers the identification of a "mode of action" in its *Guidelines for Carcinogen Risk Assessment* (USEPA 2005). Mode of action refers to the process by which an agent causes disease but at a less detailed and specific level than is intended by mechanism of action. In these guidelines, EPA modified the Hill (1965) criteria, offering its framework for evaluating evidence on mode of action. The steps for evaluating a hypothesized mode of action include (1) description of the hypothesized mode of action, (2) discussion of the experimental support for this mode of action, (3) consideration of the possibility of other modes of action, and (4) conclusions about the hypothesized mode of action. In regard to evaluating the experimental support, the *Guidelines* list strength, consistency, and specificity of association as considerations. The finding of dose-response is given weight as is proper temporal ordering. Finally, the *Guidelines* call for biologic plausibility and coherence: "It is important that the hypothesized mode of action and the events that are part of it be based on contemporaneous understanding of the biology of cancer to be accepted" (pp. 2–46). Standard descriptors for the strength of evidence are not mentioned.

Mechanisms of Action: Necessary, Sufficient, or Neither

For many of the diseases caused by smoking, multiple mechanisms are likely to be involved. For example, study results indicate that general and specific DNA injury and repair processes contribute to carcinogenesis. Causal agents have been classified as "necessary," "sufficient," or "neither necessary nor sufficient" (Rothman 1976). A necessary cause is requisite for occurrence of the disease;

Table 1.2 Causal criteria

1964 Report of the Advisory Committee to the U.S. Surgeon General	Austin Bradford Hill's criteria
1. Consistency of the association	1. Strength
2. Strength of the association	2. Consistency
3. Specificity of the association	3. Specificity
4. Temporal relationship of the association	4. Temporality
5. Coherence of the association	5. Biological gradient
	6. Plausibility
	7. Coherence
	8. Experiment
	9. Analogy

Source: U.S. Department of Health, Education, and Welfare 1964; Hill 1965.

severe acute respiratory syndrome (SARS), for example, cannot occur without infection with the SARS coronavirus. Exposure to a sufficient cause is invariably followed by occurrence of the disease. For chronic diseases, many causal factors are in the category "neither necessary nor sufficient"; cigarette smoking, for example, does not cause lung cancer in all smokers, and some cases occur among lifetime nonsmokers.

A similar formulation of "necessary" and "sufficient" might be extended to considering the mechanisms of disease production. If there is only one pathway to a disease, and a particular mechanism is included in that pathway, then the mechanism is required for the development of the disease and would be considered "necessary." A mechanism that is a component of one or more but not all pathways would be considered "sufficient." Application of this type of classification would require a depth of understanding of the interplay of mechanisms that has not been reached for the pathogenesis of most diseases caused by tobacco smoking. Consequently, the chapters of this report largely address mechanisms of disease causation one by one without placing them into categories of necessary, sufficient, or neither.

Description of Evidence on Mechanisms of Disease Production

Because evidence related to mechanisms of diseases caused by smoking is still evolving, this report uses a descriptive approach in reviewing and presenting the evidence. The chapters are based on review of the most relevant studies at the time they were written. A summary is given on the basis of the strength of evidence for each mechanism considered.

As for causal inference in regard to smoking and disease, the finding that a particular mechanism plays a role in the production of disease by smoking has implications. The finding could point to a biomarker indicating that the pathway is active, or it could indicate the possibility of new preventive therapies to obviate the particular pathway.

Scientific Basis of the Report

The statements and conclusions throughout this report are documented by citation of studies published in the scientific literature. For the most part, this report cites peer-reviewed journal articles, including reviews that integrate findings from numerous studies, and books by recognized experts. When a study has been accepted for publication but the publication has not yet been issued, owing to the delay between acceptance and final publication, the study is referred to as "in press." This report also refers, on occasion, to unpublished research such as a presentation at a professional meeting or a personal communication from the researcher. These personal references are to acknowledge experts whose research is in progress.

Development of the Report

This report of the Surgeon General was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, USDHHS. Initial chapters were written by 64 experts selected because of their knowledge of and familiarity with the topics presented here. These contributions are summarized in seven chapters evaluated by more than 30 peer reviewers. The entire manuscript was then sent to more than 20 scientists and other experts, who examined it for scientific integrity. After each review cycle, the drafts were revised by the editors on the basis of the reviewers' comments. Subsequently, the report was reviewed by various institutes and agencies within USDHHS. Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, additional studies or data may have been published.

Throughout this report, genes are represented by their abbreviations in italics. In many cases, proteins and enzymes related to these genes have the same abbreviation, presented in roman type. Definitions, alternative genetic symbols, related proteins and enzymes, and polymorphisms and variant genotypes are listed alphabetically by gene abbreviation in the table at the end of this report, "Definitions and Alternative Nomenclature of Genetic Symbols Used in This Report."

On June 22, 2009, President Barack Obama signed into law legislation granting authority to the U.S. Food and Drug Administration to regulate all tobacco products (Family Smoking Prevention and Tobacco Control Act 2009 [Public Law 111-31]). Terms used in this report reflect terms in the scientific literature and may not meet the definitions under the Tobacco Control Act.

Major Conclusions

The scientific evidence supports the following major conclusions:

1. The evidence on the mechanisms by which smoking causes disease indicates that there is no risk-free level of exposure to tobacco smoke.

2. Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases, through mechanisms that include DNA damage, inflammation, and oxidative stress.

3. Through multiple defined mechanisms, the risk and severity of many adverse health outcomes caused by smoking are directly related to the duration and level of exposure to tobacco smoke.

4. Sustained use and long-term exposures to tobacco smoke are due to the powerfully addicting effects of tobacco products, which are mediated by diverse actions of nicotine and perhaps other compounds, at multiple types of nicotinic receptors in the brain.

5. Low levels of exposure, including exposures to secondhand tobacco smoke, lead to a rapid and sharp increase in endothelial dysfunction and inflammation, which are implicated in acute cardiovascular events and thrombosis.

6. There is insufficient evidence that product modification strategies to lower emissions of specific toxicants in tobacco smoke reduce risk for the major adverse health outcomes.

Chapter Conclusions

Chapter 2. The Changing Cigarette

1. The evidence indicates that changing cigarette designs over the last five decades, including filtered, low-tar, and "light" variations, have not reduced overall disease risk among smokers and may have hindered prevention and cessation efforts.

2. There is insufficient evidence to determine whether novel tobacco products reduce individual and population health risks.

3. The overall health of the public could be harmed if the introduction of novel tobacco products encourages tobacco use among people who would otherwise be unlikely to use a tobacco product or delays cessation among persons who would otherwise quit using tobacco altogether.

Chapter 3. Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm

1. In spite of uncertainties concerning whether particular cigarette smoke constituents are responsible for specific adverse health outcomes, there is broad scientific agreement that several of the major classes of chemicals in the combustion emissions of burned tobacco are toxic and carcinogenic.

2. The design characteristics of cigarettes, including ventilation features, filters, and paper porosity, have a significant influence on the levels of toxic and carcinogenic chemicals in the inhaled smoke.

3. The different types of tobacco lamina (e.g., bright, burley, or oriental) that are combined to produce a specific tobacco blend have a significant influence on the levels of toxic and carcinogenic chemicals in the combustion emissions of burned tobacco.

4. There is no available cigarette machine-smoking method that can be used to accurately predict doses of the chemical constituents of tobacco smoke received when using tobacco products.

5. Tobacco-specific biomarkers (nicotine and its metabolites and the tobacco-specific nitrosamines) have been validated as quantitative measures of exposure to tobacco smoke among smokers of cigarettes of similar design who do not use other tobacco-containing products.
6. Although biomarkers of potential harm exist for most tobacco-related diseases, many are not specific to tobacco and levels are also influenced by diet, occupation, or other lifestyle or environmental factors.

Chapter 4. Nicotine Addiction: Past and Present

1. Nicotine is the key chemical compound that causes and sustains the powerful addicting effects of commercial tobacco products.
2. The powerful addicting effects of commercial tobacco products are mediated by diverse actions of nicotine at multiple types of nicotinic receptors in the brain.
3. Evidence is suggestive that there may be psychosocial, biologic, and genetic determinants associated with different trajectories observed among population subgroups as they move from experimentation to heavy smoking.
4. Inherited genetic variation in genes such as *CYP2A6* contributes to the differing patterns of smoking behavior and smoking cessation.
5. Evidence is consistent that individual differences in smoking histories and severity of withdrawal symptoms are related to successful recovery from nicotine addiction.

Chapter 5. Cancer

1. The doses of cigarette smoke carcinogens resulting from inhalation of tobacco smoke are reflected in levels of these carcinogens or their metabolites in the urine of smokers. Certain biomarkers are associated with exposure to specific cigarette smoke carcinogens, such as urinary metabolites of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and hemoglobin adducts of aromatic amines.
2. The metabolic activation of cigarette smoke carcinogens by cytochrome P-450 enzymes has a direct effect on the formation of DNA adducts.
3. There is consistent evidence that a combination of polymorphisms in the *CYP1A1* and *GSTM1* genes leads to higher DNA adduct levels in smokers and higher relative risks for lung cancer than in those smokers without this genetic profile.
4. Carcinogen exposure and resulting DNA damage observed in smokers results directly in the numerous cytogenetic changes present in lung cancer.
5. Smoking increases the frequency of DNA adducts of cigarette smoke carcinogens such as benzo[*a*]pyrene and tobacco-specific nitrosamines in the lung and other organs.
6. Exposure to cigarette smoke carcinogens leads to DNA damage and subsequent mutations in *TP53* and *KRAS* in lung cancer.
7. There is consistent evidence that smoking leads to the presence of promoter methylation of key tumor suppressor genes such as *P16* in lung cancer and other smoking-caused cancers.
8. There is consistent evidence that smoke constituents such as nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone can activate signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells that would normally die.
9. There is consistent evidence for an inherited susceptibility of lung cancer with some less common genotypes unrelated to a familial clustering of smoking behaviors.
10. Smoking cessation remains the only proven strategy for reducing the pathogenic processes leading to cancer in that the specific contribution of many tobacco carcinogens, alone or in combination, to the development of cancer has not been identified.

Chapter 6. Cardiovascular Diseases

1. There is a nonlinear dose response between exposure to tobacco smoke and cardiovascular risk, with a sharp increase at low levels of exposure (including exposures from secondhand smoke or infrequent cigarette smoking) and a shallower dose-response relationship as the number of cigarettes smoked per day increases.
2. Cigarette smoking leads to endothelial injury and dysfunction in both coronary and peripheral arteries. There is consistent evidence that oxidizing chemicals and nicotine are responsible for endothelial dysfunction.

3. Tobacco smoke exposure leads to an increased risk of thrombosis, a major factor in the pathogenesis of smoking-induced cardiovascular events.
4. Cigarette smoking produces a chronic inflammatory state that contributes to the atherogenic disease processes and elevates levels of biomarkers of inflammation, known powerful predictors of cardiovascular events.
5. Cigarette smoking produces an atherogenic lipid profile, primarily due to an increase in triglycerides and a decrease in high-density lipoprotein cholesterol.
6. Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without coronary heart disease.
7. The use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease produces far less risk than the risk of continued smoking.
8. The evidence to date does not establish that a reduction of cigarette consumption (that is, smoking fewer cigarettes per day) reduces the risks of cardiovascular disease.
9. Cigarette smoking produces insulin resistance and chronic inflammation, which can accelerate macrovascular and microvascular complications, including nephropathy.

Chapter 7. Pulmonary Diseases

1. Oxidative stress from exposure to tobacco smoke has a role in the pathogenetic process leading to chronic obstructive pulmonary disease.
2. Protease-antiprotease imbalance has a role in the pathogenesis of emphysema.
3. Inherited genetic variation in genes such as *SERPINA3* is involved in the pathogenesis of tobacco-caused chronic obstructive pulmonary disease.
4. Smoking cessation remains the only proven strategy for reducing the pathogenetic processes leading to chronic obstructive pulmonary disease.

Chapter 8. Reproductive and Developmental Effects

1. There is consistent evidence that links smoking in men to chromosome changes or DNA damage in sperm (germ cells), affecting male fertility, pregnancy viability, and anomalies in offspring.
2. There is consistent evidence for association of periconceptional smoking to cleft lip with or without cleft palate.
3. There is consistent evidence that increases in follicle-stimulating hormone levels and decreases in estrogen and progesterone are associated with cigarette smoking in women, at least in part due to effects of nicotine on the endocrine system.
4. There is consistent evidence that maternal smoking leads to transient increases in maternal heart rate and blood pressure (primarily diastolic), probably mediated by the release of norepinephrine and epinephrine into the circulatory system.
5. There is consistent evidence that links maternal smoking to interference in the physiological transformation of spiral arteries and thickening of the villous membrane in forming the placenta; placental problems could lead to fetal loss, preterm delivery, or low birth weight.
6. There is consistent evidence of the presence of histopathologic changes in the fetus from maternal smoking, particularly in the lung and brain.
7. There is consistent evidence that suggests smoking leads to immunosuppressive effects, including dysregulation of the inflammatory response, that may lead to miscarriage and preterm delivery.
8. There is consistent evidence that suggests a role for polycyclic aromatic hydrocarbons from tobacco smoke in the adverse effects of maternal smoking on a variety of reproductive and developmental endpoints.
9. There is consistent evidence that tobacco smoke exposure leads to diminished oviductal functioning, which could impair fertilization.
10. There is consistent evidence that links prenatal smoke exposure and genetic variations in metabolizing enzymes such as GSTT1 with increased risk of adverse pregnancy outcomes such as lowered birth weight and reduced gestation.
11. There is consistent evidence that genetic polymorphisms, such as variants in transforming growth factor-alpha, modify the risks of oral clefting in offspring related to maternal smoking.
12. There is consistent evidence that carbon monoxide leads to birth weight deficits and may play a role in neurologic deficits (cognitive and neurobehavioral endpoints) in the offspring of smokers.

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