

CHAPTER I

INTRODUCTION, OVERVIEW, SUMMARY, AND CONCLUSIONS

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Introduction

Development and Organization of this Report

This Report was developed by the Office on Smoking and Health, Center for Health Promotion and Education, Centers for Disease Control, Public Health Service of the U.S. Department of Health and Human Services as part of the Department's responsibility, under Public Law 91-222, to report new and current information on smoking and health to the United States Congress.

The scientific content of this Report reflects the contributions of more than 50 scientists representing a wide variety of relevant disciplines. These experts, known for their understanding of and work in specific content areas, prepared manuscripts for incorporation into this Report. The Office on Smoking and Health and its consultants edited and consolidated the individual manuscripts into appropriate chapters. These draft chapters were subjected to an extensive outside peer review (see Acknowledgments for individuals and their affiliations) whereby each chapter was reviewed by up to 11 experts. Based on the comments of these reviewers, the chapters were revised and the entire volume was assembled. This revised edition of the Report was resubjected to review by 20 distinguished scientists inside and outside the Federal Government, both in this country and abroad. Parallel to this review, the entire Report was also submitted for review to 12 institutes and agencies within the U.S. Public Health Service. The comments from the senior scientific reviewers and the agencies were used to prepare the final volume of this Report.

This Report contains a Foreword by the Assistant Secretary for Health, a Preface by the Surgeon General of the U.S. Public Health Service, and the following chapters and appendices:

- Chapter I. Introduction, Overview, Summary, and Conclusions
- Chapter II. Nicotine: Pharmacokinetics, Metabolism, and Pharmacodynamics
- Chapter III. Nicotine: Sites and Mechanisms of Actions
- Chapter IV. Tobacco Use as Drug Dependence
- Chapter V. Tobacco Use Compared to Other Drug Dependencies
- Chapter VI. Effects of Nicotine That May Promote Tobacco Use
- Chapter VII. Treatment of Tobacco Dependence
- Appendix A. Trends in Tobacco Use in the United States
- Appendix B. Toxicity of Nicotine

Overview

This Report of the Surgeon General on tobacco and health focuses on the pharmacologic basis of tobacco addiction. Previous Surgeon General's Reports have reviewed the medical and scientific evidence establishing that cigarette smoking and tobacco use in other forms are deleterious to health. Several reports emphasized particular diseases (e.g., 1982 Report on cancer (US DHHS 1982), 1983 Report on cardiovascular disease (US DHHS 1983a), 1984 Report on chronic obstructive lung disease (US DHHS 1984a)); some reports concentrated on specific populations (e.g., 1980 Report on women (US DHHS 1980)); and some reports dealt with particular aspects of smoking (e.g., 1986 Report on involuntary smoking (US DHHS 1986a)). These reports have been important because so many individuals engage in a behavior that causes morbidity and premature mortality.

The present Report addresses a central issue of the tobacco and health problem: Why do people smoke and in other ways consume tobacco products? Specifically, this Report reviews the pharmacologic basis of the disease-producing and life-threatening behavior of tobacco use. Psychological and social factors are also important influences on tobacco use, but a detailed review of these factors is beyond the scope of this Report. Reviews of this literature include previous reports of the Surgeon General (US DHEW 1979; US DHHS 1980, 1982, 1983a, 1984a), research monographs from the National Institute on Drug Abuse (NIDA) (Jarvik et al. 1977; Krasnegor 1978, 1979a,b,c; Grabowski and Bell 1983), and articles by scientists who study tobacco use and nicotine (Russell 1971, 1976; Gritz 1980; Henningfield 1984).

This Report reviews evidence that tobacco use is addicting and that nicotine is the active pharmacologic agent of tobacco that causes this addictive behavior. Previous Surgeon General's Reports have focused on evidence that cigarette smoking and tobacco use are health hazards. Now that those relationships are well-documented and well-known, this Report addresses addictive properties of cigarette smoking and tobacco use in order to help develop more effective prevention and cessation programs.

This Report topic is particularly timely because of recent advances and extensive data gathered in the 1980s relevant to the issue of tobacco addiction. Since the early 1900s scientific literature and historical anecdotes have provided evidence that tobacco use is a form of drug addiction. In the 1970s, however, research efforts increased considerably on various aspects of tobacco addiction, including nicotine pharmacokinetics, pharmacodynamics, self-administration, withdrawal, dependence, and tolerance. In addition, advances in the neurosciences have begun to reveal effects of nicotine in the brain and body that may help to explain why tobacco use is reinforcing and difficult to give up. These issues are addressed

in this Report. Finally, recent developments in the use of nicotine replacement in smoking cessation emphasize the importance of pharmacologic aspects of cigarette smoking.

Concepts of drug addiction or drug dependence are discussed in detail in Chapters IV and V. It is useful to begin this Report with a brief summary of main points about drug dependence that provide the foundation for the findings of the Report.

The terms “drug addiction” and “drug dependence” are scientifically equivalent: both terms refer to the behavior of repetitively ingesting mood-altering substances by individuals. The term “drug dependence” has been increasingly adopted in the scientific and medical literature as a more technical term, whereas the term “drug addiction” continues to be used by NIDA and other organizations when it is important to provide information at a more general level. Throughout this Report, both terms are used and they are used synonymously.

The main conclusions of the Report are based upon concepts of drug dependence that have been developed by expert committees of the World Health Organization, as well as in publications of NIDA and the American Psychiatric Association. These concepts were used to develop a set of criteria to determine whether tobacco-delivered nicotine is addicting. The criteria for drug dependence include primary and additional indices and are summarized below.

CRITERIA FOR DRUG DEPENDENCE

Primary Criteria

- Highly controlled or compulsive use
- Psychoactive effects
- Drug-reinforced behavior

Additional Criteria

- Addictive behavior often involves:
 - stereotypic patterns of use
 - use despite harmful effects
 - relapse following abstinence
 - recurrent drug cravings
- Dependence-producing drugs often produce:
 - tolerance
 - physical dependence
 - pleasant (euphoriant) effects

The primary criteria listed above are sufficient to define drug dependence. Highly controlled or compulsive use indicates that drug-

seeking and drug-taking behavior is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit. Such behavior is also referred to as “habitual” behavior. To distinguish drug dependence from habitual behaviors not involving drugs, it must be demonstrated that a drug with psychoactive (mood-altering) effects in the brain enters the blood stream. Furthermore, drug dependence is defined by the occurrence of drug-motivated behavior; therefore, the psychoactive chemical must be capable of functioning as a reinforcer that can directly strengthen behavior leading to further drug ingestion.

Additional criteria are often used to help characterize drug dependence. Several are associated with the drug-taking behavior itself: (1) the behavior may develop into regular temporal and physical patterns of use (repetitive and stereotypic); (2) drug use may persist despite adverse physical, psychological, or social consequences; (3) quitting episodes are often followed by resumption of drug use (relapse); (4) urges (cravings) to use the drug may be recurrent and persistent, especially during drug abstinence. Similarly, several common effects of dependence-producing drugs can strengthen their control over behavior and increase the likelihood of harm by contributing to the regularity and overall level of drug intake: (1) diminished responsiveness (tolerance) to the effects of a drug occurs, and may be accompanied by increased intake over time; (2) abstinence-associated withdrawal reactions (due to physical dependence) can motivate further drug intake; (3) effects that are considered pleasant (euphoriant) to the drug user can be provided by the drug itself. Dependence-producing drugs can also produce effects that individuals find useful. For example, many addicting drugs have therapeutic uses in medical treatments of various disorders. Most medically approved drugs that are addicting, however, are generally only available by prescription. Effects of a drug considered by the individual to be useful can promote initiation of drug use, strengthen the addiction, and contribute to relapse following cessation of use.

Tobacco and nicotine are considered in the Report in light of the above criteria. In brief, the organization of the Report is as follows: review of evidence that tobacco use is accompanied by orderly patterns of uptake of nicotine in the body and brain resulting in the development of tolerance (Chapter II); review of how effects of nicotine in the brain and the rest of the body are chemically mediated (Chapter III); review of the evidence that tobacco is addicting and that nicotine is an addicting drug (Chapter IV); comparison of tobacco use with other addictions and of nicotine with other addicting drugs (Chapter V); review of possible effects of nicotine that may promote the use of tobacco and present impediments to quitting smoking (Chapter VI); review of strategies for

helping people to achieve and maintain tobacco abstinence (Chapter VII). In addition, appendices are included that summarize information regarding trends in tobacco use (Appendix A) and information regarding the toxicity of nicotine itself (Appendix B). A summary of the main findings of the Report follows.

Major Conclusions

- 1. Cigarettes and other forms of tobacco are addicting.**
- 2. Nicotine is the drug in tobacco that causes addiction.**
- 3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.**

Brief History Relevant to this Report

Tobacco products have been used for centuries. The tobacco plant was native to the New World. The oldest cited evidence of tobacco use appears on a Mayan stone carving dated from 600 to 900 A.D. There are reports of tobacco smoking in Christopher Columbus' diary in 1492; reports of tobacco smoking appear in the logs of other European explorers of the New World in the 16th century. Since the colonial period, tobacco has been an integral part of the American economy (Robert 1949).

Tobacco use permeated the New World and quickly spread throughout the rest of the world during the 16th and 17th centuries. As use of tobacco products spread, so did controversy over the effects of these products. Throughout history, while some persons extolled the virtues of tobacco (including numerous alleged medicinal uses), others condemned its use. George Washington is attributed with exhorting the home front during the Revolutionary War, "If you can't send money, send tobacco." In contrast, Dr. Benjamin Rush condemned tobacco use in his 1798 book *Essays*. The controversy continued into the 19th century with no convincing scientific or medical evidence to support either position (Robert 1949).

In 1856-57 the British medical journal *Lancet* published opinions of 50 physicians on tobacco use. Many opponents attributed increased crime, nervous paralysis, loss of intellectual abilities, and visual impairment to tobacco use--all of these claims lacked convincing evidence. In restating the main arguments of the tobacco proponents, the *Lancet* editors wrote that tobacco use "...must have some good or at least pleasurable effects; that, if its evil effects were

so dreadful as stated the human race would have ceased to exist” (Lancet 1857).

While the health-promoting and health-damaging effects of tobacco products were being debated throughout the 17th and 18th centuries, scientists were trying to determine the chief active ingredient in tobacco. In the early 1800s the oily essence of tobacco was discovered by Cerioli and by Vauquelin. This active substance was named “Nicotianine,” after Jean Nicot, who sent tobacco seeds from Portugal to the French court at the end of the 16th century. In 1828, Posselt and Reimann at the University of Heidelberg isolated the pure form of Nicotianine and renamed it “Nikotin.” The chemical’s empirical formula, $C_{10}H_{14}N_2$, was determined in the 1840s and “nicotine” was synthesized in the 1890s (Robert 1949).

Since the late 1800s, research on the pharmacologic actions of nicotine has contributed substantially to basic information about the nervous system (Kharkevich 1980; Volle 1980). The classic work by Langley and Dickinson (1889) on nicotine’s effects in autonomic ganglia led to the postulates that chemicals transmit information between neurons and that there are receptors on cells that respond functionally to stimulation by specific chemicals. As early as the 1920s and 1930s, some investigators were concluding that nicotine was responsible for the compulsive use of tobacco products (Armstrong-Jones 1927; Dorsey 1936; Lewin 1931). Johnston (1942) concluded that, “smoking tobacco is essentially a means of administering nicotine, just as smoking opium is a means of administering morphine.”

Throughout the 20th century, research has continued to investigate the role of nicotine in tobacco use. The 1964 Report of the Surgeon General’s Advisory Committee on Smoking and Health (US PHS 1964) held that: “The habitual use of tobacco is related primarily to psychological and social drives, reinforced and perpetuated by the pharmacologic actions of nicotine on the central nervous system. Nicotine-free tobacco or other plant materials do not satisfy the needs of those who acquire the tobacco habit.” The 1964 Report, relying upon a distinction (that is no longer made) between “habituating” and “addicting” drugs, asserted that tobacco was habituating and not addicting. The distinction in 1964 between habituating drugs (including cocaine and amphetamines) and addicting drugs (including opiates and barbiturates) was based on: (1) whether the drug produced clear physical dependence; (2) whether damage was mainly to the individual user (habituating drugs) or to society (addicting drugs); and (3) the strength of the habitual behavior that developed. There was no question at the time of the 1964 Report that nicotine was the critical pharmacologic agent for tobacco use, but its role was then considered to be more similar to cocaine and amphetamines than to opiates and barbiturates. Later

in 1964 the World Health Organization dropped this semantic distinction between habituating and addicting drugs because it was recognized that habitual use could be as strongly developed for cocaine as for morphine, that social damage generally accompanied personal damage, and that behavioral characteristics of drug use could be similar for the so-called habituating and addicting drugs. In an effort to shift the focus to dependent patterns of behavior and away from moral and social issues associated with the term addiction, the term dependence was recommended.

It is now clear that even by the earlier distinction in nomenclature, cigarettes and other forms of tobacco are addicting and actions of nicotine provide the pharmacologic basis of tobacco addiction. The term “dependence producing” may also be used to describe cigarettes and other forms of tobacco use, analogous to actions of other drugs (e.g., opiates, cocaine). Since 1964, considerable additional evidence has been compiled that substantiates these conclusions. The present Report reviews this information and the relevant literature.

Previous Surgeon General’s Reports provided current reviews of the health consequences of cigarette smoking particularly relevant to public health. For example, despite the accumulating evidence, in the early 1960s there was little recognition by the public of the health hazards of smoking. Each Report examined specific information considered to be important for public dissemination. A brief review of topics addressed in these reports provides the background for the present Report.

In the late 1950s, the U.S. Public Health Service, the National Cancer Institute, the National Heart Institute, the American Cancer Society, and the American Heart Association appointed a study group to examine the available evidence on smoking and health. This study group concluded that excessive cigarette smoking is a causative factor in lung cancer.

In 1962, Surgeon General Luther Terry established an advisory committee on smoking and health. This committee released its Report on January 11, 1964, concluding that cigarette smoking is a cause of lung cancer in men and a suspected cause of lung cancer in women, and increased the risk of dying from pulmonary emphysema. The next Report was issued in 1967 (US PHS 1968a) and stated that “the case for cigarette smoking as the principal cause of lung cancer is overwhelming.” Further, the 1967 Report concluded that: “There is an increasing convergence of many types of evidence . . . which strongly suggests that cigarette smoking can cause death from coronary heart disease.” The 1967 Report also concluded that “Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary disease in the United States.”

The 1968 and 1969 Reports (US PHS 1968b, 1969) strengthened the conclusions reached in 1967. The 1971 Report provided a detailed

review of the evidence to date regarding health consequences of smoking (US DHEW 1971). The subsequent reports (1972 to 1976) continued to review the increasing evidence associating cigarette smoking with many health hazards. The 1972 Report also discussed involuntary or passive smoking (US DHEW 1972). The 1973 Report included some data on the health hazards of smoking pipes and cigars (US PHS 1973). The 1975 Report updated information on the health effects of involuntary or passive smoking (US DHEW 1975). The combined 1977-78 Report discussed smoking-related problems unique to women (US DHEW 1978).

At the time of its release, the 1979 Report was the most comprehensive review by a Surgeon General's Report of the health consequences of smoking, smoking behavior, and smoking control. In addition to providing a thorough review of the health consequences of smoking, the 1979 Report discussed the health consequences of using forms of tobacco other than cigarettes (pipes, cigars, and smokeless tobacco). Moreover, the 1979 Report expanded the scope of the previous reports and examined behavioral, pharmacologic, and social factors influencing the initiation, maintenance, and cessation of cigarette smoking. Relevant to the topic of the present Report, the 1979 Report concluded that "it is no exaggeration to say that smoking is the prototypical substance-abuse dependency and that improved knowledge of this process holds great promise for prevention of risk." Since the release of the 1979 Report, each subsequent Report has focused on a specific population or setting (women in 1980 (US DHHS 1980), the workplace in 1985 (US DHHS 1985)), a specific topic (health effects of low-tar and low-nicotine cigarettes in 1981 (US DHHS 1981) involuntary smoking in 1986 (US DHHS 1986a)), or a specific disease (cancer in 1982 (US DHHS 1982), cardiovascular diseases in 1983 (US DHHS 1983a), chronic obstructive lung disease in 1984 (US DHHS 1984a)).

In addition to the previous Surgeon General's Reports, several other developments and publications provide relevant background for the present Report. For example, numerous monographs prepared in the 1970s by the National Institute on Drug Abuse (NIDA) considered tobacco use as a form of drug dependence. In 1980, the American Psychiatric Association, in its Diagnostic and Statistical Manual of Mental Disorders, included tobacco dependence as a substance abuse disorder and tobacco withdrawal as an organic mental disorder (APA 1980). The 1987 revised edition of this manual (APA 1987), in recognition of the role of nicotine, changed "tobacco withdrawal" to "nicotine withdrawal." In 1982, the Director of NIDA testified to Congress that the position of NIDA was that tobacco use could lead to dependence and that nicotine was a prototypic dependence-producing drug. In a 1983 publication, "Why People Smoke Cigarettes," the U.S. Public Health Service supported this

position of NIDA regarding tobacco and nicotine (US DHHS 1983b). In the 1984 NIDA Triennial Report to Congress, nicotine was labeled a prototypic dependence-producing drug and the role of nicotine in tobacco use was considered to be analogous to the roles of morphine, cocaine, and ethanol, in the use of opium, coca-derived products, and alcoholic beverages, respectively (US DHHS 1984b). In 1986, a consensus conference of the National Institutes of Health and the Report of the Advisory Committee to the Surgeon General on the health consequences of using smokeless tobacco concluded that smokeless tobacco can be addicting and that nicotine is a dependence-producing (i.e., addicting) drug (US DHHS 1986b).

The present Report is the 20th such report issued by the Public Health Service on the health consequences of tobacco use. The deleterious effects of cigarette smoking are now well known. Therefore, this Report focuses on pharmacologic information to help understand why people smoke. Such information will assist health professionals in developing effective strategies to prevent initiation and to promote cessation. The literature reviewed in this Report indicates that tobacco use is an addictive behavior. It is the purpose of this Report to thoroughly review the relevant literature.

Chapter Conclusions

In addition to the three overall conclusions of this Report, there are many other substantive conclusions. These points are listed under the appropriate Chapter and Appendix headings.

Chapter II: Nicotine: Pharmacokinetics, Metabolism, and Pharmacodynamics

1. All tobacco products contain substantial amounts of nicotine and other alkaloids. Tobaccos from low-yield and high-yield cigarettes contain similar amounts of nicotine.
2. Nicotine is absorbed readily from tobacco smoke in the lungs and from smokeless tobacco in the mouth or nose. Levels of nicotine in the blood are similar in magnitude in people using different forms of tobacco. With regular use, levels of nicotine accumulate in the body during the day and persist overnight. Thus, daily tobacco users are exposed to the effects of nicotine for 24 hr each day.
3. Nicotine that enters the blood is rapidly distributed to the brain. As a result, effects of nicotine on the central nervous system occur rapidly after a puff of cigarette smoke or after absorption of nicotine from other routes of administration.
4. Acute and chronic tolerance develops to many effects of nicotine. Such tolerance is consistent with reports that initial

use of tobacco products, such as in adolescents first beginning to smoke, is usually accompanied by a number of unpleasant symptoms which disappear following chronic tobacco use.

Chapter III: Nicotine: Sites and Mechanisms of Actions

1. Nicotine is a powerful pharmacologic agent that acts in the brain and throughout the body. Actions include electrocortical activation, skeletal muscle relaxation, and cardiovascular and endocrine effects. The many biochemical and electrocortical effects of nicotine may act in concert to reinforce tobacco use.
2. Nicotine acts on specific binding sites or receptors throughout the nervous system. Nicotine readily crosses the blood-brain barrier and accumulates in the brain shortly after it enters the body. Once in the brain, it interacts with specific receptors and alters brain energy metabolism in a pattern consistent with the distribution of specific binding sites for the drug.
3. Nicotine and smoking exert effects on nearly all components of the endocrine and neuroendocrine systems (including catecholamines, serotonin, corticosteroids, pituitary hormones). Some of these endocrine effects are mediated by actions of nicotine on brain neurotransmitter systems (e.g., hypothalamic-pituitary axis). In addition, nicotine has direct peripherally mediated effects (e.g., on the adrenal medulla and the adrenal cortex).

Chapter IV: Tobacco Use as Drug Dependence

1. Cigarettes and other forms of tobacco are addicting. Patterns of tobacco use are regular and compulsive, and a withdrawal syndrome usually accompanies tobacco abstinence.
2. Nicotine is the drug in tobacco that causes addiction. Specifically, nicotine is psychoactive (“mood altering”) and can provide pleasurable effects. Nicotine can serve as a reinforcer to motivate tobacco-seeking and tobacco-using behavior. Tolerance develops to actions of nicotine such that repeated use results in diminished effects and can be accompanied by increased intake. Nicotine also causes physical dependence characterized by a withdrawal syndrome that usually accompanies nicotine abstinence.
3. The physical characteristics of nicotine delivery systems can affect their toxicity and addictiveness. Therefore, new nicotine delivery systems should be evaluated for their toxic and addictive effects.

Chapter V: Tobacco Use Compared to Other Drug Dependences

1. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.
2. Environmental factors including drug-associated stimuli and social pressure are important influences of initiation, patterns of use, quitting, and relapse to use of opioids, alcohol, nicotine, and other addicting drugs.
3. Many persons dependent upon opioids, alcohol, nicotine, or other drugs are able to give up their drug use outside the context of treatment programs; other persons, however, require the assistance of formal cessation programs to achieve lasting drug abstinence.
4. Relapse to drug use often occurs among persons who have achieved abstinence from opioids, alcohol, nicotine, or other drugs.
5. Behavioral and pharmacologic intervention techniques with demonstrated efficacy are available for the treatment of addiction to opioids, alcohol, nicotine, and other drugs.

Chapter VI: Effects of Nicotine That May Promote Tobacco Dependence

1. After smoking cigarettes or receiving nicotine, smokers perform better on some cognitive tasks (including sustained attention and selective attention) than they do when deprived of cigarettes or nicotine. However, smoking and nicotine do not improve general learning.
2. Stress increases cigarette consumption among smokers. Further, stress has been identified as a risk factor for initiation of smoking in adolescence.
3. In general, cigarette smokers weigh less (approximately 7 lb less on average) than nonsmokers. Many smokers who quit smoking gain weight.
4. Food intake and probably metabolic factors are involved in the inverse relationship between smoking and body weight. There is evidence that nicotine plays an important role in the relationship between smoking and body weight.

Chapter VII: Treatment of Tobacco Dependence

1. Tobacco dependence can be treated successfully.
2. Effective interventions include behavioral approaches alone and behavioral approaches with adjunctive pharmacologic treatment.

3. Behavioral interventions are most effective when they include multiple components (procedures such as aversive smoking, skills training, group support, and self-reward). Inclusion of too many treatment procedures can lead to less successful outcome.
4. Nicotine replacement can reduce tobacco withdrawal symptoms and may enhance the efficacy of behavioral treatment.

Appendix A: Trends in Tobacco Use in the United States

1. An estimated 32.7 percent of men and 28.3 percent of women smoked cigarettes regularly in 1985. The overall prevalence of smoking in the United States decreased from 36.7 percent in 1976 (52.4 million adults) to 30.4 percent in 1985 (51.1 million adults).
2. In 1985, the mean reported number of cigarettes smoked per day was 21.8 for male smokers and 18.1 for female smokers.
3. Smoking is more common in lower socioeconomic categories (blue-collar workers or unemployed persons, less educated persons, and lower income groups) than in higher socioeconomic categories. For example, the prevalence of smoking in 1985 among persons without a high school diploma was 35.4 percent, compared with 16.5 percent among persons with postgraduate college education.
4. An estimated 18.7 percent of high school seniors reported daily use of cigarettes in 1986. The prevalence of daily use of one or more cigarettes among high school seniors declined between 1975 and 1986 by approximately 35 percent. Most of the decline occurred between 1977 and 1981. Since 1976, the smoking prevalence among females has consistently been slightly higher than among males.
5. The use of cigars and pipes has declined 80 percent since 1964.
6. Smokeless tobacco use has increased substantially among young men and has declined among older men since 1975. An estimated 8.2 percent of 17- to 19-year-old men were users of smokeless tobacco products in 1986.

Appendix B: Toxicity of Nicotine

1. At high exposure levels, nicotine is a potent and potentially lethal poison. Human poisonings occur primarily as a result of accidental ingestion or skin contact with nicotine-containing insecticides or, in children, after ingestion of tobacco or tobacco juices.
2. Mild nicotine intoxication occurs in first-time smokers, non-smoking workers who harvest tobacco leaves, and people who

chew excessive amounts of nicotine polacrilex gum. Tolerance to these effects develops rapidly.

3. Nicotine exposure in long-term tobacco users is substantial, affecting many organ systems (Chapters II and III). Pharmacologic actions of nicotine may contribute to the pathogenesis of smoking-related diseases, although direct causation has not yet been determined. Of particular concern are cardiovascular disease, complications of hypertension, reproductive disorders, cancer, and gastrointestinal disorders, including peptic ulcer disease and gastroesophageal reflux.
4. The risks of short-term nicotine replacement therapy as an aid to smoking cessation in healthy people are acceptable and substantially outweighed by the risks of cigarette smoking.

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