

The Health Consequences Of Smoking

NICOTINE ADDICTION

*a report of the
Surgeon General*

1988



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Health Promotion and Education
Office on Smoking and Health
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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON D.C. 20201

MAY 3 1988

The Honorable James Wright
Speaker of the House
of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

I am pleased to transmit to the Congress the 1987 Surgeon General's Report on the health consequences of smoking, as mandated by Section 8(a) of the Public Health Cigarette Smoking Act of 1969. The Act requires the Secretary of Health and Human Services to transmit an annual report to Congress on the health consequences of smoking and such recommendations for legislation as the Secretary may deem appropriate.

This report, entitled The Health Consequences of Smoking: Nicotine Addiction, examines the scientific evidence that cigarettes and other forms of tobacco are addicting. The issue of tobacco addiction has been addressed in previous Surgeon General's Reports and in the medical literature beginning in the early 1900s. Because of the recent expansion of research in this area, a thorough review of this topic is warranted. Despite the significant health risks of tobacco use outlined in previous reports, many smokers have great difficulty in quitting. This report concludes that such difficulty is in large part due to the addicting properties of nicotine, which is present in all forms of tobacco.

The report further concludes that the processes that determine tobacco addiction are similar to those that determine addiction to other drugs such as heroin and cocaine. Through such understanding, health-care providers may be better able to assist tobacco users in quitting.

Private health organizations, health-care providers, community groups, and government agencies should initiate or strengthen programs to inform the public of the addicting nature of tobacco use. A warning label on the addicting nature of tobacco use should be rotated with other health warnings now required on cigarette and smokeless tobacco packages and advertisements. Preventing the initiation of tobacco use must be a priority because of the difficulty in overcoming nicotine addiction once it is firmly established. Because most cases of nicotine addiction begin during childhood and adolescence, school curricula on the prevention of drug use should also include tobacco.

Cigarette smoking, the chief avoidable cause of premature death in this country, is responsible for more than 300,000 premature deaths each year. The disease impact of smoking justifies placing the problem of tobacco use at the top of the public health agenda. The conclusions of this report provide another compelling reason for strengthening our efforts to reduce tobacco use in our society.

Sincerely,

Otis R. Bowen, M.D.
Secretary

Enclosure



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WASHINGTON, D.C. 20201

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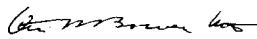
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FOREWORD

This 20th Report of the Surgeon General on the health consequences of tobacco use provides an additional important piece of evidence concerning the serious health risks associated with using tobacco.

The subject of this Report, nicotine addiction, was first mentioned in the 1964 Report of the Advisory Committee to the Surgeon General, which referred to tobacco use as "habituation." In the landmark 1979 Report of the Surgeon General, by which time considerably more research had been conducted, smoking was called "the prototypical substance-abuse dependency." Scientists in the field of drug addiction now agree that nicotine, the principal pharmacologic agent that is common to all forms of tobacco, is a powerfully addicting drug.

Recognizing tobacco use as an addiction is critical both for treating the tobacco user and for understanding why people continue to use tobacco despite the known health risks. Nicotine is a psychoactive drug with actions that reinforce the use of tobacco. Efforts to reduce tobacco use in our society must address all the major influences that encourage continued use, including social, psychological, and pharmacologic factors.

After carefully examining the available evidence, this Report concludes that:

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

We must recognize both the potential for behavioral and pharmacologic treatment of the addicted tobacco user and the problems of withdrawal. Tobacco use is a disorder which can be remedied through medical attention; therefore, it should be approached by health care providers just as other substance-use disorders are approached: with knowledge, understanding, and persistence. Each health care provider should use every available clinical opportunity to encourage or assist smokers to quit and to help former smokers to maintain abstinence.

To maintain momentum toward a smoke-free society, we also must take steps to prevent young people from beginning to smoke. First, we must insure that every child in every school in this country is educated as to the health risks and the addictive nature of tobacco use. Most jurisdictions require that school curricula include prevention of drug use; therefore, education on the prevention of tobacco use should be included in this effort. Second, warning labels regarding the addictive nature of tobacco use should be required for all tobacco packages and advertisements. Young people in particular may not be aware of the risk of tobacco addiction. Finally, parents and other role models should discourage smoking and other forms of tobacco use among young people. Parents who quit set an example for their children.

Smoking continues to be the chief preventable cause of premature death in this country. Nicotine has addictive properties which help to sustain widespread tobacco use. It is gratifying to see the decline in reported smoking prevalence and cigarette consumption in the United States during the past 25 years. However, we cannot expect to see a sustained decline in rates of smoking-related cancers, cardiovascular disease, and pulmonary disease without sustained public health efforts against tobacco use.

The Public Health Service is committed to preventing tobacco use among youth and to promoting cessation among existing smokers. We hope that this Report will assist the health care community, voluntary health agencies, and our Nation's schools in working with us to reduce tobacco use in our society.

Robert E. Windom, M.D.
Assistant Secretary for Health

PREFACE

This Report of the Surgeon General is the U.S. Public Health Service's 20th Report on the health consequences of tobacco use and the 7th issued during my tenure as Surgeon General. Eighteen Reports have been released previously as part of the health consequences of smoking series; a report on the health consequences of using smokeless tobacco was released in 1986.

Previous Reports have reviewed the medical and scientific evidence establishing the health effects of cigarette smoking and other forms of tobacco use. Tens of thousands of studies have documented that smoking causes lung cancer, other cancers, chronic obstructive lung disease, heart disease, complications of pregnancy, and several other adverse health effects.

Epidemiologic studies have shown that cigarette smoking is responsible for more than 300,000 deaths each year in the United States. As I stated in the Preface to the 1982 Surgeon General's Report, smoking is the chief avoidable cause of death in our society.

From 1964 through 1979, each Surgeon General's Report addressed the major health effects of smoking. The 1979 Report provided the most comprehensive review of these effects. Following the 1979 Report, each subsequent Report has focused on specific populations (women in 1980, workers in 1985), specific diseases (cancer in 1982, cardiovascular disease in 1983, chronic obstructive lung disease in 1984), and specific topics (low-tar, low-nicotine cigarettes in 1981, involuntary smoking in 1986).

This Report explores in great detail another specific topic: nicotine addiction. Careful examination of the data makes it clear that cigarettes and other forms of tobacco are addicting. An extensive body of research has shown that nicotine is the drug in tobacco that causes addiction. Moreover, the processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Actions of Nicotine

All tobacco products contain substantial amounts of nicotine. 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. Once in the blood stream, nicotine is rapidly distributed throughout the body.

Nicotine is a powerful pharmacologic agent that acts in a variety of ways at different sites in the body. After reaching the blood stream, nicotine enters the brain, interacts with specific receptors in brain tissue, and initiates metabolic and electrical activity in the brain. In addition, nicotine causes skeletal muscle relaxation and has cardiovascular and endocrine (i.e., hormonal) effects.

Human and animal studies have shown that nicotine is the agent in tobacco that leads to addiction. The diversity and strength of its actions on the body are consistent with its role in causing addiction.

Tobacco Use as an Addiction

Standard definitions of drug addiction have been adopted by various organizations including the World Health Organization and the American Psychiatric Association. Although these definitions are not identical, they have in common several criteria for establishing a drug as addicting.

The central element among all forms of drug addiction is that the user's behavior is largely controlled by a psychoactive substance (i.e., a substance that produces transient alterations in mood that are primarily mediated by effects in the brain). There is often compulsive use of the drug despite damage to the individual or to society, and drug-seeking behavior can take precedence over other important priorities. The drug is "reinforcing"—that is, the pharmacologic activity of the drug is sufficiently rewarding to maintain self-administration. "Tolerance" is another aspect of drug addiction whereby a given dose of a drug produces less effect or increasing doses are required to achieve a specified intensity of response. Physical dependence on the drug can also occur, and is characterized by a withdrawal syndrome that usually accompanies drug abstinence. After cessation of drug use, there is a strong tendency to relapse.

This Report demonstrates in detail that tobacco use and nicotine in particular meet all these criteria. The evidence for these findings is derived from animal studies as well as human observations. Leading national and international organizations, including the World Health Organization and the American Psychiatric Association, have recognized chronic tobacco use as a drug addiction.

Some people may have difficulty in accepting the notion that tobacco is addicting because it is a legal product. The word "addiction" is strongly associated with illegal drugs such as cocaine and heroin. However, as this Report shows, the processes that

determine tobacco addiction are similar to those that determine addiction to other drugs, including illegal drugs.

In addition, some smokers may not believe that tobacco is addicting because of a reluctance to admit that one's behavior is largely controlled by a drug. On the other hand, most smokers admit that they would like to quit but have been unable to do so. Smokers who have repeatedly failed in their attempts to quit probably realize that smoking is more than just a simple habit.

Many smokers have quit on their own ("spontaneous remission") and some smokers smoke only occasionally. However, spontaneous remission and occasional use also occur with the illicit drugs of addiction, and in no way disqualify a drug from being classified as addicting. Most narcotics users, for example, never progress beyond occasional use, and of those who do, approximately 30 percent spontaneously remit. Moreover, it seems plausible that spontaneous remitters are largely those who have either learned to deliver effective treatments to themselves or for whom environmental circumstances have fortuitously changed in such a way as to support drug cessation and abstinence.

Treatment

Like other addictions, tobacco use can be effectively treated. A wide variety of behavioral interventions have been used for many years, including aversion procedures (e.g., satiation, rapid smoking), relaxation training, coping skills training, stimulus control, and nicotine fading. In recognition of the important role that nicotine plays in maintaining tobacco use, nicotine replacement therapy is now available. Nicotine polacrilex gum has been shown in controlled trials to relieve withdrawal symptoms. In addition, some (but not all) studies have shown that nicotine gum, as an adjunct to behavioral interventions, increases smoking abstinence rates. In recent years, multicomponent interventions have been applied successfully to the treatment of tobacco addiction.

Public Health Strategies

The conclusion that cigarettes and other forms of tobacco are addicting has important implications for health professionals, educators, and policy-makers. In treating the tobacco user, health professionals must address the tenacious hold that nicotine has on the body. More effective interventions must be developed to counteract both the psychological and pharmacologic addictions that accompany tobacco use. More research is needed to evaluate how best to treat those with the strongest dependence on the drug. Treatment of tobacco addiction should be more widely available and should be

considered at least as favorably by third-party payors as treatment of alcoholism and illicit drug addiction.

The challenge to health professionals is complicated by the array of new nicotine delivery systems that are being developed and introduced in the marketplace. Some of these products are produced by tobacco manufacturers; others may be marketed as devices to aid in smoking cessation. These new products may be more toxic and more addicting than the products currently on the market. New nicotine delivery systems should be evaluated for their toxic and addictive effects; products intended for use in smoking cessation also should be evaluated for efficacy.

Public information campaigns should be developed to increase community awareness of the addictive nature of tobacco use. A health warning on addiction should be rotated with the other warnings now required on cigarette and smokeless tobacco packages and advertisements. Prevention of tobacco use should be included along with prevention of illicit drug use in comprehensive school health education curricula. Many children and adolescents who are experimenting with cigarettes and other forms of tobacco state that they do not intend to use tobacco in later years. They are unaware of, or underestimate, the strength of tobacco addiction. Because this addiction almost always begins during childhood or adolescence, children need to be warned as early as possible, and repeatedly warned through their teenage years, about the dangers of exposing themselves to nicotine.

This Report shows conclusively that cigarettes and other forms of tobacco are addicting in the same sense as are drugs such as heroin and cocaine. Most adults view illegal drugs with scorn and express disapproval (if not outrage) at their sale and use. This Nation has mobilized enormous resources to wage a war on drugs — illicit drugs. We should also give priority to the one addiction that is killing more than 300,000 Americans each year.

We as citizens, in concert with our elected officials, civic leaders, and public health officers, should establish appropriate public policies for how tobacco products are sold and distributed in our society. With the evidence that tobacco is addicting, is it appropriate for tobacco products to be sold through vending machines, which are easily accessible to children? Is it appropriate for free samples of tobacco products to be sent through the mail or distributed on public property, where verification of age is difficult if not impossible? Should the sale of tobacco be treated less seriously than the sale of alcoholic beverages, for which a specific license is required (and revoked for repeated sales to minors)?

In the face of overwhelming evidence that tobacco is addicting, policy-makers should address these questions without delay. To

achieve our goal of a smoke-free society, we must give this problem
the serious attention it deserves.

C. Everett Koop, M.D., Sc.D.
Surgeon General

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This Report was prepared by the Department of Health and Human Services under the general editorship of the Office on Smoking and Health, Ronald M. Davis, M.D., Director. The Managing Editors were Thomas E. Novotny, M.D., and William R. Lynn, Office on Smoking and Health.

Scientific editors were Neal L. Benowitz, M.D., Professor of Medicine, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, San Francisco General Hospital, University of California, San Francisco, California; Neil E. Grunberg, Ph.D., Department of Medical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Jack E. Henningfield, Ph.D., Chief, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland; and Harry A. Lando, Ph.D., Professor, Department of Psychology, Iowa State University, Ames, Iowa.

The following individuals prepared draft chapters or portions of the Report.

David B. Abrams, Ph.D., Assistant Professor of Psychiatry and Human Behavior, Brown University Program in Medicine, The Miriam Hospital, Center for Health Promotion, Providence, Rhode Island

Timothy B. Baker, Ph.D., Department of Psychology, University of Wisconsin, Madison, Wisconsin

Neal L. Benowitz, M.D., Professor of Medicine, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, San Francisco General Hospital, University of California, San Francisco, California

Thomas H. Brandon, M.S., Department of Psychology, University of Wisconsin, Madison, Wisconsin

Richard F. Catalano, Ph.D., Research Assistant Professor, Center for Social Welfare Research, School of Social Work, University of Washington, Seattle, Washington

Larry D. Chait, Ph.D., Research Associate (Assistant Professor), Department of Psychiatry, University of Chicago, Chicago, Illinois

Paul B.S. Clarke, Ph.D., Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

Richard R. Clayton, Ph.D., Professor, Department of Sociology,
University of Kentucky, Lexington, Kentucky

Allan C. Collins, Ph.D., Institute for Behavioral Genetics, School of
Pharmacy, University of Colorado, Boulder, Colorado

Thomas M. Cooper, D.D.S., Professor, Department of Community
Dentistry, University of Kentucky, Lexington, Kentucky

Lori A. Crane, M.P.H., Division of Cancer Control, Jonsson Comprehensive
Cancer Center, University of California, Los Angeles,
California

Susan Curry, Ph.D., Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, Washington

D. Layten Davis, Ph.D., Director, Tobacco and Health Research Institute, University of Kentucky, Lexington, Kentucky

Ronald M. Davis, M.D., Director, Office on Smoking and Health, Center for Health Promotion and Education, Centers for Disease Control, Rockville, Maryland

Edward F. Domino, M.D., Professor, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan

John L. Egle, Jr., Ph.D., Department of Pharmacology/Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Joan Ershler, Ph.D., Research Associate, Mt. Sinai Medical Center, Milwaukee, Wisconsin

Raymond Fleming, Ph.D., Assistant Professor, University of Wisconsin-Milwaukee, Mt. Sinai Medical Center, Milwaukee, Wisconsin

Kathleen A. Fletcher, Ph.D., M.P.H., Consultant, The University of Texas Health Science Center, Houston, Texas

Paul J. Fudala, Ph.D., Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

C. Gary Gairola, Ph.D., University of Kentucky, Tobacco and Health Research Institute, Lexington, Kentucky

David Gilbert, Ph.D., Department of Psychology, Southern Illinois University, Carbondale, Illinois

Lewayne D. Gilchrist, Ph.D., Research Associate Professor, School of Social Work, University of Washington, Seattle, Washington

Donna M. Goldberg, M.A., Annapolis, Maryland

Steven R. Goldberg, Ph.D., Preclinical Pharmacology Research Branch, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

John Grabowski, Ph.D., Department of Psychiatry and Behavioral Science, The University of Texas Health Science Center, Houston, Texas

Neil E. Grunberg, Ph.D., Department of Medical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland

- Dorothy K. Hatsukami, Ph.D., Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota
- J. David Hawkins, Ph.D., Professor, Center for Social Welfare Research, School of Social Work, University of Washington, Seattle, Washington
- Jack E. Henningfield, Ph.D., Chief, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland.
- Ronald I. Herning, Ph.D., Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland
- Matthew Owen Howard, M.S., M.S.W., Research Assistant, Center for Social Welfare Research, School of Social Work, University of Washington, Seattle, Washington
- John R. Hughes, M.D., Departments of Psychiatry, Psychology, and Family Practice, University of Vermont, Burlington, Vermont
- Edgar T. Iwamoto, Ph.D., Department of Pharmacology, College of Medicine, University of Kentucky, Lexington, Kentucky
- Murray E. Jarvik, M.D., Ph.D., The Neuropsychiatric Institute and Hospital, School of Medicine, University of California, Los Angeles, Veterans' Administration Medical Center, Brentwood Division, Los Angeles, California
- Robert C. Klesges, Ph.D., Associate Professor, Center for Applied Psychological Research, Department of Psychology, Memphis State University, Memphis, Tennessee
- Lynn T. Kozlowski, Ph.D., Head, Behavioral Research on Tobacco Use, Addiction Research Foundation, Professor of Psychology and of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario, Canada
- Howard Leventhal, Ph.D., Professor and Chairman, Department of Psychology, University of Wisconsin, Madison, Wisconsin
- Edythe D. London, Ph.D., Chief, Neuropharmacology Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland
- Scott E. Lukas, Ph.D., Assistant Professor of Psychiatry (Pharmacology), Harvard Medical School, Department of Psychiatry, Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, Massachusetts
- Alfred C. Marcus, Ph.D., Associate Director, Division of Cancer Control, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, California
- Andrew W. Meyers, Ph.D., Professor, Center for Applied Psychological Research, Department of Psychology, Memphis State University, Memphis, Tennessee
- Thomas E. Novotny, M.D., Medical Epidemiologist, Office on Smoking and Health, Center for Health Promotion and Education, Centers for Disease Control, Rockville, Maryland

Carol Tracy Orleans, Ph.D., Senior Investigator, Behavioral Medicine and Director of Smoking Cessation Services, Division of Cancer Control, Fox Chase Cancer Center, Philadelphia, Pennsylvania

John P. Pierce, M.Sc., Ph.D., Chief, Epidemiology Branch, Office on Smoking and Health, Center for Health Promotion and Education, Centers for Disease Control, Rockville, Maryland

Ovide F. Pomerleau, Ph.D., Behavioral Medicine Program, University of Michigan, Department of Psychiatry, Ann Arbor, Michigan

Amelie G. Ramirez, M.P.H., Faculty Associate, The University of Texas Health Science Center, Assistant Professor, Baylor College of Medicine, Houston, Texas

Jed E. Rose, Ph.D., Veterans' Administration Medical Center, Wadsworth and Brentwood Divisions, Los Angeles, California

J.A. Rosecrans, Ph.D., Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

David P.L. Sachs, M.D., Director, Smoking Cessation Research Institute, Palo Alto, California

Mary Anne Salmon, Ph.D., Research Associate, Health Services Research Center, University of North Carolina, Chapel Hill, North Carolina

Nina G. Schneider, Ph.D., Associate Research Psychologist, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Research Psychologist, Psychopharmacology Unit, Veterans' Administration Medical Center, Brentwood Division, Los Angeles, California

V.J. Schoenbach, Ph.D., Associate Professor, Department of Epidemiology, Research Associate, Health Services Research Center, University of North Carolina, Chapel Hill, North Carolina

Saul Shiffman, Ph.D., Associate Professor, Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania

Victor J. Strecher, Ph.D., Research Associate, Health Services Research Center, Assistant Professor, Department of Health Education, University of North Carolina, Chapel Hill, North Carolina

David M. Warburton, Professor, Department of Psychology, University of Reading, Whiteknights, Reading, United Kingdom

Elizabeth A. Wells, Ph.D., Post-Doctoral Fellow, Center for Social Welfare Research, University of Washington, Seattle, Washington

Thomas Ashby Wills, Ph.D., Assistant Professor of Psychology, Assistant Professor of Epidemiology and Social Medicine, Department of Epidemiology and Social Medicine, Ferkauf Graduate School of Psychology and Albert Einstein College of Medicine, Bronx, New York

Phillip P. Woodson, Dr.sc.nat., Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

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Leo G. Aboot, Ph.D., Department of Pharmacology, University of Rochester Medical Center, Rochester, New York

John S. Baer, Ph.D., Department of Psychology, University of Washington, Seattle, Washington

Timothy B. Baker, Ph.D., Department of Psychology, University of Wisconsin, Madison, Wisconsin

Claudia R. Baquet, M.D., M.P.H., Chief, Special Populations Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

Glen Bennett, M.P.H., Field Studies Advisor, Office of Prevention, Education, and Control, National Heart, Lung, and Blood Institute, Bethesda, Maryland

George E. Bigelow, Ph.D., Associate Professor of Behavioral Biology, Director, Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Clarice Brown, M.S., Data Analyst, Office of Prevention, Education, and Control, National Heart, Lung, and Blood Institute, Bethesda, Maryland

David M. Burns, M.D., Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of California Medical Center, San Diego, California

Donald R. Cherek, Ph.D., Department of Psychiatry and Behavioral Sciences, Mental Sciences Institute, The University of Texas Health Science Center, Houston, Texas

Paul B.S. Clarke, Ph.D., Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

Ro Nemeth-Coslett, Ph.D., Psychologist, Prevention Research Branch, Division of Clinical Research, National Institute on Drug Abuse, Rockville, Maryland

Thomas J. Crowley, M.D., University of Colorado Health Sciences Center, Denver, Colorado

Joseph W. Cullen, Ph.D., Deputy Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

K. Michael Cummings, Ph.D., M.P.H., Research Scientist, Department of Cancer Control and Epidemiology, Roswell Park Memorial Institute, Buffalo, New York

Susan Curry, Ph.D., Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, Washington

Vincent T. DeVita, Jr., M.D., Director, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Sir Richard Doll, University of Oxford, Oxford, England

Manning Feinleib, M.D., Dr.P.H., Director, National Center for Health Statistics, Centers for Disease Control, Hyattsville, Maryland

William H. Foege, M.D., Executive Director, The Carter Center of Emory University, Atlanta, Georgia

Richard R. Frecker, M.D., Ph.D., Head, Biomedical Research, Department of Pharmacology, Addiction Research Foundation, Toronto, Ontario, Canada

K.H. Ginzel, Ph.D., Professor, Department of Pharmacology and Interdisciplinary Toxicology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Russell E. Glasgow, Ph.D., Oregon Research Institute, Eugene, Oregon

Nancy P. Gordon, Sc.D., Behavioral Scientist, Division of Research, Kaiser Permanente Medical Group, Oakland, California

Roland R. Griffiths, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Ellen R. Gritz, Ph.D., Director, Division of Cancer Control, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, California

Sharon M. Hall, Ph.D., Professor, Department of Psychiatry, Center for Social and Behavioral Sciences, University of California, San Francisco, California

Louis S. Harris, Ph.D., Senior Science Advisor, National Institute on Drug Abuse, Alcohol, Drug Abuse, and Mental Health Administration, Rockville, Maryland

Ronald I. Herning, Ph.D., Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Dietrich Hoffmann, Ph.D., Associate Director, Naylor Dana Institute, Valhalla, New York

Leo Hollister, M.D., Medical Director, Harris County Psychiatry Center, Houston, Texas

Enid Hunkeler, Senior Investigator, Kaiser Permanente Medical Care Program, Oakland, California

Peyton Jacob III, Ph.D., Division of Clinical Pharmacology, San Francisco General Hospital, University of California, San Francisco, California

Jerome Jaffe, M.D., Director, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Murray E. Jarvik, M.D., Ph.D., The Neuropsychiatric Institute and Hospital, School of Medicine, University of California, Los An-

geles, and Veterans' Administration Medical Center West Los Angeles, Brentwood Division, Los Angeles, California

Martin Jarvis, M.Phil., Senior Lecturer, Addiction Research Unit, Institute of Psychiatry, London, England

Chris-Ellen Johanson, Ph.D., Department of Psychiatry, Pritzker School of Medicine, University of Chicago Drug Abuse Research Center, Chicago, Illinois

Reese T. Jones, Ph.D., Department of Psychiatry, University of California School of Medicine, San Francisco, California

Kenneth J. Kellar, Ph.D., Department of Pharmacology, Georgetown University Medical Center, Washington, D.C.

Lynn T. Kozlowski, Ph.D., Head, Behavioral Research on Tobacco Use, Addiction Research Foundation, Toronto, Ontario, Canada

Richard J. Lamb, Ph.D., Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Charles L. LeMaistre, M.D., President, University of Texas Systems Cancer Center, Houston, Texas

Claude Lenfant, M.D., Director, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

Howard Leventhal, Ph.D., Professor of Psychology, University of Wisconsin, Madison, Wisconsin

Edward Lichtenstein, Ph.D., Oregon Research Institute, Eugene, Oregon

Donald Ian Macdonald, M.D., Administrator, Alcohol, Drug Abuse, and Mental Health Administration, Rockville, Maryland

G. Alan Marlatt, Ph.D., Professor of Psychology, University of Washington, Seattle, Washington

William R. Martin, M.D., Chairman, Department of Pharmacology, University of Kentucky College of Medicine, Lexington, Kentucky

James O. Mason, M.D., Dr.P.H., Director, Centers for Disease Control, Atlanta, Georgia

J. Michael McGinnis, M.D., Deputy Assistant Secretary (Disease Prevention and Health Promotion), Washington, D.C.

A. Thomas McLellan, Ph.D., Substance Abuse Treatment Research Center, Philadelphia Veterans' Administration Medical Center and The University of Pennsylvania, Philadelphia, Pennsylvania

Nancy K. Mello, Ph.D., Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, Massachusetts

Gregory J. Morosco, Ph.D., M.P.H., Smoking Education Program Coordinator, National Heart, Lung, and Blood Institute, Bethesda, Maryland

Joseph P. Mulholland, Ph.D., Bureau of Economics, Federal Trade Commission, Washington, D.C.

Herbert W. Nickens, M.D., M.A., Director, Office of Minority Health, Public Health Service, Washington, D.C.

- Richard Peto, M.A., M.Sc., Imperial Cancer Research Fund, Cancer Studies Unit, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, University of Oxford, Oxford, England
- Roy W. Pickens, Ph.D., Director, Division of Clinical Research, National Institute on Drug Abuse, Rockville, Maryland
- John P. Pierce, M.Sc., Ph.D., Chief, Epidemiology Branch, Office on Smoking and Health, Center for Health Promotion and Education, Centers for Disease Control, Rockville, Maryland
- John M. Pinney, Executive Director, Institute for the Study of Smoking Behavior and Policy, John F. Kennedy School of Government, Harvard University, Cambridge, Massachusetts
- Michael R. Polen, M.A., Research Associate, Division of Research, Kaiser-Permanente Medical Group, Oakland, California
- William Pollin, M.D., Former Director, National Institute on Drug Abuse, Bethesda, Maryland
- David C. Ramsey, M.P.H., Health Educator, Division of Health Education, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, Georgia
- Everett R. Rhoades, M.D., Assistant Surgeon General and Director, Indian Health Service, Rockville, Maryland
- M.A.H. Russell, F.R.C.P., Addiction Research Unit, Institute of Psychiatry, University of London, London, England
- Charles R. Schuster, Ph.D., Director, National Institute on Drug Abuse, Rockville, Maryland
- Burt Sharpe, M.D., Hennepin County Medical Center, Department of Medicine, Minneapolis, Minnesota
- Donald R. Shopland, Public Health Advisor, Smoking, Tobacco, and Cancer Program, National Cancer Institute, Bethesda, Maryland
- Jerome E. Singer, Ph.D., Medical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland
- Maxine L. Stitzer, Ph.D., Associate Professor, Behavioral Biology, The Johns Hopkins School of Medicine, Behavioral Pharmacology Research, Francis Scott Key Medical Center, Baltimore, Maryland
- David N. Sundwall, M.D., Assistant Surgeon General and Administrator, Health Resources and Services Administration, Rockville, Maryland
- Dennis D. Tolsma, M.P.H., Director, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, Georgia
- Frederick L. Trowbridge, M.D., Director, Division of Nutrition, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, Georgia
- Frank J. Voccio, Jr., Ph.D., Acting Chief, Drug Abuse Staff, Center for Drug Evaluation and Research, Food and Drug Administration, Washington, DC
- Ronald W. Wilson, M.A., National Center for Health Statistics, Centers for Disease Control, Hyattsville, Maryland

Roy A. Wise, Ph.D., Department of Psychology, Concordia University, Montreal, Quebec, Canada

Faye Wright, Center for Applied Psychological Research, Department of Psychology, Memphis State University, Memphis, Tennessee

Ernst L. Wynder, M.D., President, American Health Foundation, New York, New York

James B. Wyngaarden, M.D., Director, National Institutes of Health, Bethesda, Maryland

Tomoji Yanagita, M.D., Ph.D., Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan

Frank E. Young, M.D., Commissioner, Food and Drug Administration, Rockville, Maryland

The editors also acknowledge the contributions of the following staff members and others who assisted in the preparation of this Report.

Margaret Anglin, Secretary, Office on Smoking and Health, Rockville, Maryland

Charles Appiah, Project Clerk, Smoking and Health Project, The Circle, Inc., McLean, Virginia

John L. Bagrosky, Associate Director for Program Operations, Office on Smoking and Health, Rockville, Maryland

Sonia Balakirsky, Secretary, Office on Smoking and Health, Rockville, Maryland

Carol Bean, Associate Project Director, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Tamara Blair, Production Coordinator, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Catherine E. Burckhardt, Editorial Assistant, Office on Smoking and Health, Rockville, Maryland

Gayle Christman, Word Processing Specialist, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Carol K. Cummings, Secretary, Office on Smoking and Health, Rockville, Maryland

Stephanie D. DeVoe, Programmer, Information Systems Department, ATLIS Federal Services, Inc., Rockville, Maryland

Michael C. Fiore, M.D., M.P.H., Medical Epidemiologist, Office on Smoking and Health, Rockville, Maryland

David Fry, Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Lynn Funkhauser, Word Processing Specialist, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Mary Gardner, Senior Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Amy Garson, M.P.H. student, Office on Smoking and Health, Rockville, Maryland

Arnetta G. Glover, Secretary, Office on Smoking and Health, Rockville, Maryland

William Groskopf, Library Acquisitions Specialist, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Evridiki Hatziandreu, M.D., M.P.H., Epidemic Intelligence Service Officer, Office on Smoking and Health, Rockville, Maryland

Susan A. Hawk, Ed.M., M.S., Chief, Technical Information Center, Office on Smoking and Health, Rockville, Maryland

Patricia E. Healy, Technical Information Specialist, Office on Smoking and Health, Rockville, Maryland

Terri L. Henry, Clerk-Typist, Office on Smoking and Health, Rockville, Maryland

Timothy K. Hensley, Technical Publications Writer, Office on Smoking and Health, Rockville, Maryland

Shirley K. Hickman, Data Entry Operator, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Robert S. Hutchings, Associate Director for Information and Program Development, Office on Smoking and Health, Rockville, Maryland

Karen Jacob, Senior Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Sheila Jones, Word Processing Specialist, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Rick Keir, Senior Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Julie Kurz, Graphics Specialist, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Diana Lord, Research Assistant, Department of Medical Psychology, Uniformed Services University of the Health Sciences, Bethesda, Maryland

Gerri E. Mast, Secretary, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, Georgia

Judy J. Mast, Secretary, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, Georgia

Dixie McGough, Program Manager, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Paul G. McGovern, Ph.D., Postdoctoral Research Associate, Smoking Research Group, Department of Psychology, Iowa State University, Ames, Iowa

Dan McLaughlin, Editorial Assistant, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Nancy Miltenberger, Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Cathie O'Donnell, Senior Editor, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Ruth C. Palmer, Secretary, Office on Smoking and Health, Rockville, Maryland

Russell D. Peek, Library Acquisitions Specialist, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Mary B. Pfeiffer, M.L.S., Librarian, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Margaret E. Pickerel, Public Information and Publications Specialist, Office on Smoking and Health, Rockville, Maryland

Renate Phillips, Desktop Publishing/Graphic Artist, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Karen Sherman, Production Assistant, Information Management Department, ATLIS Federal Services, Inc., Rockville, Maryland

Linda R. Spiegelman, Administrative Officer, Office on Smoking and Health, Rockville, Maryland

Tamara Shipp, Publications Assistant, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Evelyn L. Swarr, Systems Management Projects Supervisor, Information Systems Department, ATLIS Federal Services, Inc., Rockville, Maryland

Patricia Y. Thomas, Secretary, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Daniel R. Tisch, Project Director, Smoking and Health Project, The Circle, Inc., McLean, Virginia

Louise G. Wiseman, Technical Information Specialist, Office on Smoking and Health, Rockville, Maryland

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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 (Kharkovich 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 "habitivating" 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 Dependencies

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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CHAPTER II

NICOTINE: PHARMACOKINETICS, METABOLISM, AND PHARMACODYNAMICS

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Introduction

Chemicals with behavioral and physiological activity are delivered to tobacco users when they smoke a cigarette or use other tobacco products. Whether these chemicals are absorbed in quantities that are of biological significance and whether such absorption is related to the behavior of the tobacco user are critical issues in understanding their role in addictive tobacco use. The scientific study of the absorption processes, distribution within the body, and elimination from the body of drugs and chemicals is called pharmacokinetics. The study of drug and other chemical actions on the body, over time, is called pharmacodynamics.

Pharmacokinetic and pharmacodynamic studies can be done separately or together. An example of the latter is when a drug is administered and its concentrations in the blood and its behavioral and physiological actions are measured over time. Such studies can reveal relationships among the dose of a drug, levels in the blood, and effects on body functions.

The pharmacokinetics and pharmacodynamics of some tobacco smoke constituents, particularly nicotine and carbon monoxide, have been extensively studied. These studies show an orderly relationship between the use of tobacco and the absorption of nicotine. Similarly, the effects on behavioral and physiological functions, although complex, are orderly and related to the pharmacokinetics of nicotine. These data will be reviewed in this Section. Research shows that nicotine is well absorbed from tobacco; that it is distributed rapidly and in biologically active concentrations to body organs, including the brain; and that nicotine is the major cause of the predominant behavioral effects of tobacco and some of its physiologic consequences.

One effect of nicotine, development of tolerance to its own actions, is similar to that produced by other addicting drugs. Tolerance refers to decreasing responsiveness to a drug or chemical such that larger doses are required to produce the same magnitude of effect. Tolerance to many actions of nicotine occurs in animals and humans. Evidence for tolerance to nicotine and mechanisms of tolerance development will be reviewed in this Chapter (see also Chapter VI).

Although nicotine has long been considered as the primary pharmacologic reason for tobacco use, and the source of a number of the physiological effects of tobacco, thousands of other chemicals are present in tobacco. Most of these are delivered in such small quantities that they appear to have little or no behavioral consequence. However, a few chemicals do appear to have behavioral effects and there is a potential for numerous chemical interactions that conceivably could have behavioral consequences. This Chapter will conclude with an examination of tobacco smoke constituents

other than nicotine that may contribute to behavioral effects of cigarette smoking.

The toxicity of nicotine is discussed in detail in Appendix B.

Nicotine and Other Alkaloids in Various Tobacco Products

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring (Figure 1). Nicotine may exist in two different three-dimensionally structured shapes, called stereoisomers. Tobacco contains only (S)-nicotine (also called l-nicotine), which is the most pharmacologically active form. Tobacco smoke also contains the less potent (R)-nicotine (also called d-nicotine) in quantities up to 10 percent of the total nicotine present (Pool, Godin, Crooks 1985). Presumably some racemization occurs during the combustion process.

The nicotine yield of cigarettes, as determined by standardized smoking machine tests, is available for most brands. However, the amount of nicotine in cigarettes or other tobacco products is not specified by manufacturers. Because tobacco is a plant product, there are differences in the amount of nicotine among and within different types and strains of tobacco, including variations in different parts of the plant, as well as differences related to growing conditions. Table 1 shows concentrations of nicotine and other alkaloids in several different tobacco leaves used in making commercial tobacco products. Within a tobacco plant, leaves harvested from higher stalk positions have higher concentrations of nicotine than from lower stalk positions; ribs and stems of the leaves have the least (Ratkamp, Tso, Hoffmann 1973). Combining different varieties of tobacco and different parts of the plant is a way to change the nicotine concentration of commercial tobacco.

In a study of amounts of nicotine in the tobacco of 15 American cigarette brands of differing machine-determined yields (Benowitz, Hall et al. 1983), tobacco contained on average 1.5 percent nicotine by weight. Nicotine yield of the cigarettes, as defined by Federal Trade Commission smoking machine tests, was correlated inversely with nicotine concentrations in the tobacco. Thus, tobacco of lower-yield cigarettes tended to have higher concentrations of nicotine than did tobacco of higher-yield cigarettes. However, lower-yield cigarettes also contained less tobacco per cigarette, so the total amount of nicotine contained per cigarette, averaging 8.4 mg, was similar in different brands. Thus, low-yield cigarettes are low yield not because of lower concentrations of nicotine in the tobacco, but because they contain less tobacco and have characteristics which remove tar and nicotine by filtration or dilution of smoke with air. Concentrations of nicotine in commercial tobacco products are summarized in Table 2.

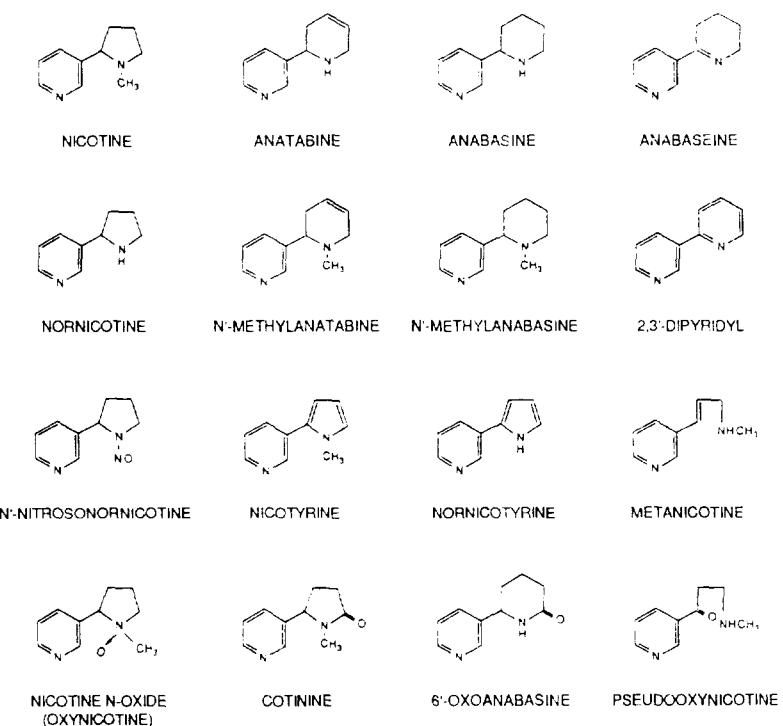


FIGURE 1.—Chemical structures of nicotine and minor tobacco alkaloids

SOURCE: Lete (1983).

Although the major alkaloid in tobacco is nicotine, there are other alkaloids in tobacco which may be of pharmacologic importance. These include nornicotine, anabasine, myosmine, nicotyrine, and anatabine (Figure 1). These substances make up 8 to 12 percent of the total alkaloid content of tobacco products (Table 1) (Piade and Hoffmann 1980). In some varieties of tobacco, nornicotine concentrations exceed those of nicotine (Schmeltz and Hoffmann 1977).

Typical quantities of the minor alkaloids in the smoke of one cigarette are: nornicotine (27 to 88 µg), cotinine (9 to 50 µg), anabasine (3 to 12 µg), anatabine (4 to 14 µg), myosmine (9 µg), and 2,3'-dipyridyl (7 to 27 µg). N'-methylanabasine, nicotyrine, nornicotyrine, and nicotine-N'-oxide have also been identified in cigarette smoke (Schmeltz and Hoffmann 1977). Puffing characteristics, especially puff frequency, influence the delivery of the component alkaloids (Bush, Grünwald, Davis 1972).

TABLE 1.—Alkaloid content of various tobaccos (mg/kg, dry basis)

Alkaloid	Dark commercial tobacco			
	A	B	Burley	Bright
Nicotine	11,500	10,000	15,400	12,900
Nornicotine	550	200	630	210
Anatabine	360	380	570	600
Anabasine	140	150	99	150
Cotinine	195	140	90	40
Myosmine	45	50	60	30
2,3'-Dipyridyl	100	110	30	10
N'-Formyl-nornicotine	175	210	140	40

SOURCE: Piade and Hoffmann (1980).

TABLE 2.—Nicotine content of various tobacco products

Product	Number of brands tested	Concentration of nicotine (mg/g tobacco)	Typical single dose ^a (g tobacco)	Nicotine in single dose ^a (mg)	Nicotine in dose typically consumed in a day
Cigarettes ^b	15	15.7 (13.3-26.9) ^c	0.54	8.4	168 mg/20 cigs
Moist snuff ^d	8	10.5 (6.1-16.6)	1.4	14.5	157 mg/15 g
Chewing tobacco ^e	2	16.8 (9.1-24.5)	7.9	133	1,176 mg/70 g

Single dose refers to a cigarette or an amount of smokeless tobacco placed in the mouth.
Range

SOURCE: ^aBenowitz, Hall et al. (1983); ^bKozlowski et al. (1982); ^cGritz et al. (1981); ^dBenowitz, Porchet et al. (in press).

Nornicotine and anabasine have pharmacologic activity qualitatively similar to that of nicotine, with potencies of 20 to 75 percent compared with that of nicotine, depending on the test system and the animal (Clark, Rand, Vanov 1965). In addition to direct activity, some of the minor alkaloids may influence the effects of nicotine. For example, nicotyrine inhibits the metabolism of nicotine in animals (Stalhandske and Slanina 1982).

The pharmacology of the minor tobacco alkaloids is discussed in more detail in the last section of this Chapter.

Pharmacokinetics and Metabolism of Nicotine

Absorption of Nicotine

Nicotine is distilled from burning tobacco and is carried proximally on tar droplets (mass median diameter 0.3 to 0.5 μm) and probably also in the vapor phase (Eudy et al. 1985), which are inhaled. Absorption of nicotine across biological membranes depends on pH (Armitage and Turner 1970; Schievelbein et al. 1973). Nicotine is a weak base with a pKa (index of ionic dissociation) of 8.0 (aqueous solution, 25°C). This means that at pH 8.0, 50 percent of nicotine is ionized and 50 percent is nonionized. In its ionized state, such as in acidic environments, nicotine does not rapidly cross membranes.

The pH of tobacco smoke is important in determining absorption of nicotine from different sites within the body. The pH of individual puffs of cigarettes made of flue-cured tobacco, the predominant tobacco in most American cigarettes, is acidic and decreases progressively with sequential puffs from pH 6.0 to 5.5 (Brunnemann and Hoffmann 1974). At these pHs, the nicotine is almost completely ionized. As a consequence, there is little buccal absorption of nicotine from cigarette smoke, even when it is held in the mouth (Gori, Benowitz, Lynch 1986). The smoke from air-cured tobaccos, the predominant tobacco in pipes, cigars, and in a few European cigarettes, is alkaline with progressive puffs increasing its pH from 6.5 to 7.5 or higher (Brunneman and Hoffmann 1974). At alkaline pH, nicotine is largely nonionized and readily crosses membranes. Nicotine from products delivering smoke of alkaline pH is well absorbed through the mouth (Armitage et al. 1978; Russell, Raw, Jarvis 1980).

When tobacco smoke reaches the small airways and alveoli of the lung, the nicotine is rapidly absorbed. The rapid absorption of nicotine from cigarette smoke through the lung occurs because of the huge surface area of the alveoli and small airways and because of dissolution of nicotine at physiological pH (approximately 7.4), which facilitates transfer across cell membranes. Concentrations of nicotine in blood rise quickly during cigarette smoking and peak at its completion (Figure 2). Armitage and coworkers (1975), measuring exhalation of radiolabeled nicotine, found that four cigarette smokers absorbed 82 to 92 percent of the nicotine in mainstream smoke, another smoker presumed to be a noninhaler absorbed 29 percent, and three nonsmokers (who were instructed to smoke as deeply as possible) absorbed 30 to 66 percent.

Chewing tobacco, snuff, and nicotine polacrilex gum are of alkaline pH as a result of tobacco selection and/or buffering with additives by the manufacturer. The alkaline pH facilitates absorption of nicotine through mucous membranes. The rate of nicotine absorption from smokeless tobacco depends on the product and the

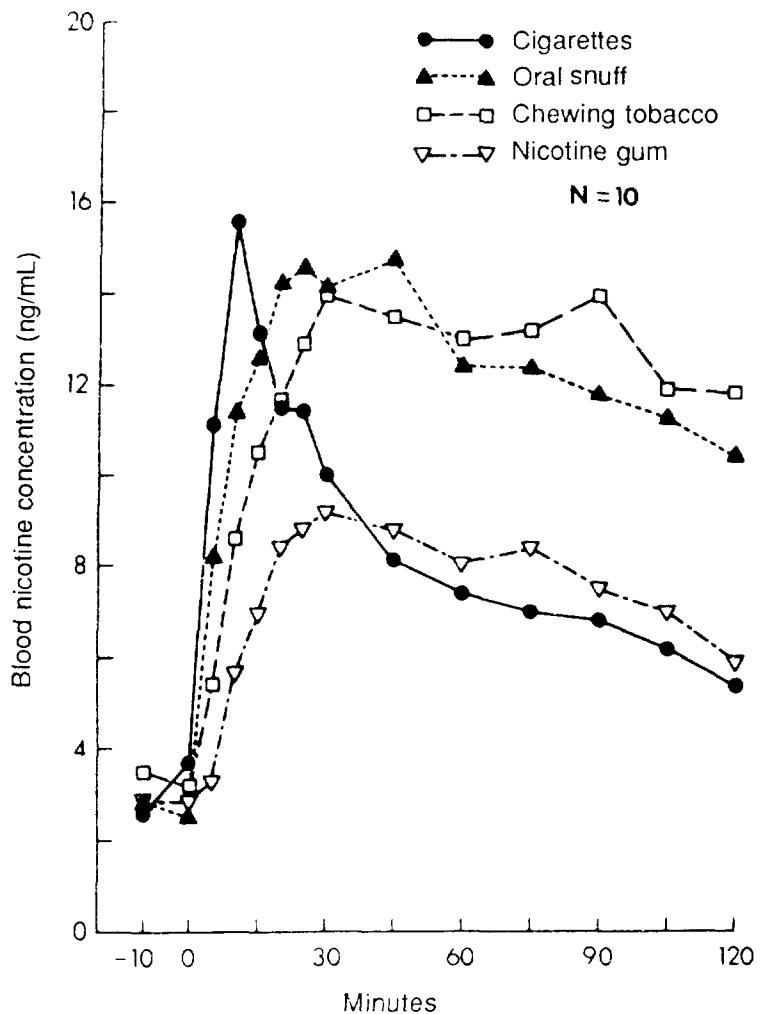


FIGURE 2.—Blood nicotine concentrations during and after smoking cigarettes (1 1/3 cigarettes), using oral snuff (2.5 g), using chewing tobacco (average, 7.9 g), and chewing nicotine gum (two 2-mg pieces)

SOURCE: Benowitz, Porcher et al., 1988.

route of administration. With fine-ground nasal snuff, blood levels of nicotine rise almost as fast as those observed after cigarette smoking

(Russell et al. 1981). The rate of nicotine absorption with the use of oral snuff and chewing tobacco is more gradual. Nicotine is poorly absorbed from the stomach due to the acidity of gastric fluid (Travell 1960), but is well absorbed in the small intestine (Jenner, Gorrod, Beckett 1973), which has a more alkaline pH and a large surface area. Bioavailability of nicotine from the gastrointestinal tract (that is, swallowed nicotine) is incomplete because of presystemic (first pass) metabolism, whereby, after absorption into the portal venous circulation, nicotine is metabolized by the liver before it reaches the systemic venous circulation. This is in contrast to nicotine absorbed through the lungs or oral/nasal mucosa, which reaches the systemic circulation without first passing through the liver. Nicotine base can be absorbed through the skin, and there have been cases of poisoning after skin contact with pesticides containing nicotine (Faulkner 1933; Benowitz, Lake et al. 1987; Saxena and Scheman 1985). Likewise, there is evidence of cutaneous absorption of and toxicity from nicotine in tobacco field workers (Gehlbach et al. 1975).

Because of the complexity of cigarette smoking processes and use of smokeless tobacco products, the dose of nicotine cannot be predicted from the nicotine content of the tobacco or its absorption characteristics. To determine the dose, one needs to measure blood levels and know how fast the individual eliminates nicotine. This topic, estimation of systemic doses of nicotine consumed from various tobacco products, will be considered in a later section after discussion of relevant pharmacokinetic issues.

Distribution of Nicotine in Body Tissues

After absorption into the blood, which is at pH 7.4, about 69 percent of the nicotine is ionized and 31 percent nonionized. Binding to plasma proteins is less than 5 percent (Benowitz, Jacob et al. 1982). The drug is distributed extensively to body tissues with a steady state volume of distribution averaging 180 liters (2.6 times body weight (in kilograms)) (Table 3). This means that when nicotine concentrations have fully equilibrated, the amount of nicotine in the body tissues is 2.6 times the amount predicted by the product of blood concentration and body weight. The pattern of tissue uptake cannot be studied in humans, but it has been examined in tissues of rabbits by measuring concentrations of nicotine in various tissues after infusion of nicotine to steady state (Table 4). Spleen, liver, lungs, and brain have high affinity for nicotine, whereas the affinity of adipose tissue is relatively low.

After rapid intravenous (i.v.) injection, concentrations of nicotine decline rapidly because of tissue uptake of the drug. Shortly after i.v. injection, concentrations in arterial blood, lung, and brain are high, while concentrations in tissues such as muscle and adipose (major storage tissues at steady state) are low. The consequence of this

TABLE 3.—Human pharmacokinetics of nicotine and cotinine

	Nicotine	Cotinine
Half-life	120 min	18 hr
Volume of distribution	180 L	88 L
Total clearance	1,300 mL/min	72 mL/min
Renal clearance	200 mL/min (acid urine)	12 mL/min
Nonrenal clearance	1,100 mL/min	60 mL/min

SOURCE: Average values based on data from Benowitz, Jacob et al. (1982) and Benowitz, Kuyt et al. (1983).

TABLE 4.—Steady state distribution of nicotine

Tissue	Tissue to blood ratio
Blood	1.0
Brain	3.0
Heart	3.7
Muscle	2.0
Adipose	0.5
Kidney	21.6
Liver	3.7
Lung	2.0
Gastrointestinal	3.5

NOTE: Tissue-to-blood nicotine concentration ratios based on 24-hr constant i.v. infusion of nicotine in rabbits.
SOURCE: Benowitz (1986b).

distribution pattern is that uptake into the brain is rapid, occurring within 1 or 2 min, and blood levels fall because of peripheral tissue uptake for 20 or 30 min after administration. Thereafter, blood concentrations decline more slowly, as determined by rates of elimination and rates of distribution out of storage tissues.

Rapid nicotine uptake into the brain has been demonstrated in animal studies. Oldendorf (1974) showed a high degree of nicotine uptake from blood in the first pass through the brains of rats. Schmiederlow and colleagues (1967) showed by autoradiographic techniques that high levels of nicotine were present in the brain 5 min after i.v. injections in mice and that most nicotine had been

cleared from the brain by 30 min. Stalhandske (1970) showed that intravenously injected ^{14}C -nicotine is immediately taken up in the brains of mice, reaching a maximum concentration within 1 min after injection. Similar findings based on positron emission tomography of the brain were seen after injection of ^{11}C -nicotine in monkeys (Mazière et al. 1976).

Nicotine inhaled in tobacco smoke enters the blood almost as rapidly as after rapid i.v. injection except that the entry point into the circulation is pulmonary rather than systemic venous. Because of delivery into the lung, peak nicotine levels may be higher and lag time between smoking and entry into the brain shorter than after i.v. injection. After smoking, the action of nicotine on the brain is expected to occur quickly. Rapid onset of effects after a puff is believed to provide optimal reinforcement for the development of drug dependence. The effect of nicotine declines as it is distributed to other tissues. The distribution half-life, which describes the movement of nicotine from the blood and other rapidly perfused tissues, such as the brain, to other body tissues, is about 9 min (Feyerabend et al. 1985). Distribution kinetics, rather than elimination kinetics (half-life, about 2 hr), determine the time course of central nervous system (CNS) actions of nicotine after smoking a single cigarette.

Nicotine is secreted into saliva (Russell and Feyerabend 1978). Passage of saliva containing nicotine into the stomach, combined with the trapping of nicotine in the acidic gastric fluid and reabsorption from the small bowel, provides a potential route for enteric nicotine recirculation. This recirculation may account for some of the oscillations in the terminal decline phase of nicotine blood levels after i.v. nicotine infusion or cessation of smoking (Russell 1976).

Nicotine freely crosses the placenta and has been found in amniotic fluid and the umbilical cord blood of neonates (Hibberd, O'Connor, Gorrod 1978; Luck et al. 1982; Van Vunakis, Langone, Milunsky 1974). Nicotine is found in breast milk and the breast fluid of nonlactating women (Petrakis et al. 1978; Hill and Wynder 1979) and in cervical mucous secretions (Sasson et al. 1985). Nicotine is also found in the freshly shampooed hair of smokers and of nonsmokers environmentally exposed to tobacco smoke (Haley and Hoffmann 1985).

Elimination of Nicotine

Nicotine is extensively metabolized, primarily in the liver, but also to a small extent in the lung (Turner et al. 1975). Renal excretion of unchanged nicotine depends on urinary pH and urine flow, and may range from 2 to 35 percent, but typically accounts for 5 to 10 percent of total elimination (Benowitz, Kuyt et al. 1983; Rosenberg et al. 1980).

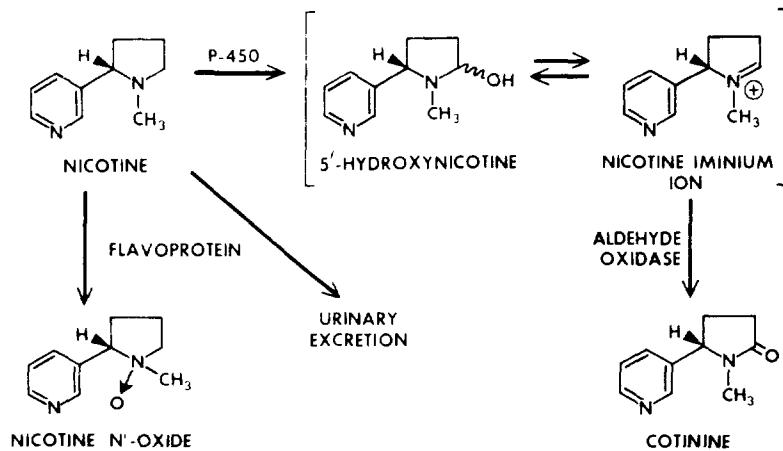


FIGURE 3.—Major pathways of nicotine metabolism

Pathways of Nicotine Metabolism

The primary metabolites of nicotine are cotinine and nicotine-N'-oxide (Figure 3). Cotinine is formed in the liver in a two-step process, the first of which involves oxidation of position 5 of the pyrrolidine ring in a cytochrome P-450-mediated process to nicotine- $\Delta^{1(5)}$ -iminium ion (Peterson, Trevor, Castagnoli 1987). In the second step the iminium ion is metabolized by a cytoplasmic aldehyde oxidase to cotinine (Hibberd and Gorrod 1983).

Cotinine itself is also extensively metabolized, with only about 17 percent excreted unchanged in the urine (Benowitz, Kuyt et al. 1983). Several metabolites of cotinine have been reported, including *trans*-3'-hydroxycotinine (McKennis, Turnbull et al. 1963), 5'-hydroxycotinine (Bowman and McKennis 1962), cotinine-N-oxide (Shulgin et al. 1987), and cotinine methonium ion (McKennis, Turnbull, Bowman 1963) (see Figure 4). Little is known about the quantitative importance of these metabolites. *Trans*-3'-hydroxycotinine appears to be a major metabolite (Jacob, Benowitz, Shulgin 1988; Neurath et al. 1987), with urinary concentrations exceeding cotinine concentrations by twofold to threefold. Cotinine N-oxide is a minor metabolite in humans, accounting for approximately 3 percent of ingested nicotine (Shulgin et al. 1987). Subsequent oxidative degradation of the pyrrolidine ring gives rise to 3-pyridylacetic acid. This compound has been identified in human urine (McKennis, Schwartz, Bowman 1964), but no quantitative data are available.

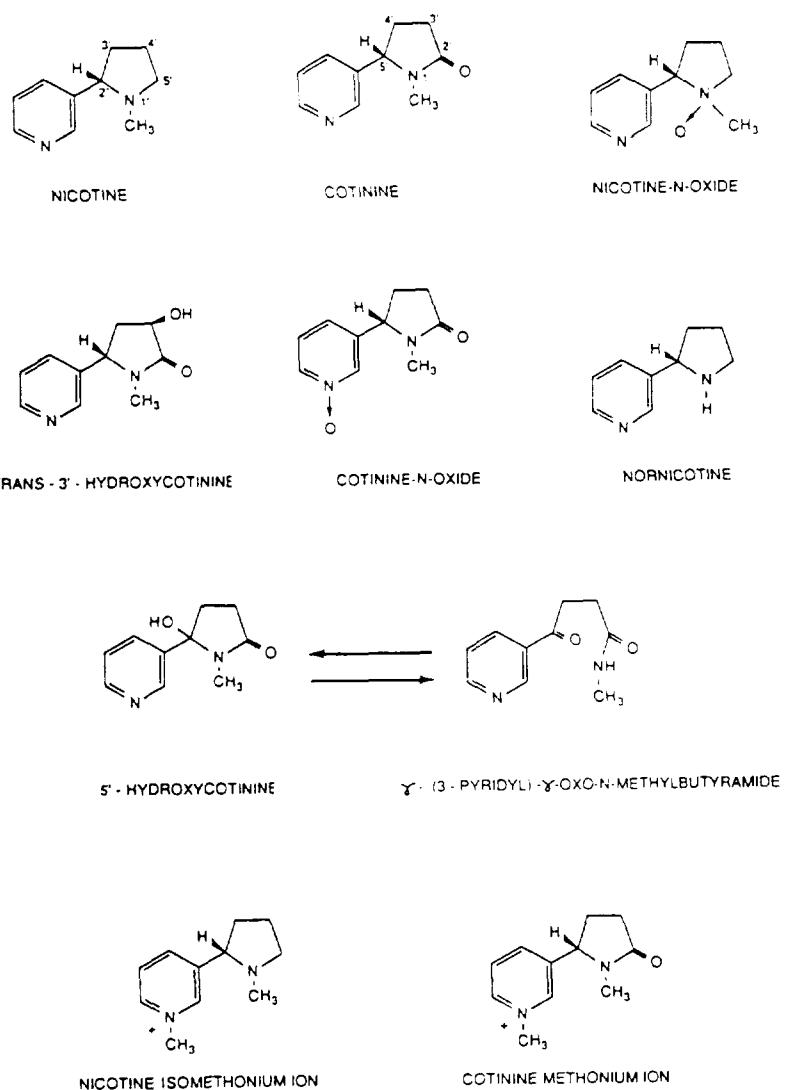


FIGURE 4.—Structures of nicotine and its major metabolites

SOURCE: P. Jacob III (with permission).

Nicotine-1'-N-oxide is quantitatively a minor metabolite of nicotine. Oxidation of the nitrogen atom of the pyrrolidine ring depends on a microsomal flavoprotein system and produces a mixture of the two diasteroisomers, 1'-(R)-2'-(S)-*cis*- and 1'-(S)-2'-(S)-*trans*-nicotine-1'-N-oxide (Booth and Boyland 1970). After i.v. injection, 100 percent of nicotine-N-oxide is excreted unchanged in the urine, indicating no further metabolism (Beckett, Gorrod, Jenner 1971a). However, after oral administration only 30 percent is recovered in the urine as nicotine-N-oxide; the remainder is recovered as nicotine and its metabolites. To evaluate the possibility of reduction of nicotine-N-oxide in the gastrointestinal tract, rectal administration of nicotine-N-oxide was performed for experimental purposes. Less than 10 percent was recovered in the urine as nicotine-N-oxide (Beckett, Gorrod, Jenner 1970). These findings indicate reduction of nicotine-N-oxide back to nicotine within the human gastrointestinal tract, believed to be a consequence of bacterial action.

Experiments in rats indicate that significant amounts of nicotine-N-oxide are converted to nicotine both *in vitro* and *in vivo* (Dajani, Gorrod, Beckett 1975a,b). Nicotine and cotinine have been measured in the blood of rats administered nicotine-N,N-dioxide and nicotine-N-oxide in drinking water (Sepkovic et al. 1984, 1986). Thus, while reduction of nicotine-N-oxide to nicotine appears to be bacterial in humans, it may be mediated by endogenous enzymes in other species.

Quantitative aspects of the conversion of nicotine to its metabolites have not been well defined. Studies of cotinine excretion in urine collected for 24 hr after i.v. nicotine injection indicate less than 10 percent of nicotine is excreted as cotinine in nonsmokers compared with an average of 25 percent in smokers (Beckett, Gorrod, Jenner 1971b). Another study, comparing 24-hr urinary excretion of cotinine with nicotine content of cigarette butts after smoking, indicated 46 percent recovery as cotinine (Schievelbein 1982). However, both of these studies underestimate the conversion of nicotine to cotinine because the urine collection period was too short. In cigarette smokers, cotinine has a half-life averaging 18 to 20 hr (Benowitz, Kuyt et al. 1983), so that in 24 hr only a little more than half of cotinine is recovered. Urine collection for at least 72 hr is necessary to recover more than 90 percent of cotinine in most subjects. In addition, since only 17 percent of cotinine is excreted unchanged (Benowitz, Kuyt et al. 1983), urinary recovery analysis underestimates the cotinine generation rate.

At steady state, the rate of metabolite excretion reflects the rate at which the metabolites are generated. After i.v. dosing, 100 percent of nicotine-N-oxide but only 17 percent of cotinine are excreted unchanged in the urine. Based on a ratio of urinary cotinine to nicotine-N-oxide of 2.9 and based on excretion of that 17 percent of

cotinine and 100 percent of nicotine-N'-oxide unchanged in the urine, the relative generation rate of cotinine compared with that of nicotine-N'-oxide is calculated to be 17 to 1 (Benowitz 1986b). Because 4 percent of nicotine is excreted as nicotine-N'-oxide (Jacob et al. 1986; Beckett, Gorrod, Jenner 1971a), about 70 percent of nicotine appears to be converted to cotinine. Quantitative data on other metabolites that may have pharmacologic activity, such as nicotine isomethonium ion and nornicotine, are not available.

Rate of Nicotine Metabolism

The rate of nicotine metabolism can be determined by measuring blood levels after administration of a known nicotine dose. In one study, cigarette smokers were given i.v. infusions of nicotine for 30 to 60 min, and total and renal clearances were computed (Benowitz, Jacob et al. 1982). Total clearance (a term which describes the capacity to eliminate a drug) averaged 1,300 mL/min. Nonrenal clearance averaged 1,100 mL/min (Table 3), which represents about 70 percent of liver blood flow. Because nicotine is metabolized mainly by the liver (data in animals indicate only a small degree of metabolism by the lung) (Turner, Sillett, McNicol 1977), this means that about 70 percent of the drug is extracted from the blood in each pass through the liver. On the average, 85 or 90 percent of nicotine is metabolized by the liver.

Renal Excretion

Nicotine is excreted by glomerular filtration and tubular secretion within the kidney. Depending on urinary pH and urine flow rate, variable amounts of nicotine are reabsorbed by the kidney tubules. In acidic urine, where nicotine is mostly ionized and tubular reabsorption is minimized, renal clearance of nicotine may be as high as 600 mL/min (urinary pH 4.4) (Benowitz, Kuyt et al. 1983; Rosenberg et al. 1980). In alkaline urine, a larger fraction of nicotine is not ionized. Tubular reabsorption of nonionized nicotine results in lower rate of excretion and reduced renal clearances as low as 17 mL/min (urine pH 7.0). When urine pH is uncontrolled, averaging 5.8, renal clearance averages about 100 mL/min, accounting for the elimination of 10 to 15 percent of the daily nicotine intake.

Nicotine and Cotinine Blood Levels During Tobacco Use

Nicotine Levels

Plasma nicotine concentrations (or concentrations in blood, which are similar) sampled in the afternoon in smokers generally range from 10 to 50 ng/mL. The increment in blood nicotine concentration after smoking a single cigarette ranges from 5 to 30 ng/mL, depending on how the cigarette is smoked (Armitage et al. 1975;

Herning et al. 1983; Isaac and Rand 1972). Peak blood levels of nicotine are similar, although the rate of nicotine increase is slower for cigar smokers and snuff and chewing tobacco users compared with that for cigarette smokers (Armitage et al. 1978; Turner, Sillett, McNicol 1977; Gritz et al. 1981; Russell, Raw, Jarvis 1980; Russell et al. 1981) (Figure 2). Pipe smokers, particularly those who have previously smoked cigarettes and who inhale, may have blood and urine levels of nicotine as high as those of cigarette smokers (McCusker, McNabb, Bone 1982; Turner, Sillett, McNicol 1977; Wald et al. 1984).

The earliest published studies of nicotine elimination kinetics reported half-lives of 20 to 40 min (Armitage et al. 1975; Isaac and Rand 1972). In those studies, drug blood levels were followed only for 30 to 60 min, which is not long enough to determine the elimination half-life. Thus, half-lives were based on blood levels which included the distribution phase. When blood levels are followed for several hours after the end of nicotine infusion, a log-linear decline of blood levels with a half-life of about 2 hr is observed (Benowitz, Jacob et al. 1982; Feyerabend, Ings, Russell 1985).

The half-life of a drug is useful in predicting its accumulation rate in the body with repetitive doses and the time course of its decline after cessation of dosing. Assuming a half-life of 2 hr, one would predict nicotine to accumulate over 6 to 8 hr (3 to 4 half-lives) of regular smoking and persist at significant nicotine levels for 6 to 8 hr after cessation of smoking. If a smoker smokes until bedtime, significant nicotine levels should persist all night. Studies of blood levels in regular cigarette smokers confirm these predictions (Figure 5) (Russell and Feyerabend 1978; Benowitz, Kuyt, Jacob 1982). Peaks and troughs follow the use of each cigarette, but as the day progresses, trough levels rise and the influence of peak levels becomes less important. Thus, nicotine is not a drug to which people are exposed intermittently and that is eliminated rapidly from the body. To the contrary, smoking represents a multiple dosing situation with considerable accumulation during smoking and with persistent levels for 24 hr of each day.

Cotinine Levels

Cotinine levels are of particular interest as qualitative markers of tobacco use and quantitative indicators of nicotine intake. Cotinine is present in the blood of smokers in much higher concentrations than nicotine. Cotinine blood levels average about 250 to 300 ng/mL in groups of cigarette smokers (Benowitz, Hall et al. 1983; Haley, Axelrad, Tilton 1983; Langone, Van Vunakis, Hill 1975; Zeidenberg et al. 1977). After stopping smoking, levels decline with a half-life averaging 18 to 20 hr (range 11 to 37 hr). But because of the long half-life, there is much less fluctuation in cotinine concentrations

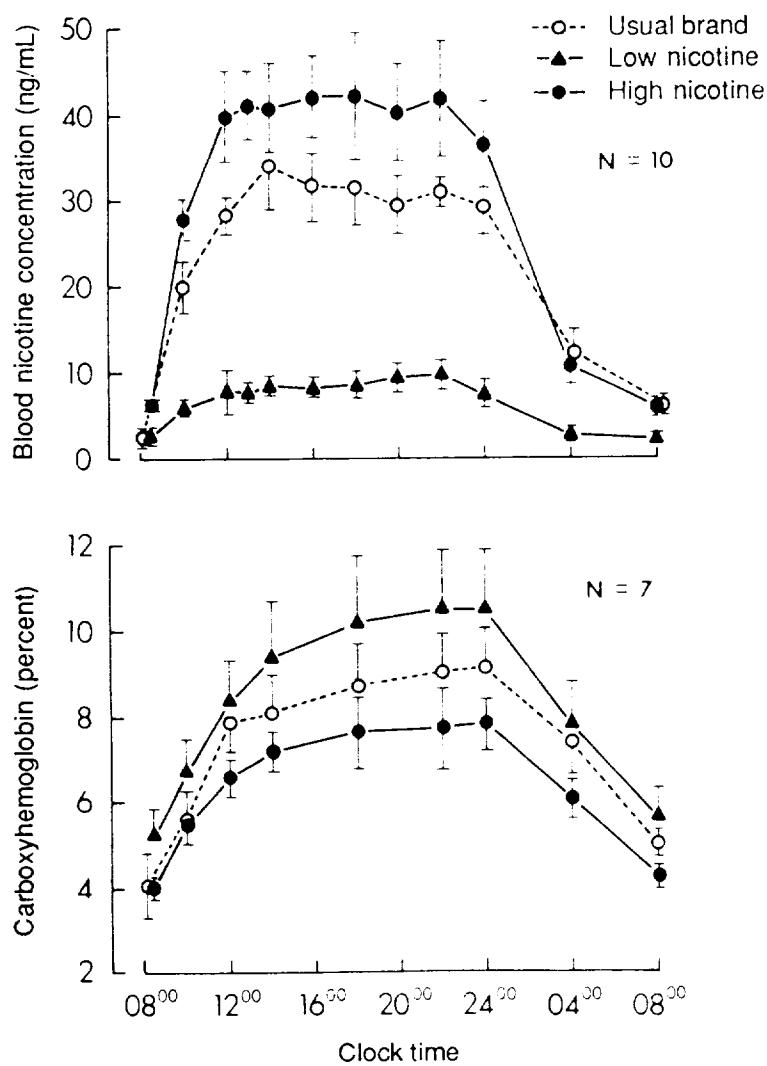


FIGURE 5.—Blood nicotine and carboxyhemoglobin concentrations in subjects smoking high nicotine (2.5 mg) and low nicotine (0.4 mg) Kentucky reference cigarettes and their usual brand (average nicotine yield, 1.2 mg) of cigarettes

NOTE: Subjects smoked on a fixed schedule of 1 cigarette every half hour from 8:30 a.m. to 11:00 p.m., for a total of 30 cigarettes/day; blood samples were collected just before the next scheduled cigarette.

SOURCE: Benowitz, Kuyt, Jacob - 1982.

throughout the day than in nicotine concentrations. As expected, there is a gradual increase in cotinine levels during the day, peaking at the end of smoking and persisting in high concentrations overnight.

Intake of Nicotine

Cigarette Smoking

Nicotine intake from single cigarettes has been measured by spiking cigarettes with ^{14}C -labeled nicotine (Armitage et al. 1975). That study of eight subjects, each smoking a single filter-tipped cigarette, indicated an intake range of 0.36 to 2.62 mg. Intake was higher in smokers than in nonsmokers. Intake of nicotine from smoking a single cigarette or with daily cigarette smoking has been estimated by methods similar to those used in drug bioavailability studies (Benowitz and Jacob 1984; Feyerabend, Ings, Russell 1985). Metabolic clearance of nicotine was determined after i.v. injection. Metabolic clearance data were then used in conjunction with blood and urinary concentrations of nicotine measured during a period of smoking to determine the intake of nicotine. In five subjects, average intake of nicotine per cigarette was 1.06 mg (range, 0.58 to 1.49 mg) (Feyerabend, Ings, Russell 1985). In 22 cigarette smokers, 13 men and 9 women who smoked an average of 36 cigarettes/day (range 20 to 62), the average daily intake was 37.6 mg, with a range from 10.5 to 78.6 mg (Benowitz and Jacob 1984). Nicotine intake per cigarette averaged 1.0 mg (range 0.37 to 1.56 mg). Intake per cigarette did not correlate with yields obtained by smoking machine using standard Federal Trade Commission methods. This is because smoking machines smoke cigarettes in a uniform way, using a fixed puff volume (35 mL), flow rate (over 2 sec), and interval (every minute). Smokers smoke cigarettes differently, changing their puffing behavior to obtain the desired amount of tobacco smoke and nicotine.

Elimination Rate as a Determinant of Nicotine Intake by Cigarette Smoking

There is considerable evidence that smokers adjust their smoking behavior to try to regulate or maintain a particular level of nicotine in the body (Gritz 1980; Russell 1976). For example, when the availability of cigarettes is restricted, habitual smokers can increase intake of nicotine per cigarette 300 percent compared with the intake of unrestricted smoking (Benowitz, Jacob, Koslowski et al. 1986).

Techniques for measuring daily intake of nicotine (Benowitz and Jacob 1984) have been applied to study the influence of elimination on nicotine intake. The rate of renal elimination of nicotine was manipulated by administration of ammonium chloride or sodium

bicarbonate to acidify or alkalinize the urine, respectively (Benowitz and Jacob 1985). Compared with daily excretion during placebo treatment (3.9 mg nicotine/day), acid loading increased (to 12 mg/day) and alkaline loading decreased (to 0.9 mg/day) daily excretion of nicotine. The total intake of nicotine averaged 38 mg/day. Average blood nicotine concentrations were similar in placebo and bicarbonate treatment conditions but were 15 percent lower during ammonium chloride treatment. Daily intake of nicotine was 18 percent higher during acid loading, indicating compensation for increased urinary loss. The compensatory increase in nicotine consumption was only partial, replacing about half of the excess urinary nicotine loss. Bicarbonate treatment had no effect on nicotine consumption, consistent with the small magnitude of effect on excretions of nicotine in comparison to total daily intake.

These results seem compatible with the suggestion of Schachter (1978) that emotional stress, which results in more acidic urine, might accelerate nicotine elimination from the body and thereby increase cigarette smoking. But caution must be exercised in applying these findings to usual smoking situations. These studies were performed under conditions of extreme urinary acidification or alkalinization, so that the changes in renal clearance would be maximized. Even with extreme differences in urinary pH, differences in overall nicotine elimination rate and smoking behavior were modest. This is because renal excretion is a minor pathway for elimination of nicotine; most is metabolized. Smaller changes in urinary pH, such as occur spontaneously throughout the day or that might be related to stressful events, would not be expected to substantially influence nicotine elimination or smoking behavior.

Biochemical Markers of Nicotine Intake

Absorption of nicotine from tobacco smoke provides a means of verification and quantitation of tobacco consumption. The general strategy is to measure concentrations of nicotine, its metabolites (such as cotinine), or other chemicals associated with tobacco smoke in biological fluids such as blood, urine, or saliva. Different measures vary in sensitivity, specificity, and difficulty of analysis. Different investigators have used blood or urinary nicotine concentrations, blood or salivary or urinary cotinine concentrations, expired carbon monoxide or carboxyhemoglobin concentrations, or plasma or salivary thiocyanate (a metabolite of hydrogen cyanide, a vapor phase constituent) concentrations as measures of tobacco smoke consumption.

Relationships among daily intake of nicotine, daily exposure to nicotine (that is, blood concentrations of nicotine integrated over 24 hr), various parameters of cigarette consumption, and different measures of nicotine intake have been examined experimentally

during ad libitum cigarette smoking on a research ward (Benowitz and Jacob 1984). The best biochemical correlate to nicotine intake and exposure in this study was a random blood nicotine concentration measured at 4 p.m. This level did not depend on when the last cigarette was smoked. This finding is consistent with the observation that nicotine levels accumulate throughout the day and plateau in the early afternoon (see Figure 5). At steady state, with regular smoking throughout the day, there should be a reasonably good correlation between nicotine concentrations and daily intake. Carboxyhemoglobin (COHb) concentrations in the afternoon were the next best markers of nicotine intake. Also, morning (8 a.m.) levels of nicotine and COHb correlated with intake, presumably reflecting persistence of nicotine and COHb in the blood from exposure on the previous day.

Although cotinine is a highly specific marker for nicotine exposure, blood levels of cotinine across subjects in this study did not correlate as closely with nicotine intake as did blood levels of nicotine or COHb (Benowitz and Jacob 1984). This is probably due to individual variability in fractional conversion of nicotine to cotinine and in the elimination rate of cotinine itself.

Because of its relatively long half-life, cotinine levels are less sensitive than nicotine levels to smoking pattern, that is, when the last cigarette was smoked. For longitudinal within-subject studies, the cotinine level would be expected to be a good marker of changes in nicotine intake. Cotinine measurements have become the most widely accepted method for assessing the intake of nicotine in long-term studies of tobacco use (see also Chapter V).

As expected by the known variation in renal clearance due to effects of urinary flow and pH, urinary concentrations of nicotine did not correlate well with nicotine intake (Benowitz and Jacob 1984). In contrast, urinary cotinine, which is less influenced by urinary flow or pH, was as good a marker as blood cotinine concentration. Salivary and urinary cotinine concentrations correlate well ($r=0.8$ to 0.9) with blood cotinine concentrations (Haley, Axelrad, Tilton 1983; Jarvis et al. 1984). Therefore, salivary or urine cotinine concentrations should be almost as useful as blood levels in indicating nicotine intake.

Analytical Methods for Measuring Nicotine and Cotinine in Biological Fluids

Determination of nicotine concentrations in biological fluids requires a sensitive and specific method, because concentrations of nicotine in smokers' blood are generally in the low nanogram per milliliter range and a number of metabolites are also present. Cotinine concentrations in blood are generally about tenfold greater than nicotine concentrations, and as a result, less sensitive analyti-

cal methodology may be acceptable. Methods with adequate sensitivity for determination of nicotine and cotinine in smokers' blood include gas chromatography (GC) (Curvall, Kazemi-Vala, Enzell 1982; Davis 1986; Feyerabend, Levitt, Russell 1975; Hengen and Hengen 1978; Jacob, Wilson, Benowitz 1981; Vereby, DePace, Mulé 1982), radioimmunoassay (RIA) (Langone, Gjika, Van Vunakis 1973; Castro et al. 1979; Knight et al. 1985), enzyme-linked immunosorbent assay (ELISA) (Bjercke et al. 1986), high performance liquid chromatography (HPLC) (Machacek and Jiang 1986; Chien, Diana, Crooks, in press), and combined gas chromatograph-mass spectrometry (GC-MS) (Dow and Hall 1978; Gruenke et al. 1979; Jones et al. 1982; Daenens et al. 1985). For reasons of sensitivity, specificity, and economy, GC and RIA are the most frequently used methods. GC-MS is a highly sensitive and specific technique, but the expense has discouraged its routine use. HPLC is less sensitive than GC for nicotine and cotinine determination. Although recently reported methods (Machacek and Jiang 1986; Chien, Diana, Crooks, in press) appear to have adequate sensitivity for determining concentrations in plasma, relatively large sample volumes are required. Concentrations of nicotine and cotinine in urine are tenfold to hundredfold greater than concentrations in plasma or saliva (Jarvis et al. 1984), and a variety of chromatographic and immunoassay techniques meet sensitivity requirements.

The choice of a particular method depends on the biological fluid to be assayed; the need for sensitivity, precision, and accuracy; and economic considerations. Chromatographic methods, particularly those utilizing high-resolution capillary columns and specific detectors such as nitrogen-phosphorus detectors or a mass spectrometer, provide the greatest specificity. On the other hand, immunoassay techniques are operationally simpler, generally require smaller samples, and may be less expensive than chromatographic methods. A drawback to immunoassay methods is the potential for cross-reactivity of the antibody with metabolites or endogenous substances. There is generally a good correlation between results obtained by GC and RIA for plasma cotinine concentrations ($r=0.94$) (Gritz et al. 1981; Biber et al. 1987). In an interlaboratory comparison study (Biber et al. 1987), cotinine concentrations in smokers' urine measured by RIA were generally higher than concentrations determined by GC, whereas in nonsmokers' urine spiked with cotinine RIA and GC values were similar. These results suggest that nicotine metabolites cross-react with the antibody against cotinine, at least in some of the RIA methods.

Pharmacodynamics of Nicotine

General Considerations

This Section will focus on the relationship between nicotine levels in the body and their effects on behavior and physiological function

(pharmacodynamics). These data show how pharmacodynamic factors determine some of the consequences of cigarette smoking. Two issues are particularly relevant in understanding the pharmacodynamics of nicotine: a complex dose-response relationship and the level of tolerance that is either preexisting or is produced by administration of nicotine.

Dose-Response

The relationship between the dose of nicotine and the resulting response (dose-response relationship) is complex and varies with the specific response that is measured. In pharmacology textbooks, nicotine is commonly mentioned as an example of a drug which in low doses causes ganglionic stimulation and in high doses causes ganglionic blockade following brief stimulation (Comroe 1960). This type of effect pattern is referred to as "biphasic." Dose-response characteristics in functioning organisms (*in vivo*) are often biphasic as well, although the mechanisms are far more complex. For example, at very low doses, similar to those seen during cigarette smoking, cardiovascular effects appear to be mediated by the CNS, either through activation of chemoreceptor afferent pathways or by direct effects on the brain stem (Comroe 1960; Su 1982). The net result is sympathetic neural discharge with an increase in blood pressure and heart rate. At higher doses, nicotine may act directly on the peripheral nervous system, producing ganglionic stimulation and the release of adrenal catecholamines. With high doses or rapid administration, nicotine produces hypotension and slowing of heart rate, mediated either by peripheral vagal activation or by direct central depressor effects (Ingenito, Barrett, Procita 1972; Porsius and Van Zwieten 1978; Henningfield, Miyasato, Jasinski 1985).

Tolerance

A second pharmacologic issue of importance is development of tolerance; that is, after repeated doses, a given dose of a drug produces less effect or increasing doses are required to achieve a specified intensity of response. Functional or pharmacodynamic tolerance can be further defined as where a particular drug concentration at a receptor site (in humans approximated by the concentration in blood) produces less effect than it did after a prior exposure. Dispositional or pharmacokinetic tolerance refers to accelerated drug elimination as a mechanism for diminished effect after repeated doses of a drug. Behavioral tolerance refers to compensatory behaviors that reduce the impact of a drug to adversely affect performance. Such tolerance can occur following intermittent exposures to a drug such that there is minimal development of functional or dispositional tolerance.

Most studies of drug tolerance have focused on tolerance which develops as a drug is chronically administered. If the tolerance develops within one or two doses, it is referred to as acute tolerance or tachyphylaxis. If tolerance develops after more prolonged use, the tolerance is referred to as acquired or chronic tolerance. Individual differences in sensitivity to the first dose of a drug also frequently exist. Those individuals who exhibit a reduced response to a specified drug dose or require a greater dose to elicit a specified level of response are said to be tolerant to the drug. This form of tolerance is referred to as first-dose tolerance, drug sensitivity, or innate drug responsiveness. For sake of clarity, this Report will reserve the term tolerance to describe reduction in the response to nicotine during the course of or following a previous exposure and will use acute drug sensitivity to describe responsiveness to an initial dose.

Studies of tolerance to nicotine began in the late 19th century. In a series of studies of fundamental importance to the understanding of the nervous system, as well as to understanding the pharmacology of nicotine, Langley (1905) and Dixon and Lee (1912) studied the effects of repeated nicotine administration on a variety of animal species and on *in vitro* tissue preparations. Several findings emerged which have been widely verified and extended to other species and responses. These include: (1) With repeated dosing, responses diminished to nearly negligible levels; (2) After tolerance occurred, responsiveness could be restored by increasing the size of the dose; (3) After a few hours without nicotine, responsiveness was partially or fully restored.

After smoking a cigarette, people who have not smoked before ("naive smokers") usually experience a number of effects that become generally uncommon among experienced smokers. For example, retrospective reports by smokers indicate that initial exposure to tobacco smoke produced dizziness, nausea, vomiting, headaches, and dysphoria, effects that disappear with continued smoking and are rarely reported by chronic smokers (Russell 1976; Gritz 1980). Tolerance may also develop to toxic effects, such as nausea, vomiting, and pallor, during the course of nicotine poisoning, despite persistence of nicotine in the blood in extremely high concentrations (200 to 300 ng/mL) (Benowitz, Lake et al. 1987).

A systematic analysis of the various forms of tobacco smoke tolerance has not been carried out. There are a few studies comparing the effects elicited by an acute exposure to tobacco in nonsmokers and smokers. Clark and Rand (1968) studied the effect of smoking cigarettes of varying nicotine content on the knee-jerk reflex and reported that high-nicotine cigarettes suppressed this reflex to a greater degree than did low-nicotine cigarettes. This effect was more pronounced at each nicotine dose in nonsmokers and light smokers compared to heavy smokers. These findings suggested that

tolerance is due to altered sensitivity to nicotine. Tolerance to nicotine is not complete because even the heaviest smokers experience symptoms such as dizziness, nausea, and dysphoria when they suddenly increase their smoking rates (Danaher 1977). Evidence indicates that the majority of the psychological actions of tobacco smoke result from nicotine (Russell 1976; Chapter VII). Thus, most of the tolerance to effects of tobacco smoke that occurs following chronic tobacco use is due to the development of tolerance to nicotine.

Acute Sensitivity

Human Studies

Studies which have indicated that individuals differ in response to tobacco smoke or nicotine have used smokers as the experimental subjects. Consequently, whether individual differences are due to differences in acute sensitivity to nicotine that have persisted during chronic tobacco use or are due to differences in the development of tolerance is unknown.

Nesbitt (1973) and Jones (1986) noted that individual smokers differ with respect to the effects of smoking a standard cigarette on heart rate, but it is not clear from these studies whether these differences in responsiveness are due to differences in sensitivity to nicotine or to differences in the dose and kinetics of nicotine. Benowitz and colleagues (1982) observed individual differences in the effects of i.v. injections of nicotine on heart rate, blood pressure, and fingertip skin temperature. Differences were not explained by differences in blood levels, indicating differential sensitivity to nicotine.

Animal Studies

Studies using laboratory animals indicate that differences in acute sensitivity to nicotine exist. Inbred rat and mouse strains differ in sensitivity to the effects of nicotine on locomotor activity (Garg 1969; Bättig et al. 1976; Schlatter and Bättig 1979; Hatchell and Collins 1980; Marks, Burch, Collins 1983b). Mouse strains also differ in the direction of the effect (increased or decreased activity). The mouse strains that differ in sensitivity to the effects of injected nicotine on locomotor activity also differ in the magnitude of response to a standard dose of tobacco smoke (Baer, McClearn, Wilson 1980). Inbred mouse strains also differ in sensitivity to the effects of nicotine on body temperature, heart rate, and acoustic startle response (Marks, Burch, Collins 1983a; Marks et al. 1985, 1986), as well as in sensitivity to nicotine-induced seizures (Tepper, Wilson, Schlesinger 1979; Miner, Marks, Collins 1984, 1986). These findings indicate that genetic factors may influence the sensitivity of rats and

mice to the first dose of nicotine. The importance of genetically determined differences in human sensitivity to the effects of nicotine administered in tobacco smoke remains to be determined.

Mechanisms of Differences in Acute Sensitivity

Differences between inbred mouse and rat strains in sensitivity to the effects elicited by a single injected dose of nicotine do not appear to result from differences in rate of nicotine metabolism (Petersen, Norris, Thompson 1984) or from differences in brain nicotine concentration following intraperitoneal injection (Hatchell and Collins 1980; Rosecrans 1972; Rosecrans and Schechter 1972). Thus, rat and mouse strains differ in tissue sensitivity to the effects of nicotine. Differences among mouse strains in sensitivity to nicotine do not appear to be due to differences in the number or affinity of brain nicotine receptors that are measured via the binding of ³H-nicotine (Marks, Burch, Collins, 1983b). Mouse stocks that are more sensitive to nicotine-induced seizures do have greater numbers of hippocampal nicotine receptors that bind ¹²⁵I-bungarotoxin (BTX) (Miner, Marks, Collins 1984, 1986). Some of the differences in sensitivity to nicotine between genetically defined stocks of animals may be related to differences in the number of nicotine receptors in specific regions of the brain.

Tachyphylaxis (Acute Tolerance)

Human Studies

Systematic studies of tachyphylaxis or acute tolerance to effects of tobacco in nonsmokers have not been reported. There is evidence that tachyphylaxis does develop to effects of tobacco and nicotine in humans. Smokers frequently report that the first cigarette of the day is the best and that subsequent cigarettes are "tasteless" (Russell 1976; Henningfield 1984). Smoking a single standard cigarette after 24 hr of abstinence increases heart rate, whereas smoking an identical cigarette during the course of a normal day fails to change heart rate (West and Russell 1987). Fewer standard puffs were required to produce nausea at the beginning of the day (following 8 to 10 hr of tobacco abstinence) or from high-nicotine cigarettes than at the end of the day or from low-nicotine cigarettes (Henningfield 1984). Complete tolerance to nausea and vomiting developed over 8 hr in a woman in the course of an accidental nicotine poisoning, despite persistently toxic blood levels of nicotine (Benowitz, Lake et al. 1987). These findings suggest that tolerance which is lost and regained during short periods of abstinence from tobacco is tolerance to nicotine.

Tolerance develops very rapidly to several effects of nicotine. Rosenberg and colleagues (1980) studied the effects of i.v. nicotine

injections on arousal level, heart rate, and blood pressure. In these experiments, six healthy smokers, 21 to 35 years of age, received six series of nicotine injections spaced 30 min apart. Each series of injections consisted of 10 2- μ g/kg injections spaced 1 min apart. Subjects reported a pleasant sensation after the first series of injections, but this response was not observed thereafter. Heart rate and blood pressure values remained above baseline, but there was little increment with successive injections, despite nicotine blood level increases which were similar to those observed after the first series of injections. In contrast, skin temperature fell progressively during the period of nicotine dosing, gradually returning to baseline at the end of the study. These data indicated rapid development of tolerance to subjective effects and heart rate and blood pressure responses, but tolerance was not complete because heart rate and blood pressure remained above baseline. Henningfield (1984) also assessed subjective responses of human subjects after i.v. injections with nicotine at 10-min intervals. The subjective response of "liking" the effects of nicotine was lost after five or six injections. Benowitz and coworkers (1982) studied the effect of a 30-min infusion of nicotine at a rate of 1 to 2 μ g/kg/min. Shortly after initiation of infusion, heart rate and blood pressure increased, but the increase did not continue even though plasma nicotine concentrations continued to rise during the continuous infusion. Maximal cardiovascular changes were seen within 5 to 10 min, whereas maximal plasma nicotine levels were not reached until 30 min. These findings indicate that tachyphylaxis to the effects of nicotine may develop in humans within 5 to 10 min, the time required to smoke one cigarette. In contrast to heart rate, skin temperature (reflecting cutaneous vascular tone) declined and rose in association with changes in blood nicotine concentrations, showing no evidence of tolerance.

The above studies indicate rapid development of tolerance to some (but not all) actions of nicotine in people. These studies were performed with cigarette smokers who had abstained from smoking the night before the study. Since significant quantities of nicotine persist in the body even after overnight abstinence, there is probably some persistence of tolerance. Experimental data supporting this conclusion were obtained in a study of cardiovascular responses to infused nicotine in smokers following either an overnight or 7-day tobacco abstinence (Lee, Benowitz, Jacob 1987). Heart rate and blood pressure responses were significantly greater after more prolonged abstinence. However, within 60 to 90 min, the blood concentration-effect relationship in subjects after brief abstinence approximated that observed after prolonged abstinence. Thus, a significant level of tolerance persists throughout the daily smoking cycle, but is lost with prolonged abstinence. Tolerance, at least after abstinence for one week, is rapidly reestablished with subsequent exposure.

Animal Studies

Many studies demonstrate that acute tolerance or tachyphylaxis develops very quickly to actions of nicotine. Barrass and coworkers (1969) demonstrated that pretreatment of mice with a single i.v. dose (0.8 mg/kg) of nicotine resulted in an increase in the LD₅₀ (dose which is lethal to 50 percent of animals) for nicotine. Maximal protection was seen 5 min after the injection, but this protection diminished steadily over the next hour. Tachyphylaxis develops to the effects of nicotine on locomotor activity. Stolerman, Bunker, and Jarvik (1974) noted that pretreating rats with a 0.75-mg/kg dose of nicotine 2 hr before challenge doses of nicotine (0.25 to 4.0 mg/kg) resulted in a shift of the nicotine dose-response curves, indicating reduced sensitivity. The ED₅₀ values (doses that are effective in producing the measured response in 50 percent of animals) for nicotine-induced decreases in locomotor activity were nearly 2.4-fold greater in nicotine-pretreated rats than in saline-pretreated animals. Nicotine pretreatment also results in tachyphylaxis to the effects of nicotine on body temperature (hypothermia) in cats (Hall 1972), water-reinforced operant responding in rats (Stitzer, Morrison, Domino 1970), discharge of lateral geniculate neurons of cats (Roppolo, Kawamura, Domino 1970), repolarization of sartorius muscle in frogs (Hancock and Henderson 1972), blood pressure elevation in rats (Wenzel, Azmeh, Clark 1971), contraction of aortic strips in rabbits (Shibata, Hattori, Sanders 1971), respiratory stimulation in cats (McCarthy and Borison 1972), and gastrointestinal contraction in squid (Wood 1969) and guinea pigs (Hobbiger, Mitchelson, Rand 1969). More recent studies have demonstrated that pretreatment with as little as one dose of nicotine will attenuate nicotine-induced elevations of plasma corticosterone (Balfour 1980) and adrenocorticotrophic hormone (ACTH) (Sharp and Beyer 1986) levels in rats (see also Chapter III).

The interval between the pretreatment and challenge doses of nicotine is a critical factor that determines whether tachyphylaxis is observed. Aceto and coworkers (1986) examined the effect of i.v. nicotine infusion on heart rate and blood pressure in the rat. Tolerance did not develop when the interval between pretreatment and challenge doses was 30 min; marked tolerance was detected when the interval was reduced to 1 min. However, Stolerman, Fink, and Jarvik (1973) observed that after a single intraperitoneal dose of nicotine to rats, acute tolerance to a second dose did not become maximal until 2 hr after the initial injection.

Mechanisms of Tachyphylaxis

Although tachyphylaxis has been described for a wide variety of nicotine's effects, very little is known about mechanisms. A nicotine

metabolite may play a role in the development of tachyphylaxis. Barrass and colleagues (1969) argued that nicotine metabolites may block nicotine receptors and thereby antagonize nicotine's lethal effects. This argument was made because pretreatment with nicotine-N'-oxide protected mice from the lethal effects of large doses of nicotine. LD₅₀ values were increased approximately ninefold by pretreatment with nicotine-N'-oxide. These authors hypothesized that this protection may involve conversion of nicotine-N'-oxide to hydroxynicotine. Their results indicated that injection of a reduction product of cotinine, believed to be hydroxynicotine, gave immediate protection, whereas maximum protection was not seen until 40 min after injection of nicotine-N'-oxide. Thus it appears that metabolism, possibly to hydroxynicotine, is required for the protective action of nicotine-N'-oxide.

Another hypothesis is that tachyphylaxis is the result of desensitization of nicotine receptors. Desensitization of the receptor involves a conformational change that results in increased affinity of the nicotinic receptor for agonists coupled with decreased ability of the receptor to transport ions (Weiland et al. 1977; Sakmann, Patlak, Neher 1980; Boyd and Cohen 1984). Desensitization of nicotinic receptors at the motor end-plate was first described by Katz and Thesleff (1957) and has since been studied by a large number of investigators, using either skeletal muscle or the electric organs of the eel, *Torpedo californica*. Although tachyphylaxis has been commonly suggested as being due to desensitization of brain nicotinic receptors, the role of desensitization in tachyphylaxis to specific behavioral effects of nicotine has not been studied. This is because concentrations of nicotinic receptors in specific areas of the brain corresponding to the behavioral effects being measured are not high enough to use available methods.

Chronic Tolerance

Human Studies

Chronic tolerance to tobacco and nicotine has not been studied systematically in human subjects, but it is clear, as noted previously, that some tolerance does develop. Tolerance is not complete; symptoms of nicotine toxicity such as nausea appear when smokers increase their normal tobacco consumption by as little as 50 percent (Danaher 1977).

These findings are consistent with the observations that smokers increase their tobacco consumption and intake of nicotine with experience. Such escalating dose patterns may be observed for several years after initiation of either cigarette smoking or smokeless tobacco use. Cigarette smokers may achieve such increases by augmenting the number of cigarettes smoked and by increasing the amount of nicotine extracted from each cigarette. For users of

smokeless tobacco, switching to products with greater nicotine delivery may also contribute to nicotine dose escalation (US DHHS 1986).

Animal Studies

Animal studies have proved useful in establishing the actual development of tolerance to nicotine, the magnitude of such tolerance, and mechanisms that underlie this tolerance. The majority of these studies have used the rat and mouse as experimental subjects.

Most of the chronic tolerance studies using the rat have focused on the effects of nicotine on locomotor activity. Depression of locomotor activity typically occurs following the injection of nicotine in doses exceeding 0.2 mg/kg in drug-naïve rats. Tolerance to this depression develops following chronic treatment (Keenan and Johnson 1972; Stolerman, Fink, Jarvik 1973; Stolerman, Bunker, Jarvik 1974). The magnitude of this tolerance is influenced by the dose and dosing interval. Tolerance persists for greater than 90 days when nicotine is injected chronically. Tolerance to the effects of injected nicotine on depression of locomotor activity could also be produced with nicotine administered in the rats' drinking water or through subcutaneously implanted reservoirs (Stolerman, Fink, Jarvik 1973).

Under certain experimental conditions, rats treated chronically with nicotine exhibit an increase in locomotor activity following nicotine challenge (Morrison and Stephenson 1972; BaA5ttig et al. 1976; Clarke and Kumar 1983a,b). A careful analysis of the response to an acute challenge dose of nicotine demonstrated that soon after the first dose of nicotine, depressed locomotor activity was observed; after 40 min or more, increased locomotor activity became apparent (Clarke and Kumar 1983b). Chronically injected rats exhibited this enhanced activity progressively earlier postinjection. More recently, Ksir and others (1985, 1987) demonstrated that chronic nicotine injections may result in enhanced locomotor activity immediately after nicotine injection if the rats were acclimated to the test apparatus for 1 hr before nicotine injection. These findings indicate that in the rat, tolerance develops to the depressant effects of nicotine and that this tolerance uncovers a latent stimulatory action.

If mice are injected chronically with nicotine, tolerance develops to the locomotor depressant effects elicited by a challenge dose of nicotine (Hatchell and Collins 1977). The degree and rate of development of tolerance appear to be influenced by the sex, as well as the strain, of the animals. Tolerance development has been studied by continuously infusing mice of several inbred strains with nicotine and assessing tolerance by measuring locomotor activity, body temperature, respiratory rate, heart rate, and acoustic startle response following nicotine challenge. Such studies have demonstrated that: (1) Tolerance to nicotine increases with the nicotine

infusion dose (Marks, Burch, Collins 1983a); (2) Tolerance is specific for nicotinic cholinergic agonists in that nicotine-infused animals are not cross-tolerant to the muscarinic cholinergic agonist oxotremorine (Marks and Collins 1985); (3) Maximal tolerance is attained within 4 days following the initiation of infusion and is lost within 8 days following the cessation of infusion (Marks, Stitzel, Collins 1985); (4) Tolerance development varies between inbred mouse strains, with some strains exhibiting marked tolerance and other strains showing very little (Marks, Romm et al. 1986); and (5) Mouse strains that fail to develop tolerance to nicotine are also relatively insensitive to the effects elicited by an acute injection of nicotine (Marks, Stitzel, Collins 1986). More recently these investigators compared the effects of continuous and pulse infusions of nicotine on tolerance development (Marks, Stitzel, Collins 1987). Pulse infusion was used to simulate the conditions obtained when tobacco is smoked. Although the total dose infused was the same in continuously infused and pulse-infused animals, marked differences in tolerance were seen. The pulse-infused animals exhibited a greater degree of tolerance. The degree of tolerance was most correlated with peak nicotine concentrations.

Chronic nicotine administration results in tolerance to a number of other nicotinic effects. Tolerance develops to depression of operant responding elicited by high doses of nicotine, such that after sufficient chronic treatment, enhanced rather than depressed operant responding is seen (Clarke and Kumar 1983c; Hendry and Rosecrans 1982). Attenuation of the effects of nicotine on electroencephalogram (EEG) activity is seen in the rat following chronic injection (Hubbard and Gohd 1975). These altered EEG responses paralleled the development of tolerance to behavioral effects described by these authors as "arousal." In contrast to the findings of Hubbard and Gohd (1975), other studies indicate that chronic tolerance does not develop to the behavioral stimulation effect of nicotine (Bättig et al. 1976; Morrison and Stephenson 1972; Clarke and Kumar 1983a,c). Likewise, little or no tolerance to nicotine-induced prostration after i.v. administration was observed after chronic exposure in rats (Abood et al. 1981, 1984).

In addition, tolerance has been reported to develop to nicotine-induced increases in plasma corticosterone, but not adrenal catecholamine release in rats (Balfour 1980; Van Loon et al. 1987). Anderson and colleagues (1985) studied the effects of chronic exposure to cigarette smoke on neuroendocrine function of the rat hypothalamus. These researchers observed that chronic exposure to cigarette smoke over a period of 9 days did not result in tolerance to the ability of acute intermittent exposure to cigarette smoke to reduce serum levels of prolactin, luteinizing hormone, and follicle stimulating hormone.

Mechanisms of Chronic Tolerance

Chronic tolerance to drugs may be due to an increase in the rate of drug metabolism or to a decrease in sensitivity of the tissue to the drug. Considerable differences exist among humans in the rate of nicotine metabolism (Benowitz et al. 1982). Metabolism is faster (shorter half-life) in smokers than in nonsmokers (Schievelbein et al. 1978; Kyerematen et al. 1982; Kyerematen, Dvorchik, Vesell 1983). The contribution of enhanced nicotine metabolism to the development of nicotine tolerance in humans is unclear. Studies of rats which clearly demonstrate that chronic nicotine treatment results in tolerance to nicotine also indicate that chronic nicotine administration does not increase the rate of nicotine metabolism in rats (Takeuchi, Kuroguchi, Yamaoka 1954) or mice (Hatchell and Collins 1977; Marks, Burch, Collins 1983b). These findings indicate that tolerance to nicotine primarily involves reduced sensitivity of target tissues.

Chronic tolerance to nicotine may be due to alterations in brain nicotinic receptors (see Chapter III for further discussion of nicotine receptors). At least two types of nicotinic receptors exist in rodent brain (Marks and Collins 1982). One of these receptor types may be measured with ^3H -nicotine or ^3H -acetylcholine (^3H -ACh) (Marks, Stitzel et al. 1986; Martino-Barrows and Keller 1987), while the other type may be measured with ^{125}I -bungarotoxin (BTX). The nicotine-binding site has higher affinity for nicotine than does the BTX site (Marks and Collins 1982). Chronic nicotine injection, once or twice daily for approximately 7 days, increased the number of ^3H -nicotine/ ^3H -ACh-binding sites in the brain (Ksir et al. 1985, 1987; Morrow, Loy, Creese 1985; Schwartz and Kellar 1983, 1985). This increase in nicotine-binding sites appeared to correlate with the emergence of nicotine-induced increases in locomotor activity in the rat. Studies of tolerance to nicotine in one inbred mouse strain (DBA) also demonstrated that chronic nicotine treatment elicits an increase in the number of brain nicotinic receptors as measured with both ^3H -nicotine and BTX as the ligands (Marks, Burch, Collins 1983a; Marks and Collins 1985; Marks et al. 1985, 1986; Marks, Stitzel, Collins 1985, 1986, 1987). These studies have also shown that the number of ^3H -nicotine-binding sites increases at lower doses of nicotine than do the BTX-binding sites. An increase in ^3H -nicotine binding (Marks, Burch, Collins 1983a) parallels development of tolerance to various responses during chronic infusion. In chronically infused DBA mice, tolerance acquisition and disappearance parallel the up-regulation and return to control, respectively, of brain ^3H -nicotine binding (Marks, Stitzel, Collins 1985). These findings suggest that the increase in ^3H -nicotine binding is related to the development of tolerance to nicotine. However, further studies indicate that factors other than receptor number must also be considered, because mouse

strains that do not develop tolerance to nicotine also demonstrate up-regulation of nicotinic receptors following chronic infusion (Marks et al. 1986; Marks, Stitzel, Collins 1986).

That chronic nicotine treatment results in a decrease in response to the drug (tolerance) and an increase in the number of nicotinic receptors was an unexpected finding. Marks, Burch, and Collins (1983a) and Schwartz and Kellar (1985) have suggested that chronic nicotine treatment results in chronic desensitization of nicotinic receptors. Chronic desensitization of the nicotinic receptor is comparable to chronic treatment with an antagonist and could be the stimulus for up-regulation of the receptors. According to this hypothesis, there is an increase in number of brain nicotinic receptors but a decrease in the absolute number of "activatable" (nondesensitized) receptors. This would result in a decreased response to nicotine (tolerance). Marks and coworkers suggest that inbred mouse strains failing to exhibit tolerance to nicotine, under the procedures used by these investigators, have brain nicotinic receptors that resensitize more rapidly than do those strains that do exhibit tolerance.

By treating rats chronically with the acetylcholinesterase inhibitor disulfoton, Costa and Murphy (1983) have found a decrease in rat brain ^3H -nicotine binding. Disulfoton-treated rats were also tolerant to the antinociceptive effects of nicotine. Thus, tolerance to nicotine effects may be seen when the number of nicotinic receptors is increased or decreased by chronic drug treatment. The observation that tolerance to at least one effect of nicotine can be obtained by a technique that decreases brain nicotinic receptor numbers supports the idea that chronic nicotine treatment results in an increase in the total number of receptors but a decrease in those that may be activated by nicotine; that is, a high fraction of the up-regulated receptors are desensitized.

In contrast to the studies reviewed above, some investigators have found no change in the number or affinity of ^3H -nicotine-binding sites in the brains of rats chronically exposed to nicotine (Abood et al. 1984; Benwell and Balfour 1985).

Other potential neurochemical explanations for tolerance to nicotine have been considered. Several reports (Westfall 1974; Giorguieff et al. 1977; Arqueros, Naquira, Zunino 1978; Giorguieff-Chesselet et al. 1979) indicate that nicotine stimulates dopamine release in vitro, and a recent study demonstrated that nicotinic agonists are less effective in stimulating dopamine release in slices of striatum obtained from rats that had been chronically treated with the nicotinic agonist dimethylphenylpiperazinium (DMPP) (Westfall and Perry 1986). These findings are consistent with the idea that chronic nicotinic agonist treatment results in a decrease in the absolute number of receptors that can be activated.

Pharmacodynamics of Nicotine and Cigarette Smoking

As the foregoing review has shown, the intensity of nicotine's effects is related to the dose given, the time since the last dose, and the level of preexisting or acquired tolerance. Since nicotine can produce effects that lead to further use (reinforcing effects) (Henningfield and Goldberg 1983) and can also produce effects that limit use (aversive effects, usually at higher dose levels) (Danaher 1977), the strength of the effect of a given dose can determine whether more or less nicotine will be subsequently taken. Thus, factors such as tolerance can affect the manner in which nicotine controls behavior (Chapter IV). Similarly, an individual's ability to develop tolerance to the toxic actions may be critical in determining whether smoking will occur and, if smoking is initiated, whether there will be an increase in the number of cigarettes consumed each day.

Pharmacodynamic considerations may help explain the pattern of cigarette smoking throughout the day. Intervals between smoking cigarettes may be determined at least in part by the time required for tolerance to disappear. With regular smoking there is accumulation of nicotine in the body resulting in a greater level of tolerance. Transiently high brain levels of nicotine following smoking individual cigarettes may partially overcome tolerance. But the effects of individual cigarettes tend to lessen throughout the day. Overnight abstinence allows considerable resensitization to effects of nicotine, and the daily smoking cycle begins again.

Pharmacodynamic observations with i.v. dosing of nicotine explain the pattern of cardiovascular changes observed in cigarette smokers. That brief infusions of nicotine increase heart rate to a maximum suggests that heart rate will increase most with the first few cigarettes of the day, but subsequently will not vary in relation to the amount of nicotine consumed. That only partial tolerance develops to heart rate acceleration due to nicotine suggests that effects on heart rate may persist as long as significant levels of nicotine persist, including overnight. These predictions were confirmed in a study in which volunteer cigarette smokers smoked either high- or low-yield nonfilter research cigarettes or abstained from smoking (Benowitz, Kuyt, Jacob 1984). Full compensation for the low-yield research cigarettes, which contained only small amounts of nicotine, was impossible. Resultant nicotine blood levels were different by fourfold. As predicted, heart rate (assessed by continuous ambulatory electrocardiogram (EKG) monitoring) increased in the morning—more on smoking than nonsmoking days—and the increase occurred with the first few cigarettes of the day. Subsequently, heart rate followed a normal circadian pattern, but was always higher during smoking than during abstinence. Also, as predicted, heart rate was no different during the smoking of low-

yield or high-yield cigarettes, despite the fourfold difference in blood nicotine concentration.

Pharmacodynamic aspects of the actions of nicotine may explain in part how cigarette smoking causes coronary heart disease (US DHHS 1983). As noted before, because of the accumulation of nicotine and its dose-response characteristics, heart rate is increased during cigarette smoking for 24 hr a day. Plasma catecholamine concentrations and urinary catecholamine excretion remain increased as well (Benowitz 1986c), consistent with the theory that cigarette smoking produces sympathetic neural activation 24 hr each day. Persistent sympathetic activation could result in the following effects: (1) Alteration in lipid metabolism, resulting in a more atherogenic lipid profile; (2) Promotion of platelet aggregation and hypercoagulability; (3) Induction of vasoconstriction and coronary spasm; and (4) Increased heart rate and myocardial contractility, thereby an increase in the oxygen demands of the heart and of circulating catecholamines, which can promote cardiac arrhythmias. These factors could accelerate atherosclerosis and contribute to acute myocardial infarction in a person with preexisting coronary atherosclerosis (Benowitz 1986a) (see also Appendix B). There is no apparent correlation between acute coronary events and the time at which a person smokes a cigarette, perhaps because of the persistent effects of nicotine throughout the day.

Constituents of Tobacco Smoke Other Than Nicotine With Potential Behavioral Effects

Tobacco smoke contains more than 4,000 constituents, many of which may have biological activity (US DHHS 1983). Although nicotine is the major pharmacologic factor which determines the use of tobacco, other constituents may also be involved. The behavioral effects of tobacco constituents other than nicotine are described in the Section below and in Chapter IV. This Section focuses more on the chemicals that may be involved, whereas Chapter IV focuses more on cigarette smoking behavior.

Minor Tobacco Alkaloids

Most of the research on the minor tobacco alkaloids has been directed to determining physiological effects, such as the effect on blood pressure and other cardiovascular responses and toxicological effects, rather than the potential for behavioral effects. The pharmacologic effects of alkaloids of the nicotine group have been discussed by Bovet and Bovet-Nitti (1948) and Clark, Rand, and Vanov (1965). Nornicotine and anabasine were found to have qualitatively similar actions but to be less potent than nicotine. Larson and Haag (1943)

reported that the potency of nornicotine as determined by effects on blood pressure in dogs was about one-twelfth that of nicotine.

Nicotine analogs have been studied for discriminative stimulus effects by using animal models (Chance et al. 1978) (see also Chapter IV). The only chemical shown to produce a positive response in that test system was 3-methylpyridylpyrrolidine. Recent research has focused on binding at specific brain receptor sites. Martin and coworkers compared binding characteristics of nicotine-related compounds (Martin et al. 1986; Sloan et al. 1985). Lobeline, anabasine, and cytisine were evaluated for effects on heart rate, blood pressure, respiration rate, minute volume, and tidal volume (Sloan et al. 1987). Lobeline and anabasine bound to low-affinity sites in the brain, whereas cytisine bound only at a high-affinity site. The binding data are consistent with the pharmacologic data, indicating that lobeline and anabasine have different pharmacologic actions than cytisine. Kanne and others (1986) and Abood and Grassi (1986) evaluated two nicotine analogs, including a new radioligand, to study brain nicotinic receptors. Kachur and others (1986) studied the pharmacologic effects of a bridged-nicotine analog (methylene bridge between the methyl of the pyrrolidine ring and the α -position of the pyridine ring). The magnitude of pressor effect depended on the particular enantiomer and dosage. These results emphasize that compounds other than nicotine may act at the nicotine receptors; however, there may be subpopulations of receptors to which different agonists and antagonists bind (Chapter III).

N-Methylated derivatives of nicotine, including nicotine isomethonium ion (N-methylnicotinium ion, NMN), have been shown to have pressor and neuromuscular effects in some species (Shimamoto et al. 1958). Nicotine isomethonium ion was first reported to be a metabolite of nicotine present in smokers' urine by McKennis and coworkers in the 1960s, and its presence in smokers' urine has been recently confirmed (Neurath et al. 1987). Recently Crooks and coworkers (Cundy, Godin, Crooks 1985) have shown that only the (R)-isomer of nicotine is converted to nicotine isomethonium ion *in vitro* in guinea pig tissue homogenates or *in vivo* in guinea pigs. Consequently, it is uncertain as to whether the nicotine isomethonium ion present in smokers' urine arrives from the small amount of (R)-nicotine present in tobacco smoke, or whether the human enzyme systems have different specifications than the guinea pig enzymes. Because little if any nicotine isomethonium ion penetrates the blood-brain barrier (Pool 1987; Aceto et al. 1983), it would appear that this metabolite could have behavioral actions only if it were formed in the CNS. These findings emphasize the complexity of the pharmacology of nicotine-related compounds. It can be concluded from research on these compounds that some do bind to specific brain receptors and may result in centrally mediated physiological changes. However,

there is inadequate evidence to date that any of these compounds produces either aversive or rewarding effects in human smokers.

"Tar" and Selected Constituents of Tobacco Smoke Which Contribute to Taste and Aroma

"Tar" is used to describe the dry particulate matter without the nicotine in tobacco smoke (Pillsbury et al. 1969). The possible role of tar in the maintenance of the cigarette smoking habit has been considered. Goldfarb and coworkers (1976) studied the effects of the tar content (determined by cigarette smoking machine testing) on the subjective reactions to cigarette smoking. Ratings of strength were not related to the tar index of the cigarettes. The results were interpreted as indicating that tar did not have a role in the maintenance of cigarette smoking behavior. In a later study, Sutton and coworkers (1982) found that when nicotine yield was held constant, smokers of lower-tar cigarettes puffed more smoke and had higher drug plasma levels. These results suggested that smokers were compensating for reduced delivery of tar by inhaling a greater volume of smoke. Because these two studies used different experimental designs, it is difficult to draw a conclusion as to the role of tar in relation to smoking behavior. However, based on knowledge about the taste and aroma constituents of cigarette smoke, it is likely that some of the chemicals in the tar fraction contribute to tobacco use, if only by providing distinct sensory stimuli (Chapter VI). Consistent with this possibility, minimal levels of tar are held by tobacco manufacturers to be important to the taste characteristics of tobacco smoke.

Several thousand compounds have been isolated from tobacco and tobacco smoke (Dube and Green 1982), and many of these may be biologically active (IARC 1986). The precursors to the carotenoids and diterpenoids, selected nitrogenous and sulfur constituents, waxes and lipids, and phenolics and acids contribute to the taste and aroma of tobacco (Enzell and Wahlberg 1980; Heckman et al. 1981; Davis, Stevens, Jurd 1976). A number of the isoprenoid compounds that influence the taste and aroma of smoke may be formed by sequential oxidation, rearrangement, and reduction reactions (Davis, Stevens, Jurd 1976). Enzell and Wahlberg (1980) described several norisoprenoid compounds which are derived from the cyclic carotenoids and are important to smoke aroma. The particular taste and aroma of a cigarette can be influenced by the selection of the grade (quality and leaf position on the plant) and type of tobacco used in the blend.

Taste and smell receptors in the pharynx, larynx, and nose provide the first sensory input to the smoker as he or she lights up, an experience which is generally perceived as pleasurable (Rose et al. 1985). The taste and smell of tobacco smoke may be important

reinforcers for tobacco smoking (Jarvik 1977)—at least following repeated association with the reinforcing effects of nicotine administration (Chapter VI). By such behavioral conditioning, sensory cues provided by tar and flavor additives could come to control the tobacco-consuming behavior of the tobacco user. Changes in smoking patterns when brands are switched and brand selection may be a response in part to the particular flavor and aroma of the product (Thornton 1978).

Carbon Monoxide

The mainstream and sidestream carbon monoxide (CO) deliveries of cigarettes are influenced by cigarette design and puffing characteristics of the smokers. Depending upon these factors, the mainstream delivery usually ranges from 10 to 20 mg/cigarette. In a study of 29,000 blood donors in 18 locations around the United States, smokers were found to have median carboxyhemoglobin (COHb) levels ranging from 3.2 to 6.2 percent (Stewart et al. 1974). Anderson, Rivera, and Bright (1977) found the COHb levels in 50 smokers to vary from 3.9 to 14.0 percent, with the mean of 8.1 percent. The mean increment in COHb immediately after smoking 1 cigarette was 0.64 percent. COHb levels gradually decrease in blood after cessation of smoking. Carbon monoxide is eliminated in expired air. The rate of elimination depends on pulmonary blood flow and ventilation. The half-life of COHb is 2 to 4 hr during daytime hours, but as COHb is related to the level of exercise, the half-life may be as long as 8 hr during sleep (Wald et al. 1975). For these reasons, many smokers awaken in the morning with substantial levels of COHb, despite not smoking overnight (Benowitz, Kuyt, Jacob 1982). Persons smoking cigarettes with lower nicotine and CO yields have only slightly lower levels of COHb when compared with those smoking higher-yield products (Wald et al. 1980, 1981; Sutton et al. 1982; Hill, Haley, Wynder 1983; Benowitz, Jacob, Yu et al. 1986).

Benowitz and colleagues (1986) studied tar, nicotine, and CO exposure in smokers switched from their usual brand to low-, high-, and ultra-low-yield cigarettes. This study indicated that there were no differences in exposure comparing low- and high-yield, but tar and nicotine exposure were reduced by about 50 percent and CO by 36 percent while smoking *ultra-low-yield* cigarettes. Switching from a high to lower yield cigarette does not significantly reduce blood COHb although switching to ultra low cigarettes has been shown to lead to a significant reduction.

The toxic effects of high CO levels are well documented (US DHHS 1983). Some studies have tried to determine whether CO levels in the blood similar to those observed in smokers can affect behavior. Beard and Wertheim (1967) and Wright, Randell, and Shephard (1973) reported performance decrements with COHb levels below 5.0

percent; however, Guillerman, Radziszewski, and Caille (1978) found no psychomotor performance effects at COHb levels of 7 and 11 percent. Thus, the data are inconclusive with regard to the possible influence of CO on psychomotor performance at levels normally encountered in smokers.

Acetaldehyde and Other Smoke Constituents

Acetaldehyde is a major constituent of tobacco smoke, with mainstream smoke levels in commercial cigarettes ranging from 0.5 to 1.2 mg/cigarette (IARC 1986). The delivery of volatile aldehydes is influenced by cigarette design, with reductions achieved by specific filtration and air dilution techniques. Yields over 5.9 mg have been reported for large cigars (Hoffmann and Wynder 1977). Acetaldehyde is the primary metabolite of ethanol, and its toxic potency is 20 to 30 times that of ethanol. Acetaldehyde has been suggested to have an adverse effect on the heart (James et al. 1970). Acetaldehyde and acrolein, another important aldehyde in the gas phase of cigarette smoke, activate the sympathetic nervous system (Egle and Hudgins 1974). Acetaldehyde, by releasing norepinephrine, results in a pressor effect (Kirpekar and Furchtgott 1972; Green and Egle 1983). Depressor effects occur at high doses of the aldehydes in guanethidine-pretreated hypertensive rats. Frecker (1983) indicated that condensation products of acetaldehyde may be active on endogenous opioid systems. Torreilles, Guerin, and Previero (1985) reviewed the synthesis and biological properties of beta-carbolines, the condensation products of tryptophan and indole alkylamines with aldehydes. Beta-carbolines occur as plant constituents, including minor constituents in tobacco. For example, harman (1-methyl-β-carboline) has been identified in tobacco and tobacco smoke (Snook and Chortyk 1984). Carbolines from other plant species have been used as hallucinogens. The research conducted to date indicates a potential pharmacologic effect of the aldehydes, especially with regard to cardiovascular physiology; however, the evidence is inadequate to determine if these volatile smoke constituents in the doses delivered in tobacco smoke contribute to the behavioral effects of cigarette smoking.

Summary and Conclusions

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 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.

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CHAPTER III

NICOTINE: SITES AND MECHANISMS OF ACTIONS

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Overview

Nicotine, in tobacco smoking concentrations, is a powerful psychoactive drug (Domino 1973; Kumar and Lader 1981; Balfour 1984). A wide variety of stimulant and depressant effects is observed in animals and humans that involves the central and peripheral nervous, cardiovascular, endocrine, gastrointestinal, and skeletal motor systems. These heterogeneous effects, along with behavioral and psychological variables, result in self-administration of tobacco, tobacco dependence, and withdrawal phenomena with abrupt cessation of tobacco smoking. This Chapter discusses sites and mechanisms of nicotine actions that may help to explain why tobacco products are self-administered.

The first Section of this Chapter provides general summaries of several major effects of nicotine in the body. Following this broad overview, the Chapter presents detailed discussions of sites and mechanisms of nicotine action that may be particularly important to understand tobacco use. Tissue distribution of nicotine, cerebral metabolic effects, and nicotine receptor binding are reviewed. Next, neuroendocrine and endocrine effects of nicotine are discussed. Then, electrophysiological effects of nicotine are presented. Finally, the effects of smoking on psychophysiological reactivity are discussed.

Peripheral Effects of Nicotine

Nicotine exerts its action on the cardiovascular, respiratory, skeletal motor, and gastrointestinal systems through stimulation of peripheral cholinergic neurons via afferent chemoreceptors and ganglia of the autonomic nervous system (ANS) (Ginzel 1967b). Inasmuch as both sympathetic and parasympathetic ganglia are stimulated by levels of nicotine derived from tobacco smoking, the end result depends on the summation of the effects of autonomic ganglion stimulation and reflex effects. The resulting peripheral physiological changes generally resemble sympathetic nervous system (SNS) arousal, but there are also some effects of nicotine and smoking that lead to physiological relaxation. For example, there is usually an increase in heart rate and blood pressure immediately following cigarette smoking. In addition, there is cutaneous vasoconstriction of the distal extremities. In contrast, nicotine can relax skeletal muscles (e.g., reduce patellar reflex) in humans and animals via effects on Renshaw cells (Domino and Von Baumgarten 1969; Ginzel and Eldred 1972; Ginzel 1987). But it also can enhance tension in some muscles (e.g., trapezius muscle) (Fagerström and Gotestam 1977). Nicotine in small doses can enhance respiration through stimulation of peripheral chemoreceptors. Yet, high nicotine doses can cause respiratory failure. (See Appendix B for a discussion of

nicotine toxicity.) The gastrointestinal effects of nicotine are complex, involving an increase in secretions and reduced motility for a short period of time.

The peripheral actions of nicotine as a cholinergic agonist have made it a valuable pharmacologic tool for studying nicotinic cholinergic actions and functioning in many physiological systems. This Chapter focuses on the mechanisms of nicotine's actions relevant to tobacco use. Several peripheral actions of nicotine, for instance muscular relaxation, may contribute to the habitual use of tobacco products (see smoking and stress in Chapter VI). However, because the central nervous system (CNS) actions of nicotine and resulting neurochemical and electrical effects mediate subsequent biological and behavioral responses, a review of these actions contributes to an understanding of the reinforcing effects of nicotine.

Central Sites of Nicotine Actions

Nicotinic binding sites or receptors in the brain have been differentiated as very high, high, and low affinity types (Shimohama et al. 1985; Sloan, Todd, Martin 1984; Sloan et al. 1985). In the rat brain, when cholinergic muscarinic receptors are blocked, the autoradiographic distribution of ^3H -acetylcholine (ACh) and ^3H -nicotine are essentially identical (Clarke and Kumar 1984; Clarke, Pert, Pert 1984). However, these brain binding sites differ from peripheral nicotinic receptors in ganglia and skeletal muscle.

Chronic nicotine administration results in up-regulation in regional rat brain ^3H -ACh binding sites measured in the presence of atropine to block the muscarinic sites (Schwartz and Kellar 1985). Up-regulation of ^3H -nicotine binding sites also has been reported after continuous nicotine infusions in mice (Marks, Burch, Collins 1983a). In contrast, most agonists that act on receptor sites in the body, when given chronically, produce a reduction (or down-regulation) in the number of receptors. Both Marks, Burch, and Collins (1983b) and Schwartz and Kellar (1983, 1985) have suggested that nicotinic cholinergic receptors undergo a functional blockade but that sufficient recovery would allow enhanced behavioral responses to low doses of nicotine to occur within 24 hr, as has been shown behaviorally by Clarke and Kumar (1983) and Ksir and coworkers (1985). This phenomenon may help to explain the tolerance to nicotine that develops with repeated exposure. However, the time course of changes in receptor number and other biological effects of nicotine must be carefully compared to determine mechanisms underlying tolerance. (See Chapter II for additional discussion.)

Several investigators have used *in vitro* autoradiography to identify ^3H -nicotine binding sites in the rat brain. These audioradiographic binding studies suggest where nicotine is acting. London, Waller, and Wamsley (1985) have found the most intense localization

of ^3H -labeled nicotine in the interpeduncular nucleus and medial habenula.

Cerebral metabolism studies also suggest key sites of action. London and colleagues (1985) have reported that nicotine stimulated local cerebral glucose utilization (LCGU) by 139 percent over that of the control in the medial habenula and by 50 to 100 percent in the superior colliculus and the anteroventral thalamic and interpeduncular nuclei. Other areas of the brain showed moderate or no significant changes. These effects of nicotine were blocked by mecamylamine, a nicotinic receptor antagonist, confirming that they acted via nicotinic receptors. Furthermore, they correlated well with the distribution of ^3H -nicotine binding in the brain except in layer IV of the neocortex, which showed nicotine binding but no change in LCGU. Sites that show increased glucose utilization after nicotine administration are probably functionally important loci of nicotinic actions. When nicotine binding and increased energy utilization both occur at a given site, it is likely to be involved in nicotine's actions.

Neuroendocrine Effects of Nicotine

Some of the actions of nicotine result from the release of ACh and other neurotransmitters, including norepinephrine (NE). Nicotinic cholinergic agonists including nicotine, carbachol, and 1,1-dimethyl-4-phenylpiperazinium (DMPP) release endogenous ACh from the presynaptic cholinergic nerve terminals in addition to stimulating postsynaptic nicotinic receptors (Chiou 1973; Chiou and Long 1969). Nicotinic agonists also release ACh from rat cerebral cortical synaptic vesicles and can release newly synthesized ^3H -ACh from synaptosomes prepared from the myenteric plexus of guinea pig ileum and from mouse cortical synapses (Briggs and Cooper 1982; Rowell and Winkler 1984). These effects are Ca^{2+} -dependent and are blocked by hexamethonium, a quaternary nicotinic receptor antagonist. In addition, nicotine-induced release of ACh in the hippocampal synaptosomes is blocked by the ion channel blocker, histrionicotoxin (Rapier et al. 1987). There is good evidence that nicotine releases ACh by a presynaptic mechanism. In contrast, presynaptic muscarinic receptors, mostly of the M_2 -subtype, inhibit ACh release. Nicotine administration increases the amounts of other chemicals in the blood and brain, including serotonin, endogenous opioid peptides, pituitary hormones, catecholamines, and vasopressin (Domino 1979; Gilman et al. 1985; Marty and colleagues 1985). These chemicals may be involved in reinforcing effects of nicotine (see Chapters IV, VI).

Electrophysiological Effects of Nicotine

Nicotine administration is accompanied by brain wave or electroencephalogram (EEG) activation in animals (Domino 1967). The EEG-activating effects of small doses of nicotine occur in intact as well as

brainstem-transected animals. Nicotine acts primarily directly on brainstem neuronal circuits to produce these effects (Domino 1967). However, stimulation of peripheral afferents (Ginzel 1987) and release of catecholamines and possibly neurotransmitters and modulators, such as serotonin or histamine, may enhance the direct central effects of nicotine.

The EEG-activating effects of nicotine result in behavioral arousal (Domino, Dren, Yamamoto 1967). In cigarette smokers, nicotine produces sedative and stimulant effects (Kumar and Lader 1981). Aceto and Martin (1982) have reviewed the large variety of nicotine effects on behavior including facilitation of memory, the increase in spontaneous motor activity, nicotine's antinociceptive properties, and its suppression of irritability. These behavioral and psychological effects are discussed in Chapters IV and VI.

Distribution and Cerebral Metabolic Effects of Nicotine

Nicotine, administered by various routes, rapidly enters the brain and also distributes to specific, peripheral organs. Nicotine produces a distinct pattern of stimulation of cerebral metabolic activity that suggests where nicotine acts in the brain. This Section reviews studies on the distribution of nicotine after its administration to experimental animals, data on the relationship between tissue levels of nicotine and the drug's biological effects, and studies on mapping the cerebral metabolic effects of nicotine in the rat brain.

Distribution of Nicotine

Tissue Distribution of Nicotine: Time Course and Other Considerations

The distribution in the body of exogenously administered nicotine has been a topic of interest for more than a century and has been reviewed several times (Larson, Haag, Silvette 1961; Larson and Silvette 1968, 1971). As early as 1851, Orfila described experiments in which he detected nicotine in various organs (e.g., liver, kidney, lungs) and in the blood of animals after nicotine administration. In the 1950s the development of radiotracer methods led to a reexamination of nicotine distribution in the body.

Werle and Meyer (1950) found that the brain, compared with other organs, contained the highest nicotine levels immediately after injection of a lethal dose in guinea pigs. Tsujimoto and colleagues (1955) found a high concentration of nicotine in the brain after the drug was administered to rabbits and dogs. Yamamoto (1955) observed that 1 hr after a subcutaneous (s.c.) injection of 5 mg/kg in the rabbit, the nicotine content was highest in the kidney. The pancreas, ileum, ventricular muscle, skeletal muscle, lung, spleen, cerebral cortex, omental fat, and liver showed progressively lower

levels of nicotine at 1 hr. None of the tissues had detectable levels at 6 hr. In the dog, the highest level at 1 hr was in the kidney, followed by the pancreas, brain, ileum, liver and omental fat, spleen, heart, muscle, and lung.

Schmilterlöw and colleagues used radiolabeled nicotine and whole-body autoradiography to study the distribution of nicotine in several species (Hansson and Schmilterlöw 1962; Appelgren, Hansson, Schmilterlöw 1962, 1963; Hansson, Hoffman, Schmilterlöw 1964; Schmilterlöw et al. 1965; Schmilterlöw et al. 1967). After radiolabeled nicotine was administered, radioactivity representing nicotine and its metabolites was concentrated in some organs, particularly the brain. Hansson and Schmilterlöw (1962) injected (S)-nicotine-methyl-¹⁴C intramuscularly or intravenously (i.v.) in mice. Within 5 min, high concentrations were found in the brain, adrenal medulla, stomach wall, and kidney. Lower concentrations were observed in the liver, skeletal muscle, and blood, but all concentrations were higher in tissue than in blood. Activity was high in the kidney from 5 min to 4 hr after the nicotine injection, with the highest activity occurring within the first hour. The adrenal medulla maintained a high concentration at 1 hr and 4 hr after injection, but little or no activity was observed at 24 hr. At 30 min, the levels were high in the walls of large blood vessels and in the bone marrow. Radioactivity disappeared rapidly from the brain.

Appelgren, Hansson, and Schmilterlöw (1962) prepared whole-body autoradiograms of mice and cats given i.v. injections of ¹⁴C-nicotine. An initial, heterogeneous accumulation of radioactivity occurred in the CNS. Fifteen minutes after the radiotracer injection, the cat brain showed distinctly more intense labeling of grey than of white matter. Also apparent was a regional distribution within grey matter areas, particularly in the hippocampus. By 30 min, radioactivity was reduced. Studies of mice demonstrated a high concentration of label in the brain at 5 min. By 30 min, the concentration was high in salivary glands, stomach contents, liver, and kidneys, while the brain was almost devoid of radioactivity. The same group also showed the accumulation of ¹⁴C-nicotine in the retina of the eye after i.v. administration (Schmilterlöw et al. 1965).

Fishman (1963) reported that in rats given randomly labeled ¹⁴C-nicotine intraperitoneally (i.p.) and killed 3 hr later, the kidney contained the highest concentration of radioactivity, followed by the lung, liver, brain, skeletal muscle, spleen, and heart. In the dog, more ¹⁴C-nicotine was present in the stomach wall than in any other tissue analyzed 3 hr after i.v. injection of radioactive nicotine.

Yamamoto, Inoki, and Iwatubo (1967) gave mice s.c. injections of 5 mg/kg methyl-¹⁴C-nicotine. Five minutes later, they found 0.5 to 1 µg/g (wet weight) of nicotine in various brain regions, including the cerebral cortex, superior and inferior portions of the brain stem, and

the cerebellum. Highest levels were detected 5 to 10 min after injection. Maximum levels in liver and whole blood were observed 2 and 10 min, respectively, after the injection.

Yamamoto, Inoki, and Iwatubo (1968) studied penetration of ^{14}C -nicotine in rat tissues in vivo and in vitro. They found that 5 mg/kg, i.p., in male Wistar rats produced the following maximum tissue-to-blood ratios of ^{14}C -nicotine activity after 10 to 20 min: kidney, 8.7; liver, 6.7; submaxillary gland, 6.2; cerebral cortex, 3.5; brainstem, 2.4; and heart, 1.8. When they incubated tissue slices with 10^{-4} M ^{14}C -nicotine for 30 min at 37°C, the relative uptake of the label was similar: kidney cortex, 2.6; liver, 2.1; submaxillary gland, 2.1; and cerebral cortex, 2.0. Penetration in slices was unaffected by uncoupling oxidative phosphorylation or blocking metabolic pathways, indicating that the uptake was not by active transport. In vivo, tissue-to-blood ratios were greater than slice-to-medium ratios, indicating that a process other than passive diffusion was involved.

Because the respiratory tract is a major route by which nicotine from tobacco smoke enters the body, Schmiederlow and coworkers (1965) sprayed ^{14}C -nicotine solution directly onto the trachea of mice. Autoradiograms from mice killed at 2 min exhibited a high amount of radioactivity in the respiratory tract and lungs and showed that nicotine enters the CNS rapidly by this route as well. At 15 min, radioactivity still persisted in the lungs, was reduced in the brain, and appeared in large amounts in the kidneys and stomach.

Uptake and distribution of nicotine from tobacco smoke have also been assessed. Harris and Negroni (1965) exposed mice to cigarette smoke and extracted nicotine from the lungs (5 to 25 µg). Mattila and Airaksinen (1966) exposed guinea pigs to the smoke of one 4-g cigar over a period of 40 min, with intermittent ventilation with fresh air, and found that the same tissues which concentrated nicotine administered by other routes also showed nicotine uptake from smoke. Organ-to-blood ratios were lung, 2.0; spleen, 3.0; intestine, 2.9; and brain, 1.1.

The use of positron-emitting radiotracers permits in vivo estimation of nicotine uptake into the brain and other organs, offering the potential of eventually relating nicotine action in the living human brain to behavioral and disease states. Maziere and coworkers (1976) prepared (S)-nicotine-methyl- ^{11}C , which they administered by i.v. injection to mice and rabbits. The time course of the radiotracer confirmed earlier studies and showed a maximum concentration in the 5 min following injection, except in the liver and spleen. Highest radioactivity was in kidneys and brain, followed by liver and lungs. The brain activity dropped rapidly, whereas the kidney concentration remained high (8 percent of injected dose) at 50 min after the injection. External imaging by a γ camera showed considerable

radioactivity in the head, kidneys, and liver. Brain activity decreased sharply over 1 hr, while activity remained high in liver and kidneys.

Maziere and coworkers (1979) used ^{11}C -nicotine and positron emission tomography (PET) in baboons and found that ^{11}C -nicotine readily penetrated into the brain and then dropped sharply with time. Radioactivity was high in the temporal lobe, cerebellum, occipital cortex, pons, and medulla oblongata. There was also a high, stable radioactivity level in the retina, consistent with the earlier observation that radioactivity from ^{14}C -nicotine is found in the retina after i.v. administration (Schmieder et al. 1965).

Heterogeneity of Nicotine Uptake: Microautoradiographic and Subcellular Studies

Appelgren, Hansson, and Schmieder (1963) used a microautoradiographic method to study the localization of nicotine within the superior cervical ganglion of the cat. Most of the radioactivity was localized in the ganglion cells, with little labeling of satellite cells and connective tissue.

Schmieder and coworkers (1967), using microautoradiograms of mouse brains after injection of ^{14}C -nicotine and ^3H -nicotine, reported that nicotine is concentrated in nerve cells. Brain areas with a high density of nerve cells, such as the molecular and pyramidal cell layers of the hippocampus and the molecular layer of the cerebellum, contained high amounts of radioactivity.

Yamamoto, Inoki, and Iwatsubo (1967) studied accumulation of ^{14}C -nicotine into subcellular fractions (nuclear, mitochondrial, nerve ending, microsomal, soluble) of mouse brain after i.p. injection of 5 mg/kg (20 $\mu\text{Ci}/\text{kg}$). Most of the radioactivity was in the soluble fraction. Less than one-tenth of the radioactivity in the soluble fraction was found in microsomes and nerve endings; however, radioactivity levels in microsomes were somewhat higher than in nerve endings.

Effects of Nicotine on Cerebral Metabolism

Following the demonstration that ^3H -nicotine binds stereoselectively and specifically in preparations of rat brain (Yoshida and Imura 1979; Martin and Aceto 1981; Marks and Collins 1982), brain binding sites were visualized (Clarke, Pert, Pert 1984) and quantified (London, Waller, Wamsley 1985) by light microscopic autoradiography. However, mapping nicotinic binding sites or identifying specific binding sites for any drug or neurotransmitter does not necessarily mean that receptors are coupled to pharmacologic actions. An example of nonfunctional, stereoselective, specific binding is that of ^3H -naloxone to glass fiber filters (Hoffman, Altschuler, Fex 1981). In addition, because the brain is a highly interconnected organ, drugs

may produce effects in brain regions remote from their initial receptor interactions. Receptor maps would show primary binding sites but not sites where important secondary actions might occur.

Functional mapping procedures, such as the use of autoradiographic techniques to measure rates of LCGU and regional cerebral blood flow, are another way to determine the sites of the *in vivo* effects of nicotine in the brain. The 2-deoxy-D-[1-¹⁴C]glucose (2-DG) method for measuring LCGU (Sokoloff et al. 1977) has been used to demonstrate a relationship between local cerebral function and glucose utilization under a wide variety of experimental conditions, including pharmacologic treatments (Sokoloff 1981; McCulloch 1982). The effects of acute, s.c. injections of nicotine on LCGU were examined by London and colleagues (1985, 1986) and by London, Szikszay, and Dam (1986), while Grünwald, Schröck, and Kuschinsky (1987) measured the effects on LCGU of constant plasma levels of nicotine produced by i.v. infusion.

Subcutaneous injections of nicotine stimulated LCGU in specific brain regions (Table 1, Figure 1), including portions of the visual, limbic, and motor systems. Effects of nicotine infusion generally paralleled those obtained with s.c. injections. The greatest increase in response to s.c. nicotine occurred in the medial habenula. Marked increases in LCGU were noted in the anteroventral thalamic nucleus, interpeduncular nucleus, and superior colliculus. Moderate increases were seen in the retrosplenial cortex, interanteromedial thalamic nucleus, lateral geniculate body, and ventral tegmental area. No significant effects were observed in the frontoparietal cortex, lateral habenula, or central grey matter. LCGU responses to s.c. injection of nicotine were completely blocked by mecamylamine, indicating the specificity of nicotine effects.

The effects of nicotine on LCGU correlate well with the distributions of ³H-nicotine binding sites (Clarke, Pert, Pert 1984; London, Waller, Wamsley 1985). Areas such as the thalamic nuclei, the interpeduncular nucleus, medial habenula, and the superior colliculus, where there is dense labeling with ³H-nicotine, show moderate to marked nicotine-induced LCGU increases. Areas with less specific binding show smaller LCGU responses to nicotine, and the central grey matter, which lacks specific ³H-nicotine binding, shows no LCGU response. Similarly, nicotine dramatically increases LCGU in the medial but not the lateral habenula, reflecting different densities of ³H-nicotine binding sites. In general, ³H-nicotine binding sites visualized autoradiographically in the rat brain are functional nicotine receptors. However, layer IV of the neocortex displays significant ³H-nicotine binding, but lacks an LCGU response.

In most brain areas, significant LCGU stimulation was obtained with 0.3 mg/kg of nicotine s.c. (London et al. 1986), a dose similar to one used successfully in training rats to distinguish nicotine from

TABLE 1.—R,S-Nicotine effects on glucose utilization in the rat brain

Brain region	Local cerebral glucose utilization ($\mu\text{mol}/100 \text{ g tissue}/\text{minute}$)	
	Saline control	Nicotine (1.75 mg/kg)
Frontoparietal cortex, layer IV	110 \pm 8.1	108 \pm 6.5
Retrosplenial cortex, layer I	98 \pm 6.5	123 \pm 5.1 ¹
Thalamic nuclei		
Anteroventral	109 \pm 6.5	201 \pm 6.1 ¹
Interanteromedial	125 \pm 8.6	175 \pm 12.3 ¹
Lateral geniculate body	82 \pm 6.8	106 \pm 4.4 ¹
Interpeduncular nucleus	99 \pm 9.8	182 \pm 9.3 ¹
Medial habenula	70 \pm 5.2	167 \pm 3.7 ¹
Superior colliculus	72 \pm 5.2	142 \pm 4.6 ¹
Central grey matter	66 \pm 4.0	77 \pm 4.3

NOTE: Results are expressed as the means plus or minus standard deviation for four rats per group.

¹Significantly different from saline control ($p \leq 0.05$).

SOURCE: London et al. (1985).



FIGURE 1.—Effect of subcutaneous R,S-nicotine (1 mg/kg, 2 min before 2-deoxyglucose) on autoradiographic grain densities, representing glucose utilization

NOTE: Photographs of x-ray film exposed to 20- μm brain sections from control rat (A) given 0.9 percent sodium chloride (1 mL/kg) and another rat (B) given nicotine; note the increased density in medial habenula (mh) and fasciculus retroflexus (fr).

SOURCE: London et al. (1986).

saline in a T-maze apparatus (0.4 mg/kg, s.c.) (Overton 1969). Nicotine-induced stimulation of LCGU in the ventral tegmental area

and the habenular complex (London et al. 1985, 1986) may relate to the reinforcing properties of the drug (see Chapter IV). These regions of the brain have been implicated in drug- and stimulation-induced reward systems, respectively (Wise 1980; Nakajima 1984). Additional studies, using specific conditions under which nicotine is reinforcing, are needed to elucidate the anatomical loci involved in nicotine-induced reward and to identify the neurophysiological mechanisms by which nicotine acts as a reinforcer.

Nicotine Receptors

Nicotine exerts diverse pharmacologic effects in both the peripheral nervous system (PNS) and CNS. The peripheral actions of nicotine are important, and some may reinforce the self-administration of nicotine. For example, stimulation in the trachea (Rose et al. 1984) seems to be involved in some of the pleasurable effects of smoking. Skeletal muscle relaxation and electrocortical arousal, both stimulated by actions of nicotine in the lung (Ginzel 1967a,b, 1975, 1987), may contribute to habitual tobacco use (Chapter VI). However, it is generally believed that the central actions of nicotine are of primary importance in reinforcing tobacco use (Chapter IV). In animals, the neuropsychopharmacologic effects of this drug are, with few if any exceptions, mediated through central sites of action. These effects are likely to contribute to the drug's reinforcing properties in animals and humans (Clarke 1987b). In addition, the effects of nicotinic antagonists on tobacco smoking in humans (Stolerman et al. 1973) and in rhesus monkeys (Glick, Jarvik, Nakamura 1970) suggest a central site of reinforcement, but do not rule out a peripheral site. To understand these actions, it is important to know exactly where nicotine acts in the body. This Section discusses evidence for nicotine receptors.

Peripheral Nicotine Receptors

In the mammalian PNS, nicotine and muscarine mimic different actions of ACh by acting at different types of cholinergic receptors. Nicotinic cholinergic receptors (nAChRs) have been subdivided according to location and sensitivity to nicotinic antagonists. Receptors of the C6 or "ganglionic" type are found principally at autonomic ganglia, in the adrenal medulla, and at sensory nerve endings; nicotinic cholinergic transmission in autonomic ganglia is selectively blocked by hexamethonium and certain other compounds. Receptors of the "neuromuscular" type (sometimes referred to as C10 type) are located on the muscle endplate, where transmission is selectively blocked by compounds such as decamethonium and alpha-bungarotoxin (α -BTX).

Higher doses of nicotine are required to stimulate nAChRs in skeletal muscle than at autonomic ganglia. Ganglionic nAChRs appear to be more sensitive than their neuromuscular counterparts, not only to the stimulant but also to the desensitizing actions of nicotine (Paton and Savini 1968). Doses of nicotine obtained by smoking cigarettes do not appear to affect the muscle endplate directly. Therefore, if the CNS were to possess both types of nAChR, doses of nicotine obtained by normal cigarette smoking might affect only the C6-receptor population. Accordingly, many of the central effects of nicotine *in vivo* and *in vitro* are reduced or blocked by nicotinic antagonists that are C6-selective in the periphery. The most widely used C6-selective antagonist is mecamylamine, which passes freely into the CNS after systemic administration. Mecamylamine antagonizes actions of nicotine in the brain and spinal cord, as revealed by behavioral (Collins et al. 1986; Goldberg, Spealman, Goldberg 1981) and electrophysiological experiments (Ueki, Koketsu, Domino 1961) and also by studies of neurotransmitter release (Hery et al. 1977; Chesselet 1984). There have been few attempts to determine whether these central nicotinic actions are also blocked by neuromuscular antagonists, while several studies support the existence of central C6 nAChRs (Aceto, Bentley, Dembinski 1969; Brown, Docherty, Halliwell 1983; Caulfield and Higgins 1983; Egan and North 1986).

The search for putative central α -BTX nAChRs has been hindered by several factors, including the central convulsant actions of α -BTX antagonists (Cohen, Morley, Snead 1981) and the probable need to deliver locally high concentrations of nicotine. Nevertheless, several studies have demonstrated actions of nicotine or cholinergic agonists that can be reduced or blocked by α -BTX, which acts selectively at neuromuscular nAChRs (Zatz and Brownstein 1981; Farley et al. 1983; de la Garza et al. 1987a).

Radioligand Binding to Putative Nicotine Cholinergic Receptors in Mammalian Brain

Many receptors for neurotransmitters in the brain have been identified through the use of radiolabeled probes (radioligands). Attempts to label putative brain nAChRs have used compounds with known potency at peripheral sites (see Table 2).

Agonist Binding

The stereospecific, saturable, and reversible binding of ^3H -nicotine to rodent brain is well-described (Romano and Goldstein 1980; Marks and Collins 1982; Costa and Murphy 1983; Benwell and Balfour 1985a; Clarke, Pert, Pert 1984). Most studies have demonstrated the existence of a population of high-affinity binding sites (reflected by a dissociation constant in the low nanomolar range) that is potently

TABLE 2.—Radioligands for putative nicotinic cholinergic receptors in mammals

Antagonists	Bind	Functional antagonism	Sites examined	Agonists
¹²⁵ I-BTX	Yes	Yes	Muscle endplate	³ H-nicotine ³ H-methyl-carbachol
	Yes	Yes	Autonomic ganglia, spinal cord	
	Yes	Yes	Brain (certain sites only)	
¹²⁵ I-naja toxin	Yes	Yes	Muscle endplate	³ H-ACh (with excess muscarinic antagonist and AChE inhibitor)
	Yes	ND ¹	Brain	
³ H-dTC	ND	Yes	Muscle, spinal cord, ganglia	
	Yes	Yes	Brain	
³ H-DHBE	ND	Yes	Muscle, autonomic ganglia	
	Yes	Yes	Brain, spinal cord	
Neosurugatoxin	ND	No	Muscle endplate	
	ND	Yes	Autonomic ganglia	
	Yes	Yes	Brain (inhibits ³ H-nicotine)	

¹ ND = no data.

inhibited by nicotinic agonists including ACh. In contrast, most nicotinic antagonists have very low affinity for this site. Binding with similar characteristics has been reported in rat brain tissue with ³H-methyl-carbachol (Abood and Grassi 1986; Boksa and Quirion 1987) and with ³H-ACh in the presence of excess atropine to prevent binding to muscarinic receptor sites (Schwartz, McGee, Kellar 1982).

In the presence of atropine, tritiated nicotine and ³H-ACh probably bind to the same population of high-affinity sites in rat brain. Thus, the two radioligands share the same neuroanatomical distribution of binding (Clarke, Schwartz et al. 1985; Marks et al. 1986; Martino-Barrows and Kellar 1987). Binding of both ligands is inhibited with similar potency by a range of nicotinic agents, is up-regulated by chronic nicotine treatment *in vivo*, is down-regulated by chronic treatment with acetylcholinesterase inhibitors, and is diminished by disulfide reducing agents *in vitro* (Marks et al. 1986; Martino-Barrows and Kellar 1987; Schwartz and Kellar 1983). Although less well studied, it appears that sites labeled by ³H-methyl-carbachol are the same as those labeled by ³H-ACh and ³H-nicotine (Abood and Grassi 1986; Boksa and Quirion 1987). High-affinity nicotine binding sites have been found in brain tissue of mice (Marks and Collins 1982), rats (Romano and Goldstein 1980), monkeys (Friedman et al. 1985), and humans (Shimohama et al. 1985; Flynn and Mash 1986; Whitehouse et al. 1986).

Some investigators have reported a second class of sites which are characterized by lower binding affinity and higher capacity for ³H-

nicotine. With no demonstrated differential anatomical distribution or stereoselectivity (Romano and Goldstein 1980; Marks and Collins 1982; Benwell and Balfour 1985b), these low-affinity sites are of questionable pharmacologic significance, but may be the result of post mortem proteolysis (Lippiello and Fernandes 1986). Careful analysis of ^3H -nicotine binding conducted in the absence of protease inhibitors has revealed the existence of five affinity sites or states (Sloan, Todd, Martin 1984). Functional studies (Martin et al. 1986) suggest that some of these different sites may represent in vivo sites of action for nicotine, although it is not clear which if any would be activated by nicotine doses obtained from typical cigarette smoking.

Radioligand Binding

Many receptors of different nicotine binding affinities have been reported. It is unclear whether these reflect different conformational states or binding sites of a single type of receptor, distinct receptor populations, or a single type of high-affinity site which has undergone proteolytic degradation. Preliminary evidence supports the existence of distinct receptor subtypes labeled by agonists. Two components of high-affinity ^3H -nicotine binding, differing in their affinity for neosurugatoxin, can be distinguished in rat brain. The relative proportion of these two components differs in different regions of the rat brain, suggesting that they are physically distinct receptors (Yamada et al. 1985).

Antagonist Binding

Most studies of nicotine binding in mammalian brain have used radioiodinated α -BTX (^{125}I -BTX), which binds with high affinity and in a saturable manner to sites in mammalian brain (Schmidt, Hunt, Polz-Tejera 1980; Oswald and Freeman 1981). This binding is selectively inhibited by nicotinic agents, including nicotine and ACh. Cobra (naja) alpha-toxin, like α -BTX, is a selective neuromuscular blocker in the mammal, and appears to label the same sites as α -BTX in mammalian brain. Binding is potently inhibited by unlabeled α -BTX and has a regional distribution resembling that of ^{125}I -BTX binding (Speth et al. 1977). The antagonist dihydro-beta-erythroidine (DHBE) binds to two sites in rat brain, but the regional distribution of binding differs from that of ^{125}I -BTX (Williams and Robinson 1984). DHBE acts with similar potency at both types of peripheral nAChR in vivo. It is not clear whether ^3H -d-tubocurarine binding is selectively inhibited by nicotinic agents. In rat brain, ^{125}I -BTX binds to a distinct population of sites that are not labeled with high affinity (nanomolar k_D) by tritiated nicotinic agonists. Radioiodinated α -BTX sites have a different neuroanatomical distribution (Marks and Collins 1982; Schwartz, McGee, Kellar 1982; Clarke, Schwartz et al.

1985) and can be physically separated from tritiated agonist binding sites by affinity chromatography (Schneider and Betz 1985; Wonnacott 1986). This type of study helps to determine the location and numbers of nicotine binding sites.

Functional Significance of Nicotinic Binding Sites

High-Affinity Agonist Binding Sites

Brain sites which bind ^3H -ACh and ^3H -nicotine with high affinity represent nAChRs that respond in some ways like the C6 type of receptor found in the periphery (Clarke 1987a). Studies using the 2-DG technique have revealed that the neuroanatomical pattern of cerebral activation following the systemic administration of nicotine in rats is strikingly similar to the distribution of high-affinity agonist binding demonstrated autoradiographically (London et al. 1985; Grunwald, Schrok, Kuschinsky 1987). Pretreatment with mecamylamine blocks the effects of nicotine on LCGU, suggesting that putative ganglionic (C6-type) receptors in the brain are associated with high-affinity agonist binding.

Most of nicotine's actions on central receptors are blocked by the C6-selective antagonist mecamylamine. The relevant nAChRs are probably those which are labeled with high affinity by tritiated agonists. However, the absence of high-affinity agonist binding sites in PC12 cells (derived from a pheochromocytoma cell line) known to express C6-type receptors (Kemp and Morley 1986) indicates that although central and ganglionic nAChRs have pharmacologic similarities, they may not be identical at the molecular level.

High-affinity agonist binding sites are relevant to long-term effects of human tobacco smoking. Recently, Benwell, Balfour, and Anderson (in press) observed that the density of high-affinity ^3H -nicotine binding in post mortem human brain is higher in smokers than in nonsmokers. The increased density of sites in smokers is consistent with studies in animals that show that chronic treatment with nicotine leads to an increased number of nicotinic receptors in the brain (Schwartz and Kellar 1983; Marks, Burch, Collins 1983b).

Alpha-Bungarotoxin Binding Sites

Although α -BTX does not block nicotinic actions in all areas of the CNS (Duggan, Hall, Lee 1976; Egan and North 1986), there are several reports of antagonism (Zatz and Brownstein 1981; Farley et al. 1983; de la Garza et al. 1987a). In the rat cerebellum, locally applied nicotine alters single-unit activity in a manner dependent on cell type: nicotine excites interneurons but inhibits Purkinje cells. Both actions are directly postsynaptic (de la Garza et al. 1987, in press(b)). The inhibitory effects of nicotine are blocked by hexame-

thonium but not by α -BTX, which does block the excitatory effects (de la Garza et al., in press(a)).

Strain differences exist in mice in the physiological and behavioral effects of nicotine, in the development of tolerance to these effects, and in the regional distribution of ^{125}I -BTX binding density (Marks, Burch, Collins 1983a; Marks, Stitzel, Collins 1986). The genetically determined variation in response is not readily explained by differences in brain nicotinic receptors. However, a classical genetic analysis indicates that the density of ^{125}I -BTX binding sites in mouse hippocampus correlates with susceptibility to seizures induced by high doses of nicotine (Miner, Marks, Collins 1984). These and other considerations (Clarke 1987a) suggest that ^{125}I -BTX may label a subtype of nAChR in the brain and that this receptor is pharmacologically akin to the nAChR found in muscle.

Although ^{125}I -BTX binding sites are found in human brain, the available evidence suggests that nicotine at doses obtained from cigarette smoking does not activate this population of brain nAChRs. Rather, the pattern of neuronal activation that follows the *in vivo* administration of nicotine in animal experiments, even in doses far greater than those likely to occur during smoking, resembles the neuroanatomical distribution of high-affinity agonist binding sites (London et al. 1985; Grunwald, Schrok, Kuschinsky 1987). However, this issue is not conclusively resolved, and a potential role for bungarotoxin binding receptors in mediating effects of smoking cannot be completely excluded.

Behavioral and Physiological Studies

The effects of mecamylamine on several responses elicited by nicotine in mice have been examined (Collins et al. 1986). The responses are of two major classes: those blocked by low doses of mecamylamine (inhibitory concentrations for 50 percent of mice tested (IC_{50}) $< 0.1 \text{ mg/kg}$) (seizures and startle response) and those blocked by higher doses (IC_{50} approximately 1 mg/kg) (effects on respiratory, heart rate, body temperature, and Y-maze activity). Strain differences are also apparent in the sensitivity to mecamylamine blockade. These findings are consistent with the existence of at least two types of central nAChR.

The Neuroanatomical Distribution of Nicotinic Binding Sites in the Brain

High-Affinity Agonist Binding Sites

Rodent

Autoradiographic maps of high-affinity nicotinic binding sites in rat brain are essentially identical for ^3H -nicotine, ^3H -ACh, and ^3H -methyl-carbachol (Clarke, Pert, Pert 1984; Clarke, Schwartz et al.

1985; London, Waller, Wamsley 1985; Boksa and Quirion 1987). Dense labeling is observed (1) in the medial habenula and interpeduncular nucleus, which appear to belong to a common cholinergic system; (2) in the so-called specific motor and sensory nuclei of the thalamus and in layers III and IV of cerebral cortex with which they communicate; (3) in the substantia nigra pars compacta and ventral tegmental area, where labeling is associated with dopaminergic cell bodies (Clarke and Pert 1985); and (4) in the molecular layer of the dentate gyrus, the presubiculum, and the superficial layers of the superior colliculus. Labeling is sparse in the hippocampus and hypothalamus.

Monkey

The autoradiographic distribution of high-affinity ^3H -nicotine binding in rhesus monkey brain is similar to that in the rat (Friedman et al. 1985). Dense labeling has been noted in the anterior thalamic nuclei and in a band within cerebral cortex layer III. The latter band is densest and widest in the primary sensory areas. Several other thalamic nuclei are moderately labeled, but as in the rat, the label is sparse in the midline thalamic nuclei. In contrast to findings for the rat, the medial habenula appears unlabeled.

Human

High-affinity agonist binding has not been mapped autoradiographically in human brain. However, assays of a few dissected brain areas suggest the following pattern: nucleus basalis of Meynert > thalamus > putamen > hippocampus, cerebellum, cerebral cortex, and caudate nucleus (Shimohama et al. 1985). Two affinity sites for ^3H -nicotine have been detected, and the regional distribution observed reflects the presence of both sites.

Alpha-Bungarotoxin Binding Sites

Because ^{125}I -BTX sites may not be relevant to tobacco smoking, they will be discussed only briefly here. There are clear differences of regional distribution not only between mice and rats, but also between different strains of mice (Marks et al. 1986). The autoradiographic distribution of ^{125}I -BTX labeling in rat brain is strikingly different from the pattern of ^3H -agonist labeling, with highest site density in hippocampus, hypothalamus, and superior and inferior colliculi (Clarke, Schwartz et al. 1985). An attempt to map ^{125}I -BTX binding in human brain was hampered by a high degree of nonspecific binding, with diffuse specific labeling in the hippocampus and cerebral cortex (Lang and Henke 1983).

Molecular Biology

Goldman and colleagues have mapped regions in the brain which contain cell bodies expressing RNA that codes for putative nAChRs. The RNA identified is homologous to cDNA clones encoding the alpha subunits of the muscle nAChR and a putative neuronal nAChR (Goldman et al. 1986; Goldman et al. 1987). These and related findings show that a family of genes exists that codes for proteins similar to, but not identical with, the muscle nAChR. The functional role of these putative nAChR subtypes in the CNS is not clear.

Central Nicotinic Cholinergic Receptors: Pre- or Postsynaptic?

Presynaptic Regulation of Neurotransmitter Release

The release of ACh from some nerve terminals in the CNS (Rowell and Winkler 1984; Beani et al. 1985) and periphery (Briggs and Cooper 1982) is increased by activation of presynaptic nicotinic "autoreceptors." Preliminary evidence from lesion experiments suggests that some nicotinic autoreceptors in the brain may be high-affinity ^3H -nicotine binding sites (Clarke et al. 1986).

Nicotine also modulates the release of certain other neurotransmitters by acting at receptors located on nerve terminals. This form of regulation has been shown for dopaminergic, noradrenergic, and serotonergic terminals (Starke 1977; Chesselet 1984). Lesion studies suggest that these receptors are labeled by ^3H -agonists (Schwartz, Lehmann, Kellar 1984; Clarke and Pert 1985; Prutsky, Shaw, Cynader 1987).

Somatodendritic Postsynaptic Actions

Much of ^3H -agonist labeling probably represents nAChRs located on neuronal cell bodies or dendrites. For example, nicotine excites neurons postsynaptically in the medial habenula, locus coeruleus, and interpeduncular nucleus, all areas of moderate to dense ^3H -agonist binding (Brown, Docherty, Halliwell 1983; Egan and North 1986; McCormick and Prince 1987).

Neuroendocrine and Endocrine Effects of Nicotine

Nicotine has direct and indirect effects on several neuroendocrine and endocrine systems (Balfour 1982; Clarke 1987a; Hall 1982). This Section reviews research on the effects of nicotine in animals and humans that are relevant to understanding cigarette smoking. Nicotine effects on cholinergic and noncholinergic nicotinic receptors, as well as on the release of catecholamines, monoamines, pituitary hormones, cortisol, and other neuroendocrine chemicals,

are discussed. Effects on single neuroregulators are emphasized, but it is important to recognize that there are extensive interrelationships among these substances (Tuomisto and Männistö 1985).

Nicotine has effects on peripheral endocrine as well as on central neuroendocrine functions. In the early 1900s researchers discovered that nicotine stimulated autonomic ganglia (ganglia were painted with tobacco solutions), inducing such effects as the release of adrenal catecholamines (Larson, Haag, Silvette 1961). As the health consequences of cigarette smoking have become clearer, many investigators have sought to determine tobacco's effects on the endocrine system, with the possibility that understanding such effects may help to explain smoking behavior. Nicotine is regarded as the major pharmacologic agent in tobacco and tobacco smoke responsible for alterations in endocrine function. However, there has not been a systematic evaluation of the effects of metabolites of nicotine or constituents of tobacco other than nicotine on the endocrine system.

The functional significance of nicotine-induced perturbations in hormonal patterns and the role of neuroregulators in smoking are poorly understood. Extensive literature using nicotinic agonists and antagonists indicates relationships between cholinergic activity and particular behavioral effects (Henningfield et al. 1983; Kumar, Reavill, Stolerman, *in press*). Similar strategies have been employed to explore the contributions of catecholamines to smoking-related behavior. However, the exploration of the importance of neuroregulators in the reinforcement of cigarette smoking is still at an early stage.

Cholinergic Effects

Nicotine has cholinergic effects in the PNS and CNS. Nicotine is a cholinergic agonist at peripheral autonomic ganglia and somatic neuromuscular junctions at low doses and becomes an antagonist at high doses (Volle and Koelle 1975). Nicotine also releases ACh in the cerebral cortex (Armitage, Hall, Morrison 1968; Rowell and Winkler 1984) and in the myenteric plexus of the peripheral ANS (Briggs and Cooper 1982). Balfour (1982) has suggested that cortical arousal (see Electrophysiological Actions of Nicotine for a detailed discussion) is mediated by ACh release but that behavioral stimulation (see Chapter IV) either is not mediated by ACh release or does not depend on the action of ACh at a muscarinic receptor.

Studies involving intracerebral administration of nicotine have been used to determine the loci of nicotine's action (Kammerling et al. 1982; Wu and Martin 1983). The injection of nicotine into the cerebral ventricles of cats, dogs, and rats produces a variety of effects including changes in cardiovascular activity, body temperature, respiration, salivation, muscle reflex tone, and electrocortical indices

of sleep and arousal; the direction and duration of effects depend on dosage and on baseline response parameters (Hall 1982).

Nicotine's cholinergic actions can affect other neuroregulators in the body (Andersson 1985). Nicotine stimulates NE release in the hypothalamus by a Ca^{2+} -dependent process that can be inhibited by prior administration of hexamethonium or ACh (Hall and Turner 1972; Westfall 1974). The mechanism resembles nicotine's effects on peripheral adrenergic nerve terminals (Westfall and Brasted 1972). At high dose levels, nicotine stimulates NE release by displacing it from vesicle stores at sites outside the hypothalamus (Balfour 1982). These actions are relevant to understanding the reinforcing effects of nicotine. For example, using drug discrimination procedures, Rosecrans (1987) has demonstrated that intact central NE and dopamine (DA) function were required to elicit the cue properties of nicotine.

Intravenous administration of nicotine modulates the release of both neurohypophyseal and adenohypophyseal hormones (Bisset et al. 1975; Hall, Francis, Morrison 1978). Hillhouse, Burden, and Jones (1975) found that the *in vitro* application of ACh to the hypophysiotropic area of the rat caused a significant increase in the basal secretion of corticotropin-releasing hormone (as measured by bioassay), which in turn controls, via the anterior pituitary, the release of the pro-opiomelanocortin (POMC) group of hormones— β -endorphin, β -lipotropin, melanocyte-stimulating hormone-releasing factor, and adrenocorticotropic hormone (ACTH) (Meites and Sonntag 1981). The humoral mechanism for the release of vasopressin has been traced from the medulla to the paraventricular nuclei of the hypothalamus (Bisset et al. 1975; Castro de Souza and Rocha e Silva 1977). Similarly, Risch and colleagues (1980) have demonstrated a cholinergic mechanism for the release of β -endorphin.

Modulation of Catecholamine and Serotonin Activity

Dale and Laidlaw (1912) found that the pressor response of the cat to nicotine was due in part to the release of epinephrine from the adrenal glands. Over the past 75 years, a large body of research has confirmed and further investigated this phenomenon. Stewart and Rogoff (1919) quantified the effect of nicotine on adrenal epinephrine release. Kotegoda (1953) observed that nicotine releases catecholamines from extra-adrenal chromaffin tissues. Watts (1961) demonstrated the effect of smoking on adrenal secretion of epinephrine. Hill and Wynder (1974) reported that increasing the nicotine content in cigarette smoke progressively increased the serum concentration of epinephrine, but not NE. Winternitz and Quillen (1977) found that the excretion of urinary catecholamines tended to be higher on smoking days than on nonsmoking days. Several recent studies have focused on the role of nicotine and the mechanisms involved in the

release of catecholamines from cultured chromaffin cells (Forsberg, Rojas, Pollard 1986). Earlier experiments by Douglas and Rubin (1961), using denervated perfused cat adrenal glands, indicated that nicotine augments catecholamine release from chromaffin cells by promoting an influx of extracellular calcium. Forsberg, Rojas, and Pollard (1986) suggested that nicotine-induced catecholamine secretion may be mediated by phosphoinositide metabolism in bovine adrenal chromaffin cells.

The anatomical localization and importance of biogenic monoamines such as serotonin (5-HT [5-hydroxytryptamine]), DA, and NE have been the subject of intense research for the past 30 years. The classic studies of Dahlstrom and Fuxe (1966) revealed that neurons containing these amines were localized in specific ascending projection systems; descending monoaminergic neurons have also been described. The physiological integrity of these systems was further demonstrated by Aghajanian, Rosecrans, and Sheard (1967), who observed that stimulation of 5-HT cell bodies localized in the midbrain raphe nucleus released 5-HT from nerve endings located in the more rostral forebrain. The recognition that these amine systems constitute a unique interneuronal communication system has played a central role in understanding underlying neurochemical and behavioral mechanisms.

The cholinergic system has undergone a similar analysis (Fibiger 1982), but the delineation of specific cholinergic pathways has been more difficult because no histochemical method has been available for ACh. It does appear, however, that the cholinergic system is similarly organized and interacts with specific biogenic amine pathways. For example, Robinson (1983) has clearly shown that both 5-HT and DA systems exert tonic inhibitory control over ACh turnover in both the hippocampus and frontal cortex regions. Lesions of the medial raphe nuclei increase the ACh turnover rate in hippocampal sites, while lesions of the dorsal raphe elicit a similar effect in frontal cortical areas. Evidence of DA control comes from the observation that the catecholamine neurotoxin, 6-OHDA, when injected into the DA-rich septal area, facilitated hippocampal ACh turnover. The research of Kellar, Schwartz, and Martino (1987) and others also suggests that nicotinic receptors may occupy a presynaptic site on select DA and 5-HT nerve endings. Westfall, Grant, and Perry (1983), using a tissue slice preparation, have shown that the DMPP-induced stimulation of nicotinic receptors in the striatum will facilitate the release of both 5-HT and DA. This preparation is devoid of cell bodies or 5-HT- and DA-containing axon terminals, suggesting that these nicotinic cholinergic receptors are primarily presynaptic. Further, hexamethonium, but not atropine, attenuated nicotine-induced amine release, confirming that these effects are nicotinic in nature.

Nicotine may have simultaneous actions on many types of neurons. Even though only one kind of receptor may be stimulated, either activation or inhibition of a particular 5-HT, NE, or DA neuron may be the ultimate outcome. Conversely, the activity of specific cholinergic neurons may also be controlled by one of these biogenic-amine-containing projection systems. Nicotine appears to produce its discriminative stimulus effect in at least one major brain area, the hippocampus. This site is rendered insensitive if DA neurons innervating this area are destroyed (Rosecrans 1987). The interrelationships of these amine pathways are important to understand nicotine's effects on behavior and its effects on the neuroendocrine system because of the central role that these amine systems play in the hypothalamic control of the pituitary.

Effects on Serotonergic Neurons

Research evaluating the relationship between nicotine and 5-HT has involved several different approaches. Hendry and Rosecrans (1982) compared the effects of nicotine on conditioned and unconditioned behaviors in rats selected for differences in physical activity and 5-HT turnover. Balfour, Khuller, and Longden (1975) observed that acute doses of nicotine were capable of attenuating hippocampal 5-HT turnover, an effect specific to the hippocampus. Fuxe and colleagues (1987) did not observe any acute changes in 5-HT function following acute nicotine dosing but did observe a significant reduction of 5-HT turnover following repeated doses (3×2 mg/kg/hr). This effect, however, was suggested to be due to cotinine, the primary metabolite of nicotine.

In addition to attempts to correlate 5-HT function with some pharmacologic effect of nicotine, investigators have evaluated potential links between 5-HT and neuroendocrine function. Balfour, Khuller, and Longden (1975) showed a relationship between 5-HT and nicotine's ability to induce the release of plasma corticosterone, presumably by activation of the pituitary-adrenal axis. Following acute nicotine injections in the rat, a reduction in 5-HT turnover correlated with an increase in plasma corticosterone. Rats exhibited tolerance to pituitary activation following repeated nicotine doses, but not to the attenuation of hippocampal 5-HT turnover. Stress antagonized nicotine-induced reductions of hippocampal 5-HT. Also, nicotine was reported to inhibit the adaptive response to adrenocortical stimulation following chronic stress (Balfour, Graham, Vale 1986). One interpretation of these data is that nicotine can modify how rats adapt to stress, which may be mediated by changes in hippocampal 5-HT function. At this point, however, it is difficult to draw firm conclusions concerning how nicotine affects 5-HT neurons and whether this neurotransmitter is involved in any of nicotine's

effects on neuroendocrine function. Hippocampal 5-HT turnover appears to be selectively attenuated by nicotine.

Effects on Catecholaminergic Neurons

Studies of the effects of nicotine on NE-containing neurons have produced mixed results. Earlier work suggested that nicotine may affect behavior via a NE component, but recent research has not supported such claims (Balfour 1982). It has been reported that nicotine releases DA from brain tissue (Westfall, Grant, Perry 1983). Lichtensteiger and colleagues (1982) observed that nicotine releases DA through an acceleration of the firing rate of DA cell bodies located in substantia nigra zona compacta when nicotine is administered via iontophoretic application or s.c. (0.4 to 1.0 mg/kg). This activation was marked by a significant increase in striatal DA turnover; DHBE, but not atropine, attenuated nigrostriatal activation. Evidence that nicotine facilitates the firing of DA cell bodies by stimulating nicotinic cholinergic receptors has recently been reported by Clarke, Hommer, and coworkers (1985), who showed a specific effect of nicotine antagonized by mecamylamine on pars compacta cell bodies. Connelly and Littleton (1983) noted that DA release from synaptosomes lacked stereoselectivity but was blocked by the ganglionic-blocking drug pempidine.

Fuxe and coworkers (1986, 1987) have studied nicotine's effects on central catecholamine neurons in relation to neuroendocrine function. These investigators use quantitative histofluorometric techniques that measure the disappearance of catecholamine stores by administering a tyrosine hydroxylase inhibitor (AMPT) to rats receiving various doses of nicotine or exposed to tobacco smoke. Tissues are then exposed to formaldehyde gas, and histofluorescence in AMPT-treated rats is evaluated in comparison to controls.

Nicotine is a potent activator of both DA and NE neuron systems located primarily in the median eminence and in areas of the hypothalamus. These effects result from a stimulation of nicotinic cholinergic receptors, generally antagonized by mecamylamine. Intermittent nicotine dosing (4 x 2 mg/kg, s.c. every 30 min) or tobacco smoke exposure (rats were exposed to one to four cigarettes with a smoking machine-determined nicotine yield of 2.6 mg; rats received 8 puffs at 10-min intervals) results in a decrease of prolactin, thyroid-stimulating hormone (TSH), and luteinizing hormone (LH) and an increase of plasma corticosterone levels. Nicotine doses of 0.3 mg/kg administered i.v. induce an overall activation of the hypothalamic-pituitary axis, causing an increase of both ACTH and prolactin that subsides within 60 min. Tolerance to the corticosterone response develops after repeated nicotine doses, and there is evidence that it develops after a single dose of nicotine (Sharp and Beyer 1986; Sharp et al. 1987). Restraint stress increases

ACTH, corticosterone, and prolactin levels and decreases DA and NE levels in hypothalamic regions. This stressor attenuates nicotine's activation of NE neurons but does not reverse its attenuating effects on prolactin.

Nicotine appears to be associated with neuroendocrine activity by NE and DA activation (Fuxe et al. 1987). Immunohistochemical studies suggest that alterations in NE function are more important for the control of the pituitary-adrenal-axis, while DA turnover appears to be crucial for nicotine's effects on prolactin, LH, and follicle-stimulating hormone (FSH). Moreover, these studies indicate that similar nAChRs are located within both DA mesolimbic and neostriatal systems.

Stimulation of Pituitary Hormones

Nicotine administration and cigarette smoking stimulate the release of several anterior and posterior pituitary hormones. Seyler and coworkers (1986) had human subjects smoke two high-nicotine (2.87 mg) cigarettes in quick succession. Plasma levels of prolactin, ACTH, β -endorphin/ β -lipoprotein, growth hormone (GH), vasopressin, and neurophysin I increased. No change was seen in TSH, LH, or FSH. The rapid smoking paradigm used by Seyler and coworkers (1986) may have contributed to the effects of nicotine. Growth hormone levels exhibited a prolonged increase after subjects smoked three cigarettes in rapid succession (Sandberg et al. 1973). In experiments conducted by Winternitz and Quillen (1977) with male habitual smokers, GH began to rise after two cigarettes, peaked at 1 hr, and then returned to control levels while smoking continued. Wilkins and colleagues (1982) also found that smoking increases GH levels and presented evidence that the effect is nicotine mediated. Coiro and coworkers (1984) reported that the increase in GH produced by clonidine was greatly enhanced by cigarette smoking, suggesting that nicotinic cholinergic and adrenergic mechanisms might interact in the stimulation of GH secretion.

The TSH plasma levels were not affected when nicotine was administered over a 60-min period to female rats (Blake 1974). In studies involving exposure to cigarette smoke, Andersen and colleagues (1982) reported a lowering of TSH secretion in rats, but as noted, Seyler and coworkers (1986) found no change in human subjects. Thus, the data on the effects of nicotine on TSH release are inconclusive at this time.

ACTH plasma levels increased after i.p. injection of nicotine in the rat (Conte-Devolx et al. 1981). In similar experiments, Cam and Bassett (1983b) found that elevated ACTH levels peaked and rapidly declined to a sustained plateau level. Sharp and Beyer (1986) reported that the effects of nicotine on ACTH in rats show a rapid and marked desensitization. Seyler and coworkers (1984) had male

subjects smoke cigarettes containing 0.48 or 2.87 mg of nicotine. No increases in ACTH or cortisol were detected after subjects smoked 0.48-mg-nicotine cigarettes. Cortisol levels rose significantly in 11 of 15 instances after smoking the high-nicotine cigarettes, but ACTH rose in only 5 of the 11 instances when cortisol increased. Each ACTH increase occurred in a subject who reported nausea and was observed to be pale, sweaty, and tachycardic. Seyler and coworkers (1984) studied smokers and concluded that ACTH release occurs only in smokers who become nauseated.

LH levels were reduced in male rats exposed to unfiltered cigarette smoke, while FSH was unchanged (Andersen et al. 1982). In experiments by Winternitz and Quillen (1977), there were no differences in LH and FSH among male cigarette smokers while smoking as compared with not smoking. Seyler and colleagues (1986) found no change in human LH or FSH levels after smoking. There is no evidence of gonadotropin release stimulated by nicotine or smoking.

Prolactin plasma levels were lowered considerably in lactating rats injected twice daily with nicotine (Terkel et al. 1973). It was suggested that failure of prolactin release following chronic nicotine administration was responsible for low milk production and starvation of pups. Blake and Sawyer (1972) found that, in lactating rats, the rapid suckling-induced release of prolactin into the blood is inhibited by s.c. injections of nicotine. Ferry, McLean, and Nikititovich-Winer (1974) reported that tobacco smoke inhalation in rats delays the suckling-induced release of prolactin. Andersen and coworkers (1982) found that prolactin secretion was reduced in male rats in a dose-dependent manner by exposure to unfiltered cigarette smoke. However, Sharp and Beyer (1986) reported that the effects of nicotine on prolactin in rats shows a biphasic effect, first increasing and then decreasing. Suppressed prolactin levels were found in female smokers who were breast feeding (Andersen et al. 1982). These researchers noted that smokers weaned their babies significantly earlier than nonsmokers. However, Wilkins and coworkers (1982) observed an increased level of prolactin in male chronic smokers.

Arginine Vasopressin

In addition to its antidiuretic effects, arginine vasopressin acts as a vasoconstrictor (Munck, Guyre, Holbrook 1984; Waeber et al. 1984). Arginine vasopressin may also act as a neuromodulator in pathways that affect behavior. It has been shown to promote memory consolidation and retrieval in rats (Bohus, Kovacs, de Wied 1978) and there are reports of memory enhancement following intranasal administration of a vasopressin analog in both normal and memory-deficient humans (LeBoeuf, Lodge, Eames 1978; Legros et al. 1978;

Weingartner et al. 1981). Nicotinic cholinergic receptors in the medial basal hypothalamus and muscarinic cholinergic receptors in the neurohypophysis (posterior pituitary) have been implicated in the release of vasopressin (Gregg 1985). Nicotine has been found to stimulate vasopressin release in a dose-related manner in animals (Reaves et al. 1981; Siegel et al. 1983) and in humans (Dietz et al. 1984; Pomerleau et al. 1983; Seyler et al. 1986). These observations are consistent with the effects of nicotine on cognitive performance (Chapter VI).

The Pro-Opiomelanocorticotropin Group of Hormones

The POMC hormones are released in response to stress and in response to corticotropin-releasing hormone (Munck, Guyre, Holbrook 1984; Krieger and Martin 1981). ACTH has behavioral effects and stimulates the release of steroids such as cortisol from the adrenal cortex. ACTH produces rapid cycling between sleeping and waking as well as sexual stimulation, grooming/scratching, blocking of opiate effects such as analgesia, and the enhancement of attention and stimulus discrimination (Bertolini and Gessa 1981). Endogenous opioids, such as β -endorphin, potentiate vagal reflexes, cause respiratory depression, lower blood pressure, block the release of catecholamines (Beaumont and Hughes 1979; Schwartz 1981), have antinociceptive effects (van Ree and de Wied 1981), and modulate neurotransmitter systems leading to amnesic effects (Izquierdo et al. 1980; Introini and Baratti 1984). It has been suggested that the primary function of the endogenous opioids is metabolic, serving to conserve body resources and energy (Amir, Brown, Amit 1980; Margules 1979; Millan and Emrich 1981).

Nicotine appears to stimulate the release of corticotropin-releasing hormone from the hypothalamus through a nicotinic cholinergic mechanism (Hillhouse, Burden, Jones 1975; Weidenfeld et al. 1983). Using an isolated perfused mouse brain preparation, Marty and coworkers (1985) demonstrated that nicotine stimulates secretion of β -endorphin and ACTH in a dose-related manner when applied directly to the hypothalamus but not when applied to the pituitary. The work of Sharp and Beyer (1986) supports this finding; they reported that the secretion of ACTH following nicotine was unaffected by adrenalectomy. Nicotine administration to rats has also been shown to increase the plasma levels of corticosterone, ACTH, and β -endorphin in a dose-related manner (Conte-Devolx et al. 1981). Termination of chronic nicotine administration reduced hypothalamic β -endorphin levels (Rosecrans, Hendry, Hong 1985). Hurlick and Corrigal (1987) have also observed that the narcotic antagonist naltrexone inhibits some nicotine-modulated behavior in mice, providing a possible link between nicotine stimulation of endogenous opioid activity and behavioral responses. Acute administration of

nicotine increases levels of plasma ACTH and corticosterone sharply (Cam and Bassett 1983b), while chronic exposure results in complete adaptation (Cam and Bassett 1984). Melanocyte-stimulating hormone was decreased and β -endorphin was increased by i.p. injections of nicotine in the rat (Conte-Devolx et al. 1981).

Risch and colleagues (1980, 1982) have accumulated evidence for cholinergic control of cortisol, prolactin, and β -endorphin release in humans. Rapid smoking increases circulating cortisol, β -endorphin, and neurophysin I (Pomerleau et al. 1983; Seyler et al. 1984; Novack and Allen-Rowlands 1985; Novack, Allen-Rowlands, Gann, in press). Moreover, in a study that examined the role of endogenous opioid mechanisms in smoking, Tobin, Jenouri, and Sackner (1982) observed that mean inspiratory flow rate increases during the smoking of a cigarette but is depressed shortly after smoking. Naloxone had no effect on the initial stimulation of respiration in response to smoking but did significantly blunt the subsequent depression of respiration. The significance of these findings for the control of cigarette smoking remains equivocal (Karras and Kane 1980; Nemeth-Coslett and Griffiths 1986; Chapter IV).

Thyroid

Most of the earlier work (1930s through 1950s) assessing the effects of nicotine on thyroid function involved histological studies of the thyroid glands from animals treated chronically with nicotine. The findings are inconsistent in that some studies suggest elevated thyroid activity and others do not (Cam and Bassett 1983a). In a more recent study of nicotine's action on the plasma levels of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), Cam and Bassett (1983a) found that a single i.p. injection of 200 μ g/kg did not alter the level of either hormone, although it did produce an increase in plasma corticosterone. As mentioned earlier, nicotine does not consistently affect TSH in animals or humans (Blake 1974; Seyler et al. 1986).

Adrenal Cortex

Several studies in animals and human subjects have reported that nicotine and cigarette smoking lead to elevated levels of corticosteroids. Kershbaum and colleagues (1968) administered nicotine i.v. to anesthetized dogs and found a 64 percent rise in plasma corticosteroids. In rats, corticosteroid concentrations increased 50 percent after i.p. administration of nicotine. Suzuki and coworkers (1973) also reported adrenal cortical secretion in response to nicotine in conscious and anesthetized dogs. The effects of nicotine on plasma corticosteroids in stressed and unstressed rats were studied by Balfour, Khuller, and Longden (1975). The administration of nicotine to unstressed rats caused a rise in corticosterone which persisted for

60 min. Nicotine did not affect plasma corticosterone concentration in rats stressed by being placed on an elevated platform. Other studies showed increased plasma corticosteroid levels after nicotine administration (Turner 1975; Cam, Bassett, Cairncross 1979; Cam and Bassett 1983b). Andersen and colleagues (1982) exposed male rats to unfiltered cigarette smoke and found a dose-related increase in corticosterone secretion. Filtered cigarette smoke was inactive.

Seifert and coworkers (1984) found that the chronic administration of 0.5 or 1.0 mg/kg of nicotine s.c. twice daily for 8 weeks to rats produced a marked decrease in plasma aldosterone levels. In this study, nicotine had no effect on plasma corticosterone concentration.

Hokfelt (1961) reported increases in plasma cortisol and urinary 17-hydroxycorticosteroids following cigarette smoking in human subjects. Kershbaum and coworkers (1968) reported similar results involving elevations of 11-hydroxycorticosteroids. Hill and Wynder (1974) found that serum corticosteroids were markedly elevated after high-nicotine (2.73 mg) cigarettes were smoked. No increase was seen with cigarettes containing less nicotine. Cryer and colleagues (1976) also found an increase in circulating levels of corticosteroids after smoking. Winternitz and Quillen (1977) reported a sharp increase in circulating cortisol after two cigarettes. The levels were maintained through the smoking period and fell gradually to normal. Wilkins and coworkers (1982) also observed increased levels of cortisol after 2-mg-nicotine cigarettes were smoked. No increases in cortisol were detected after smoking 0.48-mg-nicotine cigarettes, but cortisol rose significantly in 11 of 15 cases smoking 2.87-mg-nicotine cigarettes (Seyler et al. 1984). Consistent with these results is the observation of Puddey and colleagues (1984) that cessation of smoking is associated with a significant fall in cortisol levels.

In contrast to these findings, Tucci and Sode (1972) reported intact diurnal circadian variations of cortisol and unchanged 24-hr 17-hydroxycorticosteroids during smoking. Benowitz, Kuyt, and Jacob (1984) studied 10 subjects who either smoked their usual brand of cigarettes, some of which contained 2.5 mg nicotine, or abstained. Plasma cortisol concentrations throughout the day did not differ during smoking or abstaining. Thus, while the majority of human and animal data indicates that nicotine or smoking elevates corticosteroid levels, the effects appear to be influenced by dose, time, and perhaps other factors.

Many investigators cited above have proposed that nicotine's effects on corticosteroids are mediated by the release of ACTH. Indeed, hypophysectomy abolished the increase in adrenocortical secretion following nicotine administration (Suzuki et al. 1973; Cam, Bassett, Cairncross 1979) and nicotine-induced increase in plasma ACTH precedes the increase in cortisol (Conte-Devolx et al. 1981). However, Turner (1975) found that bilateral adrenal demedullation

abolished the rise in corticosterone in response to nicotine and suggested that the effect of nicotine is mediated via adrenal release of catecholamines and that centrally mediated stimulation is not significant. In contrast, the work of Matta and associates (1987) demonstrates that the effects of nicotine on ACTH secretion are centrally mediated. Rubin and Warner (1975) have also shown that nicotine directly stimulates isolated adrenocortical cells of the cat. The stimulant effect was dose-dependent and required the presence of calcium. These experiments also indicated that nicotine enhances the steroidogenic effect of ACTH.

Androgens

In male beagles, chronic smoking of high-nicotine/tar cigarettes was associated with decreased activity of 7α -hydroxylase active on testosterone (Mittler, Pogach, Ertel 1983). Testicular 6β - and 16α -hydroxylases were not altered, while the hepatic androgen 6β -hydroxylase activity in the testis was stimulated markedly by smoking. Serum testosterone levels were reduced to 54 percent of control levels by heavy smoking. It was concluded that chronic cigarette smoking increased hepatic metabolism of testosterone, resulting in lowered serum testosterone levels. However, it may be that total testosterone is lower while free testosterone is not.

Estrogens

Cigarette smoking is associated with antiestrogenic effects in women, including earlier menopause, lower incidence of breast and endometrial cancer, and increased osteoporosis. MacMahon and colleagues (1982) reported lower urinary estrogen levels in premenopausal smokers than in premenopausal nonsmokers and suggested that the low estrogen secretion reflected lower estrogen production, based on decreased estrone, estradiol, and estriol. However, 2-hydroxyestrogens, the major metabolites of estradiol in women, were not measured. Jensen, Christiansen, and Rodbro (1985) presented evidence for increased hepatic metabolism of estrogens as a result of smoking based on an observation of decreased serum estrogen levels in postmenopausal smokers receiving exogenous hormone therapy. This study examined 136 women treated for 1 year with different doses of estrogen. Reduction of serum estrogen was most pronounced in the highest estrogen-dose group. There was a significant inverse correlation between the number of cigarettes smoked daily and changes in serum estrogen. Michnovicz and colleagues (1986) found a significant increase in estradiol 2-hydroxylation in premenopausal women who smoked at least 15 cigarettes/day. They concluded that smoking exerts a powerful inducing effect on the 2-hydroxylation pathway of estradiol metabolism, which is likely to lead to decreased bioavailability of hormone at estrogen target tissues.

Pancreas and Carbohydrate Metabolism

The body weight of smokers is consistently lower than that of nonsmokers, and smokers tend to gain weight after cessation of smoking (see Chapter VI for a detailed discussion of these relationships). These phenomena are thought to contribute to tobacco use. Glauser and coworkers (1970) and Hofstetter and coworkers (1986) suggested that a change in metabolic rate is partially responsible for these effects. Schechter and Cook (1976) and Grunberg, Bowen, and Morse (1984) showed that rats which were administered nicotine lost body weight without reducing food intake, although the body weight changes were not as great as when eating behavior declined as well (Grunberg 1982). Grunberg (1986) has pointed out that differences in body weight between smokers and nonsmokers result from changes in energy consumption (via changes in specific food consumption) and changes in energy utilization. Recently, Grunberg and coworkers (1988) have reported reductions of insulin levels accompanying nicotine administration in rats which could result in an increase in the utilization of fat, protein, and glycogen. This finding is consistent with work of Tjälve and Popov (1973), using rabbit pancreas pieces, and studies by Florey, Milner, and Miall (1977) of human smokers versus nonsmokers. Grunberg and coworkers (1988) have suggested that the effects of nicotine on insulin levels also may be involved in the nicotine-induced decrease of sweet food preferences.

Electrophysiological Actions of Nicotine

Electrocortical Effects

The brain responds to electrical as well as to chemical stimuli. Therefore, measurements of the electrophysiological actions of nicotine complement studies of its chemical effects. In addition, electrophysiological activity reflects function that may relate to sensory and cognitive changes observed in humans after smoking (see Chapter VI). In animals, nicotine produces changes ranging from subtle latency decreases in the primary auditory pathway to seizures. The electrophysiological actions of nicotine may help to relate the anatomical and receptor data (discussed earlier in this Chapter) with sensory and cognitive data (discussed in greater detail in Chapter VI).

The human studies on electrocortical effects of nicotine have some methodological limitations. Most of the human studies had subjects smoke cigarettes and did not measure blood levels of nicotine. Also, most studies were performed on smokers whose immediate and long-term smoking history was determined by questionnaires which may not accurately reflect tolerance and physical dependence (Chapter IV). In some studies the subjects were deprived of cigarettes, but no objective measures such as expired carbon monoxide or blood

nicotine levels were collected to verify compliance with the deprivation conditions.

Spontaneous Electroencephalogram

Historically, nicotine and ACh were used in animal experiments to study the cholinergic mechanisms in the midbrain and thalamus which produced EEG and behavioral activation (Longo, von Berger, Bovet 1954; Rinaldi and Himwich 1955a,b). The administration of nicotine produced EEG activation, consisting of desynchronized low-voltage, fast activity, and behavioral arousal or alerting. These EEG and behavioral responses resembled those produced by electrical stimulation of the midbrain reticulomesencephalic activating system (Moruzzi and Magoun 1949). With the discovery by Eccles, Eccles, and Fatt (1956) of nicotinic receptors in the Renshaw cell of the spinal cord, other investigators began to study the precise pharmacology of the EEG and behavioral alerting produced by nicotine and electrical stimulation of the midbrain. Cigarette smoking in humans also produced EEG desynchronization (Hauser et al. 1958; Wechsler 1958; Bickford 1960) or EEG desynchronization with an increase in alpha frequency (Lambiase and Serra 1957). By the late 1950s and early 1960s it was generally known that nicotine or tobacco smoke caused EEG and behavioral arousal in animals and humans, but several important issues were unresolved.

The central effects of nicotine were originally thought to result from its action on the cardiovascular system (Heymans, Bouckeart, Dautrebande 1931). Early studies found that EEG desynchronization occurred when the subjects smoked nicotine cigarettes, nicotine-free cigarettes, or sucked on glass tubes filled with cotton (Hauser et al. 1958; Wechsler 1958). Schaeppi (1968) injected nicotine into the vertebral artery, carotid artery, and third and fourth ventricles of a cat's brain and was able to dissociate the effects of nicotine on the EEG from those on the cardiovascular system. Kawamura and Domino (1969) demonstrated that the EEG changes induced by nicotine could be obtained in animals whose blood pressure increase was blocked. Prevention of release of catecholamines in reserpine-pretreated animals did not interfere with the EEG desynchronization produced by nicotine (Knapp and Domino 1962).

Inhaled tobacco smoke (2-mL samples with about 2 µg/kg of nicotine) and 2 µg of nicotine injected every 30 sec in a cat encephale isolé preparation produced EEG desynchronization. EEG and behavioral activation after cigarette smoke inhalation was also observed in unanesthetized cats with implanted electrodes (Hudson 1979). Lukas and Jasinski (1983) found that i.v. doses (0.75 to 3.0 mg) in human smokers resulted in dose-dependent decreases in alpha (8 to 12 Hz EEG activity) power and EEG desynchronization. In an inpatient study where nicotine deprivation was carefully controlled and

monitored by measurement of expired carbon monoxide, the smoking of non-nicotine cigarettes did not change the EEG (Herning, Jones, Bachman 1983), but EEG changes did occur when subjects smoked nicotine-containing cigarettes. These studies confirm that nicotine has a direct action on the CNS separate from the cardiovascular effects and that the effects are produced primarily by the nicotine in inhaled tobacco smoke.

As experimental physiological manipulations, EEG recording, and EEG quantification techniques improved, the specific nature of the nicotine-induced cortical EEG changes and their relationship to behavior were found to be more complex than originally thought. The desynchronization produced by nicotine (20 to 100 µg/kg) in the cat was blocked by anterior pontine transections, but not by midpontine transections (Knapp and Domino 1962). The midbrain reticular activating system was needed for the cortical EEG desynchronization produced by nicotine. However, larger doses of nicotine injections also produced synchronous slow high-voltage EEG activity in the hippocampus (hippocampal theta). Injections of the muscarinic agonist arecoline (20 to 40 mg/kg) in the anteriorly transected midbrain preparations still produced the hippocampal theta activity without the cortical desynchronization. Atropine (1 mg/kg) and mecamylamine (1 mg/kg), but not the ganglionic antagonist trimethidinium (1 mg/kg) block the nicotine induced EEG desynchronization in an intact animal. The convulsions observed after nicotine injections (1 to 5 mg/kg in cats; 0.05 to 0.25 µg/g in mice) (Laurence and Stacey 1952; Stone, Meckelnburg, Torchiana 1958; Stümpf, Petsche, Gogolák 1962; Stümpf and Gogolák 1967) appear to be due to nicotine's ability in large doses to stimulate muscarinic cholinergic receptors in the hippocampus. Because a high concentration of labeled nicotine binds to hippocampal cells of the cat (Schmiederlöw et al. 1967) and areas adjacent to the hippocampus in the rat (Clarke, Pert, Pert 1984), the possibility that nicotine-induced limbic electrical activity contributes to its behavioral effects cannot be discounted.

Nicotine's alerting effect on the brain may also involve a peripheral component. Electrocortical and behavioral arousal occurs in the cat within 1 to 2 sec after injection of 10 to 15 µg/kg into the right atrium of the heart, originating in vagal pulmonary C fiber afferents (Ginzel 1987). The human counterpart to this finding is the observation by Murphree, Pfeiffer, and Price (1967) that an initial EEG change occurred within 5 sec after cigarette smoke inhalation, which is shorter than a chest-to-head circulation time. Another input from the periphery arises from nicotinic sites in the arterial tree. Injection of small amounts (2 to 4 µg/kg) of nicotine, even as far away from the brain as into the lower aorta or femoral artery, causes instantaneous arousal from all types of sleep (Ginzel and Lucas 1980).

The nicotine-induced release of ACh (MacIntosh and Oborin 1953; Mitchell 1963) may be responsible for the EEG desynchronization in animals (Armitage, Hall, Sellers 1969). The effect does not appear to be due to the direct action of nicotine on the cortex because the cortical cholinergic receptors are largely muscarinic (Kuhar and Yamamura 1976; Rotter et al. 1979). Lower doses of nicotine (20 µg/kg/30 sec for 20 min) induced EEG desynchronization and ACh release in the cat, whereas higher doses (40 µg/kg/30 sec for 20 min) produced either an increase or decrease in EEG desynchronization with corresponding increase or decrease in ACh release (Armitage, Hall, Sellers 1969). The effect of nicotine on the EEG was short lived relative to the release of ACh. Two separate pathways have been proposed to explain these results: an ascending cholinergic pathway mediating the cortical desynchronization and a limbic pathway mediating the ACh release.

In one strain of mice, C57BL, nicotine increased cortical high-voltage activity and decreased homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylenglycol (MHPG) production in a perfused brain preparation (Erwin, Cornell, Towell 1986). The decrease in HVA and MHPG levels reflects an increase in brain DA and NE levels. In intact C57BL mice, nicotine decreased locomotor activity (Marks, Burch, Collins 1983a). Thus, at least in one strain of mice, nicotine induces an increase in cortical EEG synchronization, a decrease in locomotor activity, and an increase in brain catecholamines. Little evidence relates the cortical desynchronization observed in animals and humans to an increase in catecholamine changes in the brain.

As trends in neuroscience research have shifted away from spontaneous EEG recording in animals to intracellular recording, receptor localization, and binding techniques, the precise quantification of the nicotine-induced EEG desynchronization and hippocampal synchronization has not been done. This type of quantification has been done in humans by power spectral analysis. This technique quantifies the EEG by the distribution and amplitude of brain waves at different frequencies. Alpha power includes EEG activity in the 8- to 12-Hz frequency range. Theta power includes EEG activity in the 4- to 7-Hz frequency range. Beta power includes EEG activity in the frequency range of 13 Hz and higher.

The comparison of nicotine-induced EEG changes in animals and humans is complicated by an important methodological difference. Animals usually have not previously been given nicotine, while in studies of humans, the subjects always are experienced tobacco smokers. Moreover, in human studies that included a deprivation period, nicotine abstinence may have produced electrophysiological changes that are reversed by smoking or nicotine.

EEG desynchronization or increased beta power was observed in smokers after smoking a tobacco cigarette (Hauser et al. 1958; Wechsler 1958; Bickford 1960; Ulett and Itil 1969). These findings essentially replicated the animal studies of nicotine. Using power spectral analysis, Ulett and Itil (1969) also observed a decrease in theta power and an increase in alpha frequency. The increase in alpha frequency was previously noted with visual inspection by Lambriase. However, the increase in theta was not. The subjects in the study by Ulett and Itil had smoked one pack or more of cigarettes/day and had been deprived of tobacco cigarettes for 24 hr when the baseline EEG was recorded. Comparisons of the postsmoking EEG were made with this baseline period. Therefore, the decrease in alpha frequency and increase in theta power relative to the data from the postsmoking session may be the result of nicotine deprivation (Chapter IV).

Knott and Venables (1978) compared the alpha frequencies of nonsmokers, 12-hr nicotine-deprived smokers, and nondeprived smokers. They observed a decrease of about 1 Hz in the dominant alpha frequency of the deprived smokers relative to the nonsmokers and nondeprived smokers in a passive eyes-closed situation. An active behavioral task and other frequencies of the EEG were not studied. Knott and Venables hypothesize that smokers were constitutionally different from nonsmokers. The slower alpha frequency was interpreted as an arousal deficit, and smoking as compensation to reduce the arousal deficit. Knott and Venables (1978) and Ulet and Itil (1969) both found an attentional deficit during tobacco deprivation.

Herning and coworkers (1983) investigated the EEG changes related to cigarette smoking in a hospitalized group of healthy smokers who smoked at least a pack and a half of tobacco cigarettes with a machine nicotine delivery of 0.8 mg or more. A serial subtraction task was administered and EEGs were recorded from subjects in an eyes-open state. Alpha frequency was not affected by periods of smoking and deprivation. However, theta and alpha power increased during periods of deprivation and decreased after smoking tobacco but not placebo cigarettes. The effects were most pronounced on theta power. Increases in theta power occurred as early as 30 min after the last cigarette, and were of the same magnitude as those after 10 to 19 hr of nicotine deprivation. The increase in EEG theta was interpreted to be a sign of tobacco deprivation (Chapter IV).

An indirect method of observing an increase in cortical activation was the measurement of alpha power changes after tobacco smoking. A number of investigators reported a decrease in alpha power or abundance with cigarette smoking (Murphree, Pfeiffer, Price 1967; Philips 1971; Caille and Bassano 1974, 1976; Murphree 1979; Herning, Jones, Bachman 1983; Cinciripini 1986), with nicotine

polacrilex gum (Pickworth, Herning, Henningfield 1986, in press), and with i.v. doses of nicotine (Lukas and Jasinski 1983). In spite of differences in the number of cigarettes regularly smoked by the subjects, the length of tobacco deprivation, the type of tobacco cigarette smoked during the experiment, and the route of administration, nicotine reduced alpha power.

Brown (1968) measured the resting EEG for heavy smokers and nonsmokers. No cigarettes were smoked. The EEG of the heavy smokers had less alpha and more beta activity. Twelve hours of nonconfirmed deprivation in the heavy smokers did not change the EEG patterns.

The EEG of neonates of mothers who smoke is not different from that of neonates of control mothers (Chernick, Childaeva, Ioffe 1983). Whether acute periods of smoking may affect the EEG of the child before birth is not known.

In limited animal and human work, individual or species differences in the effects of nicotine on the EEG have been observed. Nicotine produced a dose-dependent cortical EEG desynchronization in C3H mice and an increase in synchronized EEG similar to hippocampal theta activity in C57BL mice (Erwin, Cornell, Towell 1986). Both effects have been observed at different doses in the same preparation (Kawamura and Domino 1969). Lower doses produce EEG desynchronization, and higher doses produce hippocampal theta. Tobacco cigarette smoking decreased EEG alpha power in Type A subjects and increased theta power in Type B subjects deprived of nicotine for about 4 hr (Cinciripini 1986). The relationship between hippocampal theta in animals and cortical theta in humans is not yet understood. In nondrugged animals cortical desynchronization and hippocampal theta activity often occur simultaneously. Nicotine at low doses produces cortical desynchronization and at high doses produces both types of EEG activity. Animal data indicate that nicotine has effects on at least two systems in the brain: a midbrain area responsible for EEG desynchronization and a limbic system generating hippocampal theta activity. These findings are consistent with the observation that some smokers indicate that they smoke for nicotine's stimulating effects and others smoke for its sedating effects.

Sensory Event-Related Potentials

In animals and humans, the brainstem auditory-evoked potential technique provides a noninvasive method for studying the effects of nicotine on primary auditory sensory function. In the rat, nicotine reduced the amplitudes of Waves III and IV of the brainstem auditory-evoked response (BAER) (Bhargava and McKean 1977; Bhargava, Salamy, McKean 1978; Bhargava, Salamy, Shah 1981). Serotonergic mechanisms may mediate the nicotine-induced reduc-

tion in latency. Lavernhe-Lemaire and Garand (1985) found essentially the opposite. Nicotine increased Waves I-III and did not decrease Waves IV and V of BAER.

Auditory event-related potentials (AERPs) recorded directly from the cortex of rat have provided conflicting information about nicotine's effects on auditory transmission from the inferior colliculus to the cortical areas. Guha and Pradhan (1976), using pentobarbital anesthesia, found a dose-dependent increase in P1 (40 ms) and N1 (110 ms) of the AERP. Bhargava, Salamy, and McKean (1978), using chloralose anesthesia with atropine pretreatment, reported no nicotine-related change in P1 (11 ms), N1 (28 ms), P2 (75 ms), and N2 (121 ms) of the AERP.

After smoking, the P1 (50 ms) of the human AERP is increased during passive tasks at all intensity levels and the N1 (110 ms) is increased in both passive and active tasks (Knott 1985). The N2 (about 215 ms) to P2 (about 260 ms) component of the AERP recorded during a passive task was reduced after cigarette smoking when compared with data from the baseline deprivation test (Friedman and Meares 1980). P2 was also reduced by nicotine in the study by Knott (1985). These components also increased in amplitude as the tobacco deprivation period was lengthened. Any attempt to relate this finding to results in the anesthetized rat would be speculative because AERPs recorded from the cortex of unanesthetized animals and humans are difficult to compare (Wood et al. 1984). Alterations in AERP components in the 75- to 150-ms latency range have been attributed to change in attention. The decrease in the later N2-P2 component is more likely to reflect reduced habituation to auditory stimuli.

The effects of nicotine on visual event-related potentials (VERPs) are more complicated than those on the AERPs. In unaesthetized rabbits, i.v. nicotine (0.025 to 0.500 mg/kg) produced a complex VERP change (Sabelli and Giardini 1972). At 2 min, nicotine depressed the P1 (100 ms) and the N1 (250 ms). At 5 min, these components were enhanced. At doses below 0.050 mg/kg, the N1 was again depressed from 10 to 20 min after the injection. Pretreatment with catecholamine inhibitors diminished the nicotine-induced VERP changes. The authors suggested that the effect of nicotine on VERPs was mediated in part by catecholaminergic mechanisms.

The effects of nicotine on the human VERP using multiple flash intensities were the focus of four studies. The studies were designed to test Buchsbaum and Silverman's (1968) concept of stimulus intensity control and its modulation by nicotine. According to their theory, sensory processing in different individuals varies in at least two ways. Some persons, "augmenters," are more sensitive to higher intensities than to lower intensities, and others, "reducers," are more sensitive to lower than to higher intensities. Smokers might be

one particular type of stimulus processer and may smoke to alter or normalize stimulus intensity. In all studies the comparison was between results after 12 hr or more of unconfirmed tobacco deprivation and those after recent smoking. Components of the VERP increased after smoking in three studies (Hall et al. 1973; Friedman and Meares 1980; Woodson et al. 1982) but decreased in another study (Knott and Venables 1978). The increases and decreases occurred in components of the same latency range (75 to 250 ms) after flash onset. The fourth study differed only slightly from the others in that it used a between-subjects and not within-subject experimental design. Using a single flash intensity, Vasquez and Toman (1967) also observed a decrease in components IV (140 ms) and V (170 ms) of the VERP when compared with results after 36 hr of tobacco deprivation. Two studies found a nicotine-induced increase at earlier components (III-IV and IV-V) for the lower intensities only. The other study reported an increase in later components (V-VI and VI-VII) at the higher flash intensities. Knott and Venables (1978) observed the decrease after smoking in the middle components (IV-V and V-VI) for the lower intensities. Because of these divergent results, it is premature to conclude that smokers are exclusively augmenters or reducers who are attempting to optimally adjust stimulus intensity by smoking.

Cognitive Event-Related Potentials

Cognitive event-related potentials reflect neural events which appear to be related to different aspects of cognition, such as attention and stimulus evaluation. They usually follow the sensory components of event-related potentials when human subjects are performing active behavioral tasks. They provide information not normally available from performance measures such as reaction time. Increases or decreases in these potentials after smoking can aid in our understanding the effects of nicotine on performance.

When two task-relevant stimuli are separated by a short interval (1 to 3 sec), a negative slow wave develops between them. In particular, this contingent negative variation (CNV) develops in warned or cued reaction times, successive discrimination, and some language processing tasks. The CNV appears to reflect brain preparation to process and respond to the second stimulus. Smoked tobacco and i.v. nicotine either increase or decrease the CNV (Ashton et al. 1973, 1974, 1980; Minnie and Comer 1978). Extraverted smokers took longer to smoke and nicotine increased the CNV. Introverted subjects smoked faster and nicotine decreased the CNV. Reaction time was inversely correlated with CNV amplitude; that is, shorter reaction time was associated with larger CNV. With i.v. doses of nicotine (12.5 to 800.0 µg), larger doses produced a decrease and small doses produced an increase in the CNV in the same

subject. O'Connor (1982) studied the effects of smoking on the orienting (O wave) and expectancy (E wave) components of the CNV in introverted and extraverted subjects. The O wave was not affected by smoking. The E wave, recorded in frontal areas, was increased in extraverted subjects after smoking. The E wave has been interpreted by some investigators as cortical preparation for a response. Smoking decreased a positive parietal E wave in introverts. Nicotine's effect on the E wave suggests the possible enhancement of motor preparation in the extraverted subjects. The decrease of parietal positivity indicates a possible enhancement of stimulus-processing capacities in the introverts.

Poststimulus components P2(00) and P3(00) were affected by cigarette smoking and nicotine polacrilex gum. P2 is thought to be an index of habituation (Hillyard and Picton 1979), and P3 an index of stimulus evaluation (Johnson 1986). Both components were reduced in deprived smokers after smoking (Knott 1985; Herning and Jones 1979). Knott (1985) interprets the reduction in P2 as a more efficient habituation of sensory screening of relevant stimuli. The reduction in P3 amplitude after smoking indicates a poorer evaluation of task-relevant stimuli. The P3 latency and reaction time were reduced only by cigarettes with higher machine-tested nicotine yields (Edward et al. 1985). Such data indicate faster stimulus and response processing. These authors did not report any P3 amplitude changes. If none were present or P3 was reduced, the argument for enhanced stimulus processing would be weak. Herning and Pickworth (1985) reported both dose-dependent increases and decreases in P3 amplitude as a function of background noise levels when deprived smokers chewed nicotine polacrilex gum (4 mg and 2 mg doses). The respective increase or decrease was blocked by mecamylamine pretreatment. Thus, the effect of nicotine on stimulus evaluation remains unclear and is perhaps confounded by cognitive deficits after periods of nicotine deprivation.

Motor Potentials

O'Connor (1986) investigated the effect of tobacco smoking on motor potential and motor performance. Smoking increased the motor readiness potential in extraverts, but not in introverts. These results are consistent with his earlier finding of an increased E wave in extraverts after smoking. For introverts, smoking improved task performance, but did not increase the motor readiness potential.

Other Peripheral Effects Relevant to Tobacco Use

In addition to vast central and peripheral effects, cigarette smoking and nicotine have other peripheral effects that may contribute to tobacco use. These additional factors have received less

research attention, mainly because they involve relatively new theory or methodological approaches. For example, there is evidence that direct stimulation of the trachea is important for cigarettes to satisfy smokers (Rose et al. 1984) (Chapter IV). There is also evidence that nicotine acts directly on the lung to stimulate afferent neurons that, in turn, result in skeletal muscle relaxation and electrocortical arousal (Ginzel 1987). These effects may contribute to the relationship between smoking and stress (Chapter VI). Other research indicates that smoking affects psychophysiological reactivity, an integrative mechanism that is different from the classic, physiological approach of examining individual systems or pathways. Therefore, psychophysiological reactivity and its relevance to smoking are discussed.

Psychophysiological Reactivity and Smoking

Psychophysiological reactivity is emerging as a useful construct in smoking research, linking basic biological processes (genetic vulnerability, central neurochemical factors) to behavioral coping and other psychosocial factors. Psychophysiological reactivity refers to a physiological response to a specific stimulus or as a result of the absence of stimulation. This response can, in some cases, act as a stressor. Within the broader conceptual framework of a stress-coping model of smoking addiction (Shiffman and Wills 1985), smoking behavior can be viewed both as a potential stimulus and as a coping response that modulates psychophysiological reactivity.

Studies of psychophysiological reactivity illustrate the value of controlled laboratory procedures to study person-environment interactions. Psychophysiological reactivity reflects an interaction of the organism and the environment. It is affected by individual differences in multiple response modes (physiological, cognitive, behavioral) and takes into account the genetic and learning history and current state of the organism.

This Section reviews two separate but interrelated lines of psychophysiological reactivity research with humans. The first is the effect of smoking on psychophysiological reactivity. Related issues include identification of mechanisms that may help to reveal why some individuals smoke and the relationship between smoking and coronary heart disease (CHD). The second research line addresses the relationship among situational events (general and drug-specific), psychophysiological reactivity, and relapse.

The effects of smoking on the cardiovascular aspects of physiological reactivity have been well documented and appear to be primarily due to effects of nicotine and carbon monoxide (Suter, Buzzi, Bättig 1983; Koch et al. 1980; Rosenberg et al. 1980). In individuals with no cardiovascular disease, some of the typical effects of smoking and nicotine are elevated heart rate and blood pressure and a fall in

fingertip temperature and capillary blood flow (Richardson 1987; Ashton et al. 1982; Epstein and Jennings 1986; Henningfield et al. 1983).

Accompanying cardiovascular reactions to smoking are cognitive reactions, including perceptions of relaxation, and anxiolytic, antinociceptive, euphoric, stimulative, and dysphoric effects (Kozlowski, Director, Harford 1981). Although there is consistency in the literature with regard to the self-reported emotional changes experienced as a result of smoking, there are clear differences in response and direction of effects between individuals and within individuals over time (Best and Hackstian 1978; Gilbert 1979; Gilbert and Welser, *in press*). Smoking can produce physiological changes that are concurrent with subjective tranquilizing effects (Nesbitt 1973; Shiffman and Jarvik 1984; Gilbert 1979). This phenomenon has led investigators to emphasize the importance of incorporating physiological, psychological, and environmental factors into more biobehavioral models to better understand the cognitive and physiological components of reactivity to smoking (Pomerleau and Pomerleau 1984; Baum, Grunberg, Singer 1982; Abrams et al. 1987; Grunberg and Baum 1985). For example, nicotine has direct and indirect actions on central neuroregulatory systems and has biphasic effects of both stimulation and blockade. These factors can help explain effects such as the anxiolytic and antinociceptive phenomena (Pomerleau 1986) at a cognitive and neurochemical level, while at the same time resulting in increased heart rate and blood pressure and decreased perception of muscle tension (Epstein et al. 1984).

In addition to dosage, biphasic, and physiological factors, the influence of setting and expectancy set, the current state of the individual (smoking, deprived, stressed, not stressed), and individual differences in dependence, genetic, demographic, and learning history can all influence psychophysiological reactivity. For example, smoking a 1.3-mg-nicotine cigarette under conditions of mild sensory isolation produced consistent arousal effects (i.e., elevations in heart rate and skin conductance level with decreases in EEG alpha waves) in smokers compared with sham smoking or a situational control group. However, under conditions of stress, as induced by intermittent noise bursts, a mixed stimulant (heart rate) and depressant (EEG, skin conductance) response was observed (Golding and Mangan 1982). Woodson and coworkers (1986) also reported that during noise, smoking induced cardiovascular stimulation (i.e., heart rate acceleration, peripheral vasoconstriction) but electrodermal depression (i.e., lowered skin conductance response amplitude). These findings are consistent with the conclusions of Gilbert and Welser (*in press*) that unidimensional models are inadequate to explain the effects of smoking.

In addition to research on the impact of smoking on psychological and physiological processes, studies have also examined the combined cardiovascular effects of smoking and stress. In this context the concept of cardiovascular psychophysiological reactivity is used to help clarify the relationship among stress, smoking, and CHD (Epstein and Jennings 1986). MacDougall and colleagues (1983) randomly assigned 51 male smokers to smoking versus sham smoking and stress versus no stress conditions in a 2 x 2 factorial design. The stressor was a difficult video game performed under challenging conditions. Subjects who sham smoked under no stress showed minimal cardiovascular response. Subjects who smoked under no stress or who sham smoked under stress evidenced similar degrees of response of about a 15-bpm increase in heart rate, a 12-mmHg increase in systolic blood pressure, and a 9-mmHg increase in diastolic blood pressure. Subjects in the combined smoking and stress condition had larger increases in all cardiovascular measures. The combination of mild stress and smoking produced effects that were twice those of either condition alone. Smoking and stress combined to increase cardiovascular response in men.

In a followup study of women, using the same 2 x 2 factorial design, Dembroski and colleagues (1985) found that the combined effect of stress and smoking produced blood pressure and heart rate increases that exceeded the sum of the individual effects. However, because modifications were made in dosage and psychological challenge, the two studies were not identical. The gender differences noted could therefore reflect methodological differences, uncontrolled factors, or possibly differences between the sexes in response to the stress and smoking stimuli. Indeed, it has been noted that females may be more likely than males to smoke to regulate affect (Ikard and Tomkins 1973), are more likely to relapse after quitting (Gritz 1986), may differ in biological factors relating to stress reactivity/sensitivity (Abrams et al. 1987), and show greater changes in body weight and eating behavior in response to nicotine (Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987). (See Chapter VII for a discussion of treatment implications of these possible sex differences.)

In a conceptually related study, the relationship between physiological responses to cognitive (mental arithmetic) and physical (cold pressor) stressors was examined in female smokers and nonsmokers who either used or did not use oral contraceptives (Emmons and Weidner, in press). All subjects showed some physiological response (heart rate and blood pressure responses) to the stressors, but in smokers oral contraceptive use significantly enhanced the systolic blood pressure response to cognitive stress. This finding may be related to the fact that smokers who use oral contraceptives are 5.6-times more likely to have a myocardial infarction than are smokers

who do not use oral contraceptives, 9.7-times more likely than nonsmoking users, and 39-times more likely than nonsmokers who do not use oral contraceptives (Shapiro et al. 1979; Jain 1976; Ory 1977).

In studies of psychophysiological reactivity, it is critical to identify, measure, and control for factors that might confound or alter the intended impact of the independent variables. For instance, time since last drink and beliefs, expectations, and setting are important variables to consider in the study of alcohol addiction (Abrams and Wilson 1979; Abrams 1983; Marlatt and Rohsenow 1980). The 2 x 2 balanced placebo design (Marlatt, Demming, Reid 1973), where expectancy set (told to expect the drug or told to expect no drug) and actual content (drug versus placebo) are fully controlled, has been used extensively in the alcohol addiction field to isolate the separate and interactive elements of cognitive and pharmacologic effects. With smoking, little is known about the separate and interactive impacts of expectations of cigarettes' effects versus their actual pharmacologic effects. This is partially because it is difficult to find a method of administration that closely resembles smoking but where the required manipulations to achieve a credible balanced placebo design can be accomplished.

Another methodological concern is control over the dosage of nicotine absorbed by the smoker. Nicotine is thought to be the most important tobacco constituent responsible for the acute effects of smoking on reactivity, attention and task performance, mood, and withdrawal following cessation (Perkins et al., in press; Pomerleau, Turk, Fertig 1984; Hughes et al. 1984). However, in tobacco smoking, nicotine is accompanied by more than 4,000 other compounds (Dube and Green 1982) and smokers are known to smoke in individualized ways (Epstein et al. 1981) (Chapter IV). The coaching of puff frequency and other attempts to standardize intake of smoke are imperfect (Perkins et al., in press). An aerosol nasal spray appears to be a promising alternative to smoking in studies of behavioral and physiological effects. It allows for rapid uptake through inhalation, and a dose-response study indicates patterns of heart rate, blood pressure, and serum nicotine levels that are very similar to those obtained by smoking cigarettes of equivalent nicotine content (Perkins et al., in press).

Perkins and coworkers (in press) studied the separate and interactive effects of nicotine administered by nasal aerosols and stress on psychophysiological reactivity. The authors note that the previous studies (MacDougall et al. 1983; Dembroski et al. 1985) could be confounded because smokers usually smoke more under stress and therefore they may inhale more nicotine or alter their smoking in other ways when stressed (Mangan and Golding 1978; Rose, Ananda, Jarvik 1983) (Chapter VI). In other words, the additive effects of

stress and smoking on physiological responses could have resulted from uncontrolled changes in smoking pattern between the smokers in the no-stress and stress conditions. Perkins and colleagues (in press) studied 12 male smokers in a repeated-measures design, where subjects received all 4 conditions (stress plus nicotine, stress plus placebo, rest and nicotine, and rest and placebo) on separate days with the order of condition counterbalanced within subjects. Following the methodology of previous studies of psychophysiological reactivity, the researchers used an active stressor consisting of a video game under conditions of competitive challenge. Nicotine was administered in measured 1.0-mg doses by the aerosol nasal method (Perkins et al., in press). Consistent with observations of MacDougall and coworkers (1983), results were additive for heart rate reactivity. However, effects were less than additive for systolic and diastolic blood pressure.

Taken together, the studies of the effects of smoking cigarettes and of nicotine aerosol stimuli on the physiological responses of adult males demonstrate a consistent effect for the stimuli alone, additive in combination with stress on heart rate, and additive or less than additive with stress on blood pressure. There is some suggestion that effects may be more than additive for women, but this finding requires replication.

Psychophysiological Reactivity, Smoking Cessation, and Relapse

Psychophysiological reactivity also serves as a conceptual framework to study relapse after cessation from smoking (Shiffman 1986b; Abrams 1986). Individual differences in psychophysiological reactivity and associated coping responses, as a function of general and smoking-specific stressful stimuli, have been hypothesized to mediate relapse. For example, smokers who smoke more when stressed might be particularly vulnerable to relapse (Pomerleau, Adkins, Pertschuck 1978). This idea is consistent with the observation that relapse may be triggered by life stress events and other psychosocial demands (Ockene et al. 1982) and by high-risk situations including negative emotions, social conflicts and pressures, and the presence of alcohol or smoking cues (Marlatt and Gordon 1985; Shiffman 1979, 1982, 1984, 1986a; Abrams et al. 1986). If certain psychophysiological reactivity responses distinguish potential abstainers from relapsers, cessation may be better maintained by identifying "relapse-prone" individuals (Chapter VII).

Stressful environmental demands, sensitivity of the individual to these demands, and the repertoire of coping responses are important factors in relapse (Shiffman and Wills 1985; Abrams et al. 1987). These same factors also may contribute to initiation of smoking among adolescents. Wills (1985) provides evidence for the stress-

coping model of smoking in adolescence, relating both stress and coping patterns to substance use. Results are consistent with other findings that, in addition to peer pressure to smoke, adolescents actively seek methods of coping with their perceptions of stress (Wills 1985; Friedman, Lichtenstein, Biglan 1985; Botvin and McAlister 1981). Although these survey studies are consistent with the notion of smoking as a means of coping with psychophysiological reactivity to environmental demands, research has not yet measured reactivity in adolescents prior to smoking onset.

Observational and retrospective studies of relapse have identified other smoking-specific stressful stimuli and cognitive/psychophysiological measures of reactivity that are relevant to relapse. Situations or stimuli that cue smoking and are associated with relapse include pharmacologic dependence and withdrawal symptoms (Jarvik 1977; Pomerleau and Pomerleau, in press; Hughes et al. 1984), stimuli previously associated with smoking (e.g., coffee drinking, alcohol) (Shiffman 1984, 1986a; Best and Hakstian 1978), and urges to smoke (Myrsten, Elgerot, Edgren 1977). Situational stimuli may or may not have previously been paired with smoking and may or may not include smoking cues as a trigger for relapse.

Substance use cues themselves (e.g., the sight and smell of cigarettes) also may precipitate relapse, perhaps in combination with other stressful stimuli or in a vulnerable individual (Shiffman 1986b; Abrams et al. 1987). Models of how substance use cues are related to relapse have been proposed on the basis of classical, operant, and social learning principles. Reactions may be conditioned to stimuli repeatedly paired with smoking, resulting in craving and physiological reactivity in their presence and moderated by dependence, tolerance, and nonpharmacologic withdrawal (Siegel 1983; Cooney, Baker, Pomerleau 1983; Gritz 1980). Psychophysiological reactivity to smoking cues could mimic the prior drug response (Wikler 1965), result in a drug-opposite (compensatory) response (Siegel 1983), or have other effects on psychological processes such as perceived anxiety, urges to smoke, and self-efficacy in resisting relapse according to a social learning model of relapse (Marlatt and Gordon 1985).

Abrams and colleagues (1987) studied the psychophysiological reactivity and behavioral coping responses of male and female relapsers and quitters in four simulated situational contexts: general social situations, smoking-specific negative emotional and interpersonal role-plays, high-demand social stress, and relaxation. Compared to abstainers, relapsers had higher heart rates and higher perceived anxiety and were rated as less skillful at coping in the smoking-specific intrapersonal (negative affect) situations. There were no differences on any measures in the high-performance-demand general-social-stress procedure. There were some differences

in heart rate and self-reported anxiety in the general social situations and in heart rate in the relaxation interval, with relapsers having higher levels than abstainers. Abstainers and relapsers did not differ in heart rate, perceived anxiety, or coping skills in the high-demand social anxiety procedure, but they did differ in the other situations. The results suggest that selected situational demands prompt situation-specific psychophysiological changes.

Rickard-Figueroa and Zeichner (1985) used a within-subjects design to examine the responses of smokers to a confederate of the experimenter lighting and smoking the subject's preferred brand of cigarette behind a glass window. Cigarette paraphernalia were placed adjacent to the subject but smoking was not permitted until after the session. The cue exposure manipulation resulted in higher urges to smoke, increased systolic and diastolic blood pressure, and increased heart rate variability compared with a no-cue condition. Urges were significantly positively correlated with diastolic blood pressure, the use of active mastery to cope with urges, and the more rapid smoking of a standard cigarette after the trial.

In a study that shows some evidence for a conditioned response, Saumet and Dittmar (1985) measured finger-pulse amplitude, a measure of peripheral vasoconstrictive activity, while subjects placed an unlit cigarette into their mouths and waited for it to be lit. Heavy smokers showed an anticipatory vasoconstrictive response to the cigarette compared with light smokers and nonsmokers.

Abrams and colleagues (in press) used smoking cues and a social stressor to simulate an interpersonal situation with high risk for relapse. Relapsers, abstainers, and never smokers were examined for psychophysiological reactivity. Compared with controls (never smokers), relapsers had significant heart rate reactivity, stronger urges to smoke, and subjective anxiety. Trained raters, unaware of subject smoking status, judged relapsers as having significantly less effective coping skills to resist smoking. In a second study, the same assessment was used prospectively in a treatment outcome context to determine whether patterns of psychophysiological reactivity could discriminate between quitters who maintain abstinence from those who do not. Both heart rate reactivity and subjective anxiety were greater in quitters who relapsed at 6-month followup compared with those who continued to abstain. The groups did not differ with regard to urges to smoke or behavioral judgments of coping skill. Thus, the two studies were consistent for heart rate and perceived anxiety but not for urges or objective ratings of coping effectiveness.

In a reanalysis of the heart rate data from Abrams and coworkers (in press), Niaura and colleagues (in press) examined beat by beat event-related heart rate during the period immediately before and for the 10 sec following the lighting of a cigarette by a confederate (subjects did not smoke throughout). Prospective relapsers showed a

strong decelerative trend at the point of lighting, whereas prospective abstainers did not. The results may reflect a conditioned compensatory response (Siegel 1983) or some other information processing/attentional phenomenon (Sokolov 1963; Knott 1984). In another treatment study, Emmons (1987) examined smokers' cardiovascular reactivity to mental arithmetic or deep knee bends before and 6 months after smoking cessation. There was no change in reactivity (heart rate, systolic and diastolic blood pressure) to either stressor before and after quitting. Heightened pretreatment heart rate reactivity significantly discriminated relapse at 6-month follow-up.

Individual differences in psychophysiological reactivity may influence the likelihood of relapse. This possibility is discussed in Chapter VII.

Summary and Conclusions

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).

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CHAPTER IV

TOBACCO USE AS DRUG DEPENDENCE

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Introduction

This Chapter reviews the evidence that tobacco is a pharmacologically addicting substance and that tobacco use can be considered a form of drug addiction. Specific criteria to identify a substance as pharmacologically addicting are discussed in Chapters I and V. In brief, the criteria are: (1) that highly controlled or compulsive patterns of drug taking occur, (2) that a psychoactive or mood-altering drug is ingested by use of the substance and is involved in the resulting patterns of behavior, and (3) that the drug is capable of functioning as a reinforcer that can directly strengthen behavior leading to further drug ingestion. Addicting drugs can be characterized by other properties that include the following: they can produce pleasurable effects in users, they can cause tolerance and physical dependence, and they can have adverse or toxic effects. Drawing upon data from studies of tobacco and nicotine, involving both humans and animals, the present Chapter reviews the evidence that tobacco meets the criteria as a pharmacologically addicting substance. A specific comparison of tobacco to other pharmacologically addicting substances is provided in Chapter V.

Cigarette Smoking: Controlled Drug Self-Administration

Highly controlled or compulsive drug use refers to drug-seeking and drug-taking behavior that is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit.

Basic observations and experimental research indicate that cigarette smoking is not a random or capricious behavior that simply occurs at the will or pleasure of those who smoke. Rather, smoking is the result of behavioral and pharmacologic factors that lead to highly controlled or compulsive use of cigarettes. The highly consistent patterns of cigarette smoking illustrate the controlled nature of the behavior. For example, following initiation of smoking the individual gradually increases cigarette intake over time until he or she achieves a level that remains stable, day after day, during the smoker's lifetime (Schuman 1977; US DHHS 1987a). The dependent smoker tends to adopt a pattern in which the initial cigarette of the day is smoked soon after waking (Fagerström 1978) and in which smoking throughout the day is regular from day to day (Griffiths and Henningfield 1982; Griffiths, Henningfield, Bigelow 1982). "Occasional" cigarette smoking (or "chipping") occurs just as does occasional use of other addicting drugs (see Chapter V); however, the 1985 National Health Interview Survey showed that only 10.6 percent of current smokers smoke 5 or fewer cigarettes/day (unpublished data, Office on Smoking and Health; see also Russell 1976 and US DHHS 1987a).

Strong evidence that cigarette smoking is a highly controlled or compulsive behavior is provided by survey data showing that a majority of smokers have tried to quit or at least would like to quit. For example, several Gallup surveys have shown that a large majority of smokers report a desire to quit smoking; in fact, the proportion of smokers who would like to quit increased from 66 percent in 1977 to 77 percent in 1987 (Gallup 1987), perhaps because of a declining social acceptability of smoking and the growing awareness of the health hazards of smoking. In addition, the 1986 Adult Use of Tobacco Survey (US DHHS 1987b) showed that 65 percent of cigarette smokers had made at least one serious attempt to quit; another 21 percent said that they would try to quit "if there were an easy way to do so" (Fiore et al., in press; US DHHS 1986).

The compulsive nature of cigarette smoking is most apparent in extreme cases: for example, the laryngectomized patient who, having already suffered severe consequences of smoking, continues to smoke through a tracheostomy hole. Similarly, 50 percent or more of patients recovering from surgery for a smoking-related disease (e.g., cancer, cardiovascular disease) resume smoking while in the hospital or shortly after discharge (Burling, Singleton et al. 1986; West and Evans 1986).

In this Section, the behavioral process of cigarette smoking and the factors which determine the course of the behavior are described. Evidence that cigarette smoking is repetitious and stereotypic, common features of compulsive drug use, is reviewed in this Section, as well as evidence that actions of nicotine are responsible for patterns of smoking behavior. Initially, however, it is necessary to briefly review the methods by which the behavioral process of cigarette smoking is studied, as well as the main findings from such studies.

Measurement of Cigarette Smoking

Cigarette smoking behavior may be analyzed at different levels ranging from epidemiological surveys to the analysis of cigarette puffing. In fact, many thousands of scientific articles have been published in which some aspect of cigarette smoking is described. Much of this research has been reviewed in the tobacco research compendia of Larson and his colleagues (Larson, Haag, Silvette 1961; Larson and Silvette 1968, 1971, 1975), a previous report of the Surgeon General (US DHEW 1979), several monographs of the National Institute on Drug Abuse (NIDA) (Jarvik et al. 1977; Krasnegor 1978, 1979a,b,c; Grabowski and Bell 1983; Grabowski and Hall 1985) and in articles by others (Russell 1971, 1976; Gritz 1980; Henningfield 1984).

It is characteristic of drug dependence that the drug-seeking and self-administration behaviors become stereotypical and automatic in

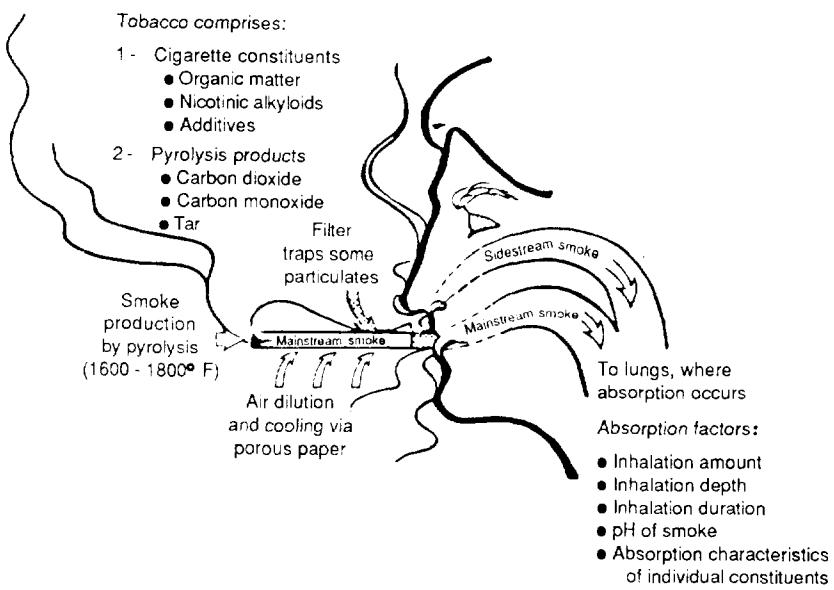


FIGURE 1.—Production and fate of cigarette smoke constituents

NOTE: Description of complexity of process by which nicotine is extracted from cigarette. Amount of nicotine ultimately absorbed is as much a function of smoker behavior as of cigarette characteristics.

SOURCE: Henningfield (1984).

appearance; cigarette smoking is no exception. The behavior of lighting, smoking, and extinguishing cigarettes, including puffing and inhaling, also becomes regular in smokers over time. The measurement techniques that permit such conclusions, however, must address a complex behavior. There are many variables (e.g., number of puffs, depth of inhalations) that might change and thereby affect the intake of tobacco smoke and its various constituents (e.g., nicotine, tar, carbon monoxide (CO)). As shown in Figure 1, the process of producing cigarette smoke constituents itself is complex (see US DHEW 1979; US DHHS 1981, for a more thorough discussion of these factors). This complexity emphasizes the importance of the use of careful measurement and multiple measures to ensure accurate characterization of cigarette smoking.

Quantification of cigarette smoking behavior has improved with the development of automated measurement techniques. These techniques permit the measurement of puffing and inhalation both in the laboratory (Gust, Pickens, Pechacek 1983; Epstein, Dickson, Stiller et al. 1982; Creighton, Noble, Whewell 1978; Herning, Hunt,

Jones 1983; Henningfield and Griffiths 1979; Puustinen et al. 1987) and outside the laboratory (Henningfield et al. 1980; Grabowski and Bell 1983). Puffing behavior is generally measured by having subjects smoke through cigarette holders that measure air flow by use of either temperature-sensitive thermistors (Gritz, Rose, Jarvik 1983; Fagerström and Bates 1981) or pressure-sensing transducers (Henningfield and Griffiths 1979; Gust, Pickens, Pechacek 1983a; Rawbone et al. 1978). Inhalation behavior has been measured by a variety of techniques, including mercury strain gauge pneumography (Rawbone et al. 1978; Herning et al. 1983), head- and arms-out whole-body plethysmography (Adams et al. 1983), and impedance (Nil, Buzzi, Bättig 1986) and inductive plethysmography (Herning, Hunt, Jones 1983; Tobin and Sackner 1982; Tobin, Jenouri, Sackner 1982). Other methods include the use of inert gas radiotracers to determine the amount of smoke inhaled (Sheahan et al. 1980; Woodman et al. 1986) and a sensor for directly measuring the concentration of smoke particles in the holder before puffing (Jenkins and Gayle 1984).

These procedures have proved to be valuable and reliable methods of measuring smoking behavior (Woodman et al. 1984; Herning, Hunt, Jones 1983). Comparisons of data obtained when simply observing smokers to data obtained when using the mechanical devices indicate that such automated measuring techniques are valid. Such comparisons reveal consistent findings on measures such as number and duration of puffs and even of patterns of puffing within cigarettes (Henningfield and Griffiths 1979; Griffiths and Henningfield 1982). However, other research suggests that the devices may alter certain characteristics of smoking such as intensity of puffing (Tobin and Sackner 1982; Ashton, Stepney, Thompson 1978; Ossip-Klein, Martin et al. 1983). In addition, some smoking behaviors, such as blocking the ventilation holes of filters of low-yield cigarettes (which can markedly influence nicotine and tar intake from the cigarette) are thwarted by the use of a cigarette holder. Nonetheless, such measurements are useful and appear to provide valid means of evaluating the effects of specific experimental manipulations.

Measurement of the intake of cigarette smoke constituents may also be obtained by analysis of various biological fluids (saliva, urine, or blood) and expired air. Chapter II reviewed the methods and practical issues of using such specimens to assess resulting levels of nicotine, cotinine (a nicotine metabolite), CO, and other tobacco-associated compounds (see also Jarvis et al. 1987; Benowitz 1983).

Use of the methods described above has led to a much better understanding of how cigarettes are smoked and factors that affect intake of smoke constituents such as CO and nicotine. In addition, these methods permit conclusions regarding which aspects of smok-

ing are most robust across individuals, which aspects are strongly influenced by pharmacologic factors, and which aspects appear to be determined by other factors. Some of these findings are reviewed in subsequent sections.

Characterization of Cigarette Smoking Behavior

Although the process of smoking a cigarette may appear to be a simple behavior, it is actually a complex series of events; a full characterization requires the measurement of a variety of interdependent indices of frequency, duration, and volume. Even the act of taking a single puff is complex. Typically, a smoker puffs a volume of smoke into the mouth, where it is held for a short period of time (Guillerm and Radziszewski 1978; Medici, Unger, Rüegger 1985). The puff itself can occur at any point during inhalation, although most commonly it occurs toward the beginning of an inhalation (McBride et al. 1984; Guillerm and Radziszewski 1978). During inhalation, the puff is diluted with ambient air which may be inhaled through the nose, the mouth, or both (Rodenstein and Stănescu 1985; McBride et al. 1984; Adams et al. 1983). The postpuff inhalation is generally longer and larger in volume than normal inspirations (Rodenstein and Stănescu 1985; McBride et al. 1984). After a variable period of breath holding, the smoker exhales, usually through the mouth (Rodenstein and Stănescu 1985).

All of the above-mentioned behavioral factors can alter nicotine absorption. The likely impact of some factors is obvious (e.g., number of puffs taken) (Kozlowski 1981); others are much more subtle (e.g., puff shape, which is a function of the air flow rate over time) (Creighton and Lewis 1978b). Analogous but distinct from puffing factors are inhalation factors (e.g., depth and duration, dilution of the puff with ambient air) which can also determine the amount of tobacco smoke constituents which are absorbed. Table 1 lists several measures of cigarette smoking that have been objectively defined and measured.

The relationships among these behavioral measures have been studied. For instance, duration and volume of puffing are generally highly correlated although they vary somewhat from smoker to smoker (Gust and Pickens 1982; Epstein et al. 1982; Adams et al. 1983; Nemeth-Coslett and Griffiths 1985; Gust, Pickens, Pechacek 1983b; Gritz, Rose, Jarvik 1983). Peak smoke flow rate has been reported to be moderately correlated with puff volume and weakly correlated with puff duration (Gritz, Rose, Jarvik 1983). The relationship between puff volume and interpuff interval is much more variable (Adams et al. 1983; Gust, Pickens, Pechacek 1983b), and puffs per cigarette and puff duration have been found to be inversely related (Lichtenstein and Antonuccio 1981).

TABLE 1.—Behavioral measures of cigarette smoking

Puffing behavior	Inhalation behavior
Puffs/cigarette	Inhalation volume
Interpuff interval	Inhalation duration
Puff duration	Breathhold duration
Butt length (weight)	Lung exposure duration
Puff volume	Percent of puff inhaled
Puff shape	
Puff flow rate (puff intensity)	
Peak flow rate (pressure)	
Latency to peak flow rate (pressure)	
Percent puffing time	

When the smoking of individual cigarettes is studied, the measures of cigarette smoking behavior and the resulting levels of biochemical markers have also been found to be highly correlated. For example, four studies found positive correlations between one or more of the behavioral measures and plasma nicotine levels (Pomerleau, Pomerleau, Majchrzak 1987; Sutton et al. 1982; Bridges et al. 1986; Herning et al. 1983). Using another approach, Zacny and associates (1987) independently varied three aspects of smoking—puff volume, inhalation volume, and lung exposure duration. They found that increases in puff volume (from 15 to 60 mL) produced proportional increases in plasma nicotine level, whereas increases in inhalation volume (from 10 or 20 to 60 percent of vital capacity) or lung exposure duration (from 5 to 21 sec) had no such effect.

CO intake (measured either from expired air or blood samples) also tends to be positively related to measures of smoking behavior, including total puff volume (Gust and Pickens 1982; Guillerm and Radziszewski 1978; Nil, Buzzi, Bättig 1984; Woodman et al. 1986) and mean puff volume (Zacny et al. 1987; Zacny and Stitzer 1986). McBride and coworkers (1984) found moderate correlations ($r=0.36$ to 0.45) between CO boost and other measures of ventilation (tidal volume, minute ventilation, and prepuff expiratory volume). These studies illustrate some of the ways that specific aspects of cigarette smoking can affect absorption of smoke constituents. These measures have been used to scientifically describe many features of cigarette smoking. A summary of findings that have emerged from such studies is presented in the next Section.

Patterns of Puffing and Inhaling

Several studies have characterized the behavior of cigarette smoking in and outside the laboratory. The values of the most frequently measured variables are shown in Table 2. Despite a wide range of variations among studies, including differences in subject population (age, gender, smoking history, type of cigarette smoked), experimental setting, method used to collect the measurements, apparatus calibration procedures, and operational definitions of the measured variables, the findings among studies are strikingly consistent.

Over the course of smoking each cigarette there are striking consistencies from cigarette to cigarette, both within and between individuals. For example, during the smoking of a single cigarette, the duration of each puff tends to decrease and/or the time between each puff (interpuff interval) tends to increase (Graham et al. 1963; Griffiths and Henningfield 1982; Nemeth-Coslett and Griffiths 1985; Herning et al. 1981; Gust, Pickens, Pechacek 1983b; Woodman et al. 1986; Buzzi, Nil, Bättig 1985; Adams et al. 1983; McBride et al. 1984; Chait and Griffiths 1982a). These trends were also found in nonlaboratory observations by Schulz and Seehofer (1978).

Although these observations reflect a tendency to decrease overall intensity of smoking over the course of the cigarette, the specific factors which produce such effects remain to be fully elucidated. The pattern has been hypothesized to be related to the nicotine dose per puff (Rickert et al. 1983; Russell et al. 1975; Chamberlain and Higenbottam 1985), because the nicotine concentration of smoke increases as the cigarette is smoked (Kozlowski 1981). However, experimental studies suggest that within-cigarette changes in puff intensity are not a simple function of the nicotine dose per puff (Nemeth-Coslett and Griffiths 1984a,b, 1985). Furthermore, puff volume may not be controlled by the same factors as puff duration (Nemeth-Coslett and Griffiths 1985). Thus, the orderliness of the behavior may be due to a variety of factors.

Various other aspects of puffing and inhaling during the smoking of single cigarettes have been studied and provide further information that helps to characterize this complex behavioral process. For example, puff shape (puff intensity over time) (McBride et al. 1984), latency to peak puff pressure (Buzzi, Nil, Bättig 1985), and inhalation volume and duration (Adams et al. 1983) did not change over the course of smoking single cigarettes. The volume expired from puff to puff during and immediately after puffing (before inhalation) was lower for early puffs than for later puffs (Adams et al. 1983). Woodman and colleagues (1986) reported that the amount of smoke actually inhaled (range, 46 to 88 percent of puff volume) decreased proportionately with puff volume as cigarettes were smoked. Finally, significant changes from cigarette to cigarette in puff volume and

TABLE 2.—Published values of common measures of smoking

Study	Number of subjects	Puffs/cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow (mL/sec)	Inhalation volume (mL)
Rawbone et al. (1978)	12	10	41		1.8			
Rawbone et al. (1978)	9	10	35		2.1	43		
Woodman et al. (1986)	9	13	18	254	1.9	49		413
Nemeth-Coslett et al. (1986a)	8	8	64	414	1.8			
Nemeth-Coslett et al. (1986b)	8	8	47	362	1.4			
Nil, Woodson, Battig (1986)	132	13	28		2.2	30	28	560
Jarvik et al. (1978)	9	10						
Russell et al. (1980b)	10	11	35					
Ashton, Stepney, Thompson (1978)	14		24		1.5			
Schulz and Seehofer (1978)	100	11	50		1.4			
Schulz and Seehofer (1978)	218	12	42		1.3			
Henningfield and Griffiths (1981)	8	10	39	351	1.0			
Stepney (1981)	19	13		400		38		
Battig, Buzzi, Nil (1982)	110	13	26		2.1	40		
Epstein et al. (1982)	63	13			2.4	21		
Russell et al. (1982)	12	15	26	324	2.3	40		
Gritz, Rose, Jarvik (1983)	8	9	47		2.2	66	48	
Ossip-Klein, Martin et al. (1983)	9	8		351	1.4			
Ossip-Klein, Martin et al. (1983)	9	12		339	1.9			
Guillerm and Radziszewski (1978)	8	12	41	390	1.9	39	35	918
Gust, Pickens, Pechacek (1983b)	8	9	48	393	1.6	44		

Study	Number of subjects	Puffs/cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow (mL/sec)	Inhalation volume (mL)
Adams et al. (1983)	10		26		1.9	44		614
Moody (1984)	517	9	26	232	2.1	44		
Nil, Buzzi, Bättig (1984)	20	15	26		1.6	40	40	
McBride et al. (1984)	9	16	25	352	2.1	42		
Medici, Unger, Rüegger (1985)	17	14	19		2.2	43	31	
Burling et al. (1985)	24	12	28	330	1.7			
Nil, Buzzi, Bättig (1986)	117	13	22		2.1	42	36	450
Hughes et al. (1986b)	46	11			1.6			
Bridges et al. (1986)	108	11				56		
Puustinen et al. (1986)	11	13	22		2.3	44		
Hilding (1956)	27	10						
Mean		11	34	346	1.8	43	36	591
Median		11	28	351	1.9	42.5	35.5	560
Range		8-16	18-64	232-414	1.0-2.4	21-66	28-48	413-918

NOTE: Data were taken from the baseline phase (or placebo treatment) of studies involving an experimental manipulation, with at least eight subjects. Values are rounded off to the nearest unit, and in some cases, were calculated from other variables or estimated from data presented in figures; missing values indicate that the variable was not measured or was not presented in the published study.

inhalation volume, as well as their ratio, were reported for individual subjects over the course of a 4-hr smoking session (Herning, Hunt, Jones 1983).

Dose-Related Determinants of Tobacco Intake

As the preceding material shows, cigarette smoking is a complex but orderly behavior; it may be qualitatively and quantitatively described. Furthermore, the behavioral process of tobacco smoke self-administration substantially determines the amount of smoke that is actually consumed. Similarly, the behavior of smoking may change in response to factors related to the delivered smoke and/or nicotine dose. These interactions are described in the present section. Much of this research has addressed issues concerning the manipulation of some aspect of cigarette and/or nicotine dose level. Such data are relevant to comparing this form of drug self-administration with other forms of drug self-administration, because one of the basic findings in studies of drug-seeking behavior is that the dose may affect the behavior. For example, when the dose (quantity) of a psychoactive drug is high, fewer doses are generally taken compared to when the dose is very low (Griffiths, Bigelow, Henningfield 1980; Chapter V).

With regard to cigarette smoking, the control and measurement of cigarette dose level is more complex than is the case with most other forms of drug delivery. For example, in opioid and alcohol studies, the amount of the morphine injected and volume of alcohol consumed can be precisely measured, but cigarette smoke can vary in levels of CO, tar, nicotine, and many other potentially important constituents (see Figure 2). The total smoke dose is positively related to the number of puffs taken per cigarette. However, total smoke dose might be changed by diluting the smoke with air or changing the number of available cigarettes. Alternatively, the smoke concentrations can be kept constant while changes are made in the concentration of nicotine delivered. This Section reviews these and several other strategies used to investigate some form of tobacco/nicotine dose manipulation and the resultant effects on cigarette smoking.

Control of Nicotine Intake

Among the most robust findings in research on cigarette smoking is the stability of nicotine intake that occurs from day to day within cigarette smokers. Several studies have collected blood samples from cigarette smokers while they are smoking their own cigarettes (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). This research has shown that blood levels of nicotine and cotinine among different cigarette smokers are stable and are relatively independent of the machine-estimated nicotine yield of the

cigarettes. Similarly, there are generally only modest correlations between the number of cigarettes smoked per day and resultant blood nicotine levels. This finding occurs because smokers consume different amounts of nicotine from their cigarettes, according to how the cigarettes are smoked. Figure 2 presents data from one of these studies.

To explain why nicotine intake is not simply determined by the machine-estimated nicotine yield of the cigarettes or the number of cigarettes smoked, many other aspects of smoking have been measured. This research is described in the remainder of this Section.

Smoke Concentration

The concentration of tobacco smoke delivered to the lung can be changed by dilution with air. Such dilution is an important means by which the low smoking-machine-estimated ratings (e.g., Federal Trade Commission ratings) of tar and nicotine are achieved in the so-called "light" or "ultra light" cigarettes (Kozlowski 1981, 1982, 1986, 1987). One way to study the possible effects of smoke dilution is to use the ventilated cigarette holders which have been marketed for persons who are trying to quit smoking. In principle, the smoker gradually reduces his or her level of dependence to nicotine by using holders of gradually increasing ventilation level. Three laboratory studies have evaluated the effects of such holders on cigarette smoking behavior (Henningfield and Griffiths 1980; Sutton et al. 1978; Martin et al. 1980). The results of all three were consistent: smoking was more intense at lower smoke concentrations and less intense at the highest concentration. In fact, in one of the studies, expired air CO levels were similar at all four concentration levels, indicating that the changes in smoking intensity were sufficient to defeat the holders' intended purpose of reducing the dose taken (Henningfield and Griffiths 1980). Using a somewhat different strategy, Zacny, Stitzer, and Yingling (1986) studied cigarette smoking with commercially available ventilated cigarettes. When the experimenter systematically blocked the filter vents of "ultra" low-yield cigarettes, there were decreases in puffs per cigarette, puff volume, and puff flow rate, and increases in interpuff interval.

These laboratory findings are consistent with findings obtained outside the laboratory when the cigarette butts of vented cigarettes are examined following smoking. Kozlowski, Rickert, Pope, and Robinson (1982) found that the cigarette butts taken from people who blocked the ventilation holes (often inadvertently) were more stained by tar and nicotine, reflecting less effective dilution and hence greater amounts of smoke delivery to the smoker. Data from a laboratory study suggest that 40 percent or more of smokers may inadvertently block the holes (Kozlowski, Rickert, Pope, Robinson,

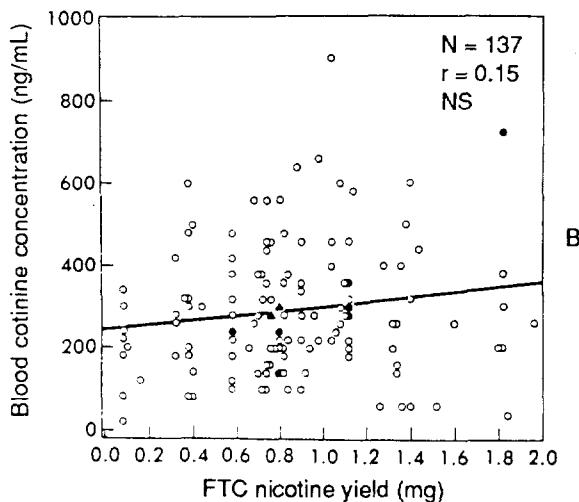
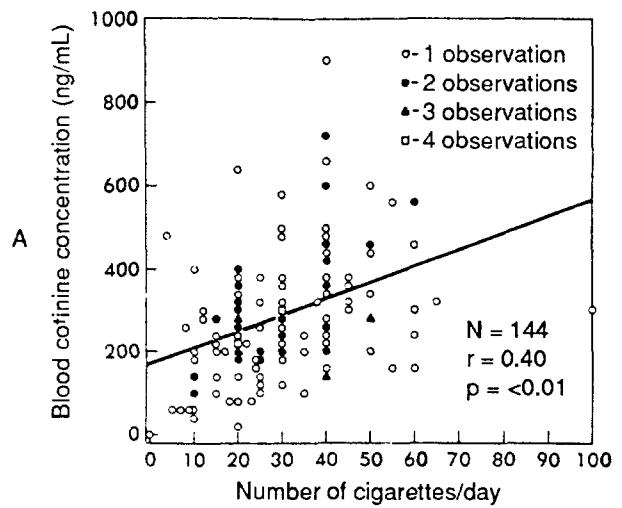


FIGURE 2.—Afternoon blood cotinine concentrations, compared by regression analysis with number of cigarettes smoked/day (A) and with U.S. Federal Trade Commission (FTC)-determined nicotine yield (B)

NOTE: The grouped smokers' values (observations 2-4) were so similar to individual values that plots overlapped. Total number of subjects in B is lower because data for a few subjects were incomplete. Morning blood cotinine concentrations (not shown) were on average slightly lower, but had similar correlations with number of cigarettes ($r=0.45$) and FTC yield ($r=0.06$).

SOURCE: Benowitz et al. (1983).

Frecker 1982). These findings imply that there is much greater exposure to cigarette smoke in the general population than one would expect based solely on the market share of ventilated cigarettes (US DHHS 1981; Kozlowski 1987).

Cigarette Length

When cigarettes are shorter, people smoke more of them (Ashton, Stepney, Thompson 1978; Goldfarb and Jarvik 1972; Gritz, Baer-Weiss, Jarvik 1976; Jarvik et al. 1978; Chait and Griffiths 1982b). Cigarette length may also affect how people smoke each cigarette. Ashton, Stepney, and Thompson (1978) found that smokers shortened their intervals between puffs and spent a greater proportion of time puffing on two-thirds-length cigarettes compared with full-length cigarettes. Russell, Sutton, and associates (1980) reported that smokers took relatively more puffs and left shorter butts when smoking shortened cigarettes. In another study, subjects smoking half-length cigarettes shortened the interval between puffs, but did not spend more time puffing on these cigarettes relative to full-length cigarettes (Chait and Griffiths 1982b). Puff duration and puff volume were inversely proportional to the length of the tobacco rod, even for the first puff of the cigarette (Chait and Griffiths 1982a; Nemeth-Coslett and Griffiths 1984a,b, 1985).

Cigarette Brand

Numerous studies have examined the effects of cigarette brand manipulations on cigarette smoking, and several reviews are available (Gritz 1980; Moss and Prue 1982; McMorrow and Foxx 1983). Such studies are of practical importance because smokers often switch to lower tar/nicotine yielding cigarette brands in an effort to reduce this exposure to toxins and to reduce their level of nicotine dependence (see Chapter VII). One finding of these studies is that the number of cigarettes smoked per day is only slightly increased when lower nicotine-yield brands are used. For this reason, it has been suggested that smokers switch to lower yield cigarette brands (1) to reduce exposure to smoke constituents and (2) to help them gradually reduce their dependence on nicotine (see discussion of these issues in US DHHS 1981 and in Chapter VII (nicotine fading)). However, as discussed earlier, several other studies indicate that there is little correlation between the nicotine rating of a cigarette and the plasma nicotine level of the smoker (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). Kozlowski (1981, 1982) has observed that increases of only one or two puffs per cigarette and possibly other more subtle changes in cigarette smoking (e.g., blocking ventilation holes and taking deeper inhala-

tions) may defeat the intended purpose of the brand-switching procedure.

Laboratory studies have provided information on the specific changes in smoking behavior that may reduce the intended impact of switching to lower yield brands of cigarettes. One confounding factor in such studies is that machine-estimated nicotine, tar, and CO yields do not necessarily change to the same degree or even in the same direction from one cigarette brand to the next (Tobacco Reporter 1985); thus, no definitive conclusions can be drawn about which specific smoke component was responsible for observed changes in smoking behavior. Nonetheless, some orderly and consistent findings emerge from a review of this literature. Several measures suggest that when tobacco smoke constituent ratings decline, smoking is more intense so that more smoke is delivered per cigarette; conversely, when tobacco smoke constituent ratings are higher, cigarette smoking becomes less intense (Frith 1971; Ashton, Stepney, Thompson 1979; Stepney 1981; Guillerm and Radziszewski 1978; Rawbone et al. 1978; Adams 1978; Creighton and Lewis 1978a; Ossip-Klein, Epstein et al. 1983; Russell et al. 1982; Ashton and Watson 1970; Epstein et al. 1981; Russell, Epstein, Dickson 1983; Tobin and Sackner 1982; Fagerström and Bates 1981; Woodman et al. 1987).

The consensus of the foregoing studies is that smokers tend to smoke in ways that minimize the effect of attempted reductions in nicotine intake; however, brand preferences can modulate nicotine intake. One study employing biochemical measures of smoke intake illustrated both of these phenomena (Benowitz and Jacob 1984). Subjects were permitted to smoke under each of three cigarette conditions: using their regular cigarette, using a higher nicotine-yield brand, and using a lower nicotine-yield brand. Subjects maintained significant nicotine intake under all three conditions, but the highest intakes of nicotine were with the subject's preferred brand. Nicotine intake from the lower nicotine-yield brands was somewhat lower than intake from the higher yield brands. Taken together, these studies indicate that brand switching may result in somewhat decreased levels of intake of nicotine and other constituents of tobacco smoke. However, because of compensatory changes in how cigarettes are smoked and in the number of cigarettes smoked, the decreases are substantially less than would have been predicted on the basis of the machine-estimated yield of the cigarettes.

Cigarette Yield of Nicotine

Research cigarettes which vary mainly in machine-estimated nicotine yield ratings but little in the yield of other constituents (e.g., tar, CO) have also been used in laboratory and nonlaboratory studies of cigarette smoking. This literature has been extensively reviewed (Russell 1971, 1976; Gritz 1980; Henningfield 1984; US DHEW 1979;

US DHHS 1981). The consensus of the literature indicates that as nicotine yield increases, the number of cigarettes smoked per day tends to decrease, although the converse relationship is not as robust (Russell 1979). Because few of these studies employed measures of smoking other than number of cigarettes smoked per day, the degree to which overall cigarette smoking behavior actually varied as a function of such manipulations may have been underestimated (Henningfield 1984).

Laboratory studies in which multiple behavioral measures of cigarette smoking were employed indicate that smoking is sensitive to nicotine dose manipulations. When cigarettes with higher nicotine yield ratings are smoked, there are decreases in measures such as puffs per cigarette, puff duration and puff volume, number of cigarettes, and expired air CO; and increases in interpuff and intercigarette interval (the specific measures were not identical for the three studies summarized) (Herning et al. 1981; Gust and Pickens 1982; McBride et al. 1984). These changes in smoking are consistent with the interpretation that intensity of smoking is inversely related to nicotine dose, indicating that compensatory changes in smoking could be affected by nicotine itself.

Urine pH

Because some nicotine is normally eliminated in the urine, manipulations of the rate of nicotine excretion might be expected to change cigarette smoking behavior (see Chapter II). Rate of renal excretion is partially determined by the acidity of the urine: lower pH values (higher acidity) increase the rate of nicotine excretion. One study showed that acidification of the urine of cigarette smokers resulted in small increases in cigarettes smoked per day, and alkalinization of urine was accompanied by only very small decreases in smoking (Schachter, Kozlowski, Silverstein 1977). A subsequent study in which urine pH was varied showed no change in cigarette smoking measures (Cherek, Mauroner, Brauchi 1982); another showed small but significant effects on nicotine intake in the expected direction (Benowitz and Jacob 1985).

The fact that there is a direct albeit weak relationship between rate of nicotine excretion and cigarette smoking has suggested to some that alkaline diets might be useful for persons trying to decrease their cigarette smoking (Fix and Daughton 1981; Fix et al. 1983; Grunberg and Kozlowski 1986). However, the relatively small amount of systemic nicotine which is eliminated by this route (approximately 2 percent in alkaline urine, 10 percent in urine without controlled pH) (Rosenberg et al. 1980; Benowitz and Jacob 1985; Chapter II) weakens its practical significance as a determinant of cigarette smoking behavior. The results of clinical studies suggest

that such therapies are not useful in the cessation of smoking (see also Grunberg and Kozlowski 1986; Schwartz 1987).

Tobacco Administration and Deprivation

When tobacco smoke itself is given or withheld, the tendency to smoke, as well as the way cigarettes are smoked, may be affected. Kumar and colleagues (1977) reported that pretreating smokers with a varying number of uniform puffs of tobacco smoke produced dose-related reductions in the subsequent number of puffs taken, volume per puff, and total puff volume during a 40-min period of smoking ad libitum. In a study of similar design, Chait, Russ, and Griffiths (1985) found that an increasing number of uniform pretreatment puffs decreased subsequent puffs per cigarette, cigarette duration, and total puff duration. Analogously, when the number of puffs available during any period of smoking (smoking "bout") during a given day was varied by the experimenter from 1 to 12 while the smokers were free to vary the interbout interval, the intervals between each smoking bout were directly related to the number of puffs that had been given (Griffiths, Henningfield, Bigelow 1982). These studies show that cigarette smoke intake is a function of time since the last cigarette or the smoke dose given at any smoking opportunity.

Whereas smoke pretreatment decreases several measures of cigarette smoke intake, other studies have found that deprivation for just 1 hr increases the tendency to smoke and elevates several measures of tobacco smoke intake (Henningfield and Griffiths 1979); furthermore, these effects were not due to "anticipation" by the subjects of the periods of smoke deprivation (Griffiths and Henningfield 1982). Several additional studies have confirmed that smoke deprivation increases one or more measures of cigarette smoking (Karanci 1985; Griffiths and Henningfield 1982; Zacny and Stitzer 1985; Epstein et al. 1981). Sutton and coworkers (1982) found a small, but statistically significant, positive correlation between time since the last cigarette and total puff volume on the subsequent cigarette. Similarly, when the interval between each smoking opportunity was varied from 7.5 to 120 min and subjects were free to take as many puffs per smoking bout as they pleased, the number of puffs per bout was directly related to the duration of the preceding interbout interval (Griffiths, Henningfield, Bigelow 1982). Restricting the number of cigarettes that may be smoked is another way to study tobacco deprivation. When smokers who on average smoked 37 cigarettes/day were permitted to smoke only 5 cigarettes/day, they consumed three times as much nicotine per cigarette compared with unrestricted smoking (Benowitz et al. 1986).

The results of studies of the effects of tobacco administration and deprivation on subsequent rates and patterns of cigarette smoking show that tobacco smoke can function as do other primary reinforc-

ers such as food, water, and dependence-producing drugs (Thompson and Schuster 1964). Such studies in themselves, however, do not reveal which of the many tobacco smoke constituents are critical. The next two sections will examine evidence that specific manipulations of nicotine and nicotine antagonists can produce analogous changes in cigarette smoking.

Nicotine Pretreatments

One of the basic ways to demonstrate that a psychoactive drug is controlling behavior is to determine if pretreatment with the drug leads to decreases in the amount subsequently taken. Such findings have been obtained with a variety of dependence-producing drugs (e.g., Griffiths, Bigelow, Henningfield 1980; Chapter V), and the strategy has been used to study the role of nicotine in cigarette smoking. These studies have shown that nicotine pretreatment by a variety of routes decreases the amount and/or intensity of subsequent cigarette smoking although the specific measures that have been reportedly affected vary across studies. It is possible that differences across studies reflect variations in sensitivity of measurement techniques and in the measures used.

Cigarette smokers may be pretreated with nicotine by giving them nicotine polacrilex gum to chew. The gum is available in similar tasting nicotine dose levels of 2 or 4 mg/piece. A similar tasting placebo preparation with no nicotine is also available. (In the United States, the placebo and 4-mg dose are only available for research.) With various combinations of nicotine gum doses it is possible to provide a wide range of dose levels. In one study, the chewing of nicotine polacrilex gum produced a dose-related (dose range = 0 to 8 mg nicotine) decrease in cigarette consumption during subsequent 90-min cigarette smoking sessions: Total puffs, total cigarettes, and expired-air CO levels were inversely related to nicotine dose; desire to smoke was also inversely related to dose but this effect varied considerably and was not statistically reliable (Nemeth-Coslett et al. 1987). Comparable findings have been obtained in several other studies, although dose manipulations were not as extensive as in the former study (Kozlowski, Jarvik, Gritz 1975; Nemeth-Coslett and Henningfield 1986; Brantmark, Ohlin, Westling 1973; Russell et al. 1976; Herning, Jones, Fischman 1985). Another study showed that nicotine given in capsule form also reduced subsequent cigarette smoking (Jarvik, Glick, Nakamura 1970), although the low dose and poor systemic absorption of nicotine given by this route (see Chapter II) required that much higher dose levels be given (10 mg).

Two studies have also demonstrated that intravenous (i.v.) administration of nicotine decreases cigarette smoking (Lucchesi, Schuster, Emley 1967; Henningfield, Miyasato, Jasinski 1983). Another study found no change in smoking following i.v. nicotine infusions (Kumar

et al. 1977); however, the dose (equivalent to about 1.7 mg, given in 10 divided doses over 10 min) was probably inadequate, as suggested by results of other studies (Nemeth-Coslett et al. 1987). The finding that even i.v.-delivered nicotine can reduce subsequent cigarette smoking confirms that neither the tobacco vehicle nor the oral/respiratory route is necessary for nicotine to control behavior. The overall consistency of findings using a variety of forms of nicotine pretreatment is evidence for a specific effect of nicotine as a determinant of cigarette smoking.

Nicotine Antagonist Pretreatments

Another way to evaluate the specific role of nicotine as a determinant of rate and pattern of cigarette smoking is to administer drugs that block the effects of nicotine on the nervous system. Nicotine antagonists (ganglionic blockers) are available as drugs (e.g., pentolinium and hexamethonium) that do not readily enter the brain but are active in the peripheral nervous system, and as drugs (e.g., mecamylamine) that do enter the brain and thus work in both the peripheral and central nervous system (CNS) (Taylor 1985b). In theory, such drug administration should produce effects that are analogous to those that would be expected if the nicotine dose of cigarettes was decreased: that is, smoke intake should increase. Moreover, if smoke intake increases, but only when the centrally acting antagonist is given, such data would suggest the critical involvement of the effects of nicotine in the brain.

Three studies showed that pretreatment of smokers with mecamylamine produced increases in cigarette smoking that resembled those expected if the nicotine dose of the cigarettes had been decreased (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau, Pomerleau, Majchrzak 1987). In each of these studies, the short-term effect of the nicotine antagonists was studied. Similarly, mecamylamine pretreatment increased the preference for high nicotine-yield cigarette smoke (apparently by reducing its nicotinic effects) when subjects were tested with a device which blends smoke from high and low nicotine-yield cigarettes (Rose, Sampson, Henningfield 1985). The role of nicotine action in the brain was demonstrated in the study by Stolerman and colleagues (1973) in which a nicotine blocker (pentolinium) that does not readily enter the brain produced no effects on cigarette smoking.

Effects of Nonnicotinic Drugs on Cigarette Smoking

In addition to nicotine and nicotine antagonists, the effects of other psychoactive drugs on cigarette smoking have been studied in the laboratory. Such studies are important insofar as they constitute drug-interaction studies whereby it may be determined if the

behavioral and physiological actions of nicotine are altered as a function of pretreatment with other drugs. In addition, studies of interactions of nicotine with other dependence-producing drugs are important because tobacco use generally precedes and accompanies use of many other dependence-producing drugs (Chapter V). Several classes of psychoactive drugs have been administered in studies in which cigarette smoking was specifically measured. In general, the results permit a categorization of these drugs into two groups: (1) those drugs that produce increases in smoking under standard test conditions, and (2) those drugs that produce little reliable effect on cigarette smoking under standard test conditions.

Sedatives, opioid agonists, and psychomotor stimulants have been shown capable of producing robust and dose-related increases in cigarette smoking. Specifically, alcohol (ethanol) has been shown to increase cigarette smoke intake (Griffiths, Bigelow, Liebson 1976; Henningfield, Chait, Griffiths 1984; Nil, Buzzi, Bättig 1984; Mintz et al. 1985; Mello et al. 1980b). In a study in which alcohol was found to increase smoking in all of five alcoholic subjects tested, pentobarbital (a depressant) was found to increase smoking in the two subjects with extensive histories of barbiturate use (Henningfield, Chait, Griffiths 1984). The effects of alcohol and pentobarbital were most robust in heavier drinkers and alcoholics (Henningfield, Chait, Griffiths 1983, 1984). The opioid agonists, heroin and methadone, increase cigarette smoking in opioid users (Mello et al. 1980a; Chait and Griffiths 1984). Methadone produced dose-related increases in number of cigarettes and puffs, and in puff duration in methadone-maintained smokers (Chait and Griffiths 1984). Analogously, number of cigarettes smoked per day gradually decreased as methadone-maintained clients had their daily methadone doses decreased over several weeks (Bigelow et al. 1981). Finally, the psychomotor stimulant *d*-amphetamine increases a variety of measures of cigarette smoking (Henningfield and Griffiths 1981; Chait and Griffiths 1983).

Three other drugs have been studied and found to produce little reliable effect on cigarette smoking. Caffeine is of interest because it might be predicted to either increase smoking by its general stimulant (amphetamine-like) effects (Rall 1985) or to decrease smoking by serving as a substitute for some of nicotine's stimulant effects (Kozlowski 1976). Laboratory studies, however, have found the effects of caffeine administration on cigarette smoking to be weak and inconsistent: two studies showed no reliable effect (Chait and Griffiths 1983; Nil, Buzzi, Bättig 1984), another showed weak decreases in smoking (Kozlowski 1976), and a fourth showed weak increases in smoking following caffeine administration (Ossip and Epstein 1981).

The opioid antagonist naloxone (naloxone blocks effects of heroin-like opioids) is another drug of interest because of the possible role of endogenous opioids as mediators of some of the effects of nicotine (Chapter III; Pomerleau and Pomerleau 1984). In a test paradigm in which several drugs have been shown to produce orderly effects on cigarette smoking (Griffiths and Henningfield 1982), naloxone produced no consistent changes in cigarette smoking over a wide range of dose levels (Nemeth-Coslett and Griffiths 1986). Another study of the effect of naloxone which employed a single dose found a reduction in smoking (Karras and Kane 1980). No clear reconciliation of these disparate findings is evident. Finally, marijuana pretreatment was found to produce no reliable effect on tobacco intake (Mello et al. 1980b; Nemeth-Coslett et al. 1986b) or on the way cigarettes were smoked (Nemeth-Coslett et al. 1986b).

Effects of Nonnicotine Constituents of Tobacco Smoke and Citric Acid Aerosol

Chemicals presumed to act primarily in the respiratory tract and not in the central nervous system may also affect smoking. The region of the trachea just below the larynx is assumed to be a site of some cigarette smoke related sensations (Cain 1980). This site corresponds to the region 2 cm below the narrow opening of the larynx where particles entering the trachea change direction (Chan and Schreck 1980).

The components of cigarette tar and volatile gases in smoke contribute to the taste, olfactory, and tracheobronchial sensations elicited by cigarette smoke. In fact, minimal levels of tar are held by tobacco manufacturers to be important to maintain product satisfaction in smokers (Tobacco Reporter 1985; Gori 1980). Besides its causal role in lung cancer and other diseases (US DHHS 1982, 1983, 1984), tar may function to mask the harshness and irritation of nicotine (Herskovic, Rose, Jarvik 1986). Consistent with this hypothesis, nicotine aerosols delivering doses of nicotine similar to those in mainstream cigarette smoke are rated as extremely harsh and irritating by cigarette smokers (Russell 1986). Similarly, some gaseous components of smoke, such as acrolein and formaldehyde, are irritating and could also contribute to the tracheobronchial sensations elicited by smoke (Lundberg et al. 1983).

Levels of tar and other constituents may also contribute to brand preference and, conversely, to the difficulty in finding readily acceptable substitutes for the cigarettes normally smoked by individuals. For example, a nonmentholated cigarette may not be a desirable substitute for a mentholated one. Moreover, when given cigarettes made of lettuce or cocoa leaves, smokers complain about the unpleasant smell and taste (Goldfarb, Jarvik, Glick 1970; Herskovic, Rose, Jarvik 1986). Tobacco research cigarettes are often

found to be less palatable than commercial brands (Benowitz, Kuyt, Jacob 1982), indicating the importance of specific tobacco blends and/or additives in determining taste and brand preferences.

The precise nature of the sensations critical to smoking satisfaction has not been elucidated, and the relative roles of taste, olfaction, and tracheobronchial sensations are not clear. One way to assess the importance of local respiratory sensations in the subjective response to cigarette smoke is to block these sensations with a short-acting topical anesthetic. Two studies have used inhalation of a 4-percent lidocaine aerosol and mouth rinses and gargling with lidocaine solutions to assess the importance of airway sensations to cigarette smokers (Rose et al. 1984, 1985). In both studies, the desirability of puffs was decreased by local anesthesia of the respiratory tract. Additionally, the decline in reported craving for cigarettes that usually occurs after smoking was diminished by local anesthesia.

A study was also conducted in which smokers inhaled a refined tobacco smoke condensate (Rose and Behm, in press). The condensate produced a low overall nicotine yield (about 0.2 mg/10 puffs), while maintaining a higher ratio of nicotine to tar and a larger particle size than that of conventional cigarette smoke. Smoke generated in this fashion was rated as stronger and harsher than smoke of equivalent nicotine content delivered by smoking a conventional low-tar and low-nicotine cigarette (Rose and Behm 1987). The subjects also reported significantly greater satisfaction and diminished desire to smoke additional cigarettes after inhaling puffs of refined smoke compared with conventional low-nicotine cigarette smoke (Rose and Behm 1987). These studies demonstrate that local sensory effects of smoke may influence the short-term subjective responses to smoking.

The inhalation of aerosols containing citric acid is a standard method of eliciting coughing in human subjects (Poundsford and Saunders 1985). One study found that smokers inhaling puffs of a nebulized 15 percent aqueous solution of citric acid reported sensations of strength and harshness comparable to those produced by their own cigarette brand and considerably stronger than those elicited by an "ultra" low-tar, low-nicotine cigarette (Rose and Hickman 1987). Moreover, some pleasure was reported to be associated with these sensations, and desire for cigarettes was decreased, suggesting that mild irritation of the respiratory airways may be involved in satiation of smoking behavior and may have a role in smoking cessation efforts (Henningfield 1987c; Chapter VII).

Nicotine: Psychoactivity, Reinforcing and Related Behavioral Mechanisms of Nicotine Dependence

As the preceding sections have shown, cigarette smoking is an orderly behavioral and pharmacologic process clearly involving

maintenance of the desired levels of nicotine in the body. These data are sufficient to label tobacco use as a form of drug self-administration in which the role of nicotine in controlling tobacco self-administration functions as do morphine, ethanol, and cocaine in the use of opium-derived products, alcoholic beverages, and coca-derived products, respectively. However, the question may be asked whether the behavior-controlling pharmacologic properties of nicotine are similar to those of prototypic dependence-producing drugs when evaluated in standard laboratory tests. More specifically, the scientific question is whether nicotine itself shares critical dependence-producing properties with drugs such as morphine, cocaine, and alcohol. Standardized testing procedures can be used in both animal and human studies to objectively determine if a drug is dependence producing. These procedures, as well as a review of how addicting drugs control behavior, is presented in Chapter V. Chapter V also presents data obtained when drugs such as morphine, cocaine, and alcohol are tested by identical procedures.

In brief, four general kinds of behavior-modifying drug effects can be differentiated on the basis of the test procedure used. These drug effects are discussed in Chapter V and include the following: (1) Drugs may produce *interoceptive* stimulus effects; that is, they can produce effects that a person or animal can distinguish from the nondrug state. Although not identical in meaning, the following terms are often used to designate interoceptive drug effects: "psychoactive," "discriminative," "subjective," "self-reported." (2) Drugs may serve as *positive reinforcers* or *rewards*, the presentation of which produces repetition and strengthening of the behaviors which led to their presentation, i.e., "drug self-administration" or "drug seeking." (3) Drugs can serve as *unconditioned stimuli*, in which case they may directly elicit various responses; these responses may subsequently be elicited by stimuli which are associated with the drug (i.e., conditioned stimuli), including the presence of environmental, or even internal, cues. (4) Drug administration or abstinence can also function as "punishers" or *aversive* stimuli.

This Section will present data from studies of nicotine with each of the four testing procedures mentioned above. The convergence of findings from several distinct approaches provides compelling evidence that nicotine is a drug that can effectively control behavior, including behavior leading to its own ingestion (i.e., dependence or addiction).

Interoceptive, Discriminative, and Subjective Effects of Nicotine

Ingested chemicals can serve as stimuli by actions on either peripheral or centrally located receptors or by indirect effects mediated through the release of various biochemicals or neurohor-

mones. In general, the term "psychoactive" is reserved for those drugs whose discriminative effects are known to result from their actions in the brain. As described by Lewin (1931) and others (Thompson and Unna 1977) it is, in part, the nature of the discriminative stimulus effects of a drug within the body that sets the dependence-producing drugs apart from other non-nutritive substances. As shown in Chapter II, all commonly used forms of tobacco are effective means of delivering nicotine to the blood from which it is rapidly transported to the brain. Research with animals has shown that nicotine produces distinct effects in the central nervous system (CNS). In addition, nicotine has diverse peripheral and hormonal actions that could serve to intensify its CNS stimulus properties. The biochemical mechanisms of these effects are discussed in Chapter III.

Three procedurally distinct methods have been used to characterize the stimulus properties of nicotine and will be discussed in the following sequence: (1) discrimination testing in animals and humans, (2) assessing subjective effects in humans, and (3) testing for state-dependent learning effects in humans. Each method has been used to help characterize the stimulus properties of a variety of drugs including nicotine (Chapter V).

Drug Discrimination Testing in Animals

Animal studies of nicotine discrimination show that nicotine produces reliable effects that are readily identified by the subjects. Such studies indicate that fundamental biobehavioral mechanisms mediate the psychoactive properties of nicotine in humans, and that such effects are not unique to human psychological processes. These data also have implications for understanding and treating tobacco dependence and are summarized below.

Specificity of the Nicotine Stimulus

Although dependence-producing drugs may overlap, to some degree, in the nature of their effects on mood and feeling, each drug class and sometimes drugs within a class produce unique effects. As this Section shows, nicotine also produces some effects that permit it to be distinguished from most other psychoactive drugs. These studies are also useful for testing new drugs that are thought to produce nicotine-like effects.

Rats can learn to accurately discriminate nicotine from placebo regardless of the route of administration as long as the nicotine reaches the brain. Most researchers have utilized the subcutaneous (s.c.) route of administration (Rosecrans and Meltzer 1981); however, more recent studies have incorporated other routes of nicotine administration and have found that rats could learn to discriminate

nicotine when given nicotine by gavage (oral tube) in a dose of 0.5 mg/kg (Howard and Craft 1987). Oral nicotine-trained rats generalized to nicotine administered via either the s.c. or transdermal routes (nicotine solution was applied to a 1.5-cm circular area on the shaved back of the rat). There was little difference in dose potency between the oral and s.c. routes; however, the transdermal route was much less potent and required eight times the oral dose to establish equivalent response patterns. Taken together, the results of these studies showed that nicotine given by a variety of routes produces time- and dose-related discriminative effects.

Several studies have compared nicotine with a variety of drugs by these drug discrimination testing procedures (Rosecrans and Meltzer 1981; Stolerman et al. 1987). Early research involved testing a wide variety of chemicals. These studies showed that nicotine-trained rats did not generalize to drugs of other classes such as the opioids, barbiturates, or hallucinogens (Rosecrans and Meltzer 1981). Of special interest was the prototypical stimulant *d*-amphetamine, because nicotine also has a variety of stimulant-like actions (Rall 1985). When nicotine-trained rats were tested with amphetamine, however, they only partially generalized to nicotine. In another study, Schechter (1981) observed higher levels of amphetamine generalization to nicotine in a group of rats trained to discriminate amphetamine from pentobarbital. Thus, nicotine may have some amphetamine-like effects which are unmasked under certain conditions.

Oxotremorine and arecoline are agonists of the cholinergic nervous system, but these drugs activate muscarinic, and not nicotinic, cholinergic receptors (Gilman et al. 1985). Consistent with the mechanisms of action of these cholinergic drugs are the findings that neither oxotremorine nor arecoline generalized to nicotine in nicotine-trained animals (Rosecrans and Meltzer 1981).

Nicotine analogs and metabolites have also been studied with the discrimination paradigm (Rosecrans and Chance 1977; Stolerman et al. 1987). Such research can help reveal the extent, if any, of the role of these nicotine-related or nicotine-derived chemicals in determining the nature of the discriminative effects that follow nicotine administration. In rats trained to discriminate 100 µg/kg of nicotine, the analogs cytisine and anabasine generalized to nicotine. The alkaloid nornicotine generalized partially to nicotine. Cotinine, the major metabolite of nicotine, was observed to generalize to nicotine only when the cotinine was given intraventricularly in relatively high doses to rats trained to discriminate relatively low dose levels (100 µg/kg) of nicotine. These data show that although metabolites of nicotine may share some stimulus properties with nicotine, the degree of generalization is weak, suggesting that the discriminative

stimulus effects of nicotine are mainly due to nicotine itself and not to the metabolites.

Synthetic analogs of nicotine have also been evaluated for their possible nicotine-like properties in discrimination studies (Rosecrans, Kallman, Glennon 1978; Rosecrans et al. 1978). Of the several compounds tested, only one, 3-methyl-pyridylpyrrolidine, a chemical isomer of nicotine, was observed to generalize to the nicotine stimulus in nicotine-trained rats. This compound was observed to be 8 to 10 times less potent than nicotine. Its effects were significantly antagonized (reduced or blocked) by mecamylamine, which also antagonizes the stimulus generated by both S- and R-nicotine; the naturally occurring tobacco constituent, S-nicotine, is also 8 to 10 times more potent as a stimulus than R-nicotine. The results of these investigations indicate that the stimulus properties of nicotine are highly specific.

A finding relevant to pharmacologic treatment efforts (see Chapter VII) involved discrimination studies with lobeline (a constituent in several over-the-counter aids for quitting smoking). Lobeline is an alkaloid with some nicotine-like ganglionic effects in the peripheral nervous system (Gilman et al. 1985). Rosecrans and Chance (1977) found that lobeline was neither discriminated as nicotine nor did it block nicotine discrimination in nicotine-trained rats. These results do not support the use of lobeline-containing compounds as treatment aids for cigarette smoking (see also Schwartz 1987; Chapter VII).

Peripheral Versus Central Discriminative Stimulus Effects of Nicotine

The degree to which the stimulus is generated via peripheral rather than central nervous system (CNS or brain) actions is also important in understanding the nature of the nicotine stimulus. As discussed in Chapter III, nicotine has many peripheral autonomic nervous system (ANS) effects which might feed back to the CNS, thereby indirectly generating or contributing to stimulus effects. Thus, changes in blood pressure, heart rate, body temperature, and hormone release could be potential mediators of the effects. Several approaches have been utilized to address the role of peripheral actions of nicotine in the generation of the discriminative stimulus. One approach is to attempt to block nicotine with an antagonist not able to enter the CNS.

In one study, animals were trained to discriminate a dose of nicotine (Rosecrans and Chance 1977). Then they were pretreated with a series of nicotinic cholinergic antagonists and with muscarinic cholinergic antagonists. After pretreatment with an antagonist, the animals were retested with the training dose of nicotine. Mecamylamine, a centrally and peripherally acting nicotine antago-

nist, was the only drug observed to completely block the nicotine stimulus. As the dose of this antagonist was increased, percent correct responses on the nicotine-correct lever, after the injection of 200 or 400 µg/kg of nicotine, decreased to placebo response levels, indicating a complete antagonism of the nicotine stimulus. In a similar study, Stolerman, Pratt, and Garcha (1982) increased the nicotine dose in an attempt to overcome the actions of mecamylamine: the blockade was not overcome by any dose of nicotine. Thus, these data suggest that mecamylamine is not a competitive antagonist (blocking at the receptor itself) but rather may functionally antagonize nicotine's effects through another mechanism (Stolerman et al. 1987).

In other studies, a 331 µg/kg dose of mecamylamine antagonized the stimulus effects of 200 µg/kg of nicotine, while 835 µg/kg was required for similar antagonism of the 400 µg/kg dose of nicotine (Rosecrans and Meltzer 1981). All such studies found that the peripherally acting nicotinic antagonist, hexamethonium, did not affect nicotine discriminations. The muscarinic antagonist, atropine, was also without effect. The possible relationships of the nicotine stimulus to brain norepinephrine and 5-hydroxytryptamine (serotonin or 5-HT) systems were also investigated through the use of the appropriate antagonists/agonists. Similarly, a quaternary analog of nicotine, which does not enter the brain, was evaluated and found to produce no evidence of generalization in nicotine-trained rats (Rosecrans et al. 1978). Such studies do not support the involvement of peripheral systems in the generation of the nicotine stimulus.

Another strategy used to investigate the central nature of the nicotine stimulus compared concentrations of nicotine in the brain with the resulting stimulus effects of nicotine (Rosecrans and Chance 1977). It was assumed that if nicotine's stimulus effects are mediated in the brain, then such effects should be related to brain levels of nicotine. This hypothesis was confirmed. In fact, it was found that before nicotine functions as a stimulus, it must achieve a minimal drug level in the brain. In addition to relating drug level in the brain to the stimulus effect induced by nicotine, Rosecrans and Chance (1977) showed that systemically administered nicotine generalized to nicotine administered intraventricularly. Taken together, the foregoing studies show that the nicotine-generated discriminative stimulus is dependent on the actions of nicotine at central nicotine receptors in the brain.

Drug discrimination research has also examined the stimulus properties of the muscarinic cholinergic agonist, arecoline. Arecoline is a constituent of the betel nut mixtures commonly chewed in the East Indies (Taylor 1985a). Three approaches have been utilized to investigate the stimulus properties of arecoline. In the first study, arecoline served as a discriminative stimulus and thereby assumed

control of behavior (Rosecrans and Meltzer 1981). These effects of arecoline were blocked by pretreatment with the muscarinic antagonist, atropine, while the quaternary compound, methyl atropine (which does not readily cross the blood-brain barrier), was ineffective. These results indicate that the stimulus can also be exerted via muscarinic stimulation and confirm that the discriminative stimulus properties of muscarinic agonists, like those of nicotinic agonists, are centrally mediated. Additional studies indicated that mecamylamine was not able to antagonize the stimulus effects of arecoline (Rosecrans and Meltzer 1981). Finally, it was found that rats could be trained to discriminate between the muscarinic and nicotinic agonists, arecoline and nicotine. Thus, there appear to be two independent central cholinergic receptor systems (muscarinic and nicotinic), each of which can exert stimulus control over behavior when appropriately stimulated. These findings have been confirmed by Stolerman and colleagues (1987).

Interactions with Noncholinergic Neurons

In a preliminary study (Takada et al., 1988) two nicotine-trained squirrel monkeys recognized beta-carboline as nicotine. Beta-carboline induces symptoms resembling anxiety in animals; these symptoms can be reduced by administration of the anxiolytic, diazepam (Shephard 1986). In addition to this observation, Colpaert (1977) reported that nicotine can antagonize the diazepam cue, and Heath, Porter, and Rosecrans (1985) noted that nicotine antagonized the effects of diazepam on punished responding in rats. Mecamylamine was also found to attenuate the nicotine-induced antagonism of diazepam's antianxiety effect. Harris and coworkers (1986) found that metrazol (a convulsant) partially generalized (35 percent) to nicotine when tested in the discrimination paradigm in nicotine-trained animals. A greater degree of generalization of the metrazol cue to nicotine (50 percent) was observed 48 hr after the cessation of a 21-day chronic nicotine regimen in rats trained to discriminate metrazol (5 mg/kg) from saline; these generalizations were not antagonized by mecamylamine. Harris and colleagues (1986) suggested that the generalization of metrazol to nicotine was a function of a nicotine abstinence-induced withdrawal syndrome resembling anxiety. These studies suggest that nicotine may act at central receptors capable of eliciting a stimulus cluster which induces anxiety (Chapter III).

Subjective Effects of Nicotine in Humans

The extensive amount of nicotine discrimination research using a variety of animal species and several routes of administration confirms that nicotine is a potent drug that can induce alterations in

nervous system function that are distinct and readily identifiable. In addition, the similar findings observed in studies using different routes of nicotine administration are consistent with the hypothesis that the tobacco vehicle is not necessary to produce nicotine-associated changes of mood and feeling. The next Section examines data from analogous studies in which humans served as research subjects.

Psychoactivity of Nicotine

The animal research described above indicates that nicotine's psychoactivity is a result of basic biological actions. Human research on nicotine corroborates the validity of the animal research. Results from studies of the interoceptive effects of nicotine in humans are analogous to those obtained in animal studies described above.

One of the first human studies that used drug discrimination procedures, as had been developed with animal subjects, was a study of nicotine discrimination. The study involved the systematic manipulation of nicotine dose levels with research cigarettes which varied primarily in the amount of nicotine delivered (Kallman et al. 1982). This study demonstrated that nicotine, as delivered by the inhalation of tobacco smoke, produces discriminative stimulus effects. The degree and rate of acquisition of the discrimination appeared to be dose dependent. The ability of the subjects to make the discriminations did not appear to be related to either autonomic (e.g., heart rate) effects of nicotine or to nicotine's effects on other self-reported measures (e.g., taste of the cigarette).

The data from Kallman and associates (1982) are consistent with those of several other studies which have found that human volunteers can differentiate among cigarettes which vary mainly in the amount of nicotine which they deliver (Goldfarb, Jarvik, Glick 1970; Goldfarb et al. 1976; Herskovic, Rose, Jarvik 1986; Rose 1984; Griffiths, Bigelow, Henningfield 1980; Henningfield, Miyasato, Johnson, Jasinski 1985). Furthermore, the conclusion that centrally mediated effects of nicotine are important in such responsivity is supported by findings that pretreatment with mecamylamine reduced responsivity to nicotine dose levels of the cigarette (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau et al. 1987). The study by Stolerman and associates (1973) also showed that such antagonism of nicotine's effects was not obtained when peripherally acting pentolinium was given.

Other research has confirmed that the tobacco vehicle is not necessary to enable the interoceptive effects of nicotine. Several studies involving i.v. administration of nicotine in human subjects have found that humans readily differentiate among nicotine dose levels given intravenously. In the earliest of these studies, i.v. injections of nicotine were given to 35 volunteers, most of whom were cigarette smokers (Johnston 1942). The conclusions of Johnston

TABLE 3.—Summary of early observations regarding psychoactivity of intravenously delivered nicotine in humans

1. "Psychic" effects are directly related to nicotine dose; nonsmokers are much more sensitive to toxic symptoms (e.g., nausea) than smokers
2. Effect of nicotine is "specific and readily distinguished from that of cocaine or codeine"*
3. Nicotine injections are "pleasant" to smokers, and are preferred by some over cigarette smoking
4. Orally given nicotine (dissolved in water) also had "psychic" action, but appeared much less potent than intravenously administered nicotine; delayed onset of effect
5. ~ 1-3 mg doses appeared tolerable and equivalent to smoking single cigarette; ~ 0.11 mg doses appeared to produce "subjective sensation" equivalent to one "deep" cigarette smoke inhalation

*More recent research indicates that higher dose levels of nicotine can produce cocaine-like effects (Henningfield, Miyasato, Jasinski 1985).

SOURCE: Johnston (1942).

that are especially relevant to characterization of the psychoactivity of nicotine are shown in Table 3.

Johnston's findings (Table 3) have been generally confirmed. Jones, Farrell, and Herning (1978) and Rosenberg and colleagues (1980) also found that human volunteers could differentiate i.v. nicotine at dose levels similar to those obtained by smoking cigarettes. In another study which extended the findings of Johnston (1942), both i.v. nicotine and nicotine inhaled from research cigarettes across a range of doses were administered to human volunteers with histories of using a variety of dependence-producing drugs (Henningfield, Miyasato, Jasinski 1985). Subjects clearly distinguished nicotine from a placebo, and the dose strength estimates were directly related to the nicotine dose level. A subsequent study showed that the immediate subjective effects of nicotine were diminished by pretreatment of subjects with mecamylamine (Henningfield et al. 1983).

In a study by Henningfield, Miyasato, Jasinski (1985), measures used to qualitatively describe the nature of the drug stimulus indicated that nicotine met criteria as a euphoriant. At higher doses nicotine was sometimes identified as a stimulant (cocaine or amphetamine); it elevated scores on the Morphine Benzedrine Group ("Euphoria" or "MBG") scale of the Addiction Research Center Inventory (ARCI) (Haertzen and Hickey 1987); and it produced dose-related increases in scores on a drug-liking scale. The high-dose cocaine/amphetamine identifications found in the study by Henningfield, Miyasato, and Jasinski (1985) were not observed by

Johnston, but such similarities between nicotine and cocaine may only be clearly identifiable by subjects experienced with both cocaine and nicotine.

Nicotine given in the polacrilex gum form has been evaluated with similar measures as described above. These studies involved giving various combinations of 2-mg- and 4-mg-nicotine pieces of polacrilex gum and placebo to cigarette smokers. Human volunteers were given the polacrilex gum to chew in doses ranging from 0 to 4 mg in one study (Nemeth-Coslett and Henningfield 1986) and 0 to 8 mg in another study (Nemeth-Coslett et al. 1987). Both studies showed that subject ratings of several effects (including "dose strength") were directly related to the total dose of nicotine that was given. In addition, similarity of the stimulus effects to those produced by cigarettes was a direct function of dose level. In these studies "liking" or "positive" effect scores were inversely related to dose level, suggesting that this nicotine delivery system has low potential for causing dependence when compared with that of cigarettes (Chapter VII). The role of centrally mediated nicotinic actions in the ability of humans to differentiate among polacrilex gum-delivered nicotine doses was confirmed in a study by Pickworth, Herning, and Henningfield (in press). These researchers found that mecamylamine pretreatment of human volunteers reduced both the EEG and subjective effects of nicotine polacrilex gum administration.

Like many other psychoactive drugs (Chapter V), nicotine can also produce unpleasant or dysphoric subjective effects that are related to the dose given and the route of administration. Such effects can be quantified by a psychological scale of the ARCI that is sometimes referred to as the "dysphoria" scale (Jasinski, Johnson, Henningfield 1984) or the "LSD" scale because it was constructed from items found to be elevated when lysergic acid diethylamide (LSD) was given to volunteers (Haertzen 1966, 1974).

In one study, Henningfield, Miyasato, and Jasinski (1985) found that both inhaled (research cigarette smoke) and i.v. nicotine produced dose-related increases in LSD scale scores. In two other studies, nicotine polacrilex gum was tested (Nemeth-Coslett and Henningfield 1986; Nemeth-Coslett et al. 1987). LSD scale scores were at least slightly increased in both studies and were significantly increased in the study by Nemeth-Coslett and Henningfield (1986). These results with nicotine polacrilex gum, combined with no increases in MBG scale scores, are consistent with the observations described earlier suggesting a low overall dependence potential for this formulation.

Sensory Effects of Nicotine

As discussed earlier in this Chapter, nonnicotine constituents of tobacco smoke can produce functional sensory effects. Nicotine, too,

can produce peripherally mediated sensory effects which could contribute to the taste of the cigarette. Although not generally termed "psychoactive" drug effects, such effects could contribute to the control over behavior as they provide discrete cues which may be associated with centrally mediated nicotinic effects. For example, nicotine has a bitter taste, elicits burning sensations when placed on the tongue, and is irritating to the oral and respiratory mucosa (Windholz et al. 1976). Increasing the nicotine delivery of cigarettes while holding tar delivery constant leads to an increase in perceived strength and harshness. The possible effects of nicotine in the upper respiratory tract on subject ratings cannot be excluded in these studies. Nicotine also stimulates mechanoreceptors sensitive to pressure and stretch (Taylor 1985b), and this local action of nicotine may also contribute to the sensory characteristics of inhaled cigarette smoke.

Hexamethonium (the nicotine receptor antagonist that only acts peripherally) has been shown to block cigarette smoke-induced edema in the tracheobronchial mucosa of rats (Lundberg, Saria, Martling 1982). Another study showed that mecamylamine produced dose-related decreases in harshness ratings of individual puffs of cigarette smoke (Rose, Sampson, Henningfield 1985). In this study, subjects were asked to rate their preference at different nicotine concentrations of the smoke: mecamylamine pretreatment shifted preferences to higher smoke concentrations for individual puffs.

Another method of producing at least some of the nicotine-related sensations of cigarette smoke is to present nicotine in vapor or aerosol form without any components of tar. Nicotine vapor is likely to be deposited mainly in the mouth and pharynx (Russell 1986); thus it would be difficult to administer a pharmacologically effective dose of nicotine without producing excessive local irritation and bad taste. However, a low dose of nicotine delivered in this fashion might simulate the sensory effects of smoking, even if the pharmacologic effects are minimal. A low-dose nicotine aerosol delivering droplets 1 to 5 μm in size would be expected to provide respiratory sensations even more similar to cigarette smoking, as particles of this size would impact mainly in the tracheobronchial region.

Three studies have evaluated the effects of a commercially marketed nicotine vapor delivery system in human subjects. The delivery system was a version of that originally described by Jacobson, Jacobson, and Ray (1979); it was marketed as a "tobacco product" through February 1987, when the Food and Drug Administration (FDA) required verification of "safety and efficacy" for continued marketing as a "nicotine delivery system" (see Chapter VII). It consisted of a cigarette-size plastic tube with a nicotine-containing polymer in the end distal from the user's mouth. It was used by sucking air through the tube and inhaling in a manner

similar to that when smoking cigarettes. When the system was used in this fashion, two studies found that plasma nicotine levels were not significantly elevated (Sepkovic et al. 1986; Henningfield 1986b). A third study found significant elevations in plasma nicotine following use of the nicotine tube (Russell et al. 1987). However, in the latter study subjects used what may be described as a heroic puffing procedure: they were instructed to puff 1 nicotine tube 10 times, at intervals of 40 sec; after a 4-min pause, subjects then "puffed and inhaled as hard and as frequently as possible, continuously for the next 20 min, with changes every 5 min to fresh cigarette [nicotine tube]." Symptoms typical of those associated with higher levels of nicotine administration were observed, i.e., dizziness, lightheadedness, and in a few subjects, nausea (Russell et al. 1987).

In another study of the nicotine vapor inhaler, four tubes in which none, one, two, or four contained nicotine (the others being denicotinized) were simultaneously puffed on by volunteers through a specially designed cigarette holder (Henningfield 1986b, 1987a). In this study, despite the fact that measurable changes in plasma nicotine levels did not occur, several responses often associated with nicotine delivery were observed: (1) subject ratings of "harshness" were directly related to dose (number of nicotine-containing tubes); (2) post-puffing increases in heart rate occurred as a function of dose; (3) subjective effects were directly related to dose; and (4) desire to smoke tobacco cigarettes was inversely related to nicotine dose level. Taken together, these results show that even with negligible systemic levels, nicotine can induce feelings of satisfaction and can reduce urges to smoke when it produces tobacco-like sensations of throat burn and harshness (Chapter VII).

Some of the short-term satisfaction derived from inhaling nicotine may explain the apparent short-term efficacy of the vapor inhaler in reducing desire to smoke despite negligible plasma nicotine levels. This is in contrast to findings obtained when nicotine is given either intravenously or in the polacrilex gum (Henningfield, Miyasato, Jasinski 1983; Nemeth-Coslett et al. 1987). Whether the effects of the nicotine vapor inhaler are conditioned responses, peripheral nicotinic actions, or both, it remains to be determined if such effects would provide long-term efficacy as tobacco replacement in the nicotine-dependent tobacco user (Chapter VII). Such effects may not be satisfactory for long-term treatment (i.e., they may not satisfactorily alleviate tobacco withdrawal), although they may prove important in providing sources of pleasure and reduction of urges in people trying to quit smoking (Henningfield 1987b).

State-Dependent Learning

The potential of nicotine to induce state-dependent learning effects as well as how such effects are studied are discussed in

Chapter VI. In the present Section, findings are summarized in so far as they are relevant to assessing the dependence potential of nicotine. In brief, state-dependent learning refers to the phenomenon whereby behavior learned in one set of cues or stimulus conditions (context) is most reliably performed when subsequently attempted in the same context and/or is adversely affected when attempted in a novel context (Chapter VI). Psychoactive drugs can produce state-dependent learning effects, apparently by providing a recognizable context based on the interoceptive stimulus cues provided by the drug (see also Chapter V). Several studies have shown that nicotine exposure can lead to state-dependent learning effects. For example, a series of studies conducted by Andersson and colleagues (Andersson 1975; Andersson and Hockey 1977; Andersson and Post 1974) and by others (Peters and McGee 1982; Warburton et al. 1986) showed that nicotine exposure in the form of tobacco smoke could induce state-dependent learning effects in humans. In a study by Lowe (1985), nicotine's part in the state complex produced by alcohol and nicotine together was also evaluated.

There are two implications of the above findings regarding the dependence potential of nicotine. The first is that state-dependent learning could contribute to the dependence potential of cigarettes, in that optimal cognitive/behavioral performance may come to depend upon the continued self-administration of tobacco. These actions might also contribute to the strength of the reinforcing effects of nicotine by producing effects on learning and/or performance (see also Chapter VI).

Nicotine as a Positive Reinforcer

The primary biobehavioral mechanism by which dependence-producing drugs maintain drug seeking is by functioning as positive reinforcers (Thompson and Unna 1977; Thompson and Schuster 1968). That is, drugs can serve as stimuli that strengthen behavior leading to their own presentation (Skinner 1953; Thompson and Schuster 1968). As discussed in Chapter V, studies in the 1960s used the drug self-administration techniques developed to study morphine and other dependence-producing drugs in animals (Weeks 1962; Thompson and Schuster 1964; Chapter V). In the first such study with nicotine, Deneau and Inoki (1967) found that monkeys would also self-administer nicotine intravenously. However, some investigators considered these findings equivocal (Russell 1979; Griffiths, Brady, Bradford 1979). In 1981, Goldberg, Spealman, and Goldberg showed conclusively that nicotine itself could function as an efficacious positive reinforcer for animals, although the range of conditions under which it was effective was somewhat more limited than for drugs such as cocaine and amphetamine. Analogous studies with humans in the 1980s (e.g., Henningfield, Miyasato, Jasinski

1983) demonstrated that intravenously administered nicotine is a reinforcer. The results leading to the foregoing conclusions are summarized in the present Section.

Animal Studies of Nicotine as a Reinforcer

Whether a drug functions as a reinforcer can depend critically on the dose of drug, the previous exposure of the subject to that or other drugs, the behavioral history of the subject, and perhaps most importantly, the immediate contingencies relating responses and subsequent injections of drug (contingencies are often referred to as schedules of reinforcement) (Barrett and Witkin 1986; Chapter V). Nicotine differs from some dependence-producing drugs (e.g., cocaine) (Griffiths, Brady, Bradford 1979) in that for animals, the conditions under which it maintains high rates of self-administration behavior appear to be more limited; however, there are other dependence-producing drugs which also serve as reinforcers under a fairly limited range of conditions (e.g., alcohol) (Mello 1973; Meisch 1977).

Table 4 (modified from Henningfield and Goldberg 1983b) is a summary of the early studies that found i.v. nicotine injection to be ineffective or marginally effective as a reinforcer as well as more recent studies that conclusively demonstrated the capacity of nicotine to function as a positive reinforcer. The studies listed in this Table employed a variety of species (ranging from rats to human volunteers), different types and parameters of drug injection schedules, a variety of training histories, and a wide range of nicotine doses. Much of the research has been reviewed in greater detail elsewhere (Goldberg and Henningfield, 1988; Swedberg, Henningfield, Goldberg, in press). The present Section only reviews some of the more recent studies that have experimentally evaluated nicotine's reinforcing effects.

Until 1981, most experiments of nicotine self-administration involved continuous reinforcement schedules in which each response by an individual subject resulted in the i.v. injection of nicotine (Table 4). Under these continuous reinforcement schedules, (1) rates of responding were very low, ranging from about 0.008 to 0.0005 responses/sec in different studies; (2) changes in nicotine dose produced only small and inconsistent changes in rates of responding; (3) the differences in rates of responding maintained by nicotine compared with saline were generally small; and (4) marked intersubject differences in self-administration of nicotine were often reported. In one series of studies (Lang et al. 1977; Singer, Simpson, Lang 1978; Latiff, Smith, Lang 1980; Smith and Lang 1980) a concurrent schedule of periodic deliveries of food pellets to food-deprived rats was found to increase rates of nicotine self-administration responding (Chapter V). The concurrent food reinforcement schedule ap-

TABLE 4.—Summary of reports in which nicotine was available under intravenous drug self-administration (S-A) procedures

Study	Species	Reinforcement schedule	Main findings	Comments
Deneau and Inoki (1967)	Rhesus monkey	FR 1; several nicotine doses tested	Two monkeys initiated S-A; others required priming procedure	Currently accepted reinforcing efficacy assessment criteria not achieved
Clark (1969)	Hooded rat	FR 1; several nicotine doses and saline tested	Nicotine a reinforcer relative to saline	No quantitative data (from study abstract)
Yanagita (1977)	Rhesus monkey	Experiment 1: FR 1; several nicotine, caffeine, and saline doses substituted for SPA	Nicotine and caffeine not reinforcers, compared with saline or SPA	(preliminary report, Yanagita et al. (1974) studies)
		Experiment 2: FR 1; several nicotine doses continuously available	Nicotine S-A rates stable in most subjects, but not clearly dose related	No direct reinforcing efficacy test
		Experiment 3: PR procedures; two nicotine doses, saline, and three cocaine doses tested	0.2 mg/kg nicotine and lowest cocaine dose (0.03 mg/kg) maintained similar response rates, which slightly exceeded rates maintained by saline	Nicotine marginally reinforcing compared with saline and higher cocaine doses
Lang, Latiff, McQueen, Singer (1977)	Hooded rat	FR 1; nicotine and saline tested in food-sated and food-deprived rats	In food-deprived (not food-sated) rats, nicotine a reinforcer, compared with saline	
Singer, Simpson, Lang (1978)	Hooded rat	CONC [(FR 1:nicotine)(FT 1 min:food pellet)] in food-deprived rats; rats subsequently food-sated	Food satiation decreased nicotine S-A rate, but nicotine a reinforcer in both conditions	Results similar to ethanol testing results

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Griffiths, Brady, Bradford (1979)	Baboon	FR 160 followed by 3-hr timeout; several nicotine doses and saline substituted for cocaine	Number of nicotine injections/day did not exceed saline	Caffeine, ephedrine, and various other similarly tested stimulants were reinforcers relative to saline
Hansen, Ivester, Moreton (1979)	Albino rat	FR 1; several nicotine doses and saline tested	Mecamylamine (centrally acting antagonist), not pentolinium (peripherally acting antagonist), altered S-A behavior	Group data suggest nicotine as a reinforcer; no clear dose-effect curve
Latif, Smith, Lang (1980)	Hooded rat	CONC [(FR 1:injection)(FT 1 min:food pellet)]; several nicotine doses and saline tested	Nicotine a reinforcer, relative to saline; mild effects of urine pH manipulations on S-A rate only during initial nicotine exposure	S-A rate inversely dose related during initial nicotine S-A behavior acquisition, not after establishment
Smith and Lang (1980)	Hooded rat	FR 1; one nicotine dose and saline tested	Nicotine a reinforcer with and without CONC food delivery schedule in food-deprived, but not food-sated, rats	
Goldberg, Speelman, Goldberg (1981)	Squirrel monkey	Second-order schedule FI 1 or 2 min (FR 10:stimulus), followed by 3-min timeout; one nicotine dose and saline tested	Nicotine maintained high rates of responding; rates decreased markedly when (1) saline replaced nicotine, (2) brief stimuli omitted, (3) subjects mecamylamine pretreated	Demonstrated importance of ancillary environmental stimuli in maintaining high rates of responding

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Dougherty, Miller, Todd, Kostenbauder (1981)	Rhesus monkey	FI 16 and second-order FI 1 min (FR 4:stimulus); several nicotine doses and saline tested	Nicotine maintained higher S-A rates than saline under FI and second-order schedules, but only a marginally effective reinforcer when continuously available	Establishing nicotine as reinforcer required several months, using procedures that establish cocaine or codeine as reinforcers in few days
Goldberg and Spealman (1982)	Squirrel monkey	FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested	Nicotine and cocaine qualitatively similar reinforcers, compared with saline; cocaine maintained higher rates of responding in 1 of 2 monkeys; mecamylamine pretreatment reduced nicotine S-A rates	Showed nicotine can be punisher, similar to electric shock
Singer, Wallace, Hall (1982)	Long-Evans rat	CONC [(FR 1:nicotine)FT 1 min:food pellet]; one nicotine dose tested	Lower nicotine S-A rates in rat group with 6-OHDA lesions in nucleus accumbens than in sham-lesions group	Range of lesion-inhibited scheduled-induced behaviors extended
Spealman and Goldberg (1982)	Squirrel monkey	Second-order FI 1, 2, or 5 min (FR 10:stimulus) and FI 5-min schedules tested; several nicotine and cocaine doses and saline tested	Nicotine and cocaine maintained similar rates of responding and patterns; nicotine, not cocaine, S-A decreased to saline-like rates when mecamylamine pretreated	Under both schedules, nicotine and cocaine reinforcing efficacy comparable

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Ator and Griffiths (1983)	Baboon	Experiment 1: FR 2 followed by 15-sec timeout; several nicotine doses, cocaine, and saline tested	Nicotine marginally reinforcing, compared with saline across narrow dose range	Inverted U-shaped initial dose-response curve; flat final curve (earlier abstract, Ator and Griffiths (1981))
		Experiment 2: FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested; FI duration varied 1-11 min	Nicotine maintained higher rates of responding than saline, but much lower than cocaine or food	Nicotine and injections/session responding rates little changed with varied FI duration
Goldberg and Henningfield (1983a, b)	Human and squirrel monkey	FR 10 followed by 1-min timeout; several nicotine doses and saline tested	Monkey and human patterns of responding qualitatively similar; nicotine injection number exceeded saline injection number in 3 of 4 of both humans and monkeys	In both humans and monkeys, evidence of nicotine having both reinforcing and punishing effects (from study abstracts)
Henningfield, Miyasato, Jasinski (1983)	Human	FR 10 followed by 1-min timeout; several nicotine doses and saline tested	Nicotine injection number generally exceeded saline injection number; nicotine injection number inversely related to nicotine dose; nicotine suppressed postsession cigarette smoking	Nicotine and intravenous cocaine subjective effects similar; nicotine had both reinforcing effects and punishing effects

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Risner and Goldberg (1983)	Beagle dog	FR 15 followed by 4-min timeout; several nicotine, cocaine, and saline doses tested; PR schedule also used	Nicotine and cocaine maintained qualitatively similar patterns of responding and were reinforcers relative to saline; mecamylamine pretreatment reduced nicotine, not cocaine, S-A	Substantially greater response rates maintained with cocaine than nicotine
Cox, Goldstein, Nelson (1984)	Wistar rat	FR 1; several nicotine doses and saline tested; a second inactive lever available to assess nonspecific activity-increasing nicotine effects	Nicotine S-A rates higher than saline, but result in part of nonspecific activity increases	Active lever responding rates low (+ 40 responses/12 hrs), only about twice as high as inactive lever rates
Prada and Goldberg (1985)	Squirrel monkey	FR 30 followed by 4-min or 10-sec timeout; one nicotine dose tested	At 4-min timeout, overall nicotine-maintained response rate range 0.3–2.4 responses/sec; at 10-sec timeout, responding poorly maintained	Nicotine iv injections and food pellet delivery maintained similar high response rates (from study abstract)
Slifer and Baister (1985)	Rhesus monkey	Experiment 1: FR 1 and CONC [(FR 1:nicotine)(FT 5-min:food pellet)]; several nicotine doses and saline tested Experiment 2: FR 10; saline and several nicotine doses substituted for cocaine	At CONC condition, nicotine S-A at rate higher than saline; at FR 1 condition, nicotine S-A without CONC food Nicotine a reinforcer relative to saline, but response rates low relative to single cocaine dose tested	At some doses, nicotine maintained higher S-A rates than at FR 1 condition saline (preliminary report, Slifer (1983)) Nicotine dose changes produced only small response rate changes

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Goldberg and Henningfield (1986)	Human and squirrel monkey	Monkeys: FR 10-200, with 1-, 2-, or 4-min timeouts Humans: FR 10-800, with 1-, 5-, 10-, or 20-min timeouts	Nicotine maintained about 1.0/sec overall rate of FR responding at high FR and timeout, in both humans and monkeys	(from text of talk)
Naruse, Asami, Ikeda, Ohmura (1986)	Rat	FR 1, FR 4, FR 8; several nicotine doses and saline tested	Higher nicotine injection doses (10 and 30 µg/kg) maintained responding above saline control levels	Nicotine a relatively weak reinforcer after 15-day availability
De la Garza and Johanson (1987)	Rhesus monkeys	FR 10; saline and several nicotine, d-amphetamine, diazepam, and perphenazine doses substituted for cocaine	Nicotine a reinforcer relative to saline, but response rates very low relative to cocaine and d-amphetamine	Food deprivation significantly increased response rate for low nicotine dose in only 1 of 3 monkeys

NOTE: FR, fixed ratio; SPA, 1:2 diphenyl-1-dimethylaminoethane-HCl; PR, progressive ratio; FT, fixed time; FI, fixed interval; CONC, concurrent.

peared to hasten acquisition of the nicotine self-administration (Smith and Lang 1980).

Since 1981, methodology for studying the reinforcing effects of nicotine has shifted away from continuous reinforcement schedules and toward schedules of self-administration in which responses are only intermittently reinforced by nicotine injection (Goldberg et al. 1983). Such intermittent schedules appear to more closely approximate the patterns of human cigarette smoking behavior in which nicotine is taken in intermittent small doses (puffs) and with even greater intervals between dosing resulting from periods of time between cigarettes (Henningfield 1984). On a variety of intermittent schedules, i.v. nicotine was shown to function as an effective reinforcer, maintaining overall rates of responding ranging from 0.1 to more than 1 response/sec (Table 4). These increases in behavioral responses maintained by nicotine were obtained without the use of food deprivation or concurrent inducing schedules of food delivery.

In one series of experiments with squirrel monkeys, Goldberg and Spealman (1982) and Spealman and Goldberg (1982) utilized a fixed-interval schedule in which the first response to occur after a 5-min interval elapsed produced an i.v. injection of nicotine followed by a 1-min period of drug nonavailability ("timeout"). Responses during the 5-min intervals had no specified consequences, and daily sessions ended after 10 intervals or 2 hr. Under these conditions, nicotine functioned as an effective reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.1 to 0.3 response/sec and were similar to those maintained by cocaine; (2) as nicotine dose per injection was increased from 3 to 300 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were about fourfold to eightfold higher than those maintained during saline substitution; and (4) daily intramuscular treatment with 1 mg/kg of mecamylamine reduced rates of responding maintained by nicotine to saline-control levels but had no effect on responding maintained by cocaine. Thus, nicotine satisfied all the criteria discussed in Chapter V as an effective reinforcer. Particularly striking was the finding that although injection doses of nicotine above 30 mg/kg produced vomiting during the session, one or more of these higher doses continued to be maintained near maximal rates of responding in four of the six monkeys studied.

The results of Goldberg, Spealman, and Goldberg (1981) showing nicotine to be an effective reinforcer have been extended in subsequent studies. For example, high rates of responding were maintained on reinforcement schedules of nicotine injection in which the number of responses per injection was fixed at some intermediate level (e.g., 1 injection/15 responses; such contingencies are termed fixed-ratio schedules). Risner and Goldberg (1983) used a 15-response fixed-ratio schedule of nicotine injection with 4-min

timeout periods following each injection in beagle dogs. Nicotine was an effective reinforcer in all dogs: (1) peak rates of responding were about 0.3 response/sec, but higher rates of responding were maintained by cocaine; (2) as the injection dose of nicotine increased from 10 to 100 mg/kg, response rates first increased and then decreased at the highest dose; (3) peak rates of responding maintained by nicotine were about fifteenfold greater than those maintained by saline; and (4) rates of responding maintained by nicotine but not by cocaine were reduced to saline levels by presession treatment with mecamylamine. Although cocaine maintained higher rates of responding than nicotine in the dog, fixed-ratio patterns of responding maintained by nicotine and cocaine were similar: a pause in responding at the start of each fixed ratio was followed by a change to steady responding at a high rate until nicotine or cocaine was injected.

In other studies Goldberg and Henningfield (1983a,b, 1986) used 10- to 30-response fixed-ratio schedules of i.v. nicotine injection in squirrel monkeys. When a 1-min timeout followed each injection, nicotine maintained rates of responding higher than did saline, although overall rates of responding were very low. When the timeout value was increased to 4 min (Prada and Goldberg 1985; Goldberg and Henningfield 1986) making maximum frequency of nicotine injection comparable to that of earlier studies by Goldberg and colleagues, nicotine maintained high rates of responding that ranged from 0.3 to 2.4 responses/sec in different monkeys.

Differences between nicotine and cocaine in their overall efficacy as intravenously delivered reinforcers have been found when the drugs are compared on progressive-ratio schedules. Risner and Goldberg (1983) studied beagles under a schedule in which the fixed-ratio requirement was increased daily until responding was no longer maintained. Cocaine maintained higher fixed-ratio values than did nicotine on this progressive-ratio schedule, although maximal fixed-ratio values for nicotine were well above those for saline. Yanagita (1977) obtained similar findings on a progressive-ratio schedule of i.v. nicotine or cocaine injection in rhesus monkeys (Chapter V).

Nicotine was also studied in the baboon using an intermittent schedule of reinforcement and was found to be a weak reinforcer. Ator and Griffiths (1983) used a 5-min fixed-interval schedule of i.v. nicotine injection in baboons with 1-min timeout periods. Peak rates of responding were higher than rates maintained during saline substitution. However, rates of responding maintained by nicotine were much lower than those maintained by i.v. injection of cocaine. In addition, as the injection dose of nicotine was increased from 10 to 560 mg/kg, rates of responding first increased and then decreased at the highest doses in one baboon. With the other two baboons, rates of responding either showed little change or decreased as injection dose

was increased. These variable dose-response data were consistent with the conclusion that nicotine was only a weak reinforcer in the baboons.

When cigarettes are smoked, a variety of environmental stimuli are intermittently associated with the pharmacologic actions of nicotine (e.g., pleasure and relief from withdrawal). These stimuli themselves appear important in controlling and strengthening repetitive cigarette smoking (e.g., removal of the sight and smell of cigarette smoking) (Gritz 1978). An experimental model for investigating the role of drug-associated stimuli is the second-order schedule of drug reinforcement. Second-order schedules of reinforcement involve the intermittent pairing or association of an environmental stimulus with the primary reinforcer; these stimuli are used as "secondary" or "conditioned" reinforcers to maintain chains of behavior leading eventually to the delivery of the primary reinforcer (Goldberg, Kelleher, Morse 1975; Katz and Goldberg, in press). These schedules add an additional component of relevance to the study of cigarette smoking: cigarette smoking involves the pairing of many such environmental stimuli (visual, olfactory, taste, and tactile) with the effects of nicotine administration.

Studies of i.v. nicotine on second-order schedules of reinforcement have shown that (1) nicotine can establish previously neutral stimuli (e.g., colored lights) as conditioned reinforcers when injections are paired with light presentations, (2) such schedules can result in high and persistent rates of drug-seeking behavior, and (3) the presentation of the stimuli themselves (in the absence of nicotine injections) could sustain substantial amounts of drug-seeking behavior. Goldberg, Spealman, and Goldberg (1981) and Spealman and Goldberg (1982) used a second-order schedule of nicotine injection in which completion of each 10-response fixed ratio during a 2-, 3-, or 5-min interval produced a brief visual stimulus; the first fixed ratio completed after the specified fixed interval elapsed produced both the visual stimulus and i.v. injection of drug. In these studies, nicotine functioned as a powerful reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.8 to 1.7 responses/sec and were similar to those maintained by cocaine; (2) as nicotine dose increased from 3 to 100 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were twofold to eightfold greater than those maintained during saline substitution; and (4) rates of responding maintained by nicotine, but not by cocaine, were reduced to saline control levels by presession administration of 1 mg/kg of mecamylamine; (5) the brief visual stimuli functioned as conditioned reinforcers, as demonstrated by the finding that rates of responding fell markedly when they were omitted during the intervals.

Taken together, the results of the studies described in this Section confirm that nicotine is self-administered in several animal species and in the absence of either tobacco or unique human cultural factors. It appears to be most effective as a reinforcer when intermittently available and when environmental stimuli are paired with nicotine delivery. Under these conditions, nicotine injections functioned to motivate behavior as did cocaine injections; however, cocaine injections maintained more total work output than did nicotine. Finally, studies with nicotine antagonists further confirmed that effects of nicotine in the brain were necessary to maintain its reinforcing actions.

Human Studies of Nicotine as a Reinforcer

The methods developed in animal studies have also been used to demonstrate the reinforcing effects of i.v. nicotine injections in human volunteers (Henningfield, Miyasato, Jasinski 1983; Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b, 1986). In these studies all subjects had histories of tobacco use and subjects were not allowed to smoke 1 hr before or during 3-hr sessions. During test sessions every 10th lever press produced an i.v. injection of either nicotine or saline followed by a 1-min timeout. In one study (Henningfield, Miyasato, Jasinski 1983), nicotine was available on some days, while saline was available on other days. In other studies (Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b), nicotine and saline were concurrently available for responding on alternate levers. With both approaches, all of the subjects initiated self-administration of nicotine. Nicotine injections were regularly spaced throughout each session, and the rate of self-administration was inversely related to dose. When saline was substituted for nicotine, rates of responding usually decreased; responding that did occur for saline occurred predominantly at the start of each session and was erratic in temporal patterns.

In another study, the fixed-ratio value was then increased to 100; following each injection, subjects then had to wait 20 min before another injection could be obtained (Swedberg, Henningfield, Goldberg, in press). Under these conditions rates of responding increased and ranged from 0.4 to 2 responses/sec, similar to those seen with squirrel monkeys and dogs in the studies previously described. These studies of i.v. nicotine self-administration demonstrated conclusively that nicotine itself can serve as an effective reinforcer in humans.

Nicotine as an Aversive Stimulus

Even dependence-producing drugs do not have invariant positive reinforcing effects; they may be aversive under some conditions (see Chapter V). Furthermore, aversive effects are an additional mechan-

ism by which drugs can modify behavior and may be important in gradually increasing the total amount of control which is exerted by the drug over the individual. Such effects of nicotine could be important in limiting the total amount of cigarette smoking or even in determining when the cigarette is discarded.

The potential effects of nicotine to produce severe discomfort and thereby limit further intake have been part of the history of nicotine which has developed over the centuries (Lewin 1931; Dixon and Lee 1912). Two types of laboratory studies have been conducted to assess possible aversive effects of nicotine. The studies, involving animals and/or humans, showed that nicotine (at high levels) can serve as a punisher to suppress behavior leading to the delivery of another reinforcer, and as an aversive stimulus or negative reinforcer to maintain behavior that either terminates or prevents injections of nicotine.

In one series of studies (Goldberg and Spealman 1982, 1983), squirrel monkeys responded on a two-component fixed-ratio schedule of food presentation. In both components, every 30th lever press produced a food pellet. In the punishment component, which was signaled by a red light, the first response in each fixed ratio produced an i.v. injection of nicotine. When responding produced 10- or 30-mg/kg injections of nicotine during the punishment component, responding was selectively suppressed in that component in a dose-related manner. When saline was injected, however, rates of responding for food were no longer suppressed. Similar findings were obtained when electric shock was compared with nicotine in the same studies. Administration of mecamylamine, but not hexamethonium, reduced the punishing effects of the nicotine, showing that the effects were centrally mediated. Furthermore, these antagonists did not reduce the aversive effects of the electric shock, confirming that the effects of nicotine were due to nicotine actions at nicotinic receptors and not to more general possible effects of nicotine.

The potential aversive effects of nicotine have been experimentally demonstrated in human subjects in a preliminary experiment by Henningfield and Goldberg (1983a). Human volunteers who had been recruited for studies of i.v. nicotine self-administration and who did not self-administer nicotine during initial sessions were tested under a concurrent schedule of nicotine avoidance and nicotine self-administration. Two levers were present, and injections of nicotine were programmed to occur every 15 or 30 min. Pressing the left lever 10 times avoided the impending injection, while pressing the right lever 10 times produced an injection. Higher doses of nicotine (1.5 to 4 mg/injection given over 10 sec) resulted in increased rates of pressing on the left lever, and fewer injections occurred. Subjects never completed the 10 responses on the alternate lever required to produce an injection. When saline was substituted for nicotine,

responding decreased and the number of injections received markedly increased. Analogously, in these same subjects scores on a visual line analog scale for rating "negative or undesirable" effects were directly related to nicotine dose, and declined to zero when saline was substituted for nicotine.

Nicotine as an Unconditioned Stimulus

The preceding studies have largely evaluated the effects of nicotine administration on some behavior which was associated with the drug by a specific behavioral contingency. But drugs can also directly elicit responses which then might become conditioned to occur in the presence of whatever stimuli were associated with those effects. The effects may be seen as positive or negative and may be associated with either increasing or declining drug levels in the body (i.e., drug taking or drug withdrawal).

Two general conditioning paradigms are used to evaluate the unconditioned stimulus effects of drugs and have been used to test nicotine: the conditioned place preference and aversion paradigm, and the conditioned taste aversion paradigm. In addition to a discussion of these paradigms, data obtained from the practical application of such findings in the treatment of tobacco dependence will be summarized.

Conditioned Place Preference and Aversion

The place preference and aversion paradigm has been increasingly used to evaluate the potential of drugs to produce dependence (Bozarth 1983). It may be used to assess the positive and negative subjective states induced by drugs and other chemicals. In the place-conditioning procedure, an animal is exposed to the effects of a drug in a novel, distinctive environment. Another environment is paired with the administration of the drug vehicle (e.g., saline). Subsequently, the subject is given a free choice of both environments while not under the influence of the drug. It is currently hypothesized that the formation of place preferences or place aversions depends on the association of the interoceptive drug effect with an external stimulus (e.g., the particular environmental context of the place-conditioning apparatus). Nicotine has been shown to condition both positive and negative effects in this paradigm.

The first published study of the place-conditioning effects of nicotine (Fudala, Teoh, Iwamoto 1985) indicated that nicotine, at doses from 0.1 to 1.2 mg/kg administered s.c. to rats, produced both a place preference and place aversion depending upon the dose. As discussed in Chapter V, the ability to condition both place preferences as well as place aversions is characteristic of several dependence-producing drugs. A dose of 0.8 mg/kg was found to condition a

place preference for previously nicotine-paired environmental cues in the greatest proportion of animals. At the lowest effective place-conditioning dose of nicotine, 0.1 mg/kg, an almost equal proportion of animals exhibited place preferences and place aversions. This investigation also indicated that mecamylamine, but not hexamethonium, blocked the place preference-producing effects of nicotine, suggesting that this nicotine-induced effect was centrally mediated.

Subsequent studies have extended the findings of Fudala, Teoh, and Iwamoto (1985) discussed above. Using a more conservative classification method in categorizing their subjects, Fudala and Iwamoto (1986) observed that nicotine produced a conditioned place preference only within the dose range previously tested. Furthermore, nicotine conditioned a place preference when the drug was administered immediately prior to conditioning sessions, but not when administered from 20 to 120 min prior to conditioning. Depending on the timing of nicotine administration, either place preferences or place aversions may be produced. For example, at doses between 0.2 and 0.8 mg/kg, a dose-dependent place aversion was induced when nicotine was administered 5 min or less following an animal's exposure to the conditioning environment (Fudala and Iwamoto 1987). One other group of investigators, Clarke and Fibiger (1987), using the same dose range of nicotine as in the two aforementioned studies, found no nicotine-induced conditioned place preference in rats. However, the two investigative groups used experimental methods that differed considerably, including differences in apparatus design, olfactory cues, number of conditioning trials performed, and time of conditioning relative to nicotine administration. The finding that nicotine administration can lead to conditioned responses in animals provides additional evidence of nicotine's potential to control behavior by this basic learning process (i.e., Pavlovian or classical conditioning, see Chapter V).

Conditioned Taste Aversion and Rapid Smoking

During conditioned taste aversion experiments, the presentation of an aversive stimulus after the consumption of a distinctively flavored solution causes rejection of the solution when it is presented at a later time (Palmerino, Rusiniak, Garcia 1980; Chapter V). A variety of dependence-producing drugs have been found to be effective at inducing taste aversions (for example, Wise, Yokel, DeWit 1976; Suzuki et al. 1983; Hunt and Amit 1987; Chapter V). Findings specific to nicotine are presented here.

Etscorn (1980) reported that a large intraperitoneal (i.p.) dose of nicotine, 2 mg/kg, conditioned taste aversions to 20 percent (weight per volume) sucrose in Swiss-Webster mice with the two-bottle choice test paradigm. Etscorn and colleagues (1986) also reported that i.p. injections of 1, 3, and 9 mg/kg of nicotine in golden Syrian hamsters

induced dose-related conditioned taste aversions to 0.1 percent sodium saccharin solutions with a single-bottle choice paradigm.

Kumar, Pratt, and Stolerman (1983) reported that s.c. injections of nicotine bitartrate could condition taste aversions to either 0.1 percent sodium saccharin or 0.9 percent sodium chloride solutions at doses as low as 0.08 mg/kg in Lister hooded rats with a two-bottle choice paradigm. The conditioned taste aversion was induced by nicotine in a dose-related manner; stronger taste aversions were induced by nicotine after four conditioning trials than after one or two trials. The S-nicotine (the nicotine form normally delivered in cigarette smoke) was approximately five times as potent as its stereoisomer in conditioning taste aversions. Mecamylamine, 0.1 to 2 mg/kg administered before each conditioning trial, blocked the development of taste aversions produced by 0.4 mg/kg of nicotine; hexamethonium, 1 to 10 mg/kg, had no effect.

Other studies have confirmed the pharmacologic specificity of nicotine-induced taste aversions; that is, Iwamoto and Williamson (1984) also found that the development of nicotine-conditioned taste aversions could be prevented in rats by pretreatment with mecamylamine, 3 mg/kg, but not with 1 mg/kg of hexamethonium. In an analogous study, the pharmacologic specificity of apomorphine-(dopamine agonist chemically derived from morphine) conditioned taste aversions was investigated in rats by establishing the response to both apomorphine and nicotine following pretreatment of the animals with pimozide (Kumar, Pratt, Stolerman 1983). Pimozide is a dopamine antagonist that blocks many of the effects of apomorphine. Pimozide pretreatment reduced the strength of the conditioned test aversions to apomorphine but not to nicotine, confirming a certain degree of pharmacologic specificity of the conditioning effects of these two chemicals. Finally, an intraventricular microinjection of 5 mg/kg of the quaternary nicotinic cholinergic ganglionic antagonist, chlorisondamine, in hooded Lister rats blocked the development of conditioned taste aversions to 0.1 percent sodium saccharin or 0.9 percent sodium chloride induced by nicotine injected 9 to 16 days after the chlorisondamine (Reavill et al. 1986).

These data indicate that nicotine, like some other drugs, is capable of conditioning taste aversions in a dose-related manner in rodents (see Chapter V). Because mecamylamine, but not hexamethonium, blocks nicotine-conditioned taste aversions, the mechanism by which nicotine conditions taste aversions appears to be centrally mediated. Conditioned taste aversion studies in which various combinations of nicotinic agonists and antagonists are given have also been useful in helping to identify specific brain mechanisms of nicotine's behavior modifying properties (see review by Stolerman, in press; also see Chapters III and V).

The fact that nicotine can be used to elicit aversive effects has been put to practical application in the treatment of cigarette smoking (Chapter V), generally to associate aversive effects of high doses of nicotine with the taste, smell, and inhalation of cigarette smoke. Variations on this procedure have been termed "rapid" smoking or "aversive" smoking procedures; the clinical results of these procedures have been mixed (see Chapter VII).

Nicotine: Withdrawal Reactions (Physical Dependence)

The preceding Sections have shown that cigarette smoking is an orderly form of drug self-administration. The role of nicotine in controlling this behavior is similar to the role of other psychoactive drugs in the determination of other forms of drug dependence (see Chapter V). Nicotine can serve as a highly effective positive reinforcer, and deprivation of cigarette smoking and presumably of nicotine itself can increase the reinforcing efficacy of cigarettes (Henningfield and Griffiths 1979). If longer periods of deprivation are associated with a discomforting withdrawal syndrome, this would constitute an additional mechanism by which the reinforcing efficacy of nicotine would be further increased. The drug effect which enables such discomforting withdrawal is physical dependence. Physical dependence refers to physiological and behavioral alterations that become increasingly manifest after repeated exposure to a pharmacologic agent. The primary indication of physical dependence is an abstinence-associated withdrawal syndrome, although tolerance is a frequent concomitant (Kalant 1978; Cochin 1970; Kalant, LeBlanc, Gibbons 1971; Eddy 1973; Clouet and Iwatsubo 1975; Yanagita 1977). Physical dependence and tolerance are discussed in greater detail in Chapter V.

Tolerance to nicotine has been studied since the 19th century and is well documented (Langley 1905; Dixon and Lee 1912; Gillman et al. 1985). As reviewed in Chapters II and V, nicotine produces tolerance to a variety of behavioral and physiological responses. Until the 1970s, however, physical dependence on tobacco was not rigorously studied, although there was evidence for a syndrome of withdrawal that could accompany abstinence from chronic cigarette smoking (Lewin 1931; Weybrew and Stark 1967) and that was significantly involved in attempts to quit smoking (Dorsey 1936). The clinical significance of the tobacco withdrawal syndrome has also been formally recognized by professional organizations such as the American Psychiatric Association (APA) (1980, 1987) and the American College of Physicians (1986). These observations, along with the evidence that nicotine produces tolerance (Chapter II), led to the conclusion that nicotine exposure produced physical depen-

dence (Jaffe 1985; Jaffe and Jarvik 1978; US DHHS 1986b; APA 1980).

Conclusions that nicotine exposure produced physical dependence were also consistent with early data which suggested that i.v. nicotine delivery seemed to relieve withdrawal from cigarettes and may have produced physical dependence in a nonsmoker (Johnston 1942). Other supporting observations included the finding that abrupt reduction of the nicotine in cigarettes (i.e., low nicotine-yield cigarettes) resulted in behavioral and physiological withdrawal signs including discomfort and the seeking of regular cigarettes (Finnegan, Larson, Haag 1945; Knapp, Bliss, Wells 1963). However, the rigorous scientific methods of the kind that were developed to evaluate withdrawal from opioids and sedatives (Himmelsbach 1942; Isbell 1948; Isbell et al. 1955; Chapter V) were not applied to the study of the tobacco withdrawal syndrome until the late 1970s. Therefore, the data available at the time of the 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health were not considered conclusive (US DHEW 1964). The present Section reviews characteristics of physical dependence on nicotine, including the relationship of nicotine intake to the magnitude of withdrawal signs and symptoms, and the role of both environmental and pharmacologic factors which influence the course of the withdrawal syndrome.

Criteria for Physical Dependence on Nicotine and Clinical Characteristics of the Withdrawal Syndrome

Similar kinds of phenomena characterize withdrawal syndromes from all drugs that produce physical dependence. If physical dependence on nicotine occurs, these same phenomena should be observed (see Chapter V; Martin 1977; Thompson and Unna 1977; Woods, Katz, Winger 1987). Based on these phenomena, criteria for establishing that physical dependence on nicotine occurs include the following: (1) Termination of cigarette smoking should be accompanied by changes in mood, behavior, and physical functioning. (2) Some of these changes should be in a direction which is opposite to those produced by cigarette smoking and should return to the baseline levels observed during chronic tobacco administration ("rebound effects"). (3) Physiological withdrawal effects should be reversible by nicotine administration.

The tobacco withdrawal syndrome as described by the APA in the revised Diagnostic and Statistical Manual (DSM III-R) (APA 1987), provides a clinical description (Table 5). Several of the symptoms of the nicotine withdrawal syndrome correspond to effects of nicotine that are either known or suspected to promote tobacco dependence as discussed in Chapter VI. It should be noted that the sequelae of tobacco abstinence include a range of responses which do not share the same underlying mechanisms. For example, some symptoms are

transient responses which are opposite those produced when nicotine is given and which subside within a few days or weeks of nicotine abstinence; such responses are presumed to reflect a physiological rebound occurring in the absence of chronic drug exposure. Other responses are also opposite those produced by nicotine administration but appear to primarily reflect the removal of nicotine exposure, and which may occur whether or not sufficient nicotine had been taken to produce physical dependence. An example of the latter type of response is body weight. Nicotine can directly suppress appetite and body weight, often below the value at which it would have been had nicotine not been taken; removal of nicotine is then accompanied by a stable increase in body weight.

Various lines of scientific evidence are available to characterize physical dependence on tobacco and to evaluate the specific role of nicotine. These data include surveys, treatment studies, and experimental laboratory studies and are briefly reviewed in this Section.

Retrospective Survey Data

Retrospective studies have been conducted with ex-smokers who were participating in major surveys (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987) or who were patients with chronic respiratory problems (Burns 1969; Mausner 1970). Other studies were conducted using subjects who responded to advertisements in newspapers (Pederson and Lefcoe 1976) or were contacted by word of mouth (Trahir 1967). The subjects in these studies had either quit smoking recently, had quit smoking for more than 1 year, or had at least one episode of remaining abstinent for 24 hr. Although the reliability of these data is limited because they are from retrospective self-reports, they provide information on the prevalence and nature of symptoms which may be experienced by smoke-deprived persons and acutely abstinent smokers.

Symptoms reported by significant numbers of ex-smokers included: "craving" for tobacco (Hughes, Gust, Pechacek 1987; Trahir 1967; Burns 1969; Mausner 1970; Pederson and Lefcoe 1976); restlessness, nervousness, or irritability (Trahir 1967; Wynder, Kaufman, Lesser 1967; Burns 1969; Mausner 1970; Hughes, Gust, Pechacek 1987); anxiety (Hughes, Gust, Pechacek 1987); impatience (Hughes, Gust, Pechacek 1987); difficulty concentrating (Trahir 1967; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); somatic or physical complaints (Hughes, Gust, Pechacek 1987; Pederson and Lefcoe 1976); increased appetite (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); increased food intake (Wynder, Kaufman, Lesser 1967); and weight gain (Trahir 1967; Wynder, Kaufman, Lesser 1967; Mausner 1970; Pederson and Lefcoe 1976).

Measures of the incidence and magnitude of signs and symptoms vary across studies, at least partly because of the diversity of the

TABLE 5.—Diagnostic categorization and criteria for nicotine withdrawal

Nicotine-induced organic mental disorder	
292.00 Nicotine Withdrawal	
	<p>The essential feature of this disorder is a characteristic withdrawal syndrome due to the abrupt cessation of or reduction in the use of nicotine-containing substances (e.g., cigarettes, cigars, and pipes, chewing tobacco, or nicotine gum) that has been at least moderate in duration and amount. The syndrome includes craving for nicotine; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain.</p>
	<p>In many heavy cigarette smokers, changes in mood and performance that are related to withdrawal can be detected within 2 hours after the last tobacco use. The sense of craving appears to reach a peak within the first 24 hours after cessation of tobacco use, and gradually declines thereafter over a few days to several weeks. In any given case it is difficult to distinguish a withdrawal effect from the emergence of psychological traits that were suppressed, controlled, or altered by the effects of nicotine or from a behavioral reaction (e.g., frustration) to the loss of a reinforcer.</p>
	<p>Mild symptoms of withdrawal may occur after switching to low tar/nicotine cigarettes and after stopping the use of smokeless (chewing) tobacco or nicotine gum.</p>
	<p>The diagnosis of Nicotine Withdrawal is usually self-evident from the person's history, and disappearance of the symptoms if smoking is resumed is confirmatory. However, withdrawal from other psychoactive substances may take place simultaneously, and produce similar symptoms.</p>
Diagnostic Criteria for Nicotine Withdrawal	
A.	Daily use of nicotine for at least several weeks
B.	<p>Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by at least four of the following signs:</p> <ul style="list-style-type: none"> (1) Craving for nicotine (2) Irritability, frustration, or anger (3) Anxiety (4) Difficulty concentrating (5) Restlessness (6) Decreased heart rate (7) Increased appetite or weight gain

SOURCE: Condensed from the American Psychiatric Association (1987).

measuring instruments and techniques used, questions asked, and populations examined. Collectively, the results of many such studies suggest that most nicotine-deprived cigarette smokers experience at least one symptom of the tobacco withdrawal syndrome, that between one-fourth and one-half show significant withdrawal, and that about one-fourth report no withdrawal at all (Pederson and Lefcoe 1976; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987; Gritz 1980; Henningfield 1984). Of those persons who retrospectively report experiencing no withdrawal symptoms, it is unclear whether they were not physically dependent, whether the assessment instruments were not sufficiently sensitive, or whether

some persons are less impaired or discomforted by withdrawal symptoms.

Prospective Data from Laboratory and Nonlaboratory Studies

Cigarette smokers have been studied both in laboratory and nonlaboratory settings using a variety of self- and observer-administered tests measuring subjective, behavioral, and physiological signs and symptoms that accompany tobacco deprivation. The studies have examined changes in functioning resulting after periods of tobacco deprivation ranging from 1 hr to 21 days. Most studies have obtained both baseline and deprivation measures; a few studies have incorporated a control group of continuing smokers or nonsmokers; and a few have obtained data after smokers resumed smoking or were given nicotine polacrilex gum. The studies included ones which were conducted while the subjects were residing on a research ward, were living in their usual environment, or were paying occasional visits to a clinic for smoking cessation treatment. The symptoms reported in these studies were similar to those obtained from the retrospective studies, demonstrating generality across method and setting. These symptoms included the following: "craving" for tobacco (Gritz and Jarvik 1973; Hatsukami et al. 1984; Gilbert and Pope 1982; Shiffman and Jarvik 1976; Cummings et al. 1985; Hughes and Hatsukami 1986), irritability or anger (Myrsten, Elgerot, Edgren 1977; Elgerot 1978; Weybrew and Stark 1967; Hughes and Hatsukami 1986), anxiety and tension (Myrsten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986), restlessness (Hughes and Hatsukami 1986), impatience (Hughes and Hatsukami 1986), depression (Hatsukami et al. 1984), problems with concentration (Hatsukami et al. 1984; Weybrew and Stark 1967; Myrsten, Elgerot, Edgren 1977; Frankenhaeuser et al. 1971; Hughes and Hatsukami 1986), drowsiness or fatigue (Weybrew and Stark 1967), sleep disturbances (Hatsukami et al. 1984; Larson, Haag, Silvette 1961; Weybrew and Stark 1967; Myrsten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986), and increased hunger or appetite (Myrsten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986).

In one study (Hughes and Hatsukami 1986), each subject had a spouse, relative, or friend rate some of the symptoms of withdrawal to verify self-report. These observer ratings of irritability, anxiety, restlessness, drowsiness, fatigue, impatience, and somatic complaints were all significantly related to their respective subject's ratings, thus adding to the validity of reports of these symptoms. These researchers found that the most common self-report symptoms were increased irritability (80 percent), anxiety (87 percent), difficulty concentrating (73 percent), restlessness (71 percent), impatience (76 percent), insomnia (84 percent), and craving for tobacco (62 percent).

Seventy-eight percent of the subjects reported four or more DSM-III criteria. This degree of prevalence was higher than that found in a retrospective study conducted by Hughes, Gust, and Pechacek (1987), possibly reflecting differences in the measuring instruments or the populations themselves.

The physiological changes which have been found to occur after cigarette deprivation include decreased heart rate (Knapp, Bliss, Wells 1963; Murphee and Schultz 1968; Parsons, Avery et al. 1975; Benowitz, Kuyt, Jacob 1984; Hatsukami et al. 1984; Weybrew and Stark 1967; Gilbert and Pope 1982; Hughes and Hatsukami 1986; West and Russell 1987; Elgerot 1978; West, Jarvis et al. 1984; Henningfield 1987a) and decreased cortical arousal as evidenced by decreases in peak alpha frequency and increases in low frequency activity which appear to be associated with drowsiness and decreased vigilance (Knott and Venables 1977, 1979; Ulett and Itil 1969; Herning, Jones, Bachman 1983; Herning 1987). Knott and Venables (1978) have also found that the visual evoked response in tobacco-deprived smokers showed faster latencies and larger amplitudes for low-stimulus intensities than among nondeprived smokers and nonsmokers. They concluded that deprived smokers experience CNS hypersensitivity and, as a result, may experience visual stimulus input more easily and strongly. Hall and colleagues (1973) reported reduced auditory evoked response (AER) amplitudes during tobacco withdrawal. Blood pressure (Benowitz, Kuyt, Jacob 1984; Murphee and Schultz 1968; Knapp, Bliss, Wells 1963) and respiratory rate (Parsons et al. 1976) have also been found to decrease during abstinence. Studies have also reported an increase in skin temperature among tobacco-deprived smokers (Gilbert and Pope 1982; Myrsten, Elgerot, Edgren 1977) or no change (West and Russell 1987), and either a decrease (Fagerström 1978) or no significant change (Hatsukami et al. 1984) in body temperature among those who are classified as more dependent. Although some studies have reported insomnia and sleep disturbance following tobacco deprivation, tobacco-deprived smokers' total sleep time may be longer during withdrawal (Soldatos et al. 1980). Reported changes in sleep pattern include decreased latency to rapid-eye-movement (REM) sleep (Kales et al. 1970), decreased latency to light (delta electroencephalogram (EEG) wave) sleep onset (Parsons, Luttrell et al. 1975; Parsons and Hamme 1976), and increased total REM sleep time (Soldatos et al. 1980; Kales et al. 1970; Parsons, Avery et al. 1975).

Another physical change found among tobacco-deprived smokers is an increase in weight (Grunberg 1986; see also Chapter VI). Weight increase has also been found among those who quit smoking in a number of longitudinal survey studies (Bosse, Garvey, Costa 1980). This increase in weight has been attributed to increased caloric intake (Hatsukami et al. 1984; Grunberg 1982; Myrsten, Elgerot,

Edgren 1977; Burse et al. 1975; Gilbert and Pope 1982; Wack and Rodin 1982), decreased basal metabolism (Glauser et al. 1970; Wack and Rodin 1982), decreased energy expenditure (Hofstetter et al. 1986), or increased activity of lipoprotein lipase (Carney and Goldberg 1984) (see also Chapter VI).

Several studies have examined the effects of cigarette deprivation and administration on reaction time and psychomotor performance. These are reviewed in detail in Chapter VI and are only briefly summarized here. Two early studies each found considerable across-subject variability, with some subjects showing distinct deprivation-induced performance impairments which were reversed by tobacco administration, and other subjects showing impairments under the tobacco administration conditions (Bates 1922; Carver 1922). Since the studies by Bates and Carver, investigators have developed increasingly sophisticated methods of performance assessment which have led to a clearer understanding of the performance-related effects of nicotine administration and deprivation (see details in Chapter VI). For example, Heimstra, Bancroft, and DeKock (1967) used a simulated driving task and found that deprived smokers made significantly more errors on tracking and vigilance tasks than did nondeprived smokers or nonsmokers, who did not significantly differ from each other. Other research has demonstrated that smokers who were allowed to smoke cigarettes during the experimental session exhibited either no decrease or an improvement in speed and accuracy in reaction time, cognitive tests, and/or vigilance performance tasks, whereas deprived smokers most frequently show some impairment in performance tasks (Myrsten et al. 1972; Franken-haeuser et al. 1971; Elgerot 1978; Kleinman, Vaughn, Christ 1973; Andersson 1975; Wesnes and Warburton 1984; Edwards et al. 1985; Snyder and Henningfield, in press; Henningfield 1986a, 1987a).

A recent study using a computerized battery of such tasks found clear impairments beginning within 8 hr of the last cigarette and improving only somewhat across 10 consecutive days of tobacco deprivation; resumption of smoking was accompanied by complete restoration of performance (Henningfield 1987a). The specificity of these performance effects of nicotine was confirmed by the findings that administration of nicotine in the polacrilex gum form produced a dose-related reversal of all performance impairments (Snyder and Henningfield, in press; Henningfield 1987a); this effect was not related to satisfaction or reduction of "craving" because the gum produced dose-related decreases in "liking" scores and produced no reliable decrease in "desire to smoke" (Henningfield 1987a).

Other changes occurring in tobacco-deprived cigarette smokers include increases in aggression scores on the Buss aggression machine (Schechter and Rand 1974) and increases in frequency of spontaneous jaw contractions (a putative analog of aggression)

(Hutchinson and Emley 1973). Analogously, monkeys withdrawn from chronic oral nicotine exposure (nicotine was placed in their drinking water) exhibited an increase in frequency of post-shock biting (Hutchinson and Emley 1973).

The magnitude of tobacco withdrawal is related to the environmental context (see Chapter V for a comparison to other dependence-producing drugs). For example, Hatsukami, Hughes, and Pickens (1985) reported that smokers who were deprived of cigarettes on an outpatient basis experienced more withdrawal symptoms than those who underwent withdrawal on a clinical research ward. These findings are consistent with those of Suedfeld and Ikard (1974), who found that deprivation of normal sensory stimulation reduced tobacco abstinence-associated discomfort. It has also been observed that the diurnal variation of withdrawal discomfort found among abstinent smokers (greater discomfort in the evenings) appears to be associated with diurnal variation in the social environment (e.g., meals, departure from work, or social contact) (Shiffman 1979).

Time Course of Responses to Nicotine Abstinence

Drug withdrawal syndromes generally include some signs and symptoms which are opposite those produced by administration of the drug and which then return to approximately the same values observed when drug intake was stable (rebound phenomena). The time course of different responses varies (Chapter V). The most recent studies show that several signs and symptoms of withdrawal appear to rebound within the first few days following cigarette abstinence; these signs and symptoms include increases in the urge to use tobacco, anxiety, problems with concentration, increased caloric intake, sleep disturbance, performance impairment, and general subjective distress (Hatsukami et al. 1984; Hughes and Hatsukami 1986; Schneider and Jarvik 1984; Cummings et al. 1985; Henningfield 1987a). Heart rate has been found to decrease to levels found among nonsmokers (Weybrew and Stark 1967) and may include some rebound, returning to stable levels between those maintained during normal cigarette smoking and those recorded during the first week of abstinence (Henningfield 1987a). The P300 response, a cognitive evoked potential component which is related to the ability to evaluate auditory stimuli (i.e., differentiate one sound from another by counting only certain sounds), showed a rebound (decrease in amplitude), with values returning to preabstinence (cigarette smoking) levels after about 3 to 5 days (Herning 1987). West, Russel, Jarvis, Pizzey, and Kadam (1984) reported that urinary epinephrine concentrations rebounded with a significant decrease during the first 3 days of abstinence followed by a significant increase. Finally, in the squirrel monkey study of nicotine abstinence-associated biting, Hutchinson and Emley (1973) found a

distinct rebound pattern in some subjects with biting levels sharply increasing and then returning to the levels observed during chronic oral nicotine administration.

Other signs and symptoms associated with tobacco abstinence do not return to levels observed during cigarette smoking. For example, weight gain has persisted for long periods of time (Blitzer, Rimm, Giefer 1977) and has also been reported to approach levels of nonsmokers (Khosla and Lowe 1971; Lincoln 1969; Chapter VI). In addition, some levels of performance impairment and associated reduction of a cognitive evoked cortical potential (N100), which is related to attention, persist at least 10 days and may last longer (Henningfield 1987a; Herning 1987).

As the preceding studies suggest, the duration of withdrawal reactions varies among studies and as a function of the measure (Shiffman 1979; West 1984). Urges to smoke cigarettes among ex-smokers have been reported to occur intermittently, although sometimes with great intensity, for up to 9 years after cessation of cigarette smoking. These reported symptoms may represent conditioned responses to environmental stimuli associated with either cigarette smoking or deprivation, may represent a protracted physiological phase of withdrawal, or both (e.g., Wikler 1965; Jasinski 1981; Chapter V).

Alleviation of Withdrawal Symptoms by Cigarette Smoking

Several studies have demonstrated that the signs and symptoms resulting from cigarette deprivation are alleviated by the resumption of cigarette smoking. These signs and symptoms include heart rate (Murphee and Schultz 1968; Weybrew and Stark 1967; Henningfield 1987a), blood pressure (Murphee and Schultz 1968), skin temperature (Myrsten, Elgerot, Edgren 1977), epinephrine and norepinephrine levels (Myrsten, Elgerot, Edgren 1977), EEG changes (Ulett and Itil 1969; Herning 1987), weight (Noppa and Bengtsson 1986), desire for food (Burse et al. 1975), hand tremor (Myrsten, Elgerot, Edgren 1977), desire to smoke (Gritz and Jarvik 1973), and fatigue, irritation, sleeplessness, problems with alertness and concentration (Weybrew and Stark 1967), and performance (Henningfield 1987a).

Hughes, Hatsukami, Pickens, and Svikis (1984) examined the consistency of tobacco withdrawal signs and symptoms using an experimental design in which periods of cigarette smoking and abstinence were alternated in the same subjects. This study demonstrated both the consistency of the withdrawal symptomatology within subjects as well as the efficacy of resumed smoking in reversing it. The most consistent withdrawal effects across subjects were supine heart rate changes, insomnia, caloric intake, irritability, restlessness, drowsiness, general mood disturbance (measured by the

Profile of Mood States), and withdrawal discomfort. Furthermore, the intensities of the withdrawal discomfort of subjects during the two deprivation periods were similar. Similarly, a study at the Addiction Research Center (Baltimore, Maryland) showed that resumption of cigarette smoking after 10 days of tobacco abstinence was accompanied by a return to preabstinence levels of all measures including EEG, evoked cortical electrical potentials, heart rate, behavioral performance, and measures of mood (Henningfield 1987a; Herning 1987).

Relationship Between Preabstinence Nicotine Intake and Magnitude of Withdrawal Syndrome

The observation that the magnitude of tobacco withdrawal reactions is directly related to preabstinence levels of nicotine intake provides specific evidence that nicotine is the pharmacologic cause of the physical dependence. The clinical significance of these relationships is that both the magnitude of the tobacco withdrawal syndrome and difficulty in quitting smoking are directly related to the daily levels of nicotine that were being ingested. The relationship has not always been observed, however, when only crude indices of nicotine dosing were used. For example, correlations between number of cigarettes smoked per day (a poor marker of nicotine intake) (Benowitz 1983; Abrams et al. 1987; Chapter II) and withdrawal reaction severity are mixed across studies. Some investigators have observed a positive correlation between the number of cigarettes smoked per day and withdrawal severity (Wynder, Kaufman, Lesser 1967; Shiffman 1979; Burns 1969; Hall, Ginsburg, Jones 1986). Others have reported no differences in severity of craving or other measures of withdrawal between light and heavy smokers or as a function of number of cigarettes smoked (Gritz and Jarvik 1973; Shiffman and Jarvik 1976; Myrsten, Elgerot, Edgren 1977; Mausner 1970). Cummings and coworkers (1985) reported that although heavy smokers reported more withdrawal symptoms than light smokers, differences between heavy and light smokers were statistically significant only with respect to irritability.

The most reliable measure of day-to-day nicotine exposure appears to be cotinine in biological specimens or nicotine itself (Benowitz 1983; Chapter II). Recent studies using such measures have found significant relationships between either nicotine or cotinine levels and severity of withdrawal reactions. Pomerleau, Fertig, and Shanahan (1983) divided subjects by their baseline plasma cotinine levels (high or low quartiles). They found that subjects in the low-cotinine quartile exhibited less withdrawal change on the Shiffman Craving and Perception of Physical Signs subscales compared with subjects in the high-cotinine quartile. They also found a significant correlation between preabstinence baseline plasma cotinine levels and absti-

nence-associated craving for cigarettes. Hatsukami, Hughes, and Pickens (1985) established a similar significant correlation between craving for tobacco and plasma nicotine level, as well as nicotine boost. Zeidenberg and associates (1977) found that preabstinence serum cotinine was correlated significantly with the degree of difficulty in smoking cessation among males but not females. Finally, West and Russell (1985b) determined that whereas preabstinence plasma nicotine levels significantly predicted craving, hunger, restlessness, inability to concentrate, and overall withdrawal severity, preabstinence rates of daily cigarette consumption did not significantly predict any withdrawal effects.

Smokeless Tobacco Withdrawal Syndrome

A study of withdrawal reactions accompanying abstinence from smokeless tobacco products helped to determine that the syndrome did not require inhalation of smoke and its constituents, which are not present in smokeless tobacco (e.g., tar and CO.). This study showed that signs and symptoms of smokeless tobacco deprivation are similar to those occurring in smokers after cigarette deprivation (Hatsukami, Gust, Keenan 1987). In persons who had been using a high nicotine containing brand of chewing tobacco, Hatsukami, Gust, and Keenan (1987) measured a number of potential withdrawal signs and symptoms over a 6-day period. Baseline data were collected during 3 days of regular smokeless tobacco use. The significant changes which occurred during smokeless tobacco deprivation relative to the baseline included decreased heart rate and an increase in craving for tobacco, confusion, eating, number of awakenings, and total scores on a withdrawal symptom checklist for both self-rated and observer-rated measures. These changes were similar to those found among cigarette smokers who underwent a similar experimental protocol, although the smokeless tobacco withdrawal syndrome appeared to be less severe than the cigarette withdrawal syndrome (Hatsukami, Gust, Keenan 1987).

Nicotine Polacrilex Gum: Treatment and Physical Dependence

Nicotine polacrilex gum has been used to evaluate the specific role of nicotine in tobacco dependence. Experimental research and clinical observations of the ability of nicotine in the polacrilex gum form to alleviate tobacco withdrawal symptomatology provide conclusive evidence that the tobacco withdrawal syndrome is pharmacologically determined by physical dependence on nicotine. To the extent that the tobacco withdrawal phenomena described above are specific to nicotine and not characteristic of the delivery system (e.g., cigarette smoke), alternate forms of nicotine delivery should be able to sustain the physical dependence. This would be evidenced by (1)

blockade of signs and symptoms of withdrawal by nicotine delivery and (2) subsequent emergence of a tobacco withdrawal-like syndrome upon abrupt abstinence from nontobacco-delivered nicotine.

Treatment of Withdrawal Symptoms

Clinical trials and experimental studies in which nicotine polacrilex gum is evaluated as a means to alleviate signs and symptoms of tobacco withdrawal are of relevance to the treatment of tobacco dependence (Chapter VII). In addition, however, such data are analogous to data from the classic "substitution" study methodology used to help determine the pharmacologic specificity of withdrawal reactions following use of opioids, sedatives, and alcohol (described in Chapter V). In brief, however, the objective is to determine if the withdrawal reaction from the primary substance upon which the person is dependent can be alleviated by administration of a test drug.

Several studies have examined the effects of nicotine polacrilex gum on tobacco withdrawal (Jarvis et al. 1982; Schneider, Jarvik, Forsythe 1984; West, Jarvis et al. 1984; Hughes, Hatsukami, Pickens, Krahn et al. 1984; Snyder and Henningfield, in press; Henningfield 1987a). These studies have examined two groups of cigarette smokers who were assigned in a double-blind fashion (with the exception of West, Jarvis, and colleagues (1984), who used a single-blind design) to receive 2-mg polacrilex gum or placebo. The duration of cigarette deprivation during which the polacrilex gum (or placebo) was used varied from 24 hr to 6 weeks. In general, the results consistently showed an attenuation of withdrawal signs and symptoms. For example, nicotine polacrilex gum significantly reduced irritability (Jarvis et al. 1982; Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984), total withdrawal discomfort (Schneider, Jarvik, Forsythe 1984; Hughes, Hatsukami, Pickens, Krahn et al. 1984), somatic complaints (Hughes, Hatsukami, Pickens, Krahn et al. 1984), sleepiness (Jarvis et al. 1982), unsociability (West, Jarvis et al. 1984), cognitive performance deficits (Snyder and Henningfield, in press; Henningfield 1987a), heart rate decreases (Schneider, Jarvik, Forsythe 1984; West, Jarvis et al. 1984; Henningfield 1987a), and EEG effects including changes in cortical evoked potentials (Herning 1987; Pickworth, Herning, Henningfield, 1988).

Other measures were less reliably alleviated; these included depression (Jarvis et al. 1982; West, Jarvis et al. 1984), anxiety/tension (Jarvis et al. 1982; Hughes, Hatsukami, Pickens, Krahn et al. 1984), difficulty concentrating (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984), and restlessness (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984). The urge to smoke cigarettes has not been found to be reliably alleviated

by nicotine polacrilex gum administration (West and Schneider 1987; West 1984; Henningfield 1987a; Hughes, Hatsukami, Pickens, Svikis 1984) except possibly at high dose levels (Nemeth-Coslett, Henningfield, O'Keefe, Griffiths 1987). Interpretation of such data is complicated by the diverse strategies used to measure the urge to smoke or "craving" as discussed further in this Section.

Of these studies, two showed nonsignificant effects of nicotine polacrilex gum on hunger (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984) and one showed significant effects in decreasing hunger (Jarvis et al. 1982). More recent research shows that the anorectic effect of nicotine polacrilex gum during tobacco abstinence is directly related to the dose level (i.e., number of doses taken per day) (Stitzer and Gross 1988; Fagerström 1987; Chapter VI). The dose-response relationship may explain the diversity in results when studies are compared; in some of these studies, dosing was either poorly controlled or not reported, or there was no verification of subject compliance with a dose regimen.

As would be expected, depending on the dose administered, the efficacy of nicotine polacrilex gum for most measures of withdrawal symptomology ranges from complete reversal of withdrawal to no effect. In a study in which periods of tobacco abstinence (3 days) were alternated with periods of cigarette smoking (4 days), subjects were given either 0-, 2-, or 4-mg-nicotine-containing pieces of the polacrilex gum (Henningfield 1987a). The subjects were given the polacrilex gum at 1-hr intervals (for 12 hr), and they chewed under the direction of research staff. Blood nicotine and cotinine levels confirmed that this procedure resulted in dose-related nicotine administration; plasma cotinine and nicotine levels at 4 mg were similar to those obtained during cigarette smoking (*ad libitum* smoking); plasma levels at 2 mg were between those at 4 and 0 mg. Measures included cognitive performance, heart rate, EEG, and self-reported symptomology. At 4 mg, all signs and symptoms of withdrawal were reduced or completely reversed except the desire to smoke. The 2-mg dose produced partial reversal of withdrawal effects.

Maintenance of Physical Dependence

Two studies have examined withdrawal effects after deprivation of nicotine polacrilex gum. West and Russell (1985a) conducted a study in which they examined withdrawal symptoms in six people who used nicotine polacrilex gum for at least 1 year. Baseline measures of possible withdrawal effects were collected during days that the subjects were chewing 2-mg pieces of nicotine polacrilex gum. These days were the first and third days of a 4-day experiment. On the second and fourth days, subjects were given either 0.5 mg unbuffered polacrilex gum (nicotine absorption is negligible in the unbuffered

formulation) to chew or no polacrilex gum. West and Russell (1985a) found significant changes for measures of withdrawal symptomology including irritability, ability to concentrate, and heart rate and for composite subjective withdrawal scores. Withdrawal reaction magnitude was slightly, but not significantly, less in the unbuffered gum than in the no gum condition.

Hughes, Hatsukami, and Skoog (1986) extended the findings of West and Russell (1985a) with a longer period of observation (1 week) and a double-blind, placebo-controlled design. In the study by Hughes, Hatsukami, and Skoog (1986), eight former smokers who had been using nicotine polacrilex gum for at least 1 month participated. The main finding was that when the maintenance dose levels (2-mg polacrilex gum) were replaced with placebo, reliable symptoms of withdrawal were produced. The effects included "craving" for tobacco, irritability/hostility, anxiety, depression, restlessness, impatience, difficulty concentrating, hunger, and total withdrawal discomfort; reports from observers verified several of the effects (i.e., observer estimates of irritability, anxiety, restlessness, impatience, and total withdrawal discomfort). The scales used to measure withdrawal discomfort in the study by Hughes and colleagues were similar to those used in a previous study of cigarette withdrawal conducted by the same investigators (Hughes and Hatsukami 1986), thus enabling an across-study comparison between abstinence from cigarettes and abstinence from nicotine in the polacrilex gum form. Intensities and numbers of withdrawal symptoms, except heart rate and insomnia, were similar.

Taken together, the results of the above-described studies with nicotine polacrilex gum have helped to confirm that tobacco withdrawal is pharmacologically caused by physical dependence on nicotine. Furthermore, the results of such work are of clinical significance because they indicate that much of tobacco withdrawal symptomology can be treated with nicotine polacrilex gum. Two studies show that nicotine polacrilex gum can maintain physical dependence; this emphasizes the importance of *gradually* giving up use of the gum to minimize the abruptness and severity of withdrawal symptoms (see Chapter VII).

Tobacco Craving

The measurement of self-reported craving for tobacco and interpretation of resulting data are among the more complicated issues in tobacco research. Findings discussed in this Chapter that nicotine polacrilex gum administration can suppress cigarette smoking and alleviate physical signs of tobacco withdrawal while having little effect on the urge to smoke indicate that such urges are not solely determined by nicotine deprivation. Similar observations regarding urges to use other dependence-producing drugs are discussed in

Chapter V (see also Childress et al., *in press*). The elicitation and alleviation of the urge to use tobacco, as for other dependence-producing substances, can be effected by a variety of pharmacologic and other environmental stimuli as well as changes in the physiological and/or behavioral state of the person (Chapter V).

Conclusions regarding the measurement and treatment of urges to use drugs are complicated because the questions about urges have been worded differently among studies. For example, subjects are sometimes asked to report their "craving." Unfortunately, subjects vary widely in their interpretations of the word "craving" and in their answers to questions about it (Kozlowski and Wilkinson 1987; Ludwig and Stark 1974). In addition, results concerning "craving" are sometimes discussed when the word was not even used in study questionnaires, and sometimes craving was inferred from other observations (e.g., self-reported discomfort or drug abstinence) (Kozlowski and Wilkinson 1987). These and other problematic issues have been discussed in several recent papers (Kozlowski and Wilkinson 1987; Shiffman 1987; West 1987; Hughes 1987; Marlatt 1987; Stockwell 1987; Henningfield 1987b; Henningfield and Brown 1987; West and Schneider 1987). One consensus that seems to emerge is that the term "craving" be replaced with "urge" or "desire" to smoke, and that subjects be asked to report the "strength" of such responses and not simply whether or not the response occurred (Kozlowski and Wilkinson 1987; Henningfield 1987b).

In consideration of the above reports and commentaries and the data reviewed in the present Chapter, the following conclusions may be drawn regarding the urge to smoke. Many means of measuring urges are reliably associated with early abstinence from tobacco; however, urges can also be elicited by a variety of other stimuli including cigarette smoking itself, tobacco-associated stimuli (e.g., sight, smell, advertisements), consumption of other psychoactive drugs, food deprivation, and mood changes. Furthermore, although urges are reliably associated with tobacco abstinence, the levels to which plasma nicotine must fall to produce it are unclear; for example, West, Russell, Jarvis, and Feyerabend (1984) found that smokers who switched to a low-nicotine cigarette reported only slight craving for their usual brand in spite of a drop in nicotine intake of around 60 percent. In addition, as discussed earlier, some sensory stimuli are effective at eliciting urges, whereas other sensory cues accompanying the inhalation of cigarette smoke may be effective at diminishing such urges (Rose et al. 1985). Chapter V provides a discussion of these issues in the context of analogous observations which have been made with other dependence-producing drugs and Chapter VII discusses the implications for replacement therapy used in treating tobacco dependence.

Alternate Nicotine Delivery Systems

Certain effects of nicotine depend little upon the specific type of delivery system that is used (see also Chapters, II, III, and VI). For instance, it appears likely that all forms of nicotine delivery resulting in systemic absorption are capable of producing tolerance and maintaining physical dependence (see also Chapter II). Similarly, it follows that a variety of nicotine delivery systems have potential utility in the treatment of cigarette smoking by the alleviation of withdrawal symptoms. However, the safety, including the potential to produce dependence, may vary considerably as a function of characteristics of the nicotine delivery system itself.

Kinds of Nicotine Delivery Systems

Because nicotine is well absorbed through the common routes of drug delivery and because the commonly used tobacco vehicle is not necessary to efficaciously deliver nicotine, nicotine can potentially be placed in a variety of vehicles and administered via a variety of delivery systems (Chapter II; Benowitz 1986; Jarvik and Henningfield, 1988). The nicotine delivery systems thus far discussed in this Chapter are tobacco smoke, nicotine polacrilex gum, i.v. nicotine, transdermal nicotine, and a nicotine vapor inhaler. Other potential therapeutic nicotine delivering systems under development include a nasal spray (Perkins et al. 1986) and nasal nicotine solutions given in droplet form (Russell, Jarvis, Feyerabend, Ferno 1983), both of which have been discussed by Russell (1988). Two other nicotine delivery systems are a chewable food product (Tobacco International 1987) and a "toothpaste" formulation which contains ground tobacco. Other nicotine delivering systems (in which the tobacco may be incidental and not necessary for nicotine delivery) are under development or consideration for over-the-counter retail marketing (R.J. Reynolds "Smokeless Cigarette" European Patent Application 1985, 1986; Cleghorn 1987; Mintz 1987).

As noted earlier, the nicotine vapor inhaler was removed from the retail market in February of 1987 by the FDA because it was a "nicotine delivery system intended to satisfy nicotine dependence" which had not been tested for safety and efficacy (Slade and Connolly 1987). At least through the end of 1987, the toothpaste-like formulation was available as an over-the-counter product but was under review by the FDA (FDA letter to Congressman Waxman); this formulation is distributed in Indian food stores. The chewable nicotine delivering product marketed by Pinkerton Inc. was test-marketed as a "tobacco product" for approximately 6 months during 1987. The FDA removed it from the market ruling that it was a "food product" ["chewing gum"] which was "unlike traditional smokeless tobacco products," and contained a "food additive [tobacco] deemed

"unsafe" for human consumption (FDA letter to Congressman Waxman).

Safety of Alternate Nicotine Delivery Systems

Alternate nicotine delivery systems may be evaluated with respect to at least three categories of safety issues. These are: (1) short- and long-term toxic effects resulting from use of the system; (2) the ease and convenience of using the system; and (3) the dependence potential of the system. All of these factors can affect initiation and maintenance of nicotine dependence.

The first safety issue is related to the direct behavioral and physiological toxicity of the preparation itself. In the moderate nicotine doses that each of these and previously marketed systems deliver, acute nicotine toxicity would not appear to be a significant health risk. However, adverse health effects from chronic exposure to nicotine may occur (see Appendix B), and other potentially absorbed constituents of the system (e.g., tar) are markedly toxic.

Existing nicotine delivery systems vary widely in their potential overall toxicity. One product was found to meet FDA criteria for safety as well as efficacy (i.e., nicotine polacrilex gum). On the other hand, cigarette smoking is a cause of lung cancer and other cancers, emphysema, heart disease, and a variety of other diseases; smokeless tobacco use causes oral cancer and other forms of gum and mouth disease (US DHEW 1979; US DHHS 1982, 1983, 1984; US DHHS 1986b).

Traditional tobacco products have historically been considered by the FDA to be outside its regulatory purview (Action on Smoking and Health vs. Harris 1980). New products, which contain either small amounts of tobacco (e.g., tobacco-containing food products) or which appear to contain possibly nonessential amounts of tobacco (e.g., possibly the case with the R.J. Reynolds smokeless cigarette (European Patent Application 1985, 1986)) and which are not regarded as traditional tobacco products, may not be exempt from such review.

The second safety issue is the potential for the product to actually sustain tobacco use by alternating use of the substitute with use of the traditional tobacco product. This is analogous to the nonmedically approved use of methadone by opioid-dependent individuals when their drug of choice (e.g., heroin) is not available, and they are not involved in treatment for opioid dependence. The use of non-tobacco nicotine products to sustain tobacco use is, similarly, medically contraindicated and hence a form of nicotine abuse (Slade 1986; Richards 1987). While any alternative nicotine delivery system can theoretically be used for this purpose, two commercial products (the chewable nicotine-delivering "food" product and the nicotine vapor inhaler) were marketed specifically as temporary substitutes for

cigarettes when it was inconvenient to smoke (Bosy 1986; Tobacco International 1987). In contrast, the instructions for use of nicotine polacrilex gum clearly specify that this preparation should not be used along with cigarettes (Physicians' Desk Reference 1988). In addition to product design and formulation, factors such as labeling, packaging, marketing, retail distribution, and regulatory oversight might influence the degree to which any particular preparation is associated with an individual's continued use of the nicotine delivery system.

The third potential safety concern is related to the dependence potential of the system. As shown in Chapter V, the potential of a drug to addict users is associated with its effects on mood, feeling, and behavior; such effects are related to the bioavailability of the drug. Systems with a controlled rate of bioavailability or a lesser rate of absorption than is obtained from conventional tobacco products may have a lesser dependence potential than tobacco products. Other factors related to availability of the preparation and cost (both economic and behavioral) may also affect the likelihood that dependence will develop in users. For example, nicotine polacrilex gum is available by prescription only, and use of the gum is recommended as a temporary treatment aid. Active chewing is required to extract the nicotine, and swallowing the nicotine too quickly reduces the amount absorbed. These factors appear relevant to the observation that less than 10 percent of all subjects entering smoking treatment trials continue to use nicotine polacrilex gum after 1 year (Tonnesen et al. 1988; Jarvis et al. 1982). Among people who have used the polacrilex gum to quit smoking and who have maintained their tobacco abstinence for 1 year or more, a higher percentage of polacrilex gum use has been reported (13 to 38 percent); however, it is not clear to what degree such use may be necessary for some people to avoid relapse to tobacco use (see further discussion of these issues in Hughes 1988; Jasinski and Henningfield 1988; Hall et al. 1985; Tonnesen et al. 1988; Chapter VII). In contrast to nicotine polacrilex gum, smokeless tobacco products (particularly one in which finely ground snuff is placed in a small tea bag-like pouch) readily lend themselves to initiating as well as to maintaining nicotine dependence (US DHHS 1986b).

Table 6 compares nicotine polacrilex gum and cigarettes on a number of dimensions, most of which have been reviewed in either Chapters II, V, or VII. As shown in the Table, there is considerable disparity between these two delivery systems: the polacrilex gum provides a generally safe and medically beneficial form of nicotine delivery; cigarettes are a known cause of substantial amounts of death and disease each year (Chapter I; US DHEW 1979; US DHHS 1981, 1982, 1983, 1984, 1985). Such a disparity in potential safety

TABLE 6.—Comparison of tobacco cigarettes and nicotine polacrilex gum on indices related to safety, including potential to cause dependence

Characteristic	Tobacco cigarettes	Nicotine polacrilex gum
Proven carcinogen	Yes	No
Availability	Widely available consumer product, including vending machine availability	Prescription only
Taste	Carefully formulated with flavor enhancers	Not formulated to provide desirable taste
Ease of nicotine extraction	Readily available with little effort	Much effort required
Nicotine kinetics	Rapid uptake	Slow uptake
Initiation of dependence	Highly effective	No reported problem
Psychoactivity	Dose-related "liking"	Dose-related "disliking"
Reinforcing effects	Powerful	Weak
Withdrawal symptoms associated with abstinence	Yes	Yes
Social factors	Often used in social settings as part of social interactions	Used for specific therapeutic benefit
Primary regulatory oversight	U.S. Bureau of Alcohol, Tobacco, and Firearms	U.S. Food and Drug Administration

across systems would suggest that any new system be submitted to evaluations of safety including dependence-potential testing.

Conclusions

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.

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CHAPTER V

TOBACCO USE COMPARED TO OTHER DRUG DEPENDENCIES

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Introduction

The present Chapter compares cigarette smoking and nicotine with other forms of drug dependence and addicting drugs. Other chapters in this Report describe the behavior of cigarette smoking, the known biobehavioral mechanisms and modulators of nicotine's actions, and techniques for achieving abstinence from smoking. As is evident from this Report, cigarette smoking is most usefully explained and characterized as a drug dependence process in which nicotine is the identified drug of dependence. It is also evident that by either the World Health Organization (WHO) definition of "drug addiction" that was issued in the 1950s (WHO 1952) or by the definitions of "drug dependence" issued since the 1960s (WHO 1964, 1969, 1981), nicotine is appropriately categorized as an addicting or dependence-producing drug. Its designation as a drug is also consistent with the definitions provided by the WHO (1981) and the Food and Drug Administration (FDA) (1987). Nicotine-delivering tobacco preparations (which include all currently marketed tobacco preparations) could, therefore, be appropriately categorized as addicting or dependence-producing drugs. In addition to evaluating nicotine with respect to definitions of dependence-producing drugs, it is also useful to compare features of tobacco dependence and the pharmacologic properties of nicotine to other drug addictions and addicting drugs, respectively. This comparison is the purpose of the present Chapter.

Two of the most widely studied drug addictions provide standards to which other addictions may be compared. They are the addictions to the opium-derived or related substances ("opioids," e.g., morphine, heroin, methadone, codeine) and to alcohol. For nearly a century, it has been widely accepted that use of these substances could lead to addictive behavior and to adverse effects. Moreover, such consequences of use develop in a sufficient number of persons that there have been recurrent regulatory efforts to restrict access and conditions of use. Cocaine and related psychomotor stimulants (e.g., amphetamine) provide an additional important standard by which to judge suspected and known addicting chemicals. These stimulants have been accepted as standards by which to evaluate the addicting potential of other stimulants since the 1950s.

It is beyond the scope of the present Chapter to review all aspects of drug dependence in detail. Rather, this Chapter summarizes primarily the pharmacologic aspects of drug dependence. In particular, the Chapter provides information that permits a comparison of the pharmacologic basis of tobacco dependence, as described in the other Chapters, with the pharmacologic basis of other forms of drug dependence. More extensive reviews of the topics to be discussed have emerged from various review panels sponsored by the National Institute on Drug Abuse (NIDA) (Krasnegor 1978, 1979a,b,c; Thompson and Johanson 1981; Grabowski, Stitzer, Henningfield 1984;

Sharp 1984) and the National Academy of Sciences (Levison, Gerstein, Maloff 1983); other reviews have been held under the auspices of professional scientific societies (Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Balster and Harris 1982; Taylor and Taylor 1984; Seiden and Balster 1985). Other important determinants and consequences of drug dependence are more thoroughly described elsewhere (Blaine and Julius 1977; Manatt 1983; Tims and Ludford 1984; Petersen 1978; Bell and Battjes 1985; Richards and Blevens 1977; Dupont, Goldstein, O'Donnell, Brown 1979; Lettieri, Sayers, Pearson 1980; Crowley and Rhine 1985).

Clinical Characteristics of Drug Dependence

Drug Dependence Defined

Before the 1960s it was fairly common to invoke factors such as "criminality," "character deficit," "immorality," and "weakness of will" in the clinical diagnosis of "drug addiction." In addition, these factors often included various social connotations. In part, it was because these attributes were not objective or scientifically based that the WHO in 1964 recommended that the term "addiction" be replaced with "drug dependence" in an effort to be more precise and descriptive in definition (WHO 1964, 1981).

According to current conceptualizations, the central and common element across all forms of drug dependence is that a psychoactive drug has come to control behavior to an extent that is considered detrimental to the individual or society (WHO 1981; APA 1987). Although the precise wording varies, the central concept of drug-dependence definitions refers to the behavior of the individual who has come under the control of a psychoactive drug, and this concept has provided the cornerstone of most definitions of dependence/addiction for at least a century (Berridge 1985) and arguably for several centuries (Murray et al. 1933; Austin 1979; Levine 1978). The involvement of a psychoactive drug is the critical feature that distinguishes drug addictions from other habitual behaviors.

In principle, the term "drug dependence" might be used to characterize any form of drug ingestion; however, the term is generally reserved for use when the chemical meets criteria as a "psychoactive" drug. These criteria are based on drug-induced changes in brain function; such changes may involve alterations in mood, feeling, thinking, perception, and other behavior. In this Chapter the term "drug dependence" or "drug addiction" refers to self-administration of a psychoactive drug in a manner that demonstrates that the drug controls or strongly influences behavior. In other words, the individual is no longer entirely free to use or not use the substance. Often times, this reduction in the degree to which use

TABLE 1.—Diagnostic criteria for psychoactive substance dependence

A. At least three of the following:

- (1) Substance often taken in larger amounts or over a longer period than the person intended
- (2) Persistent desire or one or more unsuccessful efforts to cut down or control substance use
- (3) A great deal of time spent in activities necessary to get the substance (e.g., theft), to take the substance (e.g., chain smoking), or to recover from its effects
- (4) Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (e.g., does not go to work because of hangover, goes to school or work "high," intoxicated while taking care of own children), or when substance use is physically hazardous (e.g., drives when intoxicated)
- (5) Important social, occupational, or recreational activities given up or reduced because of substance use
- (6) Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance (e.g., continuing heroin use despite family arguments about it, cocaine-induced depression, or ulcer made worse by drinking)
- (7) Marked tolerance: need for markedly increased amounts of the substance (i.e., at least a 50 percent increase) to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount
(Note: The following items may not apply to cannabis, hallucinogens, or PCP)
- (8) Characteristic withdrawal symptoms (see specific withdrawal syndromes under Psychoactive Substance-Induced Organic Mental Disorders)
- (9) Substance often taken to relieve or avoid withdrawal symptoms

B. Some symptoms of the disturbance persistent for at least 1 month, or occur repeatedly over longer period of time

SOURCE: American Psychiatric Association (1987).

is considered "voluntary" is described as "habitual" or "compulsive" drug use.

Diagnostic Criteria for Drug Dependence

The Diagnostic and Statistical Manual (DSM-III-R) of the American Psychiatric Association (APA 1987) provides a useful example of the objective criteria currently used to define drug dependence. As stated in DSM III-Revised: "The essential feature of this disorder is a cluster of cognitive, behavioral, and physiological symptoms that indicate that the person has impaired control of psychoactive substance use and continues use of the substance despite adverse consequences." Specific diagnostic criteria for psychoactive substance dependence are shown in Table 1.

The APA designated 10 classes of psychoactive substance for which use may lead to dependence: alcohol; amphetamine or similarly acting sympathomimetics; cannabis; cocaine; hallucino-

gens; inhalants; nicotine; opioids; phencyclidine (PCP) or similarly acting arylcyclohexylamines; and sedatives, hypnotics, or anxiolytics. The fact that dependence criteria are the same for all classes of drug use highlights the assumption that dependence processes are functionally similar across substances with different pharmacologic profiles.

Features of Drug Dependence

Behavior that leads to drug ingestion, as well as the various behavioral and physiological sequelae resulting from the ingestion, are determined by both drug (pharmacologic or agent) and nondrug (behavioral or environmental) factors which will be discussed in this Chapter. The nondrug determinants include characteristics of the individual ("host" characteristics) such as age, genotype, and personality.

Highly Controlled or Compulsive Drug Use

Highly controlled or compulsive drug 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. Compulsive drug use may take precedence over other important priorities.

The extent to which compulsive behavior is apparent varies across individuals and is most easily detected in extreme cases. For example, to maintain daily drug intake laryngectomized patients may smoke cigarettes through their tracheostomy hole, cocaine users may take cocaine at the risk of loss of family and job, and prostitution has been observed to occur in exchange for a variety of drugs for which availability was low or price was high.

The drug-seeking behavior itself ranges from the routine and licit procurement of cigarettes or alcohol, to the possibly more extensive behavioral repertoire necessary to obtain prescriptions for certain drugs, to the highly intricate chains of behavior required to procure many illicit drugs. Drug-seeking behavior is not determined entirely by the specific pharmacologic properties of a particular drug, however. For instance, when alcohol or tobacco has been prohibited, procurement has at times involved as much risk and involvement as the procurement of illicit drugs in the 1980s (Austin 1979; Brecher 1972).

A drug may be taken to avoid withdrawal symptoms and other undesirable sequelae of drug abstinence. This factor may contribute to the level of compulsion which develops. Addicting drugs often provide some therapeutic benefit or otherwise useful effect (Chapter VI); these effects may also contribute to the compulsive nature of drug use. Whether or not such benefits are considered to be more

important than the adverse effects of drug taking, this factor is important because it may have been prominent in initial exposure to the drug, it may have strengthened the control of the drug over behavior, and it may constitute a potential cause for relapse.

Physical Dependence and Tolerance

The observation of a withdrawal syndrome that accompanies abstinence from chronic drug exposure is the primary index of physical dependence induced by the drug (Martin 1965; Kalant 1978). Drug withdrawal syndromes are behavioral and physiological sequelae of abstinence from chronic drug administration. Tolerance refers to the diminished responsiveness to successive administration of a drug; it may occur independently of physical dependence but is a frequent concomitant (Kalant 1978). The magnitude of tolerance and physical dependence is directly related to the frequency and magnitude of the drug-dosing regimen; thus, low or infrequent drug dosing may not produce measurable levels of tolerance or physical dependence. Tolerance may develop in the absence of physical dependence; for example, infrequent dose administration may result in decreased responsiveness even though no measurable withdrawal reaction accompanies drug abstinence.

Whereas initial drug exposure may have caused marked behavioral and physiological disruption, the development of physical dependence implies that a relatively normal appearing behavioral and physiological functioning requires continued drug administration and that disruption will occur when the drug is withdrawn. For example, at certain doses, opioids, sedatives (including alcohol), and nicotine can produce marked intoxication in nontolerant individuals. As tolerance develops, these same dose levels may produce no readily observable signs of intoxication, and in the case of opioids and nicotine only extremely high doses or sudden abstinence are accompanied by disruption of ongoing behavior.

The development of tolerance to repeated drug exposure and of the onset of a withdrawal syndrome may be observed following a period of repeated drug exposure and drug abstinence, respectively, but these factors do not in themselves define a drug dependence syndrome requiring intervention to prevent relapse to drug use. It is possible to establish tolerance and physical dependence by repeated drug administration even when the animal or human never actually self-administered the drug. In animals, this is often done in experimental studies; human patients requiring pain relief may become tolerant to and physically dependent on opioid analgesics in hospital settings. Such animals and humans do not necessarily exhibit drug-seeking behavior when drug administration is terminated. Another such instance is the fetal opioid syndrome, in which treatment of the withdrawal reaction might be indicated but no

drug-seeking behavior would be present for which an intervention would be needed (Weinberger et al. 1986). Although not always essential for the occurrence of addictive drug-seeking behavior, tolerance and withdrawal phenomena are important in principle because they can serve to strengthen the control of the drug over behavior. Specifically, tolerance development can result in increased drug intake in an attempt to maintain the desired drug effects, and the onset of a drug withdrawal syndrome may constitute an aversive state which is alleviated by drug taking.

Harmful Effects

The concept that some sort of harm or disadvantage to the individual or society is a consequence of drug use is another element in most definitions of drug dependence. This concept is complex and socially determined, however. For example, drug seeking may result in illicit production and trafficking as currently occurs for illicit drugs (Drug Abuse Policy Office 1984), and had occurred for tobacco at various times when it was banned (Austin 1979; see also Warner 1982 for a discussion of recent cigarette-smuggling issues). Administration of drugs, or abstinence in the physically dependent person, may directly produce adverse behavioral and psychiatric effects ("psychotoxicity"). Finally, toxicity may also be a direct physiological effect of the addicting drug itself (e.g., liver damage caused by alcohol) or to associated toxins (e.g., transmission of the human immunodeficiency virus by needle sharing among i.v. drug users, or carcinogens delivered by tobacco smoke).

These forms of drug-associated damage can result in a variety of societal costs such as health care of drug users (including cigarette smokers), lost productivity of the work force (including tobacco-use-associated losses in productivity), and criminal justice system burdens associated with illicit drug use. Such adverse effects of drug use constitute the "liability" of drug use and may also be factors in the determination that drug use constituted "drug abuse" (Yanagita 1987). These societal aspects of drug dependence frequently invoke debates which pit the "right" to self-damage against the "right" of society to protect itself from the direct damage or costs incurred as a consequence of the individual's behavior. A historical appraisal of psychoactive substance use reveals that societies have often moved cautiously to restrict the use of drugs when there was little assumption of drug-use-associated damage.

Course of Drug Dependence

The chronic nature of drug ingestion in the severely dependent individual suggests that drug dependence processes themselves may be long lasting and resistant to termination. In contrast, the direct

effects of psychoactive drugs are generally limited to a few hours or days at most. Peak physical withdrawal signs and symptoms from opioids, sedatives, alcohol, and tobacco appear to last for about 1 to 2 weeks. However, at least for the opioids, a secondary stage of withdrawal may last for 1 year or more; this has been termed protracted withdrawal (Martin 1965; Jasinski 1981). As discussed in Chapters III and VI, an analogous protracted abstinence syndrome appears to exist in tobacco dependence and to be of importance for treatment efforts. Therefore, despite the relatively short-term duration of the effects of drug administration or withdrawal, the clinically relevant duration of drug dependence is much longer.

A major implication of post-1960s definitions of drug dependence is that drug dependence is not an absolute phenomenon, but rather may vary in degree (Jaffe 1965, 1985; Miller 1979). Often, within an individual the level of severity increases over time ("progressive" characteristic). The course may be quite variable, however. For example, an initially rapidly developed high level of use may be followed by long-term or transient remissions, while some individuals never progress at all beyond levels of use of a given drug that are sometimes considered safe and acceptable (Vaillant 1970, 1982). Such low or intermittent levels of drug use are sometimes referred to as "occasional," "controlled," "recreational" or "social" drug use or "chipping"; such use may still be problematic because there may be acute adverse consequences (e.g., auto accidents following drinking), as well as a transition to chronic drug use (as is characteristic following occasional tobacco use) and the possibility that any use involves illicit behavior (e.g., procurement of alcohol and tobacco by minors or possession of marijuana).

There are differences among drugs in the relative incidence of occasional users compared to regular daily users who meet criteria for dependence. For example, it is generally estimated that less than 15 percent of those who consume alcoholic beverages are dependent (Miller 1979). Analysis of opioid data are more problematic (Zinberg and Jacobson 1976); however, observations such as those made of Vietnam veterans show that opioid chipping is not only a well-documented phenomenon but may also be common in some social and environmental settings. Robins and colleagues found (1) that opioid chipping was a common occurrence among enlisted men in Vietnam, (2) that 88 percent of heroin-addicted Vietnam veterans used heroin occasionally upon their return to the United States, and (3) that most (approximately 90 percent) were able to avoid readdiction (Robins et al. 1977; Robins and Helzer 1975; Robins, Helzer, Davis 1975; Robins, Davis, Goodwin 1974; Robins, Davis, Nurco 1974; see also Zinberg 1972, 1980). In contrast, however, chipping appears relatively rare among tobacco users: the 1985 National Health Interview Survey showed that 10.6 percent of current smokers

smoke 5 or fewer cigarettes/day (unpublished data, Office on Smoking and Health; see also Russell 1976 and US DHHS 1987).

Polydrug Dependence and Multiple Psychiatric Diagnosis

Another feature of drug dependence is the common use of multiple substances, including tobacco, by dependent individuals. In fact, the most consistent feature of such multiple drug use is the high rate of co-occurrence of tobacco dependence along with dependence on opioids, alcohol, stimulants, and even gambling (Taylor and Taylor 1984). In addition, drugs used by individuals may sometimes vary and be interchanged as price and availability vary (e.g., cocaine is preferred by many but individuals may use opioids, or even sedatives, when cocaine is unavailable) (Kliner and Pickens 1982). Several drugs may also be taken simultaneously; for instance, heavy consumption of nicotine, alcohol, and marijuana is common. Finally, most surveys indicate that use of drugs such as cocaine, alcohol, opioids, and marijuana is accompanied (and usually preceded) by use of nicotine (US DHHS 1987).

Tobacco use concurrent with other drug dependencies is so prevalent that it is not generally considered to be of diagnostic significance or considered as a basis of multiple drug dependence diagnosis. Recently, the possible interactive nature of co-dependencies to nicotine and other drugs has been given increasing attention in drug treatment programs (Taylor and Taylor 1984; Kozlowski et al. 1984). These data are discussed later in this Chapter, as well as the issue of whether nicotine serves as a "gateway" to the use of illicit drugs.

Also of clinical significance is the concurrence of drug dependence and some other psychiatric disorder. This phenomenon is termed multiple or dual diagnosis (Meyer 1986; McLellan, Woody, O'Brien 1979; Allen and Frances 1986; Rounsaville and Kleber 1986; Jaffe and Ciraulo 1986). In general, dependence on opioids, alcohol, cocaine, and nicotine is often associated with elevated rates and levels of antisocial tendencies and extraversion, but such trends are not generally regarded as multiple diagnoses (for a review of several forms of multiple diagnosis, see Taylor and Taylor 1984). The designation of multiple diagnosis is reserved for the concurrent appearance of a clinically significant psychiatric disorder and drug dependence; the most common of such disorders would appear to be depression, anxiety, and antisocial personality (McLellan, Woody, O'Brien 1979; Rounsaville et al. 1982; Woody, McLellan, O'Brien 1984).

Spontaneous Remission

It is characteristic of drug dependence that some persons discontinue use of the drug while not engaged in a formal treatment program (i.e., "on their own") although they may have participated in a treatment program at some earlier point in time (Stall and Biernacki 1986). Spontaneous remission refers to intentional and unintentional cessation of drug use, variously referred to as "natural recovery," "maturing out," "burning out," or "self-quitting," but most frequently in current literature as "spontaneous remission." Such quitting is sometimes reported to be due to "will power" or "just deciding to quit." However, follow-up studies have revealed that significant environmental events are often associated with such quitting (for example, Vaillant 1970, 1982). Such data have suggested to some that the terms such as "self-quitting," "self-help," and "spontaneous remission" are misnomers (Fisher 1986; Fisher et al. 1988); nonetheless, because the term spontaneous remission is extant in the scientific literature, it will be used here. This Section provides a brief summary of available information comparing alcohol, opioids and tobacco with regard to their rates of spontaneous remission and of factors associated with remission from drug use.

In studies of spontaneous remission, a minimum criterion for abstinence, such as 1 year, is often imposed. Although the recorded history of drug dependence acknowledges that some people can achieve abstinence without benefit of formal intervention programs, there was little systematic study of spontaneous remission until the 1970s. Major motivations for the current interest in this phenomenon are to determine if the so-called spontaneous remitters differ in behavioral or physiological parameters from other drug-dependent persons, to identify factors which may be systematically applied in treatment settings, and to better understand the process of drug dependence itself.

The percentage of such spontaneous remitters reported in any given study appears to vary more as a function of population and study variables than as a function of drug class. For instance, data averaged across 10 studies show that approximately 30 percent of opioid-dependent persons spontaneously remit (Anglin et al. 1986) although estimates of remission rates vary from 2 percent to 65 percent (Harrington and Cox 1979; Winick 1962). On the other hand, approximately 90 percent of people who have quit smoking report that they quit without the aid of formal treatment programs or smoking cessation devices (Fiore et al., in press; see discussion of related issues in Fisher et al. 1988).

Deriving precise quantitative comparisons of rates of spontaneous remission across the various drug dependencies is problematic due to the differing criteria used to identify those who are spontaneous remitters. For example, in tobacco surveys, rates of spontaneous

remission are often estimated by retrospective self-reports from a sample of former smokers, whereas surveys of opioid and alcohol users generally include only those who were dependent enough to be involved in formal treatment programs at some time.

The factors which are associated with spontaneous remission appear to be similar across dependencies on alcohol, opioids, and tobacco (Stall and Biernacki 1986). Table 2 is a summary of findings which have been reported on factors related to spontaneous remission. As shown in the Table, influences such as health problems associated with use of the drug and social pressures are frequent precipitants of spontaneous remission among persons who were dependent on alcohol, opioids, or tobacco. Similarly, spontaneous remitters have often learned to better manage their drug "cravings" and to provide contingent reinforcement for quitting to themselves, and may even undergo significant lifestyle changes (Stall and Biernacki 1986).

These data regarding spontaneous remission support the conclusion, discussed earlier, that it is somewhat misleading to infer that spontaneous remitters are truly spontaneous or that they were not "really dependent" as is sometimes assumed (Fisher 1986; Fisher et al. 1988; US DHHS 1982). Rather, it seems more plausible that spontaneous remitters are largely those who have either learned to deliver effective treatments to themselves or for whom environmental circumstances have fortuitously changed in such a way as to provide a therapeutic situation (Fisher 1986; Stall and Biernacki 1986; Vaillant 1982, 1970). In addition, persons most likely to quit use of tobacco and opioids without benefit of formal intervention do tend to have shorter histories of use and/or be at lower levels of dependence (US DHHS 1987). Such issues, relating specifically to cigarette smoking, have been reviewed in considerable detail in a previous report of the Surgeon General (US DHHS 1982).

Chemical Detection Measures

Although drug dependence is not reliably diagnosed simply on the basis of amount of drug intake (Crowley and Rhine 1985; Jaffe 1985), it can be useful to determine whether or not a person has ingested a significant amount of a drug. For example, as is discussed later in this Chapter, many treatment programs require objective verification of drug-free patient status.

A potentially useful adjunct for objectively assessing exposure to drugs is to test for the presence of the drug in biological specimens (Walsh and Yohay 1987; Hawks and Chiang 1986). For instance, blood, urine, saliva, expired air, and other biological samples can be assayed for residual drug or drug-specific markers (e.g., metabolites). Such testing aids in determining that presumed drug-related effects were not actually symptoms of some other organic or mental

TABLE 2.—Studies concerning spontaneous remission behavior, by drug and commonly mentioned factors important to remission

Factor	Alcohol	Tobacco	Heroin
Health problems	Cahalan (1970), Goodwin et al. (1971), Knupfer (1972), Lemere (1953), Saunders et al. (1979), Stall (1983), Tuchfeld (1981)	Hecht (1978), Pederson and Lefcoe (1976)	Biernacki (1983)
Social sanctions	Cahalan (1970), Edwards et al. (1977), Goodwin et al. (1971), Knupfer (1972), Stall (1983), Thorpe and Perret (1959), Tuchfeld (1981), Vaillant (1982)	Perri et al. (1977)	Biernacki (1983), Schasre (1966), Vaillant (1966a,b, 1970)
Significant others	Edwards et al. (1977), Goodwin et al. (1971), Knupfer (1972), Saunders et al. (1979), Stall (1983), Tuchfeld (1981), Vaillant (1982)	DiClemente and Prochaska (1979), Hecht (1978), Pederson and Lefcoe (1976), Perri et al. (1977)	Biernacki (1983), Waldorf and Biernacki (1979), Vaillant (1964, 1970)
Financial problems	Cahalan (1970), Saunders et al. (1979), Stall (1983), Thorpe and Perret (1959), Tuchfeld (1981)	Hecht (1978)	Biernacki (1983)
Significant accidents	Knupfer (1972), Stall (1983), Tuchfeld (1981)	Perri et al. (1977)	Biernacki (1983), Jorquez (1983), Waldorf and Biernacki (1981)
Management of cravings	Stall (1983)	Baer et al. (1977), DiClemente and Prochaska (1979), Hecht (1978), Pederson and Lefcoe (1976), Perri et al. (1977)	Biernacki (1983), Jorquez (1983)

TABLE 2.—Continued

Factor	Alcohol	Tobacco	Heroin
Positive reinforcement for quitting	Edwards et al. (1977), Stall (1983)	Baer et al. (1977), DiClemente and Prochaska (1979), Pederson and Lefcoe (1976)	Biernacki (1983)
Internal psychic change/motivation	Edwards et al. (1977), Knupfer (1972), Saunders et al. (1979), Tuchfeld (1981)	Baer et al. (1977), Hecht (1978)	Biernacki (1983), Schasre (1966), Waldorf and Biernacki (1981)
Change in lifestyle	Edwards et al. (1977), Knupfer (1972), Saunders et al. (1979), Tuchfeld (1981)	DiClemente and Prochaska (1979), Hecht (1978)	Biernacki (1983), Jorquez (1983), Schasre (1966), Waldorf and Biernacki (1981)

SOURCE: Modified from Stall and Biernacki (1986).

disorder. One problem with such verification is that the drug level measured reflects recency as well as amount of drug use and thus may lead to either underestimation or overestimation of the typical level of drug use. Furthermore, absolute level of use does not necessarily determine whether use is pathological or detrimental. Another problem is that biochemical drug tests vary widely in both their specificity (correct drug identification) and sensitivity (minimum amount of drug detected) (see Grabowski and Lasagna 1987 and Walsh and Yohay 1987 for general reviews of such issues; and Benowitz 1983 and Muranaka et al. 1988 for a tobacco-related review; also see Chapter II).

Presently, verification of drug dependence is based largely on the behavioral factors as described below. The most useful application of testing for drug levels in the body remains the verification of compliance with treatment regimens in which drug abstinence is the goal. These and other issues regarding the methodologies and applications of chemical detection measures have been reviewed by a committee of the American Society for Clinical Pharmacology and Therapeutics (in press).

Patterns in the Development of Drug Dependence

When the relationships among drug dependencies have been studied in major epidemiological surveys (e.g., NIDA's National Household Survey (NHS) (US DHHS 1987)), two findings consistently emerge: persons who use dependence-producing drugs are often cigarette smokers, and cigarette smoking precedes and may be predictive of illicit drug use. Some of the data which have led to these conclusions are summarized in this Section.

Current Use of Cigarettes and Other Drugs

The association of current use of one drug with current use of other drugs has been studied extensively. One such study is the NHS conducted by NIDA (US DHHS 1987). The Eighth NHS, conducted in 1985, involved personal interviews with 8,038 persons 12 years of age and older, representative of the household population of the continental United States. Questions were asked about the age of respondents when they first tried a cigarette and age when they first started smoking daily. This distinction may be important when comparing cigarette use with the use of other drugs. Persons who do not make the transition from trying cigarettes to daily use may be less likely to use other drugs than those who do make this transition. A similar format was used with alcohol (i.e., age at which respondent first tried alcohol, not including childhood sips, and age of first using alcohol once a month or more). Questions about age at the onset of other drug use were limited to age at first use. In the NHS studies,

TABLE 3.—Current use of alcohol, marijuana, and cocaine among "current" cigarette smokers and nonsmokers by age group (percentages)

Age group, current drug use	'Current' cigarette use	
	No	Yes
Alcohol		
12-17	23.5	74.2
18-25	64.7	82.6
26-34	62.5	81.0
≥ 35	52.5	68.6
Marijuana		
12-17	5.8	47.3
18-25	13.7	35.4
26-34	10.6	26.0
≥ 35	1.7	3.5
Cocaine		
12-17	0.4	8.8
18-25	3.9	13.9
26-34	4.1	9.2
≥ 35	0.4	0.6

NOTE: Current use is any use reported in the 30 days prior to the interview.

SOURCE: National Household Survey on Drug Abuse, 1985. (in preparation)

current drug use is defined as any use of the drug during the 30 days preceding the interview.

Based on data from the 1985 NHS on Drug Abuse, Table 3 shows associations among use of various psychoactive substances. As shown in the table, rates of current use (i.e., during the past 30 days) of marijuana, alcohol, and cocaine are much higher among "current" cigarette smokers than among others. For example, among 12- to 17-year-olds, almost three-fourths of "current" smokers were current alcohol users compared with less than one-fourth of the youths who were not "current" smokers. Approximately 47 percent of the "current" cigarette smokers report being current marijuana users compared with 5.8 percent of the youths who were not "current" smokers.

Differences as large as those shown in Table 3 represent very strong correlations between use of cigarettes and use of other drugs. The strength of the correlation between use of cigarettes and use of other drugs, licit and illicit, suggests the potential importance of directing prevention efforts to the early gateway drugs: cigarettes and alcohol (Kandel and Yamaguchi 1985; Clayton 1986; Clayton and Ritter 1985).

Epidemiological Studies of the Progression of Drug Use

Tobacco use has been found to play a pivotal role in the development of other drug dependencies. The classic descriptive model for initiation patterns of drug use was developed by Kandel (1975), who first divided drugs into two groups of availability: licit and illicit. Kandel concluded that virtually all persons who ever used illicit drugs such as marijuana and cocaine had previously used licit drugs such as cigarettes and alcohol. Kandel's developmental stages model is based on the assumption that there are relatively invariant patterns of onset of use. The stages are:

- (1) No Use of Any Drugs
- (2) Use of Beer or Wine
- (3) Use of Cigarettes and/or Hard Liquor
- (4) Use of Marijuana
- (5) Use of Other Illicit Drugs

Although Kandel's model addresses the initiation or onset of drug use, it does not account for patterns of early use (e.g., frequency of occasions or quantity per occasion). Nonetheless, there is general agreement that the model accurately characterizes the drug initiation process in the United States as one that begins with use of licit drugs (tobacco and alcohol) and, if progression occurs, involves greater use of these substances (Kandel, Margulies, Davies 1978; Huba, Wingard, Bentler 1981; O'Donnell and Clayton 1982). This pattern has also been observed in France and Israel (Adler and Kandel 1981).

In a longitudinal study of the progression of drug use, Yamaguchi and Kandel (1984a) gathered baseline data in 1971 from subjects in the 10th and 11th grade in New York State. This representative sample was followed up in 1981 when the average age was 24.7 years. The order of onset identified by Yamaguchi and Kandel (1984a) was alcohol, cigarettes, marijuana, illicit use of psychoactive or prescriptive drugs, and other illicit drugs. Among persons who had used both alcohol and cigarettes 10 times or more, alcohol use preceded cigarette use in 70 percent of the cases for males and 55 percent of the cases for females. Among persons who had used cigarettes and marijuana 10 or more times, 67 percent of the males and 72 percent of the females reported using cigarettes first.

Using a sophisticated statistical analysis, Yamaguchi and Kandel (1984a) derived several additional conclusions including the following:

- (1) For men, the pattern of progression was one in which the use of alcohol preceded marijuana; alcohol and marijuana preceded other illicit drugs; and alcohol, cigarettes, and marijuana preceded the illicit use of other psychoactive drugs. Eighty-seven percent of the men were characterized by this pattern.

(2) For women, the pattern of progression was one in which either alcohol or cigarettes preceded marijuana; alcohol, cigarettes, and marijuana preceded other illicit drugs; and alcohol and either cigarettes or marijuana preceded the illicit use of psychoactive drugs. Eighty-six percent of women shared this pattern.

Tobacco Use as a Predictor of Other Drug Use

In an analysis of nationwide data from the high school senior class of 1980, Clayton and Ritter (1985) found that alcohol drinking and cigarette smoking were the most powerful predictors of the extent of marijuana use for both males and females. Cigarette use was a stronger predictor of marijuana use among females. Moreover, this role of cigarette smoking was especially pronounced when it had been initiated at age 17 or earlier. Similarly, data from the longitudinal study by Yamaguchi and Kandel (1984a,b) revealed that, among persons with some history of alcohol use, cigarette smoking was a powerful predictor of marijuana use.

Consistent with the above described findings regarding cigarette smoking, smokeless tobacco use has also been shown to be a predictor of other drug use, including cigarette smoking (Ary, Lichtenstein, Severson 1987). More than 3,000 male adolescents were interviewed twice, at an approximately 9-month interval, to determine their rates and levels of use of various psychoactive substances. The main findings were that (1) users of smokeless tobacco were significantly more likely to use cigarettes, marijuana, or alcohol than nonusers; (2) users of smokeless tobacco were significantly more likely to take up use of cigarettes, marijuana, or alcohol than nonusers; (3) smokeless tobacco users who were using these other substances at the time of the first interview showed substantially greater increases in levels of use of these other substances over the 6-month interval than did nonusers of smokeless tobacco; and (4) 71 percent of those who had been using smokeless tobacco at the first interview remained users at the second interview.

Cigarette smoking is also a predictor of cocaine use. White and colleagues (US DHHS 1987) began with a large sample of 12-, 15-, and 18-year-old adolescents in New Jersey and reinterviewed them at 3-year intervals. As reported in NIDA's Triennial Report to Congress (US DHHS 1987), White and coworkers found that there were several predictors of cocaine use in 18-year-olds who had been interviewed 3 years earlier: prior use of cigarettes, alcohol, and marijuana. Furthermore, at the time of the second interview (of the 18-year-olds), the cocaine users used cigarettes, alcohol, marijuana, and other drugs more often than did nonusers of cocaine.

Although alcohol use frequently precedes tobacco use, the use of alcohol only progresses to dependence (alcoholism) in about 10 to 15

percent of all drinkers (Miller 1979). Use of cigarettes, by contrast, almost inevitably escalates to a level characterized as dependent use (Russell 1976; US DHHS 1987). This is consistent with the observation that although some use of alcohol may precede tobacco use, it is prior use of tobacco and not alcohol that emerges in the above-cited studies as the stronger predictor of illicit drug use.

The 1985 High School Senior Survey by NIDA (US DHHS 1987) showed that the first dependence-producing drug tried among users of alcohol and illicit drugs was often tobacco. For example, among all respondents 12 years of age and older, first use of tobacco and alcohol occurred in the same year for 18 percent of the sample; cigarettes were used first by 62 percent of the sample, and alcohol was used first by 20 percent. Among those who tried both cigarettes and marijuana, 14 percent first tried these drugs in the same year, 75 percent tried cigarettes first, and 11 percent tried marijuana first. Among those who tried both cigarettes and cocaine, 95 percent used cigarettes first, 3 percent used them first the same year, and only 2 percent used cocaine before cigarettes. These observations show that when cigarettes and another of these dependence-producing drugs have been used by the same individual, cigarette use usually is the first of the two drugs used. One difference between cigarette smoking and the use of other common substances (e.g., milk, sugar, or aspirin) that may also precede the use of illicit drugs is that nicotine itself is a drug that produces the tolerance, physical dependence, and drug-seeking behavior that meet the criteria of a drug-dependence syndrome.

Frequency of Use of Cigarettes and Other Drugs

Measures of frequency of drug use also yield important findings. The data presented in Table 4 show the percentage of persons in three groups (never smoked, tried cigarettes but never used them daily, used cigarettes on a daily basis) who report use of alcohol, marijuana, and cocaine. The criterion for alcohol use is 5 or more consecutive drinks during at least 1 day in the past 30 days; criteria for marijuana and cocaine use involve previous use of these drugs more than 10 times during the respondent's lifetime. These criteria were used to eliminate those who merely tried the drug on a few occasions ("experimental" use). The percentages are presented separately for four age groups.

The main finding shown in Table 4 is that those who become daily cigarette smokers are considerably more likely than others to report use of these other drugs, regardless of age group. For example, among the 12- to 17-year-olds, less than 0.5 percent of the never smokers report using marijuana more than 10 times compared with 3.3 percent of those who tried but never used cigarettes daily and 22.7 percent of those who have used cigarettes daily. These data

**TABLE 4.—Use of alcohol, marijuana, and cocaine among
“never” cigarette smokers, “occasional”
cigarette smokers, and daily cigarette smokers,
by age group (percentages)**

Age group, drug use	Cigarette use pattern		
	Never smoked	Tried, never used daily	Smoked daily
Alcohol¹			
12-17	2.7	15.9	38.5
18-25	12.3	31.9	49.6
26-34	9.8	23.0	41.3
≥ 35	5.6	9.2	20.1
Marijuana²			
12-17	0.2	3.3	22.7
18-25	3.3	8.3	37.4
26-34	2.8	12.9	30.3
≥ 35	0.6	1.8	3.8
Cocaine³			
12-17	0.2	0.8	6.4
18-25	1.3	4.5	14.2
26-34	1.8	7.2	15.6
≥ 35	0.2	0.3	1.9

¹Drank five or more drinks in a row on at least 1 day in past 30 days.

²Used marijuana more than 10 times.

³Used cocaine more than 10 times.

SOURCE: National Household Survey on Drug Abuse, 1985. (in preparation)

extend those presented in Table 3: associations exist between cigarette smoking and other drug use when considering “current” use (any use in the past 30 days) (Table 3) or measures of frequency of drug use (Table 4). Similarly, a study of alcohol drinking and cigarette smoking among students in grades 7 to 12 in New York State showed a positive correlation between the frequency of consuming alcoholic beverages and both the likelihood of smoking cigarettes and daily cigarette consumption (Welte and Barnes 1987).

Initiation of Drug Use

Initiation of drug use often occurs through social contacts, independent of the pharmacologic actions of the drug. Drug seeking is then sustained and modulated through combined social and pharmacologic factors. With the possible exception of stimulants such as cocaine and amphetamine, initial exposure to many psychoactive drugs (including opioids, alcohol, and nicotine) is often associated with aversive consequences (Haertzen, Hooks, Ross 1981; Haertzen, Kocher, Miyasato 1983). For example, opioids may produce nausea; alcohol and nicotine not only produce nausea but may

produce initially aversive sensory effects in some preparations (e.g., high-concentration alcoholic beverages may taste "bad" and cigarette smoke may be "harsh"). As a consequence, lengthy periods of occasional ("experimental" or "social") drug use frequently precede the development of daily drug use.

These observations imply that nondrug factors are important in the initiation and maintenance of drug intake until dependence upon the drug itself develops (Crowley and Rhine 1985; Vaillant 1970, 1982; Marlatt and Baer 1988; Brown and Mills 1987). As discussed elsewhere in this Chapter, such factors can also modulate level of drug use as well as influence the frequency of quitting attempts and their likelihood of success (see also Chapters IV and VII in this volume and earlier Reports of the Surgeon General). The specific factors that have been identified and accepted as prominent in helping to establish initial exposure to drugs (Crowley and Rhine 1985) include availability of the drug, cost of the drug, social acceptability of the drug, and other environmental sources of pressure to use drugs.

The acceptability of the drug preparation itself can be manipulated by controlling the dose of the drug and increasing its sensory palatability. For example, the utility of some of the newer smokeless tobacco formulations as "starter" products for youth is held to be due in part to the lower concentrations of nicotine, formulations that facilitate use (e.g., snuff in pouches), as well as nontobacco flavorings (e.g., mint or cinnamon) (Henningfield and Nemeth-Coslett 1988; US DHHS 1986, 1987; Connolly et al. 1986). Such strategies of "starter product" manipulation are analogous to those used to initiate drug seeking in laboratory animals, described later in this Chapter. Such product acceptability factors, combined with the ready availability, peer pressure to use, perceptions that the products were safe, and marketing strategies aimed at increasing the social desirability of smokeless tobacco use, appear to have been largely responsible for the marked rise in use of smokeless tobacco by youth in the 1970s (Ary, Lichtenstein, Severson 1987; Christen and Glover 1987; Connolly et al. 1986; Connolly, Blum, Richards 1987; Glover et al. 1986; Guggenheimer et al. 1987; Kirn 1987; Kozlowski et al. 1982; Marty et al. 1986; Negin 1985; Silvis and Perry 1987; US DHHS 1979; Appendix A).

Vulnerability to Drug Dependence: Individual and Environmental Factors

Despite the complexity of the issues, it is useful to identify factors that differentiate individuals who appear more susceptible to drug dependence. These factors may collectively be termed vulnerability factors. Vulnerability factors are diverse, varying among individuals and within individuals at different times (Radouco-Thomas et al.

1980; Marlatt and Baer 1988; Brown and Mills 1987). Vulnerability may arise from genetic variation or from environmental sources including learning (Jones and Battjes 1985). Vulnerability factors are such that they do not necessarily compel a person to use a drug; in fact, they might be undetected in a person never exposed to a dependence-producing drug. Nonetheless, the presence of several vulnerability factors can increase the likelihood of the development of drug dependence, including cigarette smoking.

The concept of a predisposition to drug dependence arose from the observation that not all people are equally prone to becoming behaviorally dependent upon drugs (Mann et al. 1985; Radouco-Thomas et al. 1980; Jaffe 1985; M.N. Hesselbrock 1986; V.M. Hesselbrock 1986; Mirin, Weiss, Michael 1986). The multiple sources of differences in predisposition or vulnerability to drug dependence are not mutually exclusive. One is a genetic predisposition, shared by family members by virtue of their common biological heritage. Another is an experiential predisposition, shared by family members by virtue of their shared life experiences. For instance, children with parents who are dependent on drugs are at elevated risk of becoming dependent (Hawkins, Lishner, Catalano 1986; Begleiter et al. 1984; Kumpfer 1987). For tobacco, the magnitude of the effect is greater when both parents smoke than when only one parent smokes (Borland and Rudolf 1975; Green 1979). Other types of vulnerability factors are physiologic (e.g., pain, sleep deprivation) and psychiatric (e.g., anxiety, depression) conditions that may constitute undesirable states for which relief is sought by use of a drug (Crowley and Rhine 1985). Finally, as discussed earlier in this Chapter, a variety of nonpharmacologic factors are important in the initiation and development of drug dependence (e.g., price, availability); such factors may be considered vulnerability factors in their own right.

A recent area under active investigation is the identification of specific vulnerability factors in youth (Brown and Mills 1987). For example, cigarette smoking has long been associated with juvenile behavior problems (Armstrong-Jones 1927; Welte and Barnes 1987; Kumpfer 1987); more recently, scientific data have confirmed the statistical association of increased rates of cigarette smoking among juveniles with a conduct disorder diagnosis (i.e., adolescent deviance) (Sutker 1984). A related observation is that children with conduct disorders are at elevated risk of using opioids, cocaine, alcohol, tobacco, and other psychoactive drugs (Baumrind 1985). In fact, Kellam, Ensminger, and Simon (1980) found that certain indices of mental health identified in first graders were highly predictive of the use of various psychoactive drugs (including alcohol, opioids, marijuana, and nicotine) when the children were restudied in their teenage years. These studies do not directly address the degree to which juvenile behavior problems are causes or consequences of drug

use. It is plausible that either drug use or other behavior problems can exacerbate each other, possibly alternately contributing to a gradual escalation of drug use, behavior problems, or both. These observations suggest that it is especially important to prevent initiation of drug use among individuals who appear to be at increased risk (vulnerability) to developing drug dependencies.

Pharmacologic Determinants of Drug Dependence

As discussed earlier in this Chapter and in Chapter I, it is the involvement of a dependence-producing drug that sets drug addictions apart from the so-called "addictions" to other substances (e.g., food) and activities (e.g., gambling). There are scientific methods to determine if use of a substance involves a dependence-producing drug. These methods, how they are applied to study drugs such as morphine, cocaine, and nicotine, and some of the main findings from such work are reviewed in this Section.

A wide range of drugs can be used to modify behavior (e.g., as used in psychiatric treatment); however, the term drug dependence is generally reserved for dependencies which involve drugs that can sustain repetitive drug self-administration by virtue of their transient effects on mood, feeling, and behavior. Drugs that exert such effects via alteration of functioning of the brain or central nervous system (CNS) are generally termed "psychoactive" (WHO 1981). When the psychoactivity of a given drug is frequently pleasant, it is referred to as a "euphoriant," as "reinforcing," or as an "abusable" drug, although these terms are not precisely interchangeable. This framework is consistent with that described by Lewin (1931); namely, that these drugs are chemicals which are "taken for the sole purpose of producing for a certain time a feeling of contentment, ease, and comfort." Drugs which produce such effects effectively control the behavior of a wide range of species, including humans.

How Drugs Control Behavior

Drugs cause addiction by controlling the behavior of users; that is, addicting drugs come to influence behavior leading to their own ingestion. The behavioral and pharmacologic mechanisms of such control have been reviewed elsewhere (Thompson 1984) and will only be briefly summarized in this Section. Behavior, including drug taking, is biologically mediated by the electrical and chemical stimuli which arise from the nervous system. These stimuli may originate within the body and brain of the individual, but they may also arise from environmental events and be detected by sensory processes such as vision and audition. Dependence-producing drugs control behavior by activating, inhibiting, or mimicking the existing chemical circuits of the nervous system. Dependence-producing

drugs are those that readily exert control over behavior by virtue of their stimulus properties. It is useful to distinguish among four kinds of stimulus effects produced by dependence-producing drugs.

(1) Drugs can produce *interoceptive* or *discriminative* effects that a person or animal can distinguish from the nondrug state. These effects may set the occasion for the occurrence of particular behaviors. For example, the taste of alcohol or the smell of tobacco smoke can set the occasion for social interactions, and the "priming" effects of a single dose of a drug can lead to subsequent drug seeking and relapse in animals or humans with a history of use (Griffiths, Bigelow, Henningfield 1980; Colpaert 1986).

(2) Drugs may serve as *positive reinforcers* or *rewards* which directly strengthen behavior leading to their administration. The reinforcing efficacy may be related to effects termed either "stimulating," "relaxing," "pleasant," "useful," "therapeutic," or "euphoriant" or may be related to providing relief of withdrawal symptoms or other undesirable states.

(3) Drug administration or abstinence can also function as "*punishers*" or *aversive* stimuli. For example, high-dose levels of most psychoactive drugs serve as an upper boundary level of intake; analogously, decreasing drug levels can also function as aversive stimuli contributing to the strength of drug taking as a means to avoid such aversive effects (Downs and Woods 1974; Goldberg et al. 1971; Henningfield and Goldberg 1983b; Kozlowski and Herman 1984). Aversive stimuli may function as negative reinforcers by strengthening behavior that removes the stimuli (Skinner 1953). Thus, drug withdrawal symptoms are sometimes referred to as negative reinforcers that increase drug seeking.

(4) Drug administration, or abstinence following a period of chronic administration, can serve as *unconditioned stimuli*, in which case they may directly elicit various responses, e.g., vomiting at high-dose levels of opioid administration or during opioid withdrawal, light-headedness produced by rapid smoking, and a strong urge to use a drug. As will be discussed later in this Chapter, repetition of such phenomena can lead to their elicitation by drug-associated stimuli, e.g., the sight or smell of drug-associated stimuli (O'Brien, Ehrman, Ternes 1986; Wikler 1965; Wikler and Pescor 1967).

All of these processes may occur whether or not the person has correctly identified their source, i.e., is "aware" of how the drug led to the behavior (Fisher 1986). Furthermore, the biological power and generality of these processes are evidenced by the findings that they also occur in animals (Young and Herling 1986; Spealman and Goldberg 1978; Johanson and Schuster 1981).

Drugs differ widely in their potential to control behavior via such mechanisms. Dependence-producing drugs usually readily control behavior in all of the above capacities. Quantification of such

characteristics is the cornerstone of testing for the likelihood that use of a drug will lead to addiction. Observers in the 19th and early 20th centuries (e.g., Lewin 1931) had correctly determined that it was the psychological (behavioral) effects (sometimes termed "psychic" or "mental" effects) of substances that led to their habitual use. Practical methods for evaluating the behavior-modifying properties of drugs did not emerge until the behavioral sciences themselves had become sufficiently sophisticated in the 1930s and 1940s. Prior to this time, dependence-producing drugs were identified on the basis of retrospective observations of their effects. Since the 1940s, however, drug testing has grown increasingly reliable at identifying ("screening") drugs for their potential to produce dependence prior to observations of dependence outside the laboratory. In fact, highly reliable information can now be obtained on the basis of animal testing alone (Martin 1971; Thompson and Unna 1977; Brady and Lukas 1984; Bozarth 1987b).

Methods for evaluating the behavior-modifying properties of drugs were largely developed beginning in the 1940s in studies with morphine-like opioids and cocaine-like stimulants, and have only recently been systematically used to evaluate nicotine. The methods will be described in the remainder of this Section, along with a comparison between the behavioral-pharmacologic actions of nicotine and those of other drugs.

Dependence Potential Testing: Psychoactive, Reinforcing, and Related Effects

To scientifically determine if a chemical is dependence producing, a series of scientific tests may be done. These tests are jointly termed dependence potential tests. In this Chapter, Dependence Potential Testing refers to laboratory tests which measure the behavioral and physiological responses of animals and humans to drug administration and to termination of chronic drug administration. Taken together, the results of these tests can be used to objectively predict whether a drug lends itself to self-administration by persons who are exposed. The focus of the present Section is on how the methods are applied to evaluate the potential of drugs to control behavior and to produce transient alterations in mood or feeling that are predictive of self-administration. Such effects have essentially defined the dependence-producing drugs and have set them apart from other medicinals and food; drugs with such effects are sometimes termed "psychotropic" or "behaviorally active" but most commonly as "psychoactive" (President's Advisory Commission 1963; WHO 1981).

Not all psychoactive drugs lead to dependence; many drugs used to treat behavioral and psychiatric disorders are considered to have minimal dependence potential (for example, tricyclic antidepressants) or may actually produce effects that substantially impair long-

term compliance with therapeutic regimens (for example, major tranquilizers). How dependence-producing drugs are distinguished from other psychoactive drugs will be described in this Section. The next Section will discuss methods used to measure test drugs for their potential to produce tolerance and physical dependence.

In reviews and proceedings from various expert committees, the procedures to be described have been referred to as testing for "Abuse Liability," "Psychic Dependence," "Abuse Potential," "Addiction Liability," "Behavioral Dependence," and "Dependence Potential" (Brady and Lukas 1984; Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985; Thompson and Johanson 1981; Bozarth 1987b; WHO 1981). Whereas there are differences in focus that are evident when these methods are compared, the general goals and strategies are consistent. These will be briefly described in this Section. Detailed descriptions of these methods have been provided by an expert subcommittee of the Committee on Problems of Drug Dependence (Brady and Lukas 1984) and in numerous conferences involving world experts on such procedures (Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985; Thompson and Johanson 1981; Bozarth 1987b). The results of the methods are also considered in the process of reviewing the national and international regulatory status of various drugs either known or suspected to be addicting by the FDA, the Drug Enforcement Agency (DEA), and the WHO (WHO 1981, 1987).

Effects of Drugs on Mood and Feeling (Psychoactivity)

Dependence-producing drugs can change the way a person thinks, feels, and behaves. The effects may be very subtle (e.g., feelings of relaxation), or they may be profound (e.g., intoxication and impaired cognitive abilities). The scientific assessment of the effects of drugs on mood and feeling (also referred to as "psychoactive," "psychological," "interoceptive," "subjective," "psychic," or "self-reported" effects) was essentially an extension of the methods developed to assess physiological actions of drugs. By the late 1940s, several drug dependence researchers had concluded that physical dependence potential testing was of limited value in predicting whether drug-seeking behavior would develop following exposure to a given drug (Isbell 1948; Isbell and Vogel 1948). These researchers used observational techniques to measure interoceptive drug effects. Later, the reliability and general applicability of the techniques were substantially enhanced by incorporation of the methods developed by Rao (1952) for assessing changes in subjective state and the methods developed by Beecher (1959) for the measurement of pain and analgesia in humans.

These methods contributed to the development of what are generally considered the first objective questionnaires for assessing addictive drug effects by Fraser and his colleagues (Fraser and Isbell 1960; Fraser et al. 1961). A prominent feature of the questionnaires was a series of scales to evaluate the ability to feel or discriminate a drug effect, to rate the liking of the drug effect, and to identify the drug that was given from a list of widely used and abused drugs.

The next major advance in the quantification of subjective drug effects was the development of the Addiction Research Center Inventory (ARCI) by Haertzen and his colleagues (Haertzen, Hill, Belleville 1963; Haertzen 1966, 1974; Haertzen and Hooks 1969; Haertzen and Hickey 1987). The ARCI contained scales that were empirically derived to be sensitive to the effects of specific drugs and drug classes (e.g., sedatives, stimulants, hallucinogens). One of the most useful scales was developed to measure the effects of morphine and benzedrine (a prototypical opioid and stimulant, respectively); this scale was subsequently referred to as the "Morphine Benzedrine Group" or "MBG" or "Euphoriant" scale, because morphine-like and benzedrine-like drugs increased the scale scores while simultaneously producing feelings often reported as pleasurable (Haertzen, Hill, Belleville 1963; Haertzen 1974). Scores on the MBG scale are also elevated by most other addicting drugs (Jasinski 1977; Jasinski, Johnson, Henningfield 1984; Henningfield 1984). More recently, the highly specific drug discrimination testing procedures (described below) have been added to the human drug dependence potential testing armamentarium (Chait, Uhlenhuth, Johanson 1984, 1985).

To the extent to which certain common features are identified using tests such as the above, they may be categorized together, e.g., as dependence-producing or addicting drugs. This is referred to as determining "pharmacologic" equivalence. Conversely, to the extent to which these same drugs differ in certain respects, they may also be subcategorized as, for instance, analgesics, sedatives, or stimulants. Such categorization must be viewed with caution, however, because overemphasis on any particular feature of a drug can be misleading. For instance, morphine, alcohol, and amphetamine can all produce behavioral and physiological effects that are stimulant-like as well as effects that are sedative-like (Gilman et al. 1985; Dews and Wenger 1977). Nicotine has been viewed as both a stimulant ("excitant") (Lewin 1931) and a sedative (Armstrong-Jones 1927). Most commonly nicotine is now categorized as more stimulant-like than sedative-like, but with an appreciation of its diverse range of potential effects, which depend upon the dose given and the measure used (Gilman et al. 1985).

Methods and Results

Assessment of the psychoactivity of drugs in humans essentially entails giving either drug or placebo to volunteers and then asking them to report the nature of effects produced. Replicability and objectivity are increased by using standardized questionnaires such as those described above (e.g., "liking" scales, ARCI). In practice, several procedural variations are used to further enhance the reliability and validity of the results. The dose of the drug is varied to assess the nature of the dose-effect relationships; for all dependence-producing drugs, ratings of dose strength or the percentage of accurate drug identifications is directly related to the dose given. Subjects with histories of use of a variety of drugs can be asked to report which, if any, of those drugs the test drug feels like; such testing is useful to determine the extent to which the test drug produces any effects on mood and feeling that resemble those of previously studied drugs. Subjects with histories of use of a variety of drugs and who report "liking" the effects of a range of drugs can be used to help assess the dependence potential of the test drug by rating how desirable they find it to be.

Incorporation of several of these methods can add considerably to the strength of conclusions which can be drawn. For example, morphine-like opioids, pentobarbital-like barbiturates, amphetamine-like stimulants (including cocaine), alcohol, and nicotine all produce rapidly onsetting and offsetting discriminative effects; the magnitude and duration of these effects are directly related to dose; all elevate scores on the liking and MBG scales; the effects of all are directly (though complexly) related to pharmacokinetic factors such as rate of systemic absorption; all produce discriminative effects that correspond to certain physiological changes; all produce effects that can be accurately identified by an observer; all are identified as known addicting drugs by subjects with a history of use of such drugs; pretreatment with antagonists may block these effects (only opioids and nicotine have been systematically studied on this dimension). Such orderly and consistent kinds of effects across drugs confirm that they are appropriately categorized together as addicting drugs.

The selectivity and sensitivity of such procedures are illustrated in Figure 1. As shown in the Figure, when persons with multiple drug dependence histories were given drugs under double-blind conditions, they rated placebo (unconnected data point on each graph) and the nonaddicting zomepirac at a minimal level of "liking" (Jasinski, Johnson, Henningfield 1984). As a direct function of dose, however, the known addicting drugs were rated with greater liking scores. As also illustrated in Figure 1, nicotine produced comparable dose-related increases in drug liking scores as did amphetamine, morphine, and pentobarbital. Studies with human volunteers have also

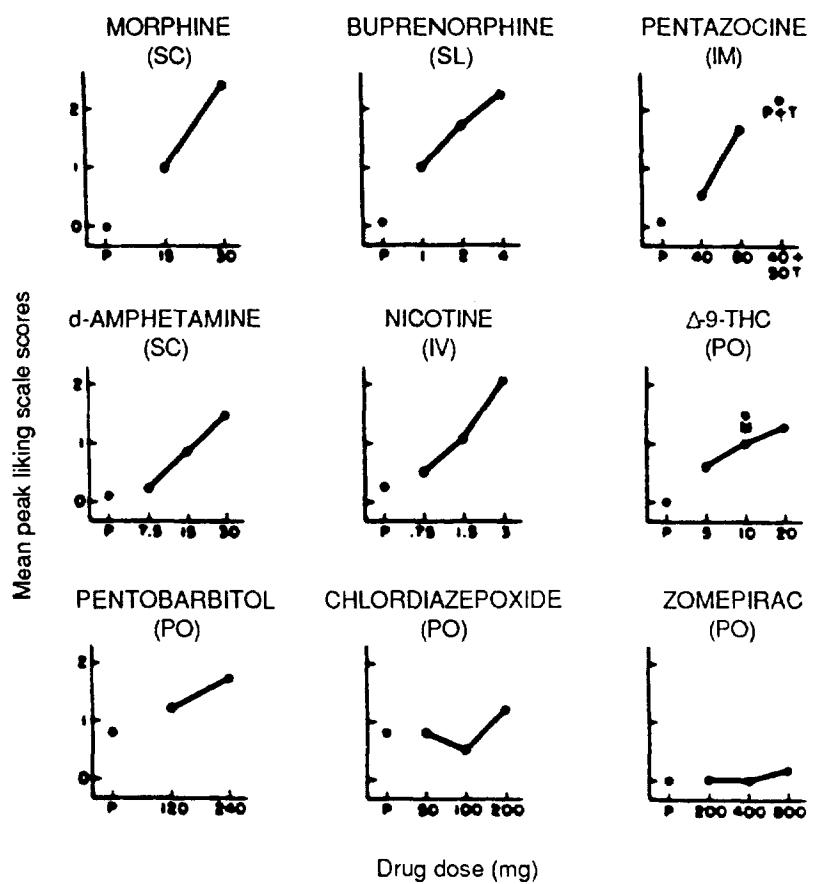


FIGURE 1.—Liking scale scores of the single-dose questionnaire

NOTE: Sample size ranges from 6 (pentobarbital and chlordiazepoxide) to 13 (d-amphetamine). The high dose of each drug (except zomepirac) produced significant ($p < 0.05$) increases in scores above placebo. Data are peak response, which occurred from approximately 1 minute (nicotine) to 5 hours (buprenorphine). Morphine and zomepirac data are from the same group of subjects as pentobarbital and chlordiazepoxide data. The P + T point on the pentazocine graph is the score given to 40 mg pentazocine combined with 50 mg tripeleannamine. The M point on the Delta-9-THC graph is the score, from the same subjects, obtained after smoking a marijuana cigarette containing 10 mg (1 percent by weight) Delta-9-THC.

SOURCE: Jasinski, Johnson, Henningfield (1984).

shown that most of the known addicting drugs (including nicotine) produced certain changes in mood and feeling that resemble those produced by morphine or benzedrine enough to significantly elevate the MBG scale scores (Griffiths, Bigelow, Henningfield 1980; Henningfield, Johnson, Jasinski 1987).

The validity of self-reported drug effects as objective indices of dependence potential has been tested using similar rating scales by observers who are blind to the condition. On the basis of their observations of subject behavior, observers report similar dose-related increases in scores on the strength of the drug effect and/or the level of drug liking for alcohol (Henningfield, Chait, Griffiths 1983), pentobarbital (Martin, Thompson, Fraser 1974; Henningfield, Chait, Griffiths 1983), morphine and heroin (Martin and Fraser 1961), amphetamine (Jasinski and Nutt 1972; Jasinski, Nutt, Griffith 1974), and a variety of other dependence-producing drugs (Jasinski 1977). A similar correspondence between subject and observer ratings was obtained when subjects were given either i.v. nicotine injections or research cigarettes which varied in nicotine dose (Henningfield, Miyasato, Jasinski 1985).

Effects on mood and feeling also correspond to a variety of physiological effects. Some of these physiological changes vary by drug class. For example, pupil diameter increases appear to correspond to early nicotine-induced subjective effects and to amphetamine and cocaine administration (Henningfield et al. 1983; Jaffe 1985), whereas pupil diameter decreases when morphine is given (Jasinski 1977). Other physiological effects show a greater degree of similarity across drug classes. For example, studies of ethanol administration in human subjects revealed that paroxysmal bursts of electroencephalogram (EEG) alpha activity paralleled subjective reports of euphoria during the ascending limb of the plasma ethanol curve (Lukas et al. 1986b,c), which also paralleled increases in plasma adrenocorticotropic hormone (ACTH) levels (Lukas and Mendelson, in press). Similar effects were observed following marijuana smoking (Lukas et al. 1985, 1986a) and acute i.v. nicotine administration (Lukas and Jasinski 1983). In turn, similar changes in EEG alpha activity have been shown to correspond with subject-reported pleasurable states which can occur in the absence of drug administration (Lindsley 1952; Brown 1970; Wallace 1970; Matejcek 1982).

Drug Discrimination Testing

Drug discrimination testing in animals is assumed to provide information analogous to the above-described procedures for assessing the effects of drugs on mood and feeling in humans (Goldberg, Spealman, Shannon 1981). Drug discrimination testing can provide two general kinds of information. First, the ability of dependence-producing drugs to control behavior by serving as positive reinforcers or punishers is associated with whether they produce interoceptive effects which are discriminated (or "felt"). Second, drugs can be compared with each other to determine the degree to which they are identified as similar or different. The methods used for drug

discrimination testing in animals were not systematized and widely utilized until the late 1960s and early 1970s (Overton 1971; Overton and Batta 1977; Schuster and Balster 1977; Järbe and Swedberg 1982).

Extension of animal discrimination study results to humans is limited by species differences and by other unique human factors that may contribute to the dependence potential of a drug. Nonetheless, animal studies are an important advance because they permit relatively inexpensive and rapid testing of a broad range of compounds and allow evaluations to be made without the possible confounding social and cultural factors. Animal studies also provide a means of gauging the biological generality of the drug discrimination data (e.g., to determine if unusual genetic characteristics are necessary for certain drug effects).

Methods and Results

These procedures and variations have been described in greater detail elsewhere (Overton and Batta 1977; Colpaert 1986; Rosecrans and Meltzer 1981). In brief, the basic method is to train animals to emit one response when given one drug and to emit another response when given either no drug (i.e., placebo) or a different drug. The animals are usually trained with either food reinforcement or the withholding of electrical shock for "correct" responses. When the animals have been trained to a level of 80 or 90 percent correct responses, they are said to be discriminating drug from placebo. Then they are ready for the testing of different doses of the training drug or different drugs. This testing is often accomplished without the use of food or shock contingencies, so that it can be determined which response the animal will make when given the test drug.

A check on the validity is to give lower doses of the training drug; the lower the dose, the less the animal should respond on the drug lever and the more on the placebo lever. A similar effect is obtained when an antagonist is given before testing with the training drug; as the dose of the antagonist is increased, the ability of the animal to discriminate the training drug decreases and the animal emits more no-drug responses. These effects have been demonstrated with both the opioids and nicotine (Overton 1971; Colpaert 1986; Rosecrans and Meltzer 1981; Chapter III); i.e., decreasing the dose of the opioid or nicotine or pretreating with an opioid or nicotine antagonist can produce decreased drug lever responding.

The specificity of the stimulus produced by a drug can also be evaluated by testing drugs. The degree to which the animals make the "drug" responses or "mistake" the test drug for the training drug is termed "generalization" and indicates the level of similarity of effects between the drugs (Colpaert and Rosecrans 1978). Morphine analogs, amphetamine analogs, pentobarbital analogs, and nicotine

analogs produce substantial amounts of generalization to morphine, amphetamine, pentobarbital, and nicotine, respectively. The fact that there is less generalization across drug classes is an index of the specificity of the drug stimulus. The cross-drug classifications which have resulted from animal discrimination studies are generally consistent with human data (Goldberg, Spealman, Shannon 1981). For instance, if an animal has been trained to press one lever when given amphetamine and another lever when given pentobarbital, it tends to press the amphetamine lever more often than the pentobarbital lever following a nicotine injection (Schecter 1981). This finding is consistent with that obtained in a study in which human volunteers frequently identified nicotine injections as amphetamine or cocaine at higher nicotine dose levels but not at the lower levels and only rarely identified the nicotine injections as sedatives (Henningfield, Miyasato, Jasinski 1985).

A more recent development is the extention of the systematic drug discrimination procedures to use with human subjects. Similar methods are used, and initial findings with drugs such as nicotine and amphetamine are comparable to the results from animal studies (Kallman et al. 1982; Chait, Uhlenhuth, Johanson 1984). Specifically human volunteers can readily learn to differentially respond to the presence or absence of these drugs, and the effects are dose related.

Drug Self-Administration

When given the mechanical means to do so, animals self-administer addicting drugs (including nicotine) much like humans; that is, drugs that function as rewards or reinforcers for humans also tend to function as reinforcers for animals. The conceptualization of dependence-producing drugs as reinforcers provided the framework for a highly predictive test strategy, the self-administration study, whereby animals or humans are given the opportunity to take drugs under laboratory conditions (Thompson and Schuster 1968). This research strategy permitted scientific analysis of the single common link across all forms of drug dependence, namely that the addictive behavior (for whatever reason) is motivated or controlled by the drug's reinforcing (rewarding) properties (Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985). Stimuli that can maintain and strengthen behavior leading to their presentation are termed "positive reinforcers" regardless of their hypothesized mechanism of action (e.g., alleviation of discomfort or production of pleasure) (Skinner 1953; Thompson and Schuster 1968). The reinforcing power or efficacy of a drug can be enhanced by a variety of conditions (e.g., deprivation of the drug which the organism had been repeatedly given, pain, food deprivation, social approval contingent on drug taking, and perceived useful effects) (Thompson and Schuster 1968; Thompson and Johanson 1981). Following

repeated exposure to a drug, a biologically mediated "drive" state can be established that did not preexist as do the drives for food, water, or sex.

The potential of a drug to serve as a reinforcer can be directly assessed and quantified in laboratory studies of drug self-administration. Essentially, a human or animal subject is given access to the drug; then his or her propensity to take the drug (i.e., to "self-administer" the drug) can be measured. The self-administration test provides the opportunity to rigorously study the main distinguishing feature of drug dependence, that is, drug-seeking behavior. As is the case in drug discrimination testing, animal data help to determine the generality of the biological basis of the addictive process for a given drug; for example, such data help to reveal if the process is unique to humans because of social, genetic, or other factors. If the drug is taken under a variety of prescribed conditions (summarized later in this Section), then it is said to be functioning as a "reinforcer" or "reward."

The validity and generality of self-administration test results were demonstrated by the observations that (1) there was a remarkable degree of consistency between patterns of drug self-administration among laboratory animals and observations concerning human drug dependence (Jasinski 1977; Griffiths, Bigelow, Henningfield 1980), (2) drugs that serve as reinforcers in self-administration studies also tend to be "liked" when given to humans, and (3) there was a high correlation among drugs which produced morphine-like euphoriant effects and those which were self-administered by animals (Griffiths and Balster 1979; Griffiths, Bigelow, Henningfield 1980; see related data in Schuster, Fischman, Johanson 1981).

Initiation of Drug Self-Administration

As discussed earlier in this Chapter, drugs cannot produce dependence without initial exposure to them. Initiation of drug use in humans is often mediated by social and other environmental sources of pressure. To determine if a drug will reinforce behavior in animals similarly requires some means of providing exposure to the drug. Strategies for establishing drug taking in animals are analogous in key respects to how humans may become dependent upon drugs. Four general categories of methods are most commonly used. The methods are not mutually exclusive and are sometimes used in combination.

The first method of establishing drug self-administration in animals is to provide initial doses ("priming" or "free sampling") and then to gradually increase the dose ("graduation"). For instance, i.v. drug infusions may be given to animals on a chronic basis while the animals are also given the opportunities to take the drug. This provides an opportunity to determine if simple exposure to the drug

is sufficient to result in drug seeking. A minor variation is to gradually increase the dose of each injection over time. This general procedure has been used to establish i.v. self-administration of *d*-amphetamine, morphine, alcohol, pentobarbital, cocaine, nicotine, and many other drugs (Deneau and Inoki 1967; Deneau, Yanagita, Seevers 1969; Yanagita 1977; Woods, Ikomi, Winger 1971; Brady and Lukas 1984; Griffiths, Bigelow, Henningfield 1980; Meisch 1987; Henningfield and Goldberg 1983a).

A second method of establishing drug self-administration is to substitute a new drug for one which was already serving as a reinforcer. Humans do this as a function of drug availability; they sometimes learn to like drugs which had not been taken previously and may even come to prefer the new drug. Using this method with animals provides a means of exposure to a new drug and may be useful in comparing one drug with another. In animal studies, cocaine is the most commonly used starter drug, because in animals (as in humans) cocaine seems to be a source of reinforcement and/or pleasure under an extremely broad range of conditions compared with most other drugs. Variations on this procedure have been used to evaluate the likelihood of self-administration of a wide range of drugs including amphetamine, barbiturates, alcohol, opioids, and nicotine (Griffiths et al. 1976, 1981; Woods 1980; Deneau 1977; Yanagita 1977; Griffiths, Bigelow, Henningfield 1980; Brady and Lukas 1984; Meisch 1987; Chapter III).

A third method is to induce the initial use of the test drug by prearranged environmental sources of "pressure" or "motivation." Induction of drug taking can be accomplished with very explicit contingencies. For example, presentation of food or withholding of electric shock can be made contingent on drug consumption (Mello and Mendelson 1971a,b). However, such direct contingencies often result in minimal response output (i.e., drug consumption) to obtain the positive reinforcer or to avoid the electric shock, and drug self-administration may not persist after the contingencies are removed (Mello 1973). For example, even when physical dependence on alcohol had developed in rhesus monkeys, the animals often rejected the drug when self-administration was not required to meet the contingency (Mello and Mendelson 1971a). Thus, these procedures have not been extensively used to generate animal models of human drug taking (Griffiths, Bigelow, Henningfield 1980).

The fourth procedure for establishing drug self-administration seems somewhat more analogous to how drug dependence may sometimes develop in humans outside the laboratory, and has been widely used to study drug self-administration in the laboratory; this method is termed the "adjunctive behavior" or "schedule-induced behavior" strategy (Falk 1983). The method involves a less direct means of inducing drug intake; in fact, the drug does not need to be

taken to obtain the reinforcer or to avoid the punisher. Rather, the animal is simply given the opportunity to take the drug; at the same time, the experimenter arranges conditions that are highly likely to engage the animal in cycles of work and breaking from work. For example, the animal may have to press a lever to obtain food. The result is that when the animal is unable to work on the food schedule (e.g., during the brief "timeouts" or "waiting" periods), the animal tends to take the drug. Eventually, the drug itself might come to function as a reinforcer in its own right, even in the absence of the environmental pressures that first led to its use. The dose level of the drug is then increased gradually over time. Variations on this procedure have been used to establish self-administration of alcohol (Falk, Samson, Winger 1972; Freed, Carpenter, Hymowitz 1970; Meisch 1975), pentobarbital (Meisch, Kliner, Henningfield 1981), nicotine (Singer, Wallace, Hall 1982), and a variety of other drugs (Brady and Lukas 1984; Meisch and Carroll 1981; Meisch 1987). Although many environmental conditions are present outside the laboratory that appear to function as do adjunctive schedules in the establishment of human drug dependence (e.g., boredom in occupational settings), there have been few experimental studies of adjunctive drug taking by humans (Falk 1983). One such study by Cherek (1982) showed that volunteers took more puffs per cigarette when they were given monetary reinforcers at regular intervals: the volunteers had to press a button to obtain the reinforcer, but their behavior did not decrease the time they had to wait for each reinforcer to become available.

Evaluation of Reinforcing Effects

Conclusive demonstration that the effects of the drug itself were the cause of the drug-seeking behavior is equivalent to showing that the drug itself is functioning as a positive reinforcer. The basic procedures were developed in animal studies (Pickens and Thompson 1968; Deneau 1977) and have been reviewed in detail elsewhere (Johanson and Schuster 1981; Balster and Harris 1982; Fischman and Schuster 1978; Yanagita 1980; Brady and Lukas 1984).

The most fundamental procedure is to verify that drug self-administration occurs under conditions in which it is "optional" or "voluntary"; that is, explicit contingencies for drug taking (e.g., to obtain food, to avoid shock, or to obtain preferred liquid) are not required. It is also necessary to ensure that the drug taking is not simply maintained by the characteristics of the vehicle (e.g., water or a flavored solution into which alcohol is placed, or the tobacco smoke in which nicotine is delivered to smokers).

If the drug is serving as a reinforcing stimulus, it should be capable of maintaining controlled behavior. For example, a complex chain of drug seeking (i.e., "procurement") might be required to

obtain the drug. An extension of this principle is to gradually increase the amount of work (i.e., the "cost") that must be expended to achieve drug delivery to determine how much the subject works ("pays") for a given drug or drug dose. For example, the ratio of lever press responses per drug injection is gradually increased in the "Progressive Ratio" procedure to determine the maximum ratio ("breaking point") that will be sustained (Yanagita 1977; Griffiths, Brady, Snell 1978a).

If the drug is serving as a reinforcer, then stimuli associated with drug administration should also come to serve as reinforcers ("conditioned reinforcers"). Of all dependence-producing drugs, the importance of this factor may be most pronounced with regard to nicotine because the various effects of nicotine may be associated with tobacco smoke and other stimuli hundreds of times each day over the course of many years of smoking. A fundamental observation is that even neutral-appearing stimuli can function as reinforcers in their own right when they are associated ("paired") with previously established reinforcers such as food, water, sex, or drugs (Skinner 1953; Thompson and Schuster 1968). For example, the taste and smell of alcohol are initially highly aversive to animals (Mello 1973), but in one study, the smell of alcohol was established as a conditioned positive reinforcer for animals: the smell of alcohol was enough to reinstate drug-seeking behavior even when the alcohol was not physically available (Meisch 1977). Seemingly arbitrary stimuli such as lights and tones can come to serve as reinforcers after association with i.v. self-administered drugs including cocaine-like stimulants, opioids, barbiturates, and nicotine (Goldberg 1970; Goldberg, Kelleher, Morse 1975; Griffiths, Bigelow, Henningfield 1980; Goldberg et al. 1983).

The basic methods described above are also used in human drug self-administration studies, although with various procedural adaptations which have been described in detail elsewhere (Nathan, O'Brien, Lowenstein 1971; Cohen, Liebson, Faillace 1971; Mello, McNamee, Mendelson 1968; Mello 1972; Meyer and Mirin 1979; Bigelow, Griffiths, Liebson 1975; Henningfield, Lukas, Bigelow 1986). As in the animal drug self-administration studies, the human volunteers must emit a measurable response that may lead to drug ingestion: for example, riding an exercise bicycle (Griffiths, Bigelow, Liebson 1979; Jones and Prada 1975) or pressing a button on a portable work station (Mello and Mendelson 1978). Such work requirements then become established as part of the chain of drug-seeking behavior. They have an advantage over non-laboratory drug-seeking behavior in that the amount of work can be carefully measured. Such data provide quantitative estimates of the time and/or work expended for drugs (see examples in the following studies and reviews: Johanson and Uhlenhuth 1978; Bigelow,

Griffiths, Liebson 1975; Mello and Mendelson 1978; Fischman and Schuster 1982; Henningfield and Goldberg 1983b; Jasinski, Johnson, Henningfield 1984).

Results from Drug Self-Administration Studies

Most categories of drugs which have been found to cause widespread drug dependence in the nonlaboratory setting have been tested with animals and humans in laboratory settings. Results of these studies have been reviewed in detail elsewhere (Griffiths, Bigelow, Henningfield 1980; Brady and Lukas 1984; Henningfield, Lukas, Bigelow 1986). Several categories of drugs have been found to be self-administered by humans and animals in the laboratory settings, to meet criteria as positive reinforcers, and to exhibit orderly relations as a function of drug dose, drug pretreatment, and other factors known to affect the intake of dependence-producing drugs. These include alcohol, morphine, pentobarbital, amphetamine, cocaine, and nicotine in the forms of cigarettes and i.v. injection.

Self-administration studies with animals are much more extensive and have also been reviewed in detail elsewhere (Johanson and Schuster 1981; Balster and Harris 1982; Fischman and Schuster 1978; Yanagita 1980; Brady and Lukas 1984; Young and Herling 1986). In brief, drug self-administration studies in animals in the 1960s showed that a range of drugs including opioids, amphetamines, barbiturates, certain organic solvents, alcohol, cocaine, and nicotine were self-administered (Weeks 1962; Thompson and Schuster 1964; Deneau, Yanagita, Seevers 1969; Deneau and Inoki 1967). All of these drugs were found to maintain powerful chains of drug-seeking behavior, even when insufficient drug was taken to produce a clinically significant degree of physical dependence (Goldberg, Morse, Goldberg 1976). Drugs that did not serve as reinforcers in these studies included caffeine, lysergic acid diethylamide (LSD), and the major tranquilizer chlorpromazine.

The speed of drug delivery can affect its reinforcing efficacy (Kato, Wakasa, Yanagita 1987). Thus, the inhaled form of cocaine ("crack") is considered more reinforcing and dependence producing than other forms of cocaine delivery, with oral cocaine apparently among the least reinforcing of the commonly used routes of delivery (see also US DHHS 1987). Analogously, nicotine taken by the slow release oral preparation (nicotine polacrilex gum) appears to be much less reinforcing than nicotine taken by quicker release oral preparations (e.g., chewing tobacco) or cigarette smoke (Chapters IV and VII).

Research findings have continued to extend the early observations (Deneau, Yanagita, Seevers 1969) that the results with animals were remarkably consistent with observations regarding human drug dependence. For example, initial exposure of humans to drugs such

as opioids and stimulants led to addictive patterns of use, whereas chlorpromazine rarely did, and LSD infrequently did (Jasinski 1977; Griffiths et al. 1980). Earlier studies had suggested that alcohol, caffeine, and nicotine were not reinforcers in animals (Mello 1973; Russell 1979; Griffiths et al. 1986). However, by the early 1970s for alcohol (Meisch and Thompson 1971; Meisch 1977, 1982) and 1981 for nicotine (Goldberg, Spealman, Goldberg 1981), it had been confirmed that these drugs could also serve as effective reinforcers for nonhumans. The relatively little research done to assess the dependence potential of caffeine has not as conclusively demonstrated that it serves as a reinforcer in animals (Griffiths and Woodson 1988b).

Drug Dose as a Determinant of Drug Intake

Drug dose per administration is a major factor that affects self-administration of dependence-producing drugs. The resultant dose-response relationships are orderly, and the data have been reviewed extensively (Griffiths, Bigelow, Henningfield 1980; Johanson and Schuster 1981; Young and Herling 1986). In brief, the relationship between the dose size available and the number of doses taken is often referred to as an inverted U-shaped function because of the shape of a graph that results when the number of injections (y-axis) is plotted as a function of dose (x-axis) across a wide range of doses to which a subject is given access.

Over the range of doses which appear to be functioning as effective reinforcers, changes in dose are accompanied by compensatory changes in number taken such that total drug intake is somewhat stabilized. It appears that a determinant of such compensatory changes in drug self-administration is the apparent upper and lower "boundaries" or "thresholds" for aversive effects that might occur when either too much drug is obtained or when insufficient drug is obtained to prevent withdrawal responses (Kozlowski and Herman 1984). It should be noted, however, that in most studies, compensatory changes in drug intake as dose level is changed are almost never perfect and are frequently quite crude (Griffiths, Bigelow, Henningfield 1980). (See Yokel and Pickens 1974 for an example of a study in which drug intake was unusually stable across a range of amphetamine doses.) Thus, the usual observation related to drug dose is that as dose is increased, the rate of drug taking decreases somewhat but more total drug is obtained. This relationship is observed in studies of i.v. nicotine in animals (Goldberg et al. 1983) and humans (Henningfield, Miyasato, Jasinski 1983) and when tobacco smoke dose is manipulated in humans (Chapter IV).

A misinterpretation of dose-response relationships by tobacco researchers, largely in the 1970s, led to the controversy that marked the so-called "titration studies" of tobacco intake. Specifically, it was

assumed that if a drug was serving as a reinforcer, then compensation for changes in dose level should have been more effective than they appeared to be. Hence, some questioned whether nicotine was serving as a reinforcer because dose-response relationships in nicotine studies appeared very crude (Russell 1979). The question that arose was not whether cigarette smokers showed compensatory changes in responses to changes in dose level; they did. In fact, the nicotine dose-response relationship has probably been better studied and established, over a wider range of conditions and techniques of study, than have dose-response relationships with any other class of drugs which are self-administered by humans (Gritz 1980; Griffiths, Bigelow, Henningfield 1980; Henningfield 1984). The question was, rather, why compensatory changes in cigarette smoke intake often appear to be inadequate to maintain stable levels of nicotine intake. There are two main problems in interpreting these data, however. The first is that in the vast majority of human cigarette smoking studies, attempts to manipulate the dose delivered were not well controlled and the measures used to assess the possible effects of intended dose manipulations were not necessarily sensitive to compensatory changes (see Chapter IV and Henningfield 1984b). The second problem is that there is simply no basis for determining what degree of compensation *should* occur, because the degree of compensation observed in animal studies varies widely by drug and test condition, and because there are relatively few human data involving drugs other than nicotine to which such a comparison might be made (Griffiths, Bigelow, Henningfield 1980; Henningfield, Lukas, Bigelow 1986).

Cost of the Drug as a Determinant of Intake

Cost of the drug is a determinant of intake in both laboratory and non-laboratory settings. Evaluation of this phenomenon is objectively carried out in the laboratory in which the amount of work required to obtain the drug can be varied. From an economic perspective, this is similar to varying the price of the commodity which is available for purchase. Such manipulations with both humans and animals have shown that cost (e.g., amount of work required) affects drug intake: usually, the lower the cost, the greater the intake. In some studies manipulations of both cost and drug dose have been carried out (e.g., Moreton et al. 1977; Lemaire and Meisch 1985). These studies show that when the dose of the drug is reduced, drug-seeking behavior may increase at first and thereby maintain fairly stable intake, but if dose continues to decrease (or cost continues to increase), the behavior will not be maintained (Lemaire and Meisch 1985). Early studies with cocaine, for example, showed that if access to cocaine was limited, either by time or work ("cost") requirements, cocaine self-administration could be maintained indef-

initely without serious apparent adverse effects (Pickens and Thompson 1968). However, if access to cocaine was nearly unlimited and the cost requirement low, monkeys might self-administer toxic dose levels (Deneau, Yanagita, Seevers 1969).

Use of tobacco in humans and intravenous nicotine self-administration by animals appear to be similarly affected by manipulations of cost as is use of other dependence-producing drugs. Specifically, as the amount of work required to obtain nicotine injections in animals is increased, the number of injections is decreased (Goldberg and Henningfield, 1988). Analogously, human cigarette smokers and other drug users can also be motivated with both positive and negative cost incentives (Bigelow et al. 1981; McCaul et al. 1984; Stitzer et al. 1982, 1986; Stitzer and Bigelow 1985). These laboratory findings with animals and humans correspond to the effects of changes in the price of cigarettes on cigarette sales (Lewit, Coate, Grossman 1981; Lewit and Coate 1982; Warner 1986a). Such relationships are also observed with other dependence-producing drugs including opioids, sedatives, alcohol, and amphetamines (Griffiths, Bigelow, Henningfield 1980; Yanagita 1977).

Place Conditioning Studies

Ingestion of dependence-producing drugs can lead to both positive and negative associations with the setting in which the drug effects were experienced. Whether the effects of a particular drug are positive or negative depends on the dose that was given and other factors that are discussed in this Section.

A scientific methodology for studying such phenomena is the "place-conditioning" or "place-preference-aversion" procedure (Bozarth 1987a). This procedure provides an indirect means of assessing the potential of a drug to establish drug seeking in the absence of any explicit contingencies on the behavior. These procedures determine if exposure to a drug in a given environmental setting enhances the preference of the animal for that setting. Conversely, the procedure can be used to determine if exposure to a drug in a specific environmental setting establishes an aversion of the animal to that setting.

Because of their convenient size and the general validity of their use as models for behavioral dependence potential testing, rats most commonly are used as subjects in place-conditioning studies. The general experimental procedure is to place the animal in one environment (e.g., one chamber of a multiple-chamber test apparatus) when a drug is given and in another environment (e.g., distinct in color, shape, or odor) when a placebo is given. Then, the animal is given access to both environments (i.e., placed in a connecting passage or placed in one chamber or the other) to determine which environment (chamber) it prefers (van der Kooy 1987; Bozarth

1987a), and, conversely, which environment it avoids. Studies have shown that conditioned preferences can be established for morphine (Bardo and Neisewander 1986), cocaine (Spyraki, Fibiger, Phillips 1982), alcohol (Stewart and Grupp 1985), and nicotine (Fudala, Teoh, Iwamoto 1985; Fudala and Iwamoto 1987; Chapter IV).

The relevance of place conditioning as a factor that increases the control of nicotine over behavior in human cigarette smokers may exceed that of other dependence-producing drugs. This possibility follows from the fact that the cigarette smoker has the ability to readily produce a critical environmental cue associated with smoking (cigarette smoke itself). Therefore, it should be possible for the smoker to "enhance" the reinforcing efficacy of a range of environments (Iwamoto et al. 1987); the highly discriminating sight, smell, and taste stimuli produced by tobacco smoke may effectively permit the smoker to establish a "preferred environment." This could contribute to the dependence potential of nicotine. The observation is also consistent with the finding that removal of the tobacco smoke-associated stimuli is accompanied by decreased pleasure and/or smoking (Gritz 1977; Goldfarb et al. 1976; Rose et al. 1987). As early as 1899 it was observed, for example, "that the pleasure derived from a pipe or cigar is abolished for many persons if the smoke is not seen, as when it is smoked in the dark" (Cushny 1899).

Constraints on Dependence Potential Testing

The main constraint on procedures used to evaluate the dependence potential of drugs is that they may fail to identify drugs which only lead to dependence under unusual or uniquely human circumstances. For example, LSD does not serve as an effective reinforcer for animals, and although its effects may be liked by humans under certain conditions, it also produce feelings of fear, paranoia, and other adverse effects (Griffiths, Bigelow, Henningfield 1980; Haertzen 1966, 1974). Caffeine provides an example of another kind of drug which is sometimes used in the face of adverse effects, even though the overwhelming majority of users do not use it in ways that are considered to be of significant adverse health effect (Gilbert 1976; Greden 1981). The anticholinergic drug atropine is another that is representative of a class of drugs that occasionally are used in nontherapeutic settings but do not appear to possess a marked dependence potential when objectively tested (Penetar and Henningfield 1986).

The wide range of factors that may result in occasional harmful use of some substances (e.g., caffeine) or which may contribute to the use of dependence-producing substances such as nicotine (Chapters IV and VI) is not routinely explored in current laboratory dependence potential tests. Thus, these drug dependence potential testing procedures appear more likely to underestimate than to overesti-

mate the pharmacologic potential of a drug to cause dependence outside of the laboratory. Furthermore, as discussed by Katz and Goldberg (1988), because a variety of drug and nondrug factors determine the actual prevalence of drug dependence outside of the laboratory, dependence potential data are most reliable when drawing qualitative conclusions. For example, such data are used to determine whether a drug is dependence producing, or whether it is more sedative- or stimulant-like.

Dependence Potential Testing: Tolerance and Withdrawal

In addition to taking control over behavior by virtue of reinforcing and other behavior modifying effects, many addicting drugs can also produce a physiological change termed physical dependence. Once physically dependent, the person may experience an even greater loss of control over use of a particular drug because abstinence from the drug may be accompanied by discomfort and heightened urges to take the drug (withdrawal syndrome).

Technically, physical dependence refers to physiological and behavioral alterations that become increasingly manifest after repeated exposure to a pharmacologic agent. As noted earlier, the primary indication of physical dependence is the observation of drug-abstinence-associated withdrawal signs and symptoms, although tolerance is a frequent concomitant (Kalant 1978; Cochin 1970; Kalant, LeBlanc, Gibbins 1971; Eddy 1973; Clouet and Iwatsubo 1975; Yanagita 1977). This phenomenon is also referred to as "neuroadaptation" or "physiological" dependence (WHO 1981; Woolverton and Schuster 1983). It should be noted that use of the term "physical" imports no greater degree of objectivity to phenomena associated with physical dependence than to the phenomenon of compulsive drug seeking: both physical dependence and drug seeking involve physiologically mediated drug receptor interactions that vary with the dose, kinetics, and type of drug. Furthermore, both of these kinds of drug-associated phenomena involve behavioral and physiological effects. For example, conventional measures of physical dependence include responses that are often considered behavioral (e.g., urge to use a drug, sleep time, food intake).

Research on opioid dependence in the 1940s focused largely on the physical dependence that developed when opioids were given to humans or certain animals (Martin and Isbell 1978). In particular, characterizing the level of tolerance that was acquired when morphine was repeatedly given, as well as the behavioral and physiological sequelae of abrupt termination of such administration, was a major contribution to the development of objective methods for testing dependence-producing drugs in general. Observations emerging from such research in the 1940s led to strategies that are still accepted as the definitive means to measure what may be termed the

TABLE 5.—Observations pertaining to the evaluation of physical dependence potential, derived from studies of morphine-like drugs

1. Repeated drug administration leads to diminished responsiveness (i.e., tolerance) that is more or less complete, depending upon the response measured. Responsiveness might be at least partially overcome by increasing the dose. The degree of tolerance that develops is generally directly related to the overall dosing level, but varies widely across various possible measures.
2. The establishment of tolerance to one opioid is shared among many opium-derived and related chemicals; the principle of "cross-tolerance" emerged as one means to further classify a dependence-producing chemical.
3. Abrupt termination of use leads to behavioral and physiological responses that often tend to be opposite of responses produced by acute drug administration. When these opposite responses actually exceed normal baseline levels (e.g., opioid-induced constipation may be replaced by diarrhea for a few days), they are termed "rebound" responses; hence the frequent labeling of withdrawal as "rebound syndrome." Together, these responses are termed "the withdrawal syndrome."
4. Severity of the withdrawal syndrome is related to the duration and dose levels of preabstinence exposure to the drug.
5. During withdrawal, readministration of the chronically given opioid can reverse the signs and symptoms of the syndrome.
6. A range of opioids can substitute for the one to which an organism was chronically exposed, thereby maintaining the level of physical dependence and preventing the onset of a withdrawal reaction. These same drugs can be used to reverse the syndrome of withdrawal precipitated by removal of the chronically given opioid. This observation provided the rational basis for the systematic development of "substitution" or "replacement" therapy for drug dependence.

NOTE: Details of the original experiments, and subsequent research upon which these observations follow, have been reviewed (Martin and Isbell 1978; Martin 1977; Sharp 1984; see also Deneau 1977).

"physical dependence potential" of a chemical (Jasinski 1977). Specifically, these tests could be used to evaluate the likelihood that (1) repeated use of a drug would lead to tolerance (physiological adaptation) such that effects of repeated use would diminish and (2) abrupt abstinence would be accompanied by a syndrome of behavioral and physiological disruption (withdrawal syndrome). Table 5 summarizes the prominent observations that emerged from these early studies (Martin and Isbell 1978; Martin 1977). These observations provide the conceptual framework within which physical dependence is assessed (Thompson and Unna 1977).

Tolerance

As noted earlier, repeated ingestion of most dependence-producing drugs leads to diminished effects unless larger doses of the drug are taken: this phenomenon is termed tolerance. One reason that tolerance is an important factor in drug dependence is that it may contribute to the escalation of drug self-administration that occurs over time. This relationship is often misinterpreted, however. Specifically, it is sometimes stated that tolerance results in a

continuous escalation of drug dose; however, lethal or aversive dose levels prevent indefinite escalation.

Procedures for assessing tolerance development rely heavily on procedures developed for assessing the direct effects of drugs (Kalant, LeBlanc, Gibbins 1971; Abood 1984). Because psychoactive drugs exert effects on numerous physiological systems and behavioral responses, almost any of a wide range of response measures can serve in studies. Perhaps the most fundamental strategy of tolerance assessment is to repeatedly present a given drug dose while measuring the subsequent responses to drug administration. When the response diminishes across drug presentations, tolerance to that response is said to have occurred. Among the most frequent measures of tolerance which have been used to assess psychoactive drugs are discrimination of drug administration, analgesia, heart rate, nausea, sedation, EEG activity, and performance on a behavioral task. Some measures (e.g., sedation from barbiturates) are more specific to certain drug classes, whereas others (e.g., pleasurable and dysphoric effects) are useful across a wider range of psychoactive drugs. A variation on the foregoing procedure is to increase the drug dose after responses have diminished to determine if the original response level can be partially or completely restored.

Cross-Tolerance

Cross-tolerance is demonstrated when pretreatment with one drug or formulation type produces tolerance to another drug or formulation type (Wenger 1983; Yanura and Suzuki 1977; Martin and Fraser 1961). For example, a person who is maintained on an adequate dose level of methadone will experience relatively little effect if he or she injects his or her usual dose of heroin (Kreek 1979). Similarly, persons given nicotine polacrilex gum may experience attenuated effects from cigarettes, including reduced satisfaction from smoking (Nemeth-Coslett et al. 1987).

Mechanisms of Tolerance

Several mechanisms of tolerance can be differentiated (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Sharp 1984; WHO 1981). For instance, if a drug impairs the ability to perform a task that produces some form of reinforcement (e.g., humans working for money or animals pressing a lever for food), the performance may return to predrug exposure levels after repeated drug exposure over time. In this example, at least four distinct mechanisms of tolerance may have been operational; they are not mutually exclusive and may co-occur (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Sharp 1984; WHO 1981; Eikelboom and Stewart 1979; Siegel 1975, 1976).

(1) The rate at which the drug was eliminated from the blood by metabolism (detoxification) or excretion (in urine, feces, sweat, or expired air) may have increased. This is frequently termed "dispositional" or "metabolic" tolerance. A general method used to assess dispositional tolerance is to measure the rate of decline in plasma drug levels after varying amounts of drug exposure.

(2) The response at the cellular level might have decreased as the drug receptor physiologically adapted to the drug or as the number of receptors was altered (thereby functioning as though the systemic dose had been reduced). This is frequently termed "functional" or "pharmacodynamic" tolerance. One method used to assess functional tolerance is to hold the plasma drug levels constant while measuring the response after varying amounts of drug exposure.

(3) The learning and motivational aspects of a behavioral situation may have resulted in compensatory behaviors that reduced the magnitude of the performance effects. This is frequently termed "behavioral" tolerance, "drug sophistication," or "behavioral adaptation." Behavioral tolerance can be assessed by presenting the drug at such long intervals so as to minimize the possible development of functional or metabolic tolerance (e.g., Stitzer, Morrison, Domino 1970), or by using a variety of other controlled procedures (Krasnegor 1978b).

(4) Another behavioral mechanism that can lead to the development of tolerance results from the classical or Pavlovian conditioning process that may occur where a drug is given. Pavlov (1927) found that drug administration could produce an unconditioned response that could subsequently occur as a conditioned response to an associated environmental stimulus. However, sometimes the conditioned response is opposite that of the drug response (Siegel 1975); when a drug-opposite response has been established, this conditioning mechanism may reduce the strength of the response to the drug itself (Goudie and Demellweek 1986).

The kinds of tolerance described above are sometimes categorized together as "acquired" tolerance, which emphasizes the fact that they have developed in an organism as a function of drug exposure (WHO 1981). Tolerance development can be affected by the unit drug dose, total daily dose, route of administration, prevailing environmental stimuli, and exposure dynamics (exposure dynamics refers to whether exposure to a drug is relatively continuous (Way, Loh, Shen 1969) or via multiple, discrete doses (Lukas, Moreton, Khazan 1982)) (see also, Dewey 1984; Adler and Geller 1984; O'Brien 1975; Bläsig et al. 1973; Okamoto, Rao, Walewski 1986). Acquired tolerance has been demonstrated to occur with opioids and with most nonopioid dependence-producing drugs, including nicotine (Martin 1977; Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Domino 1973; Chapter III). In fact, classic techniques of measuring tolerance

evolved in a series of studies involving nicotine by Langley, Dixon, and others near the end of the 19th century (Langley 1905; Dixon and Lee 1912); these researchers found that tolerance to nicotine was rapid and could be partially overcome by increasing the dose.

Constitutional Tolerance

Historically, although less commonly in recent years, tolerance has been used to differentiate individuals or populations with regard to their "preexisting" or "constitutional" level of drug responsiveness (Shuster 1984). This phenomenon has been designated "initial" tolerance by a subcommittee of the WHO (WHO 1981) and is also often referred to as "drug sensitivity" or "innate drug responsiveness." The mechanisms may be similar to those described above; for example, individuals may be born with differing numbers of receptors for a particular drug or with different abilities to detoxify a drug on the basis of enzymatic capacity of their liver. Analogously, for reasons that are not related to drug exposure, certain populations or individuals may be more effective in general at behaviorally compensating for impediments to learning or performance. Genetic, dietary, and early (including prenatal) developments are possible sources of such variation that are under study (Abood 1984).

Whereas a fairly wide range of variation among such preexisting levels of drug sensitivity has not been shown to affect the course of development of drug dependence, extreme or qualitative differences may have some impact. Such differences are sometimes held to alter the vulnerability of various individuals or populations to the development of drug addiction. One apparent example of such an effect is the markedly higher percentage of Oriental persons who, compared with most other populations in the United States, show an aversive reaction to alcohol ("flushing" response). This reaction results from slower metabolism of the alcohol metabolite, acetylaldehyde, in Orientals compared with many other ethnic groupings (Nagoshi et al. 1987). However, cultural factors also appear to strongly influence rates of alcohol use in Orientals so that even persons who show the flushing response may develop alcoholism (Sue 1987; Johnson et al. 1987).

Differences in constitutional levels of tolerance among individuals have been observed for all dependence-producing drugs, including nicotine (Chapter II). However, the importance of such individual and/or population differences remains unclear. In fact, a remarkable feature of opioids, sedatives (including alcohol), and stimulants (including nicotine) is the degree to which use has become entrenched in nearly any culture into which they have been introduced (Austin 1979). Similarly, initial exposure to opioids, sedatives, alcohol, cocaine-like stimulants, and nicotine has been shown for each to lead to drug-seeking behavior in a wide range of animal

species including primates, dogs, and rodents (Deneau 1977; Yanagita 1977; Woods, Ikomi, Winger 1971; Brady and Lukas 1984; Griffiths, Bigelow, Henningfield 1980; Meisch 1987; Meisch and Carroll 1981).

Withdrawal Syndromes

As discussed earlier, documentation of a drug withdrawal syndrome is the primary line of evidence used to decide whether a particular drug can cause physical dependence. The methods used to properly conduct such tests and provide definitive results are complex. This Section provides a summary of how such tests are conducted and some of the main findings from tests of drugs such as morphine, pentobarbital, and nicotine.

Measurement of drug withdrawal phenomena entails recording physiological, subjective, and behavioral responses that occur when drug administration is terminated, as well as those that occur following drug administration. If the organism has developed a sufficient degree of tolerance, such that levels of drug which formerly disrupted physiological and behavioral functioning have become necessary for relatively normal functioning, then the organism is said to be physically dependent. Such drug abstinence-induced disruption of functioning is termed a drug "withdrawal" or "abstinence" reaction or syndrome. The behavioral and physiological responses include some that are opposite those produced by drug administration. For instance, opioid-induced pupillary constriction, alcohol-induced muscle relaxation, and nicotine-induced tachycardia may be replaced by pupillary dilation, convulsive muscle activity, and bradycardia, respectively. Each drug withdrawal syndrome is unique to a particular drug class and animal species and also varies somewhat within individuals of a given species which are tested with the same drug. Both frequency and magnitude of withdrawal responses are typically measured.

In human studies, the range of measures available to assess withdrawal reactions is considerable. They may be designated by three categories: autonomic (e.g., blood pressure, pulse, core temperature, respiratory rate, pupillary diameter, diarrhea), somatomotor (e.g., nociception, neuromuscular reflexes, auditory and visual evoked potentials), and behavioral (e.g., irritability, sleep/awake cycle, hunger, urge to take the drug, i.e., "craving"). Himmelsbach and Andrews (1943) incorporated these distinctions into a weighted-point system used for rating the severity of these signs and symptoms of withdrawal (Fraser and Isbell 1960; Jasinski 1977). Refinements in the scaling of opioid withdrawal responses have continued (e.g., ARCI, weak opiate withdrawal scale) (Haertzen 1966; Bradley et al. 1987; Handelsman et al. 1987).

Opioid withdrawal phenomena remain the most rigorously studied and well characterized among the dependence-producing drugs. In part, this is because of the ready observability of many of the signs (e.g., dilated pupils, sweating, diarrhea). Other drugs for which withdrawal reactions are now known or suspected to occur in humans (e.g., amphetamine, cocaine, marijuana, phencyclidine) have been much less thoroughly studied than the opioids and sedatives (Mendelson and Mello 1984; Jones and Benowitz 1976). Studies with these drugs are also hindered by the fact that there are fewer readily observable signs of withdrawal, placing a greater burden on sophisticated technology (e.g., EEG and neurohormonal assessment) and procedures (e.g., performance assessment).

Two basic methods are used to measure withdrawal reactions. After a period of chronic drug administration, behavioral and physiological responses are measured following either abrupt drug abstinence ("spontaneous withdrawal") or the administration of a drug antagonist ("precipitated withdrawal") (Thompson and Unna 1977; Martin 1977).

Spontaneous Withdrawal Syndromes

Experimental studies of spontaneous withdrawal reactions include two procedures for obtaining subjects which have been chronically exposed to the drug. One procedure, termed the "direct addiction" procedure, is to administer the drug to the subject at gradually increasing dose levels, then to stabilize the dose for a predetermined time interval. Drug administration is then abruptly discontinued, and withdrawal measures are taken. This method has been used to study withdrawal from opioids, barbiturates, benzodiazepines, stimulants, ethanol, PCP, and gaseous anesthetics in a number of animal species and humans (Brady and Lukas 1984). A variation on this procedure is to abruptly withdraw subjects from a drug which they had been chronically receiving in the nonlaboratory environment. In human subjects, withdrawal reactions following cessation of use of opioids, alcohol, nicotine, sedatives, and other drugs have been studied using this procedure (Brady and Lukas 1984; Chapter IV).

A second procedure, termed the "substitution procedure," involves maintaining subjects at a given dose level of a standard or baseline drug; periodically, doses of the standard drug are replaced with either a placebo or a test drug to determine if there are signs of withdrawal that occur before the next dose of the baseline drug (Fraser 1957). This procedure provides information analogous to that obtained from studies of cross-tolerance; namely, it permits determination of whether cross-dependence exists. If the test drug prevents the expected onset of a withdrawal syndrome that should have accompanied abstinence from the maintenance drug, then it is possible that the two drugs produce similar kinds of physical

dependence. Because it is possible to suppress certain withdrawal responses by using unrelated drugs (e.g., clonidine can suppress certain aspects of morphine and nicotine (Jasinski, Johnson, Henningfield 1984)), a variety of control procedures are necessary to identify the mechanism by which the replacement drug suppressed the withdrawal responses (Martin 1977; Deneau and Weiss 1968; Yanagita and Takahashi 1973; Okamoto, Rosenberg, Boisse 1975; Jones, Prada, Martin 1976; Yanaura and Suzuki 1977).

In human subjects, both the direct addiction and substitution strategies were used to evaluate withdrawal reactions from opioids, barbiturates, and alcohol at the Addiction Research Center in the 1940s and 1950s (Himmelsbach 1941; Himmelsbach and Andrews 1943; Isbell et al. 1950, 1955). However, since those classic studies, most dependence potential studies in humans have been conducted with subjects who had been using the drug in a nonexperimental setting prior to the study. The effects of abstinence from chronic administration of opioids, barbiturates, benzodiazepines, caffeine, and nicotine have been studied using these variations of spontaneous withdrawal assessment (Benzer and Cushman 1980; Charney et al. 1981; Jaffe et al. 1983; Griffiths and Woodson 1988a; Greden 1981; Hatsukami, Hughes, Pickens 1985; Chapter IV). A disadvantage of such approaches is that it is not always possible to stabilize the subjects at a known dose level, which results in considerable cross-subject variation. The consequence of such dose-related variability is that it can raise the threshold for the detection of significant effects. This source of variability probably contributed to some of the earlier inconsistent findings regarding the nature and severity of withdrawal reactions from tobacco (see further discussions in Murray and Lawrence 1984). Early in the 20th century, analogous seemingly inconsistent data led to debates about the existence of an alcohol withdrawal syndrome (Isbell et al. 1955).

Precipitated Withdrawal Syndromes

Precipitated withdrawal responses may occur when a drug antagonist abruptly displaces the dependence-producing drug from its binding sites on receptors. The viability of this approach depends on the availability of a specific receptor antagonist which does not have other actions that would preclude assessment of a withdrawal syndrome. The antagonist is often given parenterally (e.g., intravenously or intramuscularly) to maximize its rate of onset and hence the likelihood of precipitating a withdrawal reaction.

Because of the availability of specific opioid antagonists, precipitation of withdrawal phenomena associated with abstinence from the morphine-like drugs has been most thoroughly studied using this strategy (Martin et al. 1987). The studies have shown that the process that leads to physical dependence begins with the first dose

of morphine (Higgins et al. 1987; Bickel et al. 1988) although such low levels of physical dependence are not generally considered sufficient for the clinical diagnosis of physical dependence. Analogous studies have been conducted using the antagonists of the benzodiazepines (e.g., diazepam (Lukas and Griffiths 1982, 1984)) and are one element in the conclusive demonstration that these drugs do produce physical dependence (WHO 1981, 1987). With regard to tobacco or other forms of nicotine delivery, no such comparable studies have been conducted, although, as discussed in Chapter IV, preliminary and related data suggest the theoretical possibility that nicotinic antagonists may be used to precipitate nicotine withdrawal responses (Pickworth, Herning, Henningfield, 1988).

Variability in Withdrawal Syndromes

There are multiple determinants of the course and magnitude of the withdrawal reaction from a drug. Factors which have been studied in the laboratory are similar to those which affect the development of tolerance described earlier. These include the total daily dose of the drug that was given, specific drug type, the duration of exposure, the schedule of termination, genetic constitution, gender, and the prevailing environmental stimuli (Suzuki et al. 1987; Suzuki et al. 1983; O'Brien et al. 1978; Suzuki et al. 1985; Yanagita and Takahashi 1973; Yanagita 1973). In general, the magnitude of the withdrawal reaction is directly correlated with the dose level given, the duration of exposure, and the rapidity with which drug levels at the receptor sites decrease. Conversely, lower dose levels, shorter times of exposure, and gradual dose reduction (as opposed to abrupt abstinence) can attenuate the withdrawal syndrome (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Jaffe 1985; Okamoto 1984).

Because withdrawal signs and symptoms vary among individuals using the same drug, the syndrome may not be apparent when a small number of individuals are studied. Lack of general understanding of such factors probably contributed to the fact that the nature of morphine withdrawal phenomena in humans was not rigorously documented until the studies by Himmelsbach and his coworkers in the 1940s (Himmelsbach 1941; Himmelsbach and Andrews 1943). Similarly, withdrawal responses from chronic alcohol administration were not conclusively characterized and demonstrated until the pioneering studies by Isbell and his coworkers in the 1950s (Isbell et al. 1955). Research involving comparable strategies of assessment of physical dependence on cocaine, amphetamine, marijuana, PCP, and nicotine, only began in the late 1970s. In the absence of such data, these drugs were sometimes held to be nonaddicting (e.g., President's Advisory Commission 1963). Nonetheless, for several of such drugs it had long been recognized that some drug withdrawal phenomena did occur (Jaffe 1970, 1976, 1980, 1985) and that such phenomena were

of clinical significance in the treatment of persons who were attempting to abstain from them (Jaffe 1970, 1976, 1980, 1985; Zweben 1986). For example, even prior to the rigorous studies of tobacco withdrawal phenomena in the early 1980s (Chapter IV), the Tobacco Withdrawal Syndrome had been recognized by the American Psychiatric Association (APA) as an Organic Mental Disorder in its Diagnostic and Statistical Manual (DSM) of Mental Disorders (APA 1980) on the basis of the extensive clinical observations and other sources of information prior to the 1980s (Chapter IV). The specificity of tobacco withdrawal to nicotine itself was acknowledged in the revised DSM III (APA 1987).

Cravings or Urges

Among the most frequently discussed aspects of drug dependence is the recurrent and often persistent urge to use drugs in drug-dependent persons. The urge or desire to use a drug is widely termed "craving." However, how craving is defined and how craving-related data are interpreted comprise one of the most problematic areas in drug dependence research. For example, the term craving has been used in such a variety of ways that its use may actually impede accurate communication (Kozlowski and Wilkinson 1987; Henningfield 1987). In the present Report, where possible, the term "craving" has been replaced by more descriptive terms and phrases such as "strength of an urge to use a drug" wherever the original meaning of the referent material is not changed.

Whereas the urge to use a drug is a correlate of drug abstinence, it is not an invariant one. For example, although urges to take drugs reliably increase during early abstinence from morphine- and pentobarbital-like (short-acting sedatives-hypnotics) drugs, they are not a necessary concomitant of withdrawal reactions from other opioids (e.g., cyclazocine) (Martin et al. 1965; Jasinski 1978), and alcoholics often "voluntarily" abstain and undergo withdrawal even when alcohol is available (Mello 1968; Mendelson and Mello 1966). Moreover, such urges are also evoked by stimuli associated with drugs and even by administration of the drug itself (O'Brien, Ehrman, Ternes 1986; Childress et al., in press). Thus, urges to use drugs also occur (often at high levels) when there is little other evidence that physical dependence is present (e.g., many years after drug abstinence) or when drug intake is sufficient so that no other withdrawal signs or symptoms are present.

Because drug abstinence is only one of many factors that can evoke the urge to use a drug and because such urges are not necessarily alleviated by suppressing physiological withdrawal signs, conclusions based upon such data must be carefully considered and appropriately qualified. For instance, although methadone can block withdrawal responses (at adequate dose levels), it does not reliably

diminish urges to use other opioids or opioid self-administration (Jones and Prada 1975; Grabowski, Stitzer, Henningfield 1984; Henningfield and Brown 1987). It would not be appropriate to conclude that methadone did not effectively block withdrawal reactions from morphine-like drugs simply because it did not eliminate such urges, because by other measures, methadone is effective at blocking opioid withdrawal (Kreek 1979; Jaffe 1985; Jasinski and Henningfield 1988). Analogously, as reviewed in Chapters IV and VII, most tobacco withdrawal responses are effectively suppressed by nicotine replacement even though urges to use cigarettes are not reliably diminished (see also Henningfield and Jasinski 1988).

Constraints on Physical Dependence Potential Testing

There are both practical and conceptual constraints on physical dependence potential testing. The practical constraints have been discussed above and are related to the multiple sources of variability in the intensity of withdrawal responses, which can result in failure to detect withdrawal or in unreliable data.

The main conceptual constraint is that physical dependence is neither a necessary nor sufficient condition to establish or maintain drug-seeking behavior. For instance, drug-seeking and drug-taking behaviors can persist at small doses of cocaine or morphine which produce no significant degree of physical dependence in animals (Schuster and Woods 1967; Deneau, Yanagita, Seevers 1969; Johanson, Balster, Bonese 1976; Jones and Prada 1977; Bozarth and Wise 1981) or in human subjects (Zinberg 1979). Conversely, animals in the laboratory and humans in hospitals can be made physically dependent on drugs such as opioids and barbiturates and yet never display controlled or addictive drug-seeking behavior (WHO 1981; Bell 1971). Similarly, compounds such as propranolol, cyclazocine, and nitrites have clear physical dependence potentials in that tolerance develops after repeated dosing and an abstinence syndrome appears upon cessation, yet drug-seeking or drug-taking behavior does not reliably occur (Myers and Austin 1929; Crandall et al. 1931; Rector, Seldon, Copenhaver 1955; Jasinski 1976; Jaffe 1985).

Another constraint is the difficulty in determining whether abstinence-associated symptomatology is specific to an individual or to an underlying medical disorder that became evident upon removal of the drug (Woody, McLellan, O'Brien 1984; Zweben 1986; Kosten, Rounsville, Kleber 1986; Stitzer and Gross 1988). For instance, an opioid might alleviate depression in a person with primary affective disorder. In general, as will be described below (see Chapter IV), withdrawal responses may be distinguished from abstinence-associated symptomatology by their relative consistency among indi-

viduals, by their transient nature, and by the direct relationship between their magnitude and the level of preabstinence drug intake.

Finally, although the magnitude of the withdrawal syndrome is a widely used index for assessing the degree of physical dependence, it should be noted that this single measure is not always sufficient. For instance, several studies have demonstrated that spontaneous withdrawal from chronic levo-alpha-acetylmethadol (LAAM) or buprenorphine administration failed to result in pronounced signs of withdrawal (Jasinski, Pevnick, Griffith 1978; Young, Steinfels, Khazan 1979). Such observations could lead to the false conclusion that LAAM and buprenorphine do not produce significant degrees of physical dependence, when in fact a variety of other lines of evidence confirm that they do. For example, administration of an opioid antagonist such as naloxone precipitates a marked and intense withdrawal syndrome in LAAM-maintained animals (Young, Steinfels, Khazan 1979). Analogously, Dum, Bläsig, and Herz (1981) performed a substitution type of experiment demonstrating that chronic administration of buprenorphine also results in physical dependence. The explanation for the misleadingly weak spontaneous withdrawal phenomena for LAAM and buprenorphine seems to be the slow elimination of these drugs from the plasma, which permits the body to adjust more gradually to drug abstinence. The long elimination half-life of LAAM's active metabolites (Kaiko and Inturrisi 1975) and buprenorphine's unique affinity for the opiate receptor and long elimination half-life (Cowan, Lewis, MacFarlane 1977) contribute to the lack of observed withdrawal signs after chronic exposure is terminated. A similar example exists for the long-acting benzodiazepine, diazepam. A delayed and relatively mild withdrawal syndrome appears after spontaneous withdrawal, but administration of the benzodiazepine receptor antagonist, Ro15-1788 (flumazenil), precipitates an immediate, intense abstinence syndrome (Lukas and Griffiths 1982, 1984). Analogous results are produced when the daily dose level of shorter acting drugs is gradually decreased.

A practical application of the finding that the magnitude of withdrawal reactions tends to be inversely related to rate of drug elimination is the gradual elimination of drugs from individuals who are suspected of being highly physically dependent. Such gradual elimination reduces the magnitude of the withdrawal syndrome. This is the basis of the gradual withdrawal of morphine, alcohol, or nicotine after a period of chronic intake at high dose levels (Jaffe 1985). Although gradual dose reduction of opioids and nicotine reduces the magnitude of most aspects of the withdrawal syndrome, it is not clear that such an approach improves overall treatment outcome compared with much more rapid drug cessation (i.e., "cold turkey") (Jasinski and Henningfield 1988; Chapter VII).

Therapeutic or Useful Effects of Dependence-Producing Drugs

With many dependence-producing drugs, the same biological properties that are important in their dependence-producing properties may also lend them to therapeutic application. In fact, most classes of drugs which cause dependence, including opioids, sedatives, alcohol, cocaine-like drugs, and nicotine, have been used as medicinals to treat specific medical disorders and human discomforts. Descriptions of the approved and general uses are available in the American Hospital Formulary Service (1988), the Physician's Desk Reference (Medical Economics Company 1988), the United States Pharmacopeia (Griffiths, Fleeger, Miller 1986), and Goodman and Gilman's Pharmacological Basis of Therapeutics (Gilman et al. 1985) (see also Table 6).

Although each of the drugs listed in Table 6 has a range of potential or actual therapeutic applications, past and current uses are often related to their effects on mood, feeling, and behavior. For instance, the stimulants may be used to modulate arousal level, the opioids to alleviate pain, the sedatives to alleviate anxiety; the drugs are sometimes systematically used to treat the dependence which may have previously developed on them or on another drug in the same class. Nicotine is no exception to these observations. Historically, tobacco was used to treat a range of disease states, although usually without evidence of efficacy (Corti 1931; Austin 1979). Nicotine in the polacrilex gum form is a drug approved by the FDA for treatment of nicotine dependence (see Chapter VII).

The therapeutic effects of dependence-producing drugs not only illustrate an important point of commonality among these drugs, but these effects also may be important in the drug dependence process itself. Such potential drug actions can be important in the initiation, maintenance, and relapse to drug dependence. The dependence process may have been precipitated by the therapeutic use (medically approved or self-initiated) of a drug. The dependence process may be exacerbated by the real or perceived benefit of the drug to the individual as such actions strengthen the reinforcing power of the drug. The therapeutic actions of a drug may be associated with relapse to drug use after many years of abstinence. These aspects of dependence potential as they pertain to nicotine are discussed in Chapter VI.

Adverse and Toxic Drug Effects

As discussed earlier, adverse drug effects are important clinical features of drug dependence. These effects may be used as factors in objective determinations of the overall liability associated with a drug (Yanagita 1987; Griffiths et al. 1985). For instance, chronic administration of sedatives or alcohol can produce intoxication and

TABLE 6.—Effects that may be produced by addicting drugs

Attribute	Nicotine *	Cocaine
Discriminable interoceptive (subjective) effects	+ Henningfield and Goldberg (1985), Morrison and Stephenson (1969)	+ Fischman et al. (1976)
Produce dose-related increases in self-reported "liking" scores	+ Henningfield, Miyasato, Jasinski (1985)	+ Henningfield et al. (1987)
Produce elevated response on MBG (euphoria) scale of ARC inventory	+ Henningfield, Miyasato, Jasinski (1985)	+ Fischman et al. (1976)
Positive reinforcer in animal drug self-administration studies	+ Goldberg, Spealman, Goldberg (1981), Deneau and Inoki (1967), Ando and Yanagita (1981), Henningfield and Goldberg (1983a)	+ Pickens and Thompson (1968), Deneau et al. (1969)
Positive reinforcer in human drug self-administration studies	+ Henningfield, Miyasato, Jasinski (1983)	+ Fischman and Schuster (1982)

Morphine-like	Alcohol
+ Terry and Pellens (1970)	+ Carpenter (1962)
+ Martin and Fraser (1961)	+? Mello (1968)
+ Haertzen et al. (1963)	+ Henningfield et al. (1984), Stitzer et al. (1981)
+ Headlee, Coppock, Nichols (1955), Thompson and Schuster (1964)	+ Deneau et al. (1969), Winger and Woods (1973)
+ Jones and Prada (1975)	+ Bigelow et al. (1975), de Wit et al. (1987)

TABLE 6.—Continued

Attribute	Nicotine *	Cocaine	Morphine-like	Alcohol
Place conditioning	+ Fudala, Teoh, Iwamoto (1985)	+ Spyraki, Fibiger, Phillips (1982)	+ Bardo and Neisewander (1986)	+- Stewart and Grupp (1985)
Physical dependence develops such that withdrawal accompanies abrupt abstinence	+ Hatsukami et al. (1984), Hughes and Hatsukami (1986)	+? Carroll and Lac (1987), Jones (1984)	+ Light and Torrance (1929a), Kolb and Himmelsbach (1938), Himmelsbach (1941)	+- Isbell et al. (1955)
Tolerance develops	+ Langley (1905), Domino (1978), Marks, Burch, Collins (1983), Jones, Farrell, Herning (1978)	+ Tatum and Seevers (1929), Downs and Eddy (1932), Woolverton and Schuster (1978), Wood and Emmett-Oglesby (1987)	+ Light and Torrance (1929b)	+- Goldberg (1943)
Therapeutic use in treatment of medical disorder	+ ¹ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+ ² AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+ ³ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+ ⁴ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others

TABLE 6.—Continued

Attribute	Caffeine	Marijuana
Discriminable interoceptive (subjective) effects	+ Gilbert (1976), Griffiths and Woodson (1988b)	+ Siler et al. (1933)
Produce dose-related increases in self-reported "liking" scores	+- Griffiths, Bigelow, Liebson et al. (1986), Chait and Griffiths (1983)†, Griffiths and Woodson (1988b)	+
Produce elevated response on MBG (euphoria) scale of ARC inventory	+- Chait and Griffiths (1983)	- Higgins and Stitzer (1986), Cone et al. (1986)
Positive reinforcer in animal drug self-administration studies	-? Deneau et al. (1969), Griffiths and Woodson (1988b)	- Harris et al. (1974)
Positive reinforcer in human drug self-administration studies	+? Griffiths, Bigelow, Liebson et al. (1986), Griffiths, Bigelow, Liebson (1986), Griffiths and Woodson (1988b)	+
Place conditioning	?	?

Lysergic acid diethylamide

Chlorpromazine

Hofmann (1975)

+

?

Griffiths, Bigelow, Liebson
(1979)

?

Haertzen et al. (1963)

Stitzer et al. (1981)

Hoffmeister and Wuttke
(1976)

Hoffmeister and Goldberg
(1973), Hoffmeister (1975),
Deneau et al. (1969)

?

Griffiths, Bigelow, Liebson
(1979)

?

?

TABLE 6.—Continued

Attribute	Caffeine	Marijuana	Lysergic acid diethylamide	Chlorpromazine
Physical dependence develops such that withdrawal accompanies abrupt abstinence	+ ¹ Griffiths, Bigelow, Liebson (1986), Dreisbach and Pfeiffer (1943), Horst et al (1934), Griffiths and Woodson (1988a)	+? ² Jones and Benowitz (1976), Mendelson et al. (1984), Ford and McMillan (1972), Beardsley et al. (1986)	- ³ Isbell et al. (1956)	- ⁴ Baldessarini (1980)
Tolerance develops	+ ⁵ Carney (1982), Eddy and Downs (1928), Griffiths and Woodson (1988a)	+ ⁶ McMillan et al. (1970), Weil et al. (1968), Babor et al. (1975), Cone et al. (1986)	+ ⁷ Isbell et al. (1956)	? ⁸ Baldessarini (1980)
Therapeutic use in treatment of medical disorder	+ ⁵ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+ ⁶ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	? ⁷ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+ ⁸ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others

NOTE: + indicates that drug administration produces the effect; - indicates that drug administration does not produce the effect; ? indicates that available scientific data are inadequate to draw a conclusion.

¹ Further discussion can be found in other chapters of this Report.

² As aid to stop cigarette smoking and to treat nicotine dependence.

³ As topical anesthetic (rarely used) for ear, nose, eye, and throat.

⁴(1) As strong analgesics for treatment of both acute and chronic pain, (2) treatment for myocardial infarction (analgesia, anxiolysis, and reduced left ventricular work-load and myocardial oxygen requirements), (3) for obstetric analgesia, (4) as preanesthetic medication to smooth induction, (5) treatment for pulmonary edema, (6) as cough suppressant, (7) treatment for severe diarrhea.

⁵(1) As antiseptic agent on skin, (2) intravenously to treat premature labor (uterine relaxant), (3) treatment of spasticity by local or intrathecal injection of dilute absolute alcohol solution, (4) as vehicle in dermatologic preparations (antiseptic action, astringent action, cooling effect), (5) treatment of alcohol withdrawal.

⁶(1) Incorporated with over-the-counter analgesics (e.g., aspirin) to treat ordinary headache and relieve inflammatory pain (scant scientific data to substantiate), (2) in combination with ergot alkaloid to treat migraine headache, (3) in combination with sympathomimetic agents possessing anorectic properties in weight-loss medications, (4) as stimulant, (5) treatment (clinical trials) for preterm infant apnea of undetermined origin, (6) rarely for treatment of central nervous system depressant poisoning.

⁷(1) As antiemetic for cancer chemotherapy patient, (2) glaucoma treatment.

TABLE 6.—Continued

⁷ None at present, but several proposed in past: (1) as psychotherapy aid, (2) as adjunct in alcohol and opioid addiction treatment, (3) as adjunct in terminal cancer patient therapy to reduce opioid analgesic need and induce tranquility.

⁸ (1) Management of psychotic disorder manifestations, (2) treatment for nausea and vomiting, (3) relief of presurgery restlessness and apprehension, (4) treatment for acute, intermittent porphyria, (5) as adjunct in tetanus treatment, (6) to control mania manifestations in manic-depressive illness, (7) treatment for intractable hiccups, (8) treatment of children's severe behavioral disorders characterized by combativeness or hyperexcitable behavior, (9) possible second-line treatment for nonpsychotic anxiety.

[†]"Liking" was not measured, but the increased scores on a tension and anxiety scale suggested dose-related "disliking."

severe mood swings (Mello and Mendelson 1970; Mello 1968; Isbell et al. 1950); erratic supplies of opioids may be associated with sociopathic drug-seeking and withdrawal-related mood effects (Jasinski 1977); erratic supply of tobacco can also result in disruption of ongoing activities in an effort to obtain tobacco or as a consequence of withdrawal symptoms.

Consideration of multiple factors such as the dependence potential of a drug, the extent of its actual use, and the degree to which it produces adverse effects can be used to assess the overall liability associated with the use of a drug (i.e., "abuse liability") (Brady and Lukas 1984; Griffiths et al. 1985; Yanagita 1987). For example, caffeine produces only minimal (if any) disruptive behavioral or physiological effects and is not generally regarded as posing a serious public health problem even though self-administration may be widespread (e.g., caffeine in tea or coffee) (Griffiths and Woodson 1988a,b). In contrast, drugs which produce disruptive physiological and behavioral changes even when self-administered infrequently may be considered to represent a more serious health hazard (e.g., LSD). Drugs may fall anywhere on the continuum defined by these parameters, and the relative impact on health is most effectively determined by a comprehensive assessment of these interactive behavioral and physiological dimensions (Griffiths, Brady, Snell 1978b; Griffiths et al. 1985; Brady and Lukas 1984; Yanagita 1987).

Identification of Dependence-Producing Drugs

Independent of whether use of a substance has been observed to lead to addiction, it is possible to directly and objectively test a chemical to determine if it is addicting. Such tests provide data used by Federal (e.g., FDA, Drug Enforcement Administration) and International (e.g., WHO) agencies as to how to regulate chemicals. In fact, new drugs are usually evaluated and regulated ("scheduled") before they are ever made available for medical application. Such decisions rely heavily upon the known properties of addicting drugs and on the methods used to test for such properties (both described in this Chapter). Although the physicochemical structure of the drug is one determinant of the stimulus effects produced by drug administration, simply knowing the drug structure is rarely sufficient to predict the nature and magnitude of possible drug effects (Barnett, Trsic, Willette 1978); behavioral and physiological testing in animals and humans is usually necessary. When there is convergent evidence from multiple measures of dependence potential, then the drug is appropriately regarded as addicting or dependence producing. Whether humans outside the laboratory actually become addicted will depend on additional factors such as availability, price, and social acceptability of the drug (US DHHS 1987; also see discussion by Katz and Goldberg 1988).

Table 6 provides a comparison of several drugs in terms of the major measures that have been reviewed in this Chapter. As shown in the table, drugs known to produce widespread problems in a given population are characterized by positive responses with most of these measures (cocaine, morphine-like drugs, alcohol, and nicotine). Conversely, drugs not contributing to such problems have fewer positive responses on the various tests (chlorpromazine). Intermediate drugs are associated with intermediate levels of difficulty in management of use.

Comparison Among Drugs

Within a given class of drugs, it is sometimes possible to rate their relative efficacy as reinforcers by how much behavior was affected (e.g., how many lever presses would occur or how much money would be paid) (Griffiths et al. 1981; Yanagita 1987). For instance, the slower onset/offsetting formulations of opioids, barbiturates, stimulants, and nicotine appear to have a lower dependence potential than the quicker onset and offsetting formulations (Jaffe 1985).

The practical generality of such comparisons, however, is limited because many other factors determine the overall level of dependence that might develop, the extent of social and/or personal damage, and the resulting level of social concern (Yanagita 1987; Katz and Goldberg 1988). For example, the increasing availability and decreasing relative price of cocaine in recent years are major factors contributing to increased levels of use and resultant social damage (US DHHS 1987). Analogously, the widespread ready availability and the relatively low cost of tobacco products and alcohol have probably contributed to the much higher rates of addiction and mortality associated with alcohol and tobacco than with drugs such as cocaine, even though cocaine may appear to be a more effective reinforcer in animals. Social or cultural factors may also contribute to the spread and levels of drug use. For example, sensational press reporting may have contributed to the popularization of barbiturates in the 1960s (Brecher 1972), and the mass marketing and advertising of tobacco products is likely to have contributed to the use of these products, especially among women and especially in the case of smokeless tobacco products (Ernster 1985, 1986; Warner 1986b; Davis 1987; Tye, Warner, Glantz 1987).

Four examples of drugs associated with striking changes in the prevalence of use among various populations as well as associated morbidity are: alcohol, for which use and associated diseases decreased during the Prohibition years early in the 20th century; lysergic acid diethylamide (LSD), for which use and associated hospitalizations were elevated during the 1960s; cocaine, for which use and associated hospitalizations increased during the 1970s

(Crowley and Rhine 1985; Levine 1984; Nahas and Frick 1981; Dupont, Goldstein, Brown 1979; Holder 1987; US DHHS 1987); tobacco, in which consumption of smokeless tobacco products increased among youth in 1970s and cigarette consumption increased sharply among women in the 1950s and 1960s (US DHHS 1981, 1986; Appendix A). As discussed in the aforementioned references, the changes in use of these drugs were not due to changes in the pharmacologic actions of the drug or sudden changes in genetic constitution of the populations, but rather to changes in factors such as availability, cost, social acceptability, regulatory controls, marketing efforts, and general perceptions about the risks associated with use.

Finally, various other factors contribute to the level of social concern and may be only indirectly related or unrelated to the pharmacologic properties of the drug itself. For instance, the observations on transmission of AIDS by way of shared needles among i.v. drug users and on cancer caused by tobacco smoke carcinogens have greatly increased the liability of use attributed to these drugs in recent years.

Environmental Determinants of Drug Dependence Including Behavioral Conditioning

A common feature of use of all dependence-producing drugs is that the positive (satisfaction symptoms) and negative (e.g., withdrawal symptoms) effects may become conditioned responses to associated environmental stimuli. The implications of this are important for understanding the chronic and self-sustaining nature of drug dependencies. Such conditioning is a powerful behavioral mechanism by which the drug comes to control an increasing amount of the behavior of the drug user (Thompson and Schuster 1968; Goldberg 1976a).

Some of the important environmental determinants of drug dependence are discussed elsewhere in this Chapter in the context of drug self-administration studies. These factors include: (1) the behavioral or economic cost of the drug itself or of taking the drug, (2) direct pressure to take the drug by making other reinforcers contingent upon drug taking, and (3) the other ongoing activities of the person (e.g., demanding work schedule) that tend to enhance drug taking. The focus of the present Section is on environmental stimuli that may contribute to drug dependence by evoking urges to use drugs, and by eliciting bodily responses that mimic the usual effects of either drug taking or drug withdrawal reactions.

Drug Taking as a Learned Behavior

The interface between a drug and its effects is the behavior of obtaining and ingesting the drug. Such behavior is learned behavior, and as discussed earlier in this Chapter, many of the factors that modulate this behavior are similar to those which modulate other learned behaviors including eating, exercise, and occupational skills (Thompson and Schuster, 1968). Technically, drug taking is "operant behavior" and includes "respondent" or "classically conditioned" components. The basic governing principle of operant behavior is that it occurs in the context of certain stimuli and is either strengthened or weakened by the nature of the consequence (a positive reinforcer strengthens the response and a punisher weakens the response) (Skinner 1938, 1953). Thus, for example, a friend might offer a drug (antecedent stimulus); the drug is ingested (operant behavior or response); and the effects of the drug strengthen the behavior (positive reinforcement). Respondent conditioning occurs simultaneously and further contributes to the strength of the behavior (Bouton and Swartzentruber 1986). A drug might serve as an unconditioned stimulus which elicits a relatively involuntary response (e.g., nicotine and morphine can elicit feelings of pleasure and/or nausea); when physical dependence has occurred, drug abstinence can also elicit certain responses (e.g., anxiety and urges to take the drug). Any environmental or even internal stimulus can become part of this conditioning process by repeated association with the elicited response. For example, the taste of alcohol, the smell of smoke, "thinking" about use of the substance, and the sight of cocaine- or opioid-associated paraphernalia can elicit feelings associated with either the administration or withdrawal of the drug (Childress, McLellan, O'Brien 1986a,b; Ludwig 1986; Ludwig and Stark 1974; Erben 1977; Gotestam and Melin 1983; Pickens, Bigelow, Griffiths 1973; Rickard-Figueroa and Zeichner 1985; Levine 1974).

The simultaneous operation of both operant and respondent conditioning can converge to generate and maintain powerful chains of behavior over which the individual may have little control. As shown earlier in this Chapter, highly addicting drugs are those which are very effective at reinforcing behavior and eliciting responses. Their power can be increased by factors such as drug deprivation, which may be associated with a discomforting withdrawal syndrome. In the presence of withdrawal, the person may behave in a way to relieve the discomfort of a withdrawal syndrome; in this case the withdrawal syndrome itself may be said to be functioning as a negative reinforcer. When drugs are readily available, as with tobacco for most people or opioids for physicians, these behavioral conditioning processes may be very subtle because the drug can be taken in a pattern that avoids excessive discomfort. For example, early interoceptive or subjective withdrawal cues that

are evident upon waking in the morning signal that "it is time to smoke a cigarette," and thus the smoker neither "forgets to smoke" nor experiences pronounced withdrawal symptoms.

As implied by the foregoing discussion, the strength and persistence of drug-seeking behavior are not just functions of the drug itself or of withdrawal. Rather, they are determined by many factors, such as the number of times that certain responses are associated with certain stimuli, the presence or absence of such stimuli, the subjective discomfort occurring as part of withdrawal, and the availability of the drug. The convergence of so many environmental and subjective forces can result in extremely persistent behavior that may appear disproportionate to the pleasure actually experienced when the drug is taken (e.g., the few minutes of pleasure from the postdinner cigarette or when heroin is taken after 8 to 12 hr of deprivation). In fact, the subjective pleasure itself may be very mild, and the person may describe the role of the drug as "simply maintaining feelings of normalcy or comfort" and not as "getting high" per se. The scientific basis for these observations has been actively and systematically studied since the pioneering work of Wikler and others (Wikler 1973) and has been reported and reviewed in detail elsewhere (Goudie and Demellweek 1986; O'Brien, Ehrman, Ternes 1986; Grabowski and Cherek 1983; Grabowski and O'Brien 1981; Childress, McLellan, O'Brien 1986a,b; McLellan et al. 1986; Wikler 1973; Meyer and Mirin 1979).

Drug-Associated Stimuli Modulate Drug Seeking

Stimuli associated with drug effects may come to elicit ("trigger") those same effects or sometimes opposite effects (withdrawal responses). For example, increased heart rate induced by stimulant administration may become associated with multiple environmental stimuli—the color of the tablet, the individual who provided it, and the office environment in which the drug was taken. These stimuli may act alone or in concert. One stimulus may produce a slight heart rate change; two such stimuli may produce a larger change; and the presentation of many such stimuli may have a synergistic effect. Other stimuli may counteract or facilitate these effects (Schindler, Katz, Goldberg, in press).

The response produced in relation to environmental correlates may differ qualitatively from the direct drug effect. For instance, the direct effect of a drug may be a heart rate increase, whereas the conditioned or learned response to drug-associated stimuli may be either a decrease or an increase in heart rate. Changes may be particularly evident for agents with biphasic effects such as nicotine. Whatever the direction of change in response value, the events may be of physiological and behavioral significance (for example, see Childress, McLellan, O'Brien 1986a,b; O'Brien, Ehrman, Ternes

1986; Stewart, de Wit, Eikelboom 1984; Grabowski and O'Brien 1981; Childress et al., in press). These complex conditioning processes which can function to precipitate drug taking appear to function similarly for a variety of drugs including opioids and tobacco (Ternes 1977).

Since the 1960s many researchers have shown that the role of associated stimuli is important for diverse biological reinforcers such as drugs, food, and sex. For example, Thompson and Schuster (1964) demonstrated that environmental stimuli paired with drugs could themselves come to generate drug seeking in monkeys. Schuster and Woods (1968), Davis and Smith (1976), and Carnathan, Meyer, and Cochin (1977) demonstrated that stimuli previously associated with drug taking could generate much drug-seeking behavior in animals during extinction of use when the drug is no longer available. Similar findings were obtained in a study of i.v. cocaine self-administration in which human volunteers emitted high rates of lever pressing in the presence of cocaine-associated stimuli when the drug was not available (Katz and Goldberg 1988).

Goldberg (1976b) reported that environmental stimuli associated with drug taking could help sustain substantial behavioral repertoires in monkeys often far in excess of the behavior that was maintained when just the drug was given. Similarly, Meisch found that the taste and smell of alcohol, which were normally found to be highly aversive to rats, became highly effective stimuli in their own right in the maintenance of alcohol-seeking behavior, even when alcohol was not actually available for the rats to consume (Meisch 1977). Lal and colleagues (1976) demonstrated that environmental stimuli previously associated with drug effects could, by producing drug-like responses, attenuate opiate withdrawal signs in rats. These and many other studies have shown conclusively that specific environmental stimuli associated with drug taking exert control over drug seeking, drug taking, and characteristics of the drug response itself.

Environmental conditions in many forms can contribute to sustained drug use, and specific stimulus conditions can have well-defined drug-like properties. This phenomenon, which has been well documented in laboratory settings, is recognized as being powerful in clinical pharmacology, in which "placebo" effects (conditioned responses to drug-taking conditions) may be dramatic and difficult to separate from so-called direct drug effects. Both direct drug effects and those established through learning influence physiology and behavior, thereby contributing to the strength of addictive behaviors. Recent reports suggest that conditioned effects can be attenuated for some individuals through effective treatment specifically designed to extinguish, or alter through learning, these responses (Childress, McLellan, O'Brien 1986a,b; McLellan et al. 1986).

The stimuli associated with drug effects also may generate further drug seeking and drug taking. Wikler (1973) and more recently Meyer and Mirin (1979) contributed substantially to both the conceptual framework and the data describing these complex phenomena. These investigators found that environmental stimuli which correlated with direct drug effects are pertinent to the acquisition, maintenance, and elimination of opioid taking by humans. Similar findings were observed in an intensive study of an alcoholic subject: alcohol-associated stimuli produced orderly responses including urges to drink and even drinking itself (Pickens, Bigelow, Griffiths 1973). A series of studies by Goldberg and his colleagues (Goldberg 1970; Goldberg, Kelleher, Morse 1975; Goldberg and Kelleher 1977; Goldberg, Spealman, Kelleher 1979) showed that environmental stimuli occasionally associated with morphine injections or with early withdrawal effects could lead to increased drug seeking and/or drug taking.

Conditioned Withdrawal Symptoms May Precipitate Drug Seeking

Wikler (1948) first described the discomfort of long-abstinent patients on their return to environments in which they had previously used drugs and experienced withdrawal symptoms. Subsequently, Wikler (1973), O'Brien (1975) and colleagues (O'Brien, Ehrman, Ternes 1986; O'Brien et al. 1975), and several other researchers (Siegel 1975, 1976, 1978; Eikelboom and Stewart 1979; Stewart, de Wit, Eikelboom 1984; Childress et al., in press) have made fundamental contributions to the identification of the complex interplay of factors modulating the physiological and behavioral components of abstinence. These and other studies have shown that the conditions established by abrupt withdrawal after chronic administration of a drug can serve as setting conditions which may result in further drug taking. In other words, for some individuals the onset or anticipation of abstinence symptoms may be strongly linked to reinitiation of drug self-administration. In turn, the drug effect reinforces the reinitiation of drug taking (Stewart, de Wit, Eikelboom 1984). Withdrawal symptoms and drug taking may thus become closely associated with a range of environmental stimuli. These stimuli then come to elicit abstinence symptoms and generate drug taking through a variety of powerful biobehavioral mechanisms. In fact, McNeill and colleagues (1986) have concluded that the pattern of abstinence symptoms itself may be in part determined by conditioning factors.

Environmental stimuli can lead to drug seeking by eliciting distressing conditioned withdrawal effects. Several thorough reviews on conditioning factors in drug dependence indicate that correlated behaviors and stimuli dramatically alter drug effects, withdrawal

symptoms, and other features of substance use behaviors (Goudie and Demellweek 1986; O'Brien, Ehrman, Ternes 1986; Grabowski and Cherek 1983; Grabowski and O'Brien 1981). These interacting factors have also been described in a number of prominent medical and scientific texts (Jaffe 1986, 1987), as well as in the recent Second Triennial Report to Congress from the Secretary, Department of Health and Human Services (US DHHS 1987).

One of the clearest observations of the contribution of environmental factors in tobacco withdrawal was made by Hatsukami, Hughes, and Pickens (1985). They noted that the number of withdrawal signs increased substantially when cessation occurred in the natural environment. Parallels exist in both laboratory research and naturalistic observation. Stitzer, Bigelow, and McCaul (1983) reviewed this literature and noted that individuals restrained from access to drugs for prolonged periods tend to return to use when the agents are again available; the implication is that environmental stimuli contribute to relapse. In a laboratory study, Thompson and Ostlund (1965) found that relapse to self-administration occurs rapidly for animals removed from, and then after extended periods returned to, the original environment but not for animals that undergo extinction of self-administration within that environment. In a reverse situation in humans, Robins, Davis, and Goodwin (1974) reported that individuals who experienced initial drug use in the stressful and ready-access conditions of the Vietnam war tended not to continue use on return to the United States.

Relapse to Drug Dependence

For many drug-dependent persons, achieving at least brief periods of drug abstinence is a readily achievable goal. Maintaining abstinence, or avoiding relapse, however, poses a much greater overall challenge. There is a substantial base of data for these conclusions. Treatment outcome reviews concerning opioid (Platt 1986), alcohol (Miller and Hester 1986a; Peele 1987), and tobacco (Brownell et al. 1986; Lichtenstein 1982; Schwartz 1987) dependence show that clinical interventions are often successful in producing short-term cessation of drug use but that relapse to use is a frequent posttreatment occurrence (Hunt, Barnett, Branch 1971; Brownell, Marlatt et al. 1986).

An important issue in the contemporary study of addictions is the degree to which relapse and recovery are generalizable across categories of substances (US DHHS 1986; Tims and Leukefeld 1986; Marlatt 1979; Miller and Hester 1986a,b; Schwartz 1987). This Section examines rates and predictors of relapse across drug classes with emphasis on comparisons among alcohol, opioids, and tobacco.

Implications of these observations for the prevention of relapse will be described in the next Section of this Chapter.

Definition of Relapse

In general, relapse refers to resumption of drug use following abstinence from such drug use; however, the criterion for abstinence and resumption of drug use must be specified. Principles for such specification are generally similar among drugs; however, there are drug-specific issues which complicate comparisons of data and will be discussed in this Section. Only when an individual has achieved criteria for abstinence is he or she "eligible" for the possibility of relapse. Defining abstinence over some time period as the eligibility criterion is useful because it permits distinctions to be drawn between continuous users and those who are able to "quit" drug use, however briefly. Definitions of "quit episodes" differ dramatically among published studies, leading to quite different interpretations of subsequent relapse. With regard to tobacco, a consensus conference, held under the auspices of the National Heart, Lung, and Blood Institute, recommended 24 hr of continuous abstinence from tobacco as the criterion for defining a quit episode and establishing eligibility for relapse to tobacco use (see Chapter VII). With regard to other dependence-producing drugs, patients of residential alcohol and drug abuse treatment facilities are usually deemed eligible for relapse at discharge without reference to the duration of treatment or abstinence.

Two general ways of defining relapse after a period of abstinence have appeared in the literature. Relapse has been defined as a discrete event occurring with the single use of a drug or as a process developing over time (Wesson, Havassy, Smith 1986). When relapse is defined as a discrete event, distinction is often made between first use of the primary drug of dependence and first use of any other psychoactive agent. Return to use of the primary drug holds clear potential for return to addiction (Hubbard and Marsden 1986). However, there has been less consensus regarding whether use of a substitute drug should be defined as relapse. When relapse is defined as occurring over time, the endpoint of the process has been variously defined as daily drug use for a specified period, a return to drug use at or above pretreatment or baseline level, a consequence of drug use such as readmission for treatment, a return to dependence defined by one or more diagnostic instruments, or a return to drug use at levels above criteria specified in terms of quantity and/or duration of drug use (APA 1987; Litman et al. 1983; Ossip-Klein et al. 1986; Simpson and Marsh 1986).

The choice of definition is also influenced by the treatment modality being evaluated and by the theoretical orientation of the investigator. For example, relapse is usually discretely defined in

clinical applications of aversive counterconditioning to treatment of alcohol and tobacco dependence (Boland, Mellor, Revusky 1978; Schwartz 1987). In contrast, investigations of skills training approaches to alcohol, tobacco, and other drug use treatment typically employ continuous or process measures of relapse, e.g., number of days of abstinence (Chaney, O'Leary, Marlatt 1978; Marlatt and Gordon 1985) because new skills are not lost after a slip but rather could be used repeatedly to reestablish abstinence (Catalano and Hawkins 1985).

Measurement of Relapse

Relapse is usually assessed by one of two measurement procedures (Wesson, Havassy, Smith 1986). Current drug use measures ascertain drug use at selected posttreatment intervals (e.g., 3, 6, and 12 months). Intermittent drug use occurring between these time intervals may not be captured by this procedure. Continuous status measures ascertain whether there was drug use at any point in the posttreatment interval. Current use measures typically yield higher abstinence rates than continuous status measures, because of the variable course of drug abuse careers (Pickens et al. 1985). Current use measures provide point-in-time estimates of relapse status among a sample of treated users, while continuous status measures allow for determining the percentage of individuals who have managed to achieve relatively enduring abstinence (Ossip-Klein et al. 1986). The implications of different measurement approaches for interpretation of relapse phenomena have been reviewed (Wells, Hawkins, Catalano, in press; Brownell et al. 1986).

While self-reported drug use status has been the primary method of detecting relapse, detection of the drug in biological fluids or in expired air is being used as an adjunct with increasing frequency (Wesson, Havassy, Smith 1986). As discussed earlier in this Chapter, biochemical methods of assessing drug use vary widely in their sensitivity and in the period during which drug use can be detected (Walsh and Yohay 1987).

Rates of Relapse

Hunt and his colleagues were the first to investigate commonalities in relapse processes among substances (Hunt, Barnett, Branch 1971; Hunt and Bespalec 1974; Hunt and General 1973; Hunt and Matarazzo 1970). They compared relapse rates for clients discharged from opiate, alcohol, and tobacco dependence treatment programs and noted the remarkable similarity of the relapse curves they obtained (Figure 2). Relapse was defined as any use of the primary drug of abuse. They then formulated a learning theory of relapse that was presumed to operate in alcohol, opioid, and tobacco dependence.

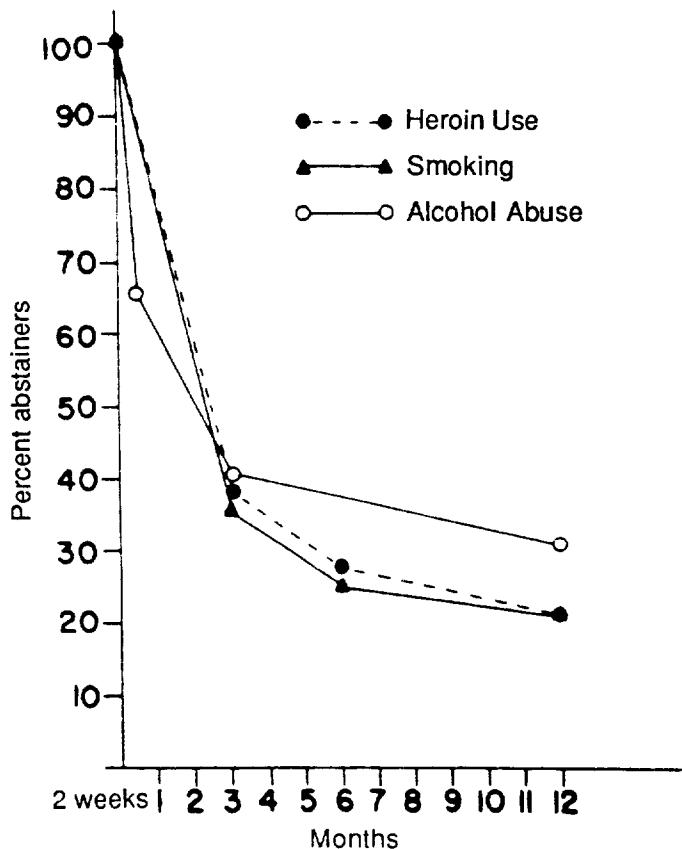


FIGURE 2.—Relapse over time for heroin use, smoking, and alcohol abuse

SOURCE: Hunt et al. (1971).

Although attempts to base theories of relapse on cumulative survival curves, such as those depicted in Figure 2, are complicated by a variety of factors (Litman, Eiser, Taylor 1979; Sutton 1979; Brownell et al. 1986), such curves do possess heuristic value. They indicate that abstinence rates fall precipitously in the early post-treatment period; that most treated smokers, alcoholics, and heroin addicts relapse to at least single use of the primary drug of use by 3-month followup; and that those who have maintained abstinence for at least 6 months are much less likely to relapse.

Similar large-scale reviews of relapse rates for multiple substances have not been published in recent years. Instead, a voluminous

literature has accrued regarding treatment effectiveness (Schwartz 1987; Miller and Hester 1986a; Platt 1986; Simpson and Sells 1982). However, data from studies of alcohol, opioid, and tobacco relapse consistently support the similarities in relapse rates and patterns across these three forms of drug dependence, as well as the operation of similar determinants of relapse. For instance, high rates of relapse characterize most treatment programs for dependence to opioids (Maddux and Desmond 1986; Platt 1986; McAuliffe 1975; McAuliffe et al. 1986; Waldorf 1983), alcohol (Belasco 1971; Bruun 1963; Robson, Paulus, Clarke 1965; van Dijk and van Dijk-Koffeman 1973; Vaillant 1982; Imber et al. 1976; Kendell and Staton 1966; Orford and Edwards 1977), and tobacco (Brandon, Tiffany, Baker 1986; Erickson, Rugg, Tunstall, Jones 1984; Hunt and Matarazzo 1973; Marlatt and Gordon 1985; Shumaker and Grunberg 1986; Schwartz 1969; see also Chapter VII). The remainder of this Section will address the parallel in the correlates of relapse to these three substances.

Correlates of Relapse

Factors found to be associated with relapse fall into three domains. Background or pretreatment factors are those that seem to heighten the individual's vulnerability to relapse (Shiffman et al. 1986). These variables may be measures of fixed pretreatment characteristics such as demographics and drug use history. Pretreatment factors appear to account for between 10 and 20 percent of the variance in posttreatment relapse (Cronkite and Moos 1980; Simpson, Savage, Lloyd 1979; Simpson and Sells 1982). Variables measured during treatment are also thought to influence the probability of relapse at posttreatment. These include treatment length, intensity, setting, type, and compliance with treatment. Treatment factors appear to account for 15 to 18 percent of the variance in drug abuse outcome studies (Simpson, Savage, Lloyd 1979). Posttreatment factors are those associated with the subject's posttreatment environment or internal state. These include degree of family support, drug use among peers, involvement in work and leisure activities, and emotional states. Posttreatment factors have been shown to account for roughly 50 percent of the variance in posttreatment relapses (Finney, Moos, Mewborn 1980) and thus may be the most important focus for relapse prevention efforts. The rest of this Section will review prominent relapse factors that have been systematically studied for opioids, alcohol, and tobacco.

Pretreatment Correlates of Relapse

Severity of Drug Dependence

Severity of pretreatment drug dependence is one determinant of the likelihood of relapse. Several studies have found that light

smokers are more likely to succeed at abstinence than heavy smokers (see Table 7 and Chapter VII). Similarly, with regard to opioid dependence, a shorter pretreatment period of dependence is associated with better posttreatment outcomes (Riordan et al. 1976), and level of drug craving was directly related to the amount of variance in relapse (McAuliffe et al. 1986). Estimating the contribution of severity of alcohol dependence to relapse is more problematic because there has been such a wide variety of measures (e.g., severity of social harm, illness, withdrawal, or craving) used among studies. Thus, the seven alcohol studies cited in Table 7 provide equivocal results, and it is unclear whether there is actually no relationship or whether variability in measurement among studies precludes meaningful conclusions. Furthermore, there is some evidence that predictions of relapse based on severity of dependence are moderated by age, marital status (Polich, Armor, Braiker 1981), and gender (Hesselbrock et al. 1983).

A factor that complicates the relationship between duration of drug dependence (as a measure of severity) and likelihood of relapse is that the age of the individual is directly related to remission (see discussion of spontaneous remission earlier in this chapter). Millman, Khuri, and Nyswander (1978) reported that length and intensity of addiction were positively associated with relapse, except that older opioid-dependent persons were more successful at avoiding relapse than younger ones. In a followup study of 38 treated methadone clients, Riordan and colleagues (1976) found that relapsed subjects were more likely than nonrelapsed subjects to have been addicted longer prior to treatment.

Psychiatric Impairment

As previously discussed, both depression and anxiety are commonly observed as dual diagnoses in persons dependent on alcohol and other psychoactive drugs. These diagnoses are also predictive of high rates of relapse and poor treatment outcomes. As shown in Table 7, several studies suggest that overall severity of psychiatric symptomatology may be an important predictor of treatment outcome. For example, McLellan and colleagues (1983) evaluated 6-month post-treatment outcomes for 460 alcoholics and 282 opioid addicts drawn from 6 rehabilitation programs. Using an intervention-based assessment of the severity of psychiatric symptomatology, they observed that patients with low psychiatric severity improved in every treatment program, while patients with high psychiatric severity showed almost no improvement in any treatment program. Patients with midrange severity levels of psychiatric disorder showed differential responses as a function of treatment modality.

TABLE 7.—Studies showing evidence for factors associated with relapse, by substance

Factors	Studies		
	Tobacco	Opioids	Alcohol
Pretreatment			
Degree of dependence	Hall, Herning et al. (1984), Pomerleau et al. (1978), Jarvik (1979), Shiffman (1979, 1984)	McAuliffe et al. (1986), Millman et al. (1978), Riordan et al. (1976)	Foy et al. (1984), Heather et al. (1983), Hesselbrock et al. (1983), Kivlahan et al. (in press), Litman et al. (1984), Orford et al. (1976), Polich, Armor, Braiker (1980)
Psychiatric impairment	No studies	Mclellan et al. (1983), Rounsville et al. (1985)	Abbot and Gregson (1981), Gregson and Taylor (1977), Heilbrun and Tarbox (1978), O'Leary et al. (1979), Donovan et al. (1984), Mclellan et al. (1983) Rounsville et al. (1987)
Criminality	No studies	Simpson and Sells (1982), DeLeon (1985)	No studies
Demographics	Tucker et al. (1985), Swan et al. (1985), Eisinger (1971), Campbell (1983)	Tucker et al. (1985), Simpson and Sells (1982)	Tucker et al. (1985), Pemberton (1967), Armor et al. (1978), Voegtlind and Broz (1949), Fox and Smith (1970)

TABLE 7.—Continued

Factors	Studies		
	Tobacco	Opioids	Alcohol
Treatment			
Length	No studies	Simpson and Sells (1982), DeLeon et al. (1982)	Miller and Hester (1986b)
Modality	Row et al. (1980), Foxx and Brown (1979), Elliott and Denney (1978), Erickson et al. (1983), Tiffany, Martin, and Baker (1986)	Simpson and Sells (1982), Bale et al. (1980)	Emrick (1974), Miller and Hester (1986a)
Use of drugs/Involvement in crime	No studies	Simpson and Sells (1982)	No studies
Positive expectations of outcome	Brandon, Tiffany, Baker (1986)	Simpson and Sells (1982)	Eastman and Norris (1982)
Posttreatment			
Family	Marlatt and Gordon (1980), Horwitz et al. (1985), Coppotelli and Orleans (1985), Mermelstein et al. (1983)	Dell Orto (1974), Levy (1972), Stanton, Todd, Steir (1979), Rhoads (1983), Wellisch and Kaufman (1975), Harbin and Mazier (1975), Hejinian and Pittel (1978), Kaufman (1985), Stanton (1978, 1979)	Finney et al. (1980), Moberg et al. (1982), Burton and Kaplan (1968), Moos and Moos (1984), Marlatt and Gordon (1980), Billings and Moos (1982a, b), Moos et al. (1979), Orford et al. (1976)
Peers	Cummings et al. (1980), Shiffman (1982), Evans and Lane (1981), Lichtenstein et al. (1977), Marlatt and Gordon (1980), Cummings et al. (1980)	Hawkins and Fraser (1987), Chaney et al. (1982), Marlatt and Gordon (1980, 1985)	Chaney et al. (1978), Marlatt (1978), Marlatt and Gordon (1980)
Isolation	No studies	Hawkins and Fraser (1987)	Stead and Viders (1979)
Lack of involvement in work		Ronnberg (1979), Savage and Simpson (1979), Simpson (1981), Simpson et al. (1986), Simpson and Lloyd (1979)	Bromet and Moos (1977), Finney et al. (1980)

TABLE 7.—Continued

Factors	Studies		
	Tobacco	Opioids	Alcohol
Lack of active leisure	Shiffman (1984)	Simpson et al. (1981), NIDA (1980)	Finney et al. (1980), Moberg et al. (1982), Moos et al. (1979), Stead and Viders (1979), Tuchfeld (1981), Tuchfeld et al. (1983)
Negative emotional states	Hatsukami et al. (1984), Marlatt and Gordon (1980), Lichtenstein et al. (1977), Mermelstein (1983), Mermelstein et al. (1986), Shiffman et al. (1986), Lichtenstein (1986)	Stephens and Cottrell (1972), Cummings et al. (1980), Marlatt and Gordon (1980), Hatsukami et al. (1981), Chaney et al. (1982)	Ludwig (1982), Marlatt (1978), Chaney et al. (1978), Finney et al. (1980), Slater and Linn (1982-1983), Pickens et al. (1985), Samsonowitz and Sjoberg (1981), Sandahl (1984), Hatsukami et al. (1981)
Negative physical states	Pomerleau (1979), Shiffman (1979)	Khatami et al. (1979), Chaney et al. (1982), Marlatt and Gordon (1980), Martin (1972)	Finney et al. (1980), Moos et al. (1979)
Skills deficits	Marlatt and Gordon (1980), Shiffman (1982, 1984), Curry and Marlatt (1985)	Brill (1963), Cheek et al. (1973), Fort (1966), Catalano and Hawkins (1985)	Miller et al. (1974), O'Leary et al. (1976), Rosenberg (1983), Miller and Eisler (1977)
Negative life events	Etringer et al. (1984)	Judson and Goldstein (1983), Rhoads (1983)	Moos et al. (1979, 1981), Finney et al. (1980), Rosenberg (1983), Hull and Young (1983), Vuchinich and Tucker (1985)
Lack of needed services	No studies	Ogborne (1978), Hawkins and Catalano (1985), McAuliffe et al. (1985)	Feit (1980), Ashley et al. (1976), Ogborne (1978), Ahles et al. (1983), Ito and Donovan (1986)

Demographic Factors

Demographic correlates of relapse have been widely studied. Consistent demographic predictors of relapse, either within or among substances, have not been identified (Tucker, Vuchinich, Harris 1985 and see Table 7). It is possible that the wide historical diversity of methods and definitions used contributes to greater apparent diversity when data are evaluated both within and among drug classes.

Treatment Correlates of Relapse

In treatment studies of opioid-dependent persons, it has been found that treatment type and duration as well as treatment expectancies affect posttreatment relapse. Length of time in treatment has been positively associated with outcomes across modalities of drug dependence treatment (McLellan et al. 1983; Simpson and Sells 1982). In addition, treatment completers have shown more positive outcomes than those who do not complete treatment regimens (DeLeon, Wexler, Jainchill 1982). Expectations of positive treatment outcome have also been related to lower relapse rates (Simpson and Sells 1982). Finally, modality of treatment has been related to treatment outcome in opioid addicts. Methadone maintenance, long-term inpatient treatment, and outpatient drug-free programs have all produced better outcomes than detoxification treatment or no treatment in both a followup study (Simpson and Sells 1982) and a prospective study (Bale et al. 1980). In the alcohol treatment literature, however, few differences have been detected among the most popular treatment techniques, including residential and outpatient modalities (Emrick 1974, 1975; Miller and Hester 1986a).

Schwartz (1987) has recently examined the effectiveness of more than 20 types of smoking cessation interventions (see Table 2 in Chapter VII). Seven methods showed good short-term results: educational techniques, nicotine chewing gum when combined with behavioral treatment, group hypnosis, physician intervention with cardiac patients, rapid smoking, satiation, and contingency contracting. Multicomponent programs that combined several interventions appeared to produce especially encouraging outcomes.

Expectations regarding alcohol's effects may enhance susceptibility to relapse. Eastman and Norris (1982) examined this relationship in 89 persons participating in outpatient treatment for alcohol dependence. At a 2-month followup, 71 percent of subjects with positive expectations about alcohol's effects had relapsed (any level of consumption was the criterion), compared with only 7 percent of subjects with negative expectations about the effects of alcohol. Analogously, in cigarette smokers, expectations regarding one's

ability to successfully abstain may also predict relapse to tobacco use (Brandon, Tiffany, Baker 1986; Chapter VII).

Posttreatment Correlates of Relapse

Evidence from a number of sources suggests that posttreatment experiences are particularly important to the relapse process. For example, Finney, Moos, and Mewborn (1980) found posttreatment factors to account for roughly half of all variance in treatment outcome. Further, recent investigations of the effectiveness of aftercare in the treatment of drug and alcohol abuse suggest that interventions which target the posttreatment interval may be particularly effective (Ahles et al. 1983; Catalano and Hawkins 1985; Catalano et al., in press; Marlatt and Gordon 1985). Specific categories of posttreatment factors associated with relapse are described below.

Family Support Factors

Family support has been a strong predictor of posttreatment success for opioid users, alcoholics, and cigarette smokers (Table 7). For example, Orford and colleagues (1976) found a marital cohesion factor to predict treatment outcome for drinking variables measured 12 months later. Similarly, in a survey of 219 subjects who were interviewed at 1-year followup after treatment in a minimal intervention smoking cessation program, abstainers reported significantly more support from spouses, parents, family, and friends than did relapsers (Horwitz et al. 1985). Similarly, Orford and colleagues (1976) found that high marital discord was a predictor of relapse drinking at the 12-month followup among treated alcoholics, whereas Burton and Kaplan (1968) found reduction in the number of areas of disagreement between the alcoholic and his or her spouse to be associated with improvement in drinking behavior. These observations are consistent with the retrospective reports of relapsed subjects indicating that interpersonal conflict that was family or peer related was a trigger for drug use following a period of abstinence (Marlatt and Gordon 1980). Taken together, these data suggest that family support plays an important role in preventing relapse to substance use and that family conflict and lack of support for posttreatment recovery may increase levels of relapse for treated users of alcohol, opioids, and tobacco.

Drug Use Among Peers

Relapse to drug use following a period of abstinence after treatment often occurs when there is peer pressure to use drugs or when drugs are offered by the nonabstinent peer. A series of reports by Marlatt, Chaney, and their associates (Chaney, O'Leary, Marlatt

1978; Chaney, Roszell, Cummings 1982; Marlatt 1979; Marlatt and Gordon 1980, 1985) examining determinants of relapse for various substances suggested that social pressure is a factor for approximately 15 to 40 percent of relapse episodes among alcohol and opioid users. In a followup study of treated heroin users, Hawkins (1979) found that 69 percent of those who returned to heroin use after drug treatment reported that they did so in response to informal pressure from peers, suggesting an even stronger effect of social factors on relapse among opioid users. Similarly, living with smokers (Shiffman 1982) and failure to avoid smoking peers (Graham and Gibson 1981) are related to relapse in treated smokers. Specifically, Shiffman (1982) found that 30 percent of the relapse cases of 183 ex-smokers were associated with the presence of other people smoking. Other investigators have also found the presence of other smokers (Lichtenstein, Antonuccio, Rainwater 1977) or social pressure to smoke (Cummings, Gordon, Marlatt 1980) to be a risk factor for relapse (Chapter VII).

Involvement in Work and Leisure Activities

Although active employment and involvement in leisure activities may be distinguished (as shown in Table 7), there are similarities in their effects on relapse. Furthermore, the factors are similar in that both may be incompatible with active involvement with some dependence-producing drugs. In brief, research on posttreatment experiences of both opioid users and alcoholics has shown a consistent positive relationship between involvement in active recreational leisure activities (sports, hobbies, crafts, and volunteer work) and reduced use of opioids, alcohol, and tobacco (Table 7). Similarly, unemployment is associated with relapse to opioids and alcohol (Table 7).

Negative Emotional States

One of the most consistent findings from retrospective studies of relapse is the involvement of negative emotional states in relapse episodes. Data supporting this conclusion regarding tobacco use are discussed in detail in Chapters VI and VII and are only briefly summarized in this Section to enable a comparison of findings with opioids and alcohol. Ludwig (1972) interviewed 161 relapsed alcoholics and reported that 25 percent relapsed in response to "psychological distress." Marlatt (1978) interviewed 48 alcoholics who relapsed within 90 days of discharge from treatment and found that 10 percent relapsed in negative mood states and 29 percent in situations arousing frustration or anger. Negative emotional states are also prominent determinants of relapse to cigarette smoking. For instance, Marlatt and Gordon (1980) reported that 43 percent of the

relapse episodes of 35 subjects who had completed a smoking cessation program were in response to negative mood states.

Drug use has also been reported as a means of alleviating negative emotional states. For example, Stephens and Cottrell (1971) studied 236 opioid users who had received 6 months of inpatient methadone treatment. One-quarter of the clients they studied relapsed, reportedly using the drug to alleviate stress or to combat personal faults or depression. Consonant with these findings, reports of former drug users suggest that approximately one-fourth to one-third of the incidents of first drug use following treatment are precipitated by negative emotional states (Cummings, Gordon, Marlatt 1980; Marlatt and Gordon 1980).

Potential sources of negative emotions cited by relapsers include stressful interpersonal interactions (e.g., anger, frustration) and negative life events such as death, illness, job loss, or change. The role of negative life events has long been recognized as an important factor that can influence psychopathology, illness, and drug dependence; recently, systematic studies of these latter factors have also been conducted (Bloom 1985). For example, Moos, Finney, and Chan (1981) found that relapsed alcoholics reported nearly twice as many negative events and approximately one-half as many positive events as either recovered alcoholics or controls (Hull and Young 1983; Vuchinich and Tucker 1985).

Another potential source of negative emotions is illness or somatic discomfort from a variety of sources. In this regard, drug dependence researchers have documented the tendency of some drug users to use drugs as a form of self-medication (see Chapter VI for tobacco-specific data). For instance, opioid dependence may develop during the course of treatment for chronic pain (Khatami, Woody, O'Brien 1979) and other forms of somatic discomfort (Marlatt and Gordon 1980; Chaney, Roszell, Cummings 1982). Similarly, physical symptoms, including allergies, back pain, headache, and insomnia, during the posttreatment period were related to opioid and alcohol use in a sample of treated alcoholics (Finney, Moos, Mewborn 1980; Moos et al. 1979). A possibly related finding is the suggestion from a number of studies that protracted withdrawal symptoms are factors in relapse to opioid (Martin 1972) and tobacco (Pomerleau 1979; Shiffman 1979) use.

As shown in this Section, relapse is characteristic among persons treated for opioid, alcohol, nicotine, and other forms of drug dependence. Rates and patterns of relapse appear to vary more as a function of treatment characteristics, client parameters, and post-treatment environmental factors than as a function of drug type when alcohol, opioids, and nicotine are compared.

Posttreatment factors appear to be the most important determinants of treatment success and relapse avoidance for users of

tobacco, opioids, and alcohol. These are summarized in Table 7. Specifically, the most common predictors, similar for alcohol, opioids, and nicotine, include posttreatment family support factors, peer substance use factors, leisure and recreational activities, and occurrence of stressful or negative affect situations in the form of intrapersonal mood states, somatic complaints, negative life events, or stressful interpersonal interactions. Additional factors that appear important include pretreatment severity of use (tobacco and opioids), length of treatment (opioids), and type of treatment (tobacco and opioids).

Treatment of Drug Dependence

Scientifically based methods of helping drug dependent persons to achieve and maintain drug abstinence are available and can be efficacious. The methods are being continually refined, however, as new data are collected on how to better address the needs of clients or patients and how to make treatments more readily available and acceptable for those who want help. This Section briefly reviews some of the kinds of treatment approaches that are available for the various drug dependencies.

Treatment strategies designed to address dependence on opioids, alcohol, nicotine, and many other dependence-producing drugs are remarkably similar. This phenomenon provides additional evidence that the processes that determine addiction are similar for the various dependence-producing drugs. Some of the differences in treatment are related to variations in detoxification strategies, which depend on the route of drug administration and on differences in the duration of drug action. There is also need to tailor the content and/or intensity of treatment delivered to groups with different substance dependencies. For example, the need for medical intervention to alleviate acute withdrawal symptoms varies among and within drug classes as a function of the physical dependence level. This Section will discuss the goals of treatment for drug dependence and three types of interventions that are commonly employed: (1) pharmacologic substitution therapy designed to suppress withdrawal, (2) interventions designed to redress deficits in skills and/or deficits in social support that are potentially related to relapse, and (3) interventions designed to bolster or sustain motivation for abstinence. These kinds of intervention strategies are not mutually exclusive, and are often used in combination to yield better overall rates of success than any single approach (Grabowski et al. 1984).

Goals of Treatment

Reducing or eliminating self-administration of the substance to which the person is dependent is the primary goal of treatment. Traditionally, there has been a tendency for treatment programs to rely on a goal of complete abstinence rather than reduction of use to manageable or nonproblematic levels. The appropriateness of this goal may, in part, vary by drug class, as well as by severity of dependence. For example, problems associated with alcohol use vary considerably, and it would appear that many persons with low levels of dependence are able to maintain stable levels of "social drinking," whereas persons with more severe levels of dependence must maintain total abstinence (Miller and Joyce 1979; Miller 1979). Because it has been estimated that only about 10 to 15 percent of adults (United States) who drink warrant the designation "problem drinker" and only a subset of these warrant the designation "alcoholic," such variation in treatment goals is not surprising (Cahalan 1970; Miller 1979). Analogously, it appears that only a small fraction of caffeinated beverage (e.g., coffee and tea) drinkers display distinct adverse consequences and apparent loss of control over caffeine intake (Griffiths and Woodson 1988)—observations consistent with the rapidly growing decaffeinated beverage market. On the other hand, with drugs for which any nonprescription use is illicit (e.g., opioids) or on which the overwhelming majority of users are dependent (e.g., only 10.6 percent of current smokers smoke 5 or fewer cigarettes/day according to the 1985 National Health Interview Survey (unpublished data, Office on Smoking and Health)), a goal of reduction of use may be especially problematic (Chapter VII). Two additional problems with low-level cigarette use as a therapeutic goal are that no level of cigarette smoking has been found safe (US DHHS 1986) and that even if the smoker is only smoking a few cigarettes, by taking more puffs per cigarette and by inhaling the smoke more deeply, the smoker might actually maintain substantial levels of tobacco toxin intake and nicotine dependence (Kozlowski 1981; Benowitz et al. 1983; Chapter IV). The percentage of persons using amphetamine or cocaine who are unable to control their intake is unknown, but because nonmedical use of these drugs is illicit and because animal and human research indicates that these drugs are powerful reinforcers (US DHHS 1987), total abstinence is similarly recommended (US DHHS 1987).

Maintenance of abstinence or avoidance of relapse is another major treatment goal. Because relapse factors can remain functional for many years in individuals who are abstaining from use of a drug to which they had been dependent (Chapters VI and VII), designing a long-range program to minimize the impact of such factors is an integral part of many drug treatment programs (e.g., Thompson, Koerner, Grabowski 1984; Stitzer et al. 1984). These factors may

include some assumed to be physiologically related to the drug dependence process (e.g., anxiety or stress), while others are assumed to function at more of a behavioral level (e.g., the sight of drug-associated stimuli).

Types of Treatment for Drug Dependence

Treatment approaches can be divided into those which involve the administration of drugs (Pharmacologic Treatment Approaches) and those which do not (Nonpharmacologic or Behavioral Treatment Approaches). Sophisticated methods involving both pharmacologic and behavioral approaches are more recent developments and show considerable promise for the treatment of dependence to alcohol, opioid, cocaine-like drugs, and nicotine (Grabowski, Stitzer, Henningfield 1984). Although considered separately in this Section, pharmacologic and behavioral treatment approaches are commonly combined and may be most effective when used in combination (Grabowski, Stitzer, Henningfield 1984; Crowley and Rhine 1985). Combined treatment approaches specific to cigarette smoking are discussed in Chapter VII.

Pharmacologic Treatment of Drug Dependence

Four pharmacologically based approaches for the treatment of drug dependence can be differentiated: (1) *replacement* or *substitution therapy* (e.g., methadone for opiate dependence), in which a more manageable (and ideally, less addicting) form of the drug is provided; (2) *blockade therapy* (e.g., naltrexone for opiate dependence), in which the behavior-controlling effects of the abused drug are blocked by pretreatment with an antagonist; (3) *nonspecific pharmacotherapy*, in which the patient is treated symptomatically (e.g, use of clonidine during opioid detoxification); and (4) *deterrent therapy*, in which administration of the treatment drug results in the occurrence of aversive effects when the abused drug is subsequently taken (e.g., the use of disulfiram to treat alcoholism (Grabowski, Stitzer, Henningfield 1984; Jaffe 1985). Each of these approaches has been described in greater detail elsewhere and will be only briefly described below (Cooper, Altman, Brown, Czechowicz 1983; Bigelow, Stitzer, Liebson 1985; Jaffe 1985; Jasinski, in press; Jasinski and Henningfield 1988; Jarvik and Henningfield, in press).

Replacement Therapy

The most widely investigated and evaluated pharmacologic treatment approach for drug dependence is replacement therapy. The general principle of replacement therapy is to provide the patient with a safer and more manageable form of drug that directly alleviates signs and symptoms normally suppressed by the substance

upon which the patient is dependent (Jaffe 1985, 1987; Jasinski and Henningfield 1988). Ideally, it should also be of lower dependence potential so that its use may be more readily discontinued than use of the original form on which the person is dependent.

Replacement therapies function through four general actions: (1) they block the onset of the physiologically mediated aspects of withdrawal; (2) they maintain a level of tolerance that attenuates the reinforcing properties of the abused chemical; (3) they treat ("suppress") other signs and symptoms such as dysphoria that may constitute vulnerability and pose an impediment to normal functioning and well-being; (4) they directly suppress drug-taking behavior, much as caloric loading can suppress eating.

The drugs that are widely used to alleviate withdrawal symptoms by providing some level of pharmacologic replacement are the following: methadone for opiate withdrawal (Cooper, Altman, Brown, Czechowicz 1983), benzodiazepines for alcohol withdrawal (Sellers et al. 1983; Newsome and Seymour 1983; Liskow and Goodwin 1987), and nicotine polacrilex gum for tobacco withdrawal (Chapters IV and VII). The potential effectiveness of these agents in prevention or relief of withdrawal symptoms has been well documented (Jaffe 1985). However, relief of early withdrawal symptoms does not necessarily yield improved overall treatment outcomes. Primary withdrawal symptoms for all dependence-producing drugs are time limited, and their duration does not span the entire high-risk period for postcessation relapse. These observations are consistent with the finding that withdrawal symptomology is only one of several potential relapse determinants.

Besides relief of withdrawal symptoms, there are several other functions that a replacement therapy might serve that would make continued long-term treatment beneficial. One of these functions is a reduction in the need for the primary addicting drug, along with a similar reduction in drug seeking. Just as importantly, the replacement therapy may reduce or eliminate symptomology (e.g., anxiety, antisocial behavior, inability to concentrate on tasks) that may interfere with the person's ability to perform in occupational settings and maintain social relationships. Analogously, nicotine replacement therapy during cigarette abstinence can reduce or eliminate tobacco intake and symptoms that interfere with normal social or occupational activities, even though urges to smoke may not be eliminated (Chapter VII).

The constraints on the efficacy of replacement therapies are generally similar across drug classes. Most importantly, the clinical application of replacement therapies is impeded by the influence of nonpharmacologic factors, which vary among individuals and/or situations (e.g., the specific drug delivery system customarily used and ritualistic aspects of the behavior). Pharmacologically related

differences may also mitigate acceptability of the replacement drug; e.g., orally administered replacements are generally not as satisfying to the user as i.v. or inhalation systems, such as the "crack" form of cocaine or tobacco smoke. In addition, replacement therapies do not reliably diminish the urge to use the drug or specific drug formulation (e.g., cigarette brand or alcoholic beverage) to which a person is accustomed. (Issues related to craving are discussed in greater detail in Chapters IV and VII; Childress et al., in press; Henningfield and Brown 1987.)

Blockade Therapy

A pharmacologic alternative to replacement therapy is to produce a pharmacologic blockade of receptors which mediate the reinforcing as well as the toxic effects of the drug (Jaffe 1985). For opioid agonists such as morphine and heroin, the short-acting antagonist naloxone can be used to reverse the effects of an overdose of the opioid agonist. The longer acting antagonist naltrexone can be given on a daily basis to opioid users to prevent them from experiencing the reinforcing and toxic effects of opioid agonists. Unfortunately, clinical trials have shown that there is frequently poor compliance with blockade therapy (Ginzburg 1986). Lack of compliance results in limited clinical utility. No clinically tested antagonist treatments are currently available for the treatment of alcohol or nicotine dependence, although experimental research with the nicotine blocker, mecamylamine, suggests that such an approach may hold promise (Chapter VII; Jarvik and Henningfield, in press).

Nonspecific Pharmacotherapy or Symptomatic Treatment

Administration of and abstinence from dependence-producing drugs produce a cascade of effects involving a variety of neurochemical and physiological effects. As discussed with regard to nicotine in Chapters III and VI, such drug actions mediate many of the desirable and undesirable effects. In principle, it is possible to target treatment approaches on a symptomatic basis.

One example of such an approach is the use of an antidepressant (desipramine) to help achieve and maintain abstinence from cocaine (Gawin and Kleber 1984); cocaine abstinence is often accompanied by symptoms of depression. Somewhat analogous is the use of clonidine to treat opioid withdrawal symptomology (Gold, Dackis, Washton 1984). Clonidine seems to exert its primary actions by suppressing aspects of opioid withdrawal that are mediated by the activity of the sympathetic nervous system (SNS). In one study, clonidine was just as effective as morphine in the reduction of certain physiological signs of opioid withdrawal (Jasinski, Johnson, Kocher 1985); however, in that study, clonidine did not reduce the self-reported

"discomfort" as effectively as did morphine. These observations are consistent with the conclusion that some but not all of the effects of the opioid withdrawal syndrome are mediated by the SNS and that treatment of these effects may provide limited but objective benefit. An analogous approach has been explored for application of clonidine in the treatment of tobacco withdrawal (Glassman et al. 1984, 1988), but conclusions are only suggestive of the possible viability of this approach (Chapter VII; Jarvik and Henningfield, *in press*).

Pharmacologic Deterrents

Drug taking can sometimes be reduced or eliminated if the consequences are immediate and/or severe enough (Crowley and Rhine 1985). There has been some effort to develop pharmacologic treatments that ensure immediate, reliable, and highly aversive (but safe) effects following self-administration of the drug of dependence. Only one such agent has provided a near approximation of these criteria: disulfiram, which is used in the treatment of alcoholism (Jaffe and Ciraulo 1985; Miller and Hester 1986a). When disulfiram has been taken, a small amount of alcohol can produce rather severe discomfort and acute illness. Reviews of controlled treatment outcome studies (Miller and Hester 1986a) suggest that many of the therapeutic effects of disulfiram may also derive from placebo effects. Thus, in some studies (e.g., Fuller and Roth 1979), outcomes have been similar for placebo and active drug groups, with only medication-compliant individuals (about 20 percent in each group) showing good outcomes.

No deterrents comparable to disulfiram in potential efficacy have been clinically tested for treatment of dependence on opioids or nicotine (see also Chapter VII). As with antagonists, a practical problem in treatments using deterrents is compliance, i.e., maintaining adequate levels of use of the medication itself. A deterrent is ineffective if it is not taken, and development of contingencies to ensure that the patient takes the deterrent has proceeded slowly (Bigelow, Stitzer, Liebson 1984, 1985; Stitzer, Bigelow, Liebson, McCaul 1984). Therefore, even if theoretically effective deterrents become available for treatment of other drug dependencies, their utility might be limited.

Behavioral Treatment Strategies

Despite the powerful sequelae which may accompany both drug administration and drug abstinence, most drug-dependent persons (possibly excluding opioid users) are not systematically treated with pharmacologic approaches. Drug dependent persons may eventually "spontaneously remit" (discussed earlier in this Chapter), but many others enter formal treatment programs that provide supportive and

behavioral therapy. Behavioral treatment approaches have a heterogeneous array of theoretical bases and means of implementation (Stitzer, Bigelow, McCaul 1983). Although the term "behavioral treatment" is often reserved for approaches which involve the systematic application of behavior modification, it is sometimes applied to any nonpharmacologic approach. Thus, behavioral strategies may involve group support, individual counseling, skills training, or family intervention (Krasnegor 1979a; Grabowski, Stitzer, Henningfield 1984). The present Section will provide a brief review of behavioral approaches aimed largely at relapse prevention.

The major challenge in the treatment of drug dependence is no longer in the initial attainment of abstinence; rather it is in the maintenance of abstinence. In fact, it is worth noting that the shift in emphasis from achievement of abstinence to the maintenance of abstinence is an important advance in treatment efficacy in itself (McAuliffe et al. 1986). This current focus has resulted in the development of nonpharmacologically based approaches aimed at what is often termed relapse prevention. In the past decade, relapse prevention interventions have been increasingly founded on empirical investigations of situational precipitants of relapse and/or have addressed factors known to predict relapse that can be manipulated (Catalano and Hawkins 1985; Catalano et al., in press; Hawkins and Catalano 1985; Marlatt and Gordon 1985; Tucker, Vuchinich, Harris 1985; Brownell et al. 1986; Todd, 1984).

A specific goal of approaches to relapse prevention is to increase the impact of those factors that are negatively associated with relapse and to decrease the impact of factors that are positively associated with relapse. These approaches have led to the development of a number of techniques that hold promise for prevention of posttreatment relapse. Some of the better documented approaches are summarized below.

Relapse Prevention Skills

Marlatt and his associates (Marlatt and Gordon 1980, 1985; Cummings, Gordon, Marlatt 1980) have developed a cognitive behavioral model of relapse which includes skills training for each phase of the relapse process. They advocate training: (1) to recognize "apparently irrelevant decisions leading to relapse"; (2) to identify and cope with personal high-risk relapse situations; (3) to practice behaviors which increase perceptions of self-efficacy and control such as reading, relaxation, and meditation; (4) to recognize the negative effects in biphasic drug action which follow immediate positive effects; (5) to cope with a slip; and (6) in some cases, to practice a relapse under controlled circumstances called a "programmed relapse" (although the general efficacy of this approach has not been confirmed).

Reports of skills training with alcoholics far outnumber reports of similar training with users of other drugs. Treatment in these studies usually involves assertion/social skills training, problem-solving training, and/or practice of high-risk situations using a combination of methods, including didactic presentation, modeling, role play, feedback, generation and evaluation of alternative problem solutions, and homework assignments. Skills improvement has been achieved as indicated by role play, self-report, and questionnaire measures, and a positive impact of skills training procedures has been shown in the treatment of alcohol use (Watson and Maisto 1983; Van Hasselt, Hersen, Millions 1978) and cigarette smoking (Shiffman 1982; Hall, Rugg et al. 1984).

The effectiveness of skills training with users of drugs other than alcohol has not been as thoroughly evaluated as for alcohol. In five single-case and uncontrolled group studies involving primarily opioid users, two reported reduced drug use at followup (Cheek et al. 1973; Polakow and Doctor 1973); four found self-reported improvements in social functioning (Cheek et al. 1973; Matefy 1973; Polakow and Doctor 1973; Wolpe 1965); and one reported improved role play performance (Callner 1973). Four studies of users of a variety of illicit drugs (Callner and Ross 1978; Hawkins, Catalano, Wells 1986; Smith 1982; Lin et al. 1982) have reported improvements in skills related to high-risk relapse situations, and one found decreased use of marijuana (Smith 1982). In one study, skill changes generalized to untrained situations and were maintained 1-year posttreatment (Hawkins, Catalano, Wells 1986). As discussed in Chapter VII, preliminary studies suggest that skills training strategies may be of some utility in the treatment of tobacco dependence. For example, Hall, Rugg, Tunstall, and Jones (1984) found that smokers receiving relapse prevention skills training were significantly less likely to relapse than smokers assigned to a discussion control condition. Subsequent studies and reviews indicate mixed results (Hall et al. 1985; Schwartz 1987).

Leisure Activity Skills

In recognition of the association of relapse with an absence of active leisure activity, a number of aftercare programs have attempted to increase participation of clients in organizations beyond work or treatment (Catalano and Hawkins 1985; McAuliffe et al. 1986; Nurco et al. 1983; Wolf and Kerr 1979). Controlled studies have shown that drug users can be encouraged to participate in voluntary community organizations and activities following inpatient treatments and that these contacts can be maintained over a 1-year period following treatment, but in these studies there were no beneficial effects in reducing relapse rates (Catalano and Hawkins 1985; Hawkins and Catalano 1985).

For alcoholics and cigarette smokers, physical exercise has been examined as a potential relapse prevention strategy. Murphy, Marlatt, and Pagano (1986) found that problem drinkers trained in running reported greater reductions in drinking at followup than did drinkers trained in meditation. In a retrospective self-report study, Koplan, Powell, Sikes, Shirley, and Campbell (1982) found at 1-year followup that of the 2,500 runners competing in the 10K Peachtree Road Race in Atlanta and returning questionnaires, 81 percent of males and 74 percent of females who smoked cigarettes before they started running had stopped smoking after they began running.

Stress Management Skills

As discussed earlier in this Chapter and in Chapters VI and VII, negative emotions associated with stressful events or interpersonal interactions have been strongly implicated in relapse precipitation. In principle, such emotional states can be addressed through stress management training, relaxation, meditation, or other "lifestyle" interventions (Marlatt and Gordon 1985; Charlesworth and Dempsey 1982). Although stress reduction techniques are frequently included as a part of drug abuse treatment, there are a surprisingly small number of well-controlled studies addressing the effectiveness of anxiety-reduction techniques with drug-abusing clients (Marlatt and Gordon 1985). As indicated earlier in this Section, there is evidence that programs which may reduce anxiety by use of aerobic exercise or relaxation practice can bring about significant reductions in alcohol use among heavy drinkers (Marlatt and Marques 1977; Marlatt et al. 1984; Murphy, Marlatt, Pagano, 1986). Further research is needed to assess the effectiveness of these techniques in reducing the use of substances following treatment for alcohol, opioid, and tobacco dependence.

Motivation Enhancing Treatments

Treatment interventions in which the primary purpose is to improve or bolster motivation for continued abstinence can take many forms. Many drug-dependent persons enter treatment as the result of some form of pressure from friends, employers, family, medical practitioners, or legal agencies. Sometimes treatments can be designed that incorporate these sources of community pressure and support for abstinence. The present Section will focus on interventions that involve social support from professional therapists, peers, and family.

Social support strategies designed to bolster environmental support for abstinence include enlistment of support from families and existing social networks, the creation of new primary social support such as self-help groups or linkages with community volunteers, and

supportive services provided by professional human service workers. Only preliminary systematic research has been conducted utilizing such interventions; however, the approach appears of similar applicability and utility in the treatment of opioid, alcohol, and tobacco dependence (Ashery 1979; Nurco et al. 1983; Leach 1973; Madsen 1974; Janis and Hoffman 1970).

Professional contact is a special kind of support strategy which has been used in drug use treatment. Typically, it involves ongoing contact with professionals from the primary treatment program. This approach may include booster sessions of individual or group counseling, followup phone calls or letters from therapists, or followup visits by counselors to former clients in the community to review progress and problems. Fitzgerald and Mulford (1985) found that bimonthly phone calls to alcoholic patients by an alcohol counselor did not affect drinking outcome. Pokorny and others (1973) found that weekly group therapy sessions following 60-day inpatient treatment for alcoholism produced relapse results equivalent to more expensive 90-day inpatient treatment with no followup. Colletti and Supnick (1980) found that weekly contact with therapists during the first month following treatment for smoking resulted in better smoking outcomes at 6 months than when subjects received no aftercare, though these differences were not maintained at 12-month followup. Chapter VII describes additional analogous strategies used to treat tobacco dependence.

Family support is a potentially cost-effective and long-lasting form of motivation enhancement. The potential importance of family support is emphasized by the correlation between stable family environment and good treatment outcomes previously discussed. In recognition of this relationship, self-help groups to assist family members of addicts and alcoholics have proliferated since the early 1970s. They include Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Families Anonymous groups for families coping with alcoholism and drug abuse (Ashery 1979; Brown and Ashery 1979), and service-agency-based aftercare groups for families (Dunlop, Skornej, Hamilton 1982). Agencies which have also focused on broader informal social networks have also arisen (Collins and Pancoast 1976; Gottlieb 1981; Speck and Attneave 1973; Whittaker and Garbarino 1983). A study by Stanton, Todd, and Steier (1979) provides support for the benefits of involving the families of opioid users in treatment. They found that in families of opioid users which received structured family therapy, there were more days free of the use of opioids, nonopiod illegal drugs, and alcohol than for opioid users whose families did not receive such treatments. While not reporting drug use outcomes, others have enlisted family members and close friends of drug dependent persons as supportive sponsors in drug treatment programs (Sorensen and Gibson 1983; Callan,

Garrison, Zerger 1975). Such networks are being increasingly developed in recent years to help tobacco dependent persons (Chapter VII; see also Schwartz 1987).

Peer support constitutes a potentially powerful motivation-enhancing approach. A difficulty of peer support is that it often involves establishing a new peer group for the drug dependent person if his or her current peer group continues to support drug use. Self-help groups such as AA and NA, for example, provide former substance abusers with a new social support network of individuals in like circumstances (Ashery 1979; Nurco et al. 1983). Descriptive followup studies of non-probability samples of AA members have suggested that AA is an effective approach for assisting some recovering alcoholics to maintain their sobriety (Leach 1973; Madsen 1974; Maxwell 1962). Several studies of the effectiveness of residential AA programs have also found better outcomes associated with participation (Alford 1980; Smith 1984, 1985). However, these studies have either failed to utilize control groups or utilized "matched" comparison groups that differ on pretreatment criteria which may influence outcome. Thus, these studies do not provide conclusive efficacy data.

A few studies have attempted to create or enhance existing peer social support, with mixed results. For example, a volunteer sponsor program for "skid-row" alcoholics was described by Fagan (1986), in which sponsor groups from churches were assigned alcoholics in a rehabilitation program. This program was not evaluated in a controlled manner. Janis and Hoffman (1970) investigated the effects of a self-help social support intervention on relapse following smoking cessation treatment. Clients paired in a high-partner-contact condition (daily calls for 5 weeks) were more successful in maintaining abstinence at 1- and 10-year followups than were clients in low-contact or control conditions. The critical dimension appeared to be quality of peer support.

Conclusions

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, re-

quire 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.

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CHAPTER VI

EFFECTS OF NICOTINE THAT MAY PROMOTE TOBACCO USE

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Despite the well-known health hazards associated with cigarette smoking and tobacco use, more than 50 million Americans continue to use these products. (See Chapter I for a brief review of health hazards and Appendix A for prevalence of use data.) Chapter IV presents evidence that tobacco use is an orderly form of drug-seeking behavior that involves nicotine self-administration. It is clear from Chapter IV that tobacco use involves several biobehavioral processes of drug dependence, including nicotine reinforcement and withdrawal. The initiation and maintenance of this dependence process may be promoted by other actions of nicotine. For example, some cigarette smokers report that smoking helps them to think better, to cope with stress, and to keep body weight under control. The fact that people believe that tobacco use has these effects may contribute to initiation, maintenance, and relapse.

This Chapter examines the evidence on the following three effects of nicotine:

- enhancement of human performance
- control of stress responses
- control of body weight.

These particular topics are presented because there is scientific literature relevant to each topic and because nicotine has been suggested to be central to each of these effects.

The three topics are discussed separately in this Chapter because the substantive material and relevant data are distinctly different for each topic. Also, the research on each topic is at a markedly different evidentiary stage at this time. Whereas studies on nicotine and performance are intriguing, there are some serious methodological concerns that force caution in the interpretation of the available experimental investigations. In contrast, the relationship between stress and smoking (i.e., that stress increases smoking) is well documented by self-report data, and several investigators have offered detailed theoretical explanations and mechanisms to account for this phenomenon. However, much of this speculation has preceded experimental investigations. In still another stage of investigation, extensive data have been gathered on the relationship between cigarette smoking and body weight, and laboratory studies have carefully assessed the role of nicotine. Explanations for the relationship between nicotine and body weight are based on investigations that were designed to test specific variables involved in this relationship. All three topics are currently receiving research attention and are considered to be important areas for more extensive investigation. This Chapter is meant to complement the information presented in Chapter IV to provide a more complete understanding of tobacco use. Most of the studies discussed in this chapter have examined effects of cigarette smoking. Some studies present data on effects of nicotine alone. The similarity in findings of

these two types of studies supports the conclusion that nicotine is responsible for the effects of cigarette smoking.

Tobacco Use, Nicotine, and Human Performance

Some cigarette smokers believe and report that smoking helps them to think and to concentrate (Russell, Peto, Patel 1974). These possibilities have been studied in the laboratory using several different tasks. Unfortunately, this research literature has methodological limitations. Most of the published studies compare smokers smoking with smokers not smoking. Few studies have included nonsmokers not smoking as a control group. When smokers smoking perform better than smokers not smoking, it is impossible to know if smoking actually improved performance, if abstinence from smoking impaired performance, or both. In addition, most studies allowing smoking and evaluating performance did not measure nicotine levels in the subjects. Therefore, the role of nicotine generally is inferred but not directly assessed. A few studies administered nicotine by oral tablets to smokers and to nonsmokers. This Section examines the effects of cigarette smoking and nicotine on attention, learning and memory, problem solving, and the control of motor function. Implications of these effects for tobacco use are discussed.

Attention

Effects of cigarette smoking on attention have been examined in the laboratory using sustained attention tasks, selective attention tests, and perceptual intrusion or distraction measures. The results using each measure are reviewed separately.

Sustained Attention

Vigilance tasks are the fundamental paradigm in the laboratory for defining sustained attention. Attention is directed to one or more sources of input for long periods of time. The subject is required to detect and respond to small, infrequent changes in the input. Performance in vigilance situations is often assessed in terms of the detection rate, i.e., the proportion of signals correctly detected, and the false-alarm rate, i.e., the number of occasions on which a signal is reported when one has not been presented. Measures of stimulus sensitivity and response criterion can be derived from the detection rate and the false alarm rate using the Theory of Signal Detectability (Green and Swets 1966) in order to assess performance. During a typical vigilance session, the detection rate decreases (the vigilance decrement), but it is also important to know if there is a decrease in false alarms, which would mean a criterion shift. If the rate at which a subject detects the stimuli falls, but there are no changes in false alarms, then there is a reduction in stimulus sensitivity.

In a study of smoking and visual vigilance, the Mackworth Clock (Mackworth 1950) was used because it produces a reliable vigilance decrement. Cigarette smokers who were allowed to smoke at 20-min intervals throughout the 80-min vigilance task maintained their stimulus sensitivity to experimental targets (Wesnes and Warburton 1978). In contrast, sensitivity was reported to drop for a group of nonsmokers and for a group of smokers who were not allowed to smoke. This finding suggests that smoking helped to maintain vigilance, but it could be that abstinence from smoking contributed to the performance decrement for smokers who were not allowed to smoke.

Tong and coworkers (1977) studied the performance of nonsmokers, smokers not smoking, and smokers smoking on a 60-min auditory vigilance task. While nonsmokers and smokers not smoking detected fewer signals as the test progressed, smokers smoking increased their number of detections. Again, it seems that smoking improved vigilance. However, this conclusion is tempered by the fact that the nonsmokers generally performed better than did the smokers on this task. Wesnes and Warburton (1978) reported that smokers maintained their initial level of stimulus sensitivity to auditory targets over an 80-min vigilance session when they smoked cigarettes at 20-min intervals. When they performed the task while smoking nicotine-free cigarettes, their sensitivity decreased over time. A similar study with a higher target density found a similar result: smoking was accompanied by maintained stimulus sensitivity (Mangan 1982). Whether smoking increased vigilance or whether abstinence decreased vigilance is not clear.

To determine whether nicotine was responsible for these effects of cigarette smoking on attention, Wesnes, Warburton, and Matz (1983) gave subjects nicotine tablets under the tongue and examined visual vigilance. The tablets consisted of nicotine placed on an alkaline matrix material to permit buccal absorption. Nicotine helped reduce the vigilance decrement by maintaining stimulus sensitivity. The nicotine tablets produced the same effects in nonsmokers, light smokers, and heavy smokers (Wesnes, Warburton, Matz 1983). Wesnes and Warburton (1978) found a similar effect of nicotine tablets on smokers but found no effect on performance by nonsmokers. Wesnes and Warburton (1984b) reported a small improvement in performance by nonsmokers given 1.5-mg-nicotine tablets; 1.0-mg- and 0.5-mg-nicotine tablets did not improve performance.

The effects of smoking on sustained reaction time performance, which has a vigilance component, were studied by Frankenhaeuser and others (1971). The experimental sessions lasted 80 min during which subjects continually performed a simple visual reaction time test. In the nonsmoking condition, the speed of reaction decreased over time; in the smoking condition, there was little change over the

session. Subjects abstained from smoking the night before participating in this study. Therefore, the smokers in the nonsmoking condition were deprived for many hours.

Wittenborn (1943) factor analyzed attention tests and found that picking out various sequences of numbers or letters from an array was most heavily loaded on what he called an "attention" or "mental concentration" factor. Williams (1980) assessed the effects of smoking by smokers on a test of this sort that involved crossing out each letter "E" found in sheets of randomly ordered letters arranged in lines of 30 letters. Smoking cigarettes produced significant improvement in performance of the letter cancellation task compared to sham smoking an unlit cigarette (Williams 1980). Because the subjects had abstained from smoking overnight before the experiment, it is not clear whether smoking improved performance or whether deprivation caused a decrease in performance.

A computer version of the letter crossing test is the Bakan task (Bakan 1959), in which a series of digits is presented at the rate of 1/sec from which subjects are required to detect certain specified three-digit sequences. Measures of both the speed and the accuracy of detection rate are made. Performance on this rapid visual information processing task after smoking was improved in both speed and accuracy above baseline levels, whereas either not smoking or smoking nicotine-free cigarettes resulted in a decline in speed and accuracy below baseline levels (Wesnes and Warburton 1983). The improvement in both speed and accuracy indicates that there is no speed and accuracy tradeoff. Higher-yield cigarettes improved performance more than low-yield ones, suggesting that nicotine is involved in these effects (Wesnes and Warburton 1984a). This interpretation is supported by studies with cigarettes with similar nicotine content but varying levels of tar and carbon monoxide (CO); cigarettes with the same nicotine content have the same effect on speed and accuracy (Warburton, in press). However, these conclusions must remain tentative until nicotine levels in the body are measured.

Analyses of performance during cigarette smoking indicate a 15-percent increase in speed and accuracy (Wesnes 1987) and improvement puff by puff (Warburton, in press). Rapid visual information processing has been studied during cigarette smoking puff by puff. Even with one puff, the probability of correct detections in the smoking conditions was higher than in the nonsmoking condition, and a single puff produced a change in reaction time (Warburton, in press). These findings suggest that smoking improves performance. However, these within-subject analyses need to be replicated and compared to nonsmoker control groups.

Selective Attention

Selective-attention tasks involve either focused or divided attention. Focused-attention tasks require subjects to attend to one source of information to the exclusion of others. Divided-attention tasks require subjects to divide their monitoring between two or more sources of information.

One study of selective attention (Tarriere and Hartemann 1964) combined central guiding with peripheral visual monitoring. The task lasted for 2.5 hr, and the measure of performance reported was the percentage of the peripheral visual signals that were missed during the session. Monitoring performance was maintained by smoking, in contrast to the large increase in the percentage of signal omissions when the subjects (all of whom were smokers) were not smoking.

In a study of divided attention, a test was based on the rapid visual information task (Warburton and Walters, in press; Wesnes and Warburton 1984a). Subjects were presented with digits at a rate of 50/min in both the visual and auditory modalities, with a different sequence for each modality. The detection of sequences in both parts of the divided attention task improved significantly after the smoking of one cigarette in comparison with not smoking. Smoking a cigarette also prevented the increase in reaction times that occurred in the control condition (smokers not smoking).

These studies show that smokers who smoke before selective attention tasks perform better than smokers who abstain from smoking before these tasks. Both the sustained and selective attention data indicate that smoking helps the smoker to perform.

Distraction

The Stroop test has been used in smoking research to examine distraction effects. The Stroop test uses three sets of displays: a list of color words printed in black, a set of color patches, and a list of color words with the words printed in incongruent colors (e.g., the word "Green" printed in blue). Subjects' word reading is faster than color naming, while naming the incongruously printed color words takes much longer than naming the patches. The time difference between naming the colors in the two conditions is the Stroop effect. This score indicates the subject's ability to focus attention on a relevant stimulus dimension of print color and to ignore an irrelevant semantic one.

The effects of nicotine on the Stroop performance of smokers and nonsmokers have been studied (Wesnes and Warburton 1978; Wesnes and Revell 1984). Wesnes and Warburton (1978) reported that nicotine reduced the size of the Stroop effect and that there were no differences between smokers and nonsmokers in the amount

of improvement produced by nicotine. This finding supports the argument that the effects of nicotine on attention are similar in smokers and nonsmokers. However, only six smokers and six nonsmokers participated in this study. Also, the performance by nonsmokers was not improved by nicotine tablets in the Wesnes and Revell (1984) study. Therefore, conclusions must be tentative until the findings of Wesnes and Warburton (1978) are replicated.

Evidence from the few distraction studies that have been reported is consistent with the results for sustained and selective attention. It may be that smoking and nicotine improve a general attentional processing capacity including improved attention to relevant stimuli (sustained and selective attention data) and ability to disregard irrelevant stimuli (distraction data). However, until studies include nonsmoker control groups and measure nicotine levels in the body, the conclusion that smoking improves attention remains plausible but equivocal. It is reasonable to conclude that the attention of smokers is better after smoking than after deprivation from cigarettes.

Learning and Memory

Numerous animal studies have demonstrated that nicotine improves learning and memory when it is administered pretrial and posttrial (Bättig 1970; Bovet-Nitti 1965; Castellano 1976; Erickson 1971; Evangelista, Gattoni, Izquierdo 1970; Stripling and Alpern 1974; Szekely, Borsy, Kiraly 1974). The effects of smoking and nicotine on human learning and memory are surprisingly complex in comparison with the effects described in reports of animal studies. Some studies of the effects of smoking on human learning and memory have shown that smoking improves this aspect of mental ability (Mangan 1983; Mangan and Golding 1978; Warburton et al. 1986). Studies of the effects of pure nicotine on human learning and memory have shown that nicotine improves memory just as smoking does (Warburton et al. 1986). However, Hull (1924) found evidence of impairment in auditory memory and in the efficiency of rote learning immediately after smoking, and later studies also have found that smoking can interfere with learning and memory, especially immediate memory (Gonzales and Harris 1980). The effects of smoking and nicotine on learning, immediate memory, delayed recall, and state-dependent memory are addressed separately.

Learning

There is no evidence for improved acquisition of information (i.e., general learning) after smoking. For example, Carter (1974) reported a higher number of correct responses from 10 smoking subjects than

from 10 nonsmoking subjects on a letter-digit substitution task for the second of 2 10-trial blocks given in the first 2 sessions (7 days apart). However, there was no difference between groups in savings (number of trials) for serial learning of a letter-digit substitution task.

Kleinman, Vaughn, and Christ (1973) had nonsmokers, 24-hr deprived smokers, and nondeprived smokers do paired-associate learning of a low- or high-meaningful list of nonsense syllables. There was no difference in learning among the groups on both trial and errors to a criterion. However, deprived smokers performed better on the high-meaningful list and worse on the low-meaningful list than did either of the other two groups.

The effects of nicotine on learning also have been investigated. Andersson and Post (1974) compared the effects of nicotine cigarettes with those of nicotine-free cigarettes in subjects learning a nonsense syllable list. Significant increases in heart rate indicated that nicotine was absorbed from the nicotine cigarettes. The first cigarette was given after the first 10 trials of learning the list, and a second cigarette, of the same kind, was given after 20 trials. The learning curves were identical for the two conditions prior to smoking. After nicotine, the number correct decreased and remained below the scores in the nicotine-free condition, but the learning curves were parallel. Thus, the rate of learning was not changed by smoking. After the second nicotine cigarette, the number of correct syllables increased significantly to the same level of acquisition performance as in the nicotine-free cigarette condition. Relative to the previous performance, nicotine had improved recall of the syllables. The difficulty in interpreting the effects of nicotine in this study is that learning and recall occurred over a 20-min period, while plasma and brain levels of nicotine would be expected to fall well below their peak levels. These data give no evidence of nicotine impairing acquisition, because the learning curves are parallel after the nicotine cigarette. However, it appeared that after the first nicotine cigarette, the information stored in the non-nicotine state was less available in the nicotine state, a phenomenon known as state-dependent learning. (See "State-Dependent Memory" below for a fuller discussion of this phenomenon.)

In another study, Andersson (1975) examined the effects of smoking on verbal rote learning using a similar procedure. Ten smokers were tested on two occasions during which they were initially given 10 successive trials followed by an 8-min break. In one condition, the subjects smoked a 2.1-mg-nicotine-delivery cigarette during this period, and in the other they simply rested. Then, another 10 trials took place, after which a 45-min break was given, followed by a final learning trial. As in the previous study, recall was significantly lower immediately after smoking. This lowered recall

tended to recover on successive trials. After the 45-min break, the recall in the two conditions was again identical.

Immediate Memory

In a study of immediate memory (Williams 1980), subjects were tested within 15 min after smoking one cigarette. They were given lists of numbers to memorize and then were immediately asked to recall them in the correct sequence (constrained recall). No main effects were significant. Controlling for presmoking performance, the number of errors increased with strength of cigarettes smoked.

Houston, Schneider, and Jarvik (1978) had 23 heavy smokers, deprived of cigarettes for 3 hr, read a list of words. The subjects were matched on a free-recall test prior to smoking. Each member of one group smoked a 1.5-mg-nicotine cigarette, and each member of the other group smoked a non-nicotine cigarette. The subjects were given three lists with free recall tests after each one. The immediate recall scores showed that the nicotine group had significantly less recall than the placebo group did. When testing was given once just after the input, however, facilitation was seen (Warburton et al. 1986). After smoking a 1.4-mg-nicotine cigarette, each of these subjects was shown a list of nouns and immediately asked to write down as many as possible. Measures of immediate recall were improved in smokers after smoking compared with not smoking.

Comparison of Immediate and Delayed Recall

Gonzales and Harris (1980) assessed the effects of smoking or abstinence on immediate and delayed memory of new and old (previously presented) words, as well as category clustering. Smokers smoking showed significantly poorer immediate and delayed recall of old words and less clustering of words into categories on the delayed recall test as compared with smokers who were not allowed to smoke before the tasks.

Mangan (1983) examined the effects of smoking a low- (0.7 mg) and a middle- (1.3 mg) nicotine-yield cigarette on paired-associate and serial learning and retention. Conditions included high and low intralist interference. Cigarettes improved retention in paired-associate learning, with task difficulty apparently having little relevance. Smoking impeded learning under low-interference conditions, but facilitated learning of high-interference sets.

Mangan and Golding (1983) studied the effects on memory of smoking deprivation and of smoking a single cigarette immediately after acquisition of a paired-associate learning task. Subjects were retested for retention of the memorized material at intervals of 30 min, 1 day, 1 week, and 1 month. At 30-min retest, nonsmokers showed superior recall compared with all smokers. After 1 month,

subjects who each smoked a low- and medium-nicotine cigarette were better than those who smoked high-nicotine cigarettes. They also achieved superior recall compared with nonsmokers.

Peeke and Peeke (1984) tested the effects of smoking one cigarette on verbal memory and attention in four experiments. In one study, subjects were allowed to smoke before the test ("pretrial smoking"), after the test ("posttrial smoking") or not at all ("no smoking"). Recall of a 50-word list was tested immediately after intervals of 10 and 45 min. Pretrial smoking resulted in improved recall 10 and 45 min after learning, but not immediately. Posttrial smoking was ineffectual. Tests at 1, 5, and 30 min after presentation of a 20-word list were compared with results from pretrial smoking. Improved recall occurred for pretrial smoking. The high-nicotine cigarette produced improved recall on both immediate- and delayed-recall tests. The low-nicotine cigarette was less effective. Light and heavy smokers did not differ in the effect of smoking on recall.

Andersson and Hockey (1977) presented words in different positions on a computer screen to smokers allowed to smoke or not allowed to smoke. In one condition, subjects had to remember the words in presentation order. In the second condition, subjects were asked to remember words, word order, and location. There were no differences between the smoking and no-smoking conditions in the percentage of words that were recalled in the correct order or for the percentage of words that were recalled correctly, regardless of word order. However, recall of position on the screen was poorer for the smoking group. When the subjects were asked to attend to all three aspects of the material, the groups did not differ significantly in their recall, although there was a trend for location to be recalled better after nicotine use than after deprivation. This study suggests that nicotine can enhance storage of information only if the subjects perceive that the information is relevant.

State-Dependent Memory

In a state-dependent design, one group of subjects learns after a dose of drug while a second group learns after a placebo or nothing. For the recall test both groups are divided: half of each group is tested with the agent presented during learning and half is switched to the other condition. If the recall scores are better for those groups that learned in the same chemical state, then state-dependent learning is said to have occurred. Numerous animal studies have provided evidence of state dependency with cholinergic drugs (Warburton 1977). The possibility that nicotine produces state-dependent learning in human subjects has been investigated in several studies.

Kunsendorf and Wigner (1985) examined state-dependent recall on text material. Subjects spent 15 min studying a 550-word article on

education and answered 6 factual questions based on the article after a 10-min break. The treatment conditions were smoking versus no smoking during the study period and during testing. When studying and testing were conducted for the same subject state (either smoking or no smoking), memory was better than when study and testing were conducted for different states.

Other investigators also have found evidence for state-dependent learning with smoking. Peters and McGee (1982) used the state-dependent design to test smoking's effect on recall and recognition memory. After smoking a 1.4-mg-nicotine cigarette, each subject was shown a list of nouns and immediately asked to write down as many as possible. There was no evidence of any difference in immediate recall, a finding in agreement with Andersson and Hockey (1977) and Houston, Schneider, and Jarvik (1978). However, on the following day, there was a state-dependent effect on the recognition test but no difference between the same-state groups.

In another recognition study (Warburton et al. 1986), smokers who were deprived of cigarettes for more than 10 hr were each given a 1.4-mg-nicotine cigarette or nothing immediately before serial presentation of a set of Chinese characters. Subjects were divided into four equal groups: Those who did not smoke prior to learning or recall; those who did not smoke prior to learning, but had a cigarette prior to recall; those who had a cigarette prior to both learning and recall; and those who had a cigarette prior to learning, but none prior to recall. Subjects who smoked prior to learning had significantly better recognition scores than the subjects who did not smoke in the first part of the experiment. There was no effect of smoking on recall performance. A significant interaction term indicated that changing the chemical state interfered with recognition.

Warburton and colleagues (1980) used nicotine tablets in the state-dependent design. After ingesting the tablet, each subject listened to words and then performed successive subtractions for 1 min to prevent rehearsal. Immediate free recall was improved. One hour later, the subjects were given either nicotine or placebo tablets. They were asked to recall as many of the words as they could in another 10-min free recall test. Long-term recall was significantly better when subjects had taken nicotine prior to learning, but was not when taken prior to recall. A significant interaction term gave evidence for a state-dependent effect of nicotine and showed that nicotine was facilitating the input of information to storage, but had no direct effect on storage or retrieval.

These findings suggest that there is a state-dependent effect of smoking on cognitive performance. The seeming impairment of immediate memory, however, complicates any simple generalizations about smoking and memory or nicotine and memory. As with the attention literature, studies need to include nonsmokers as

controls to determine whether smoking or abstinence from smoking affects learning or memory. In addition, task characteristics and individual differences among subjects must be considered in future investigations. Based on the available evidence, there are no clear effects of smoking on learning or memory.

Problem Solving

Human problem-solving capabilities involve both attention and memory. Attention is important because distraction from the task will cause a deterioration in problem-solving performance. Memory also plays a critical role in thought, both guiding the operations of the thought processes and limiting their power. Problems can be broadly categorized as well defined and ill defined. A well-defined problem has a clearly stated goal with a clear method to ascertain if the problem solving will lead to the correct solution. A well-defined problem can be solved by convergent thinking that produces logically correct answers. A simple example of a well-defined problem is addition. Ill-defined problems are solved by divergent thinking that leads to inventive solutions.

Hull (1924) found that smoking increased the rate of complex mental addition, but had no measurable effect on the accuracy of addition. Kucek (1975) found that the reduced efficiency of mental addition that was produced by doing a tracking task was ameliorated by smoking. The improvement was especially manifested in the most neurotic subjects. One interpretation of this improvement is that the attentional effects of nicotine enabled the filtering out of the distracted thoughts that interfered with performance.

A task that has elements of both convergent and divergent thinking is the Luchins Jar test (Luchins 1942), in which subjects are asked to solve a number of "numerical problems" involving the measurement of a quantity of water by means of a set of measuring jars. For the first six trials, exactly the same solution can be used, but after trial six, both the old formula and a new, easier formula are appropriate. A measure of convergent thinking is performance on the first six trials, while divergent thinking is assessed from the time taken to discover the new, easier solution. Smokers who were allowed to smoke performed better on the first half of the test in which subjects used the same solution repeatedly (convergent thinking), but were slower to change to a simpler solution when it was available, divergent thinking (Warburton 1987). While it could be argued that nicotine had impaired divergent thinking, it has been argued that it is more efficient for a subject to use a known strategy, no matter how clumsy it might be, than to attempt to invent a new one, i.e., to maintain attention (Norman 1980).

Motor Control

The effects of smoking on motor control were investigated in the early laboratory study of Hull (1924). He found a marked increase in hand tremor, a slight increase in resistance to muscular fatigue and in speed of reading reaction time, and no measurable effect on the rate of tapping or on the rate or accuracy of eye-hand reaction. These reports have received support from more recent studies (Lyon et al. 1975; Smith, Tong, Leigh 1977). West and Jarvis (1986) reported that nasal administration of nicotine increases tapping rate in nonsmokers.

Tremor

Lippold, Williams, and Wilson (1980) recorded finger tremor during a control period, sham smoking, or cigarette smoking with a strain gauge and an accelerometer. Smoking increased tremor amplitude at least twofold.

Simple Reaction Time

Cotten, Thomas, and Stewart (1971) investigated the immediate effects of smoking one cigarette on simple reaction time after each subject smoked a cigarette with a 1.5-mg nicotine yield. The mean reaction times immediately following and 5 min after smoking were significantly slower than for all other test intervals. Reaction times for the 40- and 55-min intervals were significantly faster than the reaction time before smoking.

Morgan and Pickens (1982) examined whether reaction time performance after smoking varied as a function of cigarette smoking. Twelve regular smokers were tested on a reaction time task immediately after smoking on three different occasions. In each session, they were allowed *ad libitum* smoking of their own cigarette, or *ad libitum* smoking of a standard cigarette, or they had to smoke a standard cigarette with a prescribed puff pattern. Reaction time performance was significantly faster after smoking under the latter two of the three conditions. Mean reaction times were significantly shorter for the smokers smoking than for the smokers not smoking.

Choice Reaction Time

Myrsten and Andersson (1978) compared the effects of smoking for both simple and complex reaction time tasks. In the simple reaction time testing periods, smoking prevented the significant increase in reaction time that occurred over time in the nonsmoking condition. In the complex reaction time periods, smoking significantly reduced reaction time, whereas reaction time increases were not significant in the nonsmoking condition.

Decision time and motor time scores on a choice reaction time task were measured after smoking (Lyon et al. 1975; Smith, Tong, Leigh 1977). Decision time scores were significantly decreased by smoking, and the high-nicotine cigarette had the greatest effect. Motor time scores were not improved, and hand steadiness was significantly impaired by smoking.

Smokers, deprived smokers, and nonsmokers performed a compensatory tracking task while simultaneously performing a cross-adaptive loading task (Schori and Jones 1975). With the cross-adaptive technique, the size of the subject's total work load (tracking and loading tasks combined) was individually tailored to use each subject's entire attentional capacity. No differences were detected as a function of smoking either in tracking or in loading task performance.

Smokers, deprived smokers, and nonsmokers performed a complex motor task, consisting of five subtasks, for an extended period of time at two levels of task complexity (Schori and Jones 1974). On only one subtask, on one of the two performance measures obtained, were differences as a function of smoking condition evident. Specifically, response latencies for nonsmokers were shorter than those for smokers and deprived smokers at the high level of task complexity, but were longer at the lower level. Because the performance differences were small, Schori and Jones (1974) concluded that for all practical purposes, smoking had no effect on performance.

Implications for Tobacco Use

Some cigarette smokers report that smoking helps them to think and perform. Laboratory studies of attention and state-dependent learning are generally consistent with this perception, but studies of memory and learning do not support this perception. Data on problem solving are too limited to allow clear conclusions. The improvement in attention, state-dependent learning, and some motor performance tasks are, in most cases, superior in smokers who are allowed to smoke compared with a smoking abstinence condition. Therefore, these effects may, in part, reflect reversal of the deleterious effects of smoking abstinence. In contrast to this cautious interpretation, however, it should be noted that the experiments that administer nicotine and report similar improvements in nonsmokers and smokers are consistent with the interpretation that smoking improves some cognitive performance. In light of these data, smokers' self-reports and perceptions may be correct that smoking helps them to attend, think, and perform. However, until more careful investigations are reported, conclusions concerning the effects of smoking and nicotine on human performance must remain tentative. Future studies should include nonsmokers as controls and should measure nicotine levels after smoking or abstinence.

Current methods in cognitive psychology indicate that different paradigms for evaluating memory and performance (e.g., data-dependent versus context-dependent memory measures) produce opposite effects in many cognitive tasks (Richardson-Klavehn and Bjork 1988). The effects of smoking and nicotine on these different types of tasks need to be evaluated. A recent presentation on smoking and performance, for example, reported that smoking improved performance on simple reaction tasks but impaired performance on more complex comprehension and motor performance tasks (Spilich 1987). Tasks requiring different levels of demand must be examined. Moreover, future research should evaluate performance over time to determine whether any short-term effects of smoking or nicotine on performance persist or are reversed later on. Nonetheless, the fact that smokers smoking generally perform better on some cognitive tasks (especially attention tasks) than do smokers not smoking may encourage smokers to continue smoking and may encourage relapse.

Tobacco Use, Nicotine, Stress, and Mood Regulation

Cigarette smokers commonly report that they smoke in response to stressful situations and that smoking calms them. In addition, many smokers report that smoking helps to regulate dysphoric mood or affect. Reports of a relationship between stress and smoking generally have been regarded as puzzling in light of the sympathomimetic effects (i.e., sympathetic nervous system (SNS) activating actions) of nicotine, but the consistency of these claims has brought research attention to these topics. The possibility that smoking may help to regulate dysphoric moods that involve low arousal states is easier to understand. This Section reviews the relevant research literature and presents current thinking to help explain these phenomena.

Subjective Well-Being, Stress, and Mood Regulation

The state of subjective well-being is construed as one in which positive affect (pleasure, happiness) is high and negative affect (frustration, anger, tension) is low (Watson and Tellegen 1985). Departures from an optimal state may occur because of internally generated affect (worry, anxiety) or through environmental events that strain the coping ability of the individual (Dohrenwend and Dohrenwend 1981). A state of subjective stress is postulated to be a joint function of the current environmental demands and the current coping abilities of the individual (Lazarus and Launier 1978; Lazarus and Folkman 1984). When demands exceed coping ability, a state of subjective stress may arise that manifests at the psychological level as symptoms of psychological distress and at the physiological level as changes in (SNS) arousal, changes in endocrine systems,

and decrements in specific task performance (Baum, Grunberg, Singer 1982; Cohen, Kamarck, Mermelstein 1983). In natural settings, stress may occur because of discrete events that cause a transient peak in subjective distress or in conditions that persist over considerable periods of time and thus present sources of chronic strain to affected individuals (Pearlin and Schooler 1978; Pearlin et al. 1981).

Overall mood states are related to independent contributions by dimensions of positive affect and negative affect: well-being is determined by low negative affect and by high positive affect (Diener 1984). Studies of mood states in natural settings over intermediate time periods of 1 day to 1 week show that the dimensions of negative and positive mood are independent, that is, they both occur on a regular basis in daily life and both contribute to overall mood states (Stone, Helder, Schneider 1987). Mood may be regulated both by reduction of negative affect and by increase of positive affect (Tomkins 1962, 1963; Wills and Shiffman 1985).

Subjective well-being could be improved through reducing the perceived environmental demands, through physiologically influencing stress-related arousal states, through reducing perception of unpleasant physical states, or through altering the balance of positive/negative affect in daily life. These mechanisms are relevant to understanding the relationship between stress and cigarette smoking (Tomkins 1965).

Perceived Functions of Smoking

A number of epidemiological studies have examined the perceived functions that smoking provides for users by employing large samples that are usually representative of communities; in some cases, representative national samples have been obtained. These studies ask respondents about various functions that smoking is perceived to provide for them, and the researchers aim to determine basic functional dimensions through factor analysis or cluster analysis of the motive reports. The questionnaire items used to elicit smoking functions vary considerably, including items that elicit agreement/disagreement with statements about smoking, items that elicit the frequency or likelihood of smoking in defined situations, or items that ask about a desire to smoke in certain settings. Although the methodology and sampling procedures have varied considerably across studies, there is consistency in the results. One higher order domain of intercorrelated motive dimensions indicates that smoking is perceived to provide *negative affect reduction*; another domain indicates that smoking is perceived to provide *positive affect enhancement*. Findings from the relevant studies, classified in terms of these higher-order domains, are presented in Table 1. (Survey studies also indicate that many smokers report that smoking keeps

weight down and that weight control is one of their major concerns (Charlton 1984a,b; Feldman, Hodgson, Corber 1985; Page 1983). However, for purposes of expositional clarity, this Section focuses on affect regulation and stress. Smoking and body weight are discussed in the next Section of this Chapter.)

A typical study of perceived functions was conducted in the United States by Ikard, Green, and Horn (1969) with a representative national sample of 2,094 adult respondents. In this study, subjects were presented with a list of 23 statements about smoking, representing various combinations of situation and emotion and were asked to indicate their agreement or disagreement about whether the statement was true for them. Orthogonal factor analysis of the items indicated that six basic motives were represented in the data. A factor termed "Reduction of Negative Affect" was loaded by items such as "When I feel upset about something, I light up a cigarette" and "Few things help better than cigarettes when I'm feeling upset." The domain of positive affect enhancement was represented by a factor dimension termed "Pleasurable Relaxation," which included items such as "Smoking cigarettes is pleasant and relaxing." This factor was not correlated with any of the other five factors found in the study, indicating that it is an independent functional dimension. A factor concerning addictive smoking, which included items reporting a strong desire or craving for cigarettes, was substantially correlated with the negative affect factor and for that reason is included under the domain of negative affect reduction.

Other studies of smoking motives have replicated the two domains of negative- and positive-affect regulation. Under the general domain of negative affect reduction, McKennell (1970) surveyed a representative national sample of 1,140 adolescents and adults in Great Britain and found that three factors termed "Nervous Irritation Smoking," "Smoking Alone," and "Food Substitution" were strongly intercorrelated, all representing an increased probability of smoking during unpleasant states. Coan (1973) and Leventhal and Avis (1976), in studies with college students, found almost identical factors termed "Negative Affect Reduction" and "Anxiety Reduction," which in each case were substantially correlated with another factor representing addictive smoking. Additionally, Coan (1973) found a factor termed "Distraction," which included items suggesting that smoking was sometimes used as a means of diverting attention from disturbing stimuli. (This self-report is consistent with the discussion of distraction studies presented in the first Section of this Chapter.) Best and Hakstian (1978) surveyed a sample of 331 adult commuters with an inventory about the relative strength of their urge to smoke in each of 63 situations. Intercorrelated dimensions termed "Nervous Tension," "Frustration," "Embarrassment," "Discomfort,"

TABLE 1.—Summary of studies of perceived functions of smoking

Domain/Factors	Ikard et al. (1969)	McKennell (1970)	Coan (1973)	Leventhal and Avis (1976)	Best and Hakstian (1978)	Baumann and Chenoweth (1984)
Negative affect reduction	Negative affect reduction Addictive smoking	Nervous irritation Food substitution Smoking alone	Negative affect reduction Addiction Distraction Agitated state	Anxiety reduction Addiction	Nervous tension Frustration Discomfort Anger/Impatience Restlessness	n.a. ¹
Positive affect enhancement	Pleasurable relaxation	Relaxation Social confidence smoking	Pleasurable relaxation Dependence on mental state Sensorimotor pleasure	Pleasure/Taste	Relaxation	Pleasure
Other functions	Habitual smoking Stimulation Sensorimotor manipulation Social smoking	Activity accompaniment	Habitual action Stimulation Concentration Social reward Unpleasant habit	Habit Stimulation Fiddling Social reward Inactivity/Boredom Time structuring	Automatic smoking Sensory stimulation Concentration Social smoking Positive peer relationships	Habit

NOTE: Factors of comparable content are on the same line.

¹n.a.=factors not available because relevant items not in study.

"Restlessness," and "Anger/Impatience" all indicated elevated rates of smoking in different types of negative affect situations.

Under the domain of positive-affect enhancement, findings are less consistent because studies typically included relatively few items on pleasurable aspects of smoking. Despite this methodological limitation, each of the studies contains one or two factors that represent a function of smoking to produce positive affect. A factor termed "Pleasurable Relaxation" found by Coan (1973) indicated smoking in circumstances that were relaxed and comfortable, and comparable factors termed "Pleasure" were found among adults (Leventhal and Avis 1976) and adolescents (Baumann and Chenoweth 1984). In each case, these dimensions were uncorrelated with negative affect factors or with other dimensions found in the study. Factors that were termed "Relaxation" by two investigators (Best and Hakstian 1978; McKennell 1970) represent smoking in conditions where one is alone or wants to cheer up.

The studies have indicated some additional functional dimensions not included within the two affective domains. Some dimensions represent habitual or automatic smoking that occurs without conscious attention. These self-reported dimensions are consistent with the data presented in Chapter IV that address compulsive drug-seeking properties of nicotine and tobacco use. Another common dimension represents smoking to increase stimulation, typically in conditions of inactivity or boredom; sometimes another dimension is included, indicating that smokers report that smoking helps improve concentration (Best and Hakstian 1978; Coan 1973; Leventhal and Avis 1976). This latter perceived effect is discussed in detail in the first Section of this Chapter. Dimensions representing smoking in social situations indicate that smoking occurs primarily at parties or social gatherings, and these factors typically are uncorrelated with affective dimensions.

With regard to individual differences in motives for smoking, there are some consistencies across studies. Amount of smoking tends to be greater for persons scoring high on negative affect reduction (Ikard, Green, Horn 1969; McKennell 1970), although persons scoring high on habitual smoking may have a greater frequency of smoking (Ikard, Green, Horn 1969; Leventhal and Avis 1976). Sex differences are sometimes found in functional dimensions, with females scoring higher on negative-affect reduction (Frith 1971; Ikard, Green, Horn 1969; Ikard and Tomkins 1973), whereas males score higher on habitual, relaxation, or stimulation smoking (Frith 1971; Ikard, Green, Horn 1969; McKennell 1970). Findings on external correlates of motive dimensions indicate that adolescents who score high on the Pleasure dimension are more likely to initiate or increase smoking over time (Baumann and Chenoweth 1984), and adult smokers who score high on Negative Affect reduction are more

likely to relapse after smoking cessation treatment (Pomerleau, Adkins, Perstchuk 1978).

McKennell (1970) found 65 to 75 percent of adults reporting that they perceived smoking to reduce nervous irritation, and comparable levels of endorsement were found for other dimensions of negative- and positive-affect regulation factors. Some data indicate that endorsement rates for habitual, stimulation, sensorimotor manipulation, and social confidence smoking are low in absolute terms (Ikard, Green, Horn 1969; McKennell 1970). A study of young children (Eiser, Walsh, Eiser 1986) found that mood regulation effects of smoking were clearly perceived by subjects in the 7- to 8- and 10- to 11-year-old age ranges; this suggests that perceived functions of smoking may be learned partly by observation rather than through direct experience.

The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking helps them to feel better in such situations. Additionally, smoking is perceived to increase positive mood in some situations. These data do not necessarily indicate that the various functions characterize different types of smokers; rather, they suggest that most functions are salient to an individual but are operative at different times or in different situations. Similar to the discussion of smoking and performance in the first Section of this Chapter, self-reports by smokers that they smoke under stress may indicate direct effects of smoking and nicotine or may reflect effects of smoking deprivation that are relieved by smoking. Whichever interpretation is correct, individuals certainly report that stress is associated with smoking.

Stress and Smoking

There is evidence that stress can increase the likelihood of initiation of smoking if cigarettes are available. Further, considerable evidence exists to link negative-affect states to smoking behavior. The database includes studies of stress as a risk factor for smoking initiation during adolescence and studies on stress and rates of smoking among adults.

Stress and Smoking Initiation

Several studies have shown stress to be related to the onset of smoking in early adolescence. Studies of smoking initiation typically survey a large sample of adolescents beginning at approximately 12 years of age, because the onset of cigarette smoking is greatest during the junior high school period (Fishburne, Abelson, Cisin 1980; Green 1979). Measures of psychosocial risk factors are obtained from

questionnaire scales, and indices of smoking status are usually obtained from self-report by respondents, sometimes accompanied by a biochemical index of smoking. There is evidence indicating that self-reports of smoking by adolescents are generally accurate, although the accuracy of self-report data may be increased by administration of biochemical measures (Murray et al. 1987). Convergent results from cross-sectional and prospective studies show that stress is antecedent to substance use onset and is not a consequence of the initiation of smoking (Gorsuch and Butler 1976; Kandel 1978; Kandel, Kessler, Margulies 1978; Kaplan et al. 1986).

The most direct evidence linking smoking to negative mood states is based on measures of subjective stress. A cross-sectional study by Mitic, McGuire, and Neumann (1985) surveyed a random sample of 1,684 school students in grades 7 through 12 in a medium-sized Canadian community and obtained measures indexing whether students felt nervous, anxious, or worried as a result of 12 potential problem areas. Analyses for the total sample indicated that regular and heavy smokers scored higher on perceived stress, compared with nonsmokers. A related study by Hirschman, Leventhal, and Glynn (1984) employed as the criterion variable a retrospective report of smoking experiences during the previous 2 years. Data were obtained from a stratified sample of 386 students in grades 2 through 10 in a midwestern community. Analyses of data on smoking transitions indicated that a measure of affective distress was related to rapid transitions from experimental to regular smoking. These results were obtained in multivariate analyses with control for other variables including age, peer and parental smoking, and risk-taking tendency.

Comparable findings occurred in a prospective study by Wills (1985, 1986) of a population sample of 675 students in the 7th grade in a New York City school district. Analyses for a 14-item scale of subjective stress reactions showed that high stress was related to increased levels of smoking over a 2-year period. Additional data from this cohort and a replication cohort of 901 students were obtained with measures of everyday negative events and major life events. Multivariate analyses of these data indicated that all three measures of stress were related to smoking, with major negative events being the statistically strongest predictor. These analyses indicated that the effect of stress on smoking was not attributable to other variables including sex, race, locus of control, self-esteem, social activity, and assertiveness. These findings are consistent with laboratory data indicating that females under stress are more willing to try additional cigarettes after an initial smoking experience (Silverstein et al. 1982).

It should be noted that adoption of cigarette smoking has been shown to be a risk factor for subsequent adoptions of other types of

substance use. Although many adolescents who smoke do not become regular users of other drugs, there are typically a concurrent correlation between smoking and other types of drug use (Hays, Stacy, DiMatteo 1984; Single, Kandel, Faust 1974; Revell, Warburton, Wesnes 1986) and a statistical relationship between early cigarette smoking and subsequent use of hard liquor and marijuana (Kandel 1975; Donovan and Jessor 1983). There is no direct evidence linking multiple drug use to mood regulation effects, but it has been shown that negative life events are a risk factor not only for cigarette smoking, but also for several types of other drug use (Bruns and Geist 1984; Kellam, Brown, Fleming 1982; Newcomb and Harlow 1986).

For interpretation of data on stress and smoking in adolescents, the primary methodological issue concerns a possible third confounding variable. It may be that high levels of subjective stress are most prevalent among adolescents who have difficulty adjusting to school and family because of underlying psychopathology (Depue and Monroe 1986) and who identify with the values of a deviant lifestyle that includes substance use and delinquent behavior (Jessor and Jessor 1977). The current evidence argues against this interpretation; some data show that stress-smoking correlations remain significant with control for variables such as risk-taking, perceived control, and self-esteem (Hirschman, Leventhal, Glynn 1984; Newcomb and Harlow 1986; Wills 1985), and it has been shown that negative life events that could not be self-caused by adolescents show an independent predictive relationship to smoking (Wills 1986). The current evidence, however, is minimal and does not clearly rule out the alternative interpretation. At present it can be concluded that subjective stress may be a risk factor for adolescent smoking.

Stress and Cigarette Consumption

In considering evidence on affective factors and cigarette consumption among regular users, both epidemiological and laboratory data are available. Designs in the epidemiological studies are relatively weak because studies are largely cross-sectional, making causal interpretation difficult. When longitudinal data are available, the followup periods are rather short (approximately 1 year) in relation to the probable time course of stress-smoking relationships in adult populations. The following section presents the epidemiological evidence and laboratory studies of stress and smoking.

A large body of personality research has linked measures in the category of "neuroticism" to cigarette smoking among adult populations (Kozlowski 1979). These measures, which include scales of nervousness, emotionality, and anxiety, are conceptually similar to the concept of negative affectivity as defined by Watson and Clark (1984); that is, the tendency to perceive and experience negative

affect. Theoretically, this is the most relevant construct for examining links between affective factors and smoking. Of the 50 studies reviewed by Kozlowski (1979), half showed a significant relationship between neuroticism and smoking. Three studies in this literature showed the relationship between neuroticism and smoking to be more characteristic of females than males (Cherry and Kiernan 1976; Clausen 1968; Waters 1971). These studies were mostly cross-sectional, making inferences of causality problematic because of the possibility that smoking caused feelings of anxiety and depression. Also, Cherry and Kiernan (1976) analyzed longitudinal data and found that neuroticism predicted initiation of smoking by women but neuroticism predicted decreased likelihood of quitting by men. One prospective study (Seltzer and Oechsli 1985) related personality measures obtained at age 10 to smoking status at age 16 in a sample of 1,127 subjects from health maintenance organizations in the Oakland, California, area. The prospective analyses showed that measures of anger, restless sleep, and Type A personality were significantly related to onset of smoking. These analyses were performed with control for parental socioeconomic status and smoking. Measures of neuroticism and anxiety did not discriminate smokers in these analyses.

In the laboratory, smokers tend to smoke more during stressful situations (Epstein and Collins 1977; Rose, Ananda, Jarvik 1983; Schachter et al. 1977). Individuals attempting to quit smoking tend to experience relapses into a state of continued smoking during stressful situations (Shiffman 1986). Such findings are consistent with the self-reported claims of smokers that they smoke in order to reduce stress-induced negative affect. However, there is no convincing research evidence to indicate whether smoking actually reduces stress. It may be that smoking reduces stress relative to smoking deprivation or that smoking increases during stress without attenuating it.

It has been suggested that smokers smoke as a technique to deal with stress (Wills 1985). If smoking is indeed used as a coping mechanism, individuals with poor coping skills and/or with high degrees of chronic stress would be expected to have a higher prevalence of smoking. Three prospective studies have found associations between anxious, aggressive, and generally neurotic personality traits in childhood and the tendency toward smoking later in life (Cherry and Kiernan 1976; Lerner and Vicary 1984; Seltzer and Oechsli 1985). Cross-sectional surveys have repeatedly supported these findings, showing that neurotic, depressed, angry, and rebellious individuals are more likely to smoke compared with more emotionally stable individuals (Spielberger 1986). Ninety percent or more of alcoholics smoke (Istvan and Matarazzo 1984) compared with about 30 percent of the general adult non-alcoholic population in the

United States. Individuals who commit suicide are much more likely to be smokers (Cederlof, Friberg, Lundman 1977; Doll and Peto 1976). It has been argued that individuals with personality disturbances and related psychological problems may, in some cases, be using nicotine as a form of self-medication (Brown 1973; Warburton, Wesnes, Revell 1983). It has also been noted that the symptoms of nicotine withdrawal syndrome are very similar to those of clinical depression (Gilbert and Welser, *in press*). Emotional and psychological disorders with high incidences of tobacco consumption are characterized by high degrees of negative affect, and it seems likely that, like other tobacco consumers, individuals with such disorders use tobacco as a means of coping with negative affect and stress.

Recent studies have used measures more directly linked to the experience of stress. In a survey of a sample of 505 Navy men on amphibious assault ships, Burr (1984) employed a 19-item measure indexing perceived stress from the domains of job, organization, and family and related the stress scales to a single item about smoking status. Results showed that two scales from the stress measure, indexing Role Conflict and Family Strain, were significant discriminators of smokers and nonsmokers in this sample. These results are cross-sectional, but were obtained in a multivariate analysis that included a measure of locus of control. Similar results were found in a cross-sectional study by Tagliacozzo and Vaughn (1982) in a sample of 448 hospital nurses, using a 26-item inventory of job-related stress. In this study, the stress-smoking relationship was found primarily among respondents who were younger (<28 years) and single. Billings and Moos (1983) studied a community sample of 608 adult respondents in the San Francisco area and found that heavy smokers differed from nonsmokers in showing higher levels of anxiety/depression symptoms and negative life events (during the previous year) in the areas of work strain and family illness. Correlations between stressors and amount of smoking were found primarily for heavy smokers, not for light smokers in this population. These data are consistent with findings from a community sample of 938 adults in New Haven (Lindenthal, Myers, Pepper 1972). This study found that a high level of negative events (during the previous year) was related to increased rates of smoking, with some data suggesting that this effect occurred primarily among persons scoring high on psychological impairment as measured by the Gurin Index. In this study the relationship between stress and smoking held with control for sex, race, age, marital status, and social class.

Only two studies have examined smoking and stress at more than one time point. Conway and associates (1981) studied a sample of 34 Navy officers in a training setting. Data were obtained on stressors and smoking for 14 study days over an 8-month period. The days were categorized by independent raters for stress level; additionally,

subjects made a daily rating on an eight-item scale of mood and subjective stress. Results showed that rates of smoking were significantly correlated with both the daily subjective stress measures and with the objective categorization of days for stress level. Items on perceived stress, anger, fatigue, and fear were significantly related to smoking in the overall sample, but an item on depression was not significantly correlated with smoking. Within-subject analyses of stress-smoking relationships indicated that the significant overall correlations were apparently due to a small number of individuals, but there were no data presented to discriminate these more reactive individuals from other members of the sample. A prospective study by Aneshensel and Huba (1983) was based on longitudinal data from four time periods with a community sample of 742 adult respondents in the Los Angeles area. Data on cigarette smoking, scored on a 1-to-5 scale, were obtained at baseline and at a 1-year followup interval. Results showed that a baseline measure of depression was not related to smoking either concurrently or over the 1-year interval.

The field studies are, for the most part, ambiguous with respect to causal interpretation. This difficulty is alleviated in laboratory studies in which subjects are randomly assigned to conditions and predictor variables are experimentally manipulated. Several studies of stress and smoking in laboratory settings have consistently found that stress increases rates of smoking. The stressors manipulated include threat of electric shock (Schachter et al. 1977), noise (Cherek 1985; Golding and Mangan 1982), and performance anxiety (Rose, Ananda, Jarvik 1983). These latter researchers also employed a concentration task and found that smoking increased in both the anxiety and concentration conditions, compared with a control condition. One study, using a public speaking manipulation, failed to find a significant effect of stress on smoking (Glad and Adesso 1976).

Based on epidemiological and laboratory research, it can be concluded that stress increases the rate of smoking among regular smokers. The convergence of results from cross-sectional, retrospective, and repeated-measures studies, in combination with findings from laboratory research, supports the interpretation of a causal relationship. There is some evidence suggesting that life stress has a greater impact among heavy smokers and among persons scoring high on negative-affect measures, but evidence on individual differences in this literature is minimal. The psychological mechanisms linking stress to increased smoking have not been clearly demonstrated (Leventhal and Cleary 1980; Schachter, Silverstein, Perlick 1977; Pomerleau and Pomerleau 1984). It may be that smoking attenuates stress (e.g., by regulating mood), that smoking increases during stress but does not attenuate it, or that smoking during stress is experienced as less stressful only when compared with smoking

deprivation during stress. Some laboratory studies and substantial theoretical speculations have addressed these issues and are discussed below.

Do Smoking and Nicotine Reduce Stress and Improve Mood?

There is evidence that smoking is perceived as helpful for coping with stress and dysphoric mood. A further question is whether smoking actually reduces stress or improves mood. In epidemiological studies, this question has not been directly addressed, a major limitation in the literature. There are some laboratory studies that bear on this question. This Section summarizes experimental findings concerning the effects of smoking and nicotine on stress and affect modulation.

Self-Reported Stress Reduction and Affect Modulation

Smoking-deprived smokers usually report more negative affect than do smokers who are allowed to smoke if the setting is one which tends to produce mild-to-moderate negative affect. Compared with those deprived for an hour or more, individuals allowed to smoke report less anxiety (Gilbert and Spielberger 1987; Heimstra 1973; Pomerleau, Turk, Fertig 1984; Jarvik et al., in press) as well as less anger and irritation (Cetta 1977; Heimstra 1973; Neetz 1979) during performance of a variety of slightly stressful tasks. Tobacco deprivation is also associated with self-reports of decreased alertness, lessened mental efficiency, and increased boredom during a variety of cognitive tasks (Frankenhaeuser et al. 1971; Heimstra 1973).

Experimental research suggests that nicotine is the most important, and possibly the essential, component of the affect-modulating properties of tobacco use (Gilbert and Welser, in press; Pomerleau and Pomerleau 1984). For example, studies comparing the effects of nicotine-containing gum with no-nicotine placebo gum report that nicotine reduces negative affect in nicotine-deprived habitual smokers (Hughes et al. 1984; Jarvis et al. 1982; West et al. 1984). In addition, habitual smokers assigned to smoke cigarettes of normal nicotine yield report less negative affect than those who smoke very-low-nicotine-yield cigarettes (Gilbert 1985; Perlick 1977).

However, a number of studies have not observed reduced negative affect due to smoking high- versus low-nicotine-yield cigarettes (Bowen 1969; Dubren 1975; Fleming and Lombardo 1987; Gilbert and Hagen 1980; Gilbert 1985; Hatch, Bierner, Fisher 1983). Gilbert and Welser (in press) suggest that these studies included inadequate periods of tobacco deprivation and excessively rapid smoking of multiple cigarettes (probably producing nicotine toxicity). Degree and type of stress to which subjects are exposed may also influence outcomes. There is evidence suggesting that nicotine has stress-

attenuating effects when stressor stimuli are mild or moderate, distal (anticipatory), and ambiguous, but fails to have such effects when stressors are brief, proximal, and/or intense (Gilbert and Welser, in press). More research is needed to evaluate these possibilities.

Behavioral Indices of Stress Reduction and Affect Modulation

A small number of studies that used behavioral indices of affect support the hypothesis that nicotine can reduce negative affect. Several studies report that smoking, or smoking a high-nicotine relative to a low-nicotine cigarette, is associated with reduced aggression (Cherek 1981; Schechter and Rand 1974). However, Jones and Leiser (1976) found no such effects on aggressive behavior by using similar procedures. In addition, without nonsmokers as controls, it is impossible to know whether the differences that were reported between conditions resulted from nicotine administration or nicotine deprivation.

Hughes and colleagues (1984) asked spouses to provide daily ratings of the subjects' behavioral indications of mood. These subjects had abruptly quit smoking and were randomly assigned to chew placebo gum or gum containing nicotine. Subjects who chewed the placebo gum were rated by their spouses as exhibiting significantly more anger and tension after quitting smoking, while those who chewed nicotine polacrilex gum showed little change in these emotional states. Thus, it appears that the nicotine provided by the gum replaced the nicotine previously obtained by smoking, so that there was little change in mood. However, it also appears that nicotine deprivation resulted in the tension and anger and that nicotine did not reduce these variables below baseline values.

Several studies have used pain thresholds as dependent variables in assessing the effects of smoking and nicotine on anxiety. Two studies that tested the effects of smoking cigarettes of different nicotine yield on electric shock endurance report elevated endurance thresholds in subjects who smoked relative to those who did not and in the high-nicotine-cigarette conditions relative to the low-nicotine-cigarette conditions (Nesbitt 1969; Silverstein 1982). The increased willingness to endure electric shock by individuals in the smoking and high-nicotine conditions was interpreted by these investigators and others (Schachter 1973) as indicating that nicotine reduces the anxiety associated with the electric shock. Other studies used the length of time that individuals are willing to endure pain associated with immersion of a hand or foot in ice water (the cold-pressor test) as an indicator of anxiety. These studies also showed that smoking and another means of nicotine administration (snuff) increase endurance in this test. However, the anxiolytic interpretation of increased pain thresholds has been questioned (Gilbert 1979),

because of the observation that in some situations nicotine has been reported to increase detection thresholds for tactile (including electrical) stimuli. It may be that nicotine reduces sensitivity to pain directly, rather than via reduction of anxiety. Several studies have failed to find increased shock endurance thresholds associated with smoking (Jarvik et al., *in press*; Milgrom-Friedman, Penman, Meares 1983; Shiffman and Jarvik 1984). In addition, it is unclear whether smoking and nicotine reduced these operational estimates of stress or whether smoking deprivation increased them.

Studies of the effects of acute doses of nicotine on behavioral measures of activity in animals indicate that nicotine may reduce negative affect in a number of different species (Bell, Warburton, Brown 1985; Emley and Hutchinson 1983). However, close inspection of the procedures used in these studies reveals that doses that suppress behavioral indices of emotion also may produce nicotine toxicity. Such high doses may decrease a large variety of behavioral indices due to the induction of physical distress. However, Silverman (1971), using doses of nicotine comparable to smoking doses, reported nicotine-induced reductions of aggression. Careful evaluation of studies of the effects of nicotine on indices of emotion in nonhuman subjects indicates that while these studies generally support the view that nicotine has inherent negative-affect-reducing properties independent of withdrawal effects, most have administered such high doses of nicotine as to make their relevance to habitual nicotine use in humans questionable.

Overall, evidence from experimental studies supports survey findings suggesting that tobacco use and nicotine consumption are associated with decreases in negative affect in habitual tobacco users. As was true for the learning and performance literature, caution must be exercised in generalizing about smoking and nicotine's effects on stress and mood because most laboratory studies compare smokers smoking with smokers not smoking. Few studies include the important control group of nonsmokers not smoking to allow unequivocal determinations of whether smoking and nicotine are stress reducing or whether smoking abstinence and nicotine deprivation are stress increasing. Certainly, it seems that smoking by smokers is stress reducing compared with smokers not smoking. The experimental literature suggests that smoking and nicotine may reduce negative affect most effectively in situations involving mild or moderate distal (anticipatory) anxiety and/or ambiguous stressors. The roles that individual differences in personality, temperament, and psychopathology may play in determining the nature or degree of the stress-reducing effects of nicotine are yet to be determined.

Suggested Mechanisms Underlying Nicotine's Effects on Stress and Mood

Based on the extant epidemiological literature linking stress and smoking and the laboratory studies indicating that stress increases smoking, several investigators have offered mechanisms to explain these relationships. These theoretical positions are varied and none has yet received unequivocal support to the exclusion of the other proposed mechanisms. Perhaps several or all of these mechanisms are operating. The major positions are reviewed below.

An Emphasis on Nicotine Withdrawal Symptoms

Schachter (1979) suggested that nicotine reduces negative affect in smokers simply by reducing symptoms of nicotine withdrawal. Increased irritability, anxiety, and depression are the most common symptoms of smoking withdrawal (Murray and Lawrence 1984), and these are the very emotions that appear to be most consistently reduced by acute doses of nicotine in nicotine-deprived smokers (Gilbert and Welser, *in press*). Thus, alleviation of withdrawal symptoms may account for the capacity of nicotine to reduce negative affect in nicotine-deprived smokers.

The degree to which an individual is physically dependent on nicotine may account for the variable effects observed. Perlick (1977) found that normal-nicotine-delivery cigarettes alleviated annoyance in heavy but not light smokers. On the other hand, the reduction in negative affect following nicotine administration may not be simply and solely a consequence of withdrawal symptom relief, because several investigations showing such effects used minimally deprived individuals who had not developed withdrawal symptoms (Pomerleau 1981).

A variant of this proposed mechanism suggests that smoking increases under stress and in dysphoric mood states because biological and psychological effects of stress and dysphoric moods are similar to the experience of nicotine withdrawal. From past experience, smokers learn that smoking alleviates these unpleasant states. Therefore, stressors and dysphoric moods come to elicit smoking because of conditioned responses or because of misattribution of the unpleasant experiences to nicotine withdrawal (Barefoot and Girodo 1972; Grunberg and Baum 1985). This misattribution model has some empirical support but requires careful examination.

Neurochemical Models

Evidence has been offered in support of the hypothesis that nicotine-induced release of glucocorticoids and other neuromodulators, such as the endogenous opioid beta-endorphin, may account for nicotine's capacity to reduce stress and negative affect (Gilbert 1979;

Pomerleau and Pomerleau 1984). While high doses of nicotine and rapid smoking of cigarettes after a period of smoking deprivation cause reliable increases in plasma concentrations of such neuromodulators (Seyler et al. 1986), it is not clear whether normal smoking during nonstressful conditions causes increases in these neuromodulators (Gilbert and Welser, in press). However, normal smoking in combination with mild-to-moderate stress may result in such increases. In addition, even if such neurochemical changes occur, it is not clear whether they act to modulate stress or dysphoric moods.

Biphasic Action on the Sympathetic Nervous System

Studies of human performance show that performance on simple tasks is improved by higher arousal, but performance on complex tasks is impaired by a high arousal level (Levine, Kramer, Levine 1975). In coping with the varying demands of daily life, at times it may be advantageous to vary the level of sympathetic nervous system (SNS) arousal. The ability to regulate arousal in this fashion would enable individuals to appraise stressful situations as less threatening and could result in improved performance in various conditions. There is some evidence suggesting that nicotine may have biphasic effects on SNS responses, producing either stimulatory effects or dampening effects under different conditions. Under conditions of low environmental demand, the effect of nicotine is generally to produce stimulatory or SNS arousal effects, including increases in heart rate and blood pressure (Grunberg and Baum 1985; MacDougall et al. 1983, 1986). This effect may be responsible for the perceived functions of "stimulation" or coping with "inactivity/boredom" (Best and Hakstian 1978; Coan 1973; Ikard, Green, Horn 1969; Leventhal and Avis 1976), and there is evidence indicating that smoking improves performance on simple tasks (Suraway and Cox 1986; Wesnes and Warburton 1983). At high levels of arousal, however, there is some evidence that nicotine produces central nervous system (CNS) tranquilization effects or reduces reactivity to stressful stimulation (Armitage, Hall, Sellers 1969; Ashton et al. 1974; Golding and Mangan 1982; Woodson et al. 1986). Evidence suggests that nicotine can restore high brain activation to moderate levels. In low-arousal situations, such as vigilance tasks, nicotine produces cortical activation and increased alertness (Edwards et al. 1985). Increased cortical activation could increase hedonic tone directly or indirectly by allowing the individual to perform more effectively on desired tasks and thus to experience indirect rewards such as the perception of increased self-efficacy. In contrast, nicotine has been associated with decreased cortical activation and reduced anxiety in stressful conditions (Gilbert 1985; Golding and Mangan 1982). Nicotine administration by smoking and

other means may allow individuals to achieve a hedonically more desirable level of cortical activation (Eysenck 1972).

At present, there is no direct evidence linking these physiological effects to perceived stress reduction or improved performance under stressful conditions. This position is also consistent with the findings reported in the first Section of this Chapter.

Altered Body Activity

Several mechanisms based on altered body activity may account for nicotine's stress-reducing effects. First, based on evidence that nicotine may in some situations increase the threshold for electric shock (Mendenhall 1925) and on the observation that nicotine-induced increases in cardiovascular activity typically do not produce corresponding increases in perceived heart activity (Gilbert and Hagen 1980), nicotine may reduce the intensity of emotional experiences by increasing perceptual thresholds for emotion-related feelings of bodily arousal (Gilbert 1979). The small number of studies evaluating this hypothesis have provided mixed results (Sult and Moss 1986), possibly because some have not been carried out under conditions of high stress. This elevated perceptual threshold model is consistent with the CNS arousal modulation model and with the neuromodulator model in predicting that under conditions of heightened stress, nicotine should elevate perceptual and pain-endurance thresholds.

A related possibility is that smoking reduces sensitivity to painful stimuli and sensitivity to internal proprioceptive cues that produce discomfort. Antinociceptive action (i.e., reducing perception of pain stimuli) has been documented in several animal studies (Friedman, Horvath, Meares 1974; Sahley and Berntson 1979; Tripathi, Martin, Aceto 1982). Evidence from humans is mixed, with several studies showing that smoking increases tolerance to painful stimuli (Pomerleau, Turk, Fertig 1984; Nesbitt 1973; Silverstein 1982), and the effect is attributable specifically to nicotine intake rather than to the physical act of smoking (Fertig, Pomerleau, Sanders 1986). Several studies have failed to find effects of smoking on pain thresholds (Shiffman and Jarvik 1984; Sult and Moss 1986; Waller et al. 1983). These null results may be attributable to methodological details such as gender differences or differences in current nicotine level.

Another possibility is that nicotine produces a state of tranquillity or relaxation by reducing the level of tonic and/or phasic muscular activity (Gilbert 1979). Experimental evidence strongly supports the view that nicotine depresses certain muscular reflexes (Domino 1979; Hutchinson and Emley 1973). Ginzel and Eldred (1972) and Ginzel (1987) have shown that nicotine produces muscle relaxation in the cat. Epstein and coworkers (1984) have reported that smoking by humans reduces sensitivity to perception of muscle tension.

Schachter (1973) suggests that nicotine reduces emotional experience by reducing emotion-induced phasic increases in autonomic nervous system (ANS) activity. Because nicotine typically increases activation of the ANS, this increase in tonic ANS activation should produce a ceiling effect such that the additional arousal increase associated with the onset of emotional stimulation is less than the emotion-induced arousal that occurs without nicotine. This third hypothesis assumes that phasic, rather than tonic, activation of the ANS is an important contributor to the subjective experience of emotion. Consistent with this possibility, nicotine increases tonic heart rate, but reduces phasic heart rate responses to stressors (Schachter 1973; Woodson et al. 1986).

Hedonic Systems Model

Nicotine-induced modulation of one or more systems in the brain associated with pain and pleasure may account for the capacity of nicotine to reduce negative affect and increase feeling of well-being (Eysenck 1973; Jarvik 1973). Eysenck (1973) suggests that feelings of well-being produced by nicotine and other means can be increased by influencing three hedonic systems: the primary reward, the primary aversion, and the secondary reward systems. Activating the primary system is thought to produce pleasure directly, while activating the secondary reward system produces rewarding effects indirectly, by inhibiting the aversion system. Eysenck suggests that nicotine administered during highly stressful situations may improve mood by means of the secondary system, while nicotine administered during low-arousal conditions may directly stimulate primary reward systems. Any primary rewarding effect of nicotine appears to be very subtle; many smokers and a smaller percentage of nonsmokers report pleasurable stimulant effects following the administration of nicotine (Jones, Farrell, Herning 1978). However, the subjective effects of nicotine appear to depend greatly upon expectations (Hughes et al. 1985); individuals who are not habitual tobacco users typically report that nicotine administered in any form produces unpleasant effects (Nyberg et al. 1982). In addition, the biochemical representation of affective states is not well understood (McNeal and Cimbolic 1986), and these states are a joint function of physiological and psychological factors (Reisenzein 1983; Schachter and Singer 1962). Experimental studies of stressful situations have shown that smoking produces reduction in subjective ratings of anxiety (Jarvik et al., in press; Pomerleau, Turk, Fertig 1984), but several studies have failed to find effects of smoking for subjective anxiety (Fleming and Lombardo 1987; Shiffman and Jarvik 1984) or emotional behavior (Hatch, Biernier, Fisher 1983). It appears that anxiety-reduction effects are observed primarily when smoking occurs before, rather than during, the stressful situation (Gilbert, in press).

Therefore, the anxiety reduction may result from cognitive appraisal rather than from direct reduction of negative affect, but it should be noted that comparable patterns of findings are commonly observed for most anxiolytic medications (Janke 1983).

Regarding positive affect, it has been suggested that effects of nicotine on endogenous opioid systems may relate to experienced pleasure (Pomerleau and Pomerleau 1984). There is some evidence that effects of cigarette smoke on the upper and lower respiratory airways contribute to pleasurable functions of smoking (Rose et al. 1985), but direct evidence of an influence on positive affect has not been demonstrated.

Lateralized Affective Processors Model

The capacity of nicotine to decrease negative affect may stem from its capacity to increase activation of the left cerebral hemisphere compared with the right hemisphere (Gilbert 1985). Lateralized effects on electrocortical (Elbert and Birbaumer 1987; Gilbert 1985; Gilbert, in press) and electrodermal (Boyd and Maltzman 1984) activity have been reported. These electrophysiological studies along with behavioral studies (Gilbert and Welser, in press) suggest that during stressful/high-arousal conditions, nicotine reduces right-hemisphere more than left-hemisphere parietal activation, while during low-stress situations it may activate the right hemisphere more than the left. Activation of the right hemisphere appears to be more related to the experience of negative affect (Davidson 1984), while the left hemisphere is more the biological seat of logical sequential and verbal information processing (Tucker and Williamson 1984). Thus, nicotine-induced reductions of right-hemisphere activation are associated with reductions in negative affect. Consistent with this finding, simultaneous reductions in right-hemisphere EEG activation and in negative affect have been reported while subjects viewed a stressful movie (Gilbert 1985). These lateralized effects may occur as a result of nicotine's influence on one or more relatively lateralized neurotransmitter systems (Gilbert and Hagen 1980). The lateralized effect model suggests a common biological basis for a diverse set of psychological and physiological effects of nicotine.

Hypothalamic Consummatory Drive Model

Both exposure to nicotine and the activity of the hypothalamus are linked to hunger and body weight, as well as to affective, cognitive, and perceptual processes. Stimulation of the ventromedial hypothalamus or deactivation of the dorsolateral hypothalamus produces effects similar to those produced by the administration of nicotine: decreased emotionality, decreased sensitivity to distracting stimuli,

heightened activity level, low taste responsivity, and weight loss (Nisbett 1972). Nicotine withdrawal, as well as lesions of the ventromedial hypothalamus or stimulation of the dorsolateral hypothalamus (Nisbett 1972), leads to the opposite effects: increased emotionality, increased distraction by external stimuli, decreased activity level, increased taste responsivity, and weight gain (Grunberg and Baum 1985; Perlick 1977). There are a number of commonalities between nicotine and food consumption (Grunberg and Baum 1985). Food consumption, like nicotine, reduces anxiety (Schachter 1971), and many individuals smoke (Rose, Ananda, Jarvik 1983) and/or eat more (Morley, Levine, Rowland 1983) when anxious. Nicotine may reduce aspects of the hunger drive (Grunberg and Baum 1985) and may be reinforcing for this reason. The hypothalamic consummatory drive model suggests that consummatory drive reduction by nicotine should reduce the agitation and irritability associated with a high drive state.

Indirect Models: Psychological Enhancement and Sensory Gratification

Nicotine may reduce negative affect indirectly by enhancing cognitive functioning and associated task performance (Ashton and Stepney 1982; Wesnes and Warburton 1978). The effects of smoking and nicotine on performance (reviewed earlier in this Chapter) are consistent with this interpretation. Nicotine may improve affect both directly, by one or several of the mechanisms discussed above, and indirectly, by enhancing certain psychological processes. Moreover, there is evidence that smoking improves visual sensory processing while blunting auditory distractors in humans (Friedman and Meares 1980).

Sensory experiences related to tobacco consumption may contribute to the motivation for its use and its affect and stress-related effects. Some smokers report smoking because they like handling cigarettes, watching smoke, and/or the sensory experience of smoke in the throat and lungs (Russell, Peto, Patel 1974). Experimental studies, although limited in number, have supported the view that sensory factors are important contributors to the satisfaction and craving-reduction associated with smoking (Rose et al. 1985). The strong sensory impact associated with all forms of common tobacco use may also reduce negative affect by providing distraction from negative thoughts and stimulation that relieves boredom (Gilbert and Welser, in press).

Implications for Tobacco Use

Stress is a risk factor for smoking initiation and increases cigarette smoking (e.g., puffs per cigarette) among regular users.

Smoking is stress reducing for many smokers, and nicotine appears to be involved in this effect. It is likely that the effects of nicotine on stress and on mood involve several mechanisms including alleviation of withdrawal symptoms, peripheral muscle relaxation, central neurochemical changes and electrocortical arousal, interaction with consummatory reward systems, and indirect effects such as psychological enhancement and sensory gratification. Future research needs to address and compare the possible mechanisms. Regardless of which mechanisms are operating, the relationship between stress and smoking undoubtedly reinforces habitual tobacco use and may contribute to initiation and relapse.

Tobacco Use, Nicotine, and Body Weight

Cigarette smokers weigh less than comparably aged nonsmokers, and many smokers who quit smoking gain weight (Grunberg 1986a; Rodin and Wack 1984; Wack and Rodin 1982). It has been suggested that some people smoke to prevent weight gain as the result of smoking cessation (Birch 1975; Charlton 1984b; Grunberg 1986a). Therefore, methods to control weight gain following cessation have been recommended (Birch 1975; Ducimetiere et al. 1978; Grinstead 1981; Grunberg and Bowen 1985a). How much weight gain actually occurs following smoking cessation (Albanes et al. 1987; Bosse, Garvey, Costa 1980; Rabkin 1984; Wack and Rodin 1982), the specific mechanisms (i.e., changes in dietary intake, physical activity, and/or changes in resting metabolic rate) responsible for this weight gain (Grunberg 1986b; Hofstetter et al. 1986), and whether weight gain (or fear of weight gain) affects either cessation or relapse efforts (Hall, Ginsberg, Jones 1986; Klesges and Klesges, *in press*; Kramer 1982) remain controversial. This Section reviews data relevant to the smoking/body weight relationship.

The Relationship Between Smoking and Body Weight

The relationship between smoking and body weight has been extensively examined and reported for more than 100 years (Kitchen 1889; Otis 1884). Human studies can be summarized into two broad areas: (1) cross-sectional evaluations that have compared the weights of smokers, nonsmokers, and in some cases, ex-smokers; and (2) longitudinal, within-subject evaluations that have measured weight changes in smokers, ex-smokers, and nonsmokers over time. The cross-sectional evaluations reported since 1970 are tabulated in Table 2, and the longitudinal studies reported since 1970 are summarized in Table 3. Both tables present the reference and year, a brief description of the sample design, major findings, observed moderator variables (e.g., gender, number of cigarettes per day) for weight, and major limitations of the study. Only studies published

since 1970 are summarized in this Report because there are so many studies and because reviews of earlier investigations (Bosse, Garvey, Costa 1980; Grunberg 1986a) indicate that the results are completely consistent with the studies presented in Tables 2 and 3.

Cross-Sectional Evaluations of Smoking and Body Weight

Of the 28 cross-sectional evaluations presented in Table 2, 25 (89 percent) reported that smokers weigh less than nonsmokers. An additional study (Sutherland et al. 1980) found this relationship for women but not for men and another study (Hjermann et al. 1976) found this relationship for older (45 to 49 years) but not younger (40 to 44 years) men. Only one study did not report an inverse relationship between smoking and body weight, and that study examined visitors to a "health exhibit," a population that may be health conscious and predisposed to making positive health changes (Waller and Brooks 1972). This one discrepant study included a high percentage of cigar and pipe smokers (many of whom do not inhale). While it is difficult to summarize the cross-sectional studies because of differences in reporting techniques, it was found that smokers overall weighed an average of 7.13 lb (range: 2.36 to 14.99) less than nonsmokers.

Because smoking and alcohol consumption are correlated, one study (Williamson et al. 1987) examined, through multivariate methods, the effects of smoking and alcohol consumption on body weight. This study reported that alcohol consumption accounted for approximately 44 percent of the reduction in body weight in women who smoked compared with women who did not smoke. For men, statistical adjustment for alcohol consumption did not alter the weight-lowering effect of smoking.

Cigarette consumption, age, and gender have been adequately evaluated to reach some conclusions regarding their impact on the relationship between smoking and body weight. The effect of cigarette consumption has been parametrically evaluated in eight studies. Six (Albanes et al. 1987; Hjermann 1976; Holcomb and Meigs 1972; Jacobs and Gottenborg 1981; Khosla and Lowe 1971; Lincoln 1970; Stephens and Pederson 1983) of the eight investigations (75 percent) reported a nonlinear relationship. In all of these reports, nonsmokers had the greatest body weights; moderate smokers (typically 10 to 20 cigarettes/day) had the lowest body weights; and some heavy smokers (typically >20 cigarettes/day) had body weights approaching that of nonsmokers. Two studies (Bjelke 1971; Kopczynski 1972) reported no relationship between level of smoking and weight.

The effect of age on the smoking/body weight relationship was examined in six investigations. Five of six studies (86 percent) (Albanes et al. 1987; Bjelke 1971; Hjermann et al. 1976; Jacobs and

TABLE 2.—Cross-sectional evaluations of smoking and body weight

Study	Design and sample	Major results	Moderator variables	Limitations
Albanes et al. (1987)	12,103 men and women, NHANES II Survey	Smokers weighed 5.95 lb less than nonsmokers, controlled for age, sex; smokers taller and leaner than nonsmokers, based on skinfold	Age: current smokers gained less after age 25 than either nonsmokers or ex-smokers Smoking duration: body mass index decreased with smoking duration increase Smoking rate: moderate smokers leaner than low or high rate smokers	Smoking self-report
Andrews and McGarry (1972)	All 18,631 pregnant women, Cardiff, Wales, 1965–1968	Across all heights, smoking mothers lighter than nonsmokers		Pregnant women only; birth survey record data; actual weight changes not presented
Biener (1981)	274 (174 men, 100 women) ex- smokers, worksite setting	49% women, 39% men gained weight following cessation; quitter approximate average gain: women 11 lb, men 15 lb		Retrospective postcessation gain self- report; no nonsmoker control group
Blair et al. (1980)	183 white male, 284 white female insurance company employees; average age 34	Smokers 2.64–7.5 lb lighter than nonsmokers, 0.88–15.21 lb lighter than ex-smokers; smaller skinfolds for smokers of both sexes than nonsmokers		Small sample size; white office workers only

TABLE 2.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Bjelke (1971)	8,638 male, 10,331 female respondents, mail survey, Norway general population "systematic sample"	Used "bulk index" (weight/height ²); both sexes current smokers less bulky than quitters and never smokers	Smoking rate: not related to weight Age: older respondents greater smoker/nonsmoker bulk differences Sex: women greater smoker/nonsmoker bulk differences	Self-report by mail; no weights, no statistical analyses presented
Fehily et al. (1984)	211 nonsmoking, 282 smoking men, aged 45-59, heart disease study	Smokers weighed 7.5-10.3 lb less than nonsmokers, 6.6-9.4 lb less than ex-smokers; pipe/cigar smokers weighed 2.4 lb more than nonsmokers; weight/height ² index results similar		Small, all white, restricted sample; smoking self-report
Fisher and Gordon (1985)	15% random sample, 10 U.S., Canadian clinics; 2,269 male, 2,105 female whites, aged 20-59, LRC Prevalence Study	Men: smoking nondrinkers weighed 6.6 lb less than nonsmoking nondrinkers; smoking drinkers weighed 2.2 lb less than nonsmoking drinkers Women: smoking nondrinkers weighed 2.2 lb less than nonsmoking nondrinkers; smoking drinkers weighed 4.4 lb less than nonsmoking drinkers		All white population; smoking self-report
Friedman et al. (1981)	38 smoking-discordant monozygotic twin pairs, average age 40 years	Smokers weighed 5.07 lb less than nonsmokers		Self-report by mail; small restricted sample

TABLE 2.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Garn et al. (1978b)	17,649 pregnant women, national health survey	Smoking mothers pre pregnancy weight less than nonsmoking mothers; difference: whites 2.43 lb, blacks 3.53 lb	SES and race: no smoking/weight relationship influence	Pregnant women only; self-reports
Garrison et al. (1983)	Framingham study participants; assessed 1949-1952	Nonsmokers 55% of highest weight group; smokers 80% of lowest weight group		Sample size, weights not given; no statistical evaluation
Goldbourt and Medalie (1977)	10,059 male government workers, aged 40-65	Current smokers 1/4 inch taller, 2.36 lb less than nonsmokers; ex-smokers in between; leaner skinfolds for smokers than ex-smokers and nonsmokers		Limited age range, employment group; smoking self-report
Gyntelberg and Meyer (1974)	5,249 employed men, aged 40-59, Denmark	Nondrinking smokers 1.5 percentile points lighter than nondrinking nonsmokers; light drinking smokers 2.9 percentile points lighter; heavy drinking smokers 5.9 percentile points lighter than drinking nonsmokers		All-male sample, one city; smoking self-report
Hjermann et al. (1976)	Approximately 18,000 male participants, aged 40-49, coronary risk factor screening, Oslo	Aged 45-49 smokers body weight 3.09 lb less than nonsmokers; aged 40-44 difference not significant; no group weight/height ² index differences	Smoking rate: heavy smoker (>20/day) body weights higher than lighter smoker Age: older smokers (45-49) weighed less than nonsmokers; younger smokers (40-44) no effect	Smoking self-report; limited age range; one city; all men

TABLE 2.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Holcomb and Meigs (1972)	226 manufacturing company male hourly employees, aged 55-59	Mild to moderate smokers 14 lb lighter than never smokers, ex-smokers, and heavy smokers	Smoking rate: heavy smokers (>1 pack/day) heavier than lighter smokers, equivalent to nonsmokers	Smoking self-report; limited age, incomes; all men
Huston and Stenson (1974)	184 men, British Field Regiment	<10 mm subscapular skinfold men averaged 22 cigarettes/day; ≥ 15 mm subscapular skinfold men averaged 12 cigarettes/day		Limited male sample; smoking self-report; no separate smoker/nonsmoker data
Jacobs and Gottenborg (1981)	3,291 white men and women, aged 20-59, no cardiovascular disease or elevated risk factors; randomly selected middle-class suburb census tract blacks	Smokers lighter than never smokers and quitters	Smoking rate: male moderate smokers (14-29 cigarettes/day) 6.39 lb lighter than nonsmokers, 2.65-9.93 lb lighter than light and heavy smokers; female moderate smokers 5.07 lb lighter than never smokers, 1.54-8.38 lb lighter than heavy smokers Age: moderate/never smoker weight difference increased with age	Smoking self-report; restricted population
Khosla and Lowe (1971)	10,482 male steel workers, Wales	Per weight/height ² index, smokers lighter than nonsmokers	Smoking rate: heavy smokers (>35 cigarettes/day) heavier than moderate smokers (15-34) Age: group weight differences increased after age 35	Smoking self-report; restricted population
Kittel et al. (1978)	8,284 male factory workers, Belgium	Relative weights significantly lower for cigarette smokers than never smokers, ex-smokers, and pipe/cigar smokers		Limited population, risk factor Rx program

TABLE 2.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Kopczynski (1972)	3,059 random selectees, pulmonary disease study, Poland	Nonsmokers heavier than smokers, except 20-year-old men	Sex, age, smoking rate: no smoking/weight relationship influence	Smoking self-report; weights not reported
Lincoln (1970)	3,220 male household heads, aged 41–70, across United States	Smokers weighed 3–14 lb less than nonsmokers	SES: smoker/nonsmoker weight difference increased as income decreased Smoking rate: heavy smokers (≥ 21 cigarettes/day) weighed 4 lb more, moderate smokers (11–20 cigarettes/day) 4 lb less than all-smoker average	Restricted population; men
Matsuya (1982)	90 telephone employees, Japan	Ex-smokers weighed 5.29 lb more than nonsmokers; light smokers 2.87 lb less, heavy smokers 0.44 lb less than ex-smokers		Small, nonrepresentative sample; data self-report
Nemery et al. (1983)	210 steelworkers, aged 45–55, ≥ 10 years' service, Belgium	Smokers weighed 12.13 lb less than never smokers, 14.33 lb less than ex-smokers		Restricted population; smoking self-report
Stamford et al. (1984a)	164 (56 smokers, 108 nonsmokers) premenopausal women; smokers: ≥ 20 cigarettes/day, ≥ 5 years, inhale	Smokers weighed 11.96 lb less, had lower average Quetelet Index than nonsmokers		Small sample size; premenopausal women only; data self-report
Stamford et al. (1984b)	269 adult men, fitness center screened; smokers: ≥ 20 cigarettes/day, ≥ 5 years, inhale	Smokers weighed 14.99 lb less, had 12% less body fat than nonsmokers		Select sample, exercising men; smoking self-report; heavy smokers

TABLE 2.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Stephens and Pederson (1983)	15,518 persons aged >10; questionnaire, anthropometry	Smokers weighed less than nonsmokers; female smokers weighed 1.32 lb more to 5.73 lb less than female nonsmokers; men weighed 3.09-7.7 lb less; smokers averaged 3.445 lb less than nonsmokers		White women self-report, smoking self-report; no statistical significance tests
Sutherland et al. (1980)	Random sample, 175 men and women, rural town, New Zealand	Weight/height ² index and skinfolds significantly higher in nonsmoking than smoking women; higher for nonsmoking men, but not significant	Sex: male smokers not significantly leaner than nonsmokers; smoking women lighter than nonsmoking women	Smoking self-report; small sample size
Waller and Brooks (1972)	2,169 health exhibit visitors	"Little weight difference" among current smokers, nonsmokers, and ex-smokers		Smoking self-report; bathroom scale weight; health-conscious population; high % cigar/pipe smokers; no statistical evaluations
Zeiner-Henriksen (1976)	Approximately 15,000 randomly selected Norwegians	Current smokers average and relative weight lower than nonsmokers or ex-smokers		Smoking and weight self-report, questionnaire

TABLE 3.—Longitudinal evaluations of smoking and body weight

Study	Design and sample	Major results	Moderator variables	Limitations
Blitzer et al. (1977)	57,032 women, aged 20–59, self-help weight loss groups	Quitters gained 7.0–10.2 lb more than continuing smokers	Smoking rate: weight gain/previous smoking rate proportional	Smoking and weight self-reports; all women trying to lose weight
Bosse et al. (1980)	1,749 adult men, Normative Aging Study, assessed over 5 years	Average 5-year gains: never smokers 1.81 lb; former smokers 1.87 lb; current smokers 2.00 lb; ex-smokers who quit 6.34 lb	Age: younger quitters gained more Adiposity: fatter quitters gained more Tar rate: higher pretest tar rate smokers gained most Anxiety: high related to higher gain	Smoking self-reports; all men; actual weights not presented
Burse et al. (1982)	4 paid volunteers; 11-day baseline, 21-day quit period, 20-day resumption period	3 of 4 gained weight; 1.98 lb increase during cessation; 1.76 lb loss on resumption		Very small sample, paid volunteers; short-term evaluation
Cambien et al. (1981)	1,097 Paris civil servants, aged 25–35, screened, randomly assigned, cardiovascular risk factor reduction intervention or control groups; 2-year followup evaluation	Treatment group quitters gained 4.85 lb, control group quitters 7.50 lb; nonsmokers and no-change smokers gained 1.54 lb in treatment group, 2.2 lb in control		Smoking self-report; risk factor reduction program participants
Carney and Goldberg (1984)	13 women, 5 men, aged 28–67, smoked ≥20 cigarettes/day, ≥5 years; 12 male controls; 15 smokers abstained 2 weeks	Quitters weight change range: -3.09 to +9.0 lb	Smoking rate/duration: no weight change relationship Biological variables: weight gain positively related to lipoprotein lipase activity in adipose tissue	Smoking self-report; controls weight changes not reported; short-term evaluation

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Coates and Li (1983)	373 male asbestos-exposed smokers, aged ≥ 42 ; 87% white, mean education 12.8 years; 12 months assessment after cessation effort	Continuous quitters gained 5.15 lb; continuous smokers gained 0.35 lb		Smoking self-report; all male, nonrandom sample
Comstock and Stone (1972)	502 male telephone workers, aged 40–59, mostly white; 2 assessments 5 years apart	5-year followup average gains: never smokers 2.43 lb, ex-smokers 5.07 lb, continuing smokers 2.42 lb; quitters 11.24 lb and showed greatest skinfold increases	Smoking rate: increasing quitter weight gain with heavier prequit smoking	Smoking self-report; men only
Dallosso and James (1984)	16 (8 men, 8 women) antismoking clinic participants; mean age, men 47.1, women 35.4; assessed before and 6 weeks after clinic	10 quitters gained 3.00 lb; 5 continuing smokers lost 0.99 lb		Small sample size; smoking self-report; limited followup
Emont and Cummings (1987)	125 stop-smoking clinic participants; pretreatment and 1-month followup assessments	76% quitters and slippers (≤ 5 cigarettes/day) averaged 5.8 lb gain	Nicotine gum: gain/gum use reliable negative correlation for heavy smokers; gain not related to age, sex, marital status, baseline body weight	Weight gain, smoking self-report, confounded by gum use; limited followup; incomplete data
Fagerström (1987)	28 nicotine gum users; abstinent at 6 months	Infrequent gum users gained 6.83 lb, frequent users 1.98 lb	Nicotine gum: frequent users gained less weight	Small sample size; measures unclear
Friedman and Siegelbaum (1980)	Multiphasic health checkup patients; smoked, then quit 12–18 months later (N=3,825) or continued (N=9,392)	Quitters gained 2–3 lb more than continuing smokers	Smoking rate: higher initial smoking rate related to greater weight gain after cessation	Smoking self-report; whites only data

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Garn et al. (1978b)	6,979 women followed through ≥ 2 pregnancies	Higher prepregnancy weights for habitual nonsmokers than habitual smokers: whites 3.4 lb, blacks 4.1 lb; lower habitual smoker gains between pregnancies for both races	Race: no weight/smoking relationship influence	Smoking self-reports; restricted population
Garvey et al. (1974)	870 white male veterans, aging study, assessed 4–7 years after initial assessment	Smoking/weight change significantly related; recent quitters (< 5 years) gained 4.19 lb more than smokers, nonsmokers, former smokers	Age: 40–54 quitter weight increase greatest	Smoking self-report; exact quit date unknown
Glauser et al. (1970)	7 male smokers, cessation program; assessed preprogram, 1 month postprogram	At 1-month followup, participants gained 6.4 lb		Smoking self-report; exact quit date unknown
Gordon et al. (1975)	4,798 Framingham study participants: 1,498 male smokers, 492 male nonsmokers, 1,634 female nonsmokers, 1,174 female smokers; examined short-term changes after biennial exam 1, long-term effects between biennial exams 4, 10	At entry, male smokers weighed 8.0 lb less than nonsmokers; short-term male quitters gained 3.8 lb, nonsmokers 0.5 lb, continuing smokers 0.3 lb; new smokers lost 9 lb; too few female quitters to evaluate		Smoking self-report; change analysis, men only
Gormican et al. (1980)	301 pregnancy obstetrics records, women, aged 17–35	Smoker, nonsmoker prepregnancy weight similar; no last 2 trimester weight gain difference (nonsmokers 24.6 lb, smokers 22.6 lb)		Clinic record data; pregnancy weight gain data only

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Grinstead (1981)	45 subjects (38 women, 7 men), average age 40; evaluated 6 months after cessation treatment; saliva thiocyanate verification	During program, 63% subjects averaged 2.88 lb increase, 34% averaged 2.46 lb decrease; at followup, 37% averaged 6.97 lb gain, 43% averaged 3.27 lb loss		Questionnaire, phone interview data
Gritz et al. (in press)	554 self-quitters (245 men, 309 women), mean age 41.4, 85% Caucasian, 9% black, 4% Asian, 1% Asian-American, 1% Native American; 1-year followup	35% previous quitters gained, 3% lost; at 1 year, abstainers averaged 6.1 lb gain; relapsers gained 2.71 lb while abstinent, lost 1.3 lb upon relapse; continuous smokers gained 0.3 lb		Questionnaire, phone interview data
Grossarth-Maticek et al. (1983)	1,353 subjects, Yugoslavian village of 14,000; every 2d household oldest member; evaluated 1965-1966, 1969	Smoking reduction/weight increase relationship (regression coefficient -0.30)		Smoking self-report; weights, weight changes not reported
Gunn and Shapiro (1985)	89 cessation clinic participants; all quit at initial evaluation; 3-month followup assessment	43 of 54 (80%) quitters gained 2-30 lb		Smoking, height, weight self-report; inadequate statistical evaluation
Hall et al. (1986)	255 smoker participants (122 men, 133 women), 2 smoking treatment trials; 6-, 12-month followups; biochemical verification	Abstainers gained more than smokers at 1 year	Smoking rate: pretest smoking level/postcessation weight gain positively related Chronic dieting: chronic diet subjects gained most	Multiple Rx (e.g., nicotine gum) participant data included
Hatsukami et al. (1984)	27 smokers hospitalized 7 days; 20 subjects smoked 3 days, then quit 4 days; 7 control group subjects smoked throughout	Quitters gained 1.76 lb in 4 days		Small sample size; inpatient environment

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Haworth et al. (1980)	536 women (234 nonsmokers, 302 smokers) interviewed last prenatal visit (18%) or within day after delivery (82%)	No smoker/nonsmoker pregnancy weight gain difference		Smoking self-report; pregnancy weight gain data only
Hickey and Mulcahy (1973)	150 men (124 smokers); 6-month, 2-year followups after myocardial infarction	Quitter, reducer, continuing smoker differences not significant		Smoking self-report; postmyocardial infarction may motivate healthy behavior
Holme et al. (1985)	16,202 Oslo men, aged 40–49, screening program; 1,232 (elevated cholesterol or upper quartile coronary risk score) randomly assigned diet/smoking intervention or control; 5-year followup	17% controls, 24% intervention quit; 1- to 2-year-quitter weight increased more than controls, then decreased to below prequit level		Smoking self-report; confounded by high cardiovascular disease risk health intervention; weights not reported
Howell (1971)	Retrospective, 1,121 men, aged 40–54; 15- to 20-year weight gain examinations	Light smokers (<20 cigarettes/day) gained 1.9 lb less than heavy smokers, 3.1 lb less than ex-smokers, 3.6 lb less than never smokers	Smoking rate: lower rate related to less weight gain	Retrospective report
Hughes and Hutchinson (1983)	37 smokers and 19 ex-smokers with pulmonary emphysema followed ≥ 3 years	Smokers lost 0.32 lb/yr, ex-smokers gained 1.17 lb/yr; significant difference		Smoking self-report; pulmonary emphysema population

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Jenkins et al. (1973)	2,318 men (546 never smokers, 359 previous quitters, 547 light smokers, 866 heavy smokers), aged 39–49, 11 California corporations in Western Collaborative Group Study; changes assessed since age 25; 1960–1969 study	Weight loss more likely for light and heavy smokers than never smokers and quitters		Smoking self-report; weights not presented
Kramer (1982)	175 subjects, commercial cessation program (41 nonparticipants or nonlocated, 59 quitters, 75 continuing smokers) ≥ 1-year followup	76% nonsmokers, 56% smokers gained weight; these smokers mean gain 1.7 lb, these nonsmokers mean gain 3.0 lb		All data self-report; high attrition, data loss; presentation incomplete
Lund-Larsen and Tretli (1982)	12,329 men and women, aged 20–49, cardiovascular disease project; 2 screenings 3 years apart	Smokers mean and relative weight less than nonsmokers; female quitters gained 5.95 lb, male quitters 7.84 lb; smoking-starter men lost 1.98 lb, women 5.5 lb; smokers and nonsmokers little/no change	Sex: men, women weight change/smoking cessation and initiation similar	Self-report
Manley and Boland (1983)	39 male, 55 female smokers, cessation program; randomly assigned, 1 of 3 4-week treatments or attention placebo control; 3-month followup; CO verification	31% abstinent at followup; abstainers averaged 10.93 lb gain, relapsers 6.92 lb		Relapser definition unclear

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Noppa and Bengtsson (1980)	1,302 Swedish women, aged 38-60	Current smokers leaner than nonsmokers; At 6 years, quitters gained 7.72 lb; smoking-starters lost 1.54 lb, nonchangers gained 3.09 lb		Smoking self-report
Pincherle (1971)	222 upper-class male quitters; followup \geq 1 year after first visit	28% gained weight; 22% lost		Smoking self-report; limited population; incomplete report; no weights presented
Powell and McCann (1981)	29 women, 22 men, 5-day cessation project; 2- and 6-month followup	At 2 months, 54% gained weight, range 3-20 lb, mean 8.96 lb; all subjects mean 4.69 lb		Smoking self-report; no separate abstainer, smoker data; small sample size
Puddey et al. (1985)	66 cessation program volunteers, pair-matched by age, sex, body mass index; randomly assigned experimental, control groups; 2-week baseline, 6-week treatment, 6-week followup; thiocyanate, CO verification	14 quitters gained 3.97 lb; controls 0.44 lb		Small sample size
Rabkin (1984)	40 male, 67 female smokers, assigned to 3 cessation groups; followup 3 weeks post-completion; biochemical verification	67.3% gained weight, average 1.76 lb; skinfold increase 6.6 mm	No age, age at smoking start, rate, relative weight, anxiety correlation to male or female weight change	Small sample size; weight self-report

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Rantakallio and Hartikainen-Sorriin (1981)	12,068 pregnant women, n. Finland, 1966; 15% smokers (smoked after 2 months pregnant); nonsmoking controls matched for age, parity, place of residence, marital status	No smoking/nonsmoking pregnancy weight gain difference		Pregnant women only; smoking self-report; pregnancy weight gain data only
Rush (1974)	162 low-income urban pregnant women, no known medical problems, <140 lb preconception weight; had borne low birthweight infant; randomized controlled nutritional supplementation trial	Mean pregnancy weight gain lower for smokers (0.73 lb/wk) than nonsmokers (0.90 lb/wk)	Smoking rate: higher rate related to lower pregnancy weight gain	Pregnant women only; smoking self-report; pregnancy weight gain data only
Schoenenberger (1982)	4,421 male MRFIT volunteers, aged 35–57, good health but upper 10–15% coronary risk factor score; randomly assigned to intervention or control groups; followup 3 annual visits	With MRFIT intervention, significant body weight decrease in smokers (mean 4.6 lb), nonsmokers (mean 5.8 lb), reducers (mean 3.75 lb); quitters average weight change minimal (mean 0.55 lb)		Smoking self-report; confounded by risk factor reduction program participation; restricted population
Seltzer (1974)	794 adult white male veterans, average age 45; Normative Aging Study; screened for "high" health level, geographic stability; 214 screened at 5 years	At admission, ex-smokers 5.9 lb heavier than nonsmokers, 8.1 lb heavier than current smokers; at 5 years, quitters gained 8.0 lb, continuing smokers 3.5 lb		White veterans; smoking self-report

TABLE 3.—Continued

Study	Design and sample	Major results	Moderator variables	Limitations
Stamford et al. (1986)	13 sedentary women, 48-day successful quitters; 1-year followup	At 48 days, weight increased 4.85 lb; at 1 year, quitters increased 18.07 lb; 3 relapers reduced weight to baseline levels; per hydrostatic weighing, gain was 96% fat		Small female sample; smoking self-report
Tuomilehto et al. (1985)	10,940 cardiovascular disease prevention program participants, aged 25–59, random sample, e. Finland; selectees with high blood pressure or hypertensive medicine assessed 5 years apart; smoking data from 2,264	Quitters body mass increased 2.31 lb/m ² ; starting smokers decreased 1.46 lb/m ²		Smoking self-report; hypertensives
Vandenbroucke et al. (1984)	3,091 Netherlands civil servants, spouses (1,583 men, 1,508 women), aged 40–65, general health exam; 25-year followup	76.6% lean, 65.1% obese men smoked; 22.1% lean, 11.3% obese women smoked		Smoking self-report; restricted population

Gottenborg 1981; Khosla and Lowe 1971) documented increasing weight differences between smokers and nonsmokers with advancing age. Typically, aging smokers failed to gain as much weight as aging nonsmokers.

Three evaluations systematically compared males with females (Bjelke 1971; Kopczynski 1972; Sutherland et al. 1980). Two of the three (Bjelke 1971; Sutherland et al. 1980) reported the differences in body weight between smokers and nonsmokers to be greater in females than in males.

Longitudinal Evaluations of Smoking and Body Weight

Table 3 presents the results of 43 longitudinal evaluations of the effects of smoking on body weight. Consistent with the cross-sectional evaluations, the overwhelming majority (86 percent, 37 of 43) present evidence that smokers who quit smoking gain weight, that people who quit smoking gain more weight than nonsmokers, and that people who initiate smoking lose weight relative to nonsmokers. Of the six studies that did not find these relationships, three limited their examination to smoking and weight changes in pregnant women (Gormican, Valentine, Satter 1980; Haworth et al. 1980; Rantakallio and Hartikainen-Sorri 1981), two relied on participants making broad cardiovascular risk factor reduction efforts in subjects at high risk for cardiovascular disease (Hickey and Mulcahy 1973; Holme et al. 1985), and the remaining study supplied incomplete reports of the data (Kramer 1982). Of those studies on the effects of smoking cessation on weight, the length of followup ranged from 4 days to 7 years. According to these investigations, those who quit smoking gained an average of 6.16 lb (range: 1.76 to 18.07) during the year after cessation.

Daily cigarette consumption was the only moderator variable that received sufficient attention in this group of studies reaching specific conclusions. Seven of nine studies (78 percent) (Blitzer, Rimm, Giefer 1977; Bosse, Garvey, Costa 1980; Comstock and Stone 1972; Friedman and Siegelaub 1980; Hall, Ginsberg, Jones 1986; Howell 1971; Rush 1974) reported a positive relationship between cigarette consumption and weight change; that is, as pretest cigarette consumption increased, postcessation weight gains also increased. Two studies (Carney and Goldberg 1984; Rabkin 1984) did not find a relationship between cigarette consumption and postcessation weight gain.

In summary, there is substantial evidence of an inverse relationship between cigarette smoking and body weight. Of 71 studies reported since 1970, 62 (87 percent) collectively indicate that smokers weigh less than nonsmokers and that people who quit smoking gain weight. Older smokers, females, and those smoking approximately one pack of cigarettes/day may experience the

largest weight control effects of cigarette smoking. Smokers who smoke heavily tend to gain the most weight following smoking cessation. These generalizations are consistent with reviews based on other studies reported since 1880 (Grunberg 1986a). Not all smokers who quit smoking gain weight. Further, for ex-smokers who do gain weight, the amount of weight infrequently poses a serious health risk.

The Role of Nicotine

Animal studies indicate that nicotine administration results in weight loss or decreased weight gains and that cessation of nicotine results in body weight gains greater than those of controls (Bowen, Eury, Grunberg 1986; Grunberg 1982, 1985, 1986b; Grunberg, Bowen, Morse 1984; Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987; McNair and Bryson 1983; Morgan and Ellison 1987; Schechter and Cook 1976; Wager-Srdar et al. 1984; Wellman et al. 1986). Most of these studies report inverse dose-response relationships between nicotine and body weight.

Recent research on nicotine polacrilex gum with humans corroborates the role of nicotine in body weight effects. Fagerström (1987) reported that subjects who quit smoking were much less likely to gain weight when they consistently used nicotine polacrilex gum. Abstinent subjects who regularly used the gum gained less than 2 lb at a 6-month followup. In contrast, the infrequent gum users gained almost 7 lb ($p < 0.05$). Emont and Cummings (1987) reported a significant negative relationship ($r = -0.87$) between the number of pieces of nicotine polacrilex gum chewed per day and weight gain for heavy smokers (> 26 cigarettes/day). No such relationship between gum use and weight gain was observed for lighter smokers (< 26 cigarettes/day).

Mechanisms Underlying The Relationship Between Smoking and Body Weight

The inverse relationship between smoking and body weight may result from changes in energy intake, changes in energy expenditure, or both. Energy intake involves dietary intake. Energy expenditure is affected by behavioral factors (physical activity) and biological factors (e.g., metabolism). These potential mechanisms are examined below.

Dietary Intake

Several prospective investigations have evaluated dietary intake changes following smoking cessation in humans. Hatsukami and coworkers (1984) hospitalized 27 smokers for a 7-day period. After a 3-day baseline, 20 of the subjects were deprived of smoking for 4 days

while the remaining 7 served as a control group. During this 4-day period of abstinence, caloric intake increased significantly (from 1,397 to 1,651 kcal), which corresponded with a significant 1.76-lb increase in weight. In the most comprehensive study to date, Stamford and coworkers (1986) evaluated changes in dietary intake, physical activity, and resting metabolic rate in 13 sedentary females who quit smoking for a 48-day period. Following smoking cessation, mean daily caloric consumption increased by 227 kcal, which accounted for 69 percent of the variance in postcessation weight gain (4.85 lb). Robinson and York (1986) followed 11 smokers who quit for 7 days. Mean dietary intake significantly increased, but changes in resting metabolic rate were not observed. Dallosso and James (1984) followed 10 subjects for 6 weeks after they participated in a stop-smoking clinic. There was a 4-percent drop in resting metabolic rate in smokers who quit, a drop which was reliable when the data were expressed per kilogram of body weight. The average dietary intake increased by 6.5 percent, but this difference did not reach statistical significance.

Preliminary results of a recent investigation indicate gender differences in the effects of short-term smoking cessation on body weight and food intake (Klesges, Meyers et al. 1987). Female smokers who quit for 1 week increased their body weight and dietary intake significantly more than male smokers who quit. This sex difference is consistent with animal studies (Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987). Given females' marked concerns regarding postcessation weight gain (Klesges and Klesges, in press), future studies will need to investigate possible gender differences in response to smoking cessation.

Several studies indicate that smokers may differ from nonsmokers in their intake of sweet-tasting simple carbohydrates (sugar) in particular. In a human laboratory study, Grunberg (1982) observed that smokers who were allowed to smoke ate less sweet food than smokers who were not allowed to smoke or nonsmokers. Smokers not allowed to smoke also reported the greatest preference for sweet foods. There were no differences among the three subject groups in consumption of other types of foods. Rodin (1987) conducted a prospective study in which food intake after smoking cessation was carefully evaluated. Smokers who gained weight after quitting smoking increased their sugar consumption in particular. Further, smokers increase consumption of sweet snack foods when they are deprived of cigarette smoking (Duffy and Hall, in press; Perlick 1977). On the other hand, two early investigations (Bennett, Doll, Howell 1970; Richardson 1972) found *higher* sugar consumption in smokers relative to nonsmokers. However, Richardson (1972) found that this difference was because of low-sugar intake in ex-smokers, while Bennett, Doll, and Howell (1970) argued that the differences

were largely due to increased added sugar intake because of hot beverage consumption. These two studies, which are inconsistent with the more recent studies, did not carefully measure all food intake and did not assess intentional changes in food intake to control body weight.

Several animal experiments have documented that food intake decreases during nicotine administration and increases after administration has ceased and that these changes in food intake correspond with changes in body weight (Bowen, Eury, Grunberg 1986; Grunberg 1982; Grunberg, Bowen, Winders 1986; Levin et al. 1987; McNair and Bryson 1983; Wager-Srdar et al. 1984). Consumption of sweet foods by male rats is particularly affected by nicotine (Grunberg 1982; Grunberg et al. 1985). However, nicotine also reduces bland food intake in female rats and has a greater effect on body weight of female rats than of male rats (Grunberg, Winders, Popp 1987; Grunberg, Bowen, Winders 1986; Levin et al. 1987).

Several investigations have reported that changes in body weight in animals also occur without observing decreases in food intake as the result of nicotine administration (Grunberg, Bowen, Morse 1984; Schechter and Cook 1976; Wellman et al. 1986). In one investigation, chronic exposure to cigarette smoke reduced body weight and food intake in rats; however, hamsters exposed to cigarette smoke decreased body weight without reducing food intake (Wager-Srdar et al. 1984). Several methodological factors complicate these results, including the use of different strains of animals, different routes of administration and dosages of nicotine, and whether acute versus chronic effects of nicotine were reported. However, these results indicate that more than the mechanism of food intake was involved in producing nicotine- and smoking-related weight changes.

Data from short-term human studies and several animal experiments indicate that dietary intake is involved with smoking-related energy imbalance. Based on self-reported cross-sectional surveys, it has been reported that smokers' dietary intake is the same as (Albanes et al. 1987; Fehily, Phillips, Yarnell 1984; Fisher and Gordon 1985; Matsuya 1982) or significantly higher than (Picone et al. 1982; Stamford et al. 1984a,b) that of nonsmokers while the smokers simultaneously maintained a lower body weight. Assuming that smokers are not consistently biased in their reports of dietary intake, it appears that either differences in physical activity or metabolic rate are maintaining the body weight differences between smokers and nonsmokers.

Physical Activity

The data available from cross-sectional investigations, short-term prospective studies, and animal investigations seem to indicate that changes in physical activity do not play a role in either differences in

body weight between smokers and nonsmokers or the weight gain associated with smoking cessation. Some cross-sectional investigations have found that smokers have *lower* levels of physical activity compared with nonsmokers (Kannas 1981). Others have not found differences in physical activity and physical fitness between smokers and nonsmokers (Gyntelberg and Meyer 1974; Stamford et al. 1984b; Stephens and Pederson 1983). A recent review (Blair, Jacobs, Powell 1985) that addressed the relationships among exercise, physical activity, and smoking concluded that smoking and physical activity are negatively associated; however, the relationship was extremely weak and variable.

Animal studies on the relationship between nicotine and physical activity have generally found that physical activity plays a small role or fails to correspond to decreases in weight during nicotine administration (Bowen, Eury, Grunberg 1986; Cronan, Conrad, Bryson 1985; Grunberg and Bowen 1985b). One study found that decreases in physical activity after cessation of nicotine appeared to contribute to postdrug body weight increases (Grunberg and Bowen 1985b), but this effect was quite small and occurred only in males.

A few prospective human investigations have evaluated physical activity changes following smoking cessation (Hatsukami et al. 1984; Hofstetter et al. 1986; Klesges, Brown et al. 1987; Rodin 1987; Stamford et al. 1986). These investigations found no changes in physical activity as a result of smoking cessation.

Metabolic Rate

Metabolic rate is an important consideration in energy imbalances associated with smoking cessation because approximately 75 percent of total energy expenditure is in the form of metabolism (Bernstein et al. 1983; Ravussin et al. 1982). Metabolism increases as the result of acute nicotine administration and immediate effects of smoking (Ghanem 1973; Illebekk, Miller, Mjos 1975; Robinson and York 1986; Schiavelbein et al. 1978; Wennmalm 1982). The major question, however, is whether these effects persist long enough to have a direct impact on body weight. Given that (1) smokers do not have higher levels of physical activity compared with nonsmokers (Blair, Jacobs, Powell 1985), (2) some studies report smokers' dietary intakes are the same as or higher than those of nonsmokers (Picone et al. 1982; Stamford et al. 1984a,b), and (3) smokers maintain lower body weights than nonsmokers, it is reasonable to postulate that changes in metabolism contribute to the relationship between smoking and body weight. Additionally, there are several reports in the literature on animals that have documented nicotine-induced reductions in body weight without a concomitant reduction in food intake (Grunberg, Bowen, Morse 1984; Schechter and Cook 1976; Wellman et al. 1986).

Direct evidence supporting a chronic metabolic mechanism that modulates the smoking/body weight relationship is beginning to emerge. Metabolic rate was chronically measured in a study of rat and hamster exposure to cigarette smoke (Wager-Srdar et al. 1984). Higher resting metabolic rates were observed on only one of the test days compared with the pretest in the rat investigation, while no significant differences were observed in the hamster study. Another recent investigation (Wellman et al. 1986) evaluated brown adipose tissue (BAT) thermogenesis at different levels of nicotine and caffeine injections. No differences in BAT thermogenesis were observed in response to either nicotine or caffeine. The group that received a combination of caffeine and nicotine showed a 63 percent increase in BAT thermogenesis.

The few studies that have evaluated metabolic rate changes in response to smoking cessation in humans have produced inconclusive results. Three investigations found metabolic changes after cessation in human smokers. An early report (Glauser et al. 1970) found decreases in oxygen consumption for seven male subjects who quit smoking for 1 month (neither food intake nor physical activity was monitored). A more recent investigation found a 4-percent drop in metabolic rate (reliable when data were expressed per kilogram of body weight) and no significant increase in dietary intake for 10 subjects who quit smoking for 6 weeks (Dalloso and James 1984). In the only study that used a respiration chamber, Hofstetter and others (1986) reported that total energy expenditure was 10 percent higher during a 24-hr period of smoking versus a 24-hr period of abstinence in eight smokers. No changes were observed in physical activity or mean basal (sleeping) metabolic rate (dietary intake was held constant). However, this difference in energy expenditure disappeared after 24 hr.

Three investigations did not find a change in metabolic rate as the result of smoking cessation. Burse and associates (1982, 1975) did not observe changes in resting metabolism in a sample of four smokers who quit for 3 weeks. This investigation did find reliable increases in desire for food, however. In another study, 11 smokers were studied after a 7-day period of smoking abstinence (Robinson and York 1986). Total energy expenditure following a meal did not change during the cessation period. Stamford and colleagues (1986) failed to find changes in oxygen consumption in 13 subjects who quit smoking for 48 days. This investigation did find marked dietary intake changes that accounted for 69 percent of the variance of postcessation weight gain.

There are several possible explanations for the inconsistency observed in the literature on metabolic rate. Different investigators have used different criteria (e.g., resting oxygen consumption, BAT thermogenesis) for operationalizing metabolism. It is possible that

previous dieting history (Brownell et al. 1986) and the use of nicotine polacrilex gum (Fagerström 1987) may directly impact the metabolic response to smoking cessation. It is not clear what the metabolic response to nicotine with added agents is likely to be. For example, one study found that while neither nicotine nor caffeine alone produced a change in BAT thermogenesis, the two combined increased thermogenesis by 63 percent (Wellman et al. 1986). This finding is particularly interesting given that smokers may be more likely to drink caffeinated beverages than nonsmokers (Blair et al. 1980). Finally, the available literature on human studies used very small subject groups, making it impossible to detect subtle but potentially meaningful changes in resting metabolic rate. The small sample sizes do not allow for an evaluation of variables that may potentially moderate the metabolic response to smoking cessation.

Summary of Mechanisms Literature

Changes in dietary intake appear to be involved in weight gains after cessation of smoking or cessation of nicotine administration. Physical activity plays little or no role in the relationship between smoking and body weight. The data on metabolic contributions to postcessation weight gain are suggestive, but further research is needed. Unfortunately, much of the relevant human research literature is characterized by small sample sizes, short followup evaluations, and inadequate evaluations of energy balance following smoking cessation. To date, only one investigation has comprehensively evaluated (i.e., simultaneous assessment of dietary intake, physical activity, and metabolic rate) energy balance changes as the result of smoking cessation. This was a sample of 13 sedentary females followed for 48 days (Stamford et al. 1986). Comprehensive, prospective evaluations of energy balance changes in response to smoking cessation are needed. Additionally, no study has evaluated possible long-term changes in dietary intake, physical activity, and metabolic rate as a result of smoking cessation. The longest followup period reported in the literature to date is 2 months (Dalloso and James 1984). Finally, evaluation of potential moderator variables of dietary intake, physical activity, and metabolic rate as the result of cessation is needed. Gender (Grunberg, Winders, Popp 1987; Klesges, Meyers et al. 1987), previous dieting history (Brownell et al. 1986; Hall, Ginsberg, Jones 1986), pretest levels of lipoprotein lipase (Carney and Goldberg 1984), and the use of nicotine polacrilex gum (Fagerström 1987) appear to be important variables influencing weight gain and need further investigation.

Does the Relationship Between Smoking and Weight Promote Either the Initiation or Maintenance of Smoking Behavior?

Some research attention has been given to body weight as a potential moderator of smoking initiation, maintenance, and cessation. Unfortunately, many investigations do not report weight-related issues (Borkon, Baird, Siff 1983; Eiser et al. 1985; Pederson and Lefcoe 1976; Perri, Richards, Schultheis 1977). The investigations that have evaluated these issues consistently report relationships between body weight and smoking initiation (Charlton 1984a) and maintenance (Klesges and Klesges, in press).

A survey of 16,000 school children (Charlton 1984a) in England found that the heaviest regular smokers were the most likely to agree that smoking controls weight (42.2 percent) compared with those students who never smoked (16.6 percent). Agreement increased with increased levels of smoking. More girls than boys agreed with this statement, and girls were also more likely to be regular smokers. Charlton (1984b) also reported that among the perceived effects of smoking, smokers viewed "calming the nerves" as the most popular reason (72 percent) followed by "smoking keeps your weight down" (39 percent).

Other investigations are consistent with the Charlton (1984a,b) report. In a recent study of 1,000 adolescents in Canada (Feldman, Hodgson, Corber 1985), significantly more girls than boys were concerned about becoming overweight (36 vs. 14 percent, $p < 0.001$). In girls 18 years or older, 52.6 percent of smokers reported worrying about their weight, whereas only 31 percent of nonsmokers reported weight-related concerns ($p < 0.05$). In a study of smoking intentions among 400 U.S. high school males, Tucker (1983) reported that overweight boys scored much higher on smoking intent than either normal weight or underweight boys ($p < 0.005$). Another survey evaluated gender differences in a sample of 221 college cigarette-smoking intenders and nonintenders (Page 1983). Results indicated that females were much more likely to intend to smoke than males. Females were also more likely to believe that smoking maintains body weight, and smoking intenders were also more likely to believe that smoking controls weight. Finally, in a retrospective survey of more than 1,000 young adults (Klesges and Klesges, in press), overweight females reported that they were much more likely (20 percent) to start smoking for weight-related reasons compared with normal-weight females (2 percent). No differences between overweight versus normal-weight males (8 vs. 6 percent) were observed.

Several surveys on smoking maintenance have shown that individuals report that weight control is a powerful motivator to continue to smoke. Physicians who smoked were much more likely than those who had quit (46 vs. 22 percent) to believe that smoking cessation

increases appetite and weight (Fletcher and Doll 1969). Nurses who failed to quit smoking listed (in order) loss of determination, stress, and weight gain as the major reasons for failure (Knobf and Morra 1983). Beliefs regarding the weight-control effects of smoking and quitting differentiate smokers and nonsmokers (Hill and Gray 1984; Loken 1982; Shor et al. 1981). Females are particularly worried about postcessation weight gains (Klesges and Klesges, *in press*; Sorensen and Pechacek 1987). They are more likely to endorse smoking as an active weight-loss strategy (39 vs. 25 percent) and are more likely to report relapse for weight-related reasons (20 vs. 7 percent) (Klesges and Klesges, *in press*).

The research cited above is based on self-reports of the weight-control effects of smoking and, as such, could be viewed as an excuse for smoking. Two recent worksite-based investigations evaluated whether pretest concerns regarding smoking and weight-related issues prospectively predicted cessation. Maheu (1985) evaluated 49 subjects who either received a competition-based ($n=32$) or a no-competition condition ($n=17$). In the competition-based condition, participants were told that they would be rewarded if those at their worksite lost more weight than those at a neighboring worksite. At a 3-month followup, 78 percent of the subjects in the competition and 76 percent of the subjects in the no-competition condition were reportedly abstinent. Regression analysis at followup indicated that the best pretest predictors of smoking cessation (in order) were negative responses to the questions: (1) "Do you think smoking helps control your weight?"; (2) "Did one of your parents smoke when you were young?"; and (3) "If you have tried to quit before, did you suffer any withdrawal symptoms?" Klesges, Brown, and associates (1987) found that the best predictors of cessation at posttest were pretest cotinine levels and anticipated weight gain as the result of smoking cessation. The best predictors of cessation at followup were the number of coworkers who smoked followed by anticipated cessation-related weight gain.

A recent community survey evaluated predictors of current and former smoking status in a sample of 611 nonsmokers, ex-smokers, smokers who had tried to quit smoking, and smokers who had not attempted cessation (Klesges, Somes et al. 1987). The best predictors of smokers who had never attempted cessation versus those with a history of cessation efforts were a greater concern related to weight control, followed by knowledge of the health consequences of smoking. Smokers who had not attempted cessation were significantly more likely to cite weight-control issues compared with smokers who had made active attempts at smoking cessation. Collectively, these investigations indicate that weight-related concerns may not only predict successful smoking cessation, but also attempted smoking cessation.

Weight gain following smoking cessation as a predictor of smoking relapse has been evaluated in two recent investigations. Hall, Ginsberg, and Jones (1986) found a relationship between smoking status at a 1-year followup and weight gain at 6 months; greater weight gain during the first 6 months predicted continued abstinence. This finding was contrary to expectations. In another investigation, Gritz, Carr, and Marcus (in press) found that continuous abstainers had gained an average of 6.1 lb, relapsers had gained 2.7 lb and subsequently lost half the gain (1.3 lb), and never quitters had gained only 0.3 lb. While it was expected that postcessation weight gain would be predictive of relapse, one would expect that those who have been abstinent from cigarettes would have gained more weight than those who either failed to quit or those who relapsed, because these latter groups have regained the weight reducing effects of smoking. Additional research will need to evaluate the impact of weight gain on relapsers at the point of relapse compared with the impact on abstainers at a comparable point in time. Further, it is clear that actual weight may have little relationship with subjects' perceptions of their weight status. For example, overweight males consistently view themselves as normal weight, while underweight and normal-weight females consistently view themselves as overweight (Klesges 1983). Very small weight gains in some subjects (e.g., normal-weight females) may be much more predictive of relapse than very large weight fluctuations in others (e.g., overweight males) (Klesges 1983). Future research should evaluate potential variables (e.g., gender, obesity) that may moderate the relationship between weight gain and smoking relapse.

In summary, weight-related issues may be important in the maintenance and cessation of smoking. Weight-reducing effects of smoking may encourage smoking initiation by some people, but the data on this point are currently unconvincing. Future research should focus on who (e.g., males versus females, those with a history of chronic dieting) is most at risk to smoke because of weight-related concerns. In particular, prospective studies on weight-related issues as they predict smoking initiation, cessation, and relapse are needed.

Implications for Tobacco Use

Cigarette smokers weigh less than comparably aged nonsmokers, and many smokers who quit smoking gain weight. This inverse relationship between smoking and body weight is well established, and the role of food intake and energy expenditure as mechanisms for this relationship is currently receiving research attention. The postsmoking weight gains are frequently undesired by the ex-smoker. People are quite aware of the relationship between smoking and body weight, and this relationship may encourage some people to initiate smoking and to keep smoking. However, other people may

modify food intake and avoid weight gains after cessation of smoking.

Summary and Conclusions

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.

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CHAPTER VII

TREATMENT OF TOBACCO DEPENDENCE

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Introduction

The previous chapters have established that nicotine is a drug of dependence. Chapter II provided a detailed description of the pharmacokinetics and pharmacodynamics of nicotine from various forms of tobacco. Chapter III addressed sites and mechanisms of nicotine action. Chapter IV documented addictive properties of tobacco including those related to its use as a vehicle for nicotine delivery and physiological dependence produced by nicotine administration. Chapter V demonstrated the commonalities between tobacco use and use of other drugs such as heroin and cocaine. Chapter VI discussed effects of nicotine that may promote to tobacco use.

Unfortunately, much of this work has seen limited clinical application in the treatment of the tobacco user. Most current treatment approaches are primarily psychological. Relatively few studies have addressed pharmacologic determinants of tobacco use (Pomerleau et al.). An increased understanding of the addictive properties of nicotine should lead to improved treatment approaches. Interventions for tobacco users who seek assistance should consider the addictive properties of tobacco and the ways that these can be overcome. They should also be sensitive to other effects of nicotine that may promote tobacco use. The failure to address these types of issues may be an important cause of the less-than optimal results attained by existing treatment approaches.

It is evident that smoking is maintained by both pharmacologic and psychological determinants. The relative contributions of these factors are virtually impossible to separate and are likely to vary dramatically not only among individual smokers, but perhaps also within individuals at different times and stages of their smoking histories. Pharmacologic and psychological factors become closely linked in a conditioning process in which smoking is associated with multiple cues. A typical smoker who has averaged 20 cigarettes/day over a 15-year period is likely to have taken more than 1 million puffs during the course of his or her smoking history. The highly dependent smoker who presents for treatment tends to have an even longer and more extensive history of nicotine self-administration than does the average smoker. The sheer magnitude of this overlearning appears unmatched in any other form of drug abuse.

Cues associated with smoking (an ashtray, the sight of another person smoking) can elicit strong cravings not only in current and newly abstinent smokers, but also in individuals who have achieved longer term abstinence (Abrams 1986). Some cues may extinguish relatively quickly upon cessation. Others may be more problematic, especially in long-term dependent smokers (Abrams et al., in press). Smokers who report smoking more when they are angry, frustrated, or unhappy may be especially vulnerable to a crisis even when the crisis occurs after an extended period of abstinence (Pomerleau,

Adkins, Pertschuk 1978). Cues associated with smoking that are encountered only infrequently might continue to elicit conditioned cravings over a longer time period (Abrams et al., *in press*).

Individual differences should also be considered. Conditioning histories vary among smokers, although there are also likely to be important commonalities. Some smokers have relied more heavily upon nicotine in regulating mood, especially negative affect (Chapter VI). Others have used cigarettes as a means of sustaining attention to monotonous tasks. Still others have used cigarettes more frequently as an aid to relaxation (Ikard, Green, Horn 1969; Chapter VI). Few experimental studies have related individual differences to reasons for smoking (Ikard and Tompkins 1973; Leventhal and Avis 1976).

Physiological reactions (e.g., elevated heart rate) to smoking cues have been documented to persist for extended intervals (Abrams et al., *in press*). The interaction of physiological, social, conditioning, and cognitive factors may be critical. The combination of tobacco pharmacology and users' conditioning histories can help to explain cravings even after long periods of abstinence. Expectations concerning the consequences of tobacco use also appear to be extremely important. Thus, among individuals who are currently abstinent, the anticipation of highly reinforcing physiological reactions to tobacco use is predictive of relapse (Marlatt and Gordon 1985).

It is ironic in light of the broad-spectrum treatment of other drug dependencies that tobacco prevention and cessation treatments have been focused so narrowly. Even where pharmacologic strategies have been employed (e.g., nicotine replacement therapy; Fagerström 1982b; Schneider et al. 1983), these often have not been integrated systematically with behavioral treatments. Chapter V details some of the physiological and psychosocial interventions for various drug dependencies including those on alcohol, opiates, cocaine, and other illicit substances. This body of literature may have important and largely overlooked implications for the clinical treatment of tobacco dependence.

According to the 1985 National Health Interview Survey (NHIS), there are approximately 41 million former smokers in the United States. Approximately 90 percent of former smokers report that they quit smoking without formal treatment programs or smoking cessation devices (Fiore et al., *in press*). Achieving abstinence from tobacco and other substances outside the context of formal treatment programs (spontaneous remission) is discussed in Chapter V. Not only smokers but other drug takers often discontinue use of the dependence-producing substance outside the context of formal intervention. Several common factors may be operating to influence smokers to quit (e.g., response to social pressures, observed and anticipated health consequences). Unfortunately, millions of new individuals have been recruited to smoking.

Despite the well-known health hazards of smoking and the documented difficulties in quitting, few intensive treatment options are available to the highly dependent smoker (Sachs 1986). Cigarette dependence or addiction can be as intractable as any addictive disorder (Russell 1976). Studies have found considerable similarity in relapse processes between tobacco and other drugs of dependence (Hall and Havassy 1986; Marlatt and Gordon 1980; see also Chapter V).

As shown in Chapter IV, cigarette smoking is not a random or capricious behavior; rather it is orderly and controlled. The role of nicotine in cigarette smoking is functionally similar to the roles of other addicting, psychoactive drugs in behaviors that lead to their self-administration (Chapter V; US DHHS 1984b, 1987).

A practical result of these conclusions has been the development of methods to treat cigarette smoking that are similar to methods used to treat other forms of drug dependence. An additional implication is that because cigarette smoking, like other forms of drug dependence, involves both pharmacologic and behavioral factors, treatment approaches also may involve pharmacologic agents, behavioral strategies, or a combination of these. There is some evidence, as discussed in the present Chapter, that treatment approaches which address both pharmacologic and behavioral factors are most effective.

Current data indicate that smoking prevalence is declining much more rapidly among certain segments of the population (e.g., better educated, higher income, professional) than among others (blue collar, minority, less educated, lower income) (Appendix A). Individuals from lower socioeconomic status (SES) backgrounds appear to have less access to treatment and may be less likely to enroll in treatment programs when they are available. Participants in most formal treatment programs have been from the middle and upper-middle class (US DHHS 1987). To have maximum impact upon the prevalence of smoking, interventions must be responsive to and meet the needs of lower SES smokers in a variety of circumstances.

Women represent an additional population that could benefit from tailored programming. Women may be more likely to use cigarettes for stress reduction and mood regulation (Brunswick and Messeri 1984; Mitic, McGuire, Neumann 1985). Potential weight gain may represent an especially serious concern for many female smokers (Jacobson 1981; US DHEW 1980; Chapter VI).

Knowledge of the dependence-producing aspects of tobacco underscores the need for early intervention in preventing habitual chronic tobacco use. This approach needs to be sensitive to both pharmacologic and social aspects of smoking. Intervention for children and adolescents also may need to focus upon cessation of well-established smoking patterns in addition to the prevention of smoking onset.

Treatments that assist smokers to achieve initial cessation and to maintain long-term abstinence are needed. High rates of relapse plague the vast majority of treatment programs as well as self-initiated quit attempts. Close examination of the physiological, psychological, and social factors that promote relapse should suggest more effective intervention strategies. Conceptualizing the quitting process as ongoing may also be useful (Marlatt and Gordon 1985; Prochaska and DiClemente 1983). Work is needed not only to reduce the risk of initial relapse, but to accelerate recycling of quitting attempts in the event that relapse does occur (Glasgow, Lando, Rand 1986).

Although discussed in earlier chapters in this Volume, it is appropriate to summarize some observations about cigarette smoking that are important in the development and implementation of treatment strategies.

1. Chronic tobacco use produces physical dependence such that cessation may be accompanied by a withdrawal syndrome that includes feelings of discomfort or distress, reduced capacity to work or handle stressful situations, and heightened urges to resume smoking.
2. Consumption of tobacco products, which inevitably results in administration of nicotine, can produce effects which are perceived as desirable or otherwise useful to the cigarette smoker, thereby providing a strong incentive for cigarette smoking. There is evidence that nicotine can enhance performance of smokers on certain types of attention and memory tasks. Nicotine also exerts an important role in the relationship between smoking and body weight.
3. The desire to handle cigarettes may be an important reason for smoking (Leventhal and Avis 1976). Such stereotypical behaviors are characteristic of other forms of drug addiction and other compulsive behaviors not involving psychoactive drug self-administration. For cigarette smoking, the behaviors appear to occupy small periods of time with hand-oral manipulations (Ikard, Green, Horn 1969).
4. Nicotine may reduce the aversiveness of stressors for smokers (Pomerleau, Turk, Fertig 1984). Stress has been demonstrated to increase the rate of smoking (Leventhal and Cleary 1980; Schachter, Silverstein, Perlick 1977; Chapter VI).
5. There are numerous environmental factors that can facilitate the initiation and maintenance of smoking (e.g., peer pressure, family influences, images conveyed in tobacco advertising, association with social and work activities) (Flay 1985b; Warner 1986).

Smoking treatment programs are designed to counter these important motivations to smoke. For example, skills training

treatments are designed to inculcate skills so that individuals can cope with stressors or negative affective states without smoking. Aversion treatments are designed to condition cigarette aversions so that smokers anticipate little pleasure from smoking. Nicotine polacrilex gum and nicotine fading treatments are designed to reduce the magnitude of the nicotine withdrawal syndrome. This Chapter attempts to summarize what is known about how pharmacologic and behavioral treatments exert their clinical effectiveness. Knowledge of how treatments influence smoking will be the base on which more effective treatments are designed.

This Chapter describes pharmacologic, behavioral, and combined treatments applied in clinical and laboratory settings. It concentrates on work published since the last major Surgeon General's review of smoking treatment (US DHEW 1979), but refers back to that Report for historical perspective. Pharmacologic and behavioral treatment strategies are reviewed in light of the current acceptance of tobacco use as a form of drug self-administration that has clear addictive properties as well as commonalities with other forms of drug abuse.

The review of treatment approaches is necessarily selective. Smoking interventions can be placed along a clinical-public health continuum. At the extreme clinical end are intensive and costly one-to-one interventions, often with a highly trained provider. Examples include one-to-one behavioral or psychological counseling. Proceeding somewhat toward the public health end, one finds group programs, many of them offered by nonprofit or voluntary organizations, but some also conducted on a proprietary basis. These programs typically entail 4 to 10 sessions and are usually led by facilitators with some background in health education and psychology, although trained lay facilitators are also used. Further along the public health segment of the continuum are minimal interventions emphasizing self-help manuals and including brief contact with physicians during office visits.

The current Chapter focuses primarily upon the treatment of smokers who seek assistance in quitting. There is no intent, however, to deny the importance of public health interventions that will ultimately reach a far greater number of smokers. Both clinical and public health approaches are absolutely essential. The reader is referred to previous Surgeon General's Reports and other publications for more detailed discussions of such topics as physician intervention, self-help strategies and outcomes, workplace and community interventions (US DHEW 1979; US DHHS 1982, 1984b, 1985; Schwartz 1987).

Treatment

Although most pharmacologic treatment strategies also encompass behavioral components and some studies have systematically combined pharmacologic and behavioral interventions, it is conceptually useful to consider these two major types of approaches separately.

One major pharmacologic approach has involved various nicotine replacement strategies. As discussed in Chapter V, the general principle of replacement therapies for drug dependence is to present the patient with a safer and more therapeutically manageable form of the drug that directly alleviates signs and symptoms of withdrawal and craving (Jaffe 1985). These strategies are modeled after those originally developed to treat dependence on heroin and other opiates (Henningfield and Jasinski 1988). A variety of nontobacco-based delivery systems provide potentially effective means for nicotine replacement. Experimental and theoretical aspects of each of these delivery systems have been described in part in Chapter IV. In the present Chapter, data regarding those nicotine delivery systems that are most relevant to direct treatment application will be summarized.

In addition to nicotine replacement approaches, the following additional pharmacologic treatment approaches developed for other forms of drug dependence may be applied to tobacco dependence: Nonspecific Pharmacotherapy, in which the patient is treated symptomatically; Nicotine Blockade Therapy, in which the behavior-controlling effects of the dependence-producing drug are blocked by pretreatment with an antagonist; and Deterrent Therapy, in which administration of the treatment drug results in the occurrence of aversive consequences. All three approaches have potential applications in the treatment of cigarette smoking. Each of these strategies is discussed.

Nicotine Replacement Strategies

To date, only one form of nicotine replacement has been approved by the Food and Drug Administration (FDA): nicotine polacrilex chewing gum (2-mg pieces only). Three other nicotine delivery systems that will be briefly discussed are (1) a transdermal patch for delivery of nicotine through the skin, (2) a nasal nicotine solution, and (3) a nicotine vapor inhaler (smokeless cigarette).

There is considerable current interest in nicotine replacement strategies for smoking cessation because (1) nicotine is the critical dependence-producing component in tobacco, (2) some treatment outcome data on the efficacy of the first nicotine replacement procedure to be evaluated (nicotine polacrilex gum) are encouraging, and (3) other forms of nicotine substitution may hold further

potential for more effective treatment. The assumption underlying this treatment approach is that nicotine-specific withdrawal interferes with successful cessation and can be prevented or attenuated by nicotine replacement, thereby both promoting cessation and aiding the inhibition of relapse. For a more extensive review of nicotine replacement, see Grabowski and Hall (1985) and Pomerleau and associates (1988).

Forms of Replacement and Rationale

The first reported systematic use of nicotine replacement to help people quit smoking was the intravenous administration of nicotine by Johnston (1942). This approach is not clinically practical because of the short half-life of nicotine (Chapter II) and its potential toxicity with excessively rapid administration (Appendix B). The next systematic approach was the development of nicotine polacrilex gum by Ferno, Lichtneckert, and Lundgren (1973). The weaning from nicotine would actually begin with the switch from cigarettes to gum in that nicotine polacrilex (1) produces slower-rising plasma nicotine levels than cigarettes and (2) reduces the inhaled nicotine bolus effect believed to contribute to nicotine's addictive potential in smoke (Russell and Feyerabend 1978; Chapter II).

The same rationale applies to other replacement approaches (Jarvik 1986; Russell 1986) including nicotine transdermal delivery systems, nasal nicotine solution (NNS), and smoke-free nicotine cigarettes. The different forms allow variations in delivery (dose and speed) which may influence effectiveness, relief of withdrawal, patient acceptance, and outcome.

Nicotine Polacrilex Gum

"Nicotine polacrilex" or "nicotine resin complex" (American Hospital Formulary 1987) is also commonly referred to as nicotine gum. It is a nicotine delivery system in which the nicotine is incorporated into an ion exchange resin base which permits release of nicotine in the proper environment (i.e., saliva in the mouth) when appropriate physical pressure (i.e., chewing) is applied. Twenty to thirty minutes of proper chewing can result in the release of approximately 90 percent of the nicotine (Ferno, Lichtneckert, Lundgren 1973), although there are multiple determinants of how much nicotine actually is absorbed. As discussed in Chapter II, 10 to 15 min of chewing results in the release of approximately 50 to 60 percent of the nicotine in a piece of gum. However, considerable variability exists both within and across subjects (Benowitz, Jacob, Savanapridi 1987; Nemeth-Coslett et al. 1987; Pickworth, Herning, Henningfield 1986; Chapter II). Swallowed nicotine is approximately

70 percent detoxified as a result of its first pass through the liver (Benowitz, Jacob, Savanapridi 1987; Chapter II).

Nicotine polacrilex gum does not usually lend itself to full replacement of the nicotine provided by cigarette smoking. Russell, Feyerabend, and Cole (1976) and McNabb, Ebert, and McKusker (1982) reported that 4-mg-nicotine gum produced plasma nicotine levels approximating that of a 1.2-mg-nicotine-yield cigarette. However, Benowitz, Jacob, and Savanapridi (1987) found only about 50 percent replacement of nicotine levels with 4-mg gum. Benowitz, Jacob, and Savanapridi (1987) reported that chewing 10 pieces of 2-mg gum on an hourly schedule resulted in blood levels of nicotine that were one-third of those achieved while smoking. Therefore, ad libitum chewing of the 2-mg nicotine polacrilex gum probably results in even lower nicotine levels. When nicotine polacrilex gum is chewed, drug levels in plasma rise slowly, peaking in around 20 to 30 min. Although the 4-mg nicotine polacrilex gum replaces nicotine more completely, most testing has proceeded with the 2-mg dose; only the 2-mg dose has been approved for use in the United States. It should be noted, however, that effective nicotine replacement strategies may not require the same range of nicotine blood levels as those produced by cigarette smoking. Even the 2-mg-dose nicotine polacrilex gum has increased smoking cessation rates significantly in several placebo-controlled studies (Table 1).

Withdrawal symptom relief. Several short-term trials (8 hr to 5 days) have found that nicotine polacrilex gum reduced symptoms of withdrawal in comparison to placebo controls (Hughes et al. 1984; Schneider, Jarvik, Forsythe 1984; West, Jarvis, Russell, Carruthers et al. 1984). Jarvis and associates (1982) reported relief of several symptoms for a 6-week period, with scores averaged over weekly sessions. Expectancy may also play a role in withdrawal symptom relief, as suggested in a study by Gottlieb and others (1987). Interpretation of this study is limited, however, by a brief (2-week) observation period and by the possibility that subjects failed to achieve adequate nicotine plasma levels.

In previous studies, not all symptoms were relieved with replacement nor was there consistency among the studies in which symptoms were relieved (Fagerström 1988; West 1984). Irritability was consistently relieved in all studies, whereas hunger, depression, anxiety, difficulty in concentrating, restlessness, annoyance, hostility, and somatic complaints were reduced in some but not others. The degree to which most symptoms are relieved is directly related to the dose of nicotine that is actually obtained when the polacrilex gum is used (Henningfield and Jasinski 1988). The urge to smoke (craving) is not reliably decreased by nicotine replacement (Henningfield and Jasinski 1988; West and Schneider 1987).

**TABLE 1.—Efficacy trials for nicotine polacrilex gum:
Followup abstinence rates (percentages)**

Study	Number ¹	I. Placebo-controlled studies		Followup	P
		Active gum	Placebo		
Puska et al. (1979)	160	35	28	6 mo	N.S.
Malcolm et al. (1980)	210	23	5	6 mo	p<0.05
Fee and Stewart (1982)	352	13	9	1 yr	N.S.
Fagerström (1982b)	96	49	37	1 yr	N.S.
Jarvis et al. (1982)	116	47	21	1 yr	p<0.01
British Thoracic Society (1983)	802	10	14	1 yr	N.S.
Schneider et al. (1983)	60	30	20	1 yr	N.S.
Hjalmarson (1984)	205	29	16	1 yr	p<0.05
Jamrozik et al. (1984)	200	10	8	6 mo	N.S.
Campbell et al. (1987)	985	3	2	1 yr	N.S.
Hall et al. (1987)	139	44	21	1 yr	p<0.01
II. No-gum control studies					
Study	Number ¹	Nicotine gum	No gum	Followup	P
Russell et al. (1983)	1,938	9	4	1 yr	p<0.01
Fagerström (1984)	145	25	9	1 yr	p<0.05
Hjalmarson (1985)	2,404	25	18	1 yr	p<0.05
Page et al. (1986)	227	12	9	6 mo	N.S.

TABLE 1.—Continued

Study	III. Nicotine polacrilex gum vs. other active treatment					P
	Number ¹	Gum	Comparison	Followup		
Behavioral counseling and rapid smoking						
Raw et al. (1980)	118	38	14	1 yr	p<0.01	
Hall et al. (1985)	78	36	28	1 yr	N.S.	
Skills training						
Killen et al. ² (1984)	42	23	30	10 mo	N.S.	
Acupuncture						
Clavel et al. ³ (1985)	429	12	8	13 mo	N.S.	

¹ Number of subjects based on relevant conditions; may not include all subjects assigned to treatment.² Also included a combined skills training and nicotine polacrilex gum condition.³ Included a control condition in which subjects were assigned a cigarette case programmed to lock at variable intervals.

SOURCE: Modeled after Fagerström (1988).

The studies noted above used ad libitum administration of the 2-mg gum. This level of replacement may be insufficient to reverse some of the symptoms of nicotine withdrawal. Studies which have shown little difference between the 2-mg dose and placebo are not clearly interpretable unless they have confirmed adequate dosing through biochemical markers (e.g., plasma cotinine). When the nicotine polacrilex dose has been increased to 4 mg, more complete reversal of withdrawal (Henningfield, Sampson, Nemeth-Coslett 1986), of electroencephalogram (EEG) changes with abstinence (Pickworth, Herning, Henningfield 1986), and of performance deficits during cessation (Snyder, Davis, Henningfield 1985) is observed.

Different withdrawal symptoms may also require different levels of nicotine replacement. Whether a particular withdrawal symptom is nicotine specific cannot be determined until there is systematic testing by dose and speed of delivery of nicotine replacement. In addition, recent studies show that intrasubject and intersubject variability in chewing can affect the amount of nicotine reaching the circulation (Benowitz et al. 1983; Nemeth-Coslett et al. 1985).

There is also some evidence that weight gain, a significant problem in cessation, can be reduced by nicotine replacement (Fagerström 1987). Even low-dose, 2-mg-nicotine gum has been shown to produce significantly less weight gain over a 10-week period compared with a placebo (Stitzer and Gross 1988).

Cravings-urges-desires. Findings regarding urges or craving are complicated by semantic and measurement considerations (Kozlowski and Wilkinson 1987) and by ambiguity as to what constitutes craving (West and Schneider 1987). Definitions of craving have proven elusive. It is often described as an increase in the desire or urge to use a drug. Although the term craving is used in the present context, a more appropriate phrase might be substituted, e.g., "strength of an urge to use a drug" (Chapters IV and V).

In the tobacco abstinence studies cited above, craving generally was not relieved by nicotine replacement. By contrast, significant relief of craving has been reported with 2-mg-nicotine polacrilex gum compared with placebo controls in an outcome trial (Hjalmarson 1984), in a clinical trial with NNS (Jarvis 1986), and with a nicotine patch in an acute placebo-controlled trial (Rose et al. 1985). The discrepancies may be due to how "craving" is assessed. In a study by Schneider and Jarvik (1985), treatment had no effect on "craving" but did significantly affect "urges to smoke" and "missing a cigarette" from the Shiffman-Jarvik (1976) "craving" subscale. Because nicotine seeking is believed to precede most relapse and its relief is a goal of replacement systems, appropriate operational definitions and testing are essential.

Craving should not be viewed simply as a symptom of a negative withdrawal state. Smokers clearly seek desired effects of nicotine in addition to relief from withdrawal (Chapters II and VI). Nicotine polacrilex gum may reduce negative withdrawal symptoms without providing other effects (e.g., a "high") sought by many smokers.

Efficacy trials. Table 1 summarizes efficacy trials that evaluated nicotine polacrilex gum against placebo controls, no-gum controls, or other active treatment. This Table does not include all the studies that combined nicotine polacrilex gum with behavioral interventions.

The early studies of nicotine replacement involved testing of the nicotine regulation hypothesis (e.g., the extent to which cigarette smokers show compensatory changes in their cigarette smoking behavior; Chapter IV). These studies assessed the capacity of nicotine in polacrilex gum to replace nicotine in cigarettes (Brantmark, Ohlin, Westling 1973; Russell et al. 1976; Turner et al. 1977). Several studies have demonstrated that cigarette smoking can be decreased in laboratory subjects by replacement of the nicotine normally obtained by smoking with nicotine delivered by gum (Nemeth-Coslett and Henningfield 1986). Early clinical outcome

trials, although supporting the efficacy of nicotine polacrilex gum, were flawed by statistical problems, inadequate nicotine delivery, concurrent smoking and use of gum by subjects, and lack of validation or inappropriate controls (Malcolm et al. 1980; Puska, Bjorkqvist, Koskela 1979; Raw et al. 1980). In the placebo-controlled clinical trials, nicotine polacrilex gum significantly increased success rates for as long as 6 months in some studies (Fagerström 1982a; Schneider et al. 1983) and 1 year in others (Hjalmarson 1984; Jarvis et al. 1982; Table 1). It should be noted, however, that in most of these studies, other treatment procedures (e.g., group therapy) were applied in addition to either nicotine polacrilex gum or placebo.

Subsequent efficacy trials proceeded without regard to control of dose or scheduled use of nicotine polacrilex gum. The trials may be divided into those conducted in clinic settings versus physician or dispensary trials. Different trials compared active gum with a placebo, active gum with no-gum conditions, or gum with other treatments (Fagerström 1988).

Hall and coworkers (1985) assessed nicotine polacrilex gum plus an intensive contact behavioral treatment (14 sessions over an 8-week period), nicotine polacrilex gum plus low-contact behavioral treatment (4 sessions over a 3-week period), and the intensive behavioral treatment alone. The combination of intensive behavioral treatment and nicotine polacrilex gum was significantly superior to the other interventions through 6-month followup. Differences were no longer significant at 1 year, however. In a subsequent study, Hall and colleagues (1987) assigned subjects to intensive behavioral or to low-contact smoking treatment and to 2-mg-nicotine gum or to placebo gum in a 2-by-2 factorial design. Results at 1-year followup indicated significant effects only for nicotine polacrilex gum. No differences were found between low-contact treatment and intensive behavioral intervention. In a study by Killen and colleagues (1984), the success rate of nicotine polacrilex gum combined with behavioral treatment at a 10.5-month followup was 50 percent as opposed to 23 percent for gum and 30 percent for behavioral treatment alone. However, these differences between treatment conditions were not significant.

Physician trials have resulted in lower overall success rates for all groups and some equivocal findings. These lower success rates may be attributable, at least in part, to a selection bias. Clinics may attract only a small proportion of smokers who are interested specifically in treatment. Physician trials sometimes have included all smoking patients regardless of their level of interest in quitting. The British Thoracic Society (1983) reported no differences among four conditions involving active nicotine polacrilex or placebo gum. However, this study included patients who were not actively seeking treatment and failed to instruct patients in the use of the preparation. Jamrozic and coworkers (1984), using patients who were

motivated to quit, reported no differences between patients given nicotine polacrilex or placebo gum. In that study, only 70 percent of the subjects even tried the active nicotine polacrilex gum, and only one-half of the subjects used it regularly. In a dispensary study with nicotine polacrilex versus placebo gum, all individuals started gum but most stopped use within 3 to 5 days and failed (Schneider et al. 1983).

Differences in outcome comparing the clinic setting versus physician offices have been interpreted as indicating the requirement for support treatment with nicotine polacrilex gum. However, it is not clear whether support treatment per se is necessary or whether it serves to encourage sufficient use of the preparation. In fact, compliance with gum use instructions is often unsatisfactory in both clinic and physician office settings. In a large physician trial, Russell, Merriman, and colleagues (1983) reported that 47 percent of subjects given active nicotine polacrilex gum did not use it. However, use of nicotine polacrilex gum resulted in significantly higher success rates (8.8 percent) compared with no gum (4.0 percent) at 1 year, and when patients used a total of at least three boxes of nicotine polacrilex gum, success rates tripled to 24 percent without further intervention. It is unclear whether these substantially increased success rates are a function of gum use per se or simply a reflection of a greater overall commitment to treatment.

Followup may also prove to be important for a good outcome. Fagerström (1984) assigned subjects to either short or long followup and to either nicotine polacrilex gum or no-gum conditions. Short followup consisted of one physician appointment approximately 14 days after cessation. Long followup included two physician appointments (approximately 14 and 30 days after cessation), a telephone call (after about 7 days), and a personal letter inquiring about patients' smoking status (3 months after cessation). Results at 1-year followup indicated significant differences in favor of nicotine polacrilex gum over no gum. Initial effects were also found for long over short followup. However, these effects were no longer significant at 1-year followup. At this point 27 percent of the subjects assigned long followup and nicotine polacrilex gum were abstinent, compared with 22 percent of those receiving short followup and nicotine gum, 15 percent of those assigned long followup and no gum, and 3 percent of those receiving short followup and no gum. In a recent physician trial by Hughes and associates (1988), with minimal intervention and a followup visit, significant differences in favor of active gum over placebo gum were observed at 1 and 6 months, although the differences were no longer evident at 1 year.

The high long-term relapse rate observed in their own and other published reports led Hughes and coworkers (1988) to conclude that nicotine polacrilex gum in the physician setting is not more effective

than placebo. However, the issue may be a different one. In several studies, early significant effects reported at 1 month (Fee and Stewart 1982) and 6 months (Fagerström 1982a; Hall et al. 1985; Schneider et al. 1983) disappeared at 1 year although the trends continued to favor active nicotine polacrilex gum. Rather than being interpreted as a failure for nicotine polacrilex gum versus a placebo, this may mean that what is effective treatment for initial quitting (e.g., relief of withdrawal symptoms) is different from effective long-term relapse prevention.

Another variable which may affect outcome is duration of nicotine polacrilex gum use. It has been suggested that longer use will be more effective (Russell, Raw, Jarvis 1980; Wilhelmsen and Hjalmarsson 1980), yet duration of use remains an untested and unresolved issue. The one prospective trial comparing 1- with 6-month use of nicotine polacrilex gum (Fagerström and Melin 1985) was flawed by differential clinical intervention for the 1-month group. Duration of use is also an issue in evaluating followup results. Followup is virtually never calculated as time since discontinuation of nicotine polacrilex gum. One-year followup results might be considerably shorter if the end of treatment were defined as the point at which nicotine polacrilex gum is no longer consumed. In fact, a significant proportion of subjects appear to persist in their use of this gum for at least 6 months to 1 year (Hughes 1988).

Dose and patient relationship. A few trials have used both 2- and 4-mg doses of nicotine polacrilex gum (Kornitzer et al. 1987; Toennesen et al., in press; Toennesen 1986). These studies have not found a direct effect of dose but report that dose interacts significantly with degree of nicotine dependence in the smokers tested. Four-milligram nicotine polacrilex gum improved success rates for more highly dependent smokers, whereas 2-mg nicotine polacrilex gum was superior in less-dependent smokers. The problem, once again, is that ad libitum dosing (thus uncontrolled dose-response testing) reduces the interpretability of the observed effects. Otherwise, the logic is reasonable: smokers who have a greater degree of dependence on nicotine may require treatment with higher doses than those required by less-dependent smokers.

With respect to the selection of subjects for treatment with nicotine polacrilex gum, Hall and colleagues (1985) reported a significant positive correlation between smokers with high pre-quit cotinine levels and abstinence with nicotine polacrilex gum. Jarvik and Schneider (1984) reported that individuals scoring high on the Fagerström Tolerance Scale had greater success with replacement. Other selection issues may be equally important. For example, Toennesen and coworkers (in press) reported a substantial difference in outcome at 1 year between healthy subjects (45 percent success) and those with chronic bronchitis (16.2 percent). Patient selection

and variations in severity of nicotine dependence are expected to interact with success rates for any replacement therapy (Chapter IV).

Nasal Nicotine Solution

Russell, Jarvis, and colleagues (1983) have investigated nicotine replacement in the form of an NNS. NNS is a gel-like droplet of nicotine squeezed into the nose from a small vial. NNS was formulated to provide more rapid and efficient absorption of nicotine than is possible with use of nicotine in polacrilex gum (Russell 1986; Jarvis 1986).

Russell, Jarvis, and colleagues (1983) reported average peak plasma nicotine levels of 25.7 ng/mL in three male smokers for a single cigarette (1.4-mg machine-determined nicotine yield), 8.5 ng/mL for one piece of 2-mg gum, and 14.1 ng/mL for NNS (0.1 mL of a 2 percent aqueous solution of nicotine, 2 mg, at pH 5.0 without added buffer). Higher levels with hourly dosing of NNS versus nicotine polacrilex gum were also documented (West, Jarvis, Russell, Feyerabend 1984).

Only very preliminary data are available with respect to the clinical efficacy of NNS. Jarvis (1986) reported decreased craving and encouraging abstinence outcomes in a sample of 26 consecutive new attenders at the Maudsley Smokers Clinic (approximately two-thirds of the subjects achieved initial abstinence and one-third remained abstinent at 1-year followup). The faster absorption and higher plasma nicotine levels attained with NNS as opposed to nicotine polacrilex gum suggest that NNS may be more effective and better accepted by smokers as a replacement for cigarettes. However, subjects in the Jarvis study reported NNS to be somewhat embarrassing to use in the company of others.

Nicotine Transdermal Patch

Rose, Jarvik, and Rose (1984) initially suggested that a transdermal nicotine delivery system might be an effective route of administration. In a short-term (hours) laboratory trial, Rose and colleagues (1985) reported a decrease in craving and nicotine preference in subjects using a nicotine patch versus a placebo patch.

A transdermal delivery system could eliminate some of the compliance and chewing problems associated with nicotine polacrilex gum. Steady-state administration expected from such a system may be more effective in preventing withdrawal symptoms. While the patch does not allow for self-dosing in response to smoking urges, it could potentially be used in combination with the other rapidly absorbed forms of nicotine replacement. Transdermal delivery

systems have not yet been tested in clinical trials or in nonlaboratory settings.

Nicotine Aerosols

Devices have been marketed that provide for inhalation of nicotine without other components of tobacco. One such product was on the commercial market for approximately 18 months, but was removed by the FDA (Chapter IV). Because the nicotine vapor inhaler was devoid of tobacco (other than the tobacco constituent nicotine), it was deemed by the FDA to be a nicotine delivery system. Because nicotine is regarded as a drug with clinical application (namely to treat nicotine dependence), the FDA ruled that it could not be sold until it had been shown to be safe and effective in appropriate clinical trials.

Technical engineering problems have also been encountered. The shelf life of the unrefrigerated vapor inhaler was apparently limited to approximately 1 month. In addition, this device delivers little nicotine unless there is extraordinary effort on the part of the user (Sepkovic et al. 1986). Russell and associates (1987) reported negligible plasma nicotine levels when vapor inhalers were puffed at a regular rate for 10 min. When the nicotine vapor inhalers were puffed at the rate of 10 puffs/min and 4 of these inhalers were used in a 20-min period, plasma nicotine levels increased to 17.3 ng/mL, levels similar to those seen after cigarette smoking.

If nicotine aerosols can be improved, they may be of value to smokers for whom slow-release nicotine replacement preparations are inadequate to produce the desired effects of nicotine. Such aerosols would allow nicotine replacement with some replacement also of the oral, handling, and sensory reinforcements (Rose 1986) for individuals who need to be weaned more slowly. Whether these aerosols will be effective in smoking cessation treatment is unknown.

Comparisons of Preparations

All nicotine replacement products produce side effects. Nicotine polacrilex gum may produce mouth sores, gastric upset, and hiccups. NNS produces runny nose and irritation, whereas transdermal devices can result in skin irritation. Transdermal devices have the advantages of better patient compliance with treatment and steady-state drug levels, whereas NNS and nicotine polacrilex gum have the advantage of ad libitum access to replacement. Because triggers to smoke can appear at any time, the flexibility offered by the latter may be essential. Ultimately, a combination of preparations may be most useful to control symptoms as well as to allow instant responses to smoking urges. At this point, the replacement therapies in development must undergo testing for bioavailability, safety, and

toxicity as well as testing for dose-response effectiveness in relief of withdrawal and efficacy in treatment.

Dependence on Nicotine Replacement

West and Russell (1985) and Hughes and coworkers (1986) reported the appearance of withdrawal symptoms upon abrupt cessation of nicotine polacrilex gum. However, the authors have different interpretations of these findings. Hughes and coworkers (1986) consider this phenomenon as an indication that nicotine polacrilex gum produces physical dependence. West and Russell (1986) point out that any dependence on this gum is part of the continued dependence on nicotine that originated with smoking and is bound to transfer during weaning (Chapter IV).

A more complicated issue is that of continued compulsive long-term use. The definition of excessive long-term use cannot be resolved without studies to determine the length of treatment necessary and sufficient for successful intervention. No such studies are available in the current published literature. Hughes (1988) reports that many abstinent smokers are unable to discontinue nicotine polacrilex gum use (35 to 90 percent of abstinent smokers at 6 months and 13 to 38 percent at 1 year continued to use nicotine polacrilex gum despite advice to stop).

An important additional issue is whether it is possible to initiate and maintain physical dependence on nicotine with replacement products alone. Nicotine polacrilex has been used widely with no reported cases of such development. This would suggest that nicotine polacrilex gum, through a combination of regulatory, packaging, marketing, and physical characteristics, does not readily lend itself to such abuse. Systematic investigation of the dependence-producing potential of other replacement products is needed.

Other Pharmacologic Approaches

Nonspecific Pharmacotherapy—Symptomatic Treatment

As reviewed in Chapters III and IV, administration and withdrawal from nicotine produce a number of neurohormonal and other physiological effects. These effects, as well as those on receptors in the central nervous system, mediate the various actions of tobacco (Chapters IV and VI). Because several such effects are functional in the maintenance of cigarette smoking and in relapse, it is generally assumed that addressing such factors would enhance treatment programs (Pomerleau and Pomerleau 1984; Shumaker and Grunberg 1986). Such strategies are also an integral part of many interventions for drug addiction in general, as described in Chapter V.

Prevention of relapse to tobacco may be aided by specific intervention (pharmacologic or behavioral) for needs met by the use of

tobacco. The present summary will mainly address pharmacologic methods, excluding nicotine replacement, that have been either used or suggested as means to alleviate the effects of tobacco abstinence that are considered adverse by patients themselves. The categories of such adverse effects for which pharmacologic treatment intervention appears viable are derived from the effects of tobacco in the regulation of mood, weight, performance, and the prevention of specific withdrawal-related discomfort. In addition, the results of studies involving pharmacologic approaches to directly alter cigarette consumption will be summarized.

The emphasis in this Section is upon recent research. It should be noted that there is a long history of generally unsuccessful pharmacologic treatment of smokers (Gritz and Jarvik 1977; Jarvik and Gritz 1977). Experimentation with lobeline sulfate as a smoking substitute dates back to the early 1900s (Edmunds 1904). Lobeline appears to be no more effective than a placebo in facilitating abstinence (Schwartz 1987). Medications intended to reduce withdrawal symptoms (sedatives, tranquilizers, anticholinergics, sympathomimetics, and anticonvulsants) also have failed to improve outcome relative to placebos (Gritz and Jarvik 1977).

Treatment of Discomfort Associated with Tobacco Withdrawal

The signs and symptoms of tobacco withdrawal vary to some degree in nature and severity among individuals, as shown in Chapter IV (also Hughes and Hatsukami 1985). Because symptoms can be treated independently of their origin, symptomatic therapy approaches might be useful in alleviation of tobacco abstinence-associated discomfort. This approach was used in a study by Glassman and his colleagues (1984). In this study, alprazolam (1 mg orally) and clonidine (0.2 mg orally) were compared with a placebo for heavy cigarette smokers on days when they abstained from tobacco. The subjects were exposed to one of the medication conditions on each of 3 smoking abstinence study days, which were separated by at least 3 days of normal smoking. Alprazolam, a benzodiazepine tranquilizer, was included as a control because of the known sedative effects of clonidine. Both clonidine and alprazolam were more effective than the placebo in reducing anxiety, irritability, restlessness, and tension. Only clonidine, however, successfully reduced the craving for a cigarette. Because craving tended to increase during the day, the difference between clonidine and the other two conditions became more evident as the day progressed.

Glassman and colleagues (1988) reported a clinical intervention study with clonidine in a sample of 71 smokers who consumed at least 1 pack/day and who had made at least one previous unsuccessful quit attempt. Each smoker began taking one 50- μ g tablet of clonidine ($N=33$) or a matched placebo ($N=38$) at least 3 days before

a designated quit date. Dosage was increased by one tablet every day (or as tolerated) until subjects were taking four tablets by the quit date. Subjects were seen weekly for the next 4 weeks. After 4 weeks of treatment, clonidine was gradually withdrawn (50 µg every 3 days over an average of 12 days). Success rates both at the end of 4 weeks on clonidine or placebo and at followup 6 months after discontinuance of medication favored clonidine. At 6-month followup, 27 percent of the subjects receiving clonidine and 5 percent of those on placebos reported abstinence. An unexpected finding, however, was that clonidine appeared to be effective only for women; among male subjects, drug treatment did not significantly affect outcome.

Before any recommendation of clonidine as an adjunct to smoking cessation, potentially hazardous side effects must be weighed carefully. Clonidine has been extensively used in the treatment of hypertension. Abrupt cessation has sometimes led to severe hypertension and in rare instances to hypertensive encephalopathy and even death. Far more common is sedation, which could be dangerous if individuals use this drug while driving or operating dangerous machinery.

It is interesting to compare the utility of clonidine in the treatment of tobacco withdrawal with its utility in the treatment of opioid withdrawal (Chapter V). When assessed in a paradigm analogous to that described for tobacco abstinence, clonidine was as effective as morphine in reducing certain physiological signs of opioid withdrawal (Jasinski, Johnson, Kocher 1985). However, in the study by Jasinski and colleagues, clonidine did not reduce the self-reported "discomfort" as effectively as did morphine (measures of "desire to use narcotics" or narcotic-seeking behavior were not collected).

Treatment of Abstinence-Associated Mood Changes

As discussed in Chapter VI, nicotine may serve as a regulator of mood. This observation suggests that for certain persons, selective use of minor tranquilizers, antidepressants, or even psychomotor stimulants may be beneficial in preventing relapse. Again, issues of possible side effects and drug dependence must be considered before such an approach would be recommended in clinical practice.

Laboratory studies with human subjects have shown that stressful situations lead to increased smoking and that smoking may reduce smoker distress responses to stressful stimuli and enhance reported mood (Gilbert 1979; Golding and Mangan 1982; Rose, Ananda, Jarvik 1983). Also, relapse to cigarette smoking often occurs in response to stressful situations (Gunn 1983a; Ockene et al. 1982; Shiffman 1982; Marlatt and Gordon 1980; Lichtenstein, Glasgow, Abrams 1986). There have been no clinical trials in which the targeted use of more specific anxiolytics (e.g., benzodiazepines) has been evaluated in the maintenance of tobacco abstinence. The only study involving a

benzodiazepine was that of Glassman and associates (1984), who compared alprazolam with clonidine during a brief abstinence.

Nicotine Blockade Therapy

Whereas the goal of both replacement therapies and symptomatic treatments is to relieve withdrawal by mimicking critical effects of the drug from which the person is attempting to abstain, blockade therapy provides no such potentially rewarding or therapeutic effect. Rather, the goal of blockade therapy is to reduce or eliminate any rewarding pharmacologic effects should the person attempt to resume drug use. The prototypical blockade therapy is that used in the treatment of opioid dependence (Jaffe 1985). The long-acting opiate antagonist naltrexone can be given on a daily basis to opioid abusers to prevent them from experiencing the reinforcing effects of opioid agonists. Unfortunately, only about 5 percent of opioid-abusing patients are willing to comply with such a therapeutic regimen. Success in naltrexone treatment is correlated with the following characteristics: the patient is highly motivated, well adjusted in society, and has a steady job (Greenstein et al. 1983).

Relapse to former levels of cigarette smoking begins with the first few cigarettes which are smoked. If smoking levels do not progress beyond these few cigarettes, the incident is generally referred to as a "slip" (Shumaker and Grunberg 1986). Slips can lead to relapse because they provide the stimuli which were important in maintenance of the smoking behavior in the first place. Because nicotine itself is the source of many of the effects which are sought by cigarette smokers (Chapters II, IV, and VI), blocking the effects of nicotine should assist in the prevention of relapse. As described in Chapter V, such an approach is effective in preventing relapse to opioid use if the morphine-blocking drug (opioid antagonist) is taken (see also Greenstein et al. 1983).

Pharmacologic antagonists of nicotine, the administration of which could diminish a variety of responses to nicotine, have been known for several decades (Domino 1979). Those antagonists which act both centrally and peripherally (mecamylamine), but not those which only act peripherally (e.g., pentolinium and hexamethonium), appear to have functional effects on patterns of cigarette smoking in humans. Central antagonists also alter the behavioral effects of nicotine (including self-administration) in animals (Henningfield 1984; Stolerman 1986).

Preliminary data suggest the possibility that mecamylamine could be used as an antagonist to block the nicotine-mediated reinforcing consequences of cigarette smoking. The following findings are of particular relevance: (1) Mecamylamine pretreatment produces a dose-related blockade of the ability of animals and humans to discriminate nicotine from a placebo (mecamylamine is injected in

animals and administered orally to humans) (Rosecrans and Meltzer 1981; Stolerman 1986; Henningfield et al. 1982), (2) mecamylamine pretreatment diminishes the reinforcing efficacy of intravenous nicotine administration in animals (Goldberg et al. 1983) and possibly in humans (Henningfield and Goldberg 1983), (3) mecamylamine pretreatment increases the preference for high-nicotine-delivering cigarette smoke (apparently by reducing its nicotinic effects) when subjects are tested with a device which blends smoke from high- and low-nicotine-delivering cigarettes (Rose, Sampson, Henningfield 1985), and (4) mecamylamine pretreatment increases various measures of cigarette smoking behavior and tobacco smoke intake when subjects are allowed to freely smoke (Stolerman et al. 1973; Nemeth-Coslett et al. 1986; Pomerleau, Pomerleau, Majchrzak 1987). Results from the study by Pomerleau and colleagues also suggested that the toxicity of nicotine exposure was reduced substantially by mecamylamine pretreatment.

In one clinical trial, Tennant, Tarver, and Rawson (1984) attempted to determine if mecamylamine could be used safely and efficaciously to treat cigarette smoking. Mecamylamine was given to heavy cigarette smokers in conjunction with counseling to quit smoking. Mecamylamine reduced tobacco craving in 13 of 14 subjects, and half of the subjects quit smoking within 2 weeks of initiation of mecamylamine treatment. The mean dose of mecamylamine at the time of quitting was 26.7 mg/day. Mecamylamine was not used to maintain abstinence as naltrexone is used for opioid dependence. Rather, it was used as an aid to initial quitting. In theory, because mecamylamine blocks the effects of nicotine, it should precipitate withdrawal and, therefore, would not be indicated for acute cessation. Despite this theoretical problem and the lack of placebo controls in the trial, these data suggest that nicotine blockade warrants further exploration.

The main obstacles to this treatment approach are the ganglionic blocking and antihypertensive effects of mecamylamine, the strong likelihood of considerable difficulty in obtaining adequate therapeutic compliance, and conditioned and non-nicotine-mediated reinforcers of tobacco use which may be powerful enough to sustain urges to smoke even when they are no longer associated with the pharmacologic effects of nicotine.

Deterrent Therapy

Deterrent therapy is based on the premise that pretreatment with an agent may transform smoking from a rewarding to an aversive behavior. Disulfiram treatment of alcoholism provides the pharmacologic analogy for this form of treatment (Chapter V).

With regard to cigarette smoking, the main analog to disulfiram treatment is the administration of silver acetate. Variants on this

method have been marketed for over-the-counter purchase for a number of years. The physiological basis of the approach is that sulfide salts are produced when silver acetate contacts the sulfides in tobacco smoke. The resulting silver sulfides are extremely distasteful for most people. The approach is not specific to nicotine intake, but rather to sulfide-containing smoke. Most recently, a gum preparation of silver acetate has been tested as a means to maintain abstinence from tobacco smoking (Malcolm, Currey, Mitchell, Keil 1986). The gum must be chewed upon awakening and then repeatedly during the day to assist in abstinence, because a single piece of gum is apparently only effective for a few hours. Although many over-the-counter silver acetate smoking remedies are available, their efficacy never has been validated scientifically.

Conclusions

In evaluating experimental and clinical trials involving nicotine polacrilex gum, it should be noted that actual nicotine intake may have been significantly less than had been intended or reported if there were not systematic procedures to standardize administration (Benowitz et al. 1986; Nemeth-Coslett et al. 1987; Chapters II and IV). Criteria for the determination of successful outcome in nicotine replacement studies are ambiguous. It is unclear how to interpret results in which nicotine replacement is significantly more effective than a placebo at 6 months, but not at 1 year (Fagerström 1982a; Schneider et al. 1983). Nicotine replacement may be effective in facilitating cessation and in developing early resistance to relapse (withdrawal symptoms, reported cravings for tobacco; Harackiewicz et al. 1987; Hjalmarson 1984; Hughes et al. 1984; West et al. 1984a), but may not have residual effects that prevent relapse (Chapter IV).

Overall, the outcomes of experimental and clinical trials of nicotine polacrilex gum are modestly encouraging, at least for short-term results. In the vast majority of these trials, however, nicotine polacrilex gum has been combined with additional treatment components.

The combination of low doses (with the 2-mg gum), poorly defined criteria for self-administration, compliance problems, and variable absorption of nicotine from polacrilex gum is part of the rationale for the development of alternative replacement strategies (Pomerleau et al. 1988). At the same time, additional work with nicotine polacrilex gum is continuing to address compliance and dosage problems. Availability of a 4-mg preparation might be useful for highly tobacco-dependent individuals. Little clinical application of other replacement strategies has been reported to date. Alternative forms of nicotine replacement should help to determine the relative roles of nicotine and sensory/ritual phenomena in compulsive tobacco use

and improve the therapeutic effectiveness of nicotine replacement strategies.

The precedent for the use of pharmacologically based therapies to help establish and maintain abstinence from tobacco products is the use of similar kinds of techniques to treat other substance-use disorders. It should be noted, however, that some variant on each of the pharmacologic treatment approaches described in this review has been applied to other forms of substance abuse, but with limited success. Individual differences are very important. Some smokers appear to be much more dependent upon the pharmacologic properties of nicotine (both withdrawal relief and positive mood enhancement) than are others (Chapters IV and VI). The efficacy of pharmacologic intervention may be limited by the extent to which the substance-seeking behavior and the desired effects have become functionally autonomous from the drug itself. This problem is not unique to tobacco (Henningfield and Brown 1987). It is known that treating opiate users involves considerably more than blocking physiological withdrawal; an entire lifestyle may require change (Grabowski and Hall 1985; Bigelow, Stitzer, Liebson 1986).

Behavioral Treatment Strategies

Pharmacologic strategies may have a useful role in alleviating withdrawal symptoms or in blocking gratification typically derived from smoking, but these agents do not address conditioned cues and reinforcers or the social context of tobacco use. Effective treatment of the dependent smoker requires behavioral intervention in addition to any pharmacologic agents that might be administered. Research generally indicates that pharmacologic intervention is most effective when applied in a context that includes social support and skills training (Fagerström 1988; Hall, Ginsberg, Jones 1986). Furthermore, behavioral intervention may also be useful in increasing adherence to pharmacologic treatment procedures (Epstein and Cluss 1982).

Behavioral interventions have been applied in treating dependent smokers for many years. This Section will provide an overview of that research, with an emphasis upon current approaches. The review of the literature is necessarily both selective and limited. A major review in a previous Report of the Surgeon General (US DHEW 1979) listed 452 references. Schwartz (1987) prepared a comprehensive monograph reviewing smoking cessation in the United States and Canada. Although he focused upon the period 1978-85, he included 883 references. As noted above, some topics are deliberately either excluded or minimized because they have received extensive coverage in recent Reports. These topics include physician intervention, community trials, and worksite smoking programs. Excellent reviews of other approaches such as self-help

and use of the mass media are available elsewhere (Flay 1985a; Schwartz 1987). These methods are not considered in the current Report. It is recognized, however, that self-help, mass media, physician, worksite, and community interventions can have critical impact in overall public health initiatives designed to address the smoking problem. The vast majority of smokers who have quit to date have done so in the absence of formal treatment.

Schwartz (1987) compiled a summary table listing quit rates of 416 smoking cessation trials by method. This Table is reprinted here as Table 2. The Table provides overall outcomes for a number of different intervention techniques. As discussed by Schwartz, however, considerable caution is needed in interpreting these data. Methodology in the various studies is uneven. Many studies suffered from deficient followup procedures and from an exclusive reliance upon subject self-reports. Noteworthy perhaps is the difference in outcome between nicotine polacrilex gum trials using gum alone and those combining nicotine polacrilex gum with behavioral intervention. Reported outcomes for programs including multiple components (40 percent 1-year median abstinence) are encouraging. The relative success achieved by cardiac patients indicates that treatments delivered at the time of a health crisis may be especially effective.

Aversion Procedures

Aversive strategies have involved pairing smoking with unpleasant imagery scripts (covert sensitization), with electric shock, or with the unpleasant effects produced by smoking itself (directed smoking procedures). All these techniques are designed, at least in part, to create aversions to cigarette smoke—affectionate reactions characterized by distaste, disgust, fear, or displeasure. The presumption is that such reactions will reduce the incentive to smoke. A wide variety of directed smoking strategies have been used. These include satiation, rapid smoking, and focused smoking.

Satiation

In this procedure cigarette consumption is dramatically increased prior to attempted abstinence. Smokers typically are asked to at least double their smoking intake. Despite promising early results (60 percent abstinence at 4-month followup, N=40; Resnick 1968), satiation procedures by themselves do not produce effects greater than those of attention/placebo interventions (Claiborn, Lewis, Humble 1972; Lando 1975; Sushinsky 1972).

In its most recent application, satiation has been used in multi-component programs (Best, Owen, Trentadue 1978; Lando 1977), in which its contribution to outcomes has been difficult to ascertain.

TABLE 2.—Summary of followup quit rates (percentages) of 416 smoking cessation trials, by method, reported 1959–1985

Intervention method	Quit rate (at least 6-mo followup)				Quit rate (at least 1-yr followup)			
	Number of trials	Range	Median	Percent 33%	Number of trials	Range	Median	Percent 33%
Self-help	11	0-33	17	18	7	12-33	18	14
Educational	7	13-50	36	71	12	15-55	25	25
Five-day plan	4	11-23	15	0	14	16-40	26	21
Group ¹	15	0-54	24	20	31	5-71	28	39
Medication	7	0-47	18	14	12	6-50	18.5	17
Nicotine chewing gum	3	17-33	23	33	9	8-38	11	11
Nicotine chewing gum and behavioral treatment or therapy	3	23-50	35	67	11	12-49	29	36
Hypnosis, individual	11	0-60	25	36	8	13-68	19.5	38
Hypnosis, group	10	8-68	34	50	2	14-88	—	50
Acupuncture	7	5-61	18	29	6	8-32	27	0
Physician advice or counseling	3	5-12	5	0	12	3-13	6	0
Physician intervention more than counseling	3	23-40	29	33	10	13-38	22.5	20
Physician intervention, pulmonary patients	10	10-51	24	20	6	25-76	31.5	50

TABLE 2.—Continued

Intervention method	Quit rate (at least 6-mo followup)				Quit rate (at least 1-yr followup)			
	Number of trials	Range	Median	Percent 33%	Number of trials	Range	Median	Percent 33%
Physician intervention, cardiac patients	5	21-69	44	80	16	11-73	43	63
Risk factor	—	—	—	—	7	12-46	31	43
Rapid smoking	12	7-62	25.5	33	6	6-40	21	17
Rapid smoking and other procedures	21	8-67	38	57	10	7-52	30.5	50
Satiation smoking ²	11	14-76	38	64	12	18-63	34.5	58
Regular-paced aversive smoking ²	13	0-56	29	31	3	20-39	26	33
Nicotine fading ²	7	26-46	27	29	16	7-46	25	44
Contingency contracting ²	9	25-76	46	89	4	14-38	27	25
Multiple programs ²	13	18-52	32	38	17	6-76	40	65

NOTE: Percent 33% is percentage of trials with quit rates of at least 33 percent. Median not calculated for fewer than three trials. Caution: Quit rates provided suggest overall trends. Most quit rates were based on self-reports. Some quit rates were recalculated to include all subjects, but most quit rates were based on reports by investigators. Some quit rates omitted subjects who did not complete treatment or persons who did not reply to followups. Definitions of followup may vary between trials.

¹Three group trials had 5-month followups.

²Other procedures may have been used, and some trials may be included in more than one method.

SOURCE: Schwartz (1987).

Lando (1982) conducted a dismantling strategy in which he attempted to isolate the specific contributions of individual treatment components to gauge the relative contribution of satiation to a multicomponent treatment. By itself satiation produced dismal results (15 percent 1-year abstinence, N=13). When satiation has been incorporated into multicomponent treatments that include maintenance, 1-year followup results have approached 50 percent (Lando and McGovern 1985). Lando (1986) has suggested that satiation represents a plausible preparation strategy for quitting. However, there is little evidence that satiation results in an aversion to cigarettes (Baker et al. 1984; Tiffany, Martin, Baker 1986).

Rapid Smoking

Rapid smoking typically requires smokers to inhale cigarette smoke every 6 sec until they reach the point that they would become ill if they were to continue. Whereas early interventions varied the number of rapid smoking sessions to fit client needs (Lichtenstein et al. 1973), more recent applications have tended to use standardized regimens involving six to eight sessions (Erickson et al. 1983; Hall, Rugg et al. 1984).

Multicomponent programs including rapid smoking generally yield good outcomes, but when used by itself, rapid smoking continues to yield variable results. Raw and Russell (1980) found that rapid smoking, cue exposure, and group/therapist support all produced poor outcomes when used separately (only 1 of 16 (6 percent) rapid smoking subjects was abstinent at 1 year). Similarly discouraging results have been reported by Poole, Sanson-Fisher, and German (1981) and by Corty and McFall (1984). In contrast, Hall and associates have consistently obtained high rates of success (50 percent 6-month abstinence levels) using rapid smoking alone, both with normal volunteers (Hall, Sachs, Hall 1979) and medical patients (Hall, Sachs et al. 1984).

Hall, Sachs, and colleagues (1984) observed that, in contrast to many recent applications of rapid smoking, their procedure was similar to that of early, successful rapid-smoking interventions (Lichtenstein et al. 1973). Their procedure involved (a) a single client format, (b) a warm client-therapist relationship, (c) positive expectations of success, (d) individualized scheduling, (e) office rather than home treatment, and (f) warnings against smoking outside of therapy sessions (Danaher 1977). However, Hall's research involved either elaborate physiological/medical assessment (Hall, Sachs, Hall 1979) or the use of medical patients as subjects (Hall, Sachs et al. 1984). Either of the latter two factors could have enhanced the effectiveness of rapid smoking. At this point, the weight of evidence suggests that rapid smoking by itself can have a substantial immediate impact on cessation (Poole, Sanson-Fisher, German 1981).

The long-term effects of rapid smoking do not appear to be sufficient by themselves to prevent relapse. Hall's results suggest that rapid-smoking effectiveness is greatly influenced by auxiliary treatment elements such as a warm interpersonal atmosphere, positive expectations, and admonitions regarding smoking.

Multicomponent programs involving rapid smoking have generally obtained reasonably high long-term cessation rates, i.e., 40 percent abstinence at 6 to 12 months posttreatment (Brandon, Zelman, Baker, *in press*; Erickson et al. 1983; Hall, Rugg et al. 1984; Tiffany, Martin, Baker 1986). The relative success of multicomponent programs comprising rapid smoking has been noted by earlier reviewers (Lichtenstein 1982; Pechacek 1979). Considerable research has been conducted to characterize the nature of the processes subserving rapid-smoking effectiveness. One approach to this problem is to determine whether rapid smoking results in a conditioned aversive response. In this regard, researchers have demonstrated that after rapid smoking, individuals show a conditioned tachycardia to cigarettes. The magnitude of this tachycardiac response is increased when the aversive smoking procedure produces intense gastrointestinal discomfort. The magnitude of this response is positively related to relapse latency—the greater the tachycardiac response, the longer smokers take to relapse (Erickson et al. 1983; Tiffany, Martin, Baker 1986). The similarity of these results to those found with chemical aversion treatments of alcoholism (Baker, Cannon et al. 1984; Cannon et al. 1986) suggests that part of the success of rapid smoking may be due to taste aversion learning. Thus, some aversion indices may constitute rare examples of therapy process measures that are predictive of treatment success. Previous attempts to assess aversion acquisition may have yielded inconsistent findings because the investigators attempted to relate clinical outcomes to unconditioned stimulus magnitude (e.g., number of cigarettes smoked in aversion sessions) or to unconditioned response magnitude (rapid-smoking-induced malaise) rather than to conditioned response magnitude (e.g., the cardiac response elicited by the taste of cigarettes; Glasgow et al. 1981; Norton and Barske 1977; Merbaum, Avimier, Goldberg 1979; Russell, Epstein, Dickson 1983).

Reduced-Aversion Techniques

Some investigators have compared rapid smoking and alternative low-aversion treatments for their abilities to enhance the effectiveness of a behavioral counseling or self-management treatment. Focused smoking, in which the person smokes for a sustained period but at a slow or normal rate, and rapid puffing, in which a person smokes rapidly but does not inhale, often are used as comparison conditions in order to permit assessment of specific effects of aversion (Danaher et al. 1980; Erickson et al. 1983; Hall, Rugg et al.

1984). While these treatments are unpleasant, they differ from rapid smoking in that they do not elicit the dysphoria produced by rapid smoking and they are less risky (Erickson et al. 1983; Glasgow et al. 1981; Tiffany, Martin, Baker 1986). Most research suggests that these alternative treatments produce long-term outcomes that are quite similar to, or just moderately lower than, those produced by rapid smoking (Danaher et al. 1980; Erickson et al. 1983; Hall, Rugg et al. 1984; Powell and McCann 1981; Tiffany, Martin, Baker 1986). Moreover, research shows that these treatments do not produce the conditioned cardiac response produced by rapid smoking. Thus, these treatments probably produce their effects through routes other than aversion conditioning. That low-aversion treatments produce effects comparable to those of rapid smoking indicates that aversion acquisition *per se* is not essential to successful treatment outcome. Other active components might be habituation to cigarettes, withdrawal reduction due to nicotine intake, and removal of control over smoking.

There has been concern about the possible effects of rapid smoking on the cardiovascular system. Horan and coworkers (1977) reported that rapid smoking produced elevations in blood pressure, heart rate, and carboxyhemoglobin levels as well as electrocardiographic abnormalities. Lichtenstein and Glasgow (1977) provided recommendations for screening and subject selection. Recent research suggests that the rapid-smoking procedure is fairly safe when used with healthy adults screened for such conditions as cardiovascular disease, diabetes, chronic obstructive pulmonary disease, seizure disorder, and hypertension (Hall, Sachs, Hall 1979; Sachs et al. 1979). Rapid smoking has been used safely even with medical populations (cardiac and pulmonary patients) in the presence of close medical supervision (Hall, Sachs et al. 1984). However, given that in the context of multicomponent programs focused smoking and rapid puffing yield results roughly comparable to those of rapid smoking, there appears to be little need to use rapid smoking with at-risk populations (e.g., cardiac and pulmonary patients).

Aversion therapies for smoking are constrained by some of the same limitations that apply to the use of aversion therapies for other forms of substance seeking. The aversions are rarely permanent, and the aversive conditioning is less effective in attempts to establish an aversion to substances that have had a history of repeated use.

Relaxation Training

Progressive relaxation is a popular treatment for anxiety-related disorders (Haugen, Dixon, Dickel 1958). As noted previously, smokers often report smoking to cope with anxiety and stress (Chapter VI). A large proportion of smoking relapses occurs during negative emotional states (Brandon, Tiffany, Baker 1986; Marlatt and Gordon

1980; Shiffman 1982). In theory, relaxation training should provide smokers with a means other than smoking for coping with stress and negative emotion. In a nontreatment experiment, relaxation was found to reduce levels of smoking in the face of external stress (Dobbs, Strickler, Maxwell 1981). Today, relaxation is rarely used as a sole treatment and is instead incorporated into multicomponent behavioral skills training programs (Erickson et al. 1983; Hall, Rugg et al. 1984; Hall et al. 1985; O'Connor and Stravynski 1982; Tiffany, Martin, Baker 1986); it may best be conceptualized as one of many possible stress-coping skills taught to clients. Poole, Sanson-Fisher, and German (1981) found that relaxation training did not improve the outcome of a rapid-smoking treatment. Seventy-five subjects were assigned to rapid smoking only; rapid smoking and relaxation training; rapid smoking, relaxation, and contingency contracting; or contingent rapid smoking. In none of these conditions did 1-year abstinence exceed 25 percent.

Contingency Contracting

Operant conditioning techniques have been used in smoking treatments to reward clients for not smoking and/or to punish them for smoking. The usual procedure is to collect monetary deposits from clients early in treatment with periodic repayments contingent on client achievement of abstinence goals. Variations include having the client pledge to donate money to a disliked organization or individual for every cigarette smoked, or contracting for nonmonetary rewards and punishments based on smoking status (Lando 1977; Tiffany, Martin, Baker 1986).

The rationale behind contracting techniques is that they may bolster commitment to abstinence by providing contingent concrete rewards. Contracts are in effect until withdrawal has abated and the individual has had an opportunity to begin alternative, nonsmoking activities that may be rewarding. Murray and Hobbs (1981) compared the effects of self-reinforcement (\$1 reward per day for meeting smoking reduction goal), self-punishment (\$1 forfeited for not meeting goal), combined self-reward and self-punishment, and self-monitoring alone on cessation. They found that only self-punishment led to improved outcomes: 11 of 20 subjects (55 percent) in the two self-punishment conditions reached abstinence versus only 1 of 20 subjects (5 percent) in the other two conditions. Three years posttreatment, 25 percent of self-punishment subjects still reported abstinence. A small sample size and reliance on self-report, however, indicate the need for caution in interpreting these findings.

Paxton (1980) compared multicomponent behavioral interventions with and without contingency contracting (weekly repayments if subjects were abstinent) and found that contracting significantly improved maintenance of abstinence, but only during the 8 weeks of

repayment. The end of the repayment schedule was followed by a sharp increase in relapse, and no subsequent difference between conditions was found. Overall abstinence at 6-month followup was 42 percent (25 of 60 subjects). Bowers, Winett, and Frederiksen (1987) also reported that extended contingency contracting delayed and decreased relapse, but they did not report abstinence rates. In a variation of the contracting procedure, Stitzer and Bigelow (1982) provided contingent payments of \$5 to subjects for reducing carbon monoxide (CO) levels by 50 percent. Other attempts to increase the effectiveness of contingency contracts by manipulating the length, frequency, or amount of repayment or the frequency or size of deposits have largely been unsuccessful (Paxton 1981, 1983). Yet when it is part of a multicomponent program, contingency contracting appears to aid smoking cessation, at least over the short term.

Social Support

Attempts to capitalize on the effects of social support in treatment settings have met with mixed results. Hamilton and Bornstein (1979) developed a package that included a buddy system among group members and public announcements of client successes at quitting smoking. When this package was appended to a behavioral treatment program, it significantly increased abstinence rates compared with those for behavioral treatment alone both at treatment termination (55 vs. 27 percent) and during the 6 months of followup (27 vs. 9 percent; N=12 in each of these two conditions). Etringer, Gregory, and Lando (1984) were able to improve smoking treatment outcome over the short term by emphasizing group cohesion. McIntyre-Kingsolver, Lichtenstein, and Mermelstein (1986) examined the effects of including clients' spouses in a smoking cessation program and teaching them how to be supportive of the clients' quitting attempts. At the end of treatment, 73 percent of clients in the spouse-training condition (total N=33) were abstinent compared with only 48 percent in the condition without spouse training (total N=31). This difference failed to reach significance, however, and diminished during followup. In another study, the outcome of a worksite-controlled smoking program was not affected by encouraging the social support of quitting coworkers (Malott et al. 1984). Lichtenstein, Glasgow, and Abrams (1986) summarized the results of five recent smoking cessation studies from three separate research programs (including McIntyre-Kingsolver, Lichtenstein, and Mermelstein (1986) and Malott and coworkers (1984)). Results generally indicated a positive relationship between measures of social support and treatment outcome. However, specific attempts to improve outcome by enhancing social support were uniformly unsuccessful.

Coping Skills Training

The value of coping skills training is suggested by evidence that smokers who use cognitive and/or behavioral coping responses when they are tempted to smoke reduce their likelihood of relapsing (Shiffman 1984a). The rationale for coping skills training of tobacco-dependent individuals is similar to that for such training in other forms of drug dependence. Alternative behavioral repertoires are developed that help to maintain comfortable, satisfactory functioning in the absence of drugs (Grabowski and Hall 1985; Jasinski and Henningfield 1987).

Examples of behavioral coping responses are distracting activities, escape from a stressor, relaxation, and physical activity. Cognitive coping may involve reminding oneself of the benefits of quitting or the negative consequences of smoking or simply telling oneself that smoking is not an option. Coping responses may be directed either at the smoking temptation/urge itself or at a precipitating stressor (Wills and Shiffman 1985).

Coping skills training is generally used in cessation research as part of multicomponent treatments (Brandon, Zelman, Baker, in press; Davis and Glaros 1986; Erickson et al. 1983; Hall, Rugg et al. 1984; Tiffany, Martin, Baker 1986). There is considerable variation, however, in the specific coping skills taught, in the strategies used to teach them, and in the names given to the treatment. Coping skills training appears to be effective in enhancing short-term outcomes, especially when combined with an aversive-smoking procedure. The long-term effects are less clear. This strategy has the potential for maintaining changes in smoker behavior because, presumably, once the skills are learned they may be used long after treatment has terminated. Nevertheless, in studies of maintenance of abstinence, results are mixed but generally negative (Glasgow and Lichtenstein 1987). These generally negative results may be a function of the diversity of treatments in which coping skills training is incorporated and of inadequate compliance with coping skills techniques. Adherence to coping skills instructions should be monitored more closely. Hall, Rugg, and colleagues (1984) found that the outcome differences between coping skills and discussion conditions were seen only in clients who smoked 20 or fewer cigarettes/day. It should be noted, however, that the outcome differences were computed for the number of cigarettes smoked per day and not for abstinence rates. Coping skills training may be most effective for certain subpopulations of smokers, such as less-dependent smokers (Hall, Rugg et al. 1984; Hall et al. 1985) who smoke primarily to cope with emotional stress (O'Connor and Stravynski 1982).

Stimulus Control

Stimulus control treatments are based on the assumption that a wide variety of environmental cues are associated with and serve to trigger smoking. A gradual reduction in smoking is accomplished by having clients progressively eliminate situations in which they smoke. In some cases, temporal, rather than situational, constraints upon smoking are instituted (e.g., the individual is permitted to smoke only on the half hour; Shapiro et al. 1971). In theory, a gradual reduction in smoking should result in a weaker, more manageable withdrawal syndrome.

Stimulus control procedures generally have produced weak, transient results when used alone and have been of questionable value when combined with other self-management techniques (Lando 1978). In more recent studies stimulus control has been used primarily as an element in multicomponent programs in which its effectiveness is difficult to ascertain (Best, Owen, Trentadue 1978; Colletti and Kopel 1979; Colletti, Supnick, Rizzo 1982; Karol and Richards 1981; Lando 1982; Rabkin et al. 1984).

Nicki, Remington, and MacDonald (1984) added a stimulus control component, which was designed to maximize client self-efficacy (Bandura 1977a), to a nicotine fading treatment. The combined treatment produced a 5-month abstinence rate of over 50 percent—twice that of the fading procedure alone. This level of success is unusual in research on stimulus control techniques and may be due to the self-efficacy manipulation rather than stimulus control per se. Also, as is true for so much of the smoking cessation literature, the small sample size used by Nicki and colleagues (fewer than 15 subjects per condition) requires that their results be interpreted cautiously.

Nicotine Fading

Nicotine fading (or brand switching) is based on a straightforward pharmacologic rationale. The intensity of the withdrawal syndrome, including both physical and psychological discomfort, can be reduced when the dependence-producing drug is gradually withdrawn (at least within certain limits). The procedure generally involves clients monitoring their nicotine consumption while switching (in three to six stages) to cigarette brands with progressively lower rated tar and nicotine deliveries, and then quitting completely. Chapter V supports this approach for drugs other than nicotine, and Chapter IV indicates this for nicotine as well. Foxx and Brown (1979) specifically assumed that nonabstinent nicotine fading subjects would benefit from continued smoking of low-tar and low-nicotine brands. In this study as well as in more recent nicotine fading studies, actual nicotine dose levels have been uncontrolled. At least some compensa-

tion is likely to be occurring, and nicotine reduction is undoubtedly significantly less pronounced than would be expected based upon machine-rated nicotine yields (McMorrow and Foxx 1983).

The treatment is based primarily on the idea that a gradual phaseout of smoking will minimize nicotine withdrawal symptoms. Nicotine fading can be viewed as an alternative to "cold turkey" quitting. However, to the extent that actual nicotine intake is not decreased or is decreased only minimally (Benowitz et al. 1983), this procedure might more appropriately be viewed as an additional preparation method for abrupt cessation. Furthermore, even when nicotine intake is decreased, thereby potentially reducing physiological dependence, postcessation cravings may be relatively unaffected. These continued cravings can be important in leading a newly abstinent individual to relapse. Lando and McGovern (1985) suggested that self-efficacy is increased by allowing clients to experience a series of successes (in reducing apparent nicotine intake) prior to quitting.

Nicotine fading should be distinguished from gradual reduction procedures in which smokers are instructed to progressively reduce their *number* of cigarettes. Procedures that emphasize progressive reductions in the number of cigarettes generally have been ineffective. Smokers typically report that the remaining cigarettes are more reinforcing. Furthermore, they often reach a "stuck point" beyond which additional reduction does not occur (Levinson et al. 1971).

A preliminary study by Foxx and Brown (1979) assessed a combination of nicotine fading and self-monitoring, nicotine fading alone, self-monitoring alone, and a modified American Cancer Society clinic program. Results at 18-month followup favored the combined nicotine fading and self-monitoring procedure (4 of 10 subjects or 40 percent were abstinent in this condition as opposed to no more than 10 percent of the subjects in any of the other three conditions). In several other studies, however, nicotine fading and self-monitoring produced less encouraging results (Beaver, Brown, Lichtenstein 1981; Brown et al. 1984; Foxx and Axelroth 1983; Nicki, Remington, MacDonald 1984). Lando and McGovern (1985) added a systematic behavioral maintenance procedure to nicotine fading with disappointing results (only 8 of 42 or 19 percent of subjects assigned this procedure were abstinent at 1-year followup). Lando (1987) obtained somewhat more positive findings for a treatment including nicotine fading and behavioral maintenance (35 percent abstinence at 12-month followup). However, nicotine fading subjects in this study were self-selected.

Results for nicotine fading in a field application (community rather than laboratory setting, lay rather than professional group leaders) have been encouraging (Lando 1986). Participants were

given a choice of preparation strategy (satiation or nicotine fading). Approximately 80 percent elected the nicotine fading procedure. Outcomes for nicotine fading and satiation treatments were virtually identical. Survival analyses performed on field data for several hundred participants yielded a projected permanent smoking cessation rate of 32 percent. This projection was based on relapse curves from 3- to 5-year followup data. The choice of preparation strategy may be effective in enhancing both compliance and outcome.

There is also some evidence that nicotine fading may be useful in minimal intervention programs (Prue et al. 1983; Scott et al. 1986). A strategy similar to nicotine fading involves the use of progressively stronger graduated filters (Martin et al. 1981). Hymowitz, Lasser, and Safirstein (1982) found low abstinence rates with this method and also continued use of the filters by few nonabstinent smokers after the end of treatment. Improved outcomes might occur if filters are more systematically linked with multifaceted behavioral intervention.

Controlled Smoking

Controlled-smoking programs have been developed to treat smokers who are unable or unwilling to quit completely. This approach is based in part on the assumption that reduced smoking will be associated with diminished health risk. The prototypical program attempts to decrease risk by reducing cigarette consumption, altering smoking inhalation patterns (e.g., number of puffs, duration of puffs, CO intake), and minimizing the tar and nicotine content of cigarettes (e.g., nicotine fading). A key is to change multiple aspects of the smoking behavior to minimize compensation.

Stimulus control procedures may also be used (Glasgow, Klesges, Vasey 1983). In addition, clients may be taught coping skills to use as substitutes for smoking (Frederiksen 1979). Controlled-smoking treatments have produced reductions of at least 50 percent in the rated nicotine content of cigarettes smoked, with more modest reductions in reported numbers of cigarettes, the percentage of each cigarette smoked, and CO levels (Glasgow, Klesges, Vasey 1983; Godding and Glasgow 1985; Malott et al. 1984). In general, however, by the 6-month followup the magnitude of these initial reductions had diminished by approximately one-half.

Reservations about the controlled smoking approach center around the premise that smokers can substantially diminish their health risk without total abstention. The change in health risks associated with moderate reduction is not known. Moreover, there is experimental evidence that smokers regulate their bodily levels of nicotine through compensatory changes in smoking patterns (McMorrow and Foxx 1983). These compensatory changes are not complete, however. In a short-term (3- or 4-day) restriction study, a

reduction from an average of 37 cigarettes to 5 cigarettes/day was associated with a threefold increase in the intake of tobacco toxins per cigarette (Benowitz et al. 1986). Daily exposure to tar (estimated by mutagenic activity of the urine), nicotine, and CO declined only 50 percent from the baseline. Thus, consistent with the tendency to maintain intake of nicotine, the benefit of smoking fewer cigarettes was much less than expected. Benowitz and associates used laboratory volunteers rather than smokers who were specifically concerned with reducing their levels of tar and nicotine exposure.

The basic premise of the controlled-smoking approach—that it reduces health risk—remains to be validated. Some investigators have argued that until there is clear evidence that controlled smoking actually decreases health risks, it should not be recommended as a treatment option. Finally, there is concern both that smokers who otherwise may have been successful quitters will instead be attracted to controlled-smoking programs (at this point no data are available) and that these programs may provide an illusion of safety.

If reductions in smoke exposure can be maintained over time, if a reduction in health risk can be established, and if clients can be limited to those for whom the prospect of total abstinence is highly unlikely, then reduced smoking may be an alternative for recalcitrant smokers. Given all these conditions, controlled smoking does not appear likely to represent an effective treatment. However, possible risk reduction is not the only rationale for this type of approach. Controlled-smoking interventions may appeal to a larger cross-section of smokers, may have a positive impact upon self-efficacy, and may facilitate subsequent progress toward complete abstinence. Currently, empirical data on these points are lacking.

Multicomponent Programs

In recent years, multicomponent programs have been a principal target of research. This is due to both the relatively high level of clinical success produced by these programs (Lichtenstein 1986) and the recognition that smoking is multidetermined and relatively invulnerable to any single intervention (Schwartz 1987). The most effective multicomponent programs yield almost universal short-term abstinence and long-term abstinence rates that approach or exceed 50 percent (Brandon, Zelman, Baker, in press; Elliott and Denney 1978; Erickson et al. 1983; Hall, Rugg et al. 1984; Hall et al. 1985; Fagerström 1982b; Killen, Maccoby, Taylor 1984; Lando 1977; Tiffany, Martin, Baker 1986). These results are extremely encouraging and are rarely matched in trials that place exclusive emphasis upon pharmacologic intervention. Dismantling or constructive studies have shown that combinations of treatments generally outperform any single constituent treatment (Lando 1982).

Best, Owen, and Trentadue (1978) compared satiation and rapid smoking in the context of self-management training. Subjects rehearsed possible alternatives or coping strategies for each anticipated problem situation. Suggested techniques were applied on an individualized basis and included relaxation, deep breathing, contingency contracting, social support, stimulus control, and behavioral rehearsal. The overall result with 60 subjects was 47 percent abstinence at 6-month followup.

Powell and McCann (1981) achieved successful results with a combination of lectures, self-control techniques, and aversive smoking. Aversive smoking consisted of rapid puffing without inhalation and holding the cigarette in an awkward position. Efforts were made to increase the unpleasantness of the procedures by providing ashtrays that were full of cigarette litter, dipping cigarettes in a bitter-tasting solution, and showing slides of diseased organs. Subjects were randomly assigned to one of three maintenance conditions: a 4-week support group, 4 weeks of telephone calls between subjects, or a no-contact control group. Results for the 51 subjects at 1-year followup were impressive, although there were no significant differences between conditions. The support group and the no-contact controls achieved 65 percent abstinence, and telephone contact subjects achieved 59 percent abstinence.

Hall, Rugg, and colleagues (1984) assessed two levels of relapse prevention (skills training versus discussion control) and two levels of aversive smoking (6- vs. 30-sec inhalations) in a 2-by-2 factorial design. Of 135 subjects recruited, 123 completed treatment. Of 14 treatment sessions, 8 included aversive smoking. Six sessions were devoted to relapse prevention. Specific skills training components included cue-produced relaxation, commitment enhancement, and rehearsal of commonly experienced relapse situations. Subjects assigned to the skills training condition were more likely to report use of coping skills. One-year abstinence outcomes were as follows: 52 percent for 6-sec inhalations/skills training, 39 percent for 30-sec inhalations/skills training, 34 percent for 6-sec inhalations/discussion, and 26 percent for 30-sec inhalations/discussion. Skills training was superior to the discussion control at the 1-year followup (dropouts were excluded from this analysis). No differences were observed between the 6- and 30-sec smoking procedures.

Lando (1977) compared a comprehensive treatment procedure (satiation, contingency contracts, group support, booster aversion) against a satiation control. Subjects were seen in small groups. All subjects attended six treatment sessions over a 1-week period. Subjects assigned the comprehensive intervention attended an additional seven sessions during 2 months of maintenance. Results at 6-month followup indicated 76 percent abstinence for the comprehensive procedure and 35 percent abstinence for the satiation

condition. However, it should be noted that these results were based upon a total of only 34 subjects and 2 small groups per condition.

Lando (1981) assigned 99 subjects to a 2-stage treatment (aversions and maintenance) similar to that employed in his 1977 study or to a 3-stage procedure that also included fear appeals and stimulus control. Subjects were in addition randomly assigned to intensive or minimal contact conditions. Efforts to implement a maintained reduction procedure among nonabstinent subjects were unsuccessful. One-year followup results favored the two-stage intensive contact procedure. The group of subjects in this condition achieved a 46 percent abstinence rate whereas subjects in each of the other conditions attained abstinence rates less than 20 percent. In a 3-year followup, Lando and McGovern (1982) again found 46 percent abstinence among subjects in the two-stage intensive treatment (continuous abstinence from the end of treatment in this condition was 33 percent).

Elliott and Denney (1978) developed a package treatment encompassing self-reward and punishment, cognitive restructuring, applied relaxation, behavioral rehearsal, systematic desensitization, emotional role playing, covert sensitization, and rapid smoking. This comprehensive program was compared against rapid smoking by itself and two control conditions. Six-month followup results ($N=60$) indicated a significant effect in favor of the package treatment. Subjects in this condition achieved a 45 percent abstinence rate as opposed to 17 percent for rapid smoking by itself, 12 percent for a nonspecific control, and 0 percent for an untreated control.

Erickson and colleagues (1983) assigned subjects to either rapid smoking or to a less-aversive rapid-puffing procedure. These subjects also were assigned behavioral counseling which included training in problem-solving strategies. A comparison group underwent only behavioral counseling, without any aversive smoking. Results favored the combination of rapid smoking and behavioral counseling. At 1-year followup 70 percent of rapid-smoking subjects and only 33 percent of rapid-puffing and 14 percent of behavioral counseling subjects reported abstinence. A total of only 26 subjects were included in this study.

Tiffany, Martin, and Baker (1986) assessed full-scale rapid smoking with full counseling, truncated rapid smoking with full counseling, rapid puffing with full counseling, and full-scale rapid smoking with reduced counseling. Eighty-two subjects completed treatment. During behavioral counseling, subjects learned to anticipate potential problem situations and to plan coping strategies for these situations. The full-scale rapid-smoking and rapid-puffing procedures included three trials per session. Truncated rapid smoking consisted of only one trial per session. Reduced counseling emphasized support and encouragement rather than specific behavioral

procedures. Six-month followup results favored the full-scale rapid-smoking and rapid-puffing conditions combined with full-scale counseling (59 and 55 percent abstinence, respectively). Either truncated rapid smoking or reduced counseling appeared to detract from effectiveness (35 percent of subjects in each of these conditions were abstinent at 6-month followup).

As noted in the section on methodological issues in treatment (below), many multicomponent treatments are based on clinical intuition or on the effectiveness of a treatment when used by itself and few are based on an explicit theory or model of addiction and behavioral change. Moreover, few multicomponent evaluative studies contain sound process measures that tap processes theoretically linked to particular interventions. Therefore, even though multicomponent treatments are often effective, the basis of their efficacy is little understood.

It is unclear why particular treatment elements are effective when combined. Perhaps these elements interact so that an individual who would not be especially helped by one treatment is aided by the combination. Perhaps the treatment components are additive because their individual effects are largely independent. To investigate the nature of multicomponent treatment effects, researchers might strive to develop experimental designs that are sensitive to particular components and to determine whether these reflect interactive effects when auxiliary treatments are added. It is recognized, however, that required numbers of subjects and statistical power issues often render this type of approach impractical. Furthermore, isolation of very precise or subtle treatment elements, as opposed to major differences, appears both impractical and unlikely (Lando 1982).

Some multicomponent treatments contain elements that are labeled as "maintenance" and are delivered during the postcessation, followup interval. These are based on the notion that extending therapist contact or skills training in the followup interval will prolong treatment gains. Evidence is mixed as to whether such maintenance treatments significantly enhance the long-term effectiveness of complete, multicomponent programs (Brandon, Zelman, Baker, *in press*).

Although multicomponent programs are often very effective, more is not always better (Lando 1981). Inclusion of too many procedures may overwhelm subjects and thereby reduce adherence to treatment. A point of diminishing returns may be reached by simply adding additional components to an already complex intervention. Combinations of multicomponent behavioral treatment and pharmacologic intervention may be promising for highly dependent smokers, especially for those who have been unable to achieve even short-term abstinence despite repeated attempts.

Other Treatment Strategies

Hypnosis

The usual intent of hypnosis is to increase client motivation or ability to quit smoking through posthypnotic suggestions. The most commonly used posthypnotic suggestions are variations of those originated by Spiegel (1970): (1) smoking is a poison to your body; (2) you need your body to live; and (3) you owe your body this respect and protection (Berkowitz, Ross-Townsend, Kohberger 1979; Hyman et al. 1986; Javel 1980; Perry, Gelfand, Marcovitch 1979). Suggestions may also involve problem-solving techniques (Frank et al. 1986; Javel 1980), review of the client's history of smoking (Javel 1980), desensitization to environmental cues (Wagner, Hindi-Alexander, Horwitz 1983), and an assortment of other elements (Katz 1980). Despite the variety of possible hypnotic procedures, some research reports fail to describe the procedure used (Lambe, Osier, Franks 1986; Schubert 1983). Hypnosis might most usefully be applied to the small percentage of the population that is highly susceptible to hypnotic induction. Some individuals are essentially unresponsive to hypnosis, whereas others evidence varying degrees of susceptibility. Individual differences in hypnotic susceptibility have in fact influenced outcome (Perry and Mullen 1975; West 1977), although this has not been reported by all investigators (Mott 1979).

No significant outcome differences were found when posthypnotic suggestions were compared with suggestions without hypnosis (Javel 1980), with suggestions after relaxation (Schubert 1983), with focused smoking or an attention placebo control condition (Hyman et al. 1986), or with behavior modification or health education interventions (Rabkin et al. 1984). Most studies have found hypnosis to be superior to no-treatment control groups, although Lambe, Osier, and Franks (1986) found no such difference. Followup abstinence rates reported for hypnosis in recent studies have ranged from less than 4 percent (Perry, Gelfand, Marcovitch 1979) to 60 percent (Javel 1980), with a mean of approximately 28 percent. These figures may be spuriously high because several studies reported less than 6 months of followup and most relied exclusively on subject self-report.

There is little evidence that hypnotic induction per se facilitates smoking cessation and maintenance above and beyond the effects of other treatment components (including the posthypnotic suggestions themselves) (Holroyd 1980; Katz 1980).

Acupuncture

Acupuncture involves the use of needles or staple-like attachments and commonly is given at the ear either by press needle or staple puncture. Acupuncture has gained popularity over the past 10 years (Schwartz 1987). There are few carefully controlled evaluations of

this procedure for smoking cessation. Many published reports have suffered from serious methodological shortcomings (e.g., lack of control conditions, short or nonexistent followup periods, failure to include data from all treated subjects). Six studies have compared acupuncture at the "correct" site for smoking cessation against an "incorrect" or sham site. In only one study (MacHovec and Mann 1978) was the correct site significantly superior to the sham site. As with hypnosis, most evaluations of acupuncture have relied exclusively on self-reports. At this point, there is little evidence that acupuncture relieves withdrawal symptoms or promotes smoking cessation. A combination of acupuncture and supportive counseling or skills training may be more effective (Schwartz 1987).

Treatment of Special Smoker Populations

Recognition of smoking as a dependence-producing behavior leads to important implications in treating several populations of smokers including women, blacks, and Hispanics. Current trends (Appendix A) indicate that the burdens of smoking in the future may be disproportionately felt by lower socioeconomic and minority population groups. For treatment to have optimal impact, it must meet the needs of smokers from diverse circumstances. Presently, the vast majority of those who avail themselves of formal intervention are white and are from relatively advantaged socioeconomic backgrounds.

It is not obvious that interventions for special populations should differ substantially from those that are currently available. There are indications based on smoking patterns and environmental and social factors that suggest the importance of tailored intervention. A great deal more research is needed, however. At this point, for example, it is unclear whether self-help treatment manuals oriented to specific target groups are preferable to more general manuals. Currently there are almost no materials or programs prepared especially for blacks or Hispanics. If the needs of lower SES and minority smokers are not met, the trend for smoking to be disproportionately concentrated among these groups is likely to continue. Considerations of treatment for the dependent smoker are not complete without substantial attention to issues of application and dissemination, especially to smokers not being served by current interventions.

Applying Smoking Interventions to Women

Sex Differences in Cessation and Relapse Rates

Trends in cigarette smoking among men and women in this century have followed roughly similar curves, except that increases and decreases in smoking prevalence among women have lagged 15

to 30 years behind rates for men (Harris 1983; US DHEW 1980; Appendix A). Recent declines in overall smoking prevalence are attributed to lower initiation rates among teenage males and higher cessation rates among adult males (Remington et al. 1985). The percentage of former smokers in the male population has increased more dramatically than the percentage of former smokers in the female population (Appendix A). Jarvis (1984) adjusted cigarette cessation rates in Britain and in the United States to reflect the proportion of males who switched from smoking cigarettes to smoking pipes and cigars. After this adjustment, sex differences in cigarette cessation rates disappeared for individuals under age 50.

Several recent, well-controlled prospective evaluations of cigarette cessation programs found no differences in the proportions of women and men who achieved initial cessation and/or long-term maintenance (Curry 1986; Gritz 1982; Hall, Ginsberg, Jones 1986). The question of whether previously observed gender differences in cessation and relapse rates (the magnitude of which is often small) reflect real and stable sex differences, historical effects true only in older smokers, or statistical artifacts due to analytical limitations is not resolved.

Motivation to quit. In one of the few studies addressing gender differences in motivation to quit, Curry (1986) found that successful male and female abstainers did not differ in their overall reasons for quitting (e.g., "Smoking is inconsistent with my commitment to good health"). However, women in Curry's (1986) study differed significantly from men on questions related to four more specific subdimensions of motivation: self-determination ("I will like myself better"), reinforcement ("My hair and clothes won't smell"), influence of significant others ("I can get praise from people I am close to [for quitting]"), and social consequences ("Smoking is less socially acceptable"). Perhaps these more specific reasons for quitting should be considered in tailoring the content of smoking treatments to female subjects.

Education. The personalization (perception of the personal relevance) of abstract information has been shown to be an important aspect of behavioral change in general (Mahoney 1974) and of health-related behavioral change in particular (Ben-Sira 1982; Schinke and Gilchrist 1984). Available evidence suggests that many women may not fully be aware of some important gender-specific health consequences of smoking (Shiffman 1986b; Sorensen and Pechacek 1987). Adolescent women in particular often either are not well informed or choose to ignore information on the harmful effects of smoking during pregnancy (Simms and Smith 1983; Stewart and Dunkley 1985). It may be useful to develop educational campaigns that publicize the gender-specific risks of smoking.

Information that might be used in such educational campaigns comes from studies of important adverse interactions between smoking and female physiology, especially estrogen-related processes. Several studies have found a positive association between cigarette smoking and early menopause (Baron 1984; Willett et al. 1983), estrogen-related postmenopausal osteoporosis and associated fractures (Daniell 1976; Paganini-Hill et al. 1981), and invasive cervical cancer (Brinton et al. 1986).

Social values and beliefs. Cigarette smoking is a multidetermined behavior shaped by both personal and environmental variables (Chassin, Presson, Sherman 1985; Jones and Battjes 1985). The bulk of research on smoking has assumed that the developmental pathways leading to cigarette use and later dependence are the same for males and females. Several lines of recent research suggest that this assumption is overly simplistic (Barton et al. 1982; Baumrind 1985; Ensminger, Brown, Kellam 1982; Gritz 1982; Yamaguchi and Kandel 1984). The developmental and social dynamics that propel female adolescents into smoking may differ from those operating on young males. Several studies suggest that female smokers appear attracted to cigarette smoking by a need to identify with a particular social image (Gritz 1982, 1984; Jacobson 1982; Mausner and Brandspiegl 1985). Studies of advertising influence show that women, more than men, choose cigarette brands for image reasons (Bergler 1981; Fisher and Magnus 1981). Cigarette smoking today is often associated in the media with independent women who are not only sexually desirable (and slender) but also successful in traditionally male activities (Baker, Dearborn et al. 1984; Godley, Lutzker, Lamazor, Martin 1984). Reliance on cigarettes for bolstering an important, self-selected social image may make some women resistant to educational messages on the health consequences of smoking.

Another factor bearing on women's use of cigarettes for social image reasons involves body size and weight control (Gritz 1985; Jacobson 1982; US DHEW 1980). Data from junior high students suggest that even at young ages females more than males are interested in cigarettes as a weight control aid (Charlton 1984; Chapter VI).

Achieving Abstinence

Weight gain. Women's fear of weight gain has been widely observed (US DHEW 1980). Some animal data (Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987; Levin et al. 1987) as well as preliminary results from a study with human subjects (Klesges, Meyers et al. 1987) suggest that females are more likely than males to gain weight following removal of nicotine. In contrast, Hall, Ginsberg, and Jones (1986) found that although all subjects gained weight after achieving abstinence, weight gain was no more

likely to cause female subjects than male subjects to relapse (Chapter VI). More studies are needed to determine whether fear of weight gain in the early stages of cessation is a more powerful obstacle for women than is actual weight gain later in the cessation process.

Stress management. Social, psychological, and epidemiological studies consistently report the greater importance of cognitive appraisal processes and monitoring of internal states and feelings on the part of females compared with males (Blechman 1984). Several studies have characterized women as negative-affect smokers—i.e., individuals who smoke in response to emotional discomfort and for purposes of tension reduction (Brunswick and Messeri 1984; Christen and Glover 1983; Dembroski 1984; Livson 1985; Mitic, McGuire, Neumann 1985; Rust and Lloyd 1982; US DHEW 1980). Other researchers have found that negative-affect smokers grow more reliant on cigarettes than do smokers who respond to social or external stimuli (Ockene et al. 1981; Pomerleau, Adkins, Pertschuk 1978). In current cessation studies, female subjects, compared with male subjects, have reported more stress during the quit process (Abrams et al. 1987) and more concern about finding alternatives to cigarettes for coping with stress (Abrams et al. 1987; Moreton and East 1983; Sorensen and Pechacek 1987; Chapter VI).

Social support. Women, more often than men, report a preference for interacting and learning in settings that involve close, informal, personal, dyadic, or small-group interactions (Brody 1987; Glynn, Pearson, Sayers 1983; Grady, Brannon, Pleck 1979; Linehan 1984). Both the quantity and the quality of women's participation increase in groups composed solely of women (Burden and Gottlieb 1987; Linehan and Egan 1979; Gambrill and Richey 1986). Gritz (1982) concluded that women are more successful in programs that provide social support and individualized therapist-client contact, and less successful in programs in which such support is absent or when external environmental supports are lacking. Data continue to indicate the importance of social support (and partner support in particular) for maintenance of smoking cessation among women (Coppotelli and Orleans 1985; Sorensen and Pechacek 1987).

Smoking Cessation Initiatives for Black Americans

Black Americans constitute the Nation's largest minority group, making up 12 percent of the population, and have the highest smoking rate of the major U.S. ethnic/racial groups; 34.8 percent of all black American adults smoke, compared with 29.7 percent of non-Hispanic whites and 25.7 percent of Hispanic adults (Appendix A). Blacks also suffer the Nation's highest rates of mortality and morbidity from cardiovascular diseases and cancer, including coronary heart disease and lung cancer (Cooper and Simmons 1985; US DHHS 1985, 1986). Moreover, smoking represents an especially

serious health risk for blacks, given the disproportionate incidence of infant mortality and low birth weight, hypertension, diabetes, and hazardous occupational exposures within the U.S. black population (US DHHS 1985). To date, relatively little research has been done to clarify smoking/quitting patterns and determinants among black Americans or to test smoking cessation interventions in black populations.

The 1985 Cancer Prevention Awareness Survey (US DHHS 1987) found that blacks were less likely than the general public to report hearing or reading about cancer prevention in the preceding 6 months, and were less likely to view tobacco use as a cancer risk. There is also evidence that blacks have less belief in personal control over health outcomes and disease, particularly cancer (Deniston 1981; Snow 1983; US DHHS 1987).

Sociodemographic Factors

The sociodemographic correlates of smoking status among black Americans are similar to those for the U.S. population as a whole: these include lower income, lower education levels, lower occupational status, unemployment, being male, and being unmarried (never married, separated, or divorced) (Eisinger 1971; Marcus and Crane 1987; Orleans et al. 1987; US DHHS 1985; Warneke et al. 1978).

Restricted Health Care Access

More limited access to health care, particularly to preventive health services, may also play a role in the higher black smoking rate (Eisinger 1971; Green 1975; Rogers and Shoemaker 1971; US DHHS 1985; Warneke et al. 1978). Fewer blacks (54 percent) than whites (70 percent) report a physician's office as their regular source of care, and twice as many blacks as whites say they receive their regular care from hospital outpatient clinics and emergency rooms or public health clinics (where continuous care and preventive health services are less likely) (US DHHS 1985). Therefore, it is not surprising that the 1985 National Health Interview Survey (NHIS) found fewer adult black smokers (33 percent men, 43 percent women) than white smokers (40 percent men, 47 percent women) reporting medical advice to quit smoking (Marcus and Crane 1987).

Social Norms and Advertising Influences

Peer and family modeling appears to play the usual role in the initiation and maintenance of smoking as well as in smoking cessation (Orleans et al. 1987; Warneke et al. 1978). However, the combination of a higher smoking rate among blacks and a pervasive, well-financed, black-focused tobacco advertising campaign may lead

to stronger smoking norms within the black community (Cooper and Simmons 1985; Cummings, Giovino, Mendicino 1987; Davis 1987).

Determinants of Quitting Motivation and Success Among Black Smokers

Factors influencing quitting motivation and success among black smokers appear to be similar to those among smokers in general, including beliefs in smoking-related health harms and quitting benefits; personal relevance of the health threat; a greater number of sources of support and communication about smoking health risks and quitting; the extent to which family, friends, and health professionals provide personal information about smoking risks; personal medical advice to quit; self-mastery motivation; past efforts to quit or cut down; degree of tobacco dependence; and primary group social supports for quitting and nonsmoking (Eisinger 1971; McDill 1975; Orleans et al. 1987; Pechacek and Danaher 1979; Prochaska and DiClemente 1983; Warneke et al. 1978). Again, however, considerably more research is needed.

Smoking and Quitting Patterns Among Black Americans

Although black smokers smoke fewer cigarettes per day than white smokers, they smoke brands with higher tar/nicotine yields, especially menthol brands (Friedman, Sidney, Polen 1986; Appendix A). The 1981 NHIS showed that 65 percent of black smokers smoked brands with 1.1 mg or more of nicotine, in contrast to only 35 percent of white smokers, and that 67 percent of black smokers smoked menthol cigarettes, in contrast to only 26 percent of white smokers. In fact, it has been estimated that three high-nicotine menthol brands account for more than 60 percent of cigarettes purchased by blacks (Cummings, Giovino, Mendicino 1987). Menthol additives may pose additional health risks (Cummings, Giovino, Mendicino 1987); these additives could conceivably influence puffing patterns (e.g., by reducing the perceived "harshness" of the tobacco) so as to heighten nicotine delivery or smoking risks (e.g., by enabling the smoker to tolerate inhaling more often or more deeply or to smoke the cigarette to a shorter length). However, to date no studies that address this issue have been published. National survey data (US DHHS 1985) suggest that black smokers attempt to quit at the same rate that white smokers do. However, blacks appear to be less likely to remain abstinent (Appendix A). Quitting barriers faced more often by blacks include the same sociodemographic factors that explain their higher smoking rate, including the greater life stress and more limited resources associated with lower SES.

Quit-Smoking Treatments

Quitting methods. A recent survey of black ex-smokers showed that like U.S. ex-smokers as a whole, the vast majority had quit "on their own": 9 in 10 said they relied on "willpower," and only 1 in 10 reported using formal treatment programs, self-help guides or aids, or nicotine polacrilex gum (Orleans et al. 1987). There are, to date, no published data on the extent to which black and white U.S. smokers differ specifically in their access to, or use of, quit-smoking services and resources.

Sources/treatment agents. Physicians and other health care providers are powerful sources of quit-smoking assistance (Orleans 1985) and may be especially important sources for black Americans. In the 1985 Cancer Prevention Awareness Survey (US DHHS 1987), blacks reported more often than the general population that they would be very likely to follow a doctor's advice about ways to reduce cancer risks (US DHHS 1987).

Messages/methods. It is currently unclear whether black smokers would benefit any more or less than other groups from generally effective quit-smoking strategies and treatments. When outreach has assured equal black-white access to treatments and information (broadly defined in terms of recruitment efforts, location, affordability, appeal, and readability), outcomes for black and white smokers have been similar. For instance, Windsor and colleagues (1985) offered clearly worded pregnancy-focused self-help materials on quitting to women in public health maternity clinics and found no differences in quit rates between black and white participants of similar SES. High-coronary-risk black men assigned to the Special Intervention of the Multiple Risk Factor Intervention Trial (MRFIT) achieved 6-year quit rates (43 percent) essentially comparable to those of white participants (46 percent) despite lower SES (Connett and Stamler 1984). On the other hand, preliminary unpublished results from several ongoing trials suggest that interventions developed for the general population may not be appropriate for or acceptable to lower SES minority smokers.

Channels/delivery modes. Church groups, fraternal organizations, and other groups within the black community have a unique role to play in bringing effective programs and resources to the attention of smokers and to provide support needed for compliance (Eng, Hatch, Callan 1985; Orleans et al. 1987). Besides improving treatment accessibility, these organizations have the potential to provide ongoing assistance and support for quitting efforts and nonsmoking maintenance. Eng, Hatch, and Callan (1985), for instance, describe working through black churches in rural North Carolina to offer smoking cessation, weight control, diet modification, and stress management health education and behavioral change programs. Lay health advisers were recruited to work with local professionals to

organize church-based health fairs and to provide screening and referral on an individual basis.

Interventions for Smoking Cessation Among Hispanics

As the most rapidly growing ethnic group in the United States, Hispanics have caught the attention of demographers, social scientists, and health planners, yet relatively little is known of their smoking behaviors or responses to various intervention and treatment approaches. There is recent evidence (Davis 1987) that cigarette advertising is increasingly targeted to specific groups and that Hispanics have become a major focus of sophisticated marketing approaches.

Prevalence

Smoking prevalence among Hispanic males is comparable to that among white males and considerably less than that among blacks. Smoking among Hispanic women, in contrast, is considerably lower than smoking among either white or black women (Marcus and Crane 1985). Hispanics consume considerably fewer cigarettes per day than do whites. Heavy smoking among Hispanics is relatively infrequent (Marcus and Crane 1985, 1987; Samet et al. 1982; Stern et al. 1975).

Data from the 1985 Current Population Survey indicate substantial differences in smoking status by Hispanic subgroup. More Puerto Ricans reported smoking than did other subgroups (Mexican-Americans, Cubans, and Central and South Americans). Caution is needed in interpreting these data as they are based on limited numbers of respondents. Marcus and Crane (1985) reported that the pattern of high smoking prevalence among Hispanic men and relatively low prevalence among Hispanic women held true across a number of Hispanic subgroups. Overall, the data suggest considerable ethnic diversity within the Hispanic population. Diversity in smoking prevalence among Hispanics also has been found in the Hispanic Health and Nutrition Examination Survey (HHANES) conducted between 1982 and 1984 (Appendix A). Cultural differences among divergent Hispanic groups may need to be considered in the design and content of treatment programs.

Smoking Antecedents

Markides, Coreil, and Ray (1987) used data from a three-generational study and found that smoking behavior among younger Mexican-Americans was positively correlated with that of their middle-aged parents. This association was stronger for women. In a study of Mexican-American high school students who were identified as potential school dropouts, Bruno and Doscher (1984) found more

smokers in this group than among other students. These researchers found that 56 percent of their survey population of 78 potential dropouts had increased their cigarette consumption in the previous year. Otero-Sabogal and colleagues (1986) reported that "positive social presentation" as a consequence of smoking was mentioned by Hispanics in their study group. Castro and coworkers (in press) state that smoking and other habitual behaviors do not occur in isolation, but are part of a lifestyle. Smoking has been identified by these authors and others as a "core unhealthy behavior" that is associated with other such behaviors as use of illicit drugs, alcohol abuse, driving while intoxicated, nonuse of seat belts, and a pattern of little aerobic exercise. However, on a test of knowledge about the health consequences of smoking, moderate-to-heavy cigarette smokers were the highest scorers, suggesting an intellectual awareness of the risks involved in their behavior.

Smoking Interventions

The only available study that specifically targeted Hispanics was reported by Wittenberg (1983). During a market survey for the "Healthy Mothers, Healthy Babies" campaign, focus groups were organized to gather information from minority women. Researchers held sessions with eight groups of black women and seven groups of Mexican-American women. The results of these sessions suggested that the women involved largely ignored health advice, including advice to quit smoking, believing that the negative consequences would affect the mother and not the baby. Wittenberg (1983) found that the physician was considered the most credible source of health information but that family and friends were also important sources of information, which sometimes was in conflict with professional advice. Mexican-American women cited a paucity of Spanish-speaking health providers, and both minority groups stressed the need for such providers to have a better understanding of dietary preferences and traditional cultural patterns to more adequately serve pregnant minority women. The roles of the family, the Catholic Church, and the Spanish language have been said to be at the heart of the cultural identity of Hispanics in the United States (Guernica and Kasperuk 1982; Perez-Stable 1987). These influences have not been systematically assessed or harnessed in the design of smoking intervention programs for Hispanics.

Research addressing other ethnic groups is virtually nonexistent.

Methodological Issues in Treatment Study Design and Evaluation

Since the late 1970s, researchers and theoreticians have made progress in developing theoretical comparison strategies in evaluating pharmacologic and behavioral treatment interventions. This has

gradually resulted in the use of more sophisticated analytic comparisons in at least a few studies (Brandon, Tiffany, Baker 1987; Hall, Rugg et al. 1984; Harackiewicz et al. 1987; Raw and Russell 1980; Tiffany, Martin, Baker 1986). The development of specific measures and investigator adoption of theory-driven analytic strategies (Abrams et al. 1987; Davis and Glaros 1986; Erickson et al. 1983; Hall, Rugg et al. 1984; Harackiewicz et al. 1987; Mermelstein, Lichtenstein, McIntyre 1983; Shiffman and Jarvik 1976; Tiffany, Martin, Baker 1986) should result over the next 10 years in a clearer understanding of therapeutic change processes. Integrated theoretical approaches in which treatment, subject, and context factors are considered simultaneously may prove especially fruitful.

A second major methodological concern is the typical smoking intervention study design. Most researchers, when they do use control or comparison treatments, merely pit one treatment against another, often with no clear theoretical basis. Some investigators systematically remove or add treatment elements largely on pragmatic grounds. Unfortunately, such experimental designs permit only weak inferences concerning the specific effective elements of treatment (McFall 1978).

Earlier reviews (Pechacek 1979) noted that the principal problem plaguing smoking treatment evaluation was that clinical outcomes were typically inferred from data of suspect validity. Previously, most long-term outcome data were based on client self-reports of smoking status, possibly supported by informant reports. Both self- and informant reports are vulnerable to biases that make them inadequate in research settings as sole measures of outcome (Glynn, Gruder, Jegerski 1986; Li et al. 1984; Murray et al. 1987). Fortunately, over the last 9 years biochemical verification of self-reports has become a more common practice, although it is by no means universal.

Carboxyhemoglobin estimates from breath samples and measurements of thiocyanate in urine, saliva, or plasma and of cotinine in saliva and serum have been used most frequently to assess smoking status. Carboxyhemoglobin has a relatively brief half-life and is affected by ambient CO₂ activity level, and some drugs (Ringold et al. 1962; Henningfield, Stitzer, Griffiths 1980). However, this measure is inexpensive and can provide subjects immediate feedback on an important health risk factor. Thiocyanate may remain elevated for up to 12 to 14 days after smoking cessation (Barylko-Pikielna and Pangborn 1968; Pettigrew and Fell 1973). Thiocyanate levels may be quite variable within individuals (Barylko-Pikielna and Pangborn 1968). Assays of thiocyanate are insensitive to low levels of smoking (Vogt et al. 1977) and are often poorly correlated with self-reported smoking rates or actual measures of puffing patterns (Abueg, Colletti, Rizzo 1986; Burling et al. 1985; Vogt et al. 1977). Further-

more, thiocyanate levels may be considerably affected by consumption of common foods (e.g., almonds, tapioca, cabbage, broccoli, and cauliflower; Bliss and O'Connell 1984). For these reasons, cotinine is a generally preferred assay. Cotinine, a major metabolite of nicotine, is detected above nonsmoker levels for up to 48 hr after a single cigarette is smoked (Zeidenberg et al. 1977). Cotinine levels may persist for up to 7 days after cessation of habitual smoking (Benowitz et al. 1983). Cotinine assays tend to be expensive, limiting their usefulness. Readings will not accurately reflect smoking in individuals who use nicotine polacrilex gum. Immediate feedback to subjects is not possible with thiocyanate and cotinine measures.

Biochemical assays do not provide complete information concerning posttreatment smoking status. Self-report, although not adequate when used alone, is a necessary measure. Also, when subjects are aware of the use of biochemical assays, their self-reports of abstinence agree well with assay results (Hall, Rugg et al. 1984; Hall, Sachs et al. 1984; Glynn, Gruder, Jegerski 1986; Raw and Russell 1980). However, other studies have found no improvement in the accuracy of reporting with the use of physiological measures (Bliss and O'Connell 1984).

Insufficient attention has been devoted to length and intensity of treatment as determinants of outcome (Chapter V). As noted previously, the vast majority of individuals who have quit to date have done so in the absence of formal intervention. Spontaneous remission among chronic drug users has been observed not only for tobacco but for opioids and alcohol as well (Chapter V). However, evidence of spontaneous remission does not justify a failure to treat chronic smokers who are (or who perceive themselves to be) unable to achieve abstinence on their own.

Changing social norms appear to be extremely significant in the recent decline in smoking prevalence (Appendix A). Public health approaches have the potential of reaching far larger numbers of smokers than do intensive clinical treatments, yet some individuals obviously are resistant to these normative influences. Many tobacco users do not appear responsive to minimal contact or community interventions. Sachs (1986) has argued that highly intensive clinical procedures may be cost-effective for certain populations of high-risk smokers (e.g., those who already have suffered myocardial infarctions). Some individuals persist in their tobacco use despite the presence of immediate life-threatening health problems related to their dependence.

Other issues with which the field still struggles are definitional, e.g., the operational definitions of abstinence and relapse. Studies that report abstinence rates during followup split on whether they require continuous abstinence from the end of treatment or merely abstinence at the point of followup. Abstinence levels can differ

substantially depending on which measure is used. Failure to follow a common practice in reporting outcome (or to provide sufficient information to allow independent calculations) substantially increases the difficulty of comparing success rates across studies (Bigelow and Ossip-Klein 1986).

The National Interagency Council on Smoking and Health formulated stringent standards for the evaluation of smoking cessation programs. Complete cessation including total abstinence from tobacco in all forms for a period of 1 year was defined as the primary criterion for success. Several major health agencies (the American Cancer Society, the American Heart Association, and the American Lung Association) have endorsed these standards. Biochemical validation of self-reported abstinence is not required in these guidelines. The guidelines fail to distinguish between an isolated "slip" and actual relapse in the definition of successful quitting (Ossip-Klein et al. 1986).

Many studies still fail to include enough subjects to permit adequate statistical power and to promote generalizability of results. Few cessation studies have used validity checks to determine the extent to which treatment manipulations actually were implemented effectively. This is especially important when counseling strategies are being compared (Hall, Rugg et al. 1984; Tiffany, Martin, Baker 1986). Counseling manipulations and therapist training and experience should be adequately described, and validity checks of counseling differences should be incorporated into the assessment plan. Selection of subjects represents another important issue (e.g., type of smoker, cigarette consumption, prior history of failures). Treatment outcome may be influenced substantially by the characteristics of the smokers assigned to intervention.

In sum, cessation research has made methodologically notable strides in that, in the best studies, outcomes are verified with multiple assays (including biochemical ones), the design and evaluations of treatments are now theory driven, improved therapy process measures are used, and a variety of specific pragmatic problems such as subject attrition have been reduced. These improvements are recent, however, and characterize a relatively few published studies.

Conclusions

Smoking treatment research has been marked by considerable progress since it was reviewed in the 1979 Report of the Surgeon General (US DHEW 1979), both in methodological sophistication and to a lesser extent in the consistency of success achieved by the best multicomponent cessation programs.

In contrast to the generally positive outcomes of multicomponent treatments, there is mounting evidence that no single intervention

constitutes a generally effective method. In the case of multicomponent treatment interventions, individual components should complement one another. Interventions that hold promise and deserve additional attention are low-aversion directed-smoking strategies, skill-training treatments, interventions that enhance the self-attribution of treatment success, and interventions that train individuals to obtain and use social support resources. Low-aversion smoking treatments are important because of their acceptability, ease of administration, and generally promising results when used with other treatment elements. Research on skills training should explore the extent to which enhanced clinical outcomes depend on the acquisition and actual use of specific smoking-relevant skills. Therapeutic manipulations that enhance self-attributions of success or self-efficacy estimates could have wide treatment applicability. The combination of increased knowledge and skills, self-efficacy, and social support should enhance treatment outcomes.

Investigators should make more explicit the relationship between theory and therapeutic manipulations, valid assessments should be tailored to tap processes implicated by theory in behavioral change, and greater sample sizes should be included in treatment evaluation studies. Individual differences may be important in assigning smokers to combined pharmacologic and behavioral treatment (Hughes 1986). Some smokers appear to resist pharmacologic intervention. Smokers who attribute their success to pharmacologic agents may be at increased risk for relapse when these agents are withdrawn (Davison and Valins 1969). Conversely, some smokers accept pharmacologic treatment but refuse behavioral approaches. Many of these refusals stem from required time commitments that the smokers view as excessive.

Dissemination of effective treatment strategies is critically needed. Considering the vast body of treatment literature that has accumulated, surprisingly little systematic transfer to community settings has occurred. Many treatment programs that are available (e.g., proprietary, public service) have not been subjected to rigorous evaluation. Furthermore, these programs often do not reflect recent laboratory findings. This is especially true for pharmacologic approaches. Very few applied programs adequately address nicotine replacement therapies or other potentially relevant pharmacologic adjuncts to treatment. Dissemination is especially lacking for minority and lower SES populations, which may have the greatest need for these types of services.

Relapse

As in many areas of clinical practice, therapeutic interventions have been developed and implemented in the absence of a complete

understanding of the processes being treated. Future development of smoking cessation treatments designed to maintain abstinence in the face of high relapse prevalence should benefit greatly from an expanded knowledge base that is being accumulated concerning the correlates and determinants of smoking relapse.

Research has shown that smoking cessation is a process involving several discrete stages. These stages include precontemplation, contemplation, decision, action, and maintenance (Prochaska and DiClemente 1983, 1985, 1986; DiClemente and Prochaska 1985; Prochaska et al. 1985; Velicer et al. 1985; Wilcox et al. 1985). This Section considers recent research on factors related to successful maintenance of nonsmoking once initial cessation has been achieved during the action stage. Studies of long-term outcomes in smoking cessation indicate that relapse, rather than maintenance, is the most prevalent outcome during this stage. Hunt and his colleagues (Hunt, Barnett, Branch 1971; Hunt and Matarazzo 1973) showed that over a wide range of treatments, relapse rates of 75 to 80 percent could be expected among smokers who achieved initial cessation (Figure 2, Chapter V). These findings have been replicated many times in recent treatment outcome studies (Schwartz 1987). It should be noted, however, that these relapse rates are based on single quit attempts. Cumulative long-term abstinence rates covering multiple quit attempts may be considerably better (Schachter 1982).

Defining Relapse

Given that relapse depends on the achievement of initial cessation, definitions of relapse must include a definition of cessation. In addition, many investigators distinguish between a "slip" or smoking one's first cigarette and a "relapse" or return to regular smoking (Brownell et al. 1986). The National Working Conference on Smoking Relapse recommended a duration of 24 hr of continuous tobacco abstinence to define initial cessation. A slip was defined as a "period of not more than 6 consecutive days of smoking following at least 24 hr of abstinence" (Ossip-Klein et al. 1986). Smoking beyond 6 consecutive days was then defined as a relapse. These definitions of quit episode, slip, and relapse are somewhat lenient. Many investigators require a longer period of initial abstinence (e.g., 48 hr or 1 week) for a quit episode and regard even a few smoking occasions as a relapse rather than a slip. Considerable data indicate that an initial slip is highly predictive of subsequent relapse (Brandon, Tiffany, Baker 1986; Ossip-Klein et al. 1986).

Conceptual Frameworks

Research on the relapse process has focused on two general areas: (1) identifying factors that predispose individuals to relapse or to successful maintenance and (2) identifying factors that precipitate or

immediately precede the return to smoking following initial success (Shiffman et al. 1986). Predisposing factors include characteristics of individuals and their environments that make them more or less vulnerable to relapse as they begin the maintenance process. Precipitating factors relate to the circumstances surrounding a specific relapse situation or smoking the first cigarette following a period of abstinence.

Social learning theory has provided a useful framework for much of the research on predisposing factors (Bandura 1977b; Brownell et al. 1986; Leventhal and Cleary 1980; Shiffman et al. 1986). From this perspective, the effects of environmental or behavioral elements on maintenance of nonsmoking are mediated by individual factors such as prior experience with smoking cessation and beliefs about the cessation process. In addition to personal demographic characteristics, predisposing variables examined that are consistent with this framework include smoking and quitting history, social factors (social support and the presence of smoking cues in the social environment), stress, and cognitive factors such as self-efficacy, outcome attributions, and perceptions about the consequences of quitting smoking (Chapter VI).

Marlatt and Gordon's model of the relapse process (Marlatt and Gordon 1980, 1985) has provided the foundation for much of the research on the circumstances associated with initial slips and suggests specific hypotheses regarding factors that mediate the transition from an initial slip to a full-blown relapse. This model proposes that initial smoking following a period of abstinence is likely to occur in certain types of high-risk situations. As suggested by the types of predisposing factors listed above, high-risk situations could include intrapersonal factors such as negative affect and severe withdrawal symptoms following a long history of heavy smoking. The first determinant of whether smoking occurs in a high-risk situation is whether the individual uses specific strategies to cope with the situation. Successful coping is assumed to lead to increased confidence in one's ability to maintain abstinence, thereby decreasing the probability of relapse. Failure to cope in the situation coupled with positive expectations about the effects of smoking can lead to an initial slip. The Abstinence Violation Effect (AVE) is proposed as the major mediating factor between an initial slip and a full-blown relapse. Defined as an attributional construct (Curry, Marlatt, Gordon 1987; Marlatt and Gordon 1985), the AVE is characterized by internal, stable, and global causal attributions for smoking the initial cigarette. Research on specific factors within these conceptual frameworks is reviewed below.

Predisposing Factors

Demographics

To the extent that demographic factors are related to initial cessation, the population of individuals who achieve cessation and are "eligible" for relapse is relatively homogeneous. It is not surprising, therefore, that the majority of studies that examined these variables have not found differences in relapse rates by socioeconomic status (Campbell 1983; Eisinger 1971; Evans and Lane 1981; Garvey, Heinold, Rosner, *in press*; Hirvonen 1983; Horwitz, Hindi-Alexander, Wagner 1985; Jacobs et al. 1971), age (Coppotelli and Orleans 1985; Cummings et al. 1985; Evans and Lane 1981; Hirvonen 1983; Horwitz, Hindi-Alexander, Wagner 1985; Jacobs et al. 1971), or gender (Eisinger 1971; Evans and Lane 1981; Shapiro and Gunn 1985; Horwitz, Hindi-Alexander, Wagner 1985). Exceptions to the findings for age include one study that found an inverse relationship (Garvey, Heinold, Rosner, *in press*) and two studies reporting a positive relationship between age and long-term success (Campbell 1983; Eisinger 1971). One study did report that males were more successful than were females at long-term maintenance (Hirvonen 1983).

Although women and men may be equally likely to relapse, data suggest that their return to smoking is precipitated by different factors. Hirvonen (1983) reports that men more frequently cited alcohol consumption and strong cravings as causes of relapse, whereas women more often cited the influence of other smokers and negative affect. In a prospective study, Swan and colleagues (*in press*) found that craving predicted relapse for women and not for men, while psychological withdrawal symptoms predicted relapse among men but not women. Studies that have analyzed reports of specific relapse episodes (Shiffman 1982, 1986a) have found no gender differences.

The large study by Swan and coworkers (*in press*) of treated smokers suggests that sex differences in factors associated with relapse may be pervasive. They found almost no overlap between men and women in the factors that predicted relapse. The following factors predicted relapse among women, but not men: the machine-rated nicotine delivery of cigarettes, employment status, rated likelihood of success, and lower work strain. Among men, relapse was predicted by greater stress (hassles) and higher work strain. Campbell (1983) also reports sex differences in predictors of outcome, some of which contradict Swan's findings, and Guilford (1967) reports sex differences on almost all aspects of cessation and maintenance. Although it may be premature to draw conclusions about the causes of relapse among males and females, clearly sex differences must be examined in future work.

Smoking and Quitting History

Smoking History

Most studies indicate that the length of a person's smoking history influences the process of initial cessation (Pomerleau, Adkins, Pertschuk 1978) but is unrelated to relapse (Ashenber 1983; Carl 1980; Coppotelli and Orleans 1985; Cummings et al. 1985; Evans and Lane 1981; Garvey, Heinold, Rosner, in press; Hirvonen 1983; Horwitz, Hindi-Alexander, Wagner 1985; Jacobs et al. 1971; Pomerleau, Adkins, Pertschuk 1978; Swan et al., in press). The two studies that report relationships between length of smoking history and relapse are contradictory, with one reporting that smoking longer increased relapse risk (Graham and Gibson 1971) and the other reporting an inverse relationship between the duration of smoking and the risk of relapse (Eisinger 1971).

Conflicting findings have been reported for the number of cigarettes smoked per day. Although there are some positive findings (Ockene et al. 1982; Shapiro and Gunn 1985), most studies suggest that the number of cigarettes smoked is not a good predictor of relapse (Campbell 1983; Coppotelli and Orleans 1985; Cummings et al. 1985; Eisinger 1971; Evans and Lane 1981; Graham and Gibson 1971; Hirvonen 1983; Horwitz, Hindi-Alexander, Wagner 1985; Jacobs et al. 1971; Pomerleau, Adkins, Pertschuk 1978; Swan et al., in press). A few studies do find an effect of the number of cigarettes smoked on initial cessation (Hirvonen 1983). Precessation cigarette consumption has been positively associated with the length of time between having an initial lapse and a return to regular smoking (Brandon, Tiffany, Baker 1986). It should be noted, however, that number of cigarettes is only a rough indicator of actual intake, particularly for levels above 20 cigarettes/day.

Kabat and Wynder (1987) reported that the time between waking up and smoking the first cigarette was a good predictor of outcome. This variable represents one item on the Fagerström Tolerance Questionnaire (Fagerström 1978) and appears to be strongly related to physical dependence.

Smoking Typologies

Although their predictive value has been questioned (Joffe, Lowe, Fisher 1981), smoking typologies have been widely used in an attempt to classify smokers or smoking situations (e.g., smoking for stimulation, handling, relaxation; Ikard, Green, Horn 1969). The strongest evidence for the relationship of type of smoking to relapse has been found with people who smoke to control negative affect. In a widely cited study, Pomerleau, Adkins, and Pertschuk (1978) reported that people who said they smoked when experiencing negative affect were more likely to relapse. Similarly, Campbell

(1983) reported that smokers who experience craving when emotionally upset were more likely to relapse. These findings are diluted, however, by those of other studies showing no relationship between negative-affect smoking and relapse (Coppotelli and Orleans 1985; Eisinger 1971; Garvey, Heinold, Rosner, in press; Jacobs et al. 1971).

Quitting History

Several studies have found a positive relationship between number of previous quit attempts and success in quitting smoking (Brandon, Zelman, Baker, in press; Tiffany, Martin, Baker 1986). However, other studies report no relationship between the number of prior quit attempts and relapse (Swan et al., in press; Horwitz, Hindi-Alexander, Wagner 1985; Cummings et al. 1985; Coppotelli and Orleans 1985; Ockene, Benfari et al. 1982). Some studies in fact report that subjects with fewer previous quit attempts are more successful in maintenance (Horwitz, Hindi-Alexander, Wagner 1985; Graham and Gibson 1971; Garvey, Heinold, Rosner, in press). Garvey and Hitchcock (1987) found that among recidivists, smokers with more past experience in quitting showed a slower rate of progression to regular smoking. Gottlieb and coworkers (1981) and Hirvonen (1983) also report data that suggest a positive relationship between duration of the longest previous cessation effort and successful maintenance. Clearer descriptions of quitting history with respect to both number of previous quit attempts and duration of abstinent periods would be helpful in evaluating the relationship between quit attempts and outcome.

Withdrawal and Dependence

Withdrawal symptoms, whether elicited by acute deprivation or by conditioned stimuli, are hypothesized to be the link between dependence and relapse (Baker, Morse, Sherman 1987; Shiffman 1979; Wikler 1965). The tobacco withdrawal syndrome consists of a cluster of symptoms that are typically experienced after even brief or partial tobacco deprivation (Hughes and Hatsukami 1986; American Psychiatric Association 1980, 1987; Chapter IV). The symptoms include craving for cigarettes, irritability, anxiety, difficulty in concentrating, restlessness, and increased appetite (American Psychiatric Association 1987). Some physical signs are also commonly reported, but with the possible exception of bradycardia, these appear to be less consistent (Shiffman 1979; Hughes and Hatsukami 1986). Especially significant is the fact that the syndrome has a rapid onset and generally declines within 2 weeks (Shiffman 1979; Shiffman and Jarvik 1976; Cummings et al. 1985; Gottlieb 1985).

Several studies have examined the role of withdrawal symptoms as predisposing factors for relapse. In a retrospective study, Burns

(1969) reported that recidivists cited withdrawal symptoms as the most common reason for relapse. Other retrospective studies at least partially support this finding (Garvey, Heinold, Rosner, in press; though see Evans and Lane 1981). Gottlieb (1985) found that both physical and psychological withdrawal symptoms predicted early relapse in a group of treated smokers; symptoms accounted for 14 percent of the variance in smoking after 2 weeks. Other investigators have also found that mood disturbance, a possible withdrawal symptom, predicts relapse (Hall et al. 1984; Hirvonen 1983; Manley and Boland 1983). Manley and Boland (1983) found that mood disturbance characterized relapsers even before they quit and after they resumed smoking. The literature also includes negative findings (Garvey, Heinold, Rosner, in press; Hughes and Hatsukami 1986; Swan and Denk, in press; Swan et al., in press).

Although craving is difficult to define precisely (Kozlowski and Wilkinson 1987), a number of studies have reported relationships between craving and relapse (Campbell 1983; Garvey, Heinold, Rosner, in press; Gottlieb 1985; Hirvonen 1983). The effect appears to be more marked among female smokers, with several studies reporting that it is a significant predictor of relapse only among women (Guilford 1967; Gunn 1986; Swan et al., in press).

Cognitive Factors

Concern About Weight Gain

Quitting smoking often results in weight gain (Grunberg 1986; Chapter IV). Multiple factors may contribute to postcessation weight gain, including decreased metabolism, increased food consumption, and increased preference for sweet-tasting, high-caloric foods (Grunberg 1982). Highly dependent smokers and those who tend to eat in response to specific emotional and environmental cues appear to be at greatest risk of gaining weight following smoking cessation (Emont and Cummings 1987; Hall, Ginsberg, Jones 1986; Chapter VI).

The data relating concern about weight gain to relapse are inconsistent. Klesges and Klesges (in press) found that women were more likely to report relapse for weight-related reasons. Other studies have found that concern about weight gain was not a major determinant of relapse (Fuller 1982; Greaves, Barnes, Vulcano 1983; Hirvonen 1983; Shapiro and Gunn 1985). Though there are exceptions (DiClemente 1981), studies typically report that recidivists experience less weight gain than successful abstainers (Manley and Boland 1983; Hall, Ginsberg, Jones 1986). In at least some of these studies, this cannot be confounded by the effects of continued abstinence, because the studies used prospective designs in which weight gain was assessed prior to relapse (Hall, Ginsberg, Jones

1986). Even so, the possibility remains that relapsers are more weight conscious in the first place and exert greater efforts to curtail initial weight gain (Hall, Ginsberg, Jones 1986; Herman and Polivy 1975). Smoker perceptions concerning weight gain may be critical. For some individuals, a gain of only 2 or 3 pounds may be viewed as a cause for great concern. Other individuals may be essentially indifferent to weight gains of 15 to 20 pounds.

Self-Efficacy

Bandura (1977a, 1982) proposed a common mechanism underlying behavioral change achieved by different procedures: successful psychological interventions all function by creating and strengthening expectations of personal mastery or efficacy. An efficacy expectation is the conviction that one can execute the behaviors necessary to achieve a desired outcome. Such expectations are assumed to affect the initiation of coping behavior, the amount of effort that will be expended to maintain coping behavior, and the persistence of coping behavior in the face of external and internal obstacles.

Self-efficacy is an important construct in Marlatt's theory of relapse. Marlatt's theory specifies that people's ability to resist the use of a substance (e.g., cigarettes) in a high-risk situation depends on, among other factors, their self-efficacy level (Marlatt and Gordon 1980). If people have expectations that they can cope with a smoking urge without smoking, they are less likely to relapse. Moreover, people who successfully resist temptation should experience an increase in self-efficacy. The theory also states that self-efficacy is a determinant of whether people who experience an initial lapse are able to prevent escalation to full relapse.

Various scales assumed to measure self-efficacy have predicted smoking status at followup (Coelho 1984; DiClemente 1981; Killen et al. 1984; McIntyre, Lichtenstein, Mermelstein 1983; Ockene et al. 1982; Yates and Thain 1985) and latency from treatment end to relapse (Brandon, Tiffany, Baker 1986; Brandon, Zelman, Baker, in press; Erickson et al. 1983; Tiffany, Martin, Baker 1986). Efficacy ratings have also predicted smoking intake after a controlled-smoking intervention (Godding and Glasgow 1985) and have differentiated joiners from nonjoiners of a smoking treatment program (Brod and Hall 1984).

Important qualifications, however, relate to the timing of the relapse assessment and the subject sample observed. Studies predicting relapse that are based on all treatment subjects (including those who never achieve abstinence) will achieve higher correlations with outcome than will studies assessing only abstinent subjects. Self-efficacy is a less useful predictor when measured shortly after

cessation rather than after 1 or 2 months of abstinence (Baer, Holt, Lichtenstein 1986).

Condiotte and Lichtenstein (1981) reported seven distinguishable clusters of smoking situations and found a congruence between the situation clusters for which subjects indicated low self-efficacy and the clusters that comprised their actual relapse situations. However, a conceptual replication of the use of efficacy subscales has not demonstrated utility (Baer, Holt, Lichtenstein 1986). Thus, at this point situation-specific self-efficacy assessments have not proved to be of value.

Self-efficacy may reflect the influence of diverse treatments or smoking history variables related to cessation success. Skills training, for example, might be effective to the extent that it enhances smokers' beliefs that they can cope with temptation. Aversion therapy might be effective to the extent that smokers attribute their self-punishment to their high motivation to quit and their ability to use available resources to help stay abstinent. Self-efficacy may in fact be confounded with Bandura's (1977a) concept of outcome expectancy. Rather than measuring subjects' convictions that they could execute specific coping behaviors, most of the studies simply assessed subjects' confidence that they would resist the urge to smoke in the future.

The global construct of self-efficacy is somewhat ambiguous. Self-efficacy may include not only response effectiveness, but also motivation to quit and judgment of skills necessary to undertake the quitting program. Self-efficacy as a global predictor can be useful. However, it may be more important to assess what skills individuals learn from different treatment components. A better understanding of the process of acquiring competency in quitting is needed. Knowledge of the specific treatment components that enhance self-efficacy could be significant in developing and refining effective interventions.

Outcome Attributions

Attribution theory suggests that individuals who attribute their behavioral change to internal factors are more likely to successfully maintain their change (Davison and Valins 1969). This hypothesis was supported in a study by Harackiewicz et al. (1987) which found that, for individuals participating in intrinsically oriented treatment programs (a self-help manual emphasizing individual cessation efforts either with or without nicotine polacrilex gum), internal attributions for initial success were significantly related to longer maintenance of nonsmoking. Contrary to the hypothesis, however, these investigators found that external attributions were positively related to long-term maintenance for individuals participating in extrinsically oriented treatment (nicotine polacrilex gum with a self-

help manual emphasizing a doctor's prescribed program). These findings suggest that the degree of consistency between attributions for initial success and the orientation of the cessation approach can affect the probability of relapse.

Social Factors

Smoking Cues

Most exposure to smoking-specific cues is socially mediated—e.g., watching others smoke. Such exposures have been labeled "social contagion" (Shiffman and Jarvik 1987). Few studies have assessed social contagion directly. Many studies have, however, examined the effect of having a spouse, friends, or coworkers who smoke.

The literature on the effect of spouse smoking status is surprisingly contradictory. Several studies report moderate-to-large increases in the probability of relapse among subjects with a smoking spouse (Campbell 1983; Graham and Gibson 1971; McIntyre-Kingsolver, Lichtenstein, Mermelstein 1986; Tongas, Patterson, Goodkind 1976). Some studies, though, report no effect of spousal smoking (Horwitz, Hindi-Alexander, Wagner 1985; Garvey, Heinold, Rosner, in press; Swan et al., in press).

One possible explanation for the inconsistent findings is that the influence of spousal smoking is so strong that it often prevents initial cessation. This would cause the effect to be only sporadically observed in maintenance. The effects of spouse smoking status may also be complicated by interactions with social support. The risk incurred by having a smoking spouse may be reduced or eliminated if the spouse is supportive (Mermelstein, Lichtenstein, McIntyre 1983). This may be especially true if the spouse refrains from smoking in the presence of the subject, thereby resulting in fewer exposures to smoking cues.

The data on friend smoking are clearer. Several studies find that subjects who have more smokers among their friends are more likely to relapse (Eisinger 1971; Garvey, Heinold, Rosner, in press; Ockene et al. 1982; Gottlieb et al. 1981; Goldstein 1981). One study failed to replicate this effect (Swan et al., in press). Brandon, Tiffany, and Baker (1986) found that smokers having a lapse cigarette in the presence of other smokers progressed to regular smoking more quickly than did other lapsers. The most parsimonious explanations of these social contagion effects are that people with many smoking friends tend to experience more exposure to smoking cues and that cigarettes are likely to be more readily available to them.

Social Support

Social support can serve as a buffer to reduce the negative psychological effects of stressors (Cobb 1976; Cohen, Sherrod, Clark

1986; Cohen and Wills 1985; Dean and Lin 1977). Correlational studies have found that the level of perceived social support is related to smoking cessation and maintenance. Coppotelli and Orleans (1985), for example, examined the determinants of maintenance among women who recently quit smoking. They found that a measure of "partner facilitation" (problem solving, rewarding quitting, understanding, listening, and facilitating coping responses) accounted for 32 percent of the outcome variance at 6 to 8 week postcessation. General social support from spouses, as well as smoking-specific spousal support, has been related to smoking treatment outcome (Horwitz, Hindi-Alexander, Wagner 1985; Mermelstein et al. 1986; Mermelstein, Lichtenstein, McIntyre 1983; although see Glasgow et al. 1985).

Global Support

Global support has usually been assessed as perceived support. Using the Interpersonal Support Evaluation List (ISEL; Cohen and Hoberman 1983) to measure support, Mermelstein and coworkers (1986) found that greater perceived support (having someone to talk to about personal matters) predicted maintenance at a 3-month followup. However, the ISEL was unrelated to smoking status at 6 or 12 months, and the 3-month findings were not replicated in a second study by the same investigators (Mermelstein et al. 1986). As noted above, Coppotelli and Orleans (1985) found that women who reported receiving greater support from their husbands were more likely to maintain abstinence. There was no comparison group of male subjects.

Smoking-Specific Support

Several studies have examined the role of social support directed at smoking cessation. The most thorough investigations of specific support have been conducted by researchers at the University of Oregon, who developed the Partner Interaction Questionnaire (PIQ; Mermelstein, Lichtenstein, McIntyre 1983) to assess perceived helper behaviors. These investigators found that perceived helpfulness of partner behaviors was related to cessation and maintenance. The actual number of partner behaviors was not related to outcome; however, a measure of the character of the interactions was related. A cluster of partner behaviors labeled "Support and Encouragement" (e.g., expressing understanding or pride) was related to maintenance of abstinence. In contrast, a cluster of behaviors involving "Nagging and Policing" (Mermelstein, Lichtenstein, McIntyre 1983) predicted relapse. Subsequent studies using the PIQ have only partially replicated these findings (Lichtenstein,

Glasgow, Abrams, in press; Malott et al. 1984; McIntyre-Kingsolver, Lichtenstein, Mermelstein 1986).

Other studies using other measures have also yielded mixed results. In a large prospective study, Prochaska, DiClemente, and colleagues (Prochaska and DiClemente 1983; DiClemente and Prochaska 1985; Prochaska et al. 1985) reported that social support predicted continuing abstinence. However, several other research groups have failed to find evidence that smoking-specific support aids maintenance (Evans and Lane 1981; Ockene et al. 1982; Garvey, Heinold, Rosner, *in press*).

Stress

Some studies have used the life events approach to the assessment of stress (Holmes and Rahe 1967). This technique asks subjects about major life events that have occurred since the subjects stopped smoking. Most studies have found little or no relationship between life stress events and relapse (Shapiro and Gunn 1985; Shiffman, Read, Jarvik 1985). This may be because life stress events are relatively uncommon.

Recent research on stress has begun to focus on more frequent and smaller-scale stressors, which Lazarus and colleagues (1981) and DeLongis and coworkers (1982) have called "Hassles." The Hassles Scale assesses the frequency and perceived severity of everyday stressors, such as having difficulties with coworkers or not having enough time for recreation. Swan and colleagues (Swan and Denk, *in press*; Swan et al., *in press*) found that hassles during the second month of abstinence only weakly predicted outcomes at 1 year. The effect of hassles was more reliable for men than for women.

A somewhat different approach to examining background stress was taken by Cohen and his colleagues, who developed and used the Perceived Stress Scale (PSS). The PSS measures perceived stress and demoralization without reference to particular events or sources of stress. Cohen and colleagues found that PSS scores did predict relapse and that they were strongly associated with daily cigarette consumption among recidivists.

Stress and coping theories of smoking imply that deficiencies in personal resources for coping with stress may enhance the risk of relapse (Wills and Shiffman 1985). Using the Ways of Coping checklist, Ashenbergh (1983) assessed how subjects who had quit smoking coped with stress in situations that are often associated with relapse. There were no differences between relapsers and abstainers in the kinds of coping reported, but abstainers reported using fewer coping strategies. The meaning of this finding is unclear. Abstainers could have experienced less severe stress or less severe threats to abstinence, and therefore needed fewer coping responses. Conversely, abstainer coping responses could have been more

effective, therefore mitigating the need for more coping. Also, when Ashenbergs examined recidivists, stressful situations associated with coping were found to be less likely to lead to relapse than those not associated with coping.

Precipitating Factors

High-Risk Situations

A number of studies support the theory that initial smoking following cessation tends to occur in specific types of high-risk situations. Work by Marlatt and his associates (Marlatt and Gordon 1980, 1985) has identified craving/withdrawal, intrapersonal negative emotional states (e.g., frustration, boredom, and anxiety), interpersonal conflict situations, and social pressure, both direct and indirect, as common types of high-risk situations. Shiffman (1986c) and Baer and Lichtenstein (in press) clustered data on the precipitants of relapse crises and lapses.

Data from studies of relapse episodes confirm that smoking cues are often involved in smoking relapse. Several studies report the smoking of others in the immediate environment in one-half to three-quarters of all relapse episodes (Brandon, Tiffany, Baker 1986; Colletti, Supnick, Rizzo 1981; Baer and Lichtenstein, in press; Shiffman 1982, 1986c; Cummings, Jaen, Giovino 1985). Many of these same studies report that specific smoking stimuli (usually seeing someone smoking) are responsible for precipitating 24 to 32 percent of all relapses (Shiffman 1982, 1986c; Ossip-Klein et al. 1986; Shapiro, Ossip-Klein, Stiggins 1983). Studies also report that relapse crises in which someone else is smoking are more likely to result in a smoking episode and in a shorter interval between the initial slip and relapse (Brandon, Tiffany, Baker 1986; Ossip-Klein et al. 1986; Shiffman 1982).

Abrams and his colleagues (Abrams et al., in press; Chapter III) have recently published data suggesting that individual differences in reactivity to smoking cues may influence cessation and relapse. In retrospective and prospective studies, these researchers found that recidivists responded more strongly than successful quitters to verbally presented smoking situations or to observations of another smoking. Recidivists displayed more anxiety and showed greater heart rate responses. It may be that responses elicited by smoking stimuli (Saumet and Dittmar 1985) reflect conditioned responses to nicotine effects.

Other smokers serve not only as cues for smoking but as sources of cigarettes. In half of all relapse episodes, another smoker provides the cigarettes that are smoked (Colletti, Supnick, Rizzo 1981; Baer and Lichtenstein, in press; Cummings, Jaen, Giovino 1985). This does not imply that the smokers exert social pressure to smoke; in most

cases, the ex-smoker specifically asks for a cigarette (Brandon, Tiffany, Baker 1986).

Data on relapse episodes suggest that relapse also can be cued by other stimuli or activities that have become associated with smoking through contiguity, for instance, food, drink, or relaxation (Baer and Lichtenstein, in press; Brandon, Tiffany, Baker 1986; Ossip-Klein et al. 1986; Shiffman 1986b).

Studies of specific relapse episodes consistently suggest that stress and negative affect play major roles in relapse. Findings from many studies encompassing diverse samples reveal that the majority of relapse episodes are preceded by negative affect (Brandon, Tiffany, Baker 1986; Shiffman 1982, 1986b; Marlatt and Gordon 1980; Cummings, Marlatt, Gordon 1980; O'Connell and Martin 1987; Gregory 1984; Baer and Lichtenstein, in press; Ossip-Klein et al. 1986; Shapiro, Ossip-Klein, Stiggins 1983; Giovino et al. 1986; Shapiro 1984). In some studies, as many as 9 out of 10 subjects report negative affect (Coppotelli and Orleans 1985). The most frequently reported emotion is anxiety, but boredom, depression, and anger are also common.

Data suggest that the more severe the stress surrounding a temptation to smoke, the higher the likelihood of smoking. Shiffman, Read, and Jarvik (1985) report a significant linear relationship between stress and smoking in relapse crises. There are contradictory data as to whether lapses associated with negative affect are particularly likely to progress to full relapse (Brandon, Tiffany, Baker 1986; O'Connell and Martin 1987). In sum, momentary stress and distress are major factors in relapse episodes. It should be noted, however, that these studies involve retrospective accounts of relapse episodes.

The role of negative affect in relapse may change over time. Cummings, Jaen, and Giovino (1985) report that early relapse episodes are more likely to be precipitated by stress; later in abstinence, alcohol and other appetitive cues become more prominent.

Coping Strategies

Coping strategies can be used both to prevent (anticipatory coping) and to directly respond to (immediate coping) high-risk situations. In either case, the strategies used can be behavioral, consisting of responses that are outwardly visible (e.g., leaving a party where others are smoking, engaging in physical activities), or cognitive, consisting of internal responses such as thoughts or images.

One of the most commonly used and studied anticipatory coping strategies is stimulus control—the avoidance of stimuli associated with smoking. Research on this strategy shows mixed outcomes, yielding no definitive conclusions (Evans and Lane 1981; Horwitz,

Hindi-Alexander, Wagner 1985; Prochaska and DiClemente 1983; DiClemente and Prochaska 1985). Data on the relative efficacy of cognitive and behavioral strategies weakly support the superiority of cognitive strategies. Evans and Lane (1981) report weak indications that successful maintainers were more likely to use cognitive techniques rather than behavioral ones.

Immediate coping has been assessed in studies that examined situations in which an ex-smoker was tempted to smoke. Studies of immediate coping with the temptation to smoke typically compare episodes in which smoking was averted with episodes in which relapse occurred. Shiffman (1982, 1984b, 1985) found that failure to perform any coping response was the single best predictor of smoking in a tempting situation, accounting for nearly a quarter of the variance in the outcomes of high-risk situations. This finding has been directly and indirectly supported in several other studies (Curry, Marlatt, Gordon 1987; Ossip-Klein et al. 1986; Shapiro, Ossip-Klein, Stiggins 1983; Sjoberg and Johnson 1978; Sjoberg and Samsonowitz 1978). These studies consistently show immediate coping to be effective in preventing smoking in a relapse-promoting situation. One problem with all of these studies, however, is retrospective bias. Subjects may introduce a self-justifying slant into their responses. Unfortunately, it may be virtually impossible to obtain prospective data on immediate coping.

Although there is no evidence that greater numbers of coping responses are more effective, there is evidence that it is better to use both cognitive and behavioral coping strategies when faced with a risk situation (Curry, Marlatt, Gordon 1987; Shiffman 1982, 1984b). Cognitive and behavioral coping are rather broad categories of responses. The relative efficacy of specific responses within those categories has also been examined in an attempt to identify effective and ineffective coping responses. Shiffman (1984b) examined the effectiveness of seven behavioral and eight cognitive coping strategies. Only one type of coping was not more effective than no coping: subjects who reported using self-punitive cognitions (berating oneself for being tempted to smoke) to cope were as likely to relapse as subjects who made no cognitive coping response. (See Glasgow et al. 1985, for parallel findings on cessation.) Self-punitive cognitions may diminish self-efficacy and engender negative affect, which in turn promotes smoking. Another finding from these comparative analyses was that subjects who reported "willpower" as a means of cognitive coping were significantly more likely to relapse (nearly half relapsed) than subjects who used other cognitive coping responses. Nevertheless, subjects who reported willpower fared better than subjects who made no cognitive coping response at all.

These two distinctions notwithstanding, the effectiveness of various coping responses was surprisingly uniform: 13 of the 15

responses were better than no response, but there were no significant differences among these 13 responses. Curry, Marlatt, and Gordon (1987) conducted a very similar set of analyses and arrived at a similar conclusion.

Several studies have examined whether individual differences in coping skill are associated with maintenance. The studies used similar analog methods to assess coping skill: subjects were presented with situations known to elicit desire to smoke, and their responses to these situations were rated. These studies used both retrospective and prospective analyses and had subjects respond either to written or role-played coping scenarios (Abrams et al. 1987, in press; Davis 1983; Davis and Glaros 1986; Shiffman, Maltese, Jarvik 1982). Results of retrospective analyses showed that 6-month abstainers did not differ in coping skill from recidivists (Abrams et al. 1987; Shiffman et al. 1985). Prospective studies also yielded little evidence that coping skill protects against relapse. Such studies have found no relationship between skill level and relapse likelihood, although there was evidence that high-skill subjects took longer to relapse (Abrams et al. 1987, in press; Davis 1983; Davis and Glaros 1986). Also, Davis and Glaros (1986) showed that a skill-based treatment increased the level of smoker coping skills assessed immediately posttreatment but did not enhance smoker followup performance.

Abstinence Violation Effect

Marlatt and Gordon (1980, 1985) define the Abstinence Violation Effect (AVE) as an attributional construct that mediates the transition from an initial lapse to a full-blown relapse. Curry, Marlatt, and Gordon (1987) found that individuals who smoked but did not return to regular smoking ("slipper") reported significantly greater AVEs than those who relapsed following an initial slip. Brandon, Tiffany, and Baker (1986) reported that only one-third of their subjects ($N=72$) used any coping response after a lapse and that the occurrence of coping was unrelated to relapse probability or speed of relapse.

Summary and Conclusions

1. Tobacco dependence can be treated successfully.
2. Effective interventions include behavioral approaches 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 a less successful outcome.

4. Nicotine replacement can reduce tobacco withdrawal symptoms and may enhance the efficacy of behavioral treatment.

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APPENDIX A

TRENDS IN TOBACCO USE IN THE UNITED STATES

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Introduction

The focus of this Appendix is on trends in the prevalence and demographic correlates of tobacco use. Findings from selected data sources (US DHHS 1986b; USDA 1986; US FTC 1981, 1986; US DHHS 1988) will be reported as well as findings from analyses of trend data found in these sources.

Prevalence of Smoking in the United States

Several surveys using different methodologies have reported the prevalence of current cigarette smoking in the United States. The reported prevalence of smoking between 1944 and 1986 is shown in Table 1. However, different methodologies can lead to variations in the estimation of prevalence. The same general survey methodology has been used throughout the National Health Interview Surveys (NHIS 1965 to 1985). These surveys have indicated a steady decline in smoking prevalence beginning in the late 1960s to 30.4 percent of adults 20 years of age and older in 1985. These data parallel the per capita consumption of cigarettes in the United States, which has declined each year since 1973 (Table 2). Based on population estimates and the NHIS, the total number of adult smokers (aged 20 years and older) in the United States declined from approximately 52,400,000 in 1976 to approximately 51,100,000 in 1985. The total number of former smokers increased from approximately 29,500,000 to 40,900,000 within this time period.

Trends in Cigarettes Consumed

In the United States, cigarettes are taxed at the wholesale level, in advance of retail sales. Tax data may not reflect retail sales in any particular year insofar as different inventory levels are held over time. However, the number of cigarettes taxed is a standard index used to estimate the number of cigarettes consumed over time. Total cigarette consumption as estimated by this index in the United States increased steadily from 1920 until 1981 when an estimated total of 640 billion cigarettes were smoked (Table 2). Since 1981, there has been a steady decline in consumption and the number of cigarettes smoked in 1987 is estimated at 574 billion.

These data are frequently divided by the population of adults 18 years of age and older to give a per capita estimate of consumption. It should be noted that this per capita estimate could be biased if there is a trend over time for more people to start smoking regularly under 18 years of age.

Since 1973, there has been a decline of 23 percent in the number of cigarettes smoked on a per capita basis. Although there has been a

TABLE 1.—Percentage of current cigarette smokers among adults, by year and survey, United States, 1944–1986

Year	Survey	Age (≥ years)	Current cigarette smokers (percentage)		
			Men	Women	Total
1944	GP	18	48.0	36.0	41.0
1949	GP	18	54.0	33.0	44.0
1955	CPS	18	54.2	24.5	37.6
1964	NCSH	21	52.9	31.5	40.3
1965	NHIS	17	51.1	33.3	41.7
1966	CPS	17	50.0	32.3	40.6
	NCSH	21	51.9	33.7	42.2
1967	CPS	17	49.1	32.1	40.1
1968	CPS	17	47.0	31.2	38.6
1970	NHIS	17	43.5	31.1	36.9
	NCHS	21	42.3	30.5	36.2
1974	NHIS	17	42.7	31.9	37.0
1975	NCSH	21	39.3	28.9	33.8
1976	NHIS	20	41.9	32.0	36.7
1978	NHIS	17	37.5	29.6	33.2
1980	NHIS	20	38.3	29.4	33.6
1983	NHIS	20	35.7	29.4	32.4
1985	CPS	16	31.8	25.4	28.4
	NHIS	20	33.2	27.9	30.4
1986	OSH	17	29.5	23.8	26.5

NOTE: GP, Gallup Poll; CPS, Current Population Survey (Supplement); NCSH, National Clearinghouse for Smoking and Health (Adult Use of Tobacco Survey); NHIS, National Health Interview Survey; OSH, Office on Smoking and Health (Adult Use of Tobacco Survey). NHIS data are not age adjusted.

SOURCE: US DHHS (1987c).

decline in every one of these 15 years, the rate of decline has varied from 0.2 to 7.2 percent with a mean of 1.9 percent per year (Table 2).

Trends in the Tar and Nicotine Content of Cigarettes Consumed

Data on the market share of cigarettes of different smoking machine determined tar and nicotine yield have been published by the Federal Trade Commission (FTC) from information supplied to the agency by cigarette companies. The FTC is no longer generating these data. Trends in the sales-weighted average yield of tar and nicotine for cigarettes sold are shown in Figure 1. The sales-weighted average represents the tar and nicotine content found in specific brands averaged by the quantity of sales for that specific brand.

Throughout the 1970s there was a steady decline in the sales-weighted average. This decline may have occurred because of consumer beliefs that lower-yield brands are less hazardous. The impression that low-yield brands may be less hazardous may have resulted in part from cigarette advertising implying that low-yield brands are less hazardous or safe (Davis 1987).

TABLE 2.—Total cigarette consumption and consumption per capita 18 years of age and older, 1973 to 1987, United States

Year	Total consumption (billions)	Per capita consumption (≥ 18 years old)	Per capita consumption change from previous year (percentage)
1973	589.7	4.148	
1974	599.0	4.141	-0.2
1975	607.2	4.123	-0.4
1976	613.5	4.092	-0.8
1977	617.0	4.051	-1.0
1978	616.0	3.967	-2.1
1979	621.5	3.861	-2.7
1980	631.5	3.844	-0.4
1981	640.0	3.836	-0.2
1982	634.0	3.739	-2.6
1983	600.0	3.488	-7.2
1984	600.4	3.446	-1.2
1985	594.0	3.370	-2.3
1986	583.8	3.274	-2.9
1987 (est.)	574.0	3.196	-2.4

SOURCE: USDA (1986).

From 1982 to 1985, the declining sales-weighted tar and nicotine yield leveled off. This change may be related to one or a combination of the following factors: (1) a persistent brand loyalty of some smokers to moderate- or high-yield brands because of brand image; (2) a diminishing perception that low-yield brands are less hazardous; (3) some smokers are now smoking cigarettes of such low tar and nicotine yields that further reductions in those yields may be unacceptable; i.e., the "lower boundary" of comfortable cigarette use has been reached (Kozlowski 1987; Chapter IV). The 1981 Surgeon General's Report (US DHHS 1981) cautioned that the health benefits of switching to low-yield brands are minimal compared with giving up cigarettes entirely.

Surveys of Self-Reported Cigarette Smoking in Adults

General Considerations

The validity of self-reported smoking status from community surveys affects the usefulness of these data in reporting historical trends. Respondents' sensitivity to social stigma associated with

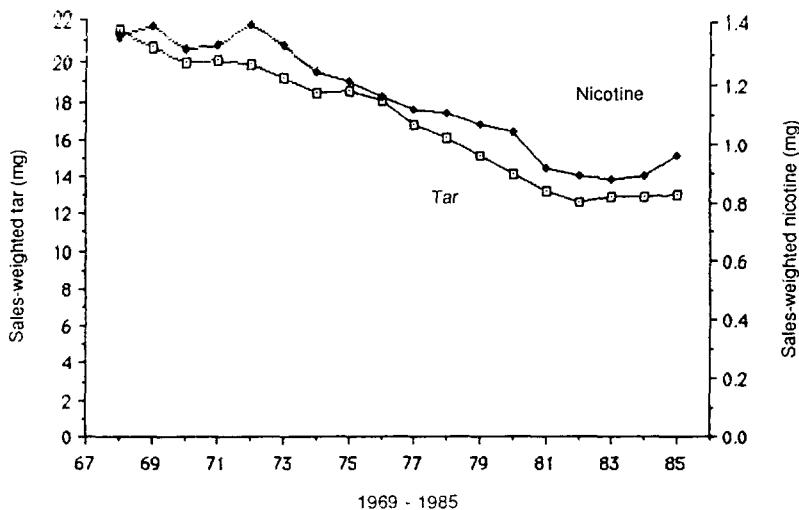


FIGURE 1.—Sales-weighted averages of tar and nicotine per cigarette, 1968–1985 (1985 data preliminary)

SOURCE: U.S. Federal Trade Commission (February 1988).

smoking is cited as a major reason why persons might underreport their smoking status (Warner 1978; Kozlowski 1986). Whereas biochemical assessment is significantly more reliable than self-reports in assessing level of nicotine intake (see Chapters II and IV), self-reported data appear valid for estimating prevalence of smoking in the population. For example, studies of patients in several settings (Petitti, Friedman, Kahn 1981; Pojer et al. 1984), as well as two large community studies (Fortmann et al. 1984; Pierce, Dwyer et al. 1987), have shown that measurements of smoking by self-report and biochemical markers give approximately the same estimates of prevalence. It is possible that the accuracy of self-reported data will vary depending on whether the data collection method is face-to-face or by telephone interview. However, biochemical validation data do not exist to allow quantification of such a difference. In addition, serious concerns have been expressed about the validity of data (Thornberry 1987) reported by one person on behalf of another (proxy response).

National Health Interview Surveys

The National Health Interview Survey (NHIS), which is conducted regularly by the National Center for Health Statistics, uses a

sampling frame developed by the U.S. Bureau of the Census and is based on a multistaged random probability sampling design. Information on behavioral health risk factors is collected in face-to-face interviews. Basic smoking information has been collected for several years, including 1965, 1976, 1978, 1979, 1980, 1983, and 1985 (data for 1965 are based on both self-report and proxy reporting; all of the more recent surveys were based on self-reports). The 1987 survey results were not available for this Report. Beginning in 1985, an adequate sample of blacks was ensured by the survey design (using the technique of oversampling). The NHIS generally has a response rate of 96 percent (Thornberry 1987). However, the smoking information is collected only by self-report in a supplement. This extra step in data collection procedures leads to a decrease in the response rate to approximately 90 percent.

Demographic Trends in Smoking Prevalence in Adults

Between 1965 and 1985, smoking prevalence decreased in all age, sex, and race categories with the exception of women aged 65 years and older (Table 3). This exception can be explained as a birth cohort effect (Warner and Murt 1982).

Both black and white males have decreased their smoking by an average of a percentage point per year over this 20-year period. However, in 1985, 41 percent of black males smoked, compared with 32 percent of white males. For all races, the largest decrease in smoking occurred in younger males; the 20- to 24-year-old age group decreased an average of 1.4 percentage points per year. The marked gradient in the degree of change per year across age groups suggests that a birth cohort effect may have occurred, with many more young males never having become regular smokers.

Proportionately fewer women smoke than men within every age group and race category except for persons 20 to 40 years old in 1985 (31.0 percent for men, 32.1 percent for women). However, the yearly rate of decline in smoking prevalence across these categories is, on average, three times less than the male rate of decline. Moreover, the decline in female smoking appears mainly in the under-44-year age group. This may indicate that uptake of smoking among women in the more recent birth cohorts is beginning to decline. Of particular importance is the almost complete lack of change in smoking prevalence among black women from 1965 to 1985.

Smoking rates among Hispanics have been reported using NHIS data (Marcus and Crane 1985, 1987), but the small sample size of this subpopulation reduces the reliability of the estimates. According to the 1985 NHIS, the prevalence of smoking among Hispanic males and females aged 18 and older was 31.3 percent and 20.8 percent, respectively (Marcus and Crane 1987). Information on Hispanic smoking is also available from the Hispanic Health and Nutrition

**TABLE 3.—Twenty-year trends in smoking prevalence
(percentage) among adults 20 years of age and
older, by sex, race, and age, United States**

Sex, race, age	1965	1976	1980	1985	Difference 1965–1985
Men					
Total ^{1,2}	52.1	41.6	37.9	32.7	-19.4
Race ¹					
White	51.3	41.0	37.1	31.8	-19.5
Black	59.6	50.1	44.9	40.6	-19.0
Age ²					
20–24	59.2	45.9	39.7	31.0	-28.2
25–34	60.7	48.5	43.1	38.2	-22.5
35–44	58.2	47.6	42.6	37.6	-20.6
45–64	51.9	41.3	40.8	33.4	-18.5
≥65	28.5	23.0	17.9	19.6	-8.9
Women					
Total ^{1,2}	34.2	32.5	29.8	28.3	-5.9
Race ¹					
White	34.5	32.4	30.0	28.3	-6.2
Black	32.7	34.7	30.6	31.6	-1.1
Age ²					
20–24	41.9	34.2	32.7	32.1	-9.8
25–34	43.7	37.5	31.6	32.0	-11.7
35–44	43.7	38.2	34.9	31.5	-12.2
45–64	32.0	34.8	30.8	29.9	-2.1
≥65	9.6	12.8	16.8	13.5	+3.9

¹ Age-adjusted prevalence rates.

² Includes white, black, and other.

SOURCE: U.S. PHS (1987).

Examination Survey (NHANES), which was conducted by the National Center for Health Statistics between 1982 and 1984. This study surveyed 9,000 Mexican-Americans in the Southwest, 4,000 Puerto Ricans in the Northeast, and 1,500 Cuban-Americans in Miami. For males aged 20 to 74 the age-adjusted smoking rates were 43 percent for Mexican-Americans, 42 percent for Cuban-Americans, and 40 percent for Puerto Rican-Americans. Among females, the smoking prevalence was 24 percent for Mexican-Americans and Cuban-Americans and 30 percent for Puerto Rican-Americans (Haynes 1987). Estimates of smoking prevalence among other minority groups may be unreliable because of small sample sizes included in the NHIS. Trend data are not available because Hispanic status was not ascertained on earlier surveys.

TABLE 4.—Smoking prevalence (percentage) among adults 18 years of age and older, by sociodemographic subgroups, United States, 1985

Subgroup	Men	Women	Total
Education			
Less than high school	40.1	31.4	35.4
High school graduate	36.6	31.0	33.4
Some college	29.9	24.9	27.3
College graduate	22.6	17.1	20.1
Postgraduate	17.3	15.1	16.5
Occupation			
Employed	33.8	30.0	32.1
White-collar	26.4	28.0	27.5
Blue-collar	40.1	33.9	39.7
Service	40.3	35.4	37.2
Unemployed	44.3	28.0	36.1
Not in workforce/Unknown	28.6	25.3	26.4
Marital status			
Never married	30.0	26.3	28.3
Divorced/Separated	48.2	42.4	44.7
Married/Cohabiting	31.9	27.7	29.7
Widowed	29.3	20.1	21.6
Income			
< \$10,000	36.3	29.7	32.3
\$10,000-19,999	37.0	29.8	33.1
\$20,000-34,999	33.1	28.1	30.7
≥ \$35,000	27.0	25.1	26.1

SOURCE: National Center for Health Statistics, National Health Interview Survey 1985.

Other Social Correlates of Smoking

The prevalence of smoking varies across sociodemographic categories. A detailed analysis of the sociodemographic correlates of smoking status in the 1985 NHIS survey is presented below.

Current smoking prevalence by sex, occupation, marital status, employment, education, and income groups for 1985 is shown in Table 4. Current smoking prevalence was inversely related to educational status. Persons who were employed were less likely to be current smokers than unemployed persons. Persons employed in white-collar jobs were less likely to be smokers than persons employed in blue-collar or service jobs. Persons with higher income and persons who were single, married, or widowed had a lower prevalence of smoking than persons with lower income or who were divorced or separated.

Because blacks were oversampled in the 1985 NHIS and subsequent sample designs, it is possible to make detailed comparisons

TABLE 5.—Percentage of current smokers in 1985, by age, race, and sex

Sex, age	White	Black
Men		
18-24	29.1	26.6
25-34	37.1	45.2
35-44	36.3	44.9
45-54	33.4	47.4
55-64	30.1	44.6
65-74	21.2	31.0
≥ 75	13.9	21.4
Women		
18-24	33.0	24.2
25-34	32.6	35.7
35-44	31.4	40.2
45-54	32.9	37.0
55-64	27.4	28.9
65-74	17.8	18.6
≥ 75	7.1	8.0

SOURCE: National Center for Health Statistics, National Health Interview Survey 1985.

between blacks and whites in smoking prevalence. Table 5 shows that across all age categories, except among those aged 18 to 24 years, blacks have higher smoking prevalence than whites. The lower smoking prevalence among blacks in this age group may reflect an older age of initiation among blacks.

In a multivariate analysis of NHIS data, controlling for sex, age, employment, poverty status, education, and marital status, blacks were no more likely to be ever smokers than whites (Novotny et al., in press). In this study, blacks were less likely than whites to quit smoking. Blacks also were less likely than whites to be heavier smokers (≥ 15 cigarettes per day).

Other Surveys Reporting Adult Prevalence of Smoking

The 1986 Adult Use of Tobacco Survey showed slightly lower rates of smoking than that expected from the trends observed in the National Health Interview Surveys (NHIS). These data, based on a telephone interview of 13,031 adults aged 17 and older, were weighted to reflect the U.S. population according to age, sex, education level, and region. An estimated 29.5 percent of males (95 percent confidence interval, 28.4 to 30.6) and 23.8 percent of females (95 percent confidence interval, 22.7 to 24.9) smoked cigarettes regularly. Differences from the NHIS may reflect differences in age of respondents (NCHS—age 18 and above, Adult Use Survey—age 17 and above), methodology (Waksberg 1978), or response rates (NCHS approximately 90 percent, Adult Use Survey approximately 74

percent). The exclusion of households lacking telephones appears to account for an underestimate of approximately 1 percentage point in telephone surveys; persons living in households without telephones have a higher smoking prevalence than those in households with telephones (US DHHS 1987c).

In 1985, a supplement to the Current Population Survey contained smoking information collected by household interviews. These data are particularly relevant because of the large sample population. However, 45 percent of responses were by proxy. Of the 114,342 persons surveyed, the overall smoking prevalence for persons 16 years of age and older was 31.8 percent for males and 25.4 percent for females (Table 1). A detailed analysis of this data set is available from the Office on Smoking and Health (Marcus and Crane 1987).

Since 1981, the Centers for Disease Control has coordinated the collection of State-specific data on several behavioral risk factors in the Behavioral Risk Factor Surveillance System (BRFSS). In 1986, 25 States and the District of Columbia participated in this telephone interview system (Table 6). Median State smoking prevalence among adults 18 years of age and older varied between 18 percent and 35 percent (US DHHS 1987c), with marked geographical distribution patterns. States east of the Mississippi appeared to have the highest smoking prevalences (US DHHS 1987d). These States also had the highest adult per capita consumption of cigarettes (Tobacco Institute 1986), as measured by sales of cigarettes taxed in each State.

Trends in Adolescent Smoking

The National Institute on Drug Abuse (NIDA) conducted household surveys on drug use in 1979, 1982, and 1985. Data were obtained from a stratified random sample of 8,000 U.S. households; approximately 2,000 interviews were conducted with respondents in the 12-to 17-year-old age group. Questions included whether any cigarettes were smoked within 30 days as well as within the previous year. These surveys indicated that approximately 26 percent of the teenage population surveyed smoked at least one cigarette at some time during 1985 (Table 7). In 1985, 15.6 percent of this population had smoked within the previous month. However, these overall mean values probably underestimate the level of experimentation and uptake of smoking during these ages due to response bias or underreporting. Comparisons with 1979 are not appropriate, because in that year, there was a markedly different definition of smoking compared with later years ("at least 100 cigarettes in lifetime" compared with "any smoking in last 30 days").

The "Monitoring of the Future" project, sponsored by NIDA, is conducted by the Institute for Social Research at the University of Michigan. It consists of a yearly survey of a representative sample of

TABLE 6.—Current smoking prevalence (percentage) in 25 States and the District of Columbia, 1986

State	Sample size	Current smokers			95 percent confidence interval
		Men	Women	Total	
Alabama	559	30.3	20.0	24.8	±4.1
Arizona	1,178	24.4	24.7	24.5	±2.8
California	1,579	25.4	23.9	24.6	±2.4
District of Columbia	1,145	32.1	22.5	26.7	±3.1
Florida	1,162	30.9	27.8	29.3	±2.8
Georgia	1,140	29.3	24.8	26.7	±2.9
Hawaii	1,551	27.8	20.3	24.1	±2.9
Idaho	1,185	30.9	16.2	23.4	±2.6
Illinois	1,142	32.7	23.6	27.9	±2.8
Indiana	1,182	31.6	23.5	27.3	±3.0
Kentucky	1,216	37.2	32.6	34.8	±3.2
Massachusetts	1,105	27.1	27.5	27.3	±3.0
Minnesota	3,023	25.3	25.0	25.1	±1.7
Missouri	873	29.4	23.0	26.0	±3.3
Montana	1,176	23.5	22.8	23.0	±2.7
New Mexico	1,139	29.9	22.4	26.1	±2.8
New York	1,135	28.7	26.1	27.4	±3.0
North Carolina	1,622	30.7	22.5	26.4	±2.4
North Dakota	1,182	27.4	25.1	26.2	±2.9
Ohio	1,158	29.4	26.9	28.1	±2.8
Rhode Island	1,535	31.0	31.1	30.9	±2.5
South Carolina	1,793	28.6	24.4	26.3	±2.4
Tennessee	1,779	30.7	25.5	28.0	±2.4
Utah	1,188	20.8	15.1	17.8	±2.5
West Virginia	1,380	32.2	26.9	29.5	±2.8
Wisconsin	1,268	31.5	21.1	26.2	±2.6

SOURCE: US DHHS (1987a).

high school seniors. This approach does not include students who do not complete high school (estimated to be about 15 percent of the population by the U.S. Bureau of Census in 1978). Dropouts tend to have a higher smoking prevalence than in-school students (Kandel 1980; Pirie, Murray, Luepker 1988); however, Johnston and O'Malley (1985) estimate that the underestimate of the true population prevalence is no more than 5 percentage points. The latter researchers argue that the magnitude of this bias is unlikely to change between the yearly surveys; thus, the estimate of the rate of change should reflect the true rate of population change.

Smoking prevalence among female high school seniors was higher than among males in 1986 (Table 8), and there are marked

TABLE 7.—Prevalence (percentage) of cigarette use among youth 12 to 17 years of age, 1979, 1982, 1985 surveys, United States

Survey year	Any use in last year	Used in last 30 days
1979 ¹	13.3	12.1
1982	24.8	14.7
1985	26.0	15.6

¹ The 1979 survey asked questions only of those who had smoked 100 cigarettes in their lifetime.

SOURCE: National Institute on Drug Abuse (1979, 1982, 1985).

TABLE 8.—Thirty-day prevalence of daily use of cigarettes by subgroups, high school class of 1986

Subgroups	N (approx.)	Percentage who used cigarettes daily in last 30 days	
		One or more	Half-pack or more
All seniors	15,200	18.7	11.4
Sex			
Men	7,100	16.9	10.7
Women	7,700	19.8	11.6
College plans			
None or under 4 years	5,100	28.2	19.2
Complete 4 years	9,100	12.8	6.4
Region			
Northeast	3,600	24.9	15.6
North-central	4,300	19.9	12.3
South	4,700	15.8	10.0
West	2,600	13.4	6.5

SOURCE: Johnston, O'Malley, Bachman (1987).

geographic differences in smoking prevalence among students. In addition, those students who plan to complete 4 years of college have a smoking rate less than half that of students without such plans.

The prevalence of daily use within the previous 30 days among high school seniors fell substantially from 1975 to 1986 for males and females (Figure 2). Since 1976, there has been an overall 35 percent reduction in smoking prevalence in this population. Most of this decline occurred between 1977 and 1981. For all students, the prevalence has fallen an average of 0.68 percentage points per year during this period (to 18.7 percent in 1986), similar to the rate of

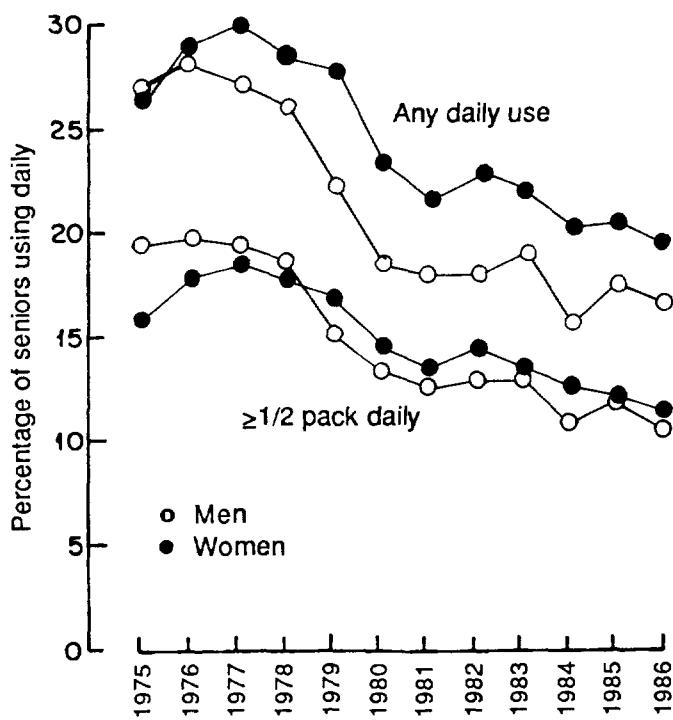


FIGURE 2.—Trends in 30-day prevalence of daily cigarette use (smoking one or more cigarettes/day) among high school seniors, by sex

SOURCE: Johnston, O'Malley, Bachman (1987).

decline noticed in adults (see Tables 1, 3). However, the rate of decline has tapered off in recent years. The smoking rates among females have consistently exceeded the rates among males.

The Monitoring of the Future Project has also followed representative samples from each graduating class since 1976. This was done by selecting two matched panels from each graduating class and following each panel in alternate years. The data obtained from these surveys are presented in Figure 3. Recently, differences in prevalence of any cigarette smoking within the last 30 days has disappeared between those still in high school and those who have graduated, suggesting that far fewer young adults are taking up smoking after high school, and that most uptake has occurred by the time of high school graduation. However, when either the 30-day prevalence of daily use or the 30-day prevalence of the use of half a

pack or more per day is considered, there is a clear marked increase in smoking prevalence in the early years after high school, suggesting that occasional and experimenting high school smokers become regular smokers once they leave school.

Trends in the Proportion of Smokers Who are Heavy Smokers

The average reported number of cigarettes smoked per day in 1985 by age, race, and sex is presented in Table 9. There are marked differences between the black and white population in the number of cigarettes reported. Both black males and females report smoking one-third fewer cigarettes per day than do their white counterparts. Even though blacks smoke fewer cigarettes per day than whites, their smoking patterns and choices of brands may provide the nicotine content necessary to maintain daily blood nicotine levels similar to whites (Chapter VII; Cummings, Giovino, Mendicino 1987). Across all race and age categories, females report smoking fewer cigarettes than males. In the over 35 age groups this difference is approximately 20 percent.

Successful quitting behavior may not be uniform across all smokers. Heavy smokers (defined as those who report smoking 25 or more cigarettes per day) are more likely to have a strong nicotine dependence (Chapter IV) and, therefore, are less likely to be successful at quitting than lighter smokers. Thus, one would expect the cross-sectional surveys over time to indicate an increasing proportion of heavy smokers as the smoking prevalence declined. These data from self-reported consumption measures are presented in Table 10. The percentage of heavy smokers reported by the 1965 survey may be biased due to the use of proxy interviews which were not used in subsequent surveys.

Between 1976 and 1985, there was no substantial change in the proportion of smokers reporting smoking 25 or more cigarettes per day. In 1985, approximately one-third of all male smokers and one-fifth of all female smokers were classified as heavy smokers. Three times as many white as black adults were classified as heavy smokers. For both males and females, the proportion peaked in the group aged 35 to 44, possibly indicative of a higher mortality rate among older smokers.

Trends in Quitting Activity

Public health efforts to reduce the prevalence of smoking concentrate on reducing the proportion of the population that begins to smoke cigarettes as well as increasing the proportion of smokers who quit. One indicator of quitting activity is the prevalence of former smokers. However, this variable is of limited use due to marked

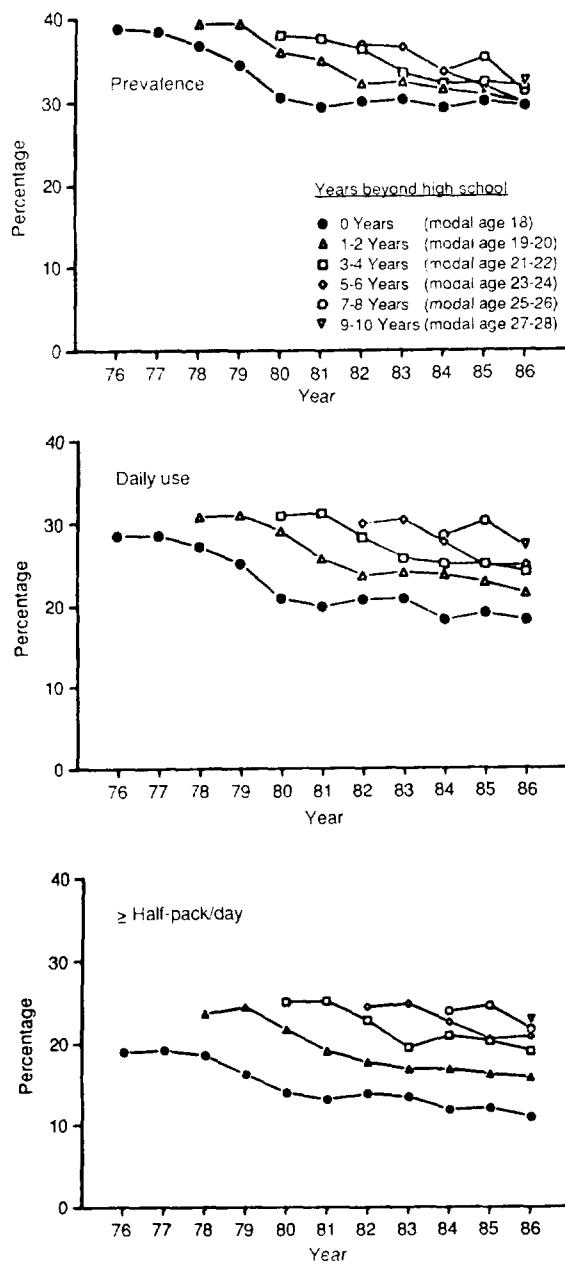


FIGURE 3.—Trends in 30-day cigarette smoking prevalence, daily use, and use of a half-pack or more per day among young adults, by age group

SOURCE: Johnston, O'Malley, Bachman (1987).

TABLE 9.—Average number of cigarettes smoked per day by current smokers, by race, age, and sex, United States, 1985

Race/Age	Men	Women	Difference
All races	21.8	18.1	3.7
Blacks	14.7	13.5	1.2
Whites	23.4	19.1	4.5
Age			
18-24	17.2	15.3	1.9
25-34	20.3	18.0	2.3
35-44	24.3	20.1	4.2
45-54	24.7	19.9	4.8
55-64	23.9	18.0	5.9
≥ 65	20.2	16.0	4.2

SOURCE: National Center for Health Statistics, National Health Interview Survey 1985.

TABLE 10.—Twenty-year trends in the proportion of smokers reporting smoking 25 or more cigarettes per day, by sex, race, and age, United States

Sex, race, age	1965	1976	1980	1985
Men				
Total	24.1	30.7	34.2	32.8
Race				
White	26.0	33.3	37.3	36.5
Black	8.6	10.8	13.8	10.7
Age				
20-24	15.4	18.5	19.8	17.1
25-34	24.3	28.7	30.1	28.5
35-44	31.5	39.2	40.7	42.3
45-64	28.0	37.4	42.6	39.3
≥ 65	13.8	18.2	25.2	25.4
Women				
Total	13.0	19.0	23.2	20.6
Race				
White	13.9	20.9	25.2	22.8
Black	4.6	5.6	8.6	6.7
Age				
20-24	9.7	14.5	15.9	12.2
25-34	15.5	20.5	24.2	21.3
35-44	17.1	21.8	32.7	27.8
45-64	13.6	21.5	24.9	22.7
≥ 65	6.4	11.8	13.1	13.4

SOURCE: National Center for Health Statistics, National Health Interview Surveys 1965, 1976, 1980, 1985.

differences in uptake of cigarettes between males and females in different birth cohorts (Warner and Murt 1982). A more meaningful index of quitting behavior has been defined as the quit ratio (Pierce, Aldrich et al. 1987)—the proportion of former smokers in a given population divided by the proportion of that population who have ever been smokers.

Trends in this quit ratio are presented in Figure 4. The quit ratio has consistently been higher among men compared with women. Quit ratios among both males and females increase with age. In 1985, nearly one-third of those persons aged 25 to 34 who reported that they had ever smoked had quit smoking by 1985. Among those aged 65 or older, the quit ratio was over 60 percent for women and 70 percent for men. Moreover, over the last 20 years, successful quitting activity has been increasing in all age groups. The quit ratio differences between men and women increased with age from 1965 to 1985 (several possible explanations for this phenomenon exist; see Chapter VII).

Trends in Cigar, Pipe, and Roll-Your-Own Cigarette Smoking

Figure 5 shows 20-year trends in pipe and cigar smoking among adult males. For both tobacco products, there has been an 80 percent decline in prevalence. In fact, cigar smoking in 1964 (30 percent) was as prevalent as cigarette smoking in 1985 (30.4 percent).

Hand-rolled cigarettes are the least expensive cigarettes to consume. According to the 1986 Adult Use of Tobacco Survey, only 0.4 percent of smokers aged 17 and older use roll-your-own cigarettes (US DHHS 1988).

Trends in Smokeless Tobacco Use

The prevalence of both snuff and chewing tobacco use by younger men has increased substantially between 1970 and 1986, as shown in Figure 6. Among women, use of smokeless tobacco products decreased between 1970 and 1986, but prevalence of use in this group has always been low. In 1986, less than 0.4 percent of females used snuff or chewing tobacco, whereas 8.2 percent of men used these products (Novotny and Lynn, *in press*). Additionally, among men, almost half of current users reported initiation of smokeless tobacco use before age 17 (Table 11).

In 1985, the NIDA National Household Survey of persons 12 years of age and older found that 12 percent of men and 1 percent of women used chewing tobacco, snuff, or other kinds of smokeless tobacco in the year of the survey. Smokeless tobacco use rates were highest among young males (12–25 years old) who were residents of nonmetropolitan areas (Rouse, *in press*).

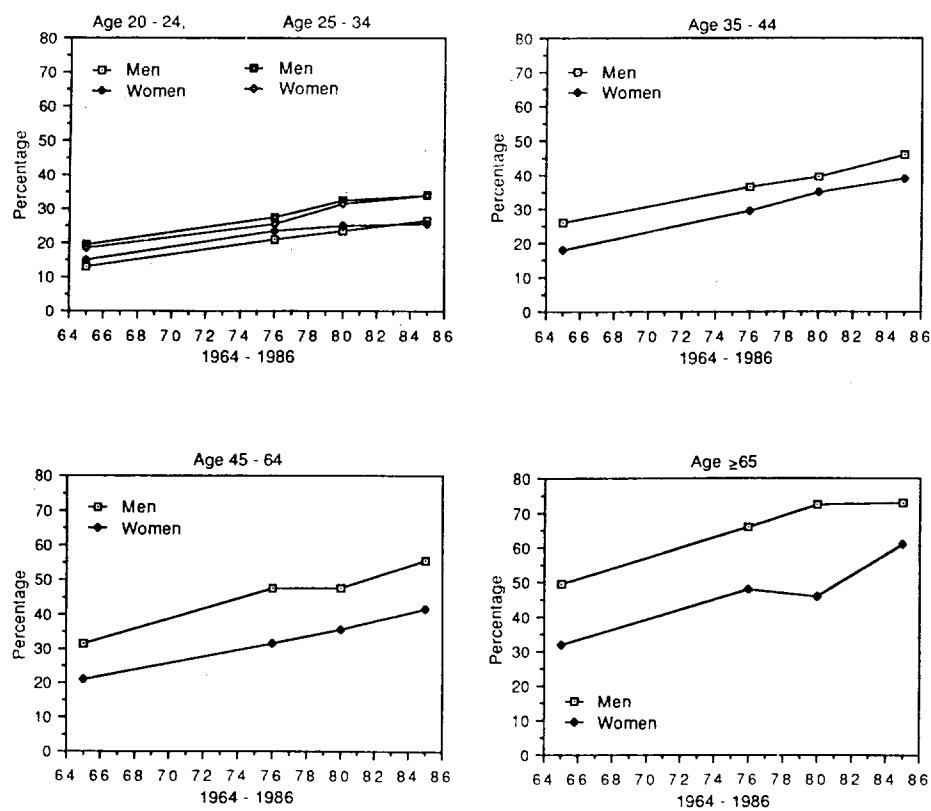


FIGURE 4.—Quit ratios (ratios of former smokers to ever smokers), by age and sex, 1965–1985

SOURCE: U.S. DHHS (1986b).

The BRFSS collected data from 25 States and the District of Columbia in 1986. In this survey, smokeless tobacco use among men ranged from 0.7 percent in New York to 21.4 percent in West Virginia (median State prevalence, 6.5 percent) (US DHHS 1987b). In addition, there was a regional pattern of use, with highest

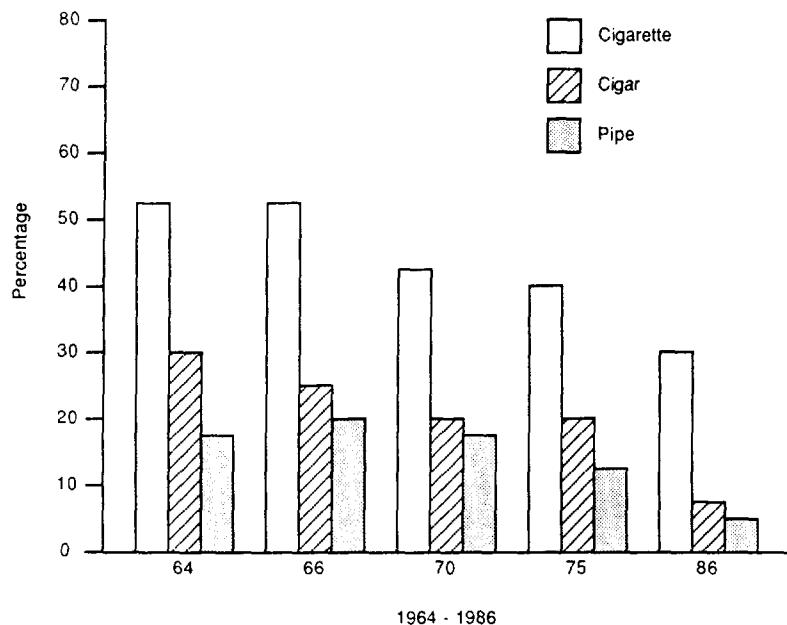


FIGURE 5.—Trends in prevalence of cigarettes, cigars, and pipes, adult men, 1964–1986

SOURCE: U.S. PHS (1970, 1975, 1986), U.S. DHHS (1987a).

prevalence found in Southern and North Central States, just as in the NIDA survey mentioned above.

Summary and Conclusions

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.

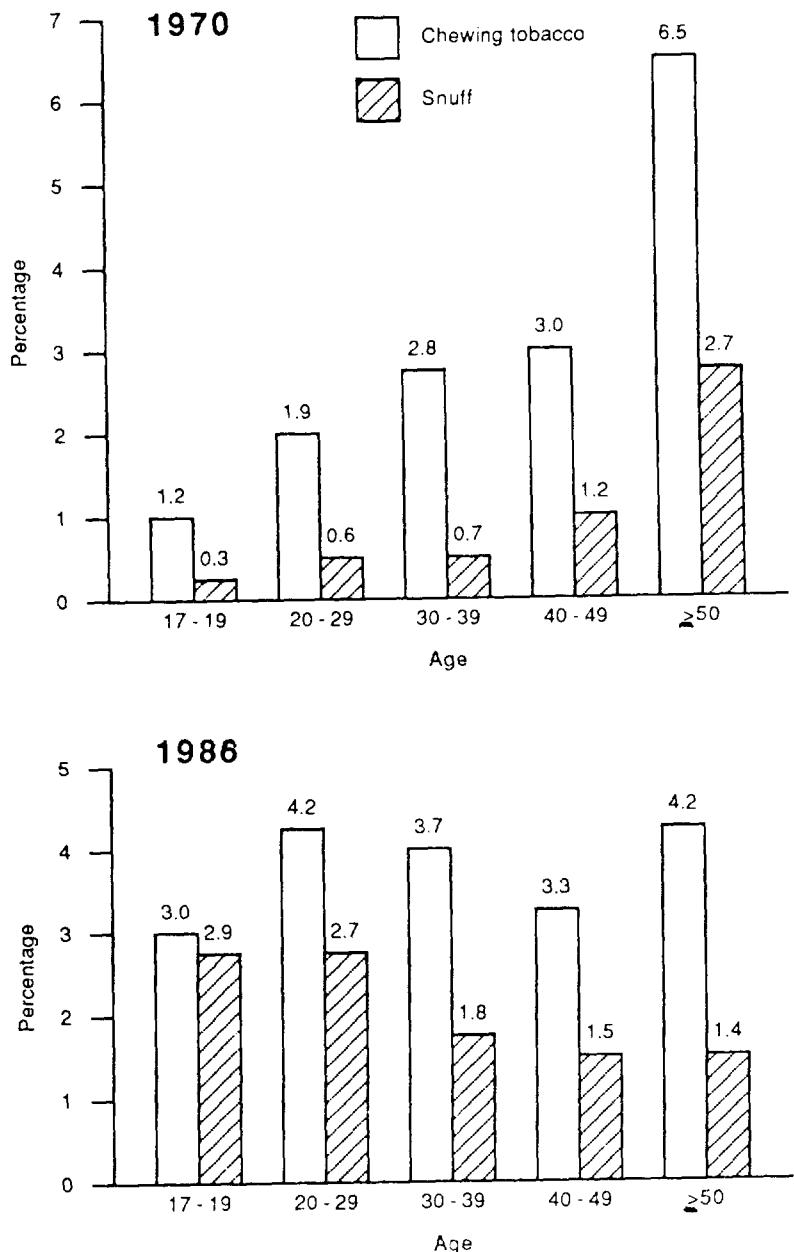


FIGURE 6.—Prevalence of chewing tobacco and snuff use among men, 1970 and 1986

SOURCE: U.S. DHHS (1986a); Novotny and Lynn (in press).

TABLE 11.—Reported age at initiation, by current smokeless tobacco users (percentage), both sexes, 1986, United States

Age at initiation	Any smokeless tobacco	Chewing tobacco	Snuff
<17 years	44.3	42.5	43.5
17-24 years	37.9	27.3	35.1
≥ 25 years	17.8	30.2	21.4

SOURCE: Novotny and Lynn. (in press).

- 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; the smoking prevalence among females has consistently been slightly higher than among males. Most of the decline occurred between 1977 and 1981.
- 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.

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APPENDIX B

TOXICITY OF NICOTINE

CONTENTS

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Introduction

Knowledge of the toxicity of nicotine is important to help understand tobacco-induced human disease as well as to assess the potential risks associated with the therapeutic use of nicotine (e.g., nicotine polacrilex gum) as an aid to assist smoking cessation.

This Appendix provides a brief overview of the toxic actions of nicotine per se, focusing on human studies wherever possible and selecting only those animal data which have direct implications in understanding mechanisms of human disease. The toxicity of cigarette smoke has been extensively reviewed in prior Surgeon General's reports (US DHHS 1982, 1983, 1984, 1985, 1986). In most cases the pathogenesis of tobacco-related diseases, including the role of nicotine, has not been fully elucidated. Therefore the potential contribution of nicotine to development of tobacco-related disease, even if unproved, will be considered.

The chemistry and general pharmacology of nicotine have been reviewed in previous chapters (Chapters II and III) of this report and are not presented in detail in this Appendix. An appreciation of the basic pharmacologic actions of nicotine is, however, a necessary foundation for understanding the issues of toxicity which are discussed in this Appendix.

Acute Intoxication

As discussed in Chapter II, nicotine is a water and lipid soluble drug which, in the free base form, is readily absorbed via respiratory tissues, skin, and the gastrointestinal tract. Nicotine may pass through skin or mucous membranes when in alkaline solutions, in which circumstance nicotine is primarily un-ionized.

In experimental animals, the dose of nicotine which is lethal to 50 percent of animals (LD_{50}) varies widely, depending on the route of administration and the species used. Intravenous (i.v.) LD_{50} doses of nicotine in mice range between 0.3 to 1.8 mg/kg body weight (Borzellica, Borman, McKennis 1962; Lindner 1963; Wirth and Gosswald 1965; Barlow and McLeod 1969). The intraperitoneal (i.p.) LD_{50} values for nicotine bitartrate in mice and rats have been found to be 13 and 83 mg/kg body weight, respectively, while the values for five inbred hamster strains varied between 125 to 320 mg/kg body weight (Bernfeld and Homburger 1972). The wide variation in sensitivity to the toxic effects of nicotine in rodents appears to be genetically determined (Garg 1969; Marks, Burch, Collins 1983; Miner, Marks, Collins 1984).

In interpreting animal toxicity data it is important to recognize that the rate of administration is an important determinant of toxicity. Rapid i.v. injections result in the highest blood and brain concentrations and produce toxicity at the lowest doses. In contrast,

with oral or i.p. administration higher doses are required to produce toxicity. This is due to presystemic ("first pass") metabolism of nicotine and the gradual time course of absorption as compared with after i.v. dosing. With intermittent dosing, such as practiced by smokers, the total dose of nicotine absorbed per day could exceed the toxic or even lethal dose of a single injection.

In humans, acute exposure to nicotine even in low doses (similar to the amounts consumed by tobacco users) elicits autonomic and somatic reflex effects as described in detail in Chapters II and III. Dizziness, nausea, and/or vomiting are commonly experienced by nonsmokers after low doses of nicotine, such as when people try their first cigarette. However cigarette smokers rapidly become tolerant to these effects (Chapter II).

A number of poisonings and deaths from ingestion of nicotine, primarily involving nicotine-containing pesticides, have been reported in humans (Beeman and Hunter 1937; McNally 1923; Franke and Thomas 1936; Saxena and Scheman 1985). The lethal oral dose of nicotine in adults has been quoted to be 40 to 60 mg (Goldfrank, Melinek, Blum 1980; Larson, Haag, Silvette 1961), but it has not been well documented. Nicotine intoxication produces nausea, vomiting, abdominal pain, diarrhea, headaches, sweating, and pallor. More severe intoxication results in dizziness, weakness, and confusion, progressing to convulsions, hypotension, and coma. Death is usually due to paralysis of respiratory muscles and/or central respiratory failure.

Dermal exposure to nicotine can also lead to intoxication. Such exposures have been reported after spilling or applying nicotine-containing insecticides on the skin or clothes (Lockhart 1933; Faulkner 1933; Benowitz et al. 1987) and as a consequence of occupational contact with tobacco leaves.

Green tobacco sickness, an occupational illness in field workers harvesting tobacco leaves, has been attributed to dermal absorption of nicotine found in the dew on tobacco leaves (Weizenecker and Deal 1970; Gehlbach et al. 1974). The levels of cotinine in the urine of exposed workers exceed those of novice smokers who had smoked three cigarettes in succession (Gehlbach et al. 1975). The symptoms of green tobacco illness are described in Table 1 (Gehlbach et al. 1975; Gehlbach, Williams, Freeman 1979). A similar syndrome has been reported in Asian Indian tobacco workers who harvest green tobacco leaves and handle cured tobacco (Ghosh et al. 1979).

Tobacco harvesters who use tobacco products, either in the forms of cigarettes or smokeless tobacco, are usually not affected by green tobacco sickness owing to development of tolerance to nicotine (Gehlbach et al. 1974). Tolerance to the toxic effects may even develop during the course of nicotine poisoning, despite the persis-

TABLE 1.—Symptoms of systemic nicotine poisoning (Green Tobacco Sickness)

Symptom	Percentage (53 cases)
Nausea, vomiting	98
Pallor	89
Weakness	81
Dizziness, lightheadedness	81
Headache	81
Sweating	56
Abdominal pain	42
Chills	36
Increased salivation	17

SOURCE: Adapted from Gehlbach et al. (1974).

tence of nicotine in the blood at extremely high concentrations (200 to 300 ng/ml) (Benowitz et al. 1987).

Acute intoxication may occur in children following ingestion of tobacco materials. Four children, each of whom ingested two cigarettes, developed salivation, vomiting, diarrhea, tachypnea, tachycardia, and hypertension within 30 min; followed by depressed respiration and cardiac arrhythmia within 40 min; and convulsions within 60 min (Malizia et al. 1983). All recovered and suffered no complication. Another six children who ingested one-half of a cigarette experienced salivation and vomiting only. In a Swedish report (Werner 1969), 355 children who ingested tobacco had only very mild symptoms. Severe poisoning has occurred in children who swallowed tobacco juice (expectorated by tobacco chewers). Although ingestions of tobacco are common, deaths due to ingestion of tobacco are extremely rare, due to early vomiting and first pass metabolism of the nicotine which is absorbed.

Conceivably, intoxication from nicotine polacrilex gum could occur after accidental use by children or nonsmokers, or if an ex-smoker gum-user consumed several pieces at once or in rapid succession. One case report describes a smoker who developed apparent symptoms of nicotine intoxication within 1 min of chewing a piece of 2-mg gum (Mensch and Holden 1984). However, based on the known absorption kinetics and the amount of nicotine in the gum, true nicotine intoxication is unlikely in this case.

Swallowing nicotine polacrilex gum appears not to be of concern for development of toxicity. Although 30 to 85 percent of the nicotine content can be released from the gum into the gastrointestinal tract, the chances of nicotine intoxication are quite low because nicotine is

released slowly (transit time of the gums through the gastro-intestinal tract is 16 to 48 hr) (Brantmark and Fredholm 1974), and because the nicotine which is released undergoes extensive presystemic metabolism. Simultaneous ingestion of 10 unchewed pieces of 4-mg gum resulted in a peak blood concentration of nicotine of less than 10 ng/ml (Brantmark and Fredholm 1974), which is similar to the level attained by a smoker after smoking a single cigarette.

Chronic Nicotine Toxicity

As attested to in the Surgeon General's reports since 1964, smoking causes coronary and peripheral vascular disease (1983), cancer (1982), chronic obstructive lung disease (1984), peptic ulcer disease, and reproductive disturbances, including prematurity (1980). Tobacco smoke is a complex mixture of chemicals, including carbon monoxide, many of which have been implicated in human disease. Nicotine may contribute to tobacco-related disease, but direct causation has not been determined because nicotine is taken up simultaneously with a multitude of other potentially harmful substances that occur in tobacco smoke and smokeless tobacco.

However, particularly now that nicotine per se may be prescribed in the form of gum or other delivery systems, the potential health consequences of chronic nicotine exposure deserve careful consideration.

Cardiovascular Disease

Smoking causes coronary and peripheral vascular disease (US DHHS 1983). Both nicotine and carbon monoxide may contribute to atherosclerotic vascular disease (Figure 1). Nicotine could contribute both to the atherosclerotic process and to acute coronary events by several mechanisms. Nicotine could promote atherosclerotic disease by its actions on lipid metabolism and coagulation, by hemodynamic effects, and/or by causing endothelial injury. Compared to nonsmokers, cigarette smokers have elevated low-density (LDL) and very-low-density lipoproteins (VLDL), as well as reduced high-density lipoprotein (HDL) levels (Criqui et al. 1986; Brischetto et al. 1983), a profile associated with an increased risk of atherosclerosis. Chronic oral nicotine feeding has been shown to increase LDL in monkeys (Cluette-Brown et al. 1986). In one patient the use of nicotine polacrilex gum was reported to increase serum total and LDL cholesterol and triglycerides (Dousset, Gutierrez, Dousset 1986). Nicotine may act by releasing free fatty acids, enhancing the conversion of VLDL to LDL, impairing the clearance of LDL and/or by accelerating the metabolism of HDL (Brischetto et al. 1983; Cluette-Brown et al. 1986; Gnasso et al. 1986; Hojnacki et al. 1986).

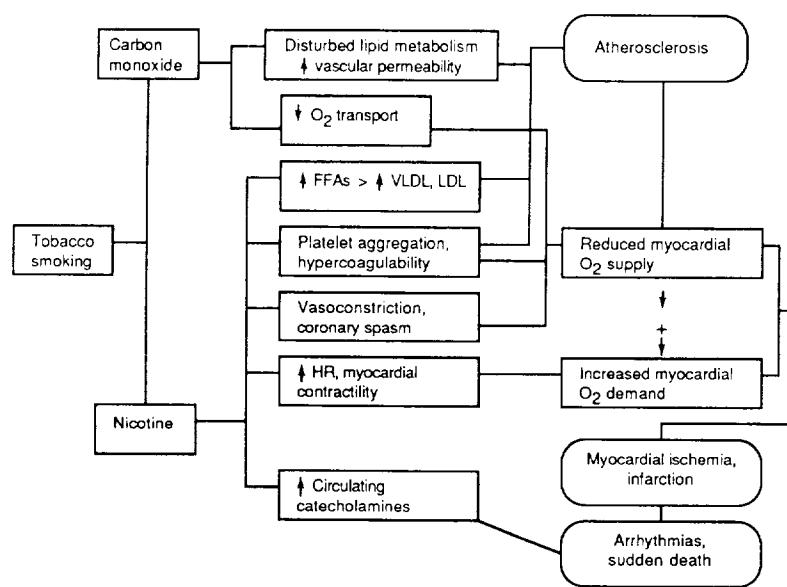


FIGURE 1.—Smoking, nicotine, and coronary heart disease

SOURCE: Benowitz (1986d).

Thrombosis is believed to play an important role in atherogenesis (Mehta and Mehta 1981). Platelets may release a growth hormone which promotes the growth of vascular endothelial cells, contributing to the atherosclerotic plaque (Packham and Mustard 1986). The blood of smokers is known to coagulate more readily than the blood of nonsmokers (Billimoria et al. 1975). According to several studies, platelets of smokers are more reactive, and have a shorter survival than those of nonsmokers (Belch et al. 1984; Siess et al. 1982; Mustard and Murphy 1963). The importance of nicotine as a determinant of platelet hyperaggregability is supported by a study showing that the blood concentrations of nicotine, after smoking different cigarettes, correlated with the platelet aggregation response (Renaud et al. 1984). Nicotine could affect platelets by increasing the release of epinephrine, which is known to enhance platelet reactivity, by inhibiting prostacyclin, an antiaggregatory hormone secreted by endothelial cells, or perhaps directly (Cryer et al. 1976; Sonnenfeld and Wennmalm 1980). Alternatively, by increasing heart rate and cardiac output and thereby increasing blood turbulence or by direct action nicotine may promote endothelial injury.

Structural damage and increased mitotic activity in the aortic endothelial cells of nicotine-treated animals have been reported (Booyse, Osikowicz, Quarfoot 1981; Zimmerman and McGeachie 1985, 1987). Nicotine has also been shown to modulate the structural and functional characteristics of cultured vascular cells (Csonka et al. 1985; Thyberg 1986). In rats, nicotine given i.v. or per os p.o. produced dose-dependent increases in circulating anuclear carcasses of endothelial cells (Hladovec 1978). In support of the relevance of animal or *in vitro* studies to humans, Davis and colleagues (1985) reported an increase in the number of endothelial cells found in venous blood (reflecting endothelial injury) and a decrease in the platelet aggregate ratios (reflecting platelet aggregation) in nonsmokers who smoked tobacco but not nontobacco (made from wheat, cocoa, and citrus plants) cigarettes.

The above findings suggest that some substance unique to tobacco, such as nicotine, may contribute to the pathogenesis of atherosclerosis and complications of atherosclerotic vascular disease. Although several potential mechanisms by which nicotine may promote atherogenesis have been considered, nicotine has not been demonstrated to produce or accelerate atherosclerosis in experimental animals. Wald and colleagues (1981) have presented an argument against the role of nicotine in promoting coronary heart disease in that pipe smokers, who consume comparable amounts of nicotine and have similar levels of nicotine but lower levels of carbon monoxide in the blood as cigarette smokers, do not share the same magnitude of increased risk for coronary heart disease. However, the possibility that nicotine inhaled in cigarette smoke, either due to rapid absorption or effects on pulmonary afferent nerves, affects the cardiovascular system differently than nicotine absorbed more slowly through mucous membranes must be considered (Benowitz and Jacob 1987).

Based on its pharmacologic actions, it is likely that nicotine plays a role in causing or aggravating acute coronary events. Myocardial infarction can be due to one or more of three precipitating factors – excessive oxygen and substrate demand, thrombosis, and coronary spasm. Nicotine increases heart rate and blood pressure and, therefore, myocardial oxygen consumption. Carbon monoxide inhaled in cigarette smoke reduces the oxygen carrying and releasing capacity of the blood. When a healthy person smokes a cigarette, coronary blood flow increases to meet the increased demand (Nicod et al. 1984). In the presence of coronary artery stenosis, coronary blood flow cannot increase and ischemia may develop, resulting in angina pectoris, myocardial dysfunction, or myocardial infarction (Jain et al. 1977). Nicotine may also directly reduce the increase in coronary blood flow which occurs in response to increased metabolic demand, or even cause an inappropriate decrease in coronary blood

flow, so that flow no longer matches increased myocardial oxygen consumption (Kaijser and Berglund 1985; Klein et al. 1984; Nicod et al. 1984; Martin et al. 1984). The decrease in coronary blood flow with smoking appears to result from alpha-adrenergically mediated coronary vasoconstriction, due to sympathetic activation and/or increased circulating catecholamines, either of which is likely to be an effect of nicotine (Winniford et al. 1986). Chronic nicotine exposure has been reported to increase the size of experimentally induced myocardial infarcts in dogs (Sridharan et al. 1985).

Nicotine consumed in the form of nicotine gum has been studied in patients with coronary artery disease. Nicotine gum (4-mg) increased myocardial contractility in healthy people, but in patients with coronary artery disease nicotine gum decreased contractility in the ischemic regions of the myocardium, consistent with aggravation of ischemia (Bayer, Bohn, Strauer 1985). In the most severe cases of coronary artery disease, overall contractility decreased after nicotine polacrilex gum. This study supports the idea that nicotine contributes to smoking-induced myocardial ischemia in susceptible people.

In addition to creating an imbalance between myocardial oxygen supply and demand, nicotine may promote thrombosis, as discussed previously. Nicotine may also induce coronary spasm by sympathetic activation or inhibition of prostacyclin. Coronary spasm has been observed during cigarette smoking (Maouad et al. 1984).

Sudden cardiac death in smokers might result from ischemia, as discussed above, combined with the arrhythmogenic effects of increased amounts of circulating catecholamines released by nicotine. However, smoking has not been demonstrated to increase the prevalence or magnitude of ventricular ectopy in patients with ischemic heart disease (Davis et al. 1985; Meyers et al. 1988). Cigarette smoking, most likely mediated by nicotine, facilitates AV nodal conduction, which could result in an increased ventricular response during atrial fibrillation (Bekheit and Fletcher 1976; Peters et al. 1988). Thus, even if the frequency of arrhythmias is not increased by smoking, the actions of nicotine may render those arrhythmias which do occur more life-threatening.

With respect to the arrhythmogenicity of nicotine, two case reports are of note. The first concerns a man who developed atrial fibrillation with a rapid ventricular response rate (150) while chewing 30 pieces of 2-mg nicotine polacrilex gum per day (Stewart and Catterall 1985). The other case was that of a man with known paroxysmal atrial fibrillation who developed a recurrence 5 min after chewing the day's first piece of nicotine gum (Rigotti and Eagle 1986).

Cigarette smoking has been associated with an increased risk of cardiomyopathy, that is a generalized reduction in contractility of

heart muscle (Hartz et al. 1984). Cigarette smoke exposure induces cardiomyopathy in rabbits (Gvozdjáková et al. 1984). A role of nicotine is suggested by a study in which dogs received injections of nicotine for 22 months and developed impaired contraction of the heart muscle with evidence of some interstitial fibrosis on anatomical examination (Ahmed et al. 1976).

Exercise tolerance in patients with intermittent claudication improves after stopping cigarette smoking (Jonason and Bergström 1987; Quick and Cotton 1982). Nicotine could aggravate peripheral vascular disease by constricting small collateral arteries and/or by inducing local thrombosis. The effect of nicotine replacement therapy on symptoms of peripheral vascular disease, as on exercise tolerance, in comparison to cigarette smoking, requires further investigation.

On balance, short-term nicotine administration, such as nicotine replacement therapy as an adjunct to smoking cessation therapy, presents little cardiovascular risk to healthy individuals. Patients with coronary or peripheral vascular disease are likely to suffer some increase in risk when taking nicotine, but considerably less risk than with cigarette smoking, which exposes them also to both carbon monoxide and higher levels of nicotine.

Hypertension

Although cigarette smoking and nicotine per se increase blood pressure, cigarette smoking alone is not a risk factor for chronic hypertension (Green, Jucha, Luz 1986). Conceivably, factors such as lower body weight or altered dietary intake, which may be associated with cigarette smoking, might lower blood pressure to compensate for any blood pressure elevation due to nicotine.

However, progression of chronic hypertension to accelerated or malignant hypertension is much more likely in cigarette smokers (Isles et al. 1979; Petitti and Klatsky 1983). Nicotine could contribute to this progression by aggravating vasoconstriction, either via sympathetic activation or inhibition of prostaglandin synthesis. Animal studies indicate that nicotine may reduce renal blood flow which, in a patient with marginal renal blood flow due to hypertensive vascular disease, could cause renal ischemia and aggravate hypertension (Downey, Crystal, Bashour 1981). Thus, there is concern about nicotine replacement therapies in patients with severe hypertension.

Tobacco, most likely due to effect of nicotine, may interact with particular hypertensive diseases. For example, a patient with pheochromocytoma (a catecholamine-secreting tumor) developed paroxysmal hypertension and angina pectoris following the use of oral snuff (McPhaul et al. 1984). Within 10 min, blood pressure increased from 110/70 mmHg to 300/103 mmHg and heart rate from

70 to 110. Rechallenge with snuff after surgical removal of the pheochromocytoma revealed only a mild blood pressure increase. Another patient with previously controlled essential hypertension presented with a blood pressure of 210/115 mmHg prior to surgery (Wells et al. 1986). A mass of snuff was found in the patient's cheek. The snuff was removed and blood pressure returned to 150/85 mmHg within 15 min.

Wound Healing

Adequate blood flow to the skin is important for wound healing. Cigarette smoking and nicotine polacrilex gum reduce skin blood flow (Fredholm and Sawe 1981; Allison and Roth 1969; Carlsson and Wennmalm 1983). In rats, exposure to cigarette smoke decreases survival of surgical flaps (Kaufman et al. 1984; Lawrence et al. 1984; Craig and Rees 1985). Cigarette smoking has been associated with a twelvefold increased risk of experiencing skin slough after facelift surgery (Rees, Liverett, Guy 1984). It is conceivable that nicotine substitution therapy might also delay wound healing, but no human data are as yet available.

Reproductive Hazards

Teratogenicity

Nicotine rapidly crosses the placenta and enters the fetus (Suzuki et al. 1974). Nishimura and Nakai (1958), Landauer (1960), and Khan and coworkers (1981) have described teratogenic effects of high doses of nicotine, which interfered with skeletogenesis in mice and chick embryos. Chronic nicotine treatments of pregnant rats throughout gestation produced subtle neurological changes which manifested themselves as behavioral or electrophysiological alterations in the offspring (Peters and Ngan 1982; Hudson, Meisami, Timiras 1973; Martin and Becker 1971). Wang, Chen, and Schraufnagel (1984) found that pre- and postnatal exposure to nicotine induced structural changes in the lungs of fetal mice. Maternal exposure to nicotine also inhibited glucose metabolism in fetal lung tissue (Maritz 1986). Thus, several studies suggest that nicotine, at least in high doses, may have toxic effects on the fetus.

Whether cigarette smoking is associated with increased rates of congenital malformations in humans is controversial. Several studies show no association or a lower incidence of malformations in offspring of smoking mothers (Comstock and Lundin 1967; Goujard, Rumeau, Schwartz 1975; Meyer and Tonascia 1977; Evans, Newcombe, Campbell 1979; Shiono, Klebanoff, Berendes 1986; Hemminki, Mutanen, Salonen 1983), but others report positive associations (Himmelberger, Brown, Cohen 1978; Fedrick 1978; Kelsey et al. 1978). One study has reported an association between paternal

smoking and the incidence of congenital malformations (Mau and Netter 1974).

Pregnancy

Cigarette smoking during pregnancy increases the risk of low birth weight, prematurity, spontaneous abortion, and perinatal mortality in humans, which has been referred to as the fetal tobacco syndrome (Nieburg et al. 1985) (also reviewed in detail in the 1980 Surgeon General's Report). Nicotine influences implantation and embryo development in some laboratory animal studies (Hudson and Timiras 1972; Card and Mitchell 1979; Hammer and Mitchell 1979). At least one adverse outcome, reduced birth weight, is correlated with the level of cotinine, the major metabolite of nicotine, in the mother's serum (Haddow et al. 1987).

Nicotine in high concentrations markedly decreases the in vitro development of rabbit preimplantation embryos and inhibits DNA synthesis (Balling and Beier 1985). Injection of nicotine, 7.5 mg twice each day from proestrus through pregnancy in rats, resulted in a delay in the entry of the ovum into the uterus, implantation, and subsequent development of the ovum (Yoshinaga et al. 1979). It was suggested that nicotine acted by delaying progesterone secretion, which is necessary to prepare the uterus for implantation, and by other disturbances of hormone release. Another study in rats reported that low doses of nicotine injected subcutaneously (0.1 mg/kg/day) from day 14 to the end of pregnancy had no effect on litter size or fetal development, but higher doses (1 mg/kg/day), comparable to those consumed by heavy smokers, reduced litter size and increased the number of still births (Hamosh, Simon, Hamosh 1979). Further research is needed to determine if there are direct adverse effects of nicotine on the embryo or fetus at levels of nicotine comparable to those observed in cigarette smokers.

A likely mechanism for the reproductive problems in pregnant cigarette smokers is placental insufficiency, which is supported by evidence of placental hypoperfusion in cigarette smoking mothers (Naeye 1978; Philipp, Pateisky, Endler 1984). The factors most likely to affect the placenta are carbon monoxide and nicotine, both agents having the potential of impairing oxygen supply to the fetus.

Inhalation of carbon monoxide results in elevation of both maternal and fetal carboxyhemoglobin (Asmussen and Kjeldsen 1975; Longo 1977). Nicotine infusion in pregnant sheep increases uterine vascular resistance and reduces uterine blood flow, effects which appear to be mediated by catecholamine release (Ayromloo, Desiderio, Tobias 1981; Resnick, Brink, Wilkes 1979). Both cigarette smoking and nicotine gum increase fetal heart rate during the second trimester in humans, consistent with sympathetic activation (Lehtovirta et al. 1983). During the third trimester in humans,

cigarette smoking or nicotine gum chewing decreases fetal heart rate and reduces fetal breathing movements, both of which may be signs of fetal hypoxia (Lehtovirta et al. 1983; Gennser, Marsal, Brantmark 1975; Manning and Feyerabend 1976). Elevated levels of catecholamines in amniotic fluid in human smokers during the third trimester indicate sympathetic activation in the fetus, consistent with fetal hypoxia and/or direct effects of nicotine (Divers et al. 1981). The above findings suggest that nicotine contributes to the adverse effects of cigarette smoking on reproduction probably by acting on the utero-placental circulation. Besides producing functional changes, carbon monoxide and nicotine might also be responsible for the injury to the intimal ultrastructure of the umbilical artery seen in smoking mothers (Asmussen and Kjeldson 1975). Fetal hypoxemia has also been considered as a contributory cause of behavioral abnormalities, such as hyperactivity, short attention span, lower scores on spelling and reading tests, which occurred at a higher frequency in children whose mothers had smoked throughout pregnancy than in those born to nonsmoking mothers (Naeye and Peters 1984).

Pulmonary Toxicity

Cigarette smoking is the major cause of chronic obstructive lung disease (US DHHS 1984). Nicotine may directly or indirectly influence the development of emphysema in smokers. It rapidly accumulates in the pulmonary epithelial cells and some of its metabolites are retained in the lung for prolonged periods (Waddell and Marlowe 1976; Szuts et al. 1978).

Chronic bronchial wall inflammation with accumulation of alveolar macrophages and polymorphonuclear neutrophils into the lung occur in response to habitual cigarette smoke exposure (Janoff 1983, 1985). Macrophages and neutrophils release elastase, an enzyme that destroys alveolar structure. Stone and colleagues (1983) found that alpha-1-antitrypsin, an inhibitor of elastase, may also be partially inactivated by cigarette smoke, probably related to effects of oxidant gases. Nicotine, which possesses chemotactic properties for neutrophils (Totti et al. 1984; Jay, Kojima, Gillespie 1986) and can stimulate the production of elastase as shown for the pancreas *in vivo* (Morosco et al. 1981), may play a role in increasing elastase levels in the lungs. In addition, nicotine may adversely affect the repair of connective tissue since it has been reported to cause structural alterations and inhibition of collagen synthesis in fibroblast cultures (Chamson et al. 1980; Chamson, Frey, Hivert 1982; Hurst and Gilbert 1979).

Several other studies suggest that nicotine may contribute to the development of emphysema in smokers. Lai and Diamond (1987) showed that repeated inhalation of smoke from high, but not from

low, nicotine cigarettes significantly augmented experimentally induced emphysema in rats. Lelcuk and coworkers (1986) reported that nicotine instilled directly into the airways induced edema. In the rat, a variety of ingredients of both the particulate and vapor phase of cigarette smoke are capable of increasing vascular permeability and producing edema in the tracheobronchial mucosa (Lundberg et al. 1983). This effect, which was traced to the stimulation of substance P-containing pulmonary vagal afferent neurons, was duplicated by nicotine (Lundberg, Saria, Martling 1982). In the guinea pig, inhaled cigarette smoke damaged the mucosal barrier and increased permeability to horseradish peroxidase by disrupting the intercellular tight junctions of the bronchial epithelium (Boucher et al. 1980). In smokers, Mason and coworkers (1983) documented an increase in pulmonary epithelial permeability in all lung regions using a radioaerosol procedure. In contrast, neither aerosolized nor injected nicotine, given over a period of 2 to 3 weeks, causes secretory cell hyperplasia (Rogers, Williams, Jeffery 1986) and there is little evidence that nicotine contributes to the development of chronic bronchitis. Further research is needed to define the magnitude of the contribution of nicotine to the pathogenesis of smoking-induced chronic lung disease.

Nicotine can also worsen pulmonary function in smokers who already have lung disease. Acute exposure to nicotine induces constriction of both central and peripheral airways (Yamatake, Sasagawa, Yanaura 1978). The increase in airway resistance by nicotine involves vagal reflexes and stimulation of parasympathetic ganglia in the bronchial wall (Nakamura et al. 1986). The magnitude of bronchoconstriction observed in experimental animals and humans following acute inhalation of cigarette smoke is correlated with the level of nicotine in the smoke (Shepherd, Collins, Silverman 1979; Rees, Chowienczyk, Clark 1982; Lee et al. 1983; Nakamura et al. 1985; Hartiala et al. 1985; Beck et al. 1986), suggesting that nicotine may be an important factor in the increased airway resistance of smokers.

Genotoxicity and Carcinogenicity

Smoking of cigarettes is causally related to cancer of the respiratory tract, the upper digestive tract, pancreas, renal pelvis, and bladder; cigarette smokers also face an increased risk for cancer of the cervix (US DHHS 1982; IARC 1986). Many carcinogenic agents have been identified in cigarette smoke, however, not a single component nor chemical group(s) of components is solely responsible for the carcinogenic activity of cigarette smoke in the various organs. Laboratory bioassays suggest that polynuclear aromatic hydrocarbons and N-nitrosamines play significant roles in the induction of cancer in smokers (US DHHS 1982; IARC 1986). Nicotine, the

principal alkaloid in tobacco smoke, has also been examined for its genotoxic and carcinogenic activity. In the Ames' *Salmonella typhimurium* mutagenesis and mammalian cell cytogenetic assays, nicotine did not possess any genotoxic activity, although it induced repairable DNA damage in the *Escherichia coli* pol A+/A- system (Bishun et al. 1972; Florin et al. 1980; Riebe, Westphal, Fortnagel 1982; Riebe and Westphal 1983).

In earlier studies, nicotine and its primary metabolites were reported to possess weak tumorigenic activity (Truhaut, De Clercq, Loisillier 1964; Boyland 1968), which subsequent investigations did not confirm (Schmähl and Osswald 1968; Martin et al. 1979; Toth 1982; LaVoie et al. 1985). Nicotine lacked cocarcinogenic activity in the urethane-induced mouse pulmonary adenoma model (Freelander and French 1956), but was found to be a cocarcinogen in the benzo(a)pyrene-tetradecanoyl phorbol acetate mouse skin tumorigenesis model (Bock 1980). The mechanism of cocarcinogenic activity is not clearly understood. Two primary metabolites of nicotine, cotinine and nicotine-N'-oxide, failed to promote N-(4-(5-nitro-2-furyl)-2-thiazyl) formamide (FANFT)-induced urinary bladder tumors in rats (LaVoie et al. 1985). On balance, it appears that nicotine does not possess direct carcinogenic activity.

During processing and pyrolysis of tobacco, nicotine can be N'-nitrosated to form N'-nitrosonornicotine and other related compounds (Figure 2) (Hoffmann and Brunnemann 1983; Hoffmann and Hecht 1985). These tobacco-specific N'-nitrosoamines are found in substantial concentrations in American snuff, as well as in mainstream tobacco smoke (Table 2), and in the saliva of snuff dippers (Hoffmann and Adams 1981; Palladino et al. 1986). Tobacco specific N-nitrosoamines are highly carcinogenic in animals and are suspected to contribute to cancer related to cigarette smoking and smokeless tobacco use (Hoffmann, LaVoie, Hecht 1985; Hoffmann and Hecht 1985). There is also concern that nicotine may be N-nitrosated within the human body. Endogenous formation of N-nitrosoproline (a noncarcinogenic marker of endogenous N-nitrosation) has been documented in cigarette smokers (Hoffmann and Brunnemann 1983; Tsuda et al. 1986). Whether nicotine-derived nitrosoamines are formed endogenously in amounts sufficient to contribute to cancer in humans exposed to nicotine per se (such as with nicotine replacement therapy) remains to be determined.

Gastrointestinal Disease

In peptic ulcer disease, cigarette smoking is a risk factor for its development, and an even stronger risk factor for delayed healing, failure to respond to therapy, and relapse (Kikendall, Eaval, Johnson 1984). In animals, nicotine potentiates peptic ulcer formation induced by histamine or pentagastrin (Konturek et al. 1971; Lee

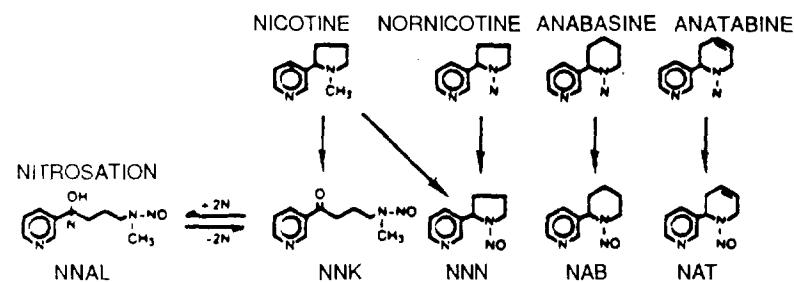


FIGURE 2.—Formation of tobacco-specific nitrosamines

NOTE: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine; NAB, N-nitrosoanabasine; NAT, N-nitrosoanatabine.

SOURCE: US DHHS (1986).

TABLE 2.—Tobacco-specific nitrosamines in commercial U.S. tobacco products

Tobacco product	NNN	NNK	NAT + NAB
Smokeless tobacco			
Chewing tobacco ¹ (ppb)	3500-8200	100-3000	500-7000
Snuff ¹ (ppb)	800-89,000	200-8300	200-4000
Mainstream smoke			
Cigarette, NF (ng/cig)	120-950	80-770	140-990
Cigarette, French Black, NF	500	220	350
Cigarette, F (ng/cig)	50-310	30-150	60-370
Little cigar, F (ng/cigar)	5500	4200	1700
Cigar (ng/cigar)	3200	1900	1900
Sidestream smoke			
Cigarette, NF (ng/cig)	1700	410	270
Cigarette, F (ng/cig)	150	190	150

NOTE: NNN, N'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, N-nitrosoanabasine; NF, without filter tip; F, with filter tip.

¹Chewing tobacco and snuff also contain < 200 ppb NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol.

SOURCE: Hoffmann, LaVoie, Hecht (1985).

and Gruber 1952). Several mechanisms by which nicotine acts in this regard have been proposed. (1) Chronic treatment in rats increases basal acid secretion, an effect which appears to be mediated by parasympathetic mechanisms (Thompson and George 1972). Chronic cigarette smoking may induce hypersecretion of acid in response to secretory stimuli. (2) Infusion of nicotine in animals and cigarette smoking by people reduces pancreatic bicarbonate secretion, which normally neutralizes acid entering the duodenum (Solomon et al.

1974; Murthy et al. 1977). This could result in increased acid delivery to the duodenum, thereby increasing the risk of ulceration. (3) Smoking may impair the mucosal barrier to acid-mediated injury. Smoking, apparently acting through nicotine, decreases mucosal blood flow and inhibits mucosal prostaglandin synthesis, both of which may impair the effectiveness of the gastric mucosal barrier, which protects the stomach lining against acid (Chujoh and Nakazawa 1981; Kawano et al. 1982; Quimby et al. 1986). (4) Cigarette smoking reduces both lower esophageal and pyloric sphincter pressures (Chattpadhyay, Greaney, Irvin 1977; Valenzuela, Defilippi, Csendes 1976), resulting in gastroesophageal reflux and duodenogastric reflux, respectively. The former may result in reflux symptoms (heartburn) (Stanciu and Bennett 1972), while the latter may cause reflux of bile acids and lysolecithin, which are known to break down the gastric mucous barrier. A direct role of nicotine is suggested by studies in opossums showing that intravenous nicotine reduces lower esophageal sphincter pressure (Rattan and Goyal 1975).

The relative importance of local exposure to nicotine (as from swallowing nicotine from nicotine polacrilex gum) versus exposure to nicotine via the bloodstream in producing the above effects is unclear. In view of the extremely high concentrations of nicotine in saliva as compared to blood, local toxicity must be considered until proven otherwise to be an additional risk of nicotine polacrilex chewing gum for patients with ulcer disease or symptoms of esophageal reflux.

Summary and Conclusions

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 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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