How Tobacco Smoke Causes Disease

The Biology and Behavioral Basis for Smoking-Attributable Disease

A Report of the Surgeon General

Executive Summary

U.S. Department of Health and Human Services

How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease

A Report of the Surgeon General

Executive Summary

2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office of the Surgeon General
Rockville, MD

Suggested Citation

U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

To download copies of this document from the Web:

Go to http://www.cdc.gov/tobacco

To order single copies of this document:

Call toll free 1-800-CDC-INFO (1-800-232-4636). Information is available in English and Spanish, 24 hours/day, 7 days/week.
For text telephone for hearing impaired, dial 1-888-232-6348.

For more information about this document:

Email tobaccoinfo@cdc.gov.

Copies of the full report (stock no. 017-023-00219-8) may be purchased from:

Superintendent of Documents, U.S. Government Printing Office
Internet: http://bookstore.gpo.gov
Phone: toll free (866) 512-1800; DC area (202) 512-1800
Fax: (202) 512-2104

Message from Kathleen Sebelius

Secretary of Health and Human Services

Tobacco use imposes enormous public health and financial costs on this nation—costs that are completely avoidable. Until we end tobacco use, more people will become addicted, more people will become sick, more families will be devastated by the loss of loved ones, and the nation will continue to incur damaging medical and lost productivity costs. Now is the time to fully implement proven and effective interventions that reduce tobacco-caused death and disease and to help end this public health epidemic once and for all.

Cigarettes are responsible for approximately 443,000 deaths—one in every five deaths—each year in the United States. The chronic diseases caused by tobacco use lead the causes of death and disability in the United States and unnecessarily strain our health care system. The economic burden of cigarette use includes more than $193 billion annually in health care costs and loss of productivity.

We can prevent the staggering toll that tobacco takes on individuals, families, and communities. This new Surgeon General's report focuses on cigarettes and cigarette smoke to provide further evidence on how cigarettes cause addiction and premature death. It identifies better approaches to helping people stop smoking and brings to light new ideas for how to lower the incidence of smoking-caused disease.

Twenty years of successful state efforts show that the more states invest in tobacco control programs, the greater the reductions in smoking, and the longer states maintain such programs, the greater and faster the impact. The largest impacts come when we increase tobacco prices, ban smoking in public places, offer affordable and accessible cessation treatments and services, and combine media campaigns with other initiatives. We have outlined a level of state investment in comprehensive tobacco control and prevention efforts that, if implemented, would result in an estimated five million fewer smokers over the next five years. Hundreds of thousands of premature deaths caused by tobacco use could be prevented, and many fewer of the nations' children would be deprived by premature death of their aunts, uncles, parents, and grandparents. Importantly, in 2009 the U.S. Food and Drug Administration received statutory authority to regulate tobacco products. This has the potential to lead to even greater progress in reducing morbidity and mortality from tobacco use.

Tobacco prevention and control efforts need to be commensurate with the harm caused by tobacco use. Otherwise, tobacco use will remain the largest cause of preventable illness and death in our nation for decades to come. When we help Americans quit tobacco use and prevent our youth from ever starting, we all benefit. Now is the time for comprehensive public health and regulatory approaches to tobacco control. We have the knowledge and tools to largely eliminate tobacco caused disease. If we seize this moment, we will make a difference in all of our communities and in the lives of generations to come.

Foreword

In 1964, the first Surgeon General's report on the effects of smoking on health was released. In the nearly 50 years since, extensive data from thousands of studies have consistently substantiated the devastating effects of smoking on the lives of millions of Americans. Yet today in the United States, tobacco use remains the single largest preventable cause of death and disease for both men and women. Now, this 2010 report of the Surgeon General explains beyond a shadow of a doubt how tobacco smoke causes disease, validates earlier findings, and expands and strengthens the science base. Armed with this irrefutable data, the time has come to mount a full-scale assault on the tobacco epidemic.

More than 1,000 people are killed every day by cigarettes, and one-half of all long-term smokers are killed by smoking-related diseases. A large proportion of these deaths are from early heart attacks, chronic lung diseases, and cancers. For every person who dies from tobacco use, another 20 Americans continue to suffer with at least one serious tobacco-related illness. But the harmful effects of smoking do not end with the smoker. Every year, thousands of nonsmokers die from heart disease and lung cancer, and hundreds of thousands of children suffer from respiratory infections because of exposure to secondhand smoke. There is no risk-free level of exposure to tobacco smoke, and there is no safe tobacco product.

This new Surgeon General's report describes in detail the ways tobacco smoke damages every organ in the body and causes disease and death. We must build on our successes and more effectively educate people about the health risks of tobacco use, prevent youth from ever using tobacco products, expand access to proven cessation treatments and services, and reduce exposure to secondhand smoke. Putting laws and other restrictions in place, including making tobacco products progressively less affordable, will ultimately lead to our goal of a healthier America by reducing the devastating effects of smoking.

The Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and other federal agencies are diligently working toward this goal by implementing and supporting policies and regulations that strengthen our resolve to end the tobacco epidemic. CDC has incorporated the World Health Organization's MPOWER approach into its actions at the local, state, and national levels. MPOWER consists of six key interventions proven to reduce tobacco use that can prevent millions of deaths. CDC, along with federal, state, and local partners, is committed to monitoring the tobacco epidemic and prevention policies; protecting people from secondhand smoke where they live, work, and play; offering quit assistance to current smokers; warning about the dangers of tobacco; enforcing comprehensive restrictions on tobacco advertising, promotion, and sponsorship; and raising taxes and prices on tobacco products.

In 2009, the *Family Smoking Prevention and Tobacco Control Act* was enacted, giving FDA explicit regulatory authority over tobacco products to protect and promote the health of the American public. Among other things, this historic legislation gave the agency the authority to require companies to reveal all of the ingredients in tobacco products—including the amount of nicotine—and to prohibit the sale of tobacco products labeled as "light," "mild," or "low." Further, with this new regulatory mandate, FDA will regulate tobacco advertising and require manufacturers to use more effective warning labels, as well as restrict the access of young people to their products. FDA will also assess and regulate modified risk products, taking into account the impact their availability and marketing has on initiation and cessation of tobacco use.

Reducing the tremendous toll of disease, disability, and death caused by tobacco use in the United States is an urgent need and a shared responsibility. All public health agencies need to partner together to develop common strategies to combat the dangers of smoking and tobacco use and defeat this epidemic for good.

This 2010 Surgeon General's report represents another important step in the developing recognition, both in this nation and around the world, that tobacco use is devastating to public health. Past investments in research and in comprehensive tobacco control programs—combined with the findings presented by this new report—provide the foundation, evidence, and impetus to increase the urgency of our actions to end the epidemic of tobacco use.

Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
and
Administrator
Agency for Toxic Substances and Disease Registry

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration

Preface

from the Surgeon General,
United States Public Health Service

In 1964, the Surgeon General released a landmark report on the dangers of smoking. During the intervening 45 years, 29 Surgeon General's reports have documented the overwhelming and conclusive biologic, epidemiologic, behavioral, and pharmacologic evidence that tobacco use is deadly. Our newest report, How Tobacco Smoke Causes Disease, is a comprehensive, scientific discussion of how mainstream and secondhand smoke exposures damage the human body. Decades of research have enabled scientists to identify the specific mechanisms of smoking-related diseases and to characterize them in great detail. Those biologic processes of cigarette smoke and disease are the focus of this report.

One-third of people who have ever tried smoking become daily smokers. This report investigates how and why smokers become addicted and documents how nicotine compares with heroin and cocaine in its hold on users and its effects on the brain. The way tobacco is grown, mixed, and processed today has made cigarettes more addictive than ever before. Because of this, the majority of smokers who try to quit on their own typically require many attempts. It is imperative that we use this information to prevent initiation, make tobacco products less addictive, and provide access to treatments and services to help smokers quit successfully.

This new report also substantiates the evidence that there is no safe level of exposure to cigarette smoke. When individuals inhale cigarette smoke, either directly or secondhand, they are inhaling more than 7,000 chemicals: hundreds of these are hazardous, and at least 69 are known to cause cancer. The chemicals are rapidly absorbed by cells in the body and produce disease-causing cellular changes. This report explains those changes and identifies the mechanisms by which the major classes of the chemicals in cigarette smoke contribute to specific disease processes. In addition, the report discusses how chemicals in cigarette smoke impair the immune system and cause the kind of cellular damage that leads to cancer and other diseases. Insight is provided as to why smokers are far more likely to suffer from chronic disease than are nonsmokers.

By learning how tobacco smoke causes disease, we learn more about how chemicals harm cells, how genes may make us susceptible, and how tobacco users become addicted to nicotine. The answers to these questions will help us to more effectively prevent tobacco addiction and treat tobacco-caused disease. Understanding the complexity of genetic, biochemical, and other influences discussed in this report offers the promise of reducing the disease burden from tobacco use through earlier detection and better treatment; however, even with all of the science presented here, it currently remains true that the only proven strategies to reduce the risks of tobacco-caused disease are preventing initiation, facilitating cessation, and eliminating exposure to secondhand smoke.

My priority as Surgeon General is the health of the American people. Although we have made great strides in tobacco control, more than 440,000 deaths each year are caused by smoking and exposure to secondhand smoke. The cost to the nation is tremendous: a staggering amount is spent on medical care and lost productivity. But most importantly there is immeasurable cost in human suffering and loss.

In 1964, Surgeon General Luther Terry called for "appropriate remedial actions" to address the adverse effects of smoking. With this report, the devastating effects of smoking have been characterized in great detail and the need for appropriate remedial action is even more apparent. The harmful effects of tobacco smoke do not end with the users of tobacco. There is no safe level of exposure to tobacco smoke. Every inhalation of tobacco smoke exposes our children, our families, and our loved ones to dangerous chemicals that can damage their bodies and result in life-threatening diseases such as cancer and heart disease. And, although not a focus of this report, we know that smokeless tobacco causes cancer and has other adverse health effects. The science is now clear that "appropriate remedial actions" include protecting everyone in the country from having to breathe secondhand smoke; making all tobacco products progressively less affordable; expanding access to proven cessation treatments

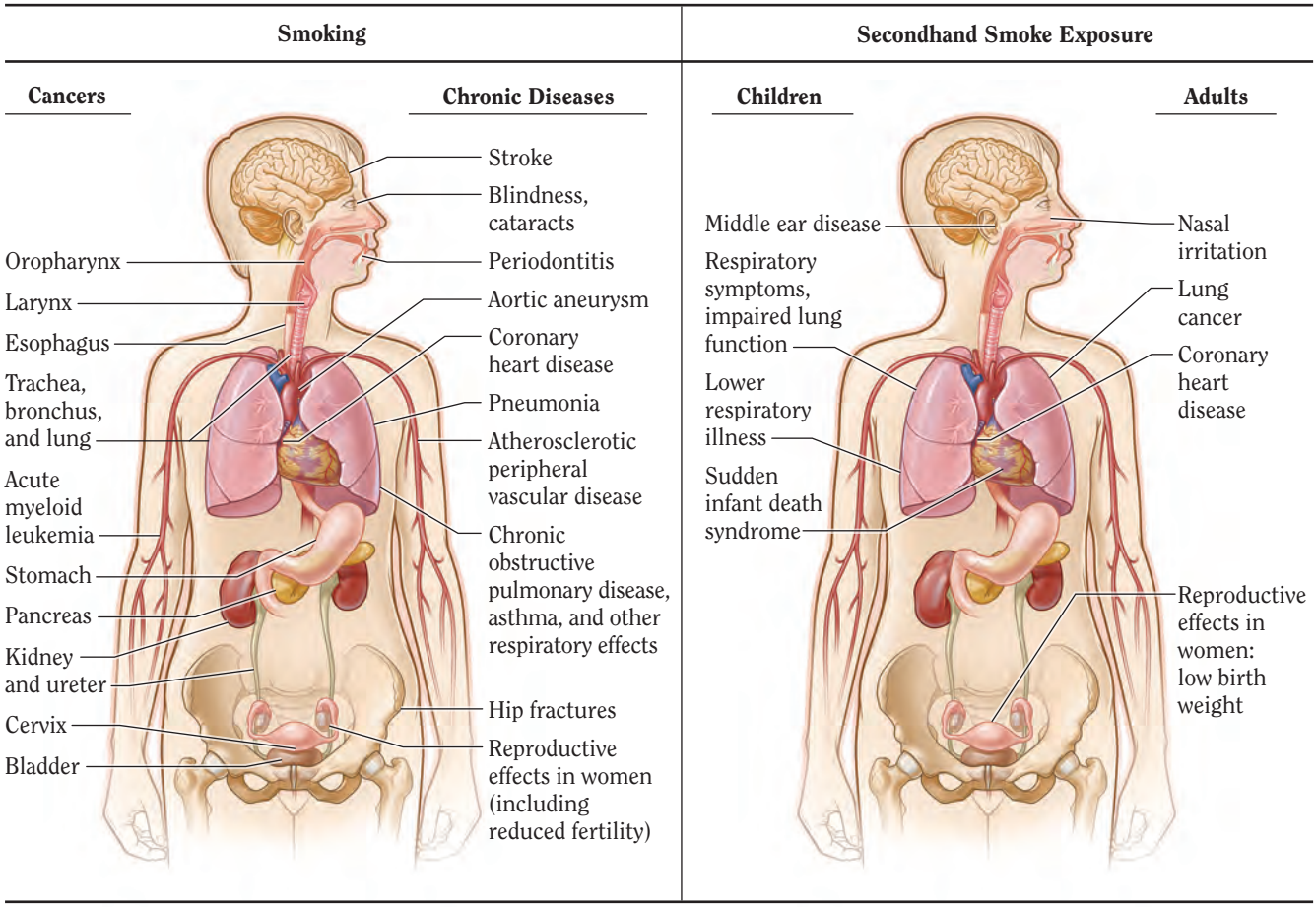
and services; taking actions at the federal, state, and local levels to counteract the influence of tobacco advertising, promotions, and sponsorship; and ensuring that all adults and children clearly understand that the result of tobacco use is addiction, suffering, reduced quality of life, and all too often, early death. Forty-five years after Surgeon General Terry called on this nation to act, I say, if not now, when? The health of our nation depends on it.

Regina Benjamin, MD, MBA
Surgeon General

Tobacco use *remains* the leading preventable cause of premature death in the United States.

For more than 50 years, the irrefutable scientific evidence has grown showing that the use of tobacco products or exposure to tobacco smoke damages the human body with deadly consequences. Predictions based on large population studies indicate that one-half of all long-term smokers, particularly those who began smoking in adolescence, will eventually die from their use of tobacco. In 1964, the Surgeon General released a landmark report that characterized the dangers of smoking as they were then understood (U.S. Department of Health, Education, and Welfare 1964). During the intervening 45 years, 29 Surgeon General's reports have documented the overwhelming and conclusive biologic, epidemiologic, behavioral, and pharmacologic evidence that tobacco use in any form is harmful and can be deadly. The past 29 reports have established a long list of health consequences and diseases caused by tobacco use and exposure to tobacco smoke (Figure 1). Since 1964, this series has considered research findings on mechanisms of disease production in assessing the biologic plausibility of associations observed in epidemiologic studies. This 30th report is a comprehensive and more detailed scientific evaluation of the

Figure 1. The health consequences causally linked to smoking and exposure to secondhand smoke



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

biologic and behavioral mechanisms of how mainstream and secondhand smoke damage the human body. The evidence and conclusions in this report on how tobacco smoke causes disease validates earlier findings, expands and strengthens the science base, and describes in great detail the multiple ways that tobacco smoke damages every organ in the body, resulting in disease and death. However, the focus of this report on the effects of tobacco smoke should not be construed to mean that noncombustible tobacco products are safe.

Evidence Summary

To reduce tobacco-attributable death and disease, public health efforts since the 1964 Surgeon General's report on smoking and health have emphasized the importance of reducing the prevalence of tobacco use. Although progress has been made, approximately one in five high school students and adults in this country continue to smoke regularly. This report provides details about how cigarettes are engineered to deliver nicotine, an addictive drug. The evidence also reviews how other chemical compounds and product design features may increase addiction. The evidence indicates that young people can quickly develop nicotine addiction and that the majority of people who begin to use tobacco products on a regular basis have great difficulty breaking this addiction.

In 2006, the Surgeon General reported that the scientific evidence was sufficient to conclude that there is no risk-free level of exposure to secondhand smoke (U.S. Department of Health and Human Services [USDHHS] 2006). This report provides a more detailed review of the mechanisms that validate that conclusion. A risk-free level of exposure to tobacco smoke (whether mainstream or from secondhand smoke) cannot be defined. A more thorough explanation of the mechanisms that cause damage to nearly every organ in the human body is provided in this report. Each inhalation of the complex mixture of combustion compounds in tobacco smoke leads to transfer of many chemical toxicants from the lungs to the blood stream, which carries them to almost every part of the body. The mechanisms by which these chemical compounds cause damage to the genetic makeup of cells, as well as inflammation of and oxidative stress (injury) to tissues throughout the body, are summarized in this report.

The 2006 Surgeon General's report on the health consequences of involuntary exposure to tobacco smoke concluded that exposure to secondhand smoke has a prothrombotic effect and causes endothelial cell dysfunction (USDHHS 2006). For cardiovascular disease, the immediate effects of even short exposures to secondhand smoke on some functions of the circulatory system appear to be as large as those seen in association with active smoking of one pack of cigarettes per day. This report provides more detailed reviews of mechanisms that can result in a rapid and sharp increase in the biologic response from low levels of exposure. Cigarette smoke and components within the smoke stimulate release or activity of factors that favor the development of thrombosis. Active smoking and involuntary exposure to cigarette smoke injure endothelial cells that line the arteries and impair endothelial function.

Prior Surgeon General's reports have concluded that there are benefits from smoking cessation at all ages (USDHHS 1990). These reports also have documented that the level of exposure, measured both by years of smoking and the amount typically smoked per day, has been found to relate in a clear, though not always linear, dose-response manner to the risks and severity of many of the major health outcomes, such as cancer and cardiovascular and pulmonary diseases. The evidence in this report provides additional details on the mechanisms by which long-term exposure to tobacco smoke damages the body. These findings emphasize the importance of helping smokers quit as early in life as possible.

The currently available evidence is insufficient to determine whether or not novel or modified tobacco products developed to be used in place of conventional cigarettes reduce exposure, individual health risks, or population harm. Evidence reviewed in this report indicates that evolving cigarette design over five decades has not reduced overall disease risk among smokers, and new designs have been used by the tobacco industry as a tool to undermine prevention and cessation efforts.

The scientific evidence reviewed in this report supports six major conclusions.

Major Conclusions of This Report

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 Summaries and Conclusions

Chapter 2: The Changing Cigarette

The evidence reviewed in this report makes clear that substantial risks may be associated with new tobacco products: (1) smokers who might have otherwise stopped smoking may continue to smoke because of perceived reduction in risk with use of new products; (2) former smokers may resume smoking because of perceived reduction in risk with use of new products; and (3) nonsmokers, particularly youth, may start to use new products because of their perceived safety. The theoretical benefit of cigarette design changes is to reduce exposure to toxicants sufficiently to reduce the risk of disease and death. However, if these products are used by persons otherwise unlikely to use a tobacco product, which would undermine efforts to prevent tobacco use, or if the products delay cessation among persons who would otherwise stop using tobacco, the overall health of the population would be harmed. The evidence also indicates that there is a critical need to conduct independent research on the design, composition, and health effects of novel and modified tobacco products. A comprehensive surveillance system to understand consumers' knowledge, attitudes, and behaviors regarding these products is also needed.

Conclusions

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

The evidence reviewed in this report describes the current understanding of the multiple factors involved in

the delivery and uptake of toxic, carcinogenic, and addictive chemicals in cigarette smoke and the mechanisms of toxicity induced by cigarette smoke. Although some uncertainty remains, the available evidence indicates that this uncertainty should not impede efforts to lower concentrations of the major classes of toxic and carcinogenic chemicals in the combustion emissions of burned tobacco. The evidence further indicates that the design characteristics of cigarettes, including the different types of tobacco blends used, have a significant influence on the levels of toxic and carcinogenic chemicals contained in the combustion emissions of burned and inhaled tobacco smoke. Biomarkers 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. Nevertheless, evidence indicates that no available cigarette machine-smoking method can predict doses of the chemical constituents of tobacco smoke any individual smoker will receive from any particular cigarette.

Conclusions

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

The 1988 Surgeon General's report, *The Health Consequences of Nicotine Addiction,* concluded that "nicotine is the drug in tobacco that causes addiction" (USDHHS 1988, p. 9). Typically, smoking initiation occurs during adolescence. Research shows that adolescent smokers report some symptoms of dependence even at low levels of cigarette consumption, and animal studies show that sensitivity to nicotine in adolescents differs from that in adults. The evidence reviewed in this report indicates that initiation and persistence of smoking and nicotine dependence show strong heritability. The powerful addicting effects of commercial tobacco products are mediated by the diverse actions of nicotine at multiple types of nicotinic receptors in the brain. In addition to biologic and genetic factors, evidence supports the substantial role played by psychological and environmental factors in the development and maintenance of nicotine dependence. The evidence is suggestive that such factors could be responsible for the varying patterns of progressing from experimentation to heavy smoking among smokers from population subgroups, as well as differences observed in severity of withdrawal symptoms and successful recovery from nicotine addiction.

Conclusions

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

Components of cigarette smoke individually and in combinaton as a potent carcinogenic mixture bring about key genetic and epigenetic processes that lead to cancer causation, as well as critical cellular pathways that further growth and development of transformed cells. Although some of these steps are now defined in great detail, the specific contribution of many tobacco carcinogens, alone or in combination, to the development of cancer has not been fully identified. Cigarette smoke contains diverse carcinogens, but polycyclic aromatic hydrocarbons, *N*-nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes, and ethylene oxide are among the most important because of their carcinogenic potency and levels in cigarette smoke. Moreover, the major pathways of metabolic activation and detoxification of some of these principal carcinogens in cigarette smoke are well established. Overwhelming evidence indicates that DNA adduct levels are higher in most tissues of smokers than in corresponding tissues of nonsmokers. This observation provides crucial support for the major pathway of cancer induction in smokers that proceeds through DNA adduct formation and genetic damage. Genetic and epigenetic changes lead to cancer through alteration of critical cellular pathways that foster uncontrolled cell growth and defeat of normal mechanisms to restrain their growth and spread. Familial predisposition and genetic polymorphisms may also play a role in the cancer risk of individual smokers.

Conclusions

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

Evidence reviewed on the acute and chronic effects of exposures on the functioning of multiple aspects of the circulatory system provides additional validation that cigarette smoking and involuntary exposure to cigarette smoke are major causes of coronary heart disease, stroke, aortic aneurysm, and peripheral arterial disease. Evidence

in this report provides additional understanding that the risk does not increase in a linear fashion with increasing exposure, and even low levels of exposure to tobacco—such as a few cigarettes per day, occasional smoking, or exposure to secondhand tobacco smoke—are sufficient to substantially increase risk of cardiac events. The constituents of tobacco smoke believed to be responsible for cardiovascular disease include oxidizing chemicals, nicotine, carbon monoxide, and particulate matter. Oxidizing chemicals, including oxides of nitrogen and many free radicals, increase lipid peroxidation and contribute to several potential mechanisms of cardiovascular disease, including inflammation, endothelial dysfunction, oxidation of low-density lipoprotein, and platelet activation. Cigarette smoking produces a chronic inflammatory state that contributes to the atherogenic disease processes and elevates levels of biomarkers of inflammation, known as powerful predictors of cardiovascular events. Cigarette smoking produces insulin resistance and chronic inflammation, which can accelerate microvascular alterations, including nephropathy, and macrovascular complications. Because smoking cessation is associated with marked improvements in the risk of myocardial infarction, sudden death, and stroke, the use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease poses a minimal risk that is far less than the risk of continued smoking.

Conclusions

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

Chronic obstructive pulmonary disease (COPD) is a broad designation that reflects underlying damage and structural changes in the lung's airways and alveoli. Two major mechanisms underlying the causation of COPD by cigarette smoking have been identified: oxidative stress (injury) and protease-antiprotease imbalance. These mechanisms are triggered by the inhalation of combustion products directly into the lungs of active and passive smokers. Although the lung has defense mechanisms that function to check injury by inhaled agents, these defenses are overwhelmed by the sustained inhalation of cigarette smoke. Acceptable doses of inhaled smoke that could be tolerated without resulting in oxidative injury and protease-antiprotease imbalance have not been identified. Cigarette smoke contains massive quantities of free radicals in its gas and tar phases, and the chemical pathways by which these free radicals produce damaging oxidative stress have been well characterized. Available evidence indicates that oxidative stress from exposure to tobacco smoke has a role in the disease processes leading to COPD; however, it is not known if oxidative stress alone is a necessary or sufficient mechanism by itself to cause COPD. Not all smokers develop COPD, and evidence indicates that inherited genetic variation may be involved. Emphysema is a prominent and highly prevalent component of the COPD disease patterns. Protease-antiprotease

imbalance has been shown to increase destructive enzyme activity that reduces the lung's elasticity by damaging its structure and causing emphysema.

Conclusions

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

Health professionals have long considered exposure to tobacco smoke harmful to reproduction, affecting aspects from fertility to fetal and child development and pregnancy outcome. Tobacco smoke contains thousands of compounds, some of which are known toxicants to reproductive health. Carbon monoxide is the toxicant in cigarette smoke that is found in the highest concentrations, and its major effect is to deprive the fetus of oxygen by binding to hemoglobin. Evidence indicates that exposure to carbon monoxide leads to birth weight deficits and may play a role in neurologic deficits (cognitive and neurobehavioral endpoints) in the offspring of smokers. Other components of tobacco smoke—including nicotine, heavy metals such as cadmium, lead, and mercury, and polycyclic aromatic hydrocarbons—have been found to be causally associated with several adverse reproductive outcomes. Exposure to the complex chemical mixture of combustion compounds in tobacco smoke may contribute to reduced fertility and other related reproductive endpoints, including earlier menopause or altered menstrual cycle parameters through similar mechanisms such as alterations in hormone function. In addition, 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. Study findings suggest that the effects of smoking on estrogen and other hormones, which may vary by gender and stage of life, may be due at least in part to effects of nicotine on the endocrine system. Evidence reviewed in prior Surgeon General's reports has suggested that smoking has antiestrogenic effects, but more recent data are less consistent, at least for nonpregnant, premenopausal women. Studies implicate that smoking affects other hormones such as progesterone, gonadotropins, and androgens (including in men).

Conclusions

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.

Chapter 9: A Vision for the Future

An expanded understanding of the health consequences and diseases caused by smoking has been a critical scientific foundation for public health and clinical actions aimed at tobacco use prevention, cessation, and protection of the nonsmoking population from secondhand smoke. Since the publication of the landmark 1964 Surgeon General's report on smoking and health, this series of reports has compiled the incontrovertible body of research evidence documenting the burden of disease and death caused by tobacco use. This report highlights various mechanisms by which tobacco smoke causes disease. The number and diversity of these mechanisms and of the resulting diseases offer yet another body of evidence indicating that tobacco use is an imminent threat to public health that must be stopped, both in this nation and around the globe. Past investments in comprehensive tobacco prevention and control programs, surveillance, and research, combined with the findings presented in this new report, provide the foundation, evidence, and impetus to begin to put the tobacco epidemic behind us forever. For our nation's public health, the time to act decisively and with resolve, to end one of the most deadly epidemics that this nation has ever known, is now.

References

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.

U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. DHHS Publication No. (CDC) 90-8416.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke. A Report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.

U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.