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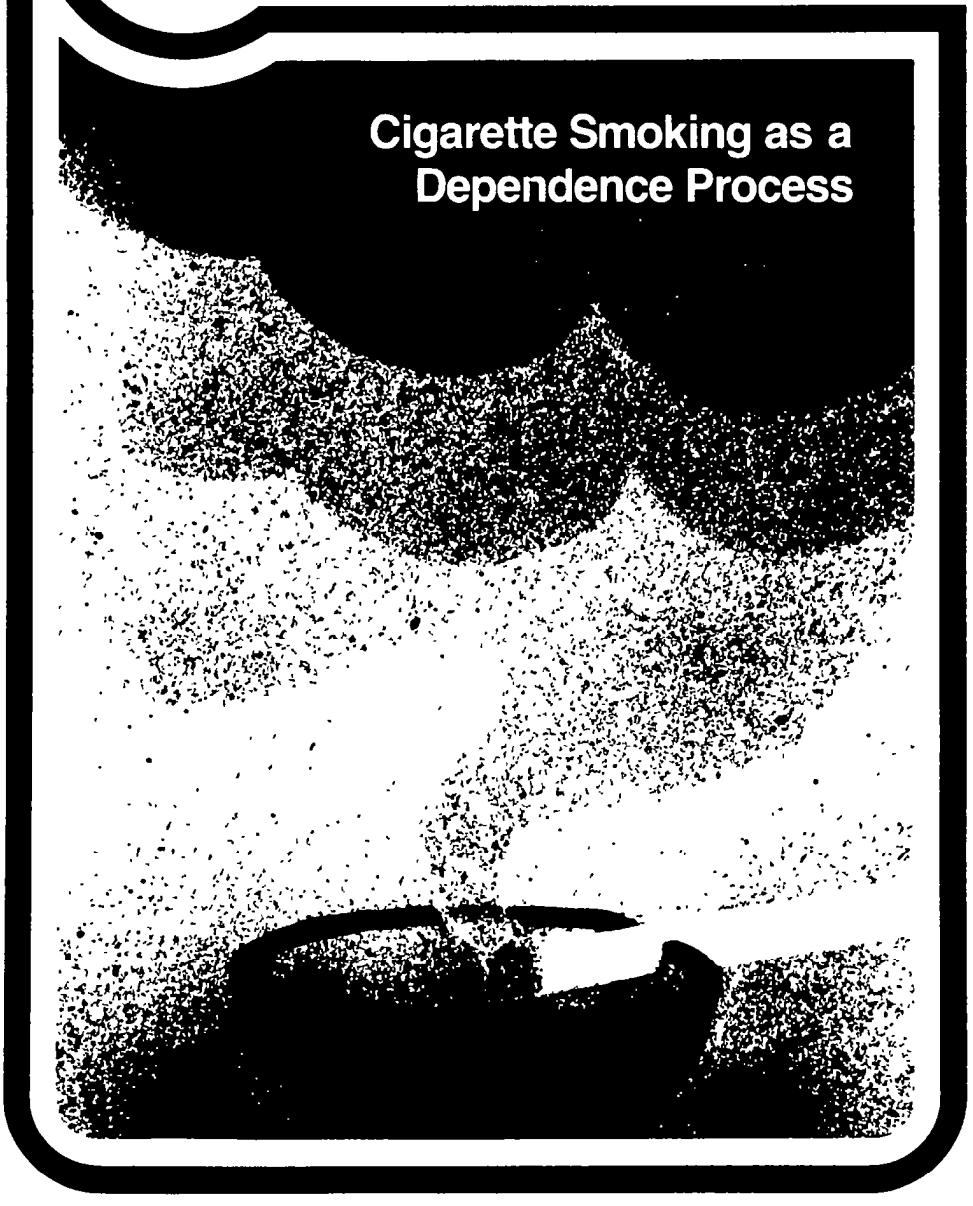

Cigarette Smoking as a Dependence Process

U S DEPARTMENT OF HEALTH EDUCATION, AND WELFARE• Public Health Service • Alcohol Drug Abuse, and Mental Health Administration

Cigarette Smoking as a Dependence Process

Editor:

Norman A. Krasnegor, Ph.D

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Foreword

The 1979 Smoking and Health report and its press coverage are giving new prominence to the health risks of smoking. At the same time, the tobacco industry advocates "personal choice" and no restrictions on smoking, and manufacturers are producing more cigarettes of lowered tar/nicotine content. Most importantly, millions of individuals--from preteens to adults--are making personal decisions about smoking: to begin to smoke; to change to cigarettes delivering less tar and nicotine (but no less carbon monoxide); to stop smoking; and, for most of those who stop, to "light up" again after a period of abstinence.

Once a person starts to smoke, future choices are less freely made, because smoking is addictive. The nature of the dependency is not well understood, and new knowledge is vitally needed. Hence the dependence process is the focal point of this volume.

The findings of researchers who are now seeking answers to questions about smoking should someday make it possible to influence more individual smoking decisions and to lessen the high economic and social costs of smoking. This will come through increased knowledge of such areas as: social and psychological factors in the initiation of smoking; just what makes cigarette smoking "rewarding"--and also dependence-producing; the effects of nicotine and the many other solid and gaseous compounds in cigarette smoke; the sites of action of nicotine in the brain and of possible compounds which may alter or block its effects; the nature of smoking withdrawal and abstinence syndromes.

This volume on Cigarette Smoking as a Dependence Process presents the results of some of the research is now beginning to answer such questions and to raise still further questions for which answers are needed. The National Institute on Drug Abuse offers this monograph with thanks to all those who are carrying forward this work and with an invitation to other qualified investigators to join them. As part of NIDA's fulfillment of its charge to carry out and support research on tobacco-smoking behavior, this book takes its place with Research Monograph No. 17, Research on Smoking Behavior (1977), and sections on smoking within monographs on the broader subject of substance abuse: No. 20, Self-Administration of Abused Substances (1978), and No. 25, Behavioral Analysis and Treatment of Substance Abuse (forthcoming).

We hope that these publications as well as the research reported are a significant contribution to the continuing effort to reduce the toll of disabilities and deaths related to cigarette smoking.

William Pollin, M.D.
Director
Division of Research
National Institute on Drug Abuse

Preface

Cigarette smoking is a dangerous habit. It can lead to a variety of ailments and serious disorders, from impaired breathing to debilitating and fatal illness, such as heart disease and cancer. Cigarette smoking is "slow-motion suicide," in the words of Joseph A. Califano, Jr., Secretary of Health, Education, and Welfare.

Such facts are widely known and accepted by most--including many who smoke. Yet, some 54 million Americans smoked 615 billion cigarettes last year. The immediate question that comes to mind is "why"?

Surveys find 90 percent of smokers saying they have tried to quit or probably would if they had an effective way to do so. In the past 15 years, 30 million smokers have quit the habit, almost all of them on their own. Again, the question is "why"?

If this habit were merely an irritating or unpleasant practice, it might be interesting to explore as another curious facet of human behavior. But the smoking habit is a case of widespread self-injury with enormous health consequences that cost the Nation an estimated $27 billion a year, not to mention the personal toll in sickness and death. We face a major public health problem created by millions of individual decisions to risk well-being for a puff of smoke. Why?

There are many theories to explain such behavior but only pieces of possible answers. Because of the magnitude of the problem, those concerned with protecting the public health are compelled to promote the prevention of smoking in the first place and to find ways to help others break the habit. To achieve those ends, we must understand the basis of the smoking habit and its mechanism. The papers collected in this monograph are steps toward that understanding.

The authors of these papers are among the first to admit that they do not have final answers, that questions far outnumber answers in this field. But good questions lead to solutions, and this effort represents a move toward that goal.

The health consequences of smoking have been studied intensively, as reflected by more than 30,000 articles on the subject and the research summarized in the 1979 Report of the Surgeon General on Smoking and Health. But, until recently, little serious research has been conducted into the reasons why the smoking habit begins and how it maintains its hold. Simply put, that is the subject of these scientific papers. To define the habit that leads individuals to act counter to common sense, and to discover why.

It is appropriate that the National Institute on Drug Abuse assume leadership in the exploration of these questions because smoking is surely the most widespread example of drug dependency. The drug, nicotine, for example, is but one of the 2,000 components of cigarette smoke and a pack-a-day smoker of cigarettes self-administers more than 50,000 puffs--or doses--a year. That is indeed drug dependency. The smoking habit is an excellent subject for research into the biological, behavioral, and psychosocial aspects of the dependency process.

This kind of research can help us learn why more than 4,000 youngsters take up the habit daily; why women, smoking in greater numbers than ever, find it more difficult than men to quit; why some individuals can break the habit "cold turkey" and others find it impossible to quit. There are many other questions that need answers: Is the smoking habit a "true" drug addiction, or is it a learned social or behavior pattern? Are there nicotine receptor sites in the central nervous system that can be blocked by medication to break the habit?

Why, in other words, do people persist in the habit despite knowledge of the health consequences? And how can they be helped?)

Such questions are explored in these papers in the hope that the theories they present, the clues they offer, and the ideas they prompt will lead to the answers we need.

John M. Pinney
Director
Office on Smoking and Health

Contents

Chapter 1

Introduction

Norman A. Krasnegor, Ph.D

Cigarette smoking is of interest to the National Institute on Drug Abuse both because of the public health problems associated with this form of substance abuse and our view that this behavior represents a prototypic dependence process. The scientific data which link cigarette smoking with risks to health have been well and amply documented in the first Surgeon General's Report on Smoking and Health (USDHEW 1964) and the recently updated version of that document (USDHEW 1979).

Despite this linkage, relatively little scientific research has been conducted to describe and analyze the cigarette smoking habit itself or the factors which are responsible for its initiation, development, maintenance, and cessation. Health risks associated with tobacco use are predicated upon the necessary existence of a chronic, habitual pattern of cigarette smoking. Scientific data which characterize the smoking habit are essential, therefore, because they can provide an understanding of the dependence process and guide the development and testing of efficacious treatment strategies.

This monograph is based upon a meeting held at the National Academy of Sciences in June 1978, sponsored by NIDA and the Committee on Substance Abuse and Habitual Behavior of the National Research Council. The intent of the meeting was to review current knowledge concerning the psychosocial, behavioral, and psychobiological factors which characterize the dependence process associated with cigarette smoking and make cessation of it difficult. This volume, which includes papers presented at the symposium, is designed to provide an overview for the scientific community on the smoking habit and an agenda to guide future research in this area.

The monograph is divided into four sections. In the first, psychosocial factors relating to the dependence process associated with cigarette smoking are explored. A stimulating discussion of how to characterize the habit is presented by Drs. Jerome Jaffe and Maureen Kanzler.

Patterns and trends in tobacco use in the United States are detailed in Dr. Dorothy Green's chapter. Cigarette smoking as a precursor

of illicit drug abuse, based on a sample of young men, is discussed by social scientist Dr. John A. O'Donnell. The dean of American researchers in the area of cigarette smoking, Dr. Daniel Horn, provides a perspective on the psychological factors involved in the establishment and maintenance of the habit.

The second section, on behavioral factors, is devoted to discussions of theoretical and empirical data on the role played by nicotine in the dependence process. Dr. Rosecrans develops arguments concerning the properties of nicotine as a discriminative stimulus. The well-known English researcher, Dr. Michael A. H. Russell, presents his perspective on the dependence liability of nicotine and the smoking dependence process. Dr. Schuster and his coworkers report findings on the effects of nicotine on smoking behavior, while Dr. Schachter discusses his social psychological experiments designed to determine the relationship of nicotine to withdrawal and addiction. The paper by Dr. Hanson and his colleagues provides convincing empirical evidence that nicotine is a reinforcer. This information is of special interest because it demonstrates an experimental model of nicotine self-administration and because it provides a method for studying pharmacological and behavioral variables associated with the reinforcing efficacy of the drug.

The third section is devoted to psychobiological phenomena associated with the smoking process. The paper by Drs. Abood and Lowy provides evidence suggesting the existence of a central noncholinergic receptor that is specific for nicotine, an exciting field of investigation. Further, the techniques described offer a methodological approach to the study of ways to centrally block the reinforcing effects of nicotine.

The papers by Drs. Jarvik and Shiffman discuss their observations respectively on the development of tolerance to cigarette smoking and the withdrawal symptoms associated with cessation of smoking. This latter work is of particular importance because abstinence symptoms have been correlated strongly with the relapse to smoking after cessation.

The final section, by Dr. Krasnegor, is a brief agenda for future research on smoking. It is hoped that this listing of research needs will be used by members of the scientific community as a focus in planning and carrying out their research and as a guide in requesting extramural funding support from the National Institute on Drug Abuse.

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Part I
Psychosocial Factors

Chapter 2

Smoking as an Addictive Disorder

Jerome H. Jaffe, M.D., and Maureen Kanzler, Ph.D.

Bishop Bartolome de las Casas, observing the use of "tabacos" by Spanish settlers in the New World, wrote that 'When reproached for such a disgusting habit, [they] replied that they found it impossible to give it up. I cannot understand what enjoyment or advantage they derive from it" (de las Casas, in Corti 1932, pp.42-43).

Today, appro mximately 450 years after de las Casas recorded those observations, we are still considering the same two questions in regard to cigarette smoking: Why don't people give it up? And what advantage or enjoyment do they derive from it? Some work has been done in the interval and some of the researchers who have contributed greatly to our knowledge are participants in this symposium. Because of their work we can now formulate some reasonable hypotheses about the origins of the "enjoyment or advantage" people derive from smoke of tobacco leaves, and we even have a considerable body of experience about helping people give up the habit. De las Casas would be happy to know that giving it up is not impossible, although for some tobacco users giving it up is difficult and relapse is common.

The title of this monograph refers to smoking as a "dependence process." Resemblance between tobacco use and consumption of other substances that produce dependence has been debated throughout history. In 1604, James I, in his Counterblaste tobacco (Corti 1932) appeared to view tobacco and the process of becoming habituated as quite analogous to the process by which a drinker of alcohol became drunkard. Three hundred years later , Sir Humphrey Rolleston, whose committee recommendations in 1926 set the tom for the British response to opiate dependence, was asked whether tobacco smoking was not properly viewed as an addiction. In his reply, Sir Humphrey differed from James I:

> This question turns on the meaning attached to the word "addiction", and may therefore be a verbal problem. The Ministry of Health's Departmental Committee on Morphine and Heroin Addiction (1926) defined an addict as a "person

> Who, not requiring the continued use of a drug for the relief of the symptoms of organic disease, has acquired, as a result of repeated administration, an over powering desire for its continuance, and in whom withdrawal of the drug leads to definite symtoms of mental or physical distress or disorder." That smoking produces a craving for more when an attempt is made to give it up... is undoubted, but it can seldom be accurately described as overpowering, and the effects of its withdrawal, though there maybe definite restlessness and instability, cannot be compared with the physical distress caused by withdrawal in morphine addicts. To regard tobacco as a drug of addiction my be all very well in a humorous sense, but it is hardly accurate (Rolleston 1926).

In at least one sense Rolleston was correct: this issue is a semantic one. And when semantic problems arise, there is always a possibility that the arguments about whether tabacco smoking is properly grouped with other forms of nonmedical drug use will divert energy from more pragmatic questions. We do not have to ascertain whether all aspects of tobacco use resemble other drug- using behaviors in all of their particulars. The problems posed by alcohol, opiate and cocaine use differ from each other in a number of significant ways.

The essential question is to what degree conceptualizing tobacco use as one of the addictive disorders is of help in directing us toward appropriate means to deal with problems that tobacco use causes.

Not all dependence on drugs results in problems for society and/or the individual. Caffeine consumption is viewed by many as appropriately claased with other forms of dependence, and caffeine dependence can be found in the International Classification of Diseases (ICD 8). There is a caffeine withdrawal syndrome and caffeine can be abused to the point where it causes problems and disrupts behavior (Gilbert 1976). But so long as the price of coffee remains within reasonable bounds, scientists and policymakers alike will think about caffeine primarily as something that adds immeasurably to the beverage served at the coffee break and without which it is difficult to start the day. For the most part, no grant applications are submitted to develop preventive treatments for caffeine dependence; there no debates in the halls of Congress about taxing it; and coffee drinkers are not forced to sit in the rear of airplanes. Perhaps some day caffeine may become of concern to behavioral scientists, but, for the present, the personal and social costs of this dependence appear to be relatively low. Tobacco dependence, on the other hand, has enormous cost to the individual who develops smoking-related diseases, and diseases in turn affect the economic well-being of society.

There are several significant areas in which tobacco use resembles other drug use, as well as a few areas in which it diverges.

When we begin to examine the ways in which tobacco use resembles other drug-using behaviors, we find ourselves asking the identical questions: What factors -- biological, psychological, sociological and pharmacological -- determine whether there will be exprimentation with the drug,a progression to casual or recreational use, or on to intensive (or excessive) use? What factors are associated with (or cause) compulsive (addictive or dependent) use, and which factors are associated with relapse after abstinence has been achieved? Although the factors are interactive, we assume with tobacco, as with other drug-using behaviors, that certain factors could act primarily at one stage while others might exert their effects at other stages.

The objective of this brief overview is not to attempt to Summarize all the factors involved in tobacco-using behavior, but to point out a few notable similarities and differences between tobacco use and the drug-using behaviors that are more commonly viewed as "addictions" and to speculate on what the future may hold.

SOME INTERESTING PSYCHOLOGICAL PARALLELS RELATED TO INITIAL USE

As with most other forms of nonmedical drug use, the initial experimentation and regular use of tobacco begin in youth. In the present climate, which is considerably less approving of cigarette use than it once was, the behavior often is seen more commonly among the less wall adjusted (Smith 1970) and less scholastically successful (Borland and Rudolph 1975; Simon and Primavera 1976). and especially among those who have friends who smoke (Iarson and Silvette 1975).

Although there is great overlap between the psychological characteristics of smokers and nonsmokers, in study after study, cigarette smokers on averaqe tend to be more extroverted (Smith 1970), more intolerant of rules, more adventuresome and risk-taking and, in some studies, more angry (Thomas 1973) than appropriately matched nonsmokers (for additional references see Larson and Silvette 1971, 1975). While it can be argued that some of these differences may be a result of smoking, they are observed even among young people just beginning to smoke (Smith 1969) and they seem to persist when the smoker becomes abstinent (Thomas 1973). Eysenck (1973) has postulated that the smoker is an extrovert who is usually at less than his or her optimal leve1 of arousal and therefore uses nicotine to raise the level of arousal. Such a view leads to a "normalizing" hypothesis to account for the maintenance of the habit hat least some smokers. Yet many of these same personality characteristics seem to be associated with exprimentation with other drugs, e.g., LSD, opiates and alcohol (Hamburg, Kraemer and Jahnke 1975: Jaffe, 1977) which are not commonly viewed as inducing arousal, an observation which is difficult to reconcile with Eysenck's hypothesis.

Most of those who begin to smoke cigarettes believe that they will some day give them up (Lieberman 1969). Very few cigarette smokers at present start out to become dependent. We most infer from their behavior that gradually the capacity to choose is eroded and, while

the user may want to believe s/he can stop at any time, the behavior indicates that this is not case. The attitudes and beliefs about the likelihood of becoming dependent are not very different among those who begin to use opiates and alcohol.

With tobacco users, as with users of other drugs, there are numerous theories that attempt to account for the transition from experimentation to continued use. With most other drugs observers are willing to attribute the ongoing behavior, at least in part, to the effects of the drug itself; but even with the opiates and alcohol, researchers recognize that, in certain social settings, the act of using the drug (rather than its pharmacological effects) may continue to provide some of the reinforcement. So it is with cigarettes -- it is a matter of degree.

Russell, Peto and Patel (1974) investigated motives for smoking in two groups -- one composed of "normal" smokers, the other an addicted group of heavy smokers attending a withdrawal clinic. A factor analysis of their responses to a questionnaire separated a "pharmacological addiction" dimension from the sensorimotor, indulgent, and psychosocial factors. The sensorimotor and indulgent factors appeared to be related to the individual's ability to experience pleasure or its enhancement by smoking and to the act of manipulating the cigarette. The psychosocial factor reflected association of cigarette smoking with a desired public image and with ease in social situations. In this, as in other studies using factor analysis (e.g., Ikard, Green and Horn 1969: Mc Kennell 1970) an addictive dimension repeatedly emerges, but is always accompanied by nonpharmacological factors. However, the mere presence of nonpharmacological factors in the maintenance of smoking does not serve to distinguish cigarette smoking from other drug-using behaviors. Social reinforcers symbolic aspects of the drug-taking behavior are also postulated to play a major role in the development of a variety of drug-using behaviors and, indeed, of deviant behaviors in general (Jessor and Jessor l977). Again, the objective here is to point to parallels rather than to survey the literature.

PHARMACOLOGICAL FACTORS IN CONTINUED USE

For many years researchers have assumed that, after smoking has been initiated through psychosocial factors, the behavior becomes habitual because the pharmacological effects of nicotine are reinforcing (for references see Ejrup 1965; Larson and Silvette 1971 and 1975; Jarvik 1973). Russell (1971 and 1976) has emphasized that a small "bolus" of nicotine reaches the brain within seconds after a puff from a tobacco cigarette is inhaled. If nicotine is a reinforcer then the hundreds of puffs inhaled each day should produce well-established puff-inhalation habit. There appears to be support for the view that it is, indeed, nicotine which is then major reinforcing component in cigarette smoking (although it may not be the only reinforcer). When nicotine and tar content are varied independently, it is the nicotine content that is correlated with ratings of strength and satisfaction (Goldfarb et al. 1976). When provided with low- or non-nicotine cigarettes,

most smokers complain bitterly or refuse to continue smoking them (see Jarvik 1973). Nevertheless, reliable laboratory evidence that nicotine is a reinforcer of drug-taking behavior has been more difficult to develop than comparable evidence for drugs like morphine, amphetamine or cocaine. In contrast to the latter drugs, which animals will self-administer over a wide range of doses, animal self-administration of nicotine has been more difficult to induce (however, see Hanson, this volume). When it does occur, it appears to be less powerful reinforcer of behavior than drugs such as cocain and amphetamine, at least as judged by the number of lever presses that the animal will make for a single dose of nicotine (Yanagita 1976).

Nicotine has both peripheral and central effects. The peripheral effects, such as inhibition of stomach contraction, acceleration of heart rate, release of epinephrine from the adrenal gland, and effects mediated by peripheral release of noradrenaline do not seem to be of major importance in reinforcings smoking. Most of these can be blocked without altering. the psychological effects in man (Carruthers 1976). The central effects are obviously more relevant. But which ones? Nicotine appears to produce multiple effects -- and in this respect the problem of identifying the site of the reinforcing effects of nicotine is unlike the problem of determining which of the multiple effects produced by the opioids or alcohol are responsible for their reinforcing properties. In man, nicotine produces an alerting pattern in the EEG and be behavioral arousal (Domino 1973: Larson and Silvette 1975). It also stimulates release of a number of hormonal substances from the CNS (Husain et al. 1975: Winternitz and Quillen 1977: Cryer et al. 1976). Animal studies indicate that nicotine releases norepinephrine and dopamine from brain tissue (See Goodman 1974; Larson and Silvette 1975; Russell 1976). Depending on the dose, it may increase or decrease the release of acetylcholine (Armitage, Hall, and Sellers 1969; Russell 1976). It may also affect brain levels of serotonin. However, with nicotine, as with other drugs, these effects on neurotransmitters do not tell us how nicotine reinforces smoking behavior.

BIOLOGICAL FACTORS IN CONTINUED AND DEPENDENT USE

Many people drink alcohol; a relatively small proportion become dependent. Not all of those who use opiates become dependent. With the latter drugs, those who become dependent tend to come from disturbed families where alcoholism and, often, a history of sociopathy or other psychiatric illness is prominent (See Jaffe 1977). One at first suspects that it is the stress of growing up in such family that leads to the later tendency to overuse alcohol or illicit drugs. However, the search for the basis of vulnerability to dependence on drugs has taken some surprising turns over the last decade. For males, a genetically transmitted biological vulnerability to alcoholism, that may be independent of disturbed family background, appears to be fairly well established (Schuckit, Goodwin, and Winokur 1972: Goodwin et al. 1973; Goodwin et al. 1974). Less defined and only suggested by the discovery of opioid receptors and endogenous opioids is a possible vulnerability to opiate addiction. Even before this discovery, some opiate users maintained that they used

opiates not to get high but to feel normal -- not to alleviate withdrawal symptoms but to experience a state of normality that the nonuser enjoys without the benefit of exogenous substances. The existence of a syndrome characterized by relative inactivity in an endogenous opioid such that exogenous substances could at least theoretically act to "normalize" the user's feeling state has not yet been demonstrated. Although the existence of a biological vulnerability to tobacco dependence is also speculative, the possibility of such a biological substrate cannot be excluded. While we are speculative, we might note one of the effects produced by cigarette smoking is a sharp rise in cortisol (wintemitz and Quillen 1977: Cryer et al. 1976). We can assume that this effect is mediated by release of ACTH. Since it seems that a molecule of ß-endorphin is released each time a molecule of ACTH is released (Guillemin et al. 1977) we cannot rule out possibility that cigarette smoking and release of B-endorpine are related. We might also note that alcohol and opiate use are not only more likely to be smokers but they smoke much more heavily (Dreher and Fraser 1968) and often find it easier to give up opiates or alcohol than cigarettes. Only the arrogance of ignorance accepts as proven that which can only be an hypothesis at present — that each and every alcoholic, opiate user, and smoker would be able to function better without the substance in question. Certainly we believe that there are millions of current tobacco users who will function better if they stop smoking, but that is not the same as assuming that all will be able to give it up without cost in terms of psychological functioning.

We need to know more about the where and the how of tobacco's effect on the brain and the rest of the central nervous system. We also need to know whether there are people who actually function better when smoking. the studies that have been carried out on heavy smokers acutely deprived of nicotine do not answer this question.

PHYSICAL DEPENDENCE AND WITHDRAWAL

The existence of physical depedence is an inference made from the observation of a stereotyped withdrawal syndrome which occurs when a chronically administered drug is discontinued. The withdrawal syndrome following smoking cessation is not as well studied as other forms of withdrawal, but few who are knowledgeable doubt that it exists. It differs in time course and character from that following alcohol or opiate deprivation. The onset smoking withdrawal symptoms may occur within hours of the last cigarette or may be delayed for days. The symptoms may last from days to months. Like the other withdrawal syndromes, there are associated physiological changes, e.g., decreased heart rate, EEG slowing. In addition to craving for tobacco, other symptoms have been reported following the cessation of smoking, such as restlessness, dullness, sleep disturbances, gastrointestinal disturbances, drowsiness, headache, amnesia, and impairment of concentration, judgment, and psychomotor performance (for references see Guilford 1966; Larson and Silvette 1975: Russell 1971; Jaffe and Jarvik 1978; Shiffman and Jarvik 1976).

As little as 90 minutes of deprivation may increase irritability (Schechter and Rand 1974).

However, there are areas of smoking withdrawal that are virtually unexplored, including the factors that determine the severity of the syndrome, the time course of its development and decay, the degree to which it can be conditioned to internal and external (enviromental) stimuli,and the ralatiation of the type and severity of the withdrawal phenomena to subject craving, to successful cesaation and to relapse after cessation.

with other drugs, the problem of tolerance is usually discussed in relation to physical dependence. It is apparent that tolerance to nicotine can develop quickly and that tolerance levels can influenced. The are now hundreds of thousands of smokers who every day purchase cigarettes delivering only 0.1 mg of nicotine. Many smokers who at first find such cigarettes to be totally unsatisfying can become accustomed to them. But we know very little about the nature of tolerance to nicotine and the factors regulating its development.

TITRATION

If smoking leads to physical dependence and if the withdrawal syndrome is an aversive state, then one might expect to find that smokers would try to avoid withdrawal by maintaining their tobacco (or nicotine) intake. Indeed, it has been proposed that heavy smokers don't get any significant positive effects from nicotine, but smoke primarily to avoid withdrawal (Schachter 1978). This general proposition has provided the basis for a number of experiments that ask the related questions: Do smokers smoke tobacco primarily to get nicotine? (i.e., Is nicotine the reinforcer in tobacco smoking?) Do smokers adjust (titrate) their level of smoking to maintain a given level of nicotine in the body? The experiments have included: (1) administration of nicotine (orally, subcutaneously, and intravenously) coupled with observation of the number of cigarettes smoked (or number of puffs taken) and/or degree of satisfaction (see Jarvik 1973; Russell 1976; kumar et al. 1977; Schuster, this volum); (2) changing the nicotine content of the tobacco and measuring the smoking patterns (Jarvik 1973) and sometimes the plasma levels of nicotine (Russell et al. 1975): and (3) administering various drugs that alter the pharmacological effects of nicotine (Jarvik 1973) or its disposition (schachter 1978) and then observing smoking behavior and the psychological effects of smoking. The evidence from most of these studies strongly supports the view that within limits heavy smokers do attempt to regulate their plasma nicotine levels by adjusting the rate and amount of tobacco smoked. Heavy smokers appear to be more consistent in reducing intake of high nicotine cigarettes to avoid unusually high plasma levels of nicotine than in increasing the number of low nicotine cigarettes to avoid unusually low levels (Russell et al. 1975). There are several possible explanations for this general finding: (1) Very high plasma nicotine levels maybe aversive for all smokers, while sharp drops in plasm levels my be aversive for only a subgroup of smokers. Alternatively,

the task of trying to maintain plasma levels of nicotine by smoking a very low nicotine cigarette may itself be aversive because of the characteristics of the cigarette, the accumulation of carbon monoxide, or because the absence of the reinforcer (nicotine) is itself a frustrating situation.

Most titration and nicotine manipulation experiments also demonStrate that in confirmed cigarette smokers factors other than nicotine contribute to the maintenance of behavior, at least over the short run. For example, although they complain bitterly, participants in experiments will continue to smoke cigarettes with little or no nicotine for a period of a week or more (Jarvik 1973). such participants are of course free to stop smoking at any time. In one experiment, an intravenous dose of nicotine equivalent to the content of single cigarette had effect at all on the latency to puff on a real cigarette or on the amount smoked (Kumar et al. 1977). That short run puffing behavior does not correspond perfectly with nicotine intake or plasma levels does not necessarily mean that tobacco smoking is a distinct form of substance-using behavior. Perfect titration of plasma levels of drug is not found in the classic addictive disorders. Alcoholics titrate alcohol levels imperfectly. Depending on environmental circumstances and schedules of reinforcement, such such individuals may tolerate major decrease in plasma levels. Similarly, some opiate-dependent subjects may continue to work for intravenous opiates when maintained on high cross-tolerance-inducing doses of methadone (Martinet al. 1973). Many, given adequate motivation, will voluntarily accept withdrawal from chronically administered opiates. In addition, addicts may continue to inject themselves and experience opiate-like effects while on blocking doses of narcotic antagonists (O'Brien 1976). It is likely that with nicotine, as with other drugs, the act of drug use itself acquires secondary reinforcing properties; and also, despite the development of tolerance, the acute effects of each dose of nicotine may continue to produce effects that are distinct from relief of withdrawal. We should not expect a perfect correlation between nicotine levels and smoking behavior any more than we expect such correlations among the "classic" addictive disorders.

CESSATION AND RELAPSE

Most smokers, like most drug users, have a remarkable capacity for denial; they appear to that the bad effects caused by drugs happen to other people. But for many smokers there comes a time when some element of self-preservation or concern about cost dictates discontinuing tobacco use. At such times an attempt to stop is often successful, at least in the short run -- just as it is for users of other drugs. But the relapse rate is high, just as it seem to be for other addictive substances. Hunt, Barnett, and Branch (1971) plotted relapse rates for heroin users, cigarette smokers, and alcoholics. The plotted curves for percent of relapse over a one-year period were virtually identical. In considering these curves we need to keep two points in mind. They represent data taken from individuals who sought "treatment." Evidence is

mounting that for both alcohol and opiate use the number of individuals who change their use patterns without formal help may exceed, by far, the number who seek formal treatment (Cahalan, Cisin, and Crossley 1969). It is estimated that, at present, thirty million nonsmoking Americans were once regular cigarette smokers. Most of these stopped without formal treatment. We do not have great deal of information on the relapse rate for this large population. It is entirely possible that those who seek formal treatment may constitute a selected group with more severe forms of dependence or a greater propensity to relapse

TREATMENT

The "treatment" of tobacco dependence, like that of other dependence disorders, has been approached from many perspectives, none of which is entirely satisfactory and some of which appear to be relatively ineffectual. This area has recently been reviewed (Bernstein and Mc Alister 1976: Schwartz 1977).

As with heroin and alcohol, the reasons for relapse in tobacco dependence appear to be multiple. Indeed, relapse is probably overdetermined and is the result of an interaction among several factors -- the personality of the individual, degree of concern about health, the functional utility of smoking, susceptibility to the pharmacological effects of tobacco, the degree to which withdrawal phenomenona become linked to enviromental stimuli, and exposure to environment situations which is some way induce smoking. What is not at all clear is the relative contribution of these various factors.

SOME POTENTIALLY IMPORTANT DIFFERENCE BETWEEN TOBACCO USE AND OTHER FORMS OF DRUG DEPENDENCE

Despite the parrallels which may be drawn between tobacco use the use of other dependence-producing substances, there are some the use of other dependence-producing substances, there are some does not induce the acute behavioral toxicity that is seen with alcohol, opiates, amphetamines, cocaine, and hallucinogens. me adverse effects of tobacco are exclusively remote and stem from chronic use rather than from occasional indulgence. There are no reports of acute fatal tobacco overdosage as a result of smoking or induced aberrant behavior. The tobacco user presents little danger to other people (albeit there may be some annoyance from the smoke and some smokers cause fires) and his/her productivity is not lowered until smoking persists for many years and leads to impairment of health. Furthermore, the liklihood that regular users of tobacco will suffer a medical illness appears to be directly related to total dose of certain tobacco constituents over time (Gori 1976). This situationoffers hope that there may be some level and some patterns of regular use which are relatively free of hazard. While this is theoretically true of other drugs, we have thus far been unsuccessful in finding ways to control their acute toxicity or their effects on behavior.

In the case of other drug-using behaviors, we believe we identified the pharmacological reinforcer. We believe that most drinkers of gin and tonic want the gin more than the fizz or the quinine, that people who drink paregoric want the morphine not the camphor. In contrast, we are not entirely certain that nicotine is the only reinforcer of tobacco-using behavior. Although Russell (1976) has stated his conviction that nicotine is the reinforcing component of cigarette smoking, there have been inconsistencies among the experiments performed over the past twenty years that remain to be resolved. Certainly, the acute effects of nicotine in the nonsmoking human volunteer have not been as thoroughly explored as have the effects of opioids, alcohol, or amphetamines in nondependent subject groups. For a substance that exerts such a remarkable hold over so many people, nicotine appears to be less than our most dramatic reinforcer in animals. There is no "mystique" about the nicotine "high" that in any way resembles that associated with the use of alcohol, opiates, cocaine, or marijuana. It is curious that it is easier to finddescriptions of the acute effects of the latter substances, which are used by only a small fraction of the population, than comparable descriptions of the subjective effects of tobacco, which is used by millions.

Compared to other drugs, the cost of a daily ration of tobacco is low. To a large degree this is because the cost of other drugs, such as alcohol, marijuana, and most synthetic substances, has been sharply increased as a result of deliberate social policies -- either through taxation or by legal prohibition that adds the costs of maintaining an illicit distribution system to the cost of the drug itself. In terms of understanding the differences between tobacco and other substances, we need to recognize that at present it remains among the relatively inexpensive commodities in most industrialized countries, and for most people it is among the the easiest to obtain. Since there is evidence to suggest that the consumption of cigarettes, like other commodities (Peto 1974, 1976; Sehm 1978) and other drugs (Popham, Schmidt, and De Lint 1975), is responsive to changes in price, a number of countries are considering taxation schedules that would reduce overall consumption. In 1976, a bill was introduced into the United States Senate that would have raised the taxes on various cigarettes in proportion to the content of tar and nicotine (Hart 1976).

The social acceptability of tobacco use and dependence is, at present, in a class by itself. In most developed countries, moderate use of alcohol is accepted and approved. Publice consumption of such beverage is part of the fabric of society. Nevertheless, it is considered dishonorable to be seen as an excessive user or to dependent on alcohol, and (despite the prominence of a number of former alcoholics) most people would rather not advertise their difficulties in keeping alcohol use at moderate levels. Most people dependent on tobacco, on the other hand, do not behave as if the continued use represents either a personal inadequancy or a behavior that ought to be kept out of the public eye.

For a long time, regular smoking, including heavy smoking, was so

common that it was almost "normal." Under such circumstances, it is understandable that textbooks and diagnostic schemes concerned with psychiatric, behavior and medical disorders made no mention of tobacco dependence (see Jaffe 1977). Curiously, the eighth edition of the International Classification of Diseases (ICD #8) listed caffeine dependence but did not include tobacco dependence. In the forthcoming ICD # 9, tobacco dependence will be included. Similarly, The American Psychiatric Association's Diagnostic and Statistical Manual, second edition (DSM-II) includes glue sniffing as a disorder but not tobacco use. In the forthcoming revision, DsM-III, a proposal has been made to include, among the substance use disorders (i.e., alcoholism, opiate dependence, etc.), a category designated "Tobacco Use Disorder." Since DSM-III is, at this time, still in draft form, the criteria for Tobacco Use Disorder cannot be considered final. It is worthwhile emphasizing, however, that just as the inclusion of alcoholism (or alcohol dependence) as a disorder does not imply that every use of alcohol is a disorder, the inclusion of the category Tobacco Use Disorder does not imply that every use of tobacco is an indication of a psychiatric abnormality. Indeed, in the current version, even the presence of physical dependence on tobacco (as evidenced by withdrawal symptomatolgy upon cessation) is not a sufficient for classifying the behavior as Tobacco Use Disorder, in an otherwise healthy individual. Mention is made of this possible change in DSM-III primarily to indicate that the climate in which tobacco use occurs is changing rapidly and this change my change the behavior itself (Jaffe 1977).

A LOOK TO THE FUTURE

If our analysis of similarities and differences in relation to other addictive disorders is accurate, what changes should use expect in the near future and what kinds of questions merit our concern? First, there will be no total victory. Despite our concern about the adverse health consequences of tobacco use in general, and about cigarette smoking in particular, a campaign against tobacco use and tobacco users is not likely to lead to an unconditional surrender -- certainly not in the near future, and probably not within foreseeable future. If history teaches us anything about the nonmedical use of drugs, it is that, within the limits of the means which free societies will tolerate, the nonmedical use of drugs that produce relaxation or pleasure can be reduced but not eliminated. This view does not imply that increased societal concern and efforts to discourage tobacco use will be without effects. It does imply that in all probability ten years from now there will still be millions of people smoking tobacco every day.

Second, we can predict that the characteristics of the population that smoke will change. History tells us that when there was no clear cut social disapproval of opiate use (as in Britain and the united states in the mid-19th century) opium and morphine were included in patent medicines and could be purchased at the local grocery store; opiates were consumed openly and dependence on opiates was widespread. When social reform and legislation focussed on the dangers of opiate use, the social climate change. "Respectable"

elements within society disavowed both medical and nonmedical use. Eventually opiate use, even in a medical context, became tinged with a hint of immorality, and nonmedical use of opiates became more and more identified with sociopathic elements (See Musto 1973). Some trends suggest that the changing attitudes toward smoking are now beginning to produce changes in the population of smokers. Not long ago cigarette smoking was a behavior that was typical of men in the upper socioeconomic grups; now, men from lower socioeconomic groups and woman from higher socioeconomic groups may be over represented (Task Force 1976). These demographic changes imply that some of those who continue to smoke at present may have a greater need to do so, or more emotional liabilities. The heavy heaviest smokers and those with the most emotional difficulties are the least likely to successfully give up smoking (Dreher Fraser 1968). The heavy smokers of tomorrow may be even more difficult to help than those of today.

Third, we can expect cigarette manufacturers to continue to compete in lowering tar levels in cigarettes. Over the past decade, both nicotineand tar levels have been reduced by all major cigarette companies. The mean tar level of the average cigarette is substantially lower than it was only five years earlier (See Wynder 1976). This trend is likely to continue until all the cigarette Manufacturers have at least one entry to compete with the very low tar/nicotine brands that deliver only 0.1 - 0.2 mg nicotine and 1 - 2 mg tar per cigarette. If the degree of dependence is a function of the daily in take of nicotine, this trend toward nicotine delivery may tend to offset the effects of the self-selection process induced by the changing social climate. The average smoker of tomorrow may have more emotional need for nicotine but may be less pharmacologically dependent. However, much depends on the degree to which tolerance develops to the effects of nicotine and to which effects.

Just as we have found no single "best approach" to alcoholism or opiate dependence, we will find no single approach to prevention and treatment of tobacco dependence. Yet it is possible that studies looking for an optimal approach will undertaken; it is equally likely that the populations using cigarettes and the patterms of use will have changed by the work is published. If the prediction that lower nicotine levels in cigarettes of the future will lead to lower levels of nicotine dependence is correct, the major problem will continue to be motivating smokers to try to stop rather than finding new and dramatic way of helping those who do seek help to succeed. On the other hand, efforts to understand the reasons for relapse will take on increasing importance.

Third party payment of costs of smoking treatment programs will be considered, discussed argued -- but our crystal ball is too murky to see the likely outcome of the argument. Since, at present, medical insurance is expected to cover the cost of treatment of the health problems caused by smoking, it would seem to be economic

common sense to cover costs of effective smoking cessation treatments. But two realities of the present health system in the U.S. make make such a change unlikely. First, with national attention riveted on spiralling cost of health care, adding the potential cost of treating fifty million smokers to the total health care bill will not be popular. Second, it is quite apparent that most smokers can stop without formal help. What criteria can be used to allocate limited treatment resources to those who really require them? what criteria might be used to define a qualified provider of treatment? And what procedures could be used to deter the development of a smoking treatment "rip-off" in which marginal practitioners submit bills for the treatment of hundreds of smokers — over and over and overagain?

We must assume that unless there develops a totally unforeseen Puritanical view of tobacco use, we will continue to be concerned with the adverse health effects of tobacco rather than the use of tobacco

per se. This being the case, the issue of less hazardous smoking viewed the studies which showed that health hazards of smoking were dose-related over time. He has computed critical values for intake of tar, nicotine, and other cigarette components below which there did not appear to be a statistically significant increased risk of morbidity. more recently, Gori and his coworkers have concluded that some cigarettes now on the market are "less hazardous" than others. The nuances of terminology are worthy of note. currently, it is considered "bad form" in the medical community to speak of "safer" cigarettes since that would imply that existing cigarettes have some degree of safety. "Less hazardous" on the other hand implies that all cigarettes are hazardous, but some may be less so. Despite his sensitivity to such semantic nuances, Gori's views have generated considerable controversy in the medical and smoking cessa-

Cigarette manufacturers are now offering cigarettes with markedly reduced tar and nicotine In general, there is a positive correlation between tar and nicotine content and amount of carbon monoxide delivered when the cigarettes are smoked on a machine (Philip Morris co. personal communication). However, there is considerable variability in CO delivery among brands with similar tar delivery. In any event, CO delivery of individual cigarette brands has not yet been made public information and may not be available for another year. Since cardiovascular disease may be more related to carboxyhemoglobin (CoHgB) levels than to nicotine and tar intake (see Aronow 1976), it is important to know what happens to the CoHgb of the smoker as, tar and nicotine are reduced. Vogt (1977) reported that CO in expired air in his subjects exhibit a dose response relationship with the number of cigarettes/day his subjects said they smoked. Vogt, working with men who volunteered for the Multiple Risk Factor Intervention Trial program, found no correlation between the amount of tar and nicotine delivered by the cigarette and the CO level; but he did not indicate the brands his subjects smoked or the proportion of subjects smoking the very low tar/nicotine brands. In our own work, we have also found that

carbon monoxide in expired air correlates substantially and positivily with the number of cigarettes smoked per day (r = .52) in a group of 34 female smokers. The correlation with CO is increased (r = .62) if the total weight of the tobacco, smoked is used in the calculations (Jaffe and Kanzler, unpublished data). Schachter (1978), reviewing his own work as well as studies of other workers on cigarette smoking, finds much support for the view that heavy smokers tend to "titrate" their body levels of nicotine. Such a view leads us to be concerned that those who attempt to reduce tar and nicotine intake by changing brands may merely smoke more cigarettes or inhale those they smoke more deeply, thereby developing higher carboxyhemoglobin levels as the price for reduced tar and nicotine intake.

In a study in which we induced twelve female smokers to switch to less hazardous brands, we did not find CO in expired breath to increase as the smokers switched to brands with lower tar and nicotine. However, in our group twelve female smokers, there was no appreciable increase in number of cigarette smoked per day. It is possible that the monitoring of CO may have served to inhibit what might have been an increase in number of cigarettes smoked under other circumstances (Jaffe et al. 1978).

There are obviously some parallels between this approach to "less hazardous" cigarette smoking and the use of methadone in the treatment of heroin use or the "responsible drinking" approach to alcohol problems. Both views assume that the drug use in question will continue and that the most pragmatic approach is to find ways to live with the drug that cause the least harm to the individual and society. But, before we can become advocates of "less hazardous" smoking we need to know more about the "tradeoffs." How much are the risks risks reduced, and are the benefits, if any, also reduced? To what extent does the body adjust to decreased nicotine intake so that lower levels produce effects similar to those once produced by higher levels? And of equal practical significance, what are the best ways to induce smokers to switch to less hazardous brands?

The "less hazardous use" approach to smoking-related problems can generate hostile reactions from some anti-smoking groups, reactions that are analogous to those that temperance and "total abstinence for alcoholics" advocates often exhibit toward the proponents of "responsible drinking" and social drinking for selected ex-alcoholics. There are also obvious parallels to the bitter schism that has divided those concerned about opiate abuse into pro- and anti-methadone maintenance camps. Many of the criticisms of the "less hazardous" smoking approach reflect realistic concerns (just as do some of the reactions to methadone maintenance and responsible drinking). For example, what level of risk would be acceptable? And for Which kinds of disability -- cancer, emphysema, heart disease?

Equally important is the concern that even discussion possibility of a less hazardous cigarette will undermine the effort to deter smoking among young people who, as with their use of other drugs, generally deny the possibility of becoming dependence or of sustaining impairment of health. We might expect that the effort

to develop information on the nature of tobacco dependence and the risks of altered patterns of tobacco use may have a number of valuable byproduction for the understanding of human biology and behavior. Certainly, there is still much to be learn about where and how tobacco produces its reinforcing effects. Can we be certain that the same sites and and receptors involved in these effects are responsible for its adverse effects on health? Is there a possibility of developing agents more selective than nicotine? Might such agents offer people who enjoy the effects of tobacco (or find that tobacco helps them regulate their internal state in some useful way) some of the same effects without the risk? In the present climate, it is difficult to forget that the discovery of endorphins was a byproduct of research that was motivated by concerns abut opiate dependence.

With tobacco, as with caffeine, dependence per se carries no social stigma. This contrasts sharply with our present attitudes toward dependence on opiates and alcohol, which elicit such grave concern that it is often difficult to persuade physicians to provide dying patients with enough opiates for relief of pain. It is possible that the increasing awareness of tobacco as a substance that induces dependence will not in itself alter or have a significant effect on the use patterns of the public at large; and that dependence will continue to be of importance only when people wish to change their behavior but find that change is exceedingly difficult or requires special help. We can expect the rediscovery of tobacco as a dependence-inducing substances to sharpen public recognition that in proportion to its impact on health we have grossly undersupported research on tobacco dependence. Over the past decade we have spent hundreds of millions of dollars on the study of diseases known to be directly caused by the prolonged use of large amounts of tobacco. But the few scientists who felt that it was important to examine tobacco dependence itself rather than the diseases it induces were viewed more with tolerance than with respect. This monograph is a sign that this attitude is changing and that the future will see more interest in the nature of tobacco dependence within the scientific community. If additional funding follows the increasing interest, we would do well to begin now to set priorities and frame the important questions.

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Chapter 3

Psychological Analysis of Establishment and Maintenance of the Smoking Habit

Daniel Horn, Ph.D.

I began studying smoking habits about 30 years ago, primarily because of an interest in the epidemiology of cancer, and continued partly to help me decide whether or not I should continue to smoke. Eventually I became persuaded that I would be better off if I stopped smoking cigarettes, and I accomplished this quite easily by continuing to smoke only a pipe. Because of the publicity associated with the publication of our American Cancer Society studies on the effect of smoking on health (Hammond and Horn 1954, 1958), I found myself the target of innumerable personal accounts of how people had given up smoking. Not only would friends and associates do this, but strangers would approach me on the commuter trains into Manhattan with detailed accounts of how they had accomplished the feat. Partly because it seemed a waste to ignore this fund of information, I began to move into a more scientific concern about the smoking habit, its development, and its alteration.

During these many years I have developed certain prejudices about statements on cigarette smoking. First, I deplore attempts by people who apply their personal standards to others' behavior to characterize it as "illogical" or "abnormal." A form of behavior that was regularly engaged in at some time by approximately three-fourths of the males in the United States born around the time of World War I, as I was, hardly seems appropriately characterized as abnormal. It was not until the early 1950's that scientific information became available which persuaded a majority of us that we would be better off if we did not smoke. Although more than half of us did eventually quit smoking, many of us found that the behavior had become so integral a part of our way of functioning that it was difficult to quit. For some, quitting demanded such an investment of effort that it seemed better to postpone trying to a later, more propitious time, but in the meantime to "hedge one's bet" by seeking a filtered cigarette.

My prejudices also encompass those who feel that only the rare individual successfully quits smoking. Roughly a million adults a year have successfully quit smoking in the past few years. During the

late 1960's, with the support of a bombardment of antismoking announcements on television, the number of persons quitting reached as high as 3 or 4 million a year (Horn 1970, 1979). Since the long term success rate during that period was between one-fourth and one-third of those who were trying to quit, we have had as many as 10 million persons trying to quit in a single year.

Also, I deplore those who characterize quitting smoking as a tortured, almost impossible process. For many people, it is easy; for most it is somewhere between easy and difficult; and only for a minority is it really difficult.

Finally, the demands of the smoking public have pushed the industry into developing and promoting cigarettes that produce lower and lower emissions of harmful ingredients. These have now been demonstrated to be of lesser degrees of harm than those being used formerly, though they are far from being demonstrated as innocuous. Average tar and nicotine levels, which have been dropping since the early 1950's, have dropped another 10 percent in the past 2 years alone and are now down to 16.6 mg of tar and 1.09 mg of nicotine (Horn, unpublished data), compared to the 42 mg of tar and 3 mg of nicotine in the cigarettes before the 1950's.

In addition to those who quit smoking and those who change to cigarettes delivering less tar and nicotine, increasing numbers of individuals do not become smokers. Until about 25 years ago, cigarette smoking was a habit that was growing rapidly in each successive cohort of males born in the United States. It began to take hold even more rapidly among successive generations of young women. This phenomenon has slowed and turned around during the past 25 years. The taking up of smoking by young men is now substantially lower than it used to be, and the growth of the habit among young women has probably now peaked, at a level appreciably below the former peak among men (Horn et al. 1959; U.S.DHETW 1972, 1976).

SMOKING AS A LEARNING PROCESS

I have explored the initiation and establishment of the smoking habit as a learning process partly, no doubt, because of the assumption that what can be learned can be unlearned. This has been basic to the descriptive model of personal choice health behavior about which I have written, summarizing much of research on smoking (Horn 1976). We have investigated the factors that characterize this class of behavior with the objective of finding out how to maximize its benefits while minimizing its harmful effects.

Initiation of the Behavior[1]

The initiation of personal choice health behavior is usually exploratory in nature. Typically, it takes place in rather young people, sometimes in young children. It is largely dependent on: first, the availability of opportunity to engage in the behavior; second, having a fairly high degree of curiosity about the effects of the behavior; and third, in finding it a way of expressing either conformity to the behavior of others (such as parents, older siblings

or age-equals) or rebellion against what are seen as unreasonable proscriptions against the behavior.

Characteristically, the greater the availability or the opportunity for expressing the behavior, the less is the necessity for a strong commitment either to conformity with the behavior of others or to rebellion against proscriptions by others (Horn et al. 1959). We know that smoking, for example, is much more common in children of parents who are themselves regular smokers, and this is partly because of the ready availability of cigarettes to children when there is already a smoker in the household and partly because use of cigarettes by older members of the family sets an example of acceptable behavior and stimulates curiosity about what makes the cigarette so attractive (Horn et al. 1959).

When smoking first begins to be widespread in a culture, it tends to be taken up with increasing frequency by successive waves of young people. Nevertheless! substantial numbers of older people may turn to it, especially if it can serve as a convenient substitute for previously well-established behavior, as was the case with cigarettes replacing cigar and pipe smoking in many male populations between 1910 and 1950. We are seeing a similar phenomenon now in Third World countries where the promotion of cigarette smoking is increasing rapidly (Eckholm 1978).

Establishment of the Behavior

The establishment of personal choice health behavior can be influenced by at least three groups of factors. In the case of cigarette smoking developing as a continuing habit in adolescents, these are, first, the costs/benefits evaluation of the behavior; second, common stereotypes that characterize perception of behavior; and third, psychological factors characterizing both personal structure and personality integration factors, particularly as they reflect the relationship of the individual and his needs to society and its demands.

The costs that go into the evaluation of the costs/benefit balance may include the harmful effects on health (both physical and mental), economic cost, and the harmful effects on society, such as economic or as a form of pollution. The benefits may include positive effects on health (both physical and mental), economic advantages, social utility (especially in terms of the facilitation of personal interactions), psychological utility (both in terms of the increase of positive effect or the reduction of negative effect) and benefits to society.

There may also be quite separate evaluations of a costs/benefits analysis for the individual and a costs/benefits analysis for society, since for some individuals, one of these may be more persuasive than the other in producing attempts to change behavior. For political leaders, the costs/benefits for society usually take precedence over the costs/benefits analysis for the individual.

When the behavior which appears to be most logical on the basis of a costs/benefits balance and the actual behavior of the individual are quite different, another set of factors consisting of rationalizations or some other set of beliefs may come into play to reduce the dissonance between the "logical" behavior and the actual behavior. In the case of cigarette smoking, the costs for the past twenty or so years have largely reflected the increasing evidence of the harmful effects of smoking on health, but in addition to that, such concerns as esthetic values, the contribution of smoking to various forms of pollution, and economic values related to the financial cost either to the individual or to society, have come into play.

The benefits are wide, ranging from the facilitation of social interaction, which is perceived or appears as one of the most valuable benefits of taking up smoking, to the reduction of tension and to the enhancement of states of pleasure which tend to be a later development in the appreciation of benefits. Such common remarks as "I can always give up smoking before it hurts me," or "I don't really smoke enough for it to do any damage," or "The kind of cigarette I smoke (or the way I smoke it) is not very likely to hurt anyone" are characteristic of beliefs of the individual who perceives potential costs as higher than benefits and yet who continues to smoke.

Perceptual stereotypes tend to develop as a kind of mythology about what smoking is like, what smokers are like, and why people smoke. These tend to be superficial and frequently inaccurate systems of beliefs and are likely to be derived either from the exaggerations of advertising on the one hand or the exaggerations of counter-advertising by antismoking groups on the other. In general, the greater the role played by superficial and inaccurate beliefs about the behavior, whether positive or negative, the more difficult it is to develop a sound decision-making process on the part of the individual or society as a whole.

A variety of patterns of psychological forces may enter into the determination of personal choice health behavior, in particular, those that reflect the conflict engendered in individuals by the demands of society and his own inner demands. In the case of smoking behavior and health, we have identified two such factors (Milne and Colman 1973). One depends on the strength of the conflict perceived by the individual between the satisfaction of his own needs and the demands imposed on him by society or by its authority figures. The second factor is a reflection of the urgency to the individual of maintaining control over his own behavior and over his own destiny as opposed to being subject either to the control of others or to the vagaries of chance as represented by "good luck" or by "bad luck."

Management of Affect

Although the factors that contribute to the establishment of the habit probably continue for a time to be important in the mainten-

ance of smoking behavior. we have found the model developed bv Tomkins (1966) and extended by us (Horn and Waingrow 1966; Ikard, Green. and Horn 19691 to describe the psychological utility of smoking in terms of its affect management capabilities describes well the use of smoking even in as young a population as college students. The use of cigarettes to help in the management of affect, by augmenting positive affective states and reducing negative affective states, is probably developed quickly; and as the number of cigarettes used per day increases usually up to the ages of 35 or 40, the individual may shift from using cigarettes for one purpose to using them for multiple purposes.

This approach to characterizing smoking behavior has been of some use in developing educational programs for altering smoking behavior, as a logical application of this knowledge carries with it implications for interfering with the establishment and maintenance of the behavior. Our critical need at this point is to identify the common patterns that predict establishment of the smoking habit and to find ways of interfering with that process.

FOOTNOTE

1. With minor changes, the sections of this paper on "Initiation of the Behavior" and "Establishment of the Behavior" were included in an article by Dr. Horn entitled "A model for the study of personal choice health behaviour," in The International Journal of Health Education, 19(2):89-98, 1976. Dr. Horn was then Director of the National Clearinghouse for Smoking and Health, Bureau of Health Education, Center for Disease Control, Department of Health, Education, and Welfare. During 1975 and early 1976 he served as a Special Consultant to the World Health Organization.

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Chapter 4

Cigarette Smoking as a Precursor of Illicit Drug Use

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This paper will focus on one question: can the variable of cigarette use be seen as a predictor, and possibly a cause, of other forms of drug use? Alcohol use and marihuana use will be employed as competitive predictors and causes.

Many surveys establish that there is a statistical association between cigarette use, or tobacco use, and use of other drugs. An association has been found for junior high and senior high school students of both sexes (Block 1975; Blum et al. 1970; Josephson 1974; Roth 1972; Shapiro 1975; Spevack and Pihl 1976; Whitehead, Smart and Laforest 1972; Wolfson et al. 1972). It has been reported at the college level (Goode 1972; Groves 1974; Johnson 1973; Steffenhagen, McAree and Nixon 1972), for U.S. military personnel in Germany (Prendergast, Preble and Tennant 1973), and for medical students (Lipp et al. 1972). Only one study (Whitehead 1974) reports no association between tobacco and most other drugs, and this was based on a methodological error; when the correct analysis is done the usual associations emerge.

None of these studies paid adequate attention to the time order in which drugs were used. Even investigators who conceptualized cigarette use as the predictor of other drug use, like Goode (1972) and Johnson (1973), made the error of measuring current cigarette use, and use of heroin and other drugs at any tune.

One study has quasi-longitudinal data. Johnston (1973) asked about use during the high school years, and separately about use in the year after high school graduation. Those who started use of any drug in that year showed a higher percentage of cigarette users in the high school years than did the continuing nonusers. This is highly suggestive, but not conclusive, because the new users of each drug were outnumbered by those who had used it in high school. Conceivably, though not probably, that early use had preceded cigarette use, which would reverse the relationship for the entire group of users.

In a true longitudinal study, Smith and Fogg (1978) measured cigarette use in 1969, when their 651 Boston students were in the 7th or 8th grade. This use predicted their classification five years later into one of three categories--nonusers, early users, and late users (of marihuana and hashish). Measures of attitudes towards smoking and smokers were also predictive.

Finally, Kandel and her associates (Kandel 1975; Kandel, Kessler and Margulies 1978) surveyed 5500 students representative of New York State high school students. Questionnaires were completed in the fall of 1971, the spring of 1972, and by almost 1000 of the seniors again in late 1972. Much of the time Kandel's variable

TABLE 1

Time Order of Use of Drugs in the National Sample (Percentages)

	Number Who Have Used Each Pair of Drugs (n = 2510)	Percentage in which		
		Drug in CAPS First	Other Drug First	Time Order unknown
ALCOHOL and				
Cigarettes	1722	59	24	17
Marihuana	1377	93	5	2
Psychedelics	548	98	2	*
Stimulantsl	578	98	2	*
Sedatives1	407	97	2	*
Heroin	147	97	3	0
Opiates1	491	94	6	*
Cocaine	351	99	1	*
CIGARETTES and				
Marihuana	1077	73	14	13
Psychedelics	451	82	10	9
Stlmulants[1]	488	81	9	9
Sedatives[1]	339	84	10	6
Heroin	134	89	6	5
Opiates[1]	409	82	11	7
Cocaine	291	90	5	5
MARIHUANA and				
Psychedelics	546	80	14	6
Stimulants[1]	562	73	21	7
Sedatives[1]	394	84	12	5
Heroin	146	90	7	3
Opiates[1]	449	77	20	3
Cocaine	350	96	1	3

[1]Quasi-medical use excluded

*Less than half of one percent

is "legal drugs," meaning cigarettes or hard liquor or beer or wine, and sometimes it is "cigarettes or hard liquor," so that it is not possible to separate out the independent effects of cigarettes. Some data make it clear that cigarette use alone, at time 1, predicted use of marihuana and other drug use at time 2, beyond the effects of hard liquor and beer or wine. But the large majority were using cigarettes and one or more kinds of alcohol at time 1, and there seem to be no data on the time order of use existing at time 1.

Kandel did regard her data as sufficient to establish that drug use involves four stages, and that each is almost a necessary condition for the next. The first involves beer and/or wine, the second hard liquor and cigarettes. Marihuana use is the third stage, and other illicit drugs the fourth.

Let us now examine the question with data collected in late 1974 and early 1975. The primary sample was a nationwide probability sample of 2510 men, then 20 to 30 years old inclusive, selected from Selective Service records. It may be regarded as representative of young men in the United States, except for Alaska and Hawaii (O'Donnell et al. 1976). A secondary sample of 294, of the same ages, was drawn from high drug use areas in New York City. It should not be regarded as representative of any population, but it is a sample of the general population, not a sample from a prison or treatment agency.

Table 1 presents the temporal relationships of alcohol, cigarette and marihuana use with each other and with other drugs. It should be noted that no drug was invariably the first. Still, the preponderance is clear, and any of the three could be an efficient predictor of the use of other drugs.

The first row of table 1 shows that alcohol normally preceded cigarettes in this sample; if the indeterminate cases are distributed like the known cases, alcohol was first in 71 percent of the cases where both were used. Cigarettes, in turn, normally preceded marihuana. It should be added that the interview inquired about regular cigarette use. The word "regular" should always be understood, though I will often omit it.

Earlier studies (O'Donnell and Clayton 1978; O'Donnell and Clayton, forthcoming) have suggested the hypothesis of a causal chain, beginning with alcohol use, leading to marihuana use, leading in turn to the use of other drugs. Cocaine is used as an example of "other drugs" in table 2. Lifetime use of marihuana is shown as an ordinal variable across the top, ranging from no use, through increasingly heavier degrees of use; the total row at the bottom shows that the percentage of those who used cocaine increases as marihuana use increases. This zero-order relationship, seen in the bottom row, is repeated in all other rows essentially unchanged, with extent of alcohol use controlled.

The zero-order relationship of cocaine use with alcohol use may be seen in the last column; again, cocaine use increases linearly with alcohol use, though not as strongly as it did with marihuana use. But this zero-order relationship disappears in each of the other columns, when marihuana use is controlled. The findings are precisely what one would expect if marihuana use comes after alcohol use but before cocaine use in the causal chain. The marihuana-cocaine relationship is not reduced by control on a prior variable, alcohol, while the alcohol-cocaine relationship disappears when controlled on an intervening variable, marihuana use.

Despite this evidence for alcohol's causal status, we have regarded marihuana use as the crucial variable. Part of the reason is an historical accident; most of the debate in the literature has been in terms of the marihuana-heroin relationship. But part relates to practical considerations. Almost all men used alcohol, and the users tended to bunch at the high use end of the scale, as can be seen from the column of n's in table 2. The marihuana variable offered a better distribution for prediction purposes.

Finally, while both alcohol and marihuana were associated with other drugs, the zero-order relationship was stronger for marihuana. Table 2 shows that the percentage of cocaine use ranged from under 1 to 58 percent as marihuana use increased from none to heavy, while the corresponding range for alcohol was only from zero to 22. This, of course, is to be expected if almost all of the effect of alcohol on cocaine use is indirect, through marihuana, with little or no direct effect.

One practical use for predictors would be in prevention of drug use. The analysis thus far suggests that one way to prevent or reduce cocaine use would be to reduce the marihuana and alcohol use that predict it. But to fall in the "heavy" categories of alcohol and marihuana use might take years of use, and the use of cocaine (or other drug) could have started before the prediction is firm. For prevention purposes, what is needed are predictors which can be easily measured at an early point in time.

Age at first use of marihuana seems to be such a predictor. Table 3 shows, for both samples, that the earlier marihuana use began, the more likely was the use of heroin and of other opiates. Similar tables, not included here, show that it is an equally powerful predictor of the use of other drugs, of illicit drug sales, and of criminal behavior.

To sum up the above and much other work, marihuana use normally, though not universally, precedes other kinds of illicit drug use, and has strong statistical associations with them, We have tested for spuriousness on the variables we have available, have seen no indications that these associations are spurious, and we believe that intervening variables between marihuana use and, for example, heroin use have been identified. These statements are sufficient for the assertion of a causal connection, by one conception of causality widely used in survey research (O'Donnell and Clayton 1978).

TABLE 2

Use of Cocaine, by Extent of Lifetime Use of Alcohol and Marihuana (Percentages)

Extent of Lifetime Use of Alcohol	n[a] (2510)	Extent of Lifetime Use of Marihuana					Total
		None (1128)	Experimental (4231	Light (231)	Moderate (227)	Heavy (501)	
None	(76)	0	_[b]	0	0	-	0
Experimental	(93)	0	0	0	0	(1 of 2)	1
Light	(491)	0	0	4	37	53	7
Moderate	(318)	0	2	0	24	40	8
Heavy	(599)	*[c]	1	2	16	54	14
Heaviest	(933)	0	1	6	20	63	22
Total	(2510)	*	1	4	22	58	

[a]Parentheses indicate numbers of individuals; figures without parentheses are percentages.

[b]A dash indicates there were no cases in the cell.

[c]An asterisk means less than one-half of one percent.

TABLE 3

Use of Heroin and Use of Opiates, Including Heroin, by Age at First Use of Marihuana, in Two Samples

A. National Sample

Age at First Use of Marihuana		Percent Used Heroin	Percent Used Opiates
16 or less	(288)	25	68
17-18	(329)	11	45
19-20	(346)	8	42
21 or more	(419)	2	30
Never used	(1128)	*	16
Total	(2510)	6	32

B. New York City Sample

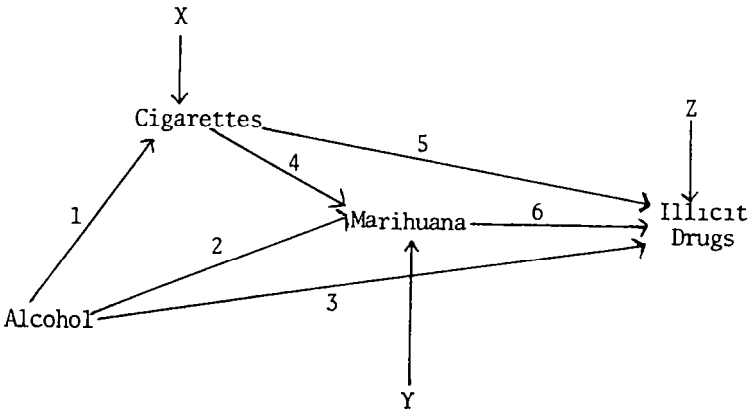
14 or less	(41)	73	80
15-16	(61)	36	62
17-18	(53)	30	51
19 or more	(65)	9	35
Never used	(74)	1	7
Total	(294)	26	43

*One user among 1128 men.

The statistical associations and time order hold for alcohol too. We have not directly examined the possibility of spurious relationships for alcohol, but it seems most unlikely that they could be completely spurious, because of the apparent causal path through marihuana. The question now becomes: do cigarettes too have some causal impact?

The question can be clarified by considering the hypothetical causal model in figure 1, where the four variables are arranged from left to right in the tune order established by table 1. The problem would be to assign values to the path coefficients of the

FIGURE 1



Hypothetical Causal Model

arrows shown, especially the values of arrows 4 and 5; does cigarette use affect marihuana use, and does it affect illicit drug use directly, in addition to whatever effect it has through marihuana use?

Problems arise because of the unnumbered arrows, which represent all other influences which impinge on the endogenous variables. There must be many variables which at one point influence a person's alcohol behavior, later his starting to use marihuana, and so on--factors such as unconventionality, rebelliousness, and curiousity. If these had been measured and could be added to the model, the model would be complex, but the solution of its linear structural equations would be straightforward. These measures are not available, however, so any attempt to use the model as it stands would confound the effects of these variables with those of the variables included in the model, producing incorrect values for the coefficients.

A second problem arises with the arrow from alcohol to cigarettes. Are we Justified in determining time order, and using a single-headed arrow, when alcohol is known to be first only 59 percent of the time? It would appear safer to take cigarette use as an exogenous variable too, and replace the arrow between it and alcohol with a symbol indicating that we are taking the correlation between the two as given and unexplained. But this in turn would mean that we can never isolate the effect of cigarettes; part of its apparent effect would be due to its correlation with alcohol use. The converse is also true; the effect of alcohol use would be partly-confounded with that of cigarette use. For both practical and theoretical reasons, therefore, we cannot expect an exact measurement of their relative influences.

We can get some hints, however, from simpler approaches. Two smoking variables are available. One, which might be labeled "Heaviest Smoking", refers to the number of cigarettes smoked daily during the heaviest period of smoking. It is related to marihuana use in table 4. There is a low degree of association--a gamma of .218.

Table 5 uses the second smoking variable, age at first regular use of cigarettes. The expected negative association with marihuana is found, but it is weak--a gamma of only -.107 when based on the age differences among cigarette users, increasing to -.248 when the nonusers also contribute to the association.

By both measures, then, it appears cigarette use may be seen as a predictor, and possibly a cause, of marihuana use, but hardly as an efficient predictor or an important cause.

To examine its relationship with other drug use, an index of non-medical drug use was constructed. This index summarizes in one number each man's lifetime use of sedatives, stimulants, psychedelics, heroin, other opiates and cocaine. The index weights each category of use, for each drug class, by the frequency of that category in the sample, so that the drugs used by fewer men, and the higher frequencies of use, receive higher scores. The range of scores in the sample is from 420 to 992, but 70 percent of the sample score below 500, because few men used drugs beyond marihuana. The relationship of cigarettes to this index was examined in two ways.

First, the index was divided into five categories and cross-tabulated against the "Heaviest Smoking" variable, within categories of lifetime extent of alcohol and marihuana use. Using Kendall's tau c and the .05 level, the pattern of findings was clear. Smoking continued to be significantly, though not strongly, associated with the index when controlled on alcohol use, suggesting that alcohol is a prior variable.

When marihuana use was controlled, the association between smoking and the index was not significant for one category, the men who did not use marihuana, but was significant in each of the other four categories where the extent of marihuana use varied. This is precisely the opposite of what happened when the alcohol association with the index was controlled on marihuana use. There, the association remained significant among the non marihuana users, but disappeared in the four categories of users. The implications may be summed up in a few statements.

1. Use of the six drug classes with which we are concerned here was rare and minimal among men who did not use marihuana.

2. The effect of alcohol on nonmedical drug use operates almost entirely through its effect on marihuana use, with little or no direct effect.

TABLE 4

Lifetime Extent of Marihuana Use, by Number of Cigarettes Used Daily During Period of Heaviest Smoking (Percentages)

Lifetime Marihuana Use	(n)[1]	Number of Cigarettes Used Daily: no. reg. cig. use (766)	Less than 1 (25)	1-4 (116)	5-14 (229)	15-24 (491)	25-34 (308)	35-44 (365)	45+ (208)
Never		60	48	54	41	38	39	34	33
Less than 10 times		16	16	16	14	17	17	20	18
10-99 times		10	16	13	14	14	12	21	20
100-999 times		9	8	14	16	17	20	12	12
1000 or more times		5	12	3	15	14	13	12	17
		100	100	100	100	100	101	99	100

gamma = .218

[1]2 cases missing; unknown on number of cigarettes used dally

TABLE 5

Lifetime Extent of Marihuana Use, by Age at First Regular Use of Cigarettes (Percentages)

Lifetime Marihuana Use	(n)[1]	14 or earlier (518)	15-16 (452)	17-18 (425)	19+ (348)	Tobacco but no reg. cig. (467)	Never Used Tobacco (299)
Never	(1128)	35	36	42	42	52	73
Less than 10 times	(423)	17	17	19	17	20	9
10-99 times	(356)	15	16	16	17	13	6
l00-999 times	(338)	15	18	14	14	10	8
1000 or more times	(264)	19	13	10	9	5	4
		101	100	101	99	100	100

gamma = -.107 (on 4 age columns)
= -.248 (on all 6 columns)

[1]One case missing; age at first use of cigarettes unknown

3. The effect of cigarette use on nonmedical drug use is direct, as well as indirect through marihuana use. But the effect is small. While statistically significant, the value of tau-c is usually below .lO with the control on marihuana, and no higher than .20 without that control.

The second approach uses the second of the two smoking variables employed earlier, age at first regular use of cigarettes. Corresponding to this are age at first use of alcohol and age at first use of marihuana. These were not grouped into categories, but the full range of ages was used, as was the full range of index scores. The correlations and some partial correlations are presented in table 6, using computer labels like "CigAge" for "Age at first regular use of cigarettes," to save space.

TABLE 6

Correlations and Partial Correlations Among Age Variables and Drug Use Index

A. Correlation Matrix (Pearson r[1])

	CigAge	MarAge	Drug Use
AlcAge	.324 (1718)	.314 (1375)	-.281 (2427)
CigAge		.242 (1074)	-.112 (1741)
MarAge			-.419 (1379)

[1]All correlations are significant at the .00l level.

B. Partial Correlations

Variables	Control on	Partial r (n)		Signif.
CigAge-Drug Use	AlcAge	-.023		
CigAge-Drug Use	MarAge	-.012	(1073)	NS
CigAge-Drug Use	AlcAge & MarAge	.037	(1072)	NS
AlcAge-Drug Use	CigAge	-.261	(1717)	.001
AlcAge-Drug Use	MarAge	-.174	(1371)	.001
AlcAge-Drug Use	CiAge & MarAge	-.177	(1072)	.001
MarAge-Drug Use	CigAge	- .407	(1073)	.001
Mar-Age-Drug Use	AlcAge	-.363	(1374)	.001
MarAge-Drug Use	CigAge & AlcAge	-.364	(1072)	.001

As might be expected, the three age variables are positively correlated--men who began to use alcohol or cigarettes or marihuana early tended to use the others at early ages too. Also as expected, each of the age variables is negatively correlated with the drug use index--the earlier a man started to use one of these three, the more likely he was to become involved in nonmedical drug use.

The marihuana correlation with drug use is -.419. This leaves most of the variance unexplained, but .4 is a quite respectable correlation in social science research, and would be enough to suggest what we already know from table 3, that age at first use of marihuana may be a useful predictor of other drug use. Further, as may be seen in the lowest panel, the correlation is hardly reduced at all by controls on the other age variables.

The correlation of Alcohol Age with Drug use is lower, at -.281, and is appreciably reduced by a control on Marihuana Age, though still significant. It might have some independent and additive predictive power.

Finally, and of most relevance here, the correlation between Cigarette Age and Drug Use is only -.112. It is statistically significant, largely because it is based on 1700 cases, but its substantive importance could not be great. And even that little importance completely disappears when the relationship is controlled on either Alcohol Age or Marihuana Age.

DISCUSSION

It is the writer's impression, though not yet confirmed by any data found in the older literature, that up to a decade or so ago it was rare for anyone without prior smoking experience to experiment with marihuana. That inhibitory factor would have produced an association between smoking and drug use, easily seen as a causal connection, and it would have been plausible to predict that a decrease in smoking would lead to a decrease in drug use.

But that inhibition, if indeed it did exist, seems to be disappearing. In late 1974, when the sample of young men was interviewed, of 299 men who had never used tobacco in any form, 27 percent had used marihuana. Of 467 who had used tobacco, but not cigarettes, 48 percent had used marihuana, while of the 1743 who had used cigarettes regularly, 62 percent used it. The differences suggest that some inhibition may still persist, but 27 and 48 are not negligible percentages. By a few years ago there were confirmed marihuana users, and users of other drugs, who quite seriously stated they would never use tobacco because tobacco has health hazards.

The association of cigarette use with drug use therefore may be partially a causal connection. It appears likely that much of it may be spurious, due to the fact that both are connected with alcohol use, and almost certainly with personality and social

variables that have been studied with respect to single substances, but not with respect to several simultaneously. Whatever the nature of the association, it is small, and would not suggest that cigarette use would be a useful predictor of later drug use.

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Chapter 5

Patterns of Tobacco Use in the United States

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From the time of World War I until the mid-1960's, when the health hazards of cigarette smoking became common knowledge, the number of smokers grew at increasingly rapid rates. After the publication of the Report of the Advisory Committee to the Surgeon General in 1964 (USDHEW 1964) both government and private organizations undertook to inform the public of the health consequences of smoking and thus to halt the increase in numbers of smokers. This paper describes the patterns of tobacco use since this effort began.

Shortly after the Surgeon General's report was issued, the National Clearinghouse for Smoking and Health (NCSH) was established in the Public Health Service. Since 1964, several surveys of tobacco use patterns among adults, teenagers, and health professionals have been conducted by private organizations for the NCSH. The data presented below are drawn from these surveys.

DEMOGRAPHIC DATA ON ADULT CIGARETTE SMOKERS

Surveys of adult tobacco use were made in 1964, 1966, 1970, and 1975 (USDHEW 1969; USDHEW 1973; USDHEW 1976a). In 1975, sample size was approximately 12,500; in each of the three earlier surveys, it was about 5,000. Additionally, except in 1964, followup studies were made of persons previously surveyed.

Age and Sex

At the time of the Surgeon General's report, a little over half the men (52.4 percent) and almost one-third of the women (32.5 percent) were cigarette smokers. (Data from the two surveys of national probability samples of adults age 21 and over conducted in the fall of 1964 and the spring of 1966 have been combined.) By 1975, these percentages had dropped to 39.3 percent of the men and 28.9 percent of the women.

In that ten-year period, the greatest decreases in smoking among men occurred during the first five years, when male smoking dropped from 52.4 percent to 42.2 percent. Decreases occurred in every

age group, except that between 1970 and 1975 there was a slight increase in the proportion of men age 65 and over who smoke.

The decrease in female smoking between 1964 and 1975 was not so large, but occurred in every age group except those age 55 and over. There was a small increase in the youngest age group--age 21-24--from 1970 to 1975, but a substantial decline as compared with the 1960's.

The increases in the proportion of smokers in the older age groups do not, of course, reflect the taking up of smoking by senior citizens, but simply the aging of a population which included large numbers of smokers. The percentages are much smaller than would have been predicted from earlier data on this cohort. The slight increase in young women who smoke follows the trend in teenage girls' smoking, discussed below.

Marital Status

In 1975, the majority of the respondents (78 percent of the men and 71 percent of the women) replied that they were married. Since married persons comprise such a large part of the total population, their smoking rates parallel those of the population as a whole. In the married group there is a slight drop since 1970 in the proportion of current smokers: from 40 percent to 38 percent for males, and from 32 percent to 28 percent for females.

About the same percentage of males who have never been married and males who are married are current smokers. Single females have a slightly higher rate than those who are married (31 percent and 28 percent respectively). Both males and females show a substantially lower smoking rate than in 1964-66 or in 1970 (61 percent of single males and 33 percent of single females were current smokers in 1964-66; comparable data for 1970 were 56 percent and 36 percent.

The highest smoking rates are among those who are divorced or separated. While only one-third of the respondents who are married and living with spouse are smokers, 60 percent of the men and 50 percent of the women who arc divorced or separated are smokers. This represents a substantial decrease from the 1970 data showing that 76 percent of the men who were divorced or separated were smokers; but at the same time, it represents an increase from the 44 percent rate for women reported in that year. This is comparable to findings in the earlier surveys.

Men who are widowed have a slightly lower smoking rate (36 percent) than those who are married (38 percent). Widowed women, however, have a much lower rate (19 percent) of cigarette smoking than do married women (28 percent). This probably reflects the lower smoking rate among older women. The proportion of smokers among both males and females in this marital category (widowed) is little different from that observed in 1964-66 or 1970.

To summarize the marital status category, the data show that men and women who are divorced or separated are more likely to be cigarette smokers than are persons who are married, widowed, or single. In all marital categories, a greater proportion of men than of women are smokers.

Educational Level

The smoking rates are lowest for those who never went to high school--37 percent for men and 18 percent for women. Because educational level is related to income, there may be a correlation between income and the cost of cigarettes for persons in this education group.

At all other educational levels there is a decided inverse relationship between the amount of education and smoking behavior, with a smaller proportion of smokers at higher educational levels. Among males, those who attended high school but not college showed 46 percent current smokers, those with some college, 36 percent, and those who graduated from college, 28 percent. Comparable proportions for women are 32 percent, 32 percent, and 21 percent. An examination of quit rates shows that half of the college graduates who ever smoked cigarettes are now former smokers.

Occupation

Among males, white collar workers (including sales personnel) are much less likely to be current smokers (36 percent) than are those in all other occupations (47 percent). This finding is consistent with the relationship between educational level and smoking behavior.

two-fifths of the women in the sample reported that they are employed outside the home. Of these employed woman, one-third are current smokers, while only 27 percent of those who classify themselves as housewives are smokers. This finding tallied with previous evidence of greater prevalence of smoking among working women.

Among the employed women, white collar workers are somewhat more likely to smoke than arc those in other occupations (34 percent and 32 percent, respectively)--a relationship opposite to that found among men.

Income

Family income is related to smoking rates with both males and females, but in different ways. Men in relatively affluent families are less likely to smoke, while women in this group are more likely to be current smokers. Only 35 percent of the men who reported an annual family income of $20,000 or mare are cigarette smokers, while 46 percent of the men in the $7,500-$10,000 range are smokers. Among women, however, there is an increase in smoking from 24 percent for those in families earning under $3,000 to 34 percent for those with incomes of $20,000 or more.

REMEDIAL ACTION--SETTING LIMITS

There has been a growing feeling that nonsmokers have a right to be allowed to breathe air free from contaminants in cigarette smoke. A dramatic change in attitude has taken place over the years toward agreement with the statement, "The smoking of cigarettes should be allowed in fewer places than it is now." Only 52 percent agreed with this statement in 1964 and 1966, but 57 percent agreed in 1970, and 70 percent in 1975. Between 1970 and 1975, this increase took place among current smokers (from 42 percent to 51 percent), among former smokers (from 61 percent to 77 percent), and among those who have never smoked (68 percent to 82 percent). This means that more than half the present smokers would like to see smoking allowed in fewer places than it is now, despite the fact that there are more and more restrictions on places where people are allowed to smoke.

Since so many people would like to see smoking allowed in fewer places, it is not surprising to find that nearly two-thirds (63 percent) of the respondents say that it is annoying to be near a person who is smoking cigarettes. Ten years ago less than half of the total number of respondents (46 percent) agreed with this, and now even more than a third of the smokers (35 percent) do so.

A ban on cigarette advertising was advocated by a little over one-third (36 percent) of the 1964 respondents. By 1970, this had increased to 60 percent, Since then, television and radio commercials advertising cigarettes have been banned. Because these two media were the most widely used for advertising cigarettes, it might be presumed that such a ban would satisfy the public. This is not so. In 1975, 56 percent believed that cigarette advertising should be stopped completely. This view is subscribed to by 51 percent of the men and 60 percent of the women. Two out of five smokers would like to see cigarette advertising stopped, perhaps because some smokers who are trying to quit find that the advertisements make it more difficult. A second possibility is that, while they continue to smoke, they are loath to see the younger generation take it up.

Because of the growing feeling that smoking should be regulated more stringently, questions were added to the 1975 survey to explore the matter of regulation more fully.

First, the question, "Do you favor stronger Federal regulations concerning cigarette smoking?" elicited 52 percent "yes" responses from men and 60 percent from women. More than 40 percent of current smokers even favor such regulations.

Another area explored was whether management has the right to prohibit smoking in its place of business. Only 16 percent of the respondents felt that management should not have the right, while 78 percent thought they should have the right; the other 6 percent were undecided. Eighty percent of the women and 75 percent of the men thought that management should have the right to prohibit

smoking. Of those who felt this way, 28 percent believed that they should be able to do this only when smoking is a safety hazard? while 72 percent said they should have this privilege whether it is a safety hazard or not.

Respondents were asked if they found it annoying to be near a person smoking cigarettes. Those who said "yes" were asked whether they found cigarette smoking more annoying than several other things that might be bothersome. The majority of these respondents expressed the belief that cigarette smoking is more annoying than someone's smoking a pipe, cracking knuckles, chewing gum, and humming or whistling. At the same time, a greater number of people said that smoking cigars is more unpleasant than cigarettes, and about the same number found cigarette smoking more annoying than drinking alcoholic beverages as found drinking alcoholic beverages more irritating than smoking.

TEENAGE SMOKING

The widespread use of cigarettes among teenagers, with its attendant health hazards, has prompted four national surveys of teenage smoking in the United States. The first was completed in January 1968 and the last in January 1974, with intermediate surveys in 1970 and 1972 (USDHEW 1972; USDHEW 1976b). About 2500 young people (12 through 18 years old) were interviewed in each survey.

Trends in Prevalence of Teenage Smoking

During the six years covered by the surveys, the proportion of boys who smoke at least once a week changed very little, except for an increase in 1970. This increase was most marked in the 17- and 18-year olds. In 1972, this proportion had dropped back to the 1968 level and remained there in 1974. Among girls, however, there has been a gradual increase in the proportion of smokers in every age group. This has had the effect of practically eliminating the difference in smoking behavior of the two sexes. In 1968, the proportion of girls reporting that they smoked cigarettes regularly was only about one-half that of boys. By 1970, this ratio had risen to almost two-thirds, and in 1972 to about 85 percent. The difference between the smoking behavior of boys and that of girls had disappeared by January 1974.

Discussion

Overall, the proportion of teenagers who smoke cigarettes regularly, including those who smoke at least once a week, has increased from 12 percent in 1968 to 16 percent in 1974. This increase has taken place almost exclusively among girls. Traditionally, cigarette smoking was a custom indulged in by men and boys and was not usual among women and girls. About the time of World War II, smoking among women began to increase, but it never quite reached the level of male smoking. In the late 1960's, men began to quit smoking, so that the proportions of men and women smokers approached each other more closely. We have already mentioned that the smoking behavior

of boys did not change appreciably during the late 1960's and early 1970's, but smoking among girls gradually increased. In fact, it rose to the point where, in 1974, boys and girls were smoking in the same proportions.

While the reasons for the disappearance of differences between boys' and girls' smoking behavior are not immediately apparent, it is likely that they are. the same as the reasons that account for the disappearance of many other differences between boys and girls, in dress, hair styles, etc. In order to understand the phenomenon of teenage smoking, it is important to recognize the differences between those who take up smoking and those who do not. Since adolescence is a period of exploration, it is natural for teenagers to experiment with smoking, just as they do with other "adult" behavior. But which experimenters become smokers and which do not? By the time a boy or girl is 18 years old, only about one in three is a smoker, although most have tried it. How do we explain the differences in behavior? One way is to look at the differences between teenage smokers and teenage nonsmokers. Until adolescence, there is no question that the family exerts the greatest of all influences upon children; but, as they grow up, outside influences become stronger. How much does the family situation affect the smoking practices of the teenager? Several characteristics of the family were examined, and all were found to be related to smoking practices.

First, teenagers in intact families (that is, those in which both parents were present) were less likely to smoke than were those in homes where there was not both a mother and a father. About one teenager in five lives in a home without both parents, some because one parent is dead or the parents divorced, and some, particularly the older teenagers, because they have left the family home and have set up their own living arrangements. They have adopted a lifestyle that is somewhat precocious; perhaps smoking is one characteristic of this lifestyle. Another family characteristic that is related to teenage smoking is socioeconomic status, as measured by education of the parents. Those with better-educated parents are less likely to smoke than are those with less well-educated parents. This is consistent with studies of adults which find that the higher the educational level a person has attained, the more likely he is to have quit smoking, if he ever did so. In spite of the notion that adolescents, in rebellion against their parents, reject the customs and beliefs of their elders, they do not turn away from their parents' smoking practices. Parents who smoke are likely to have children who smoke. In fact, teenagers with two parents who use cigarettes are more than twice as likely to smoke as are those with no parent who indulges in this habit.

Teenagers emulate older brothers and sisters, too. A boy or girl with an older sibling who smokes is extremely likely to be a smoker as well. If a teenager has both a parent and an older sibling who smoke, the likelihood of becoming a smoker is amplified. In fact, he or she is four times as likely to smoke as is one who has no smoking example in the immediate family. Smoking appears to be one of those customs which families as a whole either adopt

or do not adopt. Just as in some families a coffee pot is always on the back of the stove, in some homes cigarettes are readily available for family members to help themselves.

Teenagers not only have families who smoke; they also have friends who smoke. Almost nine out of ten smokers acknowledge that at least one of their four best friends smokes on a regular basis, while only one in three of the nonsmokers claims a smoker among his or her four best friends. At the other extreme, one in five nonsmokers claims that none of his or her four best friends has even experimented with smoking, while only one in a hundred of the smokers makes this claim.

When we discuss parents' and older siblings' smoking patterns, we can talk about their influence on teenagers, since presumably these older family members set the stage for them. But when we talk about friends' smoking, there is no way to guess who influenced whom. Did Tom's friends exert pressure to get him to smoke? Did Tom urge his friends to smoke? Did he select friends because they smoked, or did they select him because he smoked? Or do they share the same kind of lifestyle, congenial to all in this group, that includes cigarette smoking? Tom cannot tell us; no one can. It is likely, however, that Tom and his friends share a life pattern that includes smoking.

One aspect of the teenage lifestyle is the practice of working outside the home, either full time or part time. Teenagers who work at some time during the year are twice as likely to be smokers as are those who do not work. Perhaps the nonworking minority is somewhat more protected, and less likely to have achieved much independence. Those who work often participate with adults in a work situation, and therefore are more likely to experiment with smoking and other adult behaviors.

Another aspect of the teenage lifestyle is reflected in educational and vocational aspirations. The college-bound teenager probably has priorities that differ from those of peers who plan to terminate formal academic education with high school. The high school student in a college preparatory course is less likely to smoke than is one in any other course. This is consistent with the finding that offspring of parents who went to college are less likely to smoke. Thus the theory that smoking is related to socioeconomic status is supported.

HEALTH PROFESSIONALS: SMOKING AND HEALTH

People in the health professions are the authorities on matters pertaining to health. They are looked to for advice and are expected to be exemplars in preventive medicine. This is certainly true of cigarette smoking. For example, a recent survey of adults showed that more than three out of four feel that doctors should set a good example by not smoking. Thus, it is essential to know how these important exemplars see their roles, how they perceive smoking in relation to diseases, and how they act with regard to cigarette smoking both personally and professionally.

In an NCSH survey (unpublished) approximately 2,500 individuals representing each of four groups of health professionals were studied in 1975: physicians, dentists, pharmacists, and nurses. The same groups had been studied in the period between the spring of 1967 and the summer of 1969.1 One purpose of the current study was to assess the changes that have taken place during the intervening years.

Findings

In three of the four groups the proportion of smokers has decreased markedly. Only among nurses has the proportion of smokers stayed at about the same rate as in 1969. The proportion of physicians who smoked dropped from 29.6 percent in 1967 to 21.0 percent in 1975. During the same 8-year period, smoking among dentists decreased from 34.3 percent to 23.3 percent. In 1968, 34.5 percent of pharmacists smoked, compared with 27.5 percent in 1975. Nurses were smoking at about the same rate in both surveys--37.3 percent in 1969 and 38.9 percent in 1975.

Among physicians, there was little or no difference in smoking behavior by age group: 21 percent of those under 40 are current smokers, and 21 percent of those 40 and over are smokers. Both these proportions represent substantial decreases from the 1967 survey, when 33 percent of those under 40 and 29 percent of those 40 and over were smokers. The same pattern holds for dentists: in 1975, 24 percent in both the younger and older age groups were current smokers. Both were down from 1967, when 36 percent of those under 40 and 33 percent of those 40 and over were current smokers. Among pharmacists, the decrease in proportion of smokers was more noticeable in the younger age group than in the older. The percent of pharmacists under 40 who were current smokers decreased from 36 percent in 1968 to 25 percent in 1975. The corresponding percentages for those 40 and over were 35 percent in 1968 and 29 percent in 1975. As the other health professionals do, nurses under 40 show a decrease from 1969 to 1975--from 39 percent to 34 percent. However, 35 percent of the nurses 40 and over were smokers in 1969, and 42 percent were smokers in 1975. This increase reflects the fact that women 40 and over in 1975 were in the 33- to 40-year age group in 1969 and smoked at a much higher rate than the older nurses who have since left the profession.

In comparing health professionals with the adult population in general, it is appropriate to compare three of the groups with males and one group with females. Physicians in the sample included 92.9 percent males; dentists, 99.2 percent; and pharmacists, 90.0 percent. Nurses included 97.5 percent females.

A 1975 national probability sample of adults showed that 39 percent of the males and 29 percent of the females were current smokers. The proportion of smokers in each of the three predominantly male health professional groups was much lower than that of males in the general population, but nurses were smoking at a higher rate than women in general.

Three out of every five health professionals surveyed had a history of smoking, but t e majority in all groups except nursing had quit smoking. The highest quit rate was found among physicians--64 percent of all those who had ever smoked were former smokers at the time of the 1975 survey. This was closely followed by 61 percent of the dentists and 55 percent of the pharmacists who had once smoked but had quit. These proportions are higher than the quit rate of 43 percent in the male population who had ever smoked. Nurses had a quit rate of 36 percent--slightly above the quit rate of 34 percent of smokers in the female population.

Physicians have been the leaders in giving up smoking; 55 percent of former smokers have not smoked in 10 or more years. This compares with 46 percent of former smokers in the male population. Dentists were next in quitting, with 50 percent of former smokers having quit 10 or more years ago. Pharmacists began quitting at about the same time as other men in the population; 47 percent of former smokers among them quit 10 or more years ago.

Women did not start to quit smoking in large numbers as early as men. Of the former smokers among the female population in 1975. only 36 percent had not smoked for 10 or more years. However, like other health professionals, nurses lead their general population group in quitting smoking. Among their former smokers, 43 percent of nurses have not smoked for 10 or more years.

Smokers in the predominantly male health professions smoked fewer cigarettes per day than males in the general population, while there was little difference between nurses and their female counterparts in the general population. As well as smoking fewer cigarettes, physicians, dentists, and pharmacists also tended to smoke cigarettes lower in tar and nicotine than did males in the general population. While one in five in these health professions smoked cigarettes with a “tar” level of 15 mg or below, only one male in eight in the general population smoked these low “tar” cigarettes. Similarly, a larger proportion of nurses smoked low-tar cigarettes than did smokers in the general female population.

Most health professionals who are still smoking cigarettes started smoking before the relationship between smoking and disease was well known. A majority of them have made at least one attempt to stop, at rates similar to those among the general population of smokers: physicians 63 percent, dentists 64 percent, pharmacists 61 percent, nurses 55 percent, adult males 64 percent, and adult females 60 percent.

In summary, changes in the smoking habits of these groups of health professionals have been towards the reduction of smoking and, for the most part, have exceeded and predated changes among the general population. Nurses were formerly among the group of heaviest smokers in the female population. Now that there is an Increasing rate of quitting among older nurses and a reduced rate of taking up smoking by younger nurses, this is beginning to change.

Relationship between Cigarette Smoking and Selected Diseases

People in the health professions generally see cigarette smoking as either a major cause or a contributing cause of diseases of the lung. In fact, 9 out of 10 physicians and dentists say that smoking is a major or contributing cause of lung cancer, chronic bronchitis, and pulmonary emphysema. Between 80 percent and 90 percent of pharmacists and nurses agree. In every case, this represents an increase from the population holding these opinions in earlier surveys.

Even greater increases were observed in the proportion seeing smoking as a cause of heart disease. The proportion of physicians increased from 71 percent to 78 percent. Corresponding proportions for dentists were 60 percent to 75 percent; for pharmacists, 46 percent to 63 percent; for nurses, 60 percent to 74 percent.

Perception of Responsibility as a Health Professional

People in the health professions see cigarette smoking as a serious health hazard. How do they see themselves as serving to reduce the incidence of disease and death caused wholly or partly by smoking?

First, they believe it is their responsibility to set a good example by not smoking cigarettes. Ninety-one percent of physicians, 88 percent of dentists, 87 percent of nurses, and 73 percent of pharmacists agree they have this responsibility. The majority also agree it is their responsibility to convince people to stop smoking. Three-quarters of physicians and nurses, 61 percent of dentists, and 51 percent of pharmacists subscribe to this. Many in the health professions also believe they should be more active than they have been in speaking to lay groups about cigarette smoking. In fact, 82 percent of physicians, 74 percent of nurses, and 68 percent of dentists and pharmacists agree they should be more active.

Since health professionals profess a feeling of responsibility toward their patients' (or customers') smoking, smokers in these groups have changed their behavior accordingly. Health professionals are much less likely to smoke in the presence of patients or customers than they were in the earlier surveys. In all four professions, more of them report that they <u>never</u> smoke in front of a patient (or customer) (physicians, 39 to percent; dentists, 50 to 65 percent; pharmacists, 22 to 41 percent; nurses, 60 to 89 percent) . Although a slightly smaller proportion of nurses, compared with doctors and dentists, feel that they should set a good example, they include the largest proportion who say they do not smoke in front of patients. Perhaps they face more restrictions of where they are allowed to smoke at their places of work. Indeed, 80 percent of the nurses who are presently employed say that smoking is restricted to certain times or places, or prohibited entirely, at the place where they work.

Just as health professionals feel increasingly that they should be doing something about smoking, they are less pessimistic than they were earlier about their ability to effect change. For example, in 1967 three-fourths of the physicians agreed that "there is no method around today to really help a smoker who wants to quit but can't do it on his own." By 1975, fewer than half of them agreed with this statement. The proportion of dentists agreeing with it dropped from 58 percent to 33 percent. It is interesting to note that nurses have been most optimistic about the possibility of helping people to quit.

USE OF OTHER FORMS OF TOBACCO

Since the mid-1960's, the proportion of pipe smokers among males has decreased from about one in five to about one in eight. Among women, it has remained at less than one in a hundred. Cigar smoking has also decreased, from 28 percent in the 1964-1966 surveys to 18 percent in 1975 in males. Women have not usually smoked cigars; fewer than 1 percent reported smoking cigars in any of the surveys. The use of snuff has remained at about 3 percent for males and less than 2 percent for females over the time of the surveys. Chewing tobacco is used, and has been used, by about 6 percent of the males and 1 percent of the females (USDHEW 1976a). These forms of tobacco are used by such a sma11 percent of the population that little attention has been paid to trying to decrease the prevalence of their use.

SUMMARY

Overall, then, the picture of decrease in cigarette smoking is an encouraging one, with the exception of the increased rate of smoking among teenage girls. However, this change probably reflects the tenor of the times and an alteration in the concept of what has traditionally been considered "feminine" behavior.

FOOTNOTE

1. The 1975 survey was conducted for NCSH by Chilton Research Service; the 1967 and 1969 surveys were conducted by National Opinion Research Center.

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Part II
Behavioral Factors

Chapter 6

Nicotine as a Discriminative Stimulus to Behavior: Its Characterization and Relevance to Smoking Behavior

John A. Rosecrans, Ph.D.

INTRODUCTION

One of the major objectives of research being conducted in our laboratory over the last decade has been to determine the neurochemical and pharmacological mechanisms by which nicotine produces its behavioral effects in experimental animals. The goal of this research has been to assist in identifying which of nicotine's effects may contribute to its use in tobacco by humans. The generalization of our findings to tobacco use, however, is contingent upon our ability to develop behavioral procedures which are specific to nicotine and analogous to nicotine's effects in humans. Much progress has been made in this regard, and it is felt that we have been successful in developing an animal model of nicotine effects which will provide important information relevant to drug dependency problems.

The experimental model developed in this laboratory relies upon the ability of nicotine to exert stimulus control of behavior (Rosecrans and Chance 1977; 1978). In this approach an animal or human subject is required to discriminate between drug and non-drug states in order to receive a positive reinforcement. For example, food-deprived rats are trained to press one of two levers (for liquid reinforcement) in an operant chamber after they are administered nicotine (200-400 µg/kg s.c.), while the opposite lever is reinforced following saline administration on a different day. After repeated daily exposure to this procedure, the animal soon learns to detect the effects of nicotine. Thus, the drug is acting as a discriminative stimulus.

Human subjects can be studied in an analogous way. In studies just initiated in our laboratory, human subjects can obtain a financial reward for pressing the correct lever in a similar two-lever drug discrimination task, In this situation each subject must detect differences in nicotine level when allowed to smoke cigarettes differing in nicotine content (0.3 vs. 1.3 mg nicotine per cigarette).

Tar content, taste, and other parameters have been equalized to prevent the smoker from using other cues to solve the problem. As with our animal studies, human subjects will be allowed access to the discrimination task following random exposure in each session to either the high or low nicotine cigarette. This latter experiment is extremely important, as it will allow us to determine whether nicotine can be studied in human subjects using procedures developed from our animal experiments.

USES OF THE MODEL

It should be understood that we are not studying the effects of nicotine on behavior. Rather, these procedures are used to measure drug detection. This is an important distinction, since drugs from different pharmacological classes may be shown to induce the same degree of behavioral disruption in animals, but may not be similar in terms of quality as a discriminative stimulus (DS). Put in another way, a rat may exhibit equivalent behavioral disruption by specific doses of both d-amphetamine and morphine, but it will be able to discriminate between them because of the qualitatively different DS properties. These procedures, therefore! provide a very specific model which can be used to study the mechanism of drug action within a given pharmacological class.

The discriminative stimulus model has provided us with a unique tool by which to study nicotine. To determine mechanism of action or central cite of action, several neuropharmacological manipulations can be utilized in animals trained to detect nicotine, to attenuate or mimic the nicotine DS. In the experiments to be summarized in this paper, rats are first trained to discriminate between doses of nicotine and saline. Once this is achieved, animals can be challenged with suspected antagonists or given experimental or known compounds to determine if such compounds produce effects similar to those of nicotine. From such studies one can determine: 1) the receptor mechanisms involved, or 2) the structure-activity relationships involved in the nicotine-receptor interaction. In addition, such studies can be conducted centrally via chronically implanted cannulae at various sites to study the locus of action of the nicotine DS within the brain. Neurochemical interactions have been studied by evaluating the ability of nicotine to produce its DS effects in rats chronically depleted of specific biogenic amines. At present, we are also exploring ways of studying ongoing brain area biogenic amine function under nicotine and saline conditions, via the use of radioisotopes and centrally placed push-pull cannula.

Specific Behavioral Techniques Used in Animal Studies

At approximately 10 weeks of age, rats were trained to press first one lever, then the other, in a two-lever operant chamber. Discrimination training began with four preliminary training sessions of 15 minutes duration in which each correct bar press was reinforced (Chance et al. 1977). Subsequent sessions started with a 2.5 minute period during which no responses were reinforced; a variable interval of 15 seconds (VI - 15 sec) schedule was in effect for the remaining

12.5 minutes. Every session was preceded by 10 minutes with subcutaneous injection of either nicotine or saline. During the four preliminary training sessions, nicotine and saline injections were alternated daily; thereafter, 2 days of one treatment were followed by 2 days of the other. By means of this double alternation schedule of drug administration, each treatment was preceded equally often by a session with the same and the opposite treatment. One lever was reinforced after the injection of nicotine, and the opposite lever was reinforced following saline. For half of the subjects, the right lever was rewarded after nicotine and the left lever was rewarded after saline. These conditions were reversed for the remaining animals.

After 40 discrimination training sessions, responding was relatively stable. The same animals continued to receive either 200 or 400 µg/kg of nicotine and saline according to a double alternation sequence. However, test sessions 2.5 minutes in duration were interposed during which no responses were reinforced. An odd number of training sessions, usually one or three, separated two successive test sessions. All experimental manipulations were accomplished during test sessions, That is, drug antagonism or drug generalization studies were conducted during these test sessions. During test sessions, rats made 85-95 percent of their responses on the nicotine-correct lever following a training of nicotine, while response rates following a dose of saline were only l0-15 percent on the same lever. Thus, these animals exhibited an ability to discriminate between nicotine and saline of 70-85 percent.

NICOTINE AS A DISCRIMINATIVE STIMULUS: MECHANISM AND SITE OF ACTION

The DS approach has been very useful in studying the mechanism of action of nicotine, especially since this drug appears to elicit behavioral changes within other tasks which are contingent on baseline arousal levels prior to drug exposure (Rosecrans 1971a; 1971b. Thus, nicotine produced stimulant effects when the baseline arousal levels were low, while reverse effects were observed if arousal levels were high. These variable effects, while important to the overall behavioral pharmacology of nicotine, cause difficulty in attempts to correlate behavior with central mechanisms or neurochemical events. The advantage of DS procedures is that the subjects are not responding to a specific effect of the drug on behavior, but to the presence of the drug within the CNS. Furthermore, the specificity of and sensitivity to the nicotine cue did not change in relation to time-duration or dose-response relationships across different schedules of reinforcement which elicit high (FR 10 sec) or low (DRL 10 sec) rates of responding (Chance et al. 1977). Furthemore, to learn a DS task, an experimental subject must develop some degree of behavioral tolerance to a specific training dose of nicotine to perform the operant schedule.

Domino (1967) was one of the first to investigate nicotine's CNS mechanisms in a systematic way and clearly showed that nicotine acts at specific non-muscarinic receptor sites. He and coworkers,

by studying various neurophysiological parameters in cats, showed that nicotine's arousal effects could be antagonized by mecamylamine, a centrally acting nicotinic blocking drug, but not by the muscarinic blocker, atropine. In addition, they were unable to block the nicotine effect by the quarternary nicotinic peripheral blocker, hexamethonium, indicating nicotine's central site of action. These workers also showed that arecoline (a muscarinic agonist) had the exact opposite profile (atropine, but not mecamylamine, blocked arecoline's arousal effect), suggesting that each drug was acting on separate N-cholinergic and M-cholinergic receptors. This research was extended using the DS paradigm (Schechter and Rosecrans 1971; Hirschhorn and Rosecrans 1974) and an identical profile for the action of nicotine was observed (see table 1).

TABLE 1

Mechanism of the Nicotine (200-400 µg/kg s.c.) DS: Drug Antagonism Studies

Drug Antagonist	Receptor Blocked	Results vs. Nicotine
Mecamylamine (s.c.) 1 mg/kg; 30 min prior	N-cholinergic central acting	complete antagonism
Hexamethonium (s.c.) 1 mg/kg; 10 min prior	N-cholinergic peripheral acting	no effect
Atropine (s.c.) 0.5-20 mg/kg; 30 min prior	M-cholinergic central acting	no effect
Dibenamine (i.p.) 10-20 mg/kg; 30 min prior	α-adrenergic	no effect
Propranolol (i.p.) 1-4 mg/kg; 30 min prior	ß-adrenergic	no effect
α-Methyl-paratyrosine (i.p.) 30-200 mg/kg; 2 hr prior	catecholamine synthesis I	some blockade
p-Chlorophenylalanine (p.o.) 300 mg/kg; 72 hr prior	5-hydroxytryptamine synthesis	no effect

Thus, it appears that the behavioral effects of nicotine are contingent upon stimulation of a specific N-cholinergic receptor. The possibilities that other animal systems may be involved and that there may be a dopamine (DA) neuron link have also been considered (Rosecrans, Chance, and Schechter 1976). Research conducted in this laboratory indicates that rats trained to discriminate nicotine (400 µg/kg, s.c.) vs. saline will generalize to nicotine injected into the hippocampus; hut if the rats are dopamine-depleted (65 percent), no generalization to the trained s.c. nicotine cue occurs following injection of nicotine into the hippocampus. Additional support that DA is involved with nicotine's pharmacological effects

comes from human research in which smokers appear to have a lower incidence of Parkinson's disease than nonsmokers (Kessler 1973). The theoretical model proposed suggests that nicotine is somehow metabolized to nicotinic acid. which will alter the amount of DOPA available to DA neurons. Support for this theoretical model has also been obtained at the Medical College of Virginia in studies where nicotinic acid, given to rats orally, facilitated the accumulation of DA following i.p. doses of DOPA (Black 1977). The hippocampus may thus be a primary site of nicotinic action and DA may also be involved in the action of nicotine (figure 1). DA systems, however, appear to affect cholinergic systems quite indirectly, via either the septum or N. Accumbens.

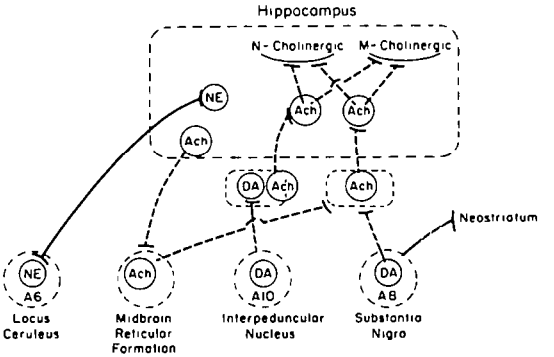
Schechter and Rosecrans (1972a) also studied arecoline in this paradigm and showed that atropine, but not mecamylamine, antagonized its DS effects. Methylatropine, a peripherally acting muscarinic blocker, was unable to antagonize the DS, indicating arecoline produced its effect via a central M-cholinergic stimulation. Schechter and Rosecrans (1972b) also showed that rats could be trained to discriminate nicotine from arecoline, which suggests that there are separate central N- and M-cholinergic receptors.

Other research (Rosecrans and Chance 1977) has indicated that peripheral doses of nicotine (100-400 µg/kg, S.C.) will generalize to nicotine administered via the intraventricular (iv-t) route of doses ranging from 16-32 µg. The mechanism of ivt generalization also appears to be a function of N-cholinergic stimulation. In addition, generalization studies involving nicotine metabolites (cotinine) have indicated that nicotine is not producing its effects via some active metabolite. Support for this has also been obtained by correlating behavior to brain area nicotine levels (Rosecrans and Chance 1977). Time-duration and dose-response experiments indicated a close relationship between behavior and physiological drug level. This research delineates how nicotine produces stimulus control of behavior in rats. Parametric studies have provided information describing the duration and mechanism of action of nicotine (Rosecrans and Chance 1977).

SPECIFICITY OF THE NICOTINE DS

Four years ago a research program designed to search out known chemical compounds which might produce DS effects similar to those of nicotine was initiated in this laboratory. We began by studying d-amphetamine under a variety of training conditions and observed this stimulant to be quite unlike nicotine (Chance et al. 1977). In addition, other types of stimulants such as caffeine and magnesium pemoline were found to be devoid of nicotine-like effects. The responses elicited indicated that the rats studied perceived these compounds as unlike either nicotine or saline. Response rates on the nicotine-current lever never averaged 60 percent following doses of d-amphetamine, indicating that a CNS effect was perceived but was qualitatively different from nicotine. In addition, drugs such as LSD or morphine elicited only saline-like responding.

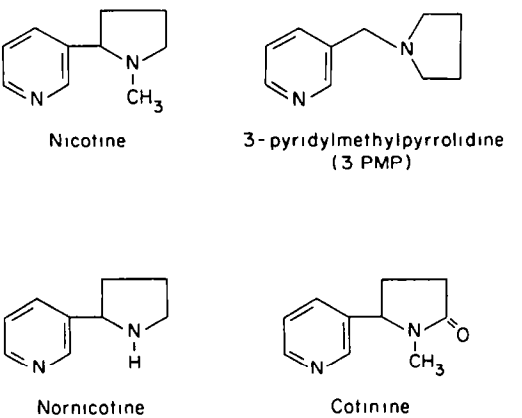
FIGURE 1



CATECHOLAMINE - CHOLINERGIC INTERRELATIONSHIPS

A description of the interrelations between catecholamine and neuron connections. Abbreviations are: DA = dopamine; ACh = acetylcholine; NE = norepinephrine.

FIGURE 2



Structures of nicotine analogs and metabolites. Respective ED-50 generalization doses with nicotine were as follows: Nicotine = 52.4 µg/kg; 3PMP = 263.4 µg/kg; nornicotine = 960.5 µg/kg; cotinine did not generalize with nicotine.

To complete this study we also evaluated a series of nicotine and pyridine derivatives. Nicotine metabolites such as cotinine were inactive, but nornicotine did produce a partial generalization. Interestingly, lobeline, a compound considered to act like nicotine, was also without effect (Schechter and Rosecrans 1972c). The consensus of studies indicated that only one compound, 3 PMP (figure 2), which is a chemical isomer of nicotine, had a significant nicotine-like effect (Rosecrans et al. 1978). In fact, Kallman et al. (1978) have shown that 3 PMP appears to act like nicotine centrally. That is, it appears to be producing its stimulus effects by stimulating N-cholinergic receptors.

Finally, it should be added that the ability to exert stimulus control of behavior is not a property only of nicotine. Most psychoactive drugs exert DS control of behavior. In many instances there is a good correlation between stimulus strength, drug abuse, and therapeutic potential within a specific psychopharmacological class of compounds (Over-ton 1978). The intriguing aspect of nicotine in relation to other psychoactive drug classes is its apparent specificity. It should be kept in mind, however, that we have been limited in our research to the numbers of chemical compounds available for study. The picture could change as other chemicals are synthesized.

RELEVANCE TO SMOKING BEHAVIOR

To understand better how our research efforts may correlate to real world events, a model describing the sequence of events leading to drug dependency in man has been developed (figure 3). We have broken the sequence into three stages, which helps separate out all the contingencies involved in the development of drug dependency. The DS properties of a specific agent appear to us to fit into stages II and III.

For a drug to be abused, it first must be recognized by the individual (Discriminative Stimulus). Thus, there must be a state change, which is contingent upon the detection level of the individual. This, plus the quality of the state change, will have a direct bearing on the probability that the drug will be used again (Reinforcement Potential). For example, cocaine produces strong qualitative state changes in animals and is rapidly self-administered, suggesting it to be reinforcing. LSD, on the other hand, also produces a profound state change, but the probability of continued self-administration is low, suggesting it may be somewhat aversive. Nicotine produces a potent DS effect in animals, but some will argue that it does not produce the same rate of continued self-administration observed with other reinforcing drugs. At least, many investigators have had difficulty demonstrating self-administration of nicotine by animals. Thus, what is it about nicotine which leads to its being used initially? This is an issue we have discussed much in our laboratory, and as yet we have not developed an adequate hypothesis, at least in terms of a behavioral or neurochemical mechanism. We are satisfied at this time that the nicotine DS model does provide us with a good animal analog to human drug effects and that much of the information we obtain appears quite relevant to how this drug produces its effects in man.

In the process associated with nicotine use, the drug may not always be the primary reinforcer for smoking behavior. Instead, other psychological and sociological variables associated with the act of smoking may also be primary reinforcers, and nicotine becomes a secondary reinforcer once the habitual use stage occurs (figure 3). At this stage the discriminative stimulus properties of nicotine become important. The repeated pairing of task performance with the nicotine may provide the necessary signal for maintenance of the smoking behavior. This phenomenon, sometimes called state-dependent learning, is also a prominent property of other psychoactive drugs (Weingartner 1978; Overton 1978), and there is no reason to believe that it is not also the case with nicotine.

Our hypothesis, then, suggests that the maintenance of smoking behavior (or the dependency stage) may be in part related to the state-dependent or discriminative stimulus properties of nicotine. Experimental evidence for such a hypothesis is lacking in man, but we do have some support for such a concept in animal subjects (Rosecrans and Chance 1977). In one study, rats were trained in a one-trial learning paradigm to avoid a shock under saline or nicotine conditions. After the initial training sessions rats were reexposed to the apparatus 24 hours later. The data jndicated that rats trained in the nicotine state avoided the shock less often after a repeated exposure unless nicotine was readministered prior to the test session. Thus, nicotine provided the stimulus which enabled the rat to avoid being shocked.

According to our hypothesis a smoker would need to maintain a constant level of nicotine to adequately perform certain behaviors. This point is speculative, though, and should be tested. However, the specific nature of the nicotine DS suggests that this property of nicotine is one of the many factors important for the maintenance of smoking behavior.

DIRECTIONS FOR FUTURE RESEARCH

There are three research areas that need to be expanded:

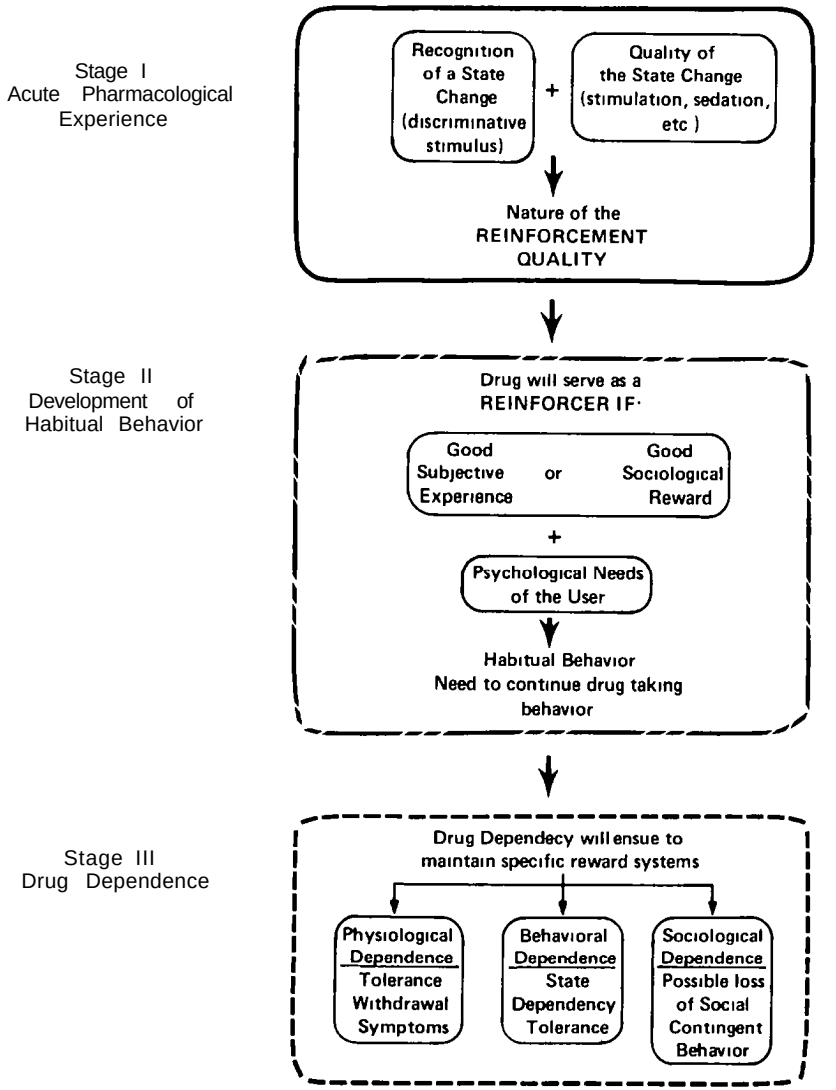
1) Sites and mechanisms of nicotine action

There is much to be learned about the way in which nicotine produces its effects. Until now, little effort has been given to pursuing how and where nicotine exerts its many pharmacological effects. In this respect, areas to be further explored include: a) brain sites of nicotine action; b) neurochemical mechanisms, specifically DA-ACh interactions (figure 1); and c) studies investigating the mechanisms of behavioral tolerance, physical dependence, and state-dependent learning. This last area is of special importance as it relates to dependence in human subjects.

2) Human research

The hypothesis developed in this paper suggests that nicotine could be acting as a reinforcer of smoking behavior via its DS or state-

FIGURE 3



An overview of the sequence of events leading to drug dependence, as viewed by this laboratory.

dependent properties. This question needs to be studied in depth in human subjects. The necessary methodologies have been developed, and what is needed now is some fundamental research into the question.

3) Organic molecular mechanisms of nicotine: therapeutic implications

The fact that millions of humans smoke tobacco suggests that many people obtain some benefit from this behavior. Furthermore, if this behavior can be associated with nicotine, then one could suggest that nicotine could have potential as a therapeutic agent. The history of the pharmacology of marihuana is relevant to this point. At present, much research is being devoted to studying the possible therapeutic potential of the tetrahydrocannabinols and synthetic derivatives, even though many consider this drug to be potentially dangerous. Thus, one wonders if some time should be devoted to studying nicotine analogs with the same point of view. Such research would serve two purposes. First, a nicotine-like compound could conceivably be developed which has psychotherapeutic potential. Second, a research program designed to synthesize nicotine analogs would also assist us in determining the structure and configuration of the nicotine receptor.

ACKNOWLEDGMENTS

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Chapter 7

Nicotine Self-Administration in Rats

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INTRODUCTION

Contrasted with the voluminous and still burgeoning literature devoted to laboratory study of the self-administration of morphine, cocaine, amphetamine and the barbiturates, studies of the self-administration of nicotine have been few in number. The entire literature available to us is less than a dozen papers; Clark (1969), Lang et al. (1977), and Hanson, Ivester and Morton (1977) reported data collected with rats, Deneau and Inoki (1967) and Yanagita (1973) with primates.

The reasons for this apparent neglect of a compound self-administered by a large percentage of the human population are uncertain. Techniques for such studies have long been available, and the feasibility of the study of the self-administration of nicotine was demonstrated by Deneau and Inoki (1967) 10 years ago. It is likely that the less dramatic effects demonstrable in the laboratory with nicotine compared to the effects possible with morphine or cocaine may have overshadowed the potential importance of such studies and have resulted in investigators directing their efforts toward the study of substances yielding more striking and voluminous data.

The studies of nicotine self-administration to be reported in this paper were undertaken based on the assumption that nicotine is the substance in tobacco smoke that leads to man's use of tobacco. It was further assumed that such studies were relevant to understanding smoking in humans, and as a model could lead to a successful pharmacological "treatment" for smoking.

METHODS

Because of their small size, ease of maintenance,and the possibility of assembling a large colony for study, the rat was chosen as an experimental animal. Four hundred to 500-gram male albino

rats (Sprague-Dauley-derived, Buckshire Corporation) were lm-planted with Weeks-Davis type jugular cannulae using ether anesthesia. After recovery from the anesthetic, the rats were fitted with Weeks-type "saddle and leash" restraint devices to protect the catheters and placed in individual operant conditioning cages. For two days following surgery the rats were infused with nicotine solution or saline every 30 minutes; on the third day operant conditioning levers were placed in the chambers and all further Infusions were dependent on lever depressions. Thirteen-second injections of 0.1 ml of solution were delivered following every lever depression (FR 1). Responses emitted during an infusion were ignored.

Food and water were available at all times; the room housing the rats was maintained at 21-22°C; lights were on in the room 12 hours daily from 6:00 a.m. to 6:00 p.m. Patency of individual catheters was checked at weekly intervals or following the completion of a particular study. All data collected with a particular rat for a study were discarded if testing indicated that the catheter had failed.

A group of 42 identical test cages were used for the studies to be reported. Rats were randomly assigned to test chambers and to studies. Where noted, more than a single compound was tested in individual rats. A total of 276 rats were used to collect the data.

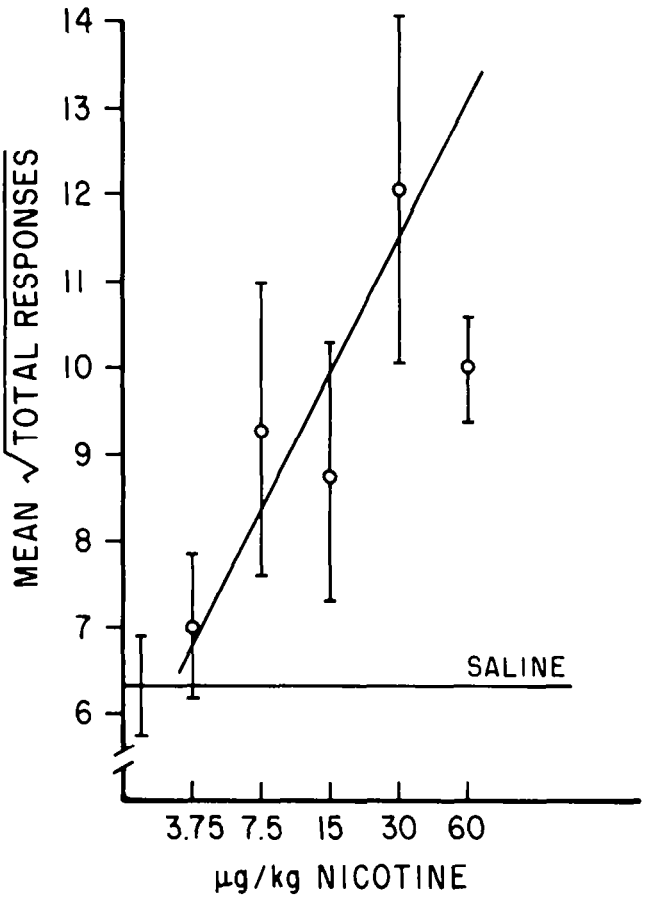
RESULTS

Self-Administration of Nicotine; Dose-Response Relationship

Groups of 9-10 rats (N=59) were implanted with jugular cannulae and placed in the test chambers with the operant levers removed. Every 30 minutes for two days the rats were given automatic injections of saline, or 3.75, 7.5, 15, 30, or 60 µg/kg of nicotine. At the end of the 48-hour period the automatic injections were stopped and the operant conditioning levers were placed in the chambers; for the next 10 days each lever press resulted in an injection of the same dose of nicotine or saline as was given in the pretreatment period.

The data collected are shown in figure 1 as mean square root responses for each of the groups. The horizontal line indicates the mean number of responses emitted by the saline control group over the l0-day test period. The vertical lines are standard errors. A linear function fitted to the data by the method of least squares is also shown. The value for 60 µg/kg of nicotine was omitted from this estimation. Doses greater than 60 µg/kg resulted in even lower response rates, suggesting that for naive rats doses of 30-60 µg/kg are maximally reinforcing; it can be noted, however, that doses in excess of 100 µg/kg, which resulted in convulsions following each injection, were self-administered at rates significantly higher than saline controls.

FIGURE 1



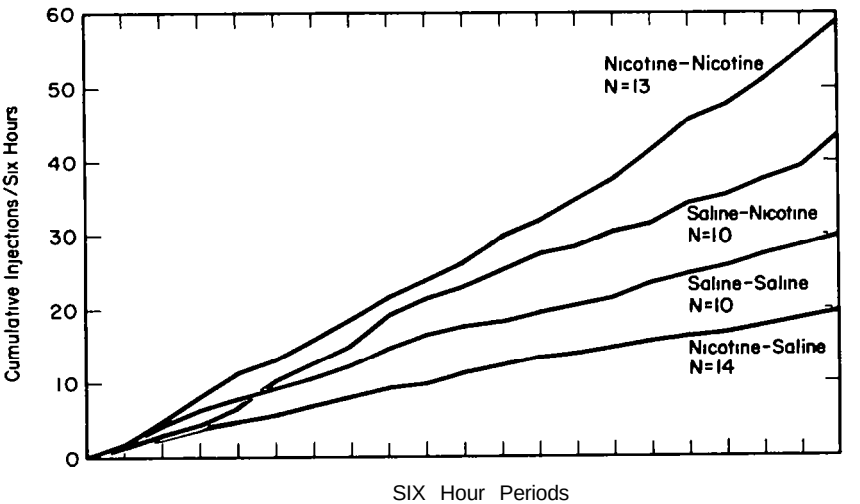
Dose response *relationship for self-administration* of *nicotine. Data points represent average number of infusions of various nicotine solution over a 10-day period. The horizontal line is the saline control group mean; the vertical lines show standard errors.*

It was concluded based on these data that rats will self-administer nicotine at rates significantly higher than control levels over a relatively wide range of doses, and that it is possible to demonstrate a relationship between dose level and rate of self-administration.

Effects of Pretreatment with Nicotine on Nicotine Self-Administration

Groups of 10-14 rats were implanted with jugular catheters and placed in individual cages as in the preceding experiment. The rats were assigned randomly to two groups receiving automatic injections of either saline or nicotine (60 µg/kg) every 30 minutes. After two days the rats were divided into four groups and assigned to one of four treatment conditions, self-administering nicotine or saline after pretreatment with either saline or nicotine.

FIGURE 2



Cumulative response curves of self-admnistration of nicotine (160 µg/kg) or saline over a 5-day period following pretreatment with injections every 30 minutes of either nicotine (60 µg/kg) or saline for two days. The curves are identified by the treatments given during the two phases of the study. The mean values on the final day of the study are significantly different.

The data, collected over a 5-day period of self-administration, are shown in figure 2 as cumulative curves. Only the data collected during the last three days of the study were analyzed. The means of the groups were significantly different from each other. The shape of the curves indicated that both groups self-administering nicotine were increasing their rates of response while the other two groups self-administering saline were decreasing their average response rates over the 5-day period.

It was concluded that a significant increase in response rates as a result of nicotine self-administration compared with saline is demonstrable in as short a period as 5 days. Pretreatment with automatic nicotine injections was found to significantly increase the rate at which nicotine is self-administered, compared with animals pretreated with saline. Pretreatment with automatic nicotine injections was found to significantly depress the rate of saline self-administration: the decreased rates might be considered in some way analogous to withdrawal symptoms seen following exposure to opiates. Further study of this effect is indicated.

Based on these data, in order to facilitate training, all rats except for those used in special studies were subjected to a 2-day period of automatic injections of nicotine before being allowed to self-administer the compound.

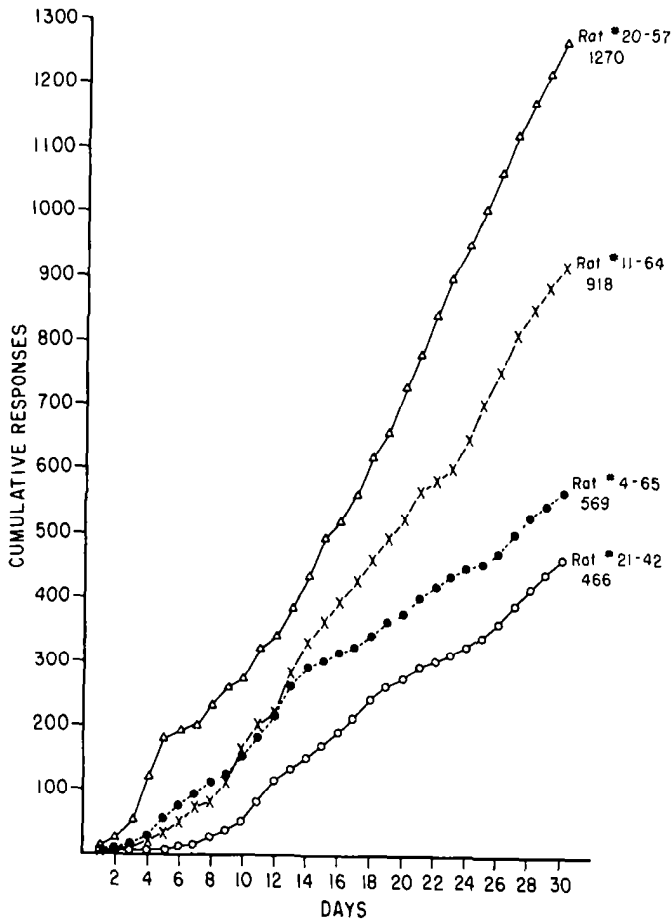
Course of Nicotine Self-Administration

The data examined so far were gathered over very short periods of time (up to 10 days) following first exposure to lever-controlled injections of nicotine. If longer periods of exposure are considered, the trend toward increasing daily dosages noticed in figure 2 becomes even more pronounced. Data collected with 4 rats self-administering nicotine (60 µg/kg) over a 30-day period are shown in figure 3 as cumulative curves. The rats, which were selected to represent a range of response rates, showed an overall acceleration in response rates.

It is possible this tendency to increase daily dose levels is due to the development of tolerance, either to the reinforcing actions of nicotine (requiring higher dosages) or alternatively, to the limiting side effects produced by nicotine (allowing higher dose levels). This tendency to increase the rate of administration has been noted in all rats studied to date. Correlated with the increase in total nicotine intake is a slow but consistent increase in the amount of nicotine necessary to induce a convulsion.

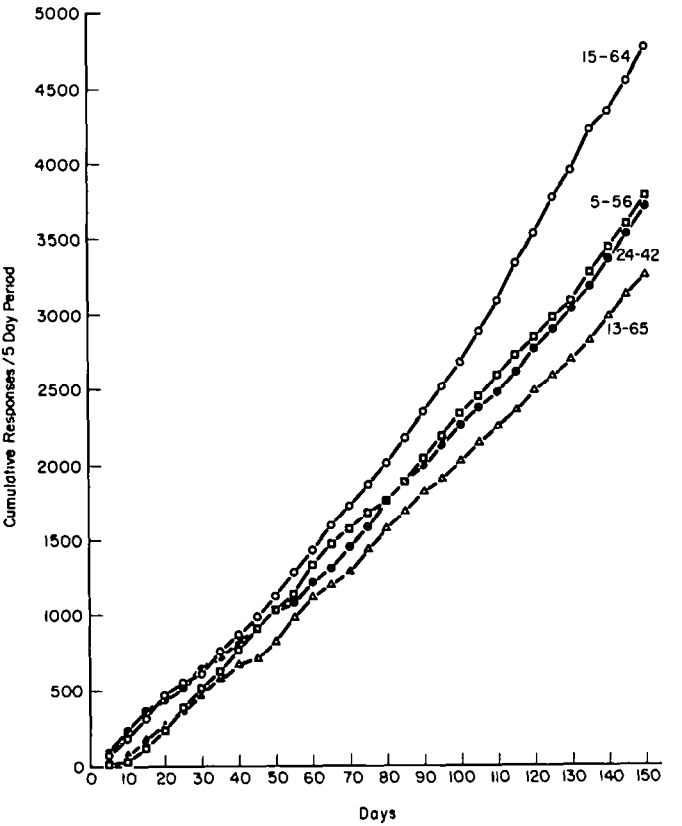
That this phenomenon is not restricted to short exposures is illustrated in figure 4. In a manner similar to that in figure 3, cumulative curves, representing responding over a 5-month period, are shown for 4 additional rats. The increments in this case equal 5 days, which "washes out" minor day-to-day fluctuations. The cumulative curves of these animals also show accelerating rates of response. It should be noted that all 4 of these rats were subjected to a variety of pharmacological treatments, which changed response rates on a daily basis but did not seem to have affected the overall course of responding.

FIGURE 3



Cumulative curves of self-administration of nicotine for 4 rats over a 30-day period. The total number of responses for each animal is indicated under its respective identification number.

FIGURE 4



Cumulative curves of self-administration of nicotine for 4 rats over a period of five months. The numbers are for animal identification.

During the last 5-day period shown in the figure, the rat with the greatest nicotine intake (Number 15-64) averaged 44 responses a day, equalling 2.64 mg/kg of nicotine, a high but by no means unusual rate of self-administration.

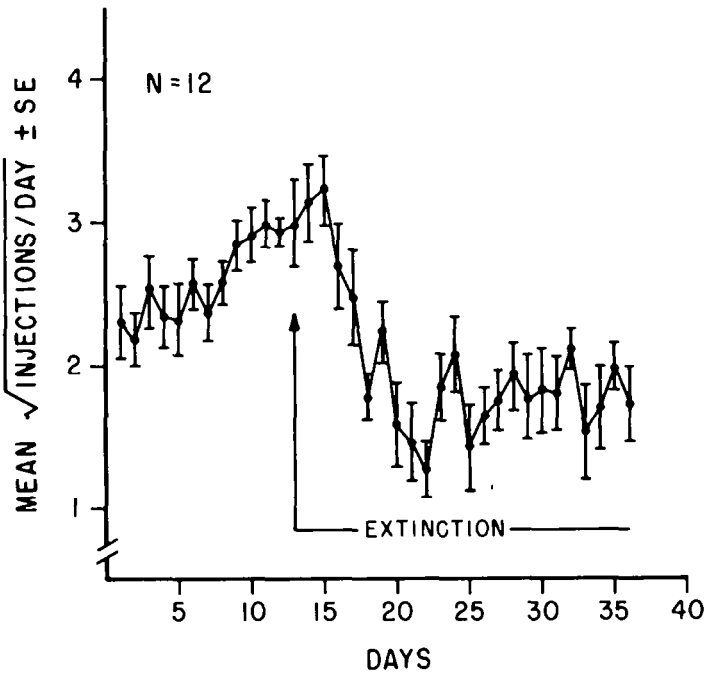
Extinction of Lever Pressing Reinforced by Nicotine

Reports of systematically collected extinction data following reinforcement with drug infusions are practically nonexistent in the self-administration literature. The data that are available are almost entirely devoted to the study of "cross-self-administration" of selected compounds and are usually single animal studies. [See, however, Yokel and Pickens (1976)]. We felt that

in order to unequivocally categorize nicotine as a reinforcing substance, extinction data was necessary.

Following our standard procedure, 12 rats were implanted with cannulae, placed in individual cages, pretreated for 2 days with nicotine infusions (60 µg/kg) every 30 minutes and on the third day given operant conditioning levers. All further nicotine infusions were dependent on lever depressions. After 12 days of self-administration, saline was substituted for the nicotine solution. and lever pressing was recorded for 24 more days (extinction).

FIGURE 5



Extinction of lever pressing following reinforcement by nicotine infusions. Data shown are means and standard errors of the data transformed to square roots. Extinction was begun on the twelfth day of the study, as indicated by the vertical arrow.

The data collected are shown in figure 5 expressed as the means and standard errors of the square roots of the values. The group of rats showed the usual increase in response rate for the first 12 days of the study. The mean rate of response on Day 12 was approximately 50 percent higher than on Day 1, a statistically significant difference (paired values t-test). After withdrawal of nicotine the mean rates continued to increase on Days 13-15,

the difference in mean rates reaching significance compared with Day 12 by Day 15. The rates thereafter decreased day by day, reaching the lowest point on Day 22 followed by a slight overall increase through Day 36. The rate of responding in extinction was significantly different from the mean rate on Day 12 by Day 18 and thereafter.

Nicotine self-administration appears to generate extinction data comparable to that following other types of reinforcement. The prolonged period of increased rates of response at the beginning of extinction is unusual but is somewhat similar to the effects we have seen in extinction following reinforcement with morphine. Considering the fact that the animals were reinforced on a FR 1 schedule and were exposed to this schedule and to extinction 24 hours a day, the course of extinction was dramatically prolonged, which again is very similar to extinction following morphine (unpublished data).

The Effects of Selected Compounds on Nicotine Self-Administration

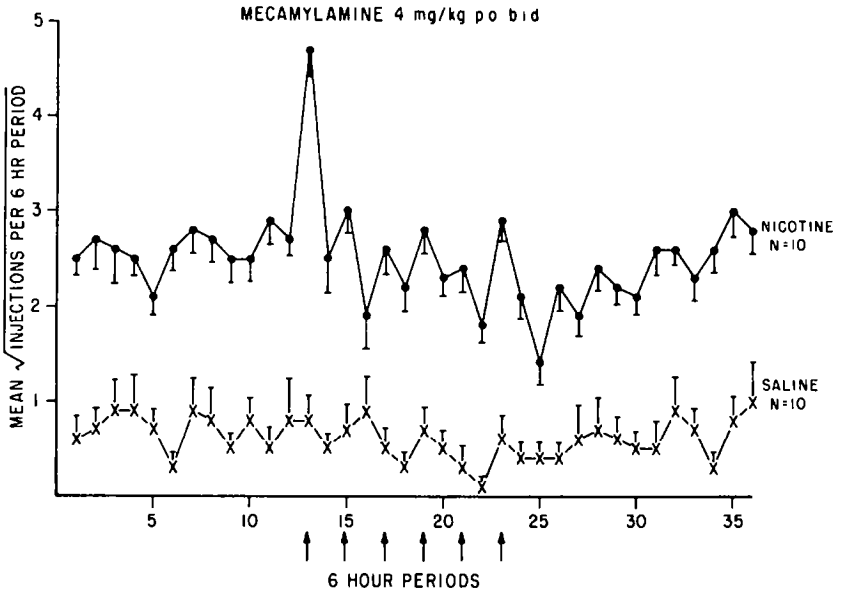
The effects of 9 compounds were studied in groups of rats self-administering nicotine (60 µg/kg). Compounds with a range of pharmacological actions were selected, all of which have received intensive study in a variety of behavioral and neurophysiological experiments.

Groups of 10 or more rats self-administering either nicotine solution or saline were selected from the colony for a particular study. Individual rats were used repeatedly; however, no rat was used more than once for the study of a particular compound. No rat was selected for study that had not been in the colony for at least 3 weeks; nicotine-self-administering animals were not selected for study unless their average daily response rate fell outside the 95 percent confidence limits of an historical saline-self-administering reference group and showed clear evidence of circadian rhythm in responding (greater number of responses during 12-hour dark period).

All compounds were administered orally twice daily for 3 days (9:00 a.m. and 9:00 p.m.) after a 3-day period of twice daily dosing with water at the same times. Data were also collected for 3 days following drug administration as an additional control. The patency of the catheters was tested on Day 10 of the study.

The data collected are shown in figures 6-14 as the means and standard errors of the square roots of the number of injections for consecutive 6-hour periods over the 3-day period. The arrows below the abscissa indicate the times of dosing. The doses selected for study were large enough in all cases to show pharmacological activity in some appropriate test system. All dosages of the compounds were calculated as the weight of the base compound and administered dissolved or suspended in water.

FIGURE 6



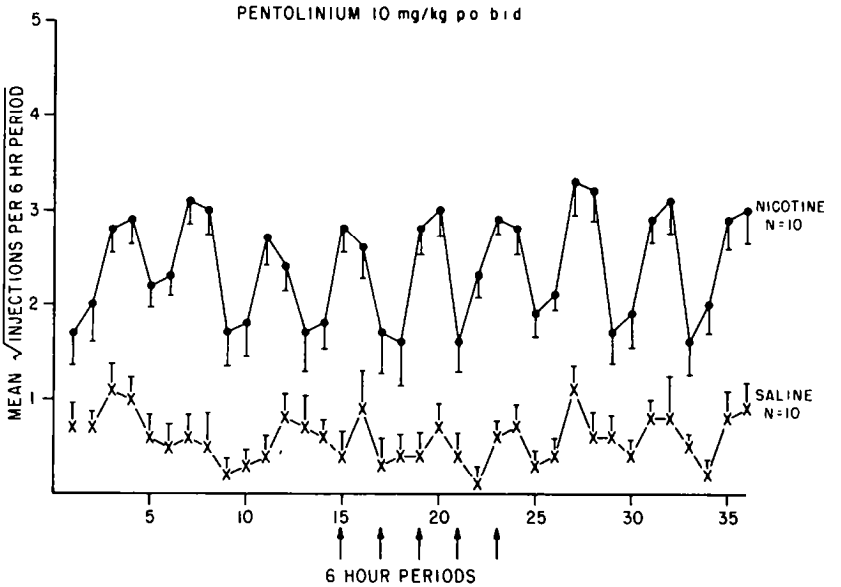
Effects of 4 mg/kg mecamylamine b.i.d. on nicotine and saline self-administration. The vertical lines indicate standard error of the mean. Mecamylamine was administered at the times indicated by the arrows; dosing with water was done at comparable time periods for the preceding 3 days.

Mecamylamine and Pentolinium: The effects of 4 mg/kg p.o. of the ganglionic blocker, mecamylamine, are shown in figure 6. The difference between the two curves was significant at all time intervals, the mean response rate of the nicotine group being generally 7 times that of the saline group. Although it is more pronounced in the later figures, a clear circadian rhythm is in evidence for the data collected preceding treatment. Following the first dose of mecamylamine, a dramatic and highly significant increase (approximately 4-fold) in nicotine self-administration occurred. The rats appeared active and slightly tremulous within 5 minutes of dosing. Repeated lever responses were emitted during the next 15-20 minutes followed by quiescence and assumption of the usual sleep posture. The total effect lasted *no* more than 45 minutes. No overt signs of high nicotine dosage were seen. The remaining doses did not produce similar effects but resulted in a slow decrease in response rates. The average number of nicotine injections for the 24-hour period immediately following the 3-day mecamylamine treatment period was significantly lower than the average number of responses emitted the day preceding treatment. A similar, but nonsignificant, decrease was also seen for the control group. The last 3 days of the study

resulted in a slow daily increase in response rates. Mean responses on the last day of the study are not significantly different from the mean responses on the last pretreatment day, suggesting the original control levels had been recovered.

This effect of mecamylamine, considering the known nicotine-blocking activity of this compound [Stone, Meckelnburg, and Torchiana (1958)] , was not unexpected. The dramatic increase in self-administration following mecamylamine appears very similar to the effect seen following the administration of naloxone to rats self-administering morphine (unpublished data), and perhaps in similar fashion could be understood as a direct receptor blockade. The marked lack of effect following the remaining five doses in the series is puzzling and no ready explanation is presently available.

FIGURE 7



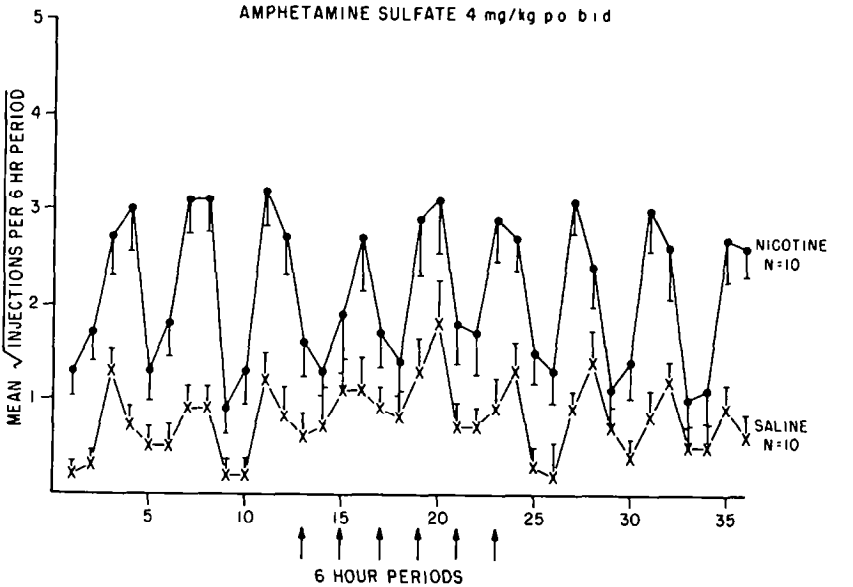
Effects of pentolinium, 10 mg/kg p.o. b.i.d. See figure 6 for details of the study.

For comparison with mecamylamine, the peripheral ganglionic blocker pentolinium was tested in groups of rats self-administering nicotine or saline. The data collected are shown in figure 7.

The distinctive pattern of responding controlled by the light-dark cycle is clearer with these groups of rats. The separation in response rates between the two groups is clear and was statistically significant throughout the study. In sharp contrast to the effects produced by mecamylamine, pentolinium had no measurable effect on either nicotine or saline self-administration.

These data lend much weight to the conclusion that the effects seen with mecamylamine were due to the central nervous system activity of the compound and, by extrapolation, that the locus of the reinforcing activity of nicotine is also in the central nervous system.

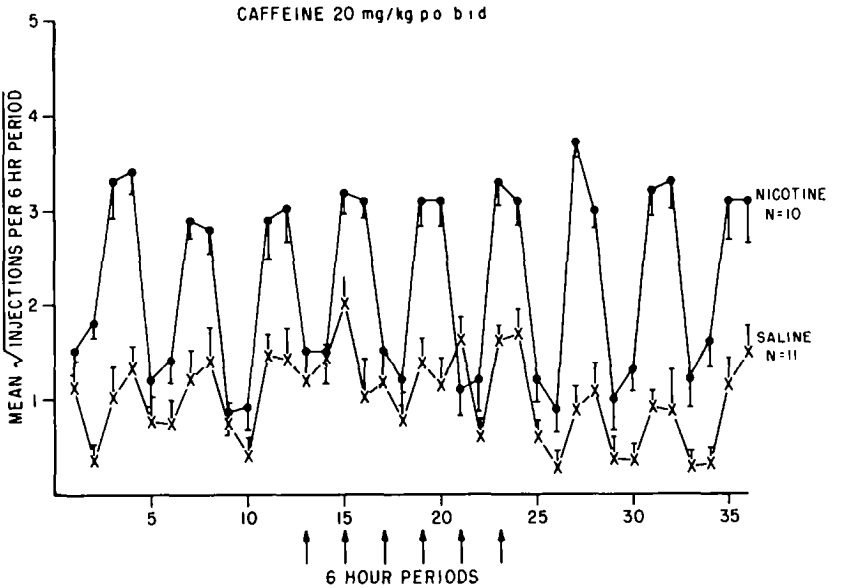
FIGURE 8



Effects of amphetamine, 4 mg/kg p.o. b.i.d. See *figure 6 for details.*

Amphetamine and Caffeine: Figures 8 and 9 show the effects of the central nervous system stimulants, amphetamine and caffeine, on nicotine and saline self-administration. The doses tested, amphetamine, 4 mg/kg p.o. and caffeine, 20 mg/kg p.o., produced increased activity and, in the case of amphetamine, stereotype within 15 minutes following the first dose and throughout the testing period. The rate of responding was significantly increased for the animals self-administering saline during the drug test period for both amphetamine and caffeine. No significant change in nicotine self-administration was seen following dosing with caffeine at any interval; however, amphetamine produced a statistically significant increase in responding during the usually inactive periods when the room lights were on (i.e., the 13th, l4th, 17th, 18th, etc., 6-hour recording periods) compared with similar data collected before and after dosing. Response rates were not significantly changed during the "dark periods."

FIGURE 9

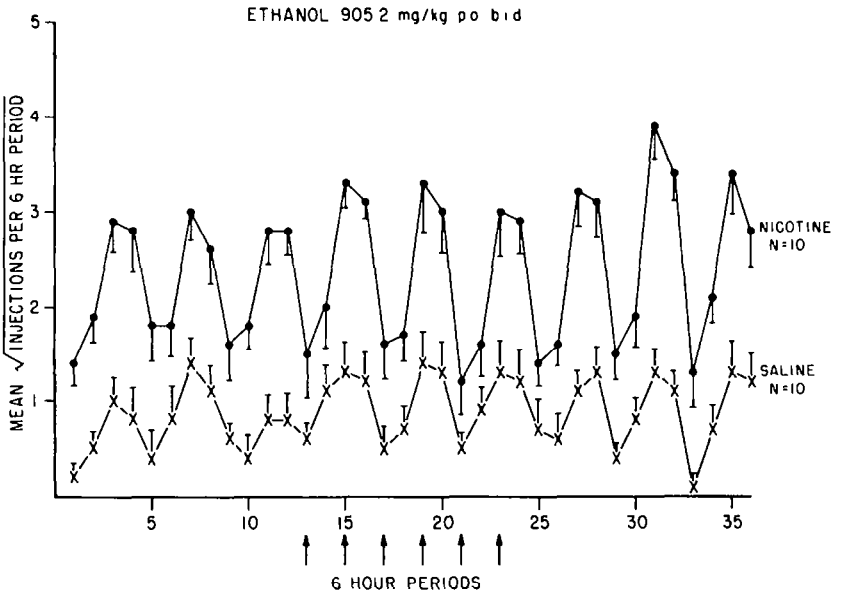


Effects of caffeine, 20 mg/kg p.o. b.i.d. See figure 6 for details.

These effects would appear to be due to general increases in activity and not to any interaction with the pharmacological agents studied. It is interesting to note that the rats did not increase responding (increase nicotine intake) above the control level during the normal periods of high responding (dark periods), even though the immediate effects of dosing as well as the long-term effects would have been present. It is possible that limiting side effects of nicotine may have controlled the actual maximal amount tolerated, and the rats were demonstrating something akin to titration of the dose of nicotine.

Ethanol, Chlordiazepoxide, Phenobarbital and Diphenylhydantoin: The data collected with ethanol, chlordiazepoxide, phenobarbital and diphenylhydantoin are shown in figures 10, 11, 12 and 13. These four compounds, although differing widely in their pharmacological activities and tested at doses which produced observable sedation and ataxia, unexpectedly increased nicotine self-administration following the 3-day dosing period, compared with predosing control levels. This Increased responding was not seen in the saline self-administering control groups. In the case of chlordiazepoxide and diphenylhydantoin, the increase in rates occurred soon after dosing was initiated in the case of diphenylhydantoin had reached levels some three times higher than the predosing control levels by the last day of the study.

FIGURE 10

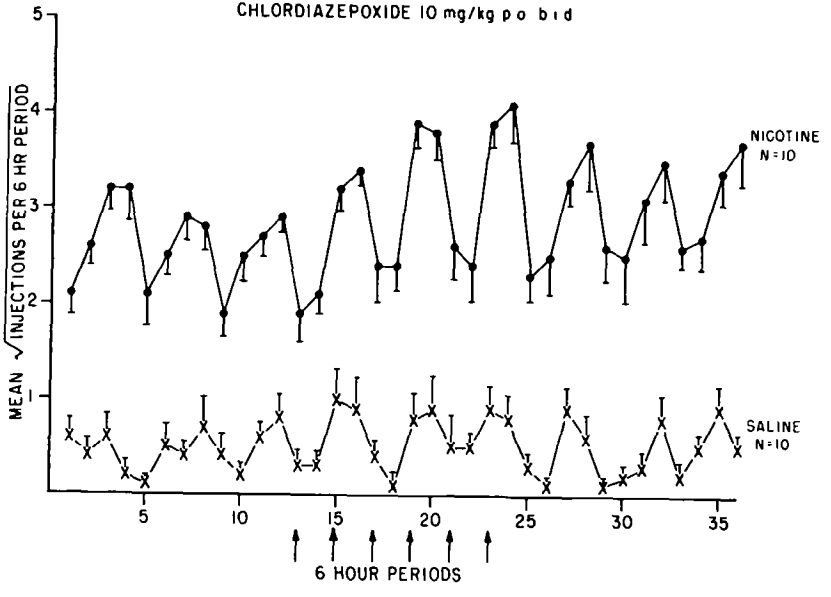


Effects of ethanol, 905 mg/kg p.o. b.i.d. See figure 6 for details.

An explanation for this unexpected effect is not readily available. The fact that the saline self-administering group did not show a comparable increase suggests that simple stimulation was not a factor. Since the response rates remained high or continued to Increase after dosing had stopped, some fundamental change may have occurred, perhaps a change in the metabolic rate of nicotine, or possibly an increase in tolerance to the limiting side effects of nicotine. Some support is offered for this first possibility by the known ability of these compounds to modify enzymatic systems. Assuming that convulsions and the preconvulsant state are some of the limiting side effects of nicotine, dosing with anticonvulsants, such as phenobarbital and dilantin, could possibly unmask the reinforcing properties of high doses of nicotine by preventing these side effects and thereby "allowing" higher dosages of nicotine to be self-administered, leading to the more rapid development of tolerance.

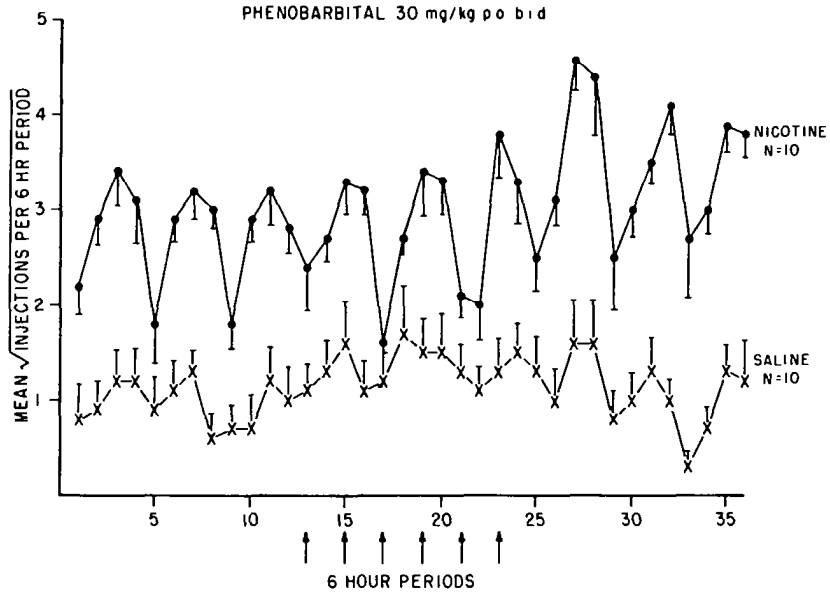
From the data available, none of these four compounds could be considered to have a specific effect on nicotine self-administration.

FIGURE 11



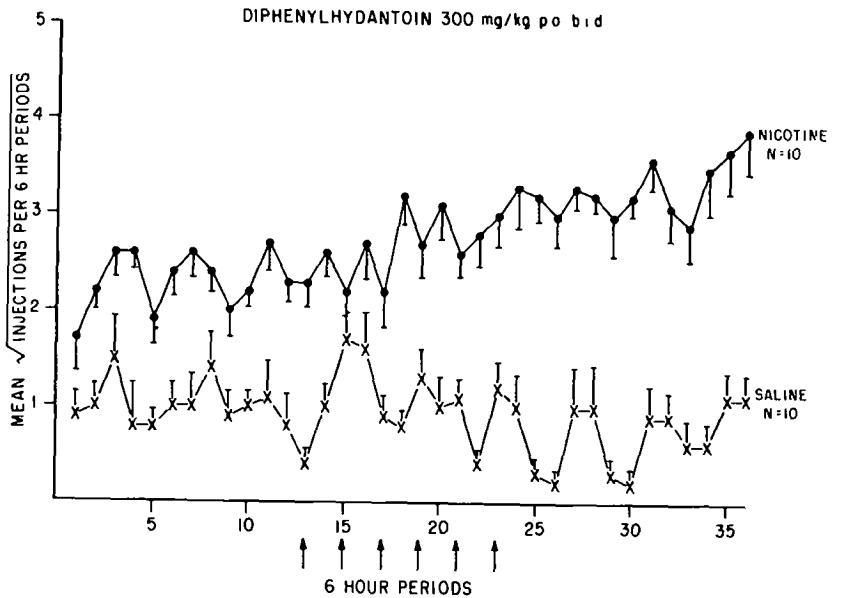
Effects of chlordiazepoxide, 10 mg/kg p.o. b.i.d. See figure 6 for details.

FIGURE 12



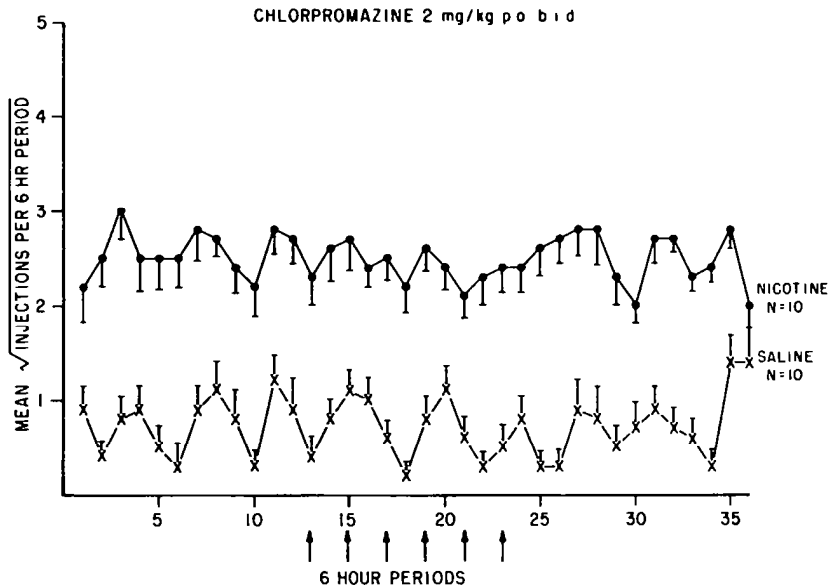
Effects of phenobarbital, 30 mg/kg p.o. b.i.d. See figure 6 for details.

FIGURE 13



Effects of diphenylhydantoin, 300 mg/kg p.o. b.i.d. See figure 6 for details.

FIGURE 14



Effects of chlorpromazine, 2 mg/kg p.o. b.i.d. See figure 6 for details.

Chlorpromazine: The data collected with chlorpromazine are shown in figure 14. The dose used, 2 mg/kg p.o., produced ataxia and sedation which became more pronounced with succeeding doses. In spite of the severity of the side effects produced by the dosing regimen, there were no significant changes in the overall rates of nicotine self-administration other than disruption of the normal circadian rhythm. The saline self-administration control group, surprisingly, did not show a similar effect. The response rates for this group were, of course, very low. Normal patterns of responding were recovered 2 days after cessation of dosing; at approximately the same time sedation and ataxia were no longer noted.

DISCUSSION

While clearly possessing reinforcing properties, nicotine can only be classified as relatively weak in this regard when it is compared with morphine, amphetamine, or cocaine (Pickens et al. 1978). Of particular interest in the study of nicotine self-administration, and a factor which differentiates it from other compounds, is the remarkably slow onset of self-administration in the rat, complemented by the tendency gradually to increase the daily dosage over extended periods of exposure. This slow increase in the daily rate of nicotine self-administration could be explained as due to the development of tolerance either to the reinforcing properties or to the limiting side-effects of nicotine. Concurrent administration with an appropriate dose of the peripherally-acting ganglionic blocker, pentolinium, might yield data of interest in this regard since at least some of nicotine's side effects, but not its actions on the central nervous system, would be blocked by this treatment.

The difficulties experienced by Lang et al. (1977) in demonstrating the reinforcing properties of nicotine are easily understood considering they studied acquisition of lever pressing for only 90 hours. It would seem likely that longer periods of exposure would have yielded data comparable to those presented here.

The surprising resistance to extinction generated following a short period of reinforcement by nicotine suggests that "feedback" from this reinforcement system is poor; we would expect that partial schedules of reinforcement would be poorly supported by nicotine. To date we know of no studies of partial reinforcement schedules using nicotine infusions as a reinforcer. It would appear, however, that any attempt to demonstrate the control of lever pressing by partial schedules of reinforcement would be most likely to succeed if done after a significant daily intake of nicotine had been established. The implications of this unusual resistance to extinction are obvious in any comparison with human smoking and may be of use in understanding the problems of withdrawal from smoking.

The effects on nicotine self-administration of standard compounds studied clearly demonstrate the difficulties in achieving pharmacological manipulation of nicotine self-administration. Mecamylamine, which is a specific blocker of nicotine's actions, produced a dramatic but short-lived increase in nicotine self-administration. Several explanations are possible; the most likely would appear to be a direct blockade of nicotine at the receptor site in the central nervous system, the appropriate comparison being with the interaction of naloxone and morphine. If this is true, an effort to identify specific nicotine receptor sites would be of value. Still to be accommodated in such an explanation is the unusual resistance to extinction observed (the rats were self-administering saline in extinction, the perfect analog of "blockade" of nicotine) following a short period of nicotine reinforcement. Also to be explained is the apparent ineffectiveness of additional doses of mecamylamine in either increasing or decreasing nicotine self-administration.

The constancy of the rates of nicotine self-administration following heroic doses of a stimulant, such as amphetamine, or depressants, such as chlorpromazine or phenobarbital suggests that in spite of all its apparent fragility as a reinforcer, in these studies of nicotine we were dealing with a major behavioral control which was not easily disrupted. The implications for the study of smoking are again obvious.

RECOMMENDATIONS FOR FURTHER RESEARCH

1. Systematic studies of self-administration of nicotine should be extended to other species, such as the monkey, even though the rat may well remain the test animal of choice.

2. Self-administration of the main metabolites of nicotine should be studied, since it is possible the "reinforcing" properties of nicotine are shared with those of a metabolic byproduct.

3. To better bring nicotine into the mainstream of self-administration studies, partial schedules of reinforcement could be studied with either rats or primates.

4. While technically somewhat difficult, the study of "sensitive" schedule-controlled behaviors, reinforced by food and water concurrently with nicotine self-administration, might allow the study of the nicotine abstinence syndrome in laboratory animals.

5. Comparative studies of several representative compounds, using resistance to extinction as a measure of reinforcing "potency," might allow the ordering of compounds in terms of abuse potential. Techniques other than substitution or repeated extinction would probably be most fruitful.

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Chapter 8

The Effects of *d*-Amphetamine, Meprobamate, and Lobeline on the Cigarette Smoking Behavior of Normal Human Subjects

C. R. Schuster, Ph.D., B. R. Lucchesi, M.D., Ph.D., and G. S. Emley, M.S.

In the mid 1960's at the University of Michigan my colleagues, B.R. Lucchesi and C.S. Emley, and I conducted a series of experiments designed to investigate the effects of various drugs on the cigarette smoking behavior of normal volunteer subjects. One of our major interests was the role of nicotine in cigarette smoking behavior.

The subjects used in this experiment were male and female volunteers ranging in age from 21 to 30 years. Each volunteer was given an interview and a complete physical and psychiatric examination before being accepted as a subject. They were told that the purpose of the experiment was to determine the effects of psychoactive drugs on several types of performance tasks and to see how these behavioral changes correlated with changes in various physiological systems. At the end of the experiment the subjects were completely informed of the details of the experiment and the drugs they had been given.

Each subject was confined to a soundproof room for six hours per day for a minimum of 12 experimental days. Heart rate, EKG and blood pressure were continuously monitored. Smoking was permitted ad libitum and a standard breakfast and lunch were provided. Behavioral procedures including time estimation, hand steadiness and a vigilance or monitoring task were scheduled at various times throughout the six hour session. All experimental days had identical testing schedules. The number of cigarettes smoked during the six hour period was recorded and the residual portion of each cigarette was weighed at the end of each session. The subjects were instructed to report any subjective effects attributable to the drug.

In the first experiment we investigated the effects of intravenously infused nicotine bitartrate. The results of this experiment have been presented in detail elsewhere (Lucchesi, Schuster and Emley 1967). In summary, this study demonstrated that doses of 2-4 mg/hour of intravenously infused nicotine produced a small but

significant decline in cigarette smoking frequency and the amount of each cigarette consumed, as estimated by weighing the butts at the end of the day. Of great importance is the fact that at this dosage of nicotine the subjects did not report any unpleasant side effects and were unable to discriminate the drug days from saline control days. Further, the nicotine infusion produced no changes in any of the behaviors generated by the performance tasks, suggesting that its effect on cigarette smoking behavior was specific. We interpreted our data as suggesting that cigarette smoking was a form of drug-seeking behavior and that the drug was nicotine. That the infusion of nicotine produced only small decrements in cigarette smoking behavior could readily be attributable to the fact that cigarette smoking was under strong stimulus control and that the act itself had through association with nicotine become a powerful conditioned reinforcer. Although recent experimental evidence has seriously questioned this role of nicotine (Kumar et al. 1977), it is still my opinion that cigarette smoking is a form of drug-seeking behavior and that nicotine is the drug being sought.

EXPERIMENTS WITH d-AMPHETAMINE, MEPROBAMATE, AND LOBELINE

In subsequent experiments, which have not been reported previously, we studied the effects of orally administered lobeline, d-amphetamine and meprobamate on cigarette smoking behavior. These drugs were selected because at the time these experiments were conducted they were being used alone or in combination by clinical investigators attempting to develop a program of pharmacotherapy for aiding smokers to reduce or cease their cigarette use.

Lobeline is an alkaloid which is the principal constituent of Lobelia,which is obtained from the herb, Lobelia lnflata. Lobeline shares many of the actions of nicotine and cross tolerance has been demonstrated. Because of the pharmacologic similarity, lobeline has been suggested as a substitute for nicotine in people attempting to decrease their tobacco use (Dorsey 1936). Various commercial preparations containing lobeline have been marketed as smoking deterrents.

Neprobamate and amphetamine were suggested as pharmacotherapeutic aids in smoking programs to alleviate the anxiety (meprobamate) or sleepiness (amphetamine) associated with the cessation of cigarette smoking.

The experiments to be reported here differ from the clinical work in that WC used naive subjects who were unaware of the drug being administered. They did not come to us for aid in reducing their cigarette consumption and were not aware that we were studying their cigarette smoking behavior. In contrast, in all of the clinical investigations the subjects were selected because of a desire to stop smoking.

The method used in this study was identical to that used in the first study except that the drugs were given orally rather than intravenously. All drugs were encapsulated in identical gelatin

capsules. The subjects took 2 capsules with milk just before breakfast. The d-amphetamine was given in dosages of 5.0, 7.5, and in some cases 10 mg. The meprobamate was given in dosages of 400 and 800 mg. The drug sessions were always randomized with placebo sessions. Following the testing of these drugs, the subjects were given 3 placebo capsules daily which they took with each meal for 3 consecutive days. This was followed by a 5 day chronic lobeline regimen. The lobeline capsules (2 mg/ tablet) which were made from commercially available lobeline sulfate (with antacids) were crushed, mixed with lactose, and encapsulated in a gelatin capsule. The subjects took 3 lobeline capsules per day (one with each meal) for 5 consecutive days and were tested in the experimental procedure on days 1, 3, and 5 of the chronic regimen. This was the dosage regimen suggested by the manufacturer for the use of this product.

Six subjects were used in this series of studies. One subject failed to complete the lobeline portion of the study, reducing the number of subjects to five during the final stage of the experiment.

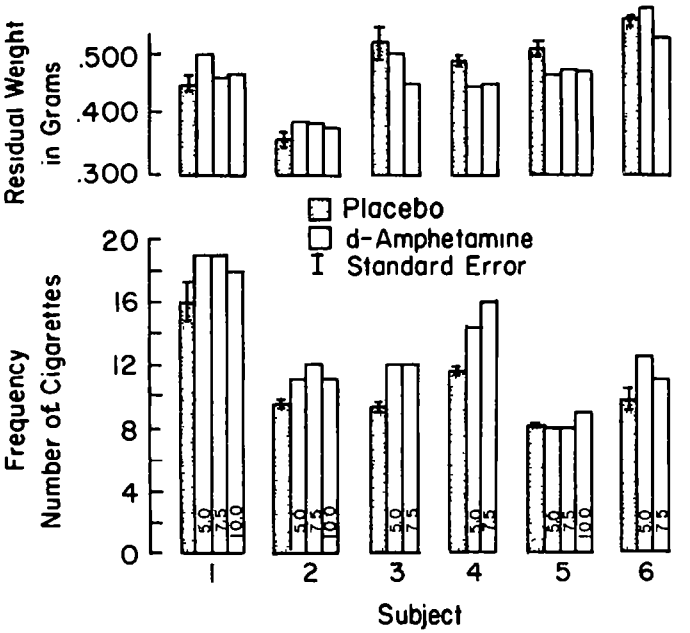
Figure 1 (bottom section) shows the number of cigarettes smoked during the placebo control and d-amphetamine sessions for each subject . The placebo values are means of at least 6 sessions. The d-amphetamine data represents individual sessions. This illustrates that for subjects 2, 3, 4 and 6 there was a significant Increase in cigarette smokng frequency during the d-amphetamine sessions. The upper graph shows the corresponding residual weights of the cigarettes. It can be seen that the amount of each cigarette consumed was not consistently affected by d-amphetamine. On the other hand, there was no decrease in the amomt of each cigarette consumed, at least as revealed by the weight of the cigarette butts.

Figure 2 shows the corresponding data for meprobamate sessions and placebo sessions. As can be observed, there was no significant change attributable to meprobamate at the dosages of 400 and 800 mg in cigarette smoking frequency or the residual weights of cigarettes consumed.

Figure 3 shows the effects of chronic lobeline on cigarette smoking. Lobeline did not produce a decline in the number of cigarettes smoked or the amount consumed in any of the 5 subjects tested. In fact, subject 1 actually showed a sizable increase in the number of cigarettes smoked as well as the amount consumed on day 5 of the chronic lobeline regimen.

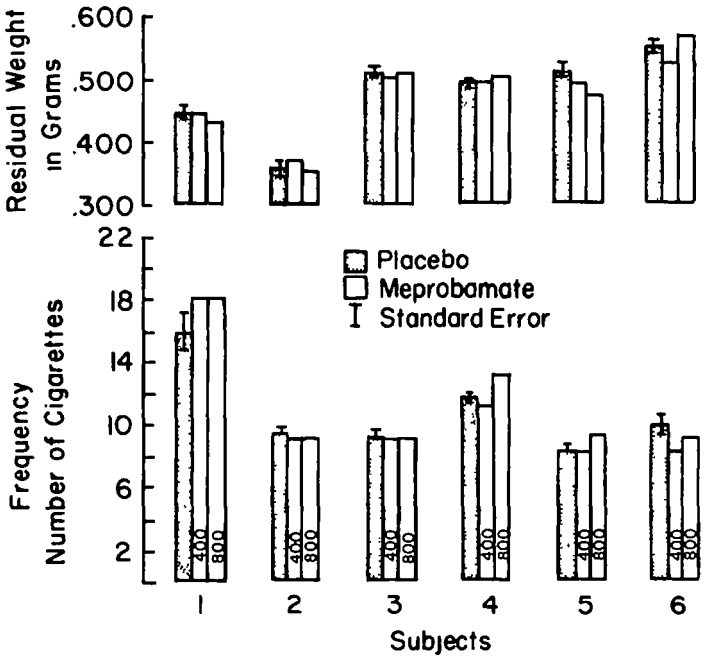
From these data it can be concluded that only d-amphetamine had any significant effect upon cigarette smoking frequency under the present experimental conditions. At the dosage levels employed, d-amphetamine produced both physiological and behavioral effects.

FIGURE 1



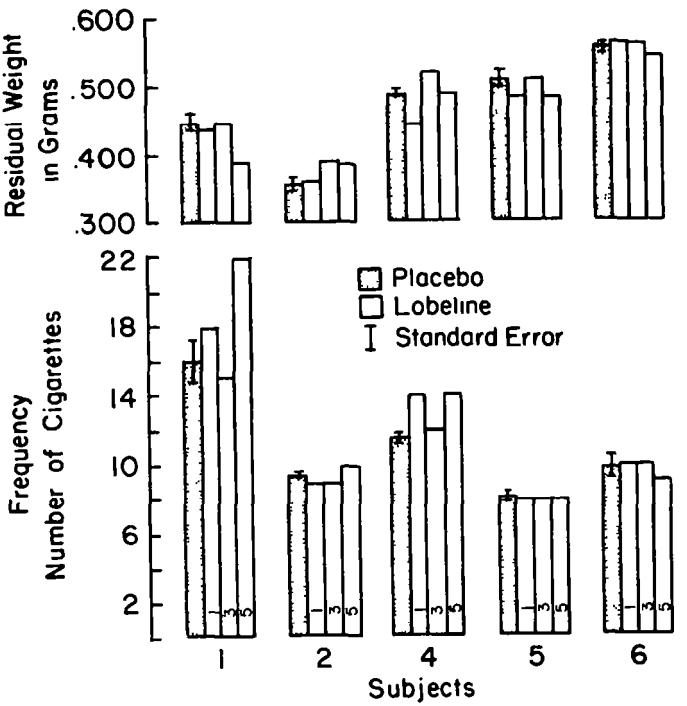
The effects of various doses of d-amphetamine on the cigarette smoking behavior of six subjects. The top panel shows the average weight of the unsmoked portion of the cigarette and the lower panel shows the number of cigarettes smoked. The data for the placebo condition represent the average of six sessions and the vertical brackets indicate the standard error. The data for the drug sessions represent the single determination at each dose level.

FIGURE 2



The effects of various doses of meprobamate on the cigarette smoking behavior of six subjects. The top panel shows the average weight of the unsmoked portion of the cigarette and the lower panel shows the number of cigarettes smoked. The data for the placebo condition represent the averaqe of six sessions and the vertical brackets indicate the standard error. The data for the drug sessions represent the singe determination at each dose level.

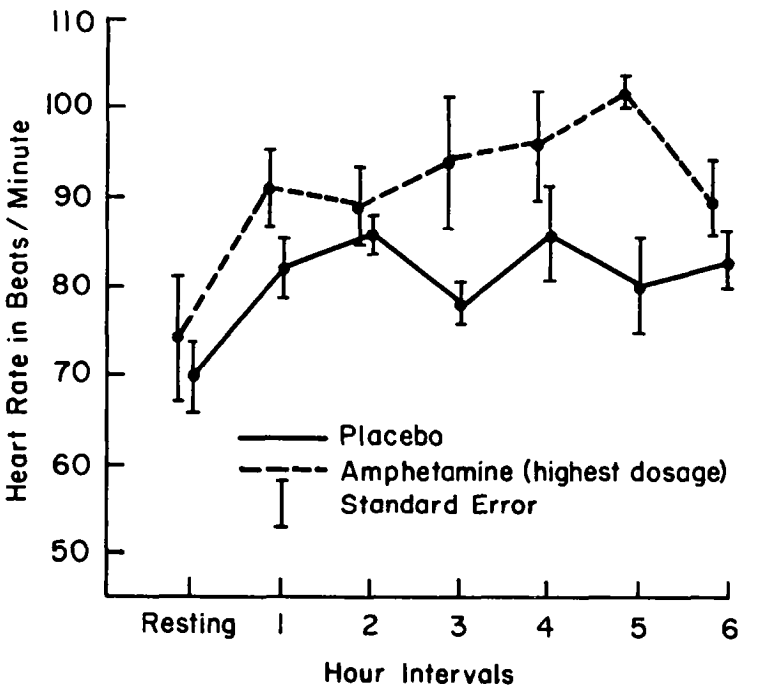
FIGURE 3



The effects of repeated administration of lobeline on the cigarette smoking behavior of five subjects. The top panel shows the weight of the unsmoked portion of the cigarette and the lower panel shows the number of cigarettes smoked. Placebo sessions represent an average of six sessions and the lobeline data are for sessions conducted on days 1, 3, and 5 of the chronic dosing regimen.

Figure 4 shows the mean heart rate under placebo conditions and for the highest dosage of d-amphetamine (7.5 or 10 mg). It is clear that on days when subjects received these doses of d-amphetamine, heart rate was consistently elevated over the 6 hour session. In addition systolic blood pressure showed a small but consistent increase over the 6-hour session. These effects probably represent a combination of the sympathomimetic actions

FIGURE 4



The effects of d-amphetamine on heart rate over the six-how session average for the six subjects, The placebo data represent an average of six sessions for each subject. The drug data are derived from a singe session in which the highest dose of d-amphetamine was administered.

of d-amphetamine and the effects of increased nicotine intake, since the subjects were smoking more frequently. It is of importance to note that d-amphetamine also produced increased rates of responding on the vigilance task. This suggests that the actions of d-amphetamine on smoking frequency were not specific.

In contrast, neither lobeline nor meprobamate produced any changes in heart rate, blood pressure, or behavior generated by the performance tasks. Further, with the exception of drowsiness reported by one subject at the 800 mg dose of meprobamate, subjects did not report any subjective effects associated with the administration of any of the drugs.

If this study had been conducted more recently, a number of additional measures could have been obtained. Clearly, blood nicotine levels would provide important additional data. For example, it is conceivable that the drugs employed in this study might have altered puff frequency and/or duration. Further, the depth of inhalation of smoke might have been changed by these drugs. Measures of blood nicotine levels would be the ideal way to resolve these questions. Unfortunately, at the time these experiments were carried out, the methodology for the measurement of nicotine levels in blood was not available.

CONCLUSIONS

Despite the limitations of this study, I believe we can still reach some important conclusions. First, lobeline sulfate at the recommended dosages does not produce any effect upon cigarette smoking behavior under the same conditions where nicotine does. It thus seems unlikely that lobeline has comparable pharmacologic actions allowing it to substitute for nicotine.

The data on d-amphetamine as well are of interest for theoretical reasons. It has been suggested that the mechanism underlying the reinforcing action of nicotine is its ability to produce EEG arousal through its actions on the ascending reticular activating system (Jarvik 1970). If this is the case, one would assume that d-amphetamine should substitute for nicotine since it as well produces EEG arousal through stimulation of the ARAS. The fact that amphetamines cause an increase in cigarette smoking frequency clearly does not support this hypothesis.

The fact that meprobamate failed to alter cigarette smoking frequency does not necessarily indicate that anxiety is not a factor in the control of cigarette smoking frequency. The efficacy of meprobamate as an anti-anxiety agent is highly questionable. Clearly, studies with more efficacious drugs (e.g., the benzodiazepines) are necessary.

One final observation concerns the stability of cigarette smoking frequency observed in the subjects of these experiments under the placebo conditions. The small size of the standard errors bracket-

ing the placebo averages indicates that there was little variance in both the measures of cigarette smoking frequency and the amount of each cigarette consumed. Observation of the times when subjects smoked indicated that this occurred with high probability during "break" times from the performance tasks. It would be of great interest to determine in future research whether smoking frequency could be altered by manipulation of the timing of these "break" periods. This would help to clarify the relative importance of pharmacologic and environmental control over cigarette smoking patterning and frequency.

ACKNOWLEDGMENT

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Chapter 9

Tobacco Dependence: Is Nicotine Rewarding or Aversive?

M. A. H. Russell, M.B., MRCP, MRCPsych

To understand tobacco smoking is like doing a large and very difficult jigsaw puzzle. I shall focus on the role of nicotine in tobacco use partly because it may be a kind of straight edge to the puzzle which we can usefully begin to piece together without getting lost among all the pieces that go in the middle. But the role of nicotine interests me for another very practical reason. If it is an important factor, and if most people do smoke chiefly to dose themselves with nicotine, the present low-tar, low-nicotine approach to safer cigarettes is obviously wrong, and it would be more logical to develop low-tar, medium-nicotine (or even high-nicotine) cigarettes (Russell 1976a).

We know that tobacco smoking is highly dependence-producing. We know that nicotine has numerous pharmacological effects, peripherally and in the brain, which are potentially reinforcing. We know that it has effects on behavior and performance which are potentially reinforcing. We know that it induces tolerance in animals and that they become dependent on nicotine injections to maintain performance. We know that most smokers absorb nicotine in amounts sufficient to produce these rewarding effects, that they acquire tolerance to some of its actions, and that they suffer from physical as well as psychological withdrawal effects when they stop smoking. We also know that the rapid absorption of nicotine through the lungs produces intravenous-like high-nicotine boli in the blood which reach the brain within a few seconds after each inhaled puff. The possibility that this produces a rapid puff-by-puff pharmacological reinforcement in the reward centers in the brain some 70,000 times a year would go a long way toward explaining the high dependence-producing potency of cigarette smoking (Russell 1976b).

If we could prove that nicotine is what smokers seek, we could be confident that the puzzle was virtually completed. Unfortunately this is not the case and we cannot escape the nagging fact that powerful addictive syndromes occur where pharmacological factors clearly play no part. One does not have to look far for examples such as gambling, nail-biting, and the desire for sweet tastes

or high-fat and high-cholesterol foods. With tobacco smoking there are numerous nonpharmacological components which could make it equally dependence-producing. Nicotine titration studies have attempted to prove that people smoke for nicotine. But, as I shall go on to show, these data do not disprove (indeed they can be better fitted to support) the hypothesis that people smoke and inhale for nonpharmacologic effects such as taste, aroma, sensorimotor ritual, and the local irritation by nicotine and other components of tobacco to sensory receptors in the lungs and respiratory tracts, and that the pharmacological effects of nicotine are aversive and tend to inhibit inhalation rather than reinforce it.

Definition of "Dependence" and "Addiction"

If we agree that tobacco smoking is for many a form of dependence, what does this mean? There are some who restrict the term "addiction" to compulsive syndromes which are maintained largely by the need to relieve or avoid physical withdrawal effects. The issue of "physical" versus "psychological" dependence is a somewhat false dichotomy, as the two are so interwoven. I use the terms "dependence" and "addiction" interchangeably to refer to a state in which the urge or need for something is so strong that the individual suffers or has great difficulty in going without it! and in extreme cases cannot stop doing it, or using it, when it is available. How high a degree of dependence is required before the condition is labelled a "dependence disorder" or "addiction" is somewhat arbitrary.

I would like to emphasize one point. It is the strength of the urge or need which is important, not whether it is predominantly pharmacologically or nonpharmacologically determined. Strong social or psychological rewards can produce a higher degree of dependence than weak pharmacological ones.

To what extent, then, does tobacco smoking depend on pharmacological as opposed to social or other nonpharmacological reinforcement? And to what extent do smokers smoke for positive rewards (pharmacological, nonpharmacological or acquired by conditioning) as opposed to seeking relief from, or avoidance of, unpleasant withdrawal effects (pharmacological, nonpharmacological or conditioned)? In other words, how much is smoking maintained by positive versus negative reinforcement?

Expressed Motives of Smokers

Many smokers find it difficult to explain why they smoke. Some will say they smoke because they find it pleasurable, that it helps them to relax, or simply that they are addicted. There are obvious pitfalls to accepting such statements at face value. When people find themselves doing something frequently and to some extent against their better judgment, they may tend to attribute this to pleasure, addiction, or some such "rational" explanation. They are, however, unable to tell us what makes the behavior pleasurable, relaxing, or addictive. Nevertheless, the statements of smokers them-

selves are an essential starting point in determining the motives underlying the dependence.

A number of people, such as Horn in the U.S.A. (Ikard, Green and Horn 1969) and McKennell (1973) in Britain, have used factor analysis to make systematic studies of the responses of smokers to questions on motives for smoking. We have done a similar study (Russell, Peto, and Patel 1974) using a 34-item questionnaire combining various aspects of the earlier work of Horn and Mckennell. We obtained six factors representing various motives for smoking: psychosocial, indulgent, sensorimotor, stimulation, addictive, and automatic. Unlike previous studies, we did not obtain a sedative smoking factor. Items designed to form a sedative factor loaded instead on the addictive and stimulation factors. It is not intended here to discuss the factor structure, but it may be that the negative affect and agitation which smoking apparently sedates are generated by cigarette withdrawal, and that in such cases "sedative" smoking is withdrawal relief smoking rather than smoking for sedation of negative affect due to other causes.

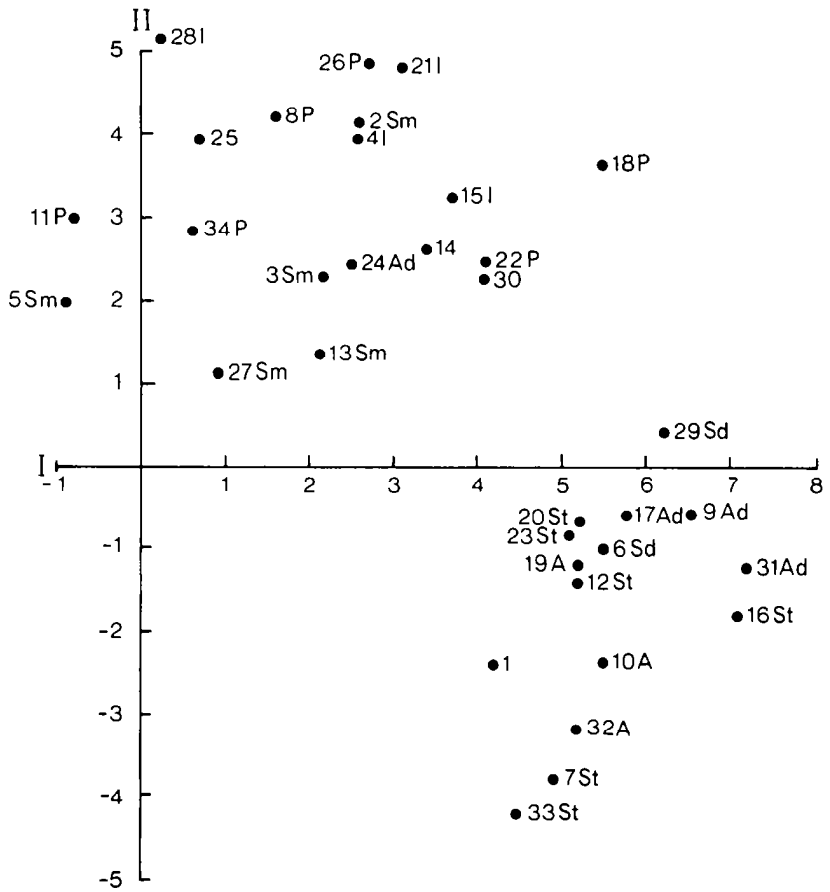
The most striking finding of our study was the clear-cut separation of the factors and their items into two distinct clusters, which we interpreted as representing pharmacological and nonpharmacological motives. This is shown in figure 1 where the items have been plotted according to their loadings on the first two unrotated factors, which respectively accounted for 18 percent and 8 percent of the variance. The "pharmacological" cluster was comprised of the addictive, automatic, stimulation, and sedative smoking items. The psychosocial, sensorimotor, and indulgent factor items were all in the "nonpharmacological" cluster. Some validation is provided by the correlation of the "pharmacological" group of factors with cigarette consumption; it was these factors that also differentiated a criterion group of addicted heavy smokers attending a withdrawal clinic from the main sample of normal smokers (figure 2). The questionnaire has since been modified and further validation will be sought by examining the relation of factor scores to blood nicotine and COHb levels and to clinical outcome.

Pharmacological studies have shown that in smoking doses nicotine is predominantly a stimulant drug but that it also has some sedative actions (Russell 1976b). The self-report data of smokers suggested similar effects! and this led us to label the two main item clusters as "pharmacological" and "nonpharmacological." The addictive factor items were concerned with craving and the relief of withdrawal symptoms, or, in other words, with negative reinforcement smoking. The high correlation between the positive effects of stimulation and the negative addictive factor items suggests that once sufficient nicotine is taken in to provide stimulation, withdrawal effects are likely to occur. This does not appear to ha pen to the same extent with indulgent smoking (smoking for pleasure). How much the pleasurable aspects depend on nicotine is obviously an important question.

As a final caution, it should be emphasized that stimulation, sedation, and withdrawal relief smoking do not necessarily indicate

FIGURE 1

Loadings of 34 items on the first two unrotated factors

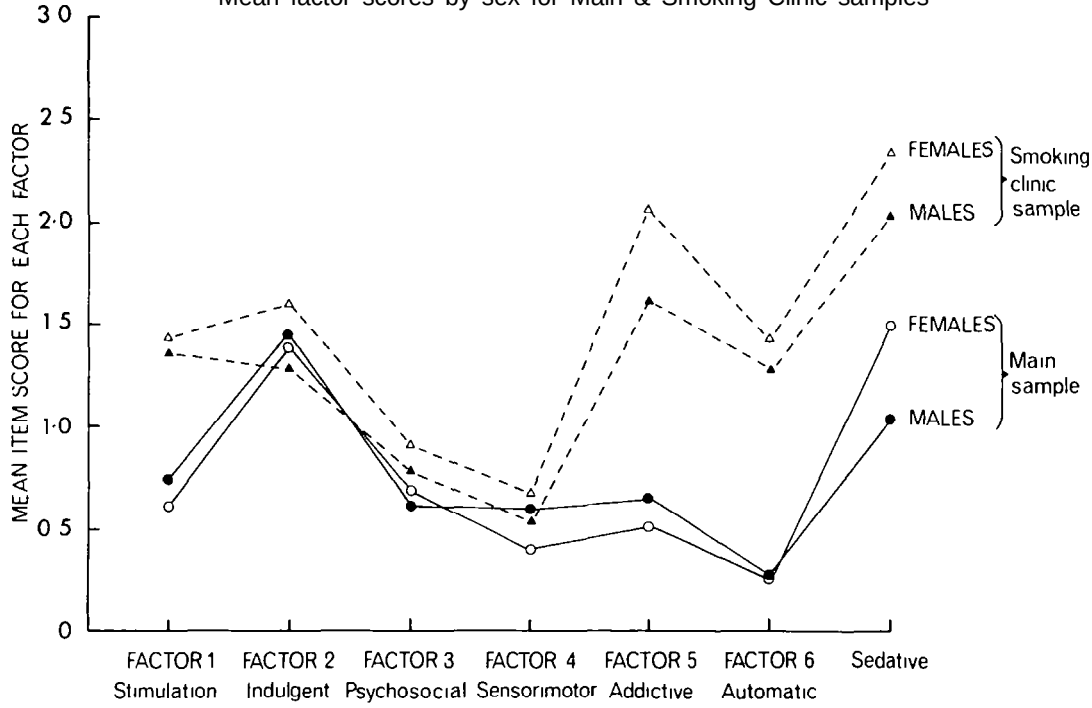


St Stimulation, I: Indulgent, P: Psychosocial, Sm: Sensorlmotor, Ad: Addlctwe, A: Automatic, Sd: Sedative.

Loadings of 34 questionnaire items on the first two unrotated factars. The upper left cluster is comprised of "nonpharmacologica1" motives for smoking from the psychosocial, sensorimotor, and indulgent smoking factors. The "pharmacological" items representing stimulation, sedative, addictive, and automatic smoking are all in the lower right cluster. (Reprinted with permission from Russell, M.A.H.; Pete, J.; and Patel, U.A. The classification of smoking by factorial structure of motives. Journal of the Royal Statistical Society, Series A, 137:373-333, 1974. © 1974, Royal Statistical Society.)

FIGURE 2

Mean factor scores by sex for Main & Smoking Clinic samples



Mean factor scores by sex for "Main" sample of normal smokers (N=175) and "Smoking Clinic" sample (N=103). There is no difference between the samples in scores on the indulgent, psychosocial and sensorimotor factors, but the differences on the other factors are highly significant (p<.001). (Reprinted with permission from Russell, Peto, and Patel, 1974. ©1974, Royal Statistical Society. See citation, figure 1.)

pharmacological mediation. It is possible that a similar factor structure with the same two main clusters of items could have been obtained by applying a similar questionnaire to regular gamblers. Nevertheless, the evidence so far available from this kind of approach suggests that smoking depends on a mixture of pharmacological and nonpharmacological motives and that pharmacological motives dominate in the case of addicted heavy smokers.

Onset and Maintenance of Smoking

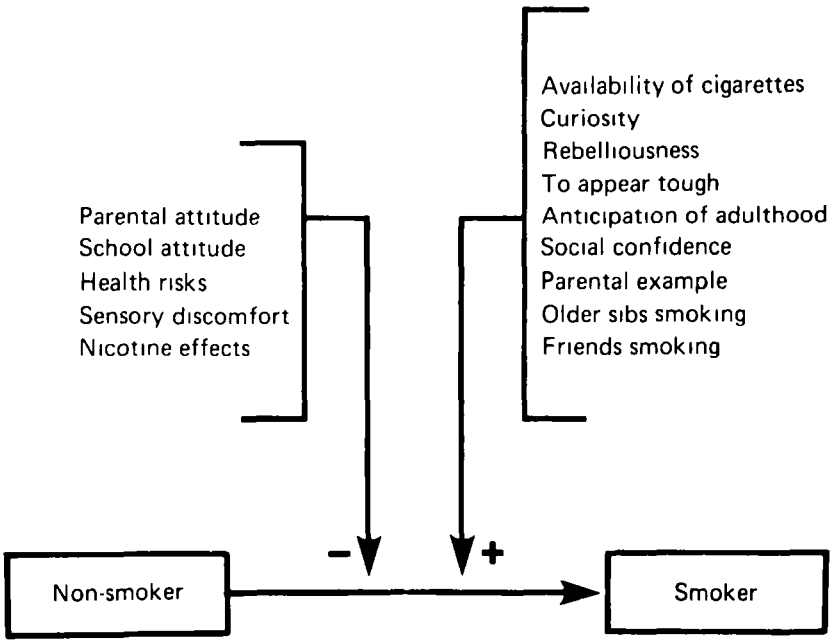
Daniel Horn (this volume) has discussed the factors involved in the establishment and maintenance of the smoking habit-two quite distinct processes. He has perhaps paid insufficient attention to one outstanding British study by Bynner (1969, 1970) which greatly clarifies the process of recruitment to smoking in schoolboys. It is also worth emphasizing the finding of McKennell and Thomas (1967) that of those teenagers who smoke more than a single cigarette, only 15 percent avoid going on to become regular dependent smokers. Why this escalation should be almost inevitable may be explained in the following way: The first few cigarettes are usually unpleasant, but skill is quickly acquired to limit the intake of smoke to a comfortable level. Tolerance to the unpleasant side effects of nicotine soon develops, thus lowering the threshold for further attempts. If the psychosocial rewards are sufficiently strong to cause the act to be repeated in the face of the side effects and physical discomfort, there is little chance that it will not continue, as the side effects rapidly disappear. The factors controlling the onset of smoking are summarized in figure 3, and those determining its maintenance are shown in figure 4.

In the early stages, smoking is intermittent and is usually confined to social situations. A few remain occasional social smokers for many years. But, in the majority, consumption gradually rises and ceases to be confined to social situations. After a few years smoking occurs with great regularity. Inhalation also increases gradually in most smokers until nicotine is absorbed in sufficient quantities to exert numerous potentially rewarding pharmacological effects. It is not known, however, whether the establishment of inhalation coincides with or determines the development of a regular smoking pattern. Many smokers then progress to a further stage of smoking for a predominantly negative reason: avoidance or relief of the effects of withdrawal. What proportion of smokers reach this stage, how long it takes, and to what extent the withdrawal effects are mediated by pharmacological as opposed to nonpharmcological factors are unknown.

Noninhaled Smoking

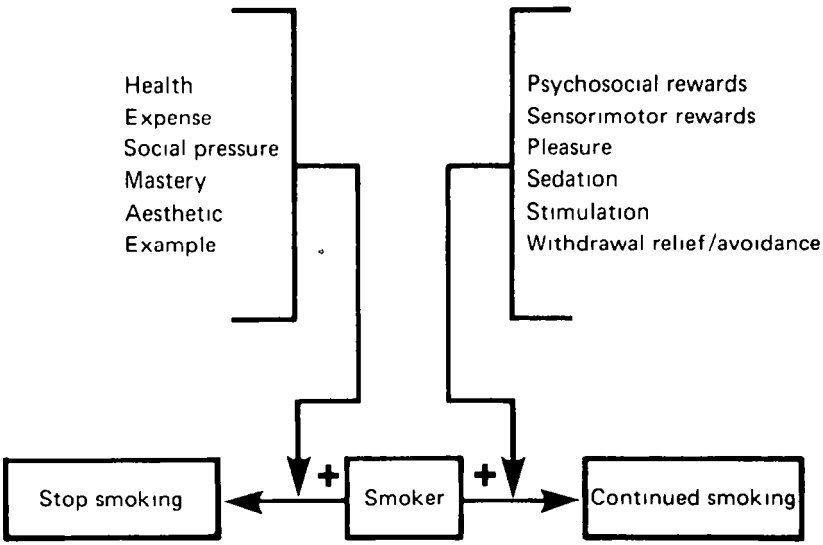
Some cigarette smokers do not inhale and consequently absorb little nicotine. Systematic comparison of noninhalers and inhalers could throw much light on the importance of pharmacological vs. nonpharmacological factors, but to my knowledge this has not been done. Apart from novices and occasional social smokers, some heavy (two-pack-a-day) smokers do not inhale; this is confirmed by low plasma nicotine

FIGURE 3



The main psychosocial factors determining the onset of smoking. On the right are the positive reinforcers or incentives to smoke. Anticipation of adulthood includes an impatience to be grown up and a tendency to participate in the activities of older teenagers, such as drinking, taking an interest in the opposite sex, going to dances and coffee bars, and staying out late. On the left are the factors that discourage smoking; two of these-the sensory discomfort of the first few cigarettes and the unpleasant side effects of nicotine-soon disappear as the act is repeated, thereby lowering the threshold for mother attempts. (Reprinted with permission from Russell, M. A. H. The smoking habit and its classification. The Practitioner, 212: 791-800, 1974. ©1974, The Practitioner.

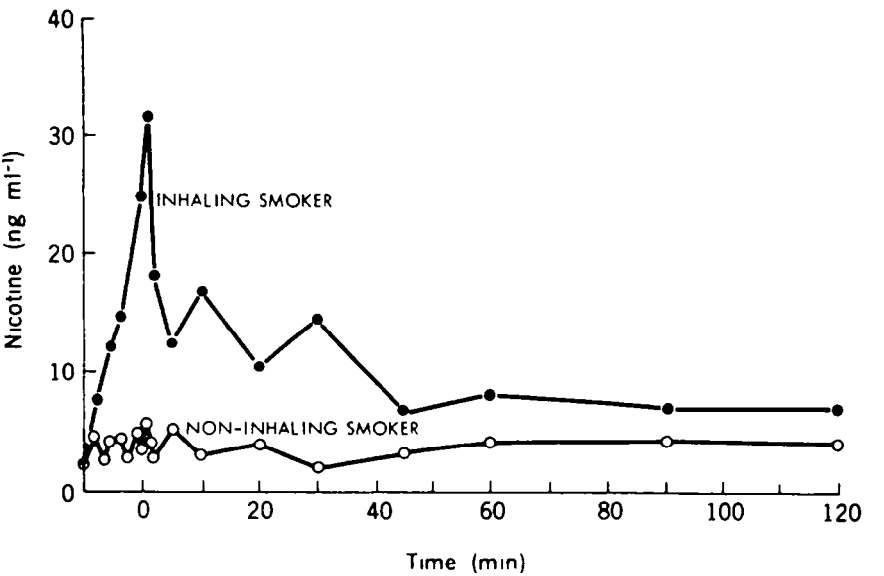
FIGURE 4



Factors controlling the maintenance and discontinuance of smoking. For most people below middle age, the factors motivating continued smoking are stronger than the motives to stop. The "Mastery" motive is the wish to show will power and gain control over the habit. "Aesthetic" refers to the feeling that smoking is dirty and messy, while "Example" concerns those who wish to stop to set a good example to children or other impressionable groups. (Reprinted with permission from Russell, M.A.H. The smoking habit and its classification. The Practitioner, 212:791-800, 1974. ©1974, The Practitioner.)

and COHb levels (figure 5). Such smokers may, however, be highly dependent in terms of craving and difficulty in giving up smoking. We do not know how many cigarette smokers are noninhalers, nor do we know whether they have lower ratings of dependence (with or without control for daily consumption). To study this would require measures of COHb or expired air CO, for smokers themselves do not reliably Know the extent to which they inhale.

FIGURE 5



Plasma nicotine concentration in an inhaling smoker and a noninhaler during and after smoking one cigarette. The inhaler smoked only one pack a day and had little difficulty giving up smoking. The noninhaler smoked more than three packs a day and suffered intense craving when he tried unsuccessfully to quit. (Reprinted from Feyerabend, C.; Levitt. T.: and Russell. M.A.H. A rapid estimation of nicotine in-biological fluids. Journal of Pharmacy and Pharmacology, 27:433-436, 1975, with permission. ©1975, Journal of pharmacy and Pharmacology.)

Though less rapid than absorption through the lungs, it is generally held that with snuffing, tobacco-chewing, and noninhaled pipe and cigar smoking, absorption of nicotine through the nose or mouth is sufficient to provide a pharmacologically rewarding effect. The role of pH in determining the rate of absorption is crucial (Russell 1976b). Nicotine-containing chewing gum with a buffer to keep the pH in the mouth at about 8.5 produces plasma nicotine levels comparable to inhaled cigarette smoking, but absorption is much slower (Russell, Feyerabend, Cole 1976; Russell et al. 1977). The few snuff users we have tested have had high plasma nicotine levels. But what about noninhaled pipe and cigar smoking? Although the pH of air-cured tobacco smoke is alkaline (about pH 8.5), is the buffering capacity of the smoke sufficient to bring the pH of saliva in the mouth up to this level? I am not aware of any studies which show this. There is, however, one recent English study which suggests that nicotine absorption from noninhaled cigar smoking may be minimal (Turner, Sillett, McNicol 1977).

TABLE 1

Blood Nicotine and COHb Levels from Cigar Smoking in Primary and Secondary Pipe and Cigar Smokers*

	Before	20 min	40 min	60 min	120 min
NICOTINE (ng/ml)					
1° (N=5)	3.3	4.0	4.3	5.1	4.5
2° (N=5)	12.8	30.7	45.6	36.2	24.7
COHb (%)					
l° (N=5)	0.8	1.0	1.0	0.9	1.0
2° (N=5)	2.9	6.6	8.4	9.6	8.1

The cigar was discarded at 60 minutes.

Abstracted from Turner, J.A.M.; Sillett, R.W.; and McNichol, M.W. Effect of carboxyhaemoglobin and plasma nicotine concentrations in primary pipe and cigar smokers and ex-cigarette smokers. British Medical Journal, 2:1387-1387, 1977. ©1977, British Medical Journal. Reproduced by permission.

**Primary pipe and cigar smokers are those who have never been regular cigarette smokers. Secondary pipe and cigar smokers are ex-cigarette smokers who have switched to a pipe or cigars, which they then tend to inhale (Castleden and Cole, 1973; Cowie, Sillett and Ball, 1973).*

Turner and his colleagues measured plasma nicotine and COHb levels of smokers before, during, and after the smoking of a large cigar (12.4 an, 6.2 g). The results in table 1 show clearly that the noninhaling primary pipe and cigar smokers absorbed virtually no nicotine. The authors claim that these smokers were nevertheless addicted in terms of craving and suffering when they could not smoke. The authors believed that their study seriously challenges the role of nicotine in tobacco dependence. They did not, however, make systematic ratings of dependence. True primary pipe and cigar smokers are an atypical minority of the smoking population. The fact that ex-cigarette smokers who switch to a pipe or cigars often continue inhaling is an indication that, once experienced, the inhalation of tobacco smoke is difficult to forgo.

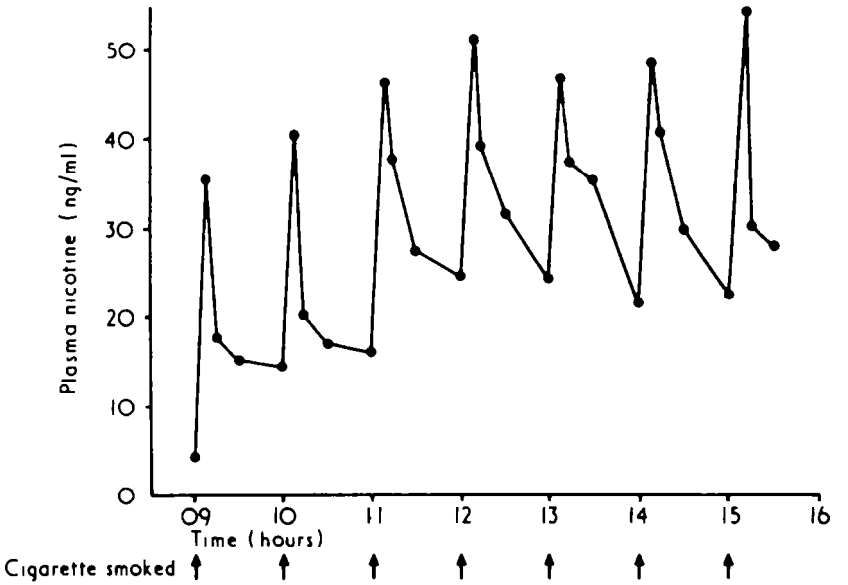
Though further study is obviously necessary, it would seem that strong dependence may occur in cigarette smokers, pipe smokers, and cigar smokers who do not inhale and who consequently absorb little nicotine. This suggests that tobacco dependence can be mediated by nonpharmacological factors such as taste, smell, sensorimotor ritual, and the like. Indeed, nicotine itself may contribute to the flavor, sharpness, irritancy, etc., and may be rewarding for these effects apart from its pharmacological actions.

Nicotine Intake from Cigarette Smoking

It comes as no surprise to find wide individual variation among smokers in blood nicotine levels just after a cigarette. Values range from below 10 ng/ml to more than 50 ng/ml, with an average for heavy smokers of around 35 ng/ml. Neither is it unexpected that the individual smoker tends to obtain a fairly consistent peak nicotine level after each cigarette, whether it is smoked in the morning or afternoon, from one day or week to the next.

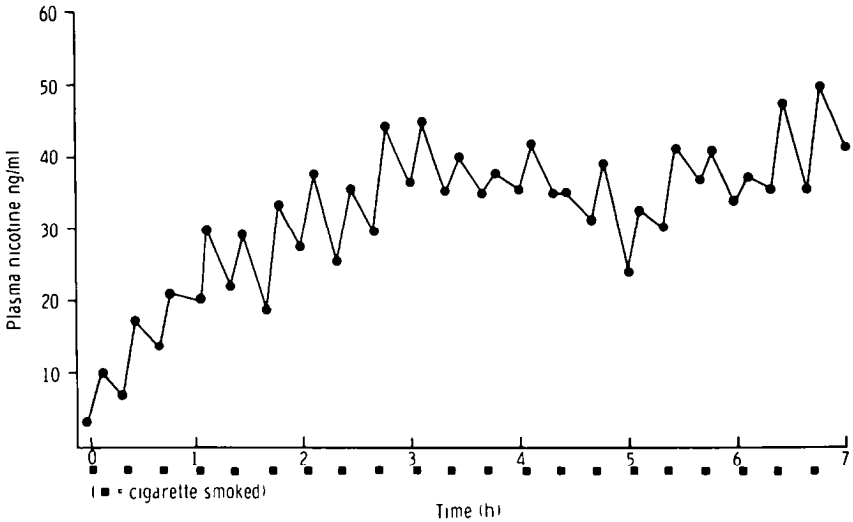
Of the majority of smokers, who do inhale, we are nowhere near the stage of knowing whether they smoke for some positive effect of the blood nicotine peaks, whether they smoke to avoid the pharmacological effects of falling below a certain blood nicotine trough, or indeed whether the nicotine intake and its pharmacological effects are merely incidental to inhalation which is determined by nonpharmacological factors. It would seem from preliminary pharmacokinetic findings (Russell and Feyerabend, 1978) that the predominant blood profile for inhalers who smoke one cigarette per hour or less is one of repeated high nicotine peaks (figure 6), whereas the accumulation of nicotine in the body of those who smoke at least one cigarette every 30 minutes would tend to show smaller peaks relative to the overall level (figure 7). They might more likely, therefore, be motivated by the need for "trough maintenance." Very tentatively I suggest that if nicotine has a pharmacologically reinforcing role, trough maintenance may be the main motive for the addicted smoker, while optimal peak effects may be more important to indulgent smokers, who smoke less heavily. The peak blood nicotine levels of the two types, however, do not appear to differ greatly, and peak blood nicotine does not correlate with cigarette consumption, r = .02 (Russell et al. 1975 and 1977).

FIGURE 6



Plasma nicotine concentrations in an inhaling smoker while smoking at a rate of one cigarette per hour for seven hours. Although there is some accumulation of nicotine, the predominant profile is one of prominent blood nicotine peaks following each cigarette. This illustrates the characteristic pattern of the "peak seeker" type of smoker mentioned in the text. (Figure reproduced with permission from Russell, M.A.H.; Feyerabend, C.; and Cole, P.V. Plasma nicotine levels after cigarette smoking and chewing nicotine gum. British Medical Journal, 1:1043-1046, 1976. ©1976, British Medical Journal.)

FIGURE 7



Plasma nicotine concentrations in an inhaling smoker while smoking at a rate of three cigarettes per hour for seven hours. Blood samples were taken just before and two minutes after each cigarette. The blood nicotine builds up to a "steady state" with peaks which are small relative to the overall level. This illustrates the characteristic pattern of the "trough-maintainer" type of smoker suggested in the text. (Reprinted from Russell, M.A.H., and Feyerabend, C. Cigarette smoking: a dependence on high nicotine boli. Drug Metabolism Review, 8•29-57, 1978, by courtesy of Marcel Dekker, Inc., ©1978.)

It is tempting to postulate a three-stage process, with smokers beginning to smoke for psychosocial reasons, the majority then learning to inhale and progressing to smoking for the effects of the sharp blood nicotine peaks that follow each cigarette (peak-seekers), and some finally going on to a third stage of negative reinforcement smoking to avoid the withdrawal effects of dropping below a certain blood nicotine level (trough-maintainers).

As mentioned, however, the issue is far more complex: Noninhalers may also progress to a second stage of regular indulgent smoking for positive nonpharmacological rewards, as well as to a third stage of negative withdrawal relief smoking mediated by nonpharmacological factors. Further complexities arise from interactions between pharmacological and nonpharmacological components, due to conditioning and other processes. Plausible as all this may seem, with many resemblances to other drug addictions, it has yet to be established that smokers do indeed smoke for the pharmacological effects of nicotine rather than for nonpharmacological reasons.

Use of low-Tar, Low-Nicotine Cigarettes

What can be learned from studies of the use of low-nicotine cigarettes? Among English cigarette smokers, only 10 percent of men and 18 percent of women regularly smoke low-nicotine brands. Most low-nicotine brands smoke in Britain have standard deliveries of 0.6 to 0.8 mg nicotine; yet it is still possible to maintain high blood nicotine levels, of 40 ng/ml or more, by smoking these brands. It is only when the nicotine yield is reduced to 0.4 mg or less that this becomes difficult, and relatively very few people smoke cigarettes of this type.

The lack of popularity of low-nicotine cigarettes may seem to provide evidence of a need for nicotine. Similarly, the tendency when smoking them to smoke more cigarettes or take larger and more frequent puffs and inhale more deeply has been interpreted as reflecting a need to titrate nicotine. There is a serious objection to this interpretation, however. low-nicotine cigarettes also have low yields of other consituents, such as tar, which contribute to the taste and satisfaction of the smoke. Indeed, they are often also difficult to light and to smoke.

Regulation of Nicotine Intake

Self-regulation of nicotine intake, or nicotine titration, is probably the most useful approach for studying the role of nicotine in smoking. It has been comprehensively discussed by Schachter (this volume). As he points out, there are numerous studies showing that smokers modify their smoking patterns to compensate for a reduction of the tar and nicotine yields of their cigarettes. But, as mentioned above, owing to the high correlation (70.9) of tar and nicotine yields, we cannot know

from such studies whether the smokers are regulating their intake of nicotine rather than tar or some other factor.

Only one study, by Goldfarb et al. (1976), has used cigarettes in which tar and nicotine yields were independently varied. The number of cigarettes smoked was unaffected by tar yield but varied inversely with nicotine yield, although insufficiently to maintain urinary nicotine excretion constant. While most studies have shown that compensation on low nicotine cigarettes is often only partial (Russell 1976b, Sutton et al. 1978), we have found that smokers lower their intake very accurately when switched to high nicotine cigarettes. Blood nicotine levels on cigarettes yielding 3.2 mg nicotine averaged 29 ng/ml, compared to 30 ng/ml on cigarettes yielding 1.3 mg nicotine (Russell et al. 1975). It seems, therefore, that that self-regulation downwards to avoid an excessive intake may be more sensitive and complete than compensation upwards to avoid a reduction in nicotine and/or tar intake.

There have been very few direct studies of nicotine titration, i.e., those which avoid confoundment with tar intake and other factors. They have, however, with one exception, been most convincing in their support for nicotine titration. For example, Stolerman et al. (1973) showed that central cholinergic blockade with mecamylamine caused smokers to increase the number of cigarettes smoked by 26.5 percent and the number of puffs by 25.3 percent compared to placebo. In the study by Lucchesi et al. (1967), intravenous nicotine infusion reduced the number of cigarettes smoked by an average of 29.8 percent compared to saline. Furthermore, 22 mg of IV nicotine bitartrate (about 7.3 mg base) caused a mean decrease of about 2.5 cigarettes during the 6-hour infusion period. The nicotine delivered by 2.5 cigarettes in the mid-1960's, though not stated by the authors, would have been about 7 mg. Titration of similar accuracy was demonstrated during Schachter's manipulation of urinary nicotine excretion via its pH (Schachter, Kozlowski and Silverstein 1977). It would take too long to go fully into our own failure to replicate Lucchesi's findings (Kumar et al. 1977). This could have had something to do with the extreme artificiality of our experimental conditions. Although our subjects continued to puff at baseline levels during and just after the IV nicotine, it is possible that they titrated by inhaling less. We did not measure blood nicotine levels, so we do not know whether or not this was so.

The sensitivity of the nicotine titration demonstrated in these more direct studies is in keeping with the view that self-regulation of nicotine intake downwards is more sensitive and complete than compensation upwards. One other direct approach has been to study the effect on smoking behavior of nicotine-containing chewing gum. Two studies have shown a modest inhibitory effect (Kozlowski, Jarvik and Gritz 1975; Russell et al. 1976). In our study (table 2), a dose of 20 mg nicotine per day taken in the gum reduced cigarette consumption by 17 percent ($p < .05$) and COHb by 41 percent ($p < .01$) compared to placebo gum. About 90 percent of the nicotine in the gum is released, but much of this is no doubt swallowed, absorbed in the gut,

TABLE 2

Effect of Nicotine Chewing Gum on Plasma Nicotine Levels During ad libitum Smoking (means of 41 subjects)

	No gum	Placebo gum	Nicotine gum
Cigarettes per day	33.3	23.0	20.9
COHb(%)	8.5	7.2	6.3
Plasma nicotine (ng/ml)	30.1	24.7	27.4

Note: One piece of gum containing 2 mg nicotine was chewed hourly for 30 min to a total of ten pieces per day. The specific effect of nicotine (as opposed to the effect of placebo gum) accounted for 17% of the reduction in daily cigarette consumption (23.0-20.9) ÷ (33.3-20.9) x 100 = 17. By similar calculation it accounted for 41% of the reduction in COHb and hence degree of inhalation.

Adapted from Russell, Wilson, Feyerabend, and Cole. Effect of nicotine chewing-gum smoking behaviour and as an aid to cigarette withdrawal. British Medical Journal, 2:391-393, 1976. © 1976, British Medical Journal. Reprinted by permission.)

and metabolized in the liver before reaching the systemic circulation. It is not known how much of the 20 mg daily dose would have been absorbed through the mouth. Nevertheless, despite the extra nicotine from the gum, the average plasma level of 27.4 ng/mg (table 2) was not significantly different from the base-line level of 30.1 ng/ml when smoking normally without gum, showing once again fairly accurate downward titration. On the placebo gum, the small decrease in plasma nicotine ($p < .05$) suggests that a drop in plasma nicotine may be better tolerated than an excess.

Adaptation and Compensation

Theoretically, a smoker may adjust to a dilution of nicotine (and tar) content of smoke either by adapting to a lower dose or by compensating to maintain intake, smoking more cigarettes or increasing the intensity of puffing and inhalation. The degree of compensation may range from nil, to partial, to complete. The reduction of nicotine (and tar) intake to which adaptation is required will obviously vary accordingly. Adaptation to a lower dose will only be complete when any negative affect or discomfort has subsided. The time courses of adaptation and of compensatory changes in smoking pattern

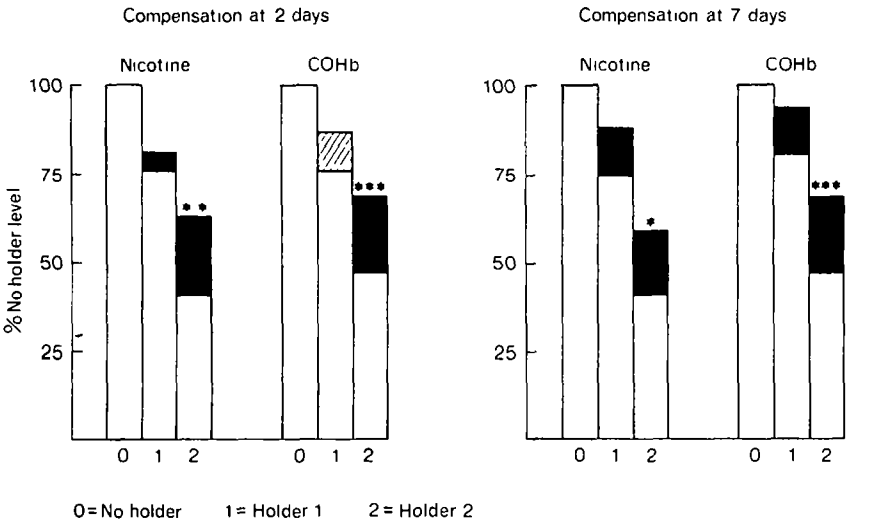
may differ, and they may also interact. For example, the degree of compensation may be reduced as adaptation to a lower intake reduces the urge for a higher intake. Increase in the intensity of puffing may generate discomfort of a different kind (from that generated by the reduced intake), to which adaptation of a different kind may or may not occur. For example, to increase puff volume from 40 ml to 60 ml to maintain smoke intake per puff may involve little effort, but an increase from 60 ml to 80 ml may make the smoker aware of some awkwardness or discomfort. There are further complexities. For example, a smoker may be able to take a larger puff of diluted smoke, sufficient to maintain nicotine (and tar) dosage per puff, but the dilution may reduce impact and flavor below an acceptable level. Response to such interactions will vary, depending on the degree to which the smoker requires to maintain nicotine (and tar) intake on a per puff basis or on a per cigarette or per unit of time basis. Furthermore, the unit of time may refer to the time taken to smoke one cigarette or to longer periods in which several cigarettes are smoked.

Most studies of smokers' responses to changing to low-nicotine cigarettes have been focused on demonstrating a significant compensatory change in a group of smokers. They have been less concerned with individual differences and have not attempted to measure the degree of compensation. We have recently examined the extent to which smokers compensate for the dilution of smoke produced by ventilated cigarette holders (Sutton et al. 1978). There *were* no changes in the number of cigarettes smoked. However, measures of plasma nicotine and COHb showed, on average, partial compensation of about 40 percent on Holder 2 (60 percent dilution), but on Holder 1 (20 percent dilution) there was no significant compensation (see figure 8). Individual differences were marked, ranging from full compensation to none at all. About half the subjects were clear-cut noncompensators. A similar 50/50 differentiation of individual smokers into compensators and noncompensators has been observed by others (Cherry and Forbes 1972; Freedman and Fletcher 1976; Forbes et al. 1976).

A further finding, shown in figure 8, was that the degree of compensation on Holder 2 did not change between 2 days and 7 days, but adaptation to the lower nicotine intake did improve over this time. Withdrawal symptoms subsided and subjective satisfaction on Holder 2 increased. How much this difference in the short term trends of these two processes would be reflected in the long term is obviously an important question. The adaptation acquired over this short period was transient. Plasma nicotine and COHb had returned to former levels five days after the holders were abandoned. The only long term study, by Freedman and Fletcher (1976), suggested that adaptation acquired over several months could be maintained and that smokers who had adapted to a lower tar and nicotine intake at mouth level (based on butt analysis) did not increase it again when they reverted to smoking stronger cigarettes.

These findings highlight the fact that compensation is, on average, only Partial and that some smokers compensate while others do not. This contrasts strikingly with the very accurate downward titration

FIGURE 8



*Amount of compensation when using ventilated cigarette holders, based on the means of 18 subjects. The observed and "expected" blood nicotine and COHb levels on the holders are expressed as percentages of the mean no-holder levels. The "expected" levels are based on the dilution factors of the two holders, about 20 percent for Holder 1 and 60 percent for Holder 2. The shaded areas represent the difference between the observed and "expected" levels, which is a measure of the amount of compensation. The lined area (for COHb on Holder 1 at 2 days) indicates a negative O-E difference, i.e., observed levels were lower than "expected" levels. Thus, though there was significant compensation on Holder 2 on all measures, there was clearly none on Holder 1. Significance of O-E differences: *p<.02, **p<.01, ***p<.001. (From Sutton, S.R.; Feyerabend. C.; Cole, P. V.; and Russell, M. A. H. Adjustment of smokers by ventilated cigarette holders. Clinical Pharmacology and Therapeutics, 24. 395-405, 1978. ©1978, The C. V. Mosby Co.*

of nicotine in the experiments cited previously and may be partly explained by the fact that it requires some effort by the smoker to increase smoke intake but no effort to reduce it. Although satisfaction is reduced when the smoke is diluted, this is not necessarily due entirely to failure to maintain nicotine intake. Other factors such as the effort of compensation, loss of taste and impact of the smoke in the mouth, throat, and lungs may contribute. It would appear on balance that smokers tolerate a decrease in nicotine intake better than an increase.

The Role of Nicotine

Our uncertainty about the role of nicotine in tobacco dependence is reflected in the title of this conference where tobacco and nicotine are linked, ambiguously, as "tobacco/nicotine." As I see it, the stroke between them proclaims loudly what we don't know, and it is on this issue that I have tried to focus.

In terms of unequivocal evidence that people smoke for nicotine, even the few direct studies which purport to show that people smoke to obtain a pharmacological effect from nicotine and that titration indicates a need for nicotine, could be interpreted as showing nicotine to be pharmacologically aversive. Thus, when Lucchesi administered nicotine intravenously, smoking was inhibited (Lucchesi, Schuster, and Emley 1976); but when Stolerman blocked the pharmacological effects of nictotine, his subjects could smoke more (Stolerman et al. 1973). Similarly, Schachter's subjects could smoke more when nicotine excretion was increased (Schachter, Kozlowski, and Silverstein 1977). In other words, these studies could be seen as showing that excessive nicotine is aversive; they do not show that smaller amounts are pharmacologically rewarding. Can we be sure that people are not dependent on inhalation for nonpharmacological reasons such as taste, smell, ritual, sensory stimulation to the lungs and respiratory tract-to which nicotine might contribute? Are people perhaps addicted to inhalation for nonpharmacological rewards but inhibited from indulging more because they find excessive nicotine pharmacologically aversive? Simply because nicotine has so many pharmacological effects in smoking doses, it does not necessarily follow that these effects are reinforcing rather than aversive. Is there, indeed, any evidence that nicotine is rewarding?

Evidence that nicotine can be pharmacologically rewarding is scanty. Firstly, throughout history people have never shown a strong inclination to inhale smoke, however aromatic or flavorful, which does not contain a psychoactive drug. This historical evidence is compelling but only circumstantial. On the other hand, there is a surprising lack of evidence beyond the anecdotal level that animals will learn to self-inject nicotine as avidly as they do other addictive drugs. Until attending this conference I was aware of only two incomplete reports (Clark 1969; Deneau and Inoki 1967). The careful studies of Hanson and his colleagues (this volume) are a major contribution to this area. A preliminary reservation is that they may not have shown conclusively that their rats were indeed

seeking nicotine as opposed to increasing the rate of lever-pressing due to its stimulant action. The study design did not include a free choice situation, which could have gone a long way to settle this question.

Apart from the historical evidence and animal self-administration studies, there is the well-known pioneer study by Johnston (1942). He reported that when smokers were given hypodermic injections of nicotine they "almost invariably thought the sensation pleasant." He also reported that the craving following withdrawal of cigarettes was relieved by injection of nicotine. Has Johnston, all those years ago, done what all of us have failed to do, namely shown that nicotine is both a positive and negative reinforcer for human smokers? Unfortunately, he has not. His studies were uncontrolled and nonblind. However, his approach to the question has been more direct and relevant than any of our efforts. We still lack a direct study in humans to show that nicotine is pharmacologically reinforcing. Whether or not it is rewarding in optimal doses, it certainly seems to become aversive when these are exceeded, and the implications for safer cigarettes remain the same. Less tar and CO will be taken in by smokers if their cigarettes combine a low tar and low CO delivery with a medium to high, rather than low, nicotine delivery.

Summary and Conclusions

The role of nicotine in tobacco dependence is discussed. Review of the data available in the literature raises many questions but provides few answers beyond the following conclusions.

(1) Pharmacological reinforcement is not an essential feature of addictive behavior.

(2) There are many nonpharmacological factors involved in tobacco smoking, and these appear to be sufficient to generate strong dependence in smokers who do not inhale.

(3) The low acceptability of low-nicotine cigarettes is not necessarily due to the low nicotine. Nonpharmacological factors are also involved.

(4) Smokers who inhale seem to tolerate a decrease in nicotine intake better than an increase.

(5) Simply because nicotine has many pharmacological effects in smoking doses, it does not follow that these effects are reinforcing rather than aversive.

(6) Evidence is scanty that animals will self-inject nicotine as avidly as they do other addictive drugs.

(7) Apart from circumstantial historical evidence that people have never shown a strong inclination to inhale smoke that does not con-

tain a psychoactive drug, there is no direct experimental study which shows that nicotine is pharmacologically rewarding or reinforcing in humans.

(8) Whether or not nicotine is pharmacologically rewarding in optimal doses, it seems to become aversive when these doses are exceeded.

(9) The hypothesis that people smoke and inhale for nonpharmacological rewards, including the taste and irritancy of nicotine itself, but are inhibited from smoking more because they find excessive nicotine pharmacologically aversive, has not yet been disproved.

(10) The implications for safer cigarettes remain the same no matter whether nicotine is rewarding or aversive. The safer cigarette should have a low tar, low CO, but medium to high rather than low nicotine yield.

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Chapter 10

Regulation, Withdrawal, and Nicotine Addiction

Stanley Schachter, Ph.D.

Most of us who do research on smoking have at some time championed the hypothesis that cigarette smoking, with nicotine as the active agent, is an addiction. Sometimes, however, it is difficult to figure out why that conviction is so strong. The data supporting the proposition are not particularly good; in fact, looked at with a ruthless eye, they are rather flimsy. I intend to review and evaluate the data relevant to the addiction hypothesis and to attempt to understand just why they are so weak.

Most studies of the addiction hypothesis have focused on the regulation of nicotine intake. I know of twelve studies in which subjects were supplied with high- or low-nicotine cigarettes and a record kept of how much they smoked. Two of these (Finnegan, Larson, and Haag 1945, Goldfarb, Jarvick, and Glick 1970) found no differences--subjects smoked no more low- than high-nicotine cigarettes. One study (Ashton and Watson 1970) found exquisitely precise regulation, and nine (Frith 1971; Goldfarb et al. 1976; Herman 1974; Jarvik et al. 1970; Johnston 1942; Kozlowski et al. 1975; Kumar et al. 1977; Russell et al. 1973; and Schachter 1977b) did find that subjects smoked more low- than high-nicotine cigarettes. It was not precise regulation, by any means; but in all cases subjects did smoke somewhat more of the low- than of the high-nicotine cigarettes. So far so good: in 10 of 12 studies the amount smoked varied inversely with the nicotine content of the cigarette.

Though these studies indicate some degree of regulation, they do not as yet establish just what is being regulated; for, as we know, the nicotine and tar contents of cigarettes covary. When I last correlated the nicotine and tar contents of commercially available cigarettes, the correlation coefficient was +.91. We note then that two of these twelve studies attempted in some fashion to manipulate tar and nicotine content independently. Both studies (Goldfarb et al. 1976; Schachter 1977b) found the same result--smokers track nicotine content, not tar content.

There have been three studies which preloaded subjects either with nicotine chewing gum or nicotine capsules (Brantmark et al. 1973;

Jarvik et al. 1970; Kozlowski et al. 1975). All report the same effect: Subjects on nicotine gum or capsules smoke less than subjects on placebo. The effects in all cases are quite small but statistically significant. In addition, Stolerman et al. (1973) have demonstrated that administration of a nicotine antagonist increases cigarette smoking.

Finally, there have been two studies using the IV infusion technique. Lucchesi, Schuster, and Emley (1967) find good evidence for regulation, and the study by Kumar et al. does not. In other contexts (Schachter 1977a), I have spelled out why I think this is so. It looks as if a reasonable case can be made for the proposition that smoking is addicting and something of a case for the proposition that nicotine or one of its metabolites is the addicting agent.

Why then do I speak of the data supporting the proposition as "flimsy"? For two reasons: First, when we speak of regulation, we tend to think in terms of fairly precise set-point models. Presumably there is a "nicostat" sensing nicotine and regulating intake so as to keep nicotine at some constant level. Yet with a single exception (Ashton and Watson 1970), the data indicate extraordinarily crude and imprecise regulation. A typical instance of just how crude can be seen in Table 1, which presents the data of a study I did some years ago (Schachter 1977b) on a group of long time, very heavy smokers. In alternate weeks, subjects smoked high- or low-nicotine cigarettes. The low-nicotine cigarettes contained 0.3 mg of nicotine per cigarette; the high-nicotine cigarettes contained 1.3 mg of nicotine--more than a fourfold difference. Though all of the subjects did smoke somewhat more low- than high-nicotine cigarettes, on the average they smoked only 25 percent more low-nicotine cigarettes--hardly the exquisite titration that set-point models suggest.

The second reason for discomfort with the addiction hypothesis is that exceptions to an addiction model are so common. Though it is known (Isaac and Rand 1972) that plasma-level nicotine is zero on awakening in the morning, there are heavy smokers who will not light up their first cigarette of the day till afternoon. There are smokers who smoke only at parties or while they are working, and otherwise not at all. Some orthodox Jewish smokers, forbidden to smoke on the Sabbath, appear able to do so without a whimper. And so on.

Just how to cope with such blatant exceptions is problematic. Perhaps it is necessary to invent typologies (e.g., McKennell 1973; Russell 1974; Tomkins 1968) to accommodate the distressing apparent variety of smokers, but I find this an unsatisfying scientific strategem and admission of defeat.

As a working hypothesis, I propose instead that we consider virtually all long-time smokers as addicted and attempt to understand the exceptions to maintaining a constant nicotine level in terms of such notions as self-control, concern with health, restraints, and so on. Certainly all smokers are aware of the dangers and

TABLE 1

The Effects of Nicotine Content on Cigarette Smoking

Subjects	Cigarettes Smoked per Day: Low (0.3 mg) Nicotine	High (1.3 mg) Nicotine	% Increase High to Low Cigarettes
JA	31.25	21.50	+ 45.3
SS	55.00	40.50	+ 35.8
RR	42.50	30.75	+ 38.2
RS	22.75	20.00	+ 13.8
DR	70.75	58.75	+ 20.4
RA	30.25	26.25	+ 15.2
JE	48.00	44.25	+ 8.5
Mean	42.93	34.57	+ 25.3

expense of smoking. To the extent that such concerns are prominent, the smoker probably inhibits smoking by such devices as imposing an upper limit on daily consumption, scheduling smoking, restricting smoking to particular occasions, and so on. All of these are devices which are designed to lower consumption and which would tend to mask such behavioral manifestations of addiction as tracking nicotine content. If this is correct, we should also expect other less obvious manifestations of addiction to be present. Of these I would suggest that the key will be the withdrawal syndrome. Obviously, anyone can give up smoking, limit daily intake, or restrict smoking to particular times or occasions if he is willing and able to put up with the withdrawal syndrome. If it is correct that virtually all longtime smokers are addicted, it should be anticipated that smokers who do not smoke in the morning will be grumpier and more irritable at that time of day than in the afternoon; that heavy smokers who switch to very low-nicotine brands will be chronically more volatile than heavy smokers who don't switch, and so on.

In order to test this sort of expectation, Perlick (1977) designed an experiment in which she measured irritability in two groups of smokers and a control group of nonsmokers. Unrestrained, heavy smokers were compared with a matched group of mostly former heavy smokers who, though still smoking, were deliberately cutting down. In fact, most of this second group were smoking less than half of their former regular intake.

We have, then, two groups of experimental subjects: one smoking to heart's content and the other deliberately restricting intake by any or all of a variety of devices such as switching to low-nicotine brands, buying only one pack a day, smoking only on the hour, and so on.

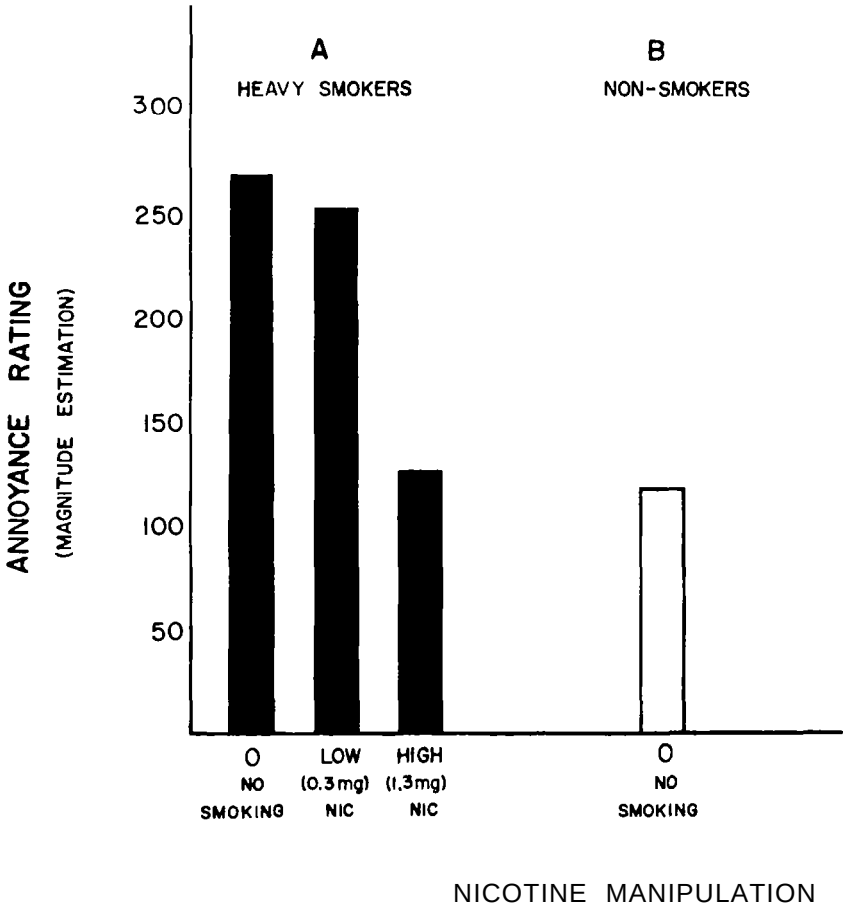
Within the context of a study of aircraft noise, these subjects individually watched a television drama and rated how annoying they found each of a series of simulated overflights. The laboratory had been designed by Eugene Galanter to look like a living room in Queens, near Kennedy Airport. Every 30 seconds or so a horrendous racket pervaded the room as the stereo audio system reproduced the noise of a jet taking off or landing. There were three experimental conditions: In one, the subjects were permitted ad lib smoking of high-nicotine (1.3 mg) cigarettes; in a second, ad lib smoking of low-nicotine (0.3 mg) cigarettes; finally, in a third condition, they were prevented from smoking.

Before getting to the results, let us examine the actual amount. of smoking by these two groups of smokers during the experiment. Do they behave during the experiment as on questionnaires they say they do in real life? They do. In those conditions in which they were permitted to smoke, restrained smokers took an average of 20.6 puffs (3.3 cigarettes) during the two-hour experimental session. This is just about half the amount smoked by unrestrained smokers, who puffed an average of 39.5 times (5.3 cigarettes).

Let us examine next the impact of the nicotine manipulation on the heavy, unrestrained smokers. The logic of the general argument demands the demonstration that irritability is a consequence of nicotine shortage. The data are presented in Figure 1. Along the ordinate is plotted the average annoyance rating. It can be seen that when permitted ad lib smoking of high-nicotine cigarettes, unrestrained smokers are just about as irritated by this noxious series of noises as are the control nonsmokers. However, when prevented from smoking or permitted to smoke only low-nicotine cigarettes, their irritability increases markedly. It does appear that, for the unrestrained smoker, irritability is a clear consequence of depleted nicotine. Incidentally, Perlick found precisely the same pattern for eating behavior, which is also presumed to be one of the key nicotine withdrawal symptoms. At one point during the experiment subjects had the opportunity to nibble freely at the contents of a large jar of jelly beans. Subjects in the no- or low-nicotine conditions ate twice as many jelly beans as did high-nicotine or nonsmoker subjects.

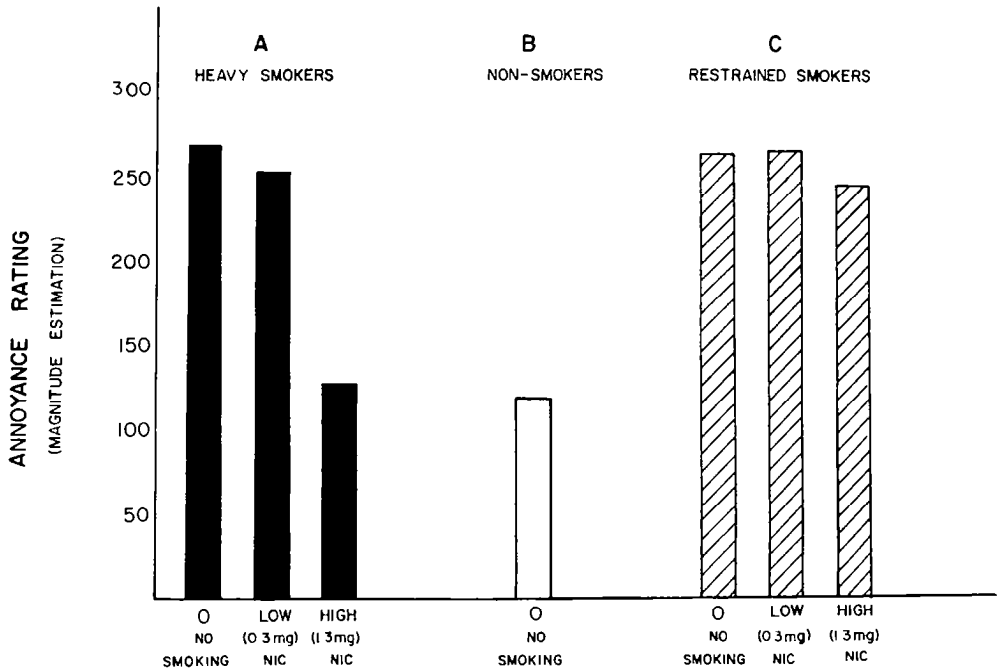
Let us turn next to the group of highly restrained smokers. If it is correct that the price of successful self-control is a chronic state of withdrawal, we should anticipate high irritability in all conditions, for even in the high-nicotine condition these former heavy smokers are getting considerably less nicotine than was their wont. The results are presented in Figure 2, where it can be seen that in all conditions these highly restrained smokers are irritable. Further, Perlick showed that these restrained smokers eat more when

FIGURE 1



The effects of nicotine on the irritability of heavy smokers and nonsmokers.

FIGURE 2



The effects of nicotine deprivation on the irritability of heavy smokers, nonsmokers, and restrained smokers.

given free access to jelly beans and also do not do as well at a proofreading task requiring concentration. Restrained smokers, then, appear to be chronically more irascible, to nibble more, and to have poorer concentration than unrestrained smokers. It is possible to control and restrict smoking, but at a price, and the price appears to be a chronic state of withdrawal.l It does appear that one of the exceptions to a purely addictive view of smoking is in reality no exception. I suspect that this will be the case with most of these exceptions, and that by taking account of withdrawal we can understand those studies (Finnegan, Larson, and Haag 1945; Goldfarb, Jarvik, and Glick 1970) that fail to show nicotine regulation. I would certainly suggest that any future studies of nicotine regulation make systematic provision for the measurement of withdrawal. I would also suggest that of the numerous possible indices of withdrawal, weight change may be by far the simplest and most reliable. Given what we know of the effects on weight of giving up smoking and what we know of the effects of nicotine deprivation on eating, it's not an unreasonable guess that those subjects who fail to regulate nicotine will be the most likely to increase weight.

I would like to conclude that by jointly considering withdrawal and regulation we can cope with the numerous apparent exceptions to an addictive model of cigarette smoking and also dispose of the hateful necessity to invent typologies to account for the apparent diversity of types of smokers. Though I do believe that this conclusion is valid for most smokers and smoking phenomena, I am not yet ready to declare it universal, for there does seem to be at least one "type" (dreadful word) of smoker for whom none of this seems to make sense. This is the sort of person who has smoked for most of his or her life and has never smoked more than 10 or 15 cigarettes a day. This person inhales, smokes medium- to high-nicotine cigarettes, but by his own self-description gives no indication that he is addicted. He may not light up his first cigarette of the day until cocktail time and can go for days without smoking and not think about it, until he goes to a party or some such event. Further, he insists that he is in no way trying to cut down or limit his smoking. Despite extensive and long-time exposure to nicotine, we seem to have a nonaddicted and nonaddictable animal.

For years I have tried to prove that among his other attributes this "type" of smoker is a liar, but so far with no success. In a first attempt to study regulation in this group, I was able to identify four such people and ran them simultaneously with the group already described in the study in which subjects smoked either 0.3 mg or 1.3 mg nicotine cigarettes in alternate weeks (Schachter, 1977b). These subjects, as a group, gave no sign of regulation, for two of them smoked more of the high-nicotine and two smoked more of the low-nicotine cigarettes.

Since my theme has been, "If they don't regulate, look for withdrawal," let us next examine this "type" of smoker for indications of withdrawal. Perlick was able to locate 15 such smokers, who incidentally were roughly matched with her group of restrained former heavy smokers. Both groups had smoked for about 8.5 years and both groups currently

averaged about 11.5 cigarettes a day. The irritability data for this group are presented on the right hand side of Figure 3. They stand in fascinating contrast to all of the other groups of subjects, for their irritability rating has absolutely no relationship to the nicotine manipulation. In all three conditions, their annoyance rating is quite low and on a par with the two groups that are not suffering withdrawal--nonsmokers and heavy smokers in the high nicotine conditions.

One obvious problem in interpreting these data is that two hours without smoking may be small deprivation to someone who smokes only 10-15 cigarettes a day. It may be that with a longer period of deprivation even these subjects would manifest withdrawal. However, several sub-analysts suggest that this would not be the case. First, even for such subjects, one might expect that annoyance ratings made at the end of the experimental period would be higher than those made at the beginning. This is certainly the case for the heavy and the restrained smokers in the nicotine deprivation condition. Both groups are markedly more annoyed at the end of the experiment than at the beginning. There is no such effect at all for this group, of apparently nonaddicted smokers; they are just as tranquil at the end of the experiment as at the beginning.

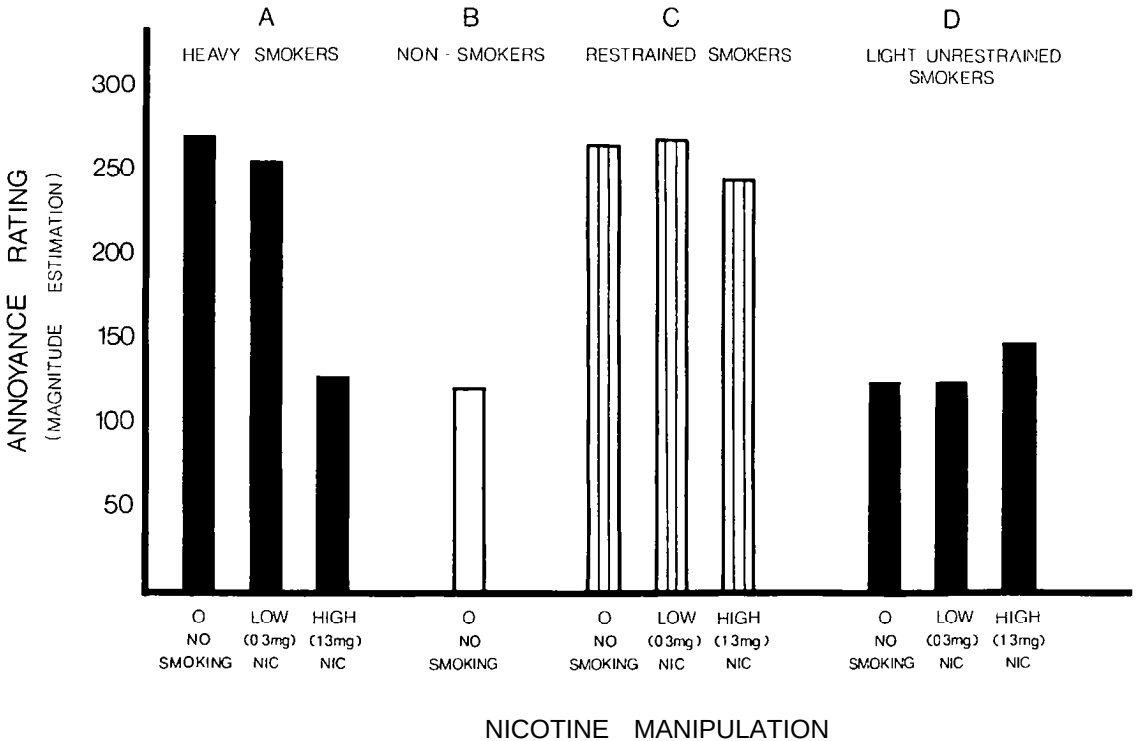
Secondly, thanks to a questionnaire, Perlick knew when the subjects had smoked their last cigarette before coming to the experiment. If it is simply a matter of time, one would expect that those who had smoked their last cigarette long before coming to the experiment would be more irritable than those who had smoked shortly before the experiment. Not so. For this group of subjects, there is no relationship between time of last pre-experiment cigarette and the mean level of annoyance during the experiment.

There is, then, experimental evidence suggesting that some smokers are not addicted and apparently are nonaddictable. Some of these subjects have smoked for 30 years and never smoked more than 10 or so cigarettes a day. I think there are few such people--perhaps 5 to 10 percent of the smoking population--but I harp on them because I suspect that they are an extraordinary scientific resource. If we can understand these “freaks,” we may begin to make steps in discovering what addiction is about.

FOOTNOTE

1. One alternative interpretation of these data must be considered. It is conceivable that naturally irascible people are more likely to restrain their smoking. If so, these results could be attributable to self-selection rather than withdrawal. Acutely aware of this possibility, Perlick (1977) compared these groups on numbers of personality and demographic variables and found no differences between the two groups.

FIGURE 3



The effects of nicotine deprivation on the irritability of heavy smokers, nonsmokers, restrained smokers, and light unrestrained smokers.

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Part III
Psychobiological Factors

Chapter 11

Acute and Chronic Effects of Nicotine in Rats and Evidence for a Noncholinergic Site of Action

L. G. Abood, Ph.D., K. Lowy, M.D., and H. Booth

Since the discovery that acetylcholine is a neurotransmitter in the autonomic nervous system and that its action consists of a muscarinic and nicotinic component, the action of nicotine has been attributed mainly to effects on nicotitic cholinergic synapses (Domino 1965; Larson and Silvette 1975). Although the action of nicotine in the autonomic nervous system or in certain brain areas can be understood in terms of either its agonistic or antagonistic action at nicotinic cholinergic synapses, a close perusal of the literature reveals that its neuropharmacological effects are considerably more complex and cannot be entirely explained by this mechanism. Recently we have observed that when the natural form of nicotine, which is the (-)-isomer, is injected directly into a rat's lateral or third ventricle, there occurs a characteristic prostration-immobilization syndrome lasting for from 0.5 - 2 min (Abood et al. 1978). The syndrome can be prevented or antagonized by the intraventricular administration of a number of newly synthesized nicotine or piperidine derivatives, but not by a variety of antinicotinic or numerous psychotropic agents. These observations, along with those involving electrophysiological and receptor binding measurements, led to the conclusion that the prostration syndrome may not be mediated by cholinergic mechanisms.

Additional pharmacological and electrophysiological studies on the acute effects of nicotine as well as observations on the chronic effects following continuous intraventricular infusion of nicotine into the lateral ventricles of freely moving rats are described in this report.

MATERIALS AND METHODS

All studies were performed on male Sprague-Dawley rats weighing between 150-200 g. The anesthetized rat was introduced into a Kopf stereotactic instrument, and a stainless steel cannula (#220 DK 1 rat cannula, obtained from David Kopf) was inserted stereotactically, aiming at either the lateral or third ventricle

It was attached to the skull by means of acrylic cement and four small set screws. A bipolar Formvar coated nichrome electrode of 0.2 mm thickness and 3/4 mm vertical tip separation was inserted with leads into the region of the dorsal hippocampus.

Electrical Recordings From Conscious Rats

Electrical recordings were made from freely moving conscious rats by way of a light shielded flexible cable leading into a Grass P-15-B preamplifier set for an amplification of 1000 and a filter band between 3-30 cycles/set. The amplifier output was connected to an FM tape recorder and a Grass dynagraph. Analysis of electrical activity was accomplished by two LINC-8 programs operating on the output from the tape recorder. Spectral analysis was done LINC-8 of a fast Fourier transform program modified for use by LINC-8. Another program was used to plot histograms of amplitude distribution recorded from representative sections of the tape recordings.

^{3}H-Nicotine Binding to Glass and Tissue

In an effort to develop a receptor binding assay for nicotine, an extensive investigation was undertaken utilizing various neural membrane preparations, synaptosomes, brain homogenates, and brain slices; however, none of these proved to be satisfactory. The ligands used in this exploratory study were ^{125}I-α-bungaratoxin, ^{14}C-d-tubocurarine, and 3H-nicotine. The techniques for measuring binding to cell-free preparations included equilibrium dialysis, centrifugation, gel filtration, and filtration through glass fiber filters. Although some stereospecific or specific nicotine binding could be demonstrated with fresh rat brain slices, the most satisfactory data were obtained by measuring 3H-nicotine binding directly to Whatman GE/F glass fiber filters in the absence of any tissue preparations.

The procedure for measuring 3H-nicotine binding to glass fiber filters is described elsewhere (Abood et al. 1978). Briefly, it consists of filtering a solution (0.05M Tris, pH 7.5) of 10^{-8}M ^{3}H-nicotine (0.2 curies/mole) in the absence or presence of 10-5M (-) or (+)-nicotine or nicotine analogues and then filtering in vacuo through Whatman GF/B glass fiber filters (2.1 cm). After washing the filters with 10 ml 0.05M Tris, pH 7.5, the filter is transferred to vials and radioactivity measured by liquid scintillation. Although some success was obtained in measuring specific nicotine binding to fresh rat brain slices, no specific or stereospecific binding was demonstrable to synaptosomes, neural membranes, or brain homogenates, employing all known techniques for measuring binding (see "Results").

Chronic Intraventricular Infusion of Nicotine

Chronic microinfusion of nicotine into the lateral ventricles of rats was accomplished by means of Alzet osmotic minipumps Model

1701 (Wei and Loh 1976). The minipump was inserted subcutaneously and was connected by means of a fine catheter to a 24 gauge stainless steel cannula stereotactically implanted into the lateral ventricles. The reservoir of the minipump contained 170 µl of 10 mg/ml solution of nicotine HCl, and the delivery rate was about 1 µl/hr (i.e.,10 µg nicotine/hr). In order to determine the reliability of the minipumps, they were tested for their remaining Contents 1-2 weeks later either by measuring optical absorbance at 260 nM or by the use of ^{3}H-nicotine and measuring residual radioactivity.

RESULTS

Psychopharmacological Effects of Nicotine Given Intraventricularly

Within 1-10 sec following the intraventricular administration of 2-10 µg of (-)-nicotine HCl the rats became prostrate and immobile, manifesting occasional seizures and tremors together with various autonomic changes (tachycardia, hyperpnea, and urination-defecation). The dose-response relationship was monotonic in this range. In order to produce a comparable response with (+)-nicotine, the required dose was at least 100 times greater than for (-)-nicotine. A variety of agents were tested for their ability to prevent the prostration immobilization syndrome of (-)-nicotine, including a series of synthetic derivatives of nicotine and piperidine (table 1). When 10 µg of either the benzyl or 4-azido-2-nitrophenyl derivatives of either piperidine or nicotine was given intraventricularly 2 min prior to 4 µg of (-)-nicotine, the prostration syndrome could be prevented. A wide variety of psychotropic neurotransmitters, cholinergic agents (e.g., naloxone, d-tubocurarine anticholinergics, and physostigmine), and d-tubocurarine were ineffective. Azapetine, an α-adrenergic blocker having a structural relationship to nicotine, possessed moderate antagonist activity. Neither chlorpromazine nor diazepam had any effect in antagonizing nicotine or on binding.

^{3}H-Nicotine Binding to Glass Fiber Filters

In general, a good correlation was observed between the behavioral antagonism of a given agent and its ability to compete with ^{3}H-nicotine for binding to glass fiber filters (table 1). The most effective antagonists-such as N-ANPP, N-benzyl and N-ONPS derivatives of nicotine, and piperidine-were also the most effective agents in blocking nicotine binding. The (+)-isorcler of nicotine, which possessed about 1 percent of the efficacy of (-)-nicotine in producing the prostration syndrome, was 10 percent as effective as the natural nicotine in blocking binding. Although some stereospecific and specific binding of nicotine could be demonstrated with fresh brain slices, the magnitude of the binding was small and somewhat variable; therefore, such data were not included. No specific binding to neural membranes, synaptosomes, or homogenates prepared from rat brain was demonstrable.

TABLE 1

Antagonism of various agents to prostration syndrome in rats and to ^{3}H-nicotine binding to glass filters. The dose of (-)-nicotine was 4 µg, which was given 1 min after the test agent. All drugs were given intraventricularly at doses of 10 µg, except for (+)-nicotine and piperidine, which were given at 100 µg. At least **8** rats were used for each drug tested behaviorally, while the standard error in the binding studies is within 6 percent of the mean. Binding is expressed as moles x 10^{14}/glass fiber filter. N-ANPP = 4-azide-2-nitrophenyl; N-ONPS = 2-nitrophenylsulfenyl.

Agent	% Behavioral Antagonism	^{3}H-nicotine binding	
		Moles x 10^{14} Glass	% competition Glass
Control	-	12.0	
(-)-nicotine	0	3.6	70
(+)-nicotine	33	11.0	8
N-benzyl nicotine	92	7.0	42
N-ANPP-nicotine	83	6.5	45
N-benzyl piperidine	75	6.0	50
N-ANPP piperidine	72	6.0	50
N-ONPS-piperidine	35	9.0	25
N-ONPS-nicotine	40	10.0	17
piperidine	40	11.5	4
butaclamol	slight	12.0	0
decamethonium	0	0.5	19
3-quinuclidinyl benzilate	slight	11.8	2
oxotremorine	0	9.9	17
naloxone	0	12.0	0
α-lobeline	0	11.5	4
azapetine	moderate	10.0	17
chlorpromazine	slight	11.5	4
diazepam	0	11.7	2

Electrical Recordings of Dorsal Hippocampus After (-) and (+)-Nicotine and Benzyl Nicotine

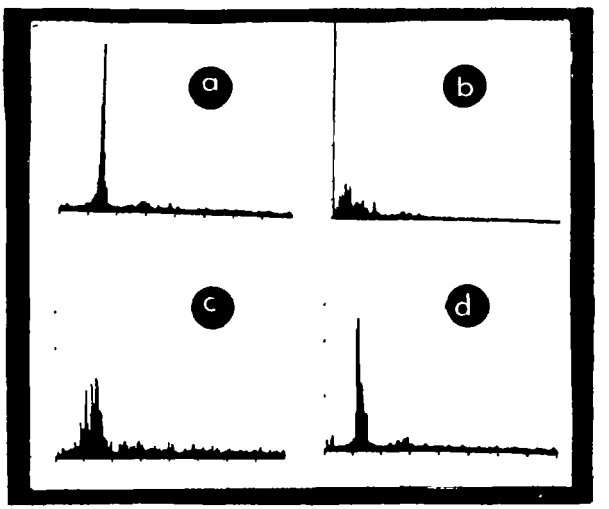
Spontaneous electrical activity recorded from the dorsal hippocampus of unanesthetized, freely moving rats before and after the administration of 4 µg of (-)-nicotine bitartrate revealed marked changes in both the frequency and amplitude of the electrical pattern (figure 1 a-d; figure 2 a-d). Frequency analyses of the electrical record are presented as oscillographic displays from fast Fourier transform (figure 1 a-d). The control record indicated a frequency range of 6-8 cycles/sec with a minor component in the 12-14 cycles/sec range (figure 1 a). Within 1 min after the administration of 4 µg of (-)-nicotine, when the rat was completely prostrate and immobile, the 5-8 cycle/sec activity greatly diminished (figure 1 b). When 10 µg of N-benzyl nicotine was given intraventricularly about 30 sec after the record in figure 1 b, the electrical pattern within 30 sec reverted to one resembling the control (figure 1c). For comparison, a frequency histogram is presented of a record from an animal given 200 µg of (+)-nicotine bitartrate, a dose which produced only minimal prostration, muscle weakness, and inactivity (figure 1d). A slight shift to lower frequencies was noted, with a peak value at about 5 cycles/sec. A computer analysis was performed on the amplitudes of the electrical recordings, and the results are presented in the form of histograms (lower tracings, figure 2 a-d). During the control period the amplitudes varied over a large range between 200-400 µV. After (-)-nicotine, when the animal was prostrate, the higher amplitudes at 400 µV disappeared, while the major component was at 200 µV. The flattening of the electrical recording after (-)-nicotine is evident in the upper tracing (figure 2b). After 10 µg of benzyl nicotine, the electrical record and the amplitude distribution resembled the control pattern; however, the 300-400 µV amplitude components did not reach the control level (figure 2c). After 200 µg of (+)-nicotine, the histogram and electrical pattern varied only slightly from the control records, the major difference being an increase in the 200 µV component (figure 2d).

Electrical Activity of Hippocampus During Nicotine Infusion

The electrical activity was recorded from the dorsal hippocampus of freely roving rats throughout the period of the intraventricular infusion of nicotine *at* a rate of 10 µg/hr (figure 3 a-d). The electrical pattern of the hippocampus is displayed in the upper oscillographic tracings of figure 3a and 3b; and in the tracing below is displayed a corresponding amplitude histogram of the upper record. The amplitude range before the infusion began had a broad spectrum ranging up to 400 µV (figure 3a); but after 48 hours of infusion the amplitude range narrowed considerably, with a maximum of 100 µV (figure 3b). After 6 days of infusion the amplitude histogram and electrical record resembled the control record (figure 3c), and two days following the removal of the minipump the records were unchanged (figure 3d). A spec-

tral analysis of the frequency employing fast Fourier transform revealed after 1.6 hours of nicotine a broad spectrum up to 30/ sec with a major component in 5-7/sec range (figure 4a). After 48 hours of nicotine infusion the higher frequency components almost vanished and only the 5-7/sec component remained (figure 4b). After 6 days of infusing nicotine, the frequency spectrum returned to the pattern seen in the control (figure 4c); and two figure 4d). removal of the minipump the pattern remained unchanged

FIGURE 1

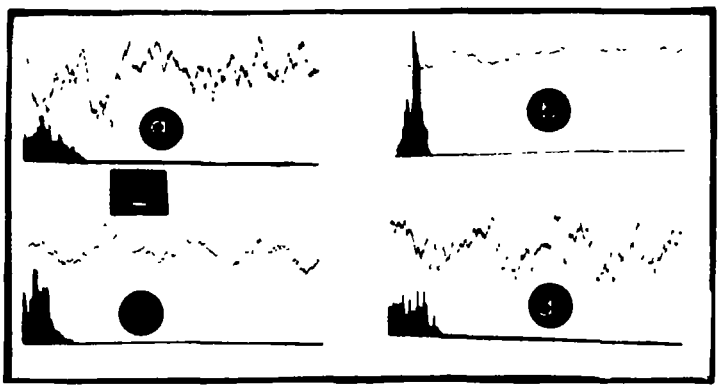


Spectral frequency analyses of electrical recordings of rat dorsal hippocampus after (-)- or (+)-nicotine and N-benzyl nicotine. a = control, b = 1 min after 4 µg (-)-nicotine, c = same rat given 200 µg (+)-nicotine 2 days later (control record identical), d = a rat given 10 µg N-benzyl nicotine 30 sec after (-)-nicotine. The records are typical of at least 5 individual rats for each drug. See text. Each dot on the abscissa represents a scale of 5 cycles/sec.

Chronic Nicotine Administration and Tolerance

In an effort to determine whether tolerance developed with repeated intraventricular administration of nicotine, rats were exposed to various dosage regimes of nicotine (table 2). When rats received 10 µg of nicotine for 3 consecutive days, they all responded (prostration immobilization syndrome) on day 1, while

FIGURE 2



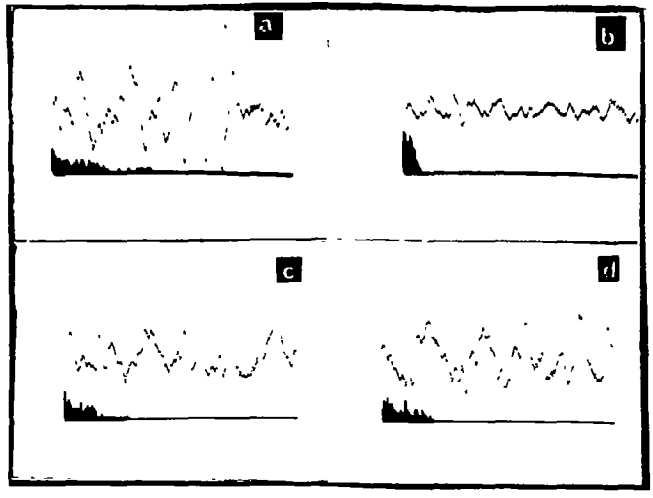
Electrical record and amplitude histograms corresponding to record described in figure 1 a-d. The bar represents a scale of 10^{-4} V on the abscissa.

TABLE 2

Effects of various dosage regime on behavioral response of rats to nicotine. From 5-10 rats were represented in each schedule. Nicotine was administered into left lateral ventricles.

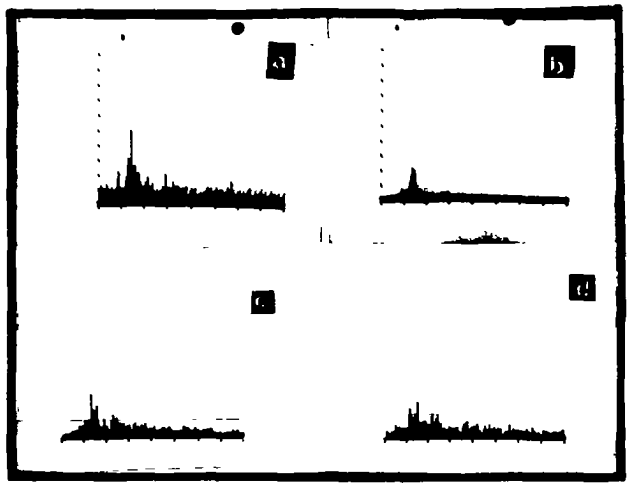
Dosage Schedule	Incidence of Prostration Syndrome
10 µg nicotine daily for 3 consecutive days	All of rats responded day 1, 50 percent on day 2, 20 percent on day 3, 90 percent response after 3 days recovery. Tolerance.
10 µg nicotine every other day for 10 days	Most rats fully responded for each day drug was given. No tolerance.
2 µg nicotine day 1, 4 µg day 2, 10 µg day 3	Response on day 4 to 10 µg nicotine.
Alzet minipump (10 µg/hr for 10 days.	Normal response to 10 µg nicotine on day after infusion ended.

FIGURE 3



Amplitude histogram of hippocampal electrical activity following chronic intraventricular infusion of nicotine. Same rat and legend as in figure 4 a-d.

FIGURE 4



Frequency analysis of hippocampal electrical activity following chronic intraventricular Infusion of nicotine. a = control, b = 48 hrs of nicotine infusion, c = 6 days of nicotine, d = 2 days after infusion was discontinued.

50 percent responded on day 2 and only 20 percent on day 3. If 10 µg of nicotine was given every other day for 10 days, most of the rats responded each day the drug was given. After 10 µg of nicotine was given for 5 consecutive days, none of the rats responded to 10 µg of nicotine on day 6; however, most of the animals responded on the second day after discontinuing the nicotine. If rats were given 2 µg of nicotine on the first day, 4 µg on the second day, and 10 µg of nicotine on the third day, they all responded to 10 µg of nicotine on the fourth day.

Effect of Nicotine on Drain Levels of Met-Enkephalin

Regional brain levels of met-enkephalin were measured in rats sacrificed 1-2 minutes following the intraventricular injection of 10 µg of nicotine. The animals were still prostrate at the time of sacrifice. No significant differences were observed between the saline- and nicotine-injected rats in any of the three brain regions (table 3). The determinations were made by Dr. S. Chanda, utilizing the technique of radioimmune assay.

TABLE 3

Effect of nicotine on enkephalin of rat brain regions.

Enkephalin = TYR-GLY-GLY-PHE-MET in pmoles/g wet wt. All rats received 10 µg nicotine intraventricularly 1-2 minutes before sacrifice. Results are average of 6 rats.

	Nicotine	Saline
Telencephalon	128 ± 39	97 ± 29
Diencephalon	149 ± 55	152 ± 36
Mesencephalon	223 ± 48	243 ± 34

DISCUSSION

The major conclusion from this study is that the action of nicotine in producing the prostration immobilization syndrome does not appear to be mediated by cholinergic mechanisms in the brain. Among the reasons for this conclusion are the following: 1) the syndrome cannot be simulated by a number of cholinergic agents in doses up to 100 µg; included among such agents were acetylcholine, oxotremorine, pilocarpine, physostigmine, and a-lobeline; 2) a variety of agents know-n to block the nicotinic cholinergic receptor were ineffective in either preventing or reversing the behavioral effect of nicotine; and 3) the nicotine and piperidine analogues which were effective in blocking the behavioral effect of nicotine did not interfere with the binding

of ^{125}I-α-bungarotoxin or ^{3}H-d-tubocurarine to neural membranes (Abood et al. 1978). In an effort to determine the possible relationship of nicotine to town neurotransmitters, a wide variety of substances, in addition to those described, were injected intraventricularly (in doses up to 100 µe) and found to have no similar effect. These included noradrenalin, dopamine, serotonin, glutamic acid, γ-sminobutyric acid, met-enkephalin, and morphine, as well as a variety of antagonists to known neurotransmitters. It would appear, therefore, that this behavioral effect of nicotine is quite unique and distinct, while being largely unrelated to any known neurotransmitter system.

The brain sites associated with the prostration syndrome exhibit a high degree of stereospecificity, the natural (-)-isomer of nicotine being at least 100 times as effective as the (+)-isomer. Since the optical purity of the stereoisomers can be determined with only about 99 percent accuracy, it is conceivable that the (+)-isomer is completely inactive. Domino (1965) compared the two isomers of nicotine on established conditioned avoidance and seizure threshold in rats as well as hypertension in dogs and concluded that the (-)-isomer was only 8 times as active as the (+)-isomer. Pfeiffer (personal communication) reported a similar difference in man with the two Isomers. Although the (+)-nicotine used by both investigators was not as optically pure as the material used in the present study, the difference between the results cannot be accounted for by the difference in purity. A more plausible explanation is that the ventricular sites associated with the prostration syndrome are distinct from those involved in the behavioral and peripheral parameters measured by Domino (1965).

Another conclusion from this study is that tolerance in rats to the behavioral effect of nicotine develops after repeated injections, but the responsiveness returns to the initial level within 2 days following the last injection. Even after the rats received a continuous infusion of nicotine for **7** days, they still responded 1 day after stopping infusion to 10 µg of nicotine injected into the lateral ventricles. With continuous infusion of nicotine into the lateral ventricles, a marked change occurred in electrical pattern of the dorsal hippocampus 24 hours after infusion began, but the electrical activity returned to normal by the end of the third day. Despite the fact that the electrical pattern changed so markedly, there were no marked behavioral effects during 7 days of infusing nicotine.

FUTURE OBJECTIVES AND DIRECTIONS

The present study raises a number of important questions concerning both the acute and chronic effects of nicotine on behavior. The most fundamental question pertains to the nature of the prostration-immobilizatlon syndrome produced by nicotine administered intraventricularly to rats and its possible relationship to the behavioral effects of tobacco in man. It is recognized that the doses used to produce this effect in rats are comparatively large, so that any comparison with smoking would be

difficult and somewhat conjectural. Some similarity has been observed in EEG changes associated with smoking in man (Murphee et al. 1967; Philips 1971) and after intravenous administration of small doses of nicotine in cats (Domino and Yamamoto 1965). Nicotine in both cats and man produces a desynchrony in the EEG, which has been interpreted as both an "arousal" (Domino and Yamamoto 1965; Philips 1971) and an opposite tranquilizing effect (Murphee et al. 1967). In our studies with intraventricularly administered nicotine, both the electrical recordings and behavioral responses tend to suggest that the preponderant effect is a depressant one; however, at lower doses (1 µg) the rats appear more active and hyperexcitable. Precise and detailed psychophysical measurements are needed in order to distinguish the two kinds of effects in animals as well as man.

Another question concerns the nature and localization of the sites for nicotine's action in the brain. If, as the present study seems to suggest, the sites are noncholinergic and may be unrelated to other known neurotransmitters, the question then arises as to chemical nature of the endogenous substrate for this particular site. As to the location of the sites, they would appear to be somewhere within or near the lining of the lateral or third ventricles. To date it has not been possible to produce the prostration syndrome by injecting nicotine directly into brain structures immediately adjacent to the ventricles or into innumerable deeper brain structures.

Since a large number of neurohumoral substances, including biogenic amines and neuropeptides, are present in the hypothalamus (Hokfelt et al. 1978), and since synaptic terminals for known neurotransmitters have been detected in the linings of the lower third ventricles, the hypothalamus has been considered as a possible site for nicotine. Although the injection of nicotine into the ventricular region in the vicinity of the hypothalamus will elicit the prostration syndrome, the administration of nicotine into various nuclei of the hypothalamus has falled to produce any behavioral response. In view of the fact that a number of neuropeptides, such as B-endorphin, enkephalins, substance P, and angiotensin II are associated with the hypothalamus, the possibility exists that nicotine may promote their release and that the behavioral effects are due directly to the peptides. Nicotine has been shown to promote the release of catecholamines from the hypothalmus (Hall and Turner 1972) and to inhibit the release of serotonin (Goodman and Weiss 1973), but neither neurotransmitter mimics the action of nicotine. The brain is also known to contain amines which possess nicotinic cholinergic actions, the most noteworthy being piperidine (Von Euler 1944; Abood et al. 1961). Although piperidine possesses tranquilizing (Abood et al. 1961) and soporific actions (Dolezalova et al. 1973), it does not produce the prostration syndrome seen with intraventricularly administered nicotine.

It does not appear from the present studies that the behavioral

effects of nicotine are associated with changes in the levels of brain met-enkephalin. Another finding that would tend to exclude the involvement of endogenous opioid peptides in the action of nicotine is that naloxone did not prevent or modify the behavioral effects of nicotine. Furthermore, morphine itself did not mimic or prevent the effects of nicotine.

Finally, some comment should be made concerning the inability to demonstrate specific nicotine binding to neural tissue, whereas both specific and stereospecific binding is readily demonstrable to glass. One possibility is that the sites are either destroyed during disruption of the tissue or that released endogenous substances interfere with binding. Another is that the binding affinity is too low to detect with the ^{3}H-nicotine used, a problem that might be rectified with material having a 100-fold greater specific activity. The fact that the response to nicotine is so fleeting (often lasting only 10-30 seconds) is suggestive of a relatively low affinity. Since nicotine would appear to be highly potent when injected intraventricularly, the receptors may be close to the site of administration. Since many drugs bind stereospecifically to glass, it is difficult to attach much significance to the fact that nicotine also binds stereospecifically. It is of interest, nevertheless, that the data with the glass filters correlate well with the in vivo effects of the various nicotine derivatives. Conceivably, the technique could be useful as an initial screening for nicotine agonists or antagonists.

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Chapter 12

Tolerance to the Effects of Tobacco

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The question of whether cigarette smoking or other forms of tobacco use can be considered an addiction comparable to addiction to heroin or alcohol always sparks a lively debate. For one thing, there appear to be different styles of tobacco use. For another, there is some question about how often heroin or alcohol use results in addiction. And, finally, there is not even uniform agreement on the meaning of "addiction." The definition I prefer is that of Jaffe (1975): "Addiction...(is) ...a behavioral pattern of compulsive drug use, characterized by overwhelming involvement with the use of a drug, the securing of its supply, and a high tendency to relapse after withdrawal."

Tolerance and dependence are two phenomena which are closely related to addiction to heroin and alcohol. In this paper I want to consider evidence concerning tolerance to tobacco and its components. Since prominent theories of physical dependence consider tolerance to be the basis of this state (Jaffe and Sharpless 1968; Martin 1968; Goldstein et al. 1974), this paper may be considered complementary to that of Shiffman (this volume), who deals with the dependence question. I can think of no example of a drug to which dependence occurs which does not also involve tolerance. On the other hand, tolerance may occur without dependence, for example, to phenothiazines, or to antihistamines.

Tolerance is manifested by a decreasing response to repeated administration of the same dose of a drug, or by the requirement for increasing doses in order to elicit the same response. Tolerance to different effects of a given drug may vary widely.

Of the many thousands of substances contained in tobacco and tobacco smoke (Schmeltz and Hoffman 1976), three are of primary biological importance: "tar," carbon monoxide, and nicotine. There is evidence that tolerance can develop to the effects of each of these, and their interaction has scarcely been studied. Although there is evidence that tolerance may develop to other components such as acetone and phenol, it is unclear how much they contribute to the pharmacological actions of cigarettes,

Three kinds of tolerance are apt to occur with tobacco use as with other drug use: (1) drug dispositional or metabolic tolerance; (2) tissue or pharmacodynamic tolerance; and (3) behavioral tolerance. The first refers to methods that the body uses to eliminate the drug or to deactivate it. For most chemicals derived from tobacco, the liver is the organ most heavily responsible for detoxifying or transforming them into inactive and eliminable forms. The kidney is also important, especially for alkaloids whose water solubility varies with the pH of the solution. The second refers to changes in the ability of receptors to be activated by the drug at its final site of action. The third refers to the way in which the subject using the drug changes his behavior to adapt to the effects which the drug repeatedly produces.

TAR

"Tar" is defined as the total particulate matter (TPM) collected by a Cambridge filter after subtracting moisture and nicotine. The polycyclic aromatic hydrocarbons are generally blamed for a substantial portion of the carcinogenic activity of "tar." They are also powerful enzyme inducers and are undoubtedly responsibe for much of the tolerance produced by smoking to themselves and a variety of other compounds. The tar content of cigarette smoke for all brands is determined yearly by the Federal Trade Commission which publishes a listing, along with nicotine content. Tar and nicotine tend to covary and thus their effects may be confounded. Obviously, tar is obtained in the smoke from pipes and cigars, but not from chewing tobacco and snuff. The latter do not deliver pyrolysis products such as carbon monoxide and may thus be somewhat safer than smoked tobacco.

It is known now that hepatic microsomal enzyme formation is induced by a number of carcinogens in the tar fraction of cigarette smoke, including benzpyrene (Oates et al. 1975). This means that smokers are rendered tolerant to both the therapeutic and toxic effects of a wide variety of drugs (Swett 1974). Even the enzymes in platelets are activated (Horns et a1.1976). Paradoxically, just because of this type of enzyme induction, cigarette smokers are more resistant to the effects of carcinogens but not enough to prevent a wide variety of cancers.

Some examples of the effects of induction of microsomal enzymes are cited by Hunter and Chasseaud (1976). Arylhydrocarbon hydroxylase is regularly induced by smoking. Benzpyrene hydroxylase and aminoazo dye N-methylase were higher in placentae of pregnant smoking women than of nonsmokers. Metabolism of benzodiazepines, of propoxyphene, pentazocine and phenacetin is increased in smokers. Xanthines such as theophylline are also metabolized more quickly in smokers (Powell et al. 1977).

CARBON MONOXIDE

While levels of carbon monoxide achieved in the human body following cigarette smoking do not appear to be higher enough to materially affect psychological performance (Stewart 1975), the long term effects may be quite significant. There are some (McGill 1977) who contend that the atherogenic effects of cigarettes are largely due to carbon monoxide. Indeed, the chronically high levels of carboxyhemoglobin found in smokers can induce both a polycythemia and increase in hemoglobin levels. These compensatory changes enable the smoker to cope with the oxygen deficit produced by cigarettes. Furthermore, since the latent oxygen carrying capacity of the blood is increased by smoking, sudden cessation should make a smoker more capable of functioning at high altitudes for a short while than a nonsmoker.

NICOTINE

For most drug dependencies it has been shown that pharmacodynamic tolerance is more important than drug dispositional tolerance. For example, animals and humans tolerant to alcohol and barbiturates show significantly less sedation and ataxia than do nontolerant subjects at the same blood concentrations. Since the liver and the kidneys largely control the blood concentration, one would have to assume that tolerance must be occurring in the brain. Methods of determining blood levels of nicotine with gas chromatography or radioimmunoassay are too recently developed to have produced many studies in tolerance.

In a recent study, Jones and colleagues (1978) showed that smokers could tolerate higher intravenous doses of nicotine than nonsmokers. Smokers reported generally pleasanter effects from 700 mcg. of nicotine intravenously than nonsmokers from 300 mcg. In addition to the chronic tolerance demonstrated by the smokers, both smokers and nonsmokers manifested acute tolerance. When the same dose of nicotine was injected at about hourly intervals, each succeeding injection elicited less of a response. This resembles tachyphylaxis, and it may represent occupation of the receptor by the drug or by some other substance such as a catecholamine released by the nicotine, or it may imply depletion of catecholamines.

The fate of 1 mg of nicotine base injected intravenously in humans (actually as nicotine hydrogen tartrate) was intensively investigated by Beckett (1971). They found that smokers excrete nicotine significantly faster than nonsmokers. None of the smokers reported any nausea from the nicotine injections, but this was reported in varying degrees by all nonsmokers. Haines et al. (1974) reported that the plasma concentrations of nicotine were actually higher in smokers than nonsmokers one minute after smoking, but these results were confounded by the fact that nonsmokers were instructed to smoke cigarettes. Obviously smokers were able to inhale more effectively than nonsmokers in part because they had acquired tolerance to the aversive effects of cigarette smoke on the respiratory passages. Indeed, some of the tolerance that smokers show to

cigarette smoke may be correlated with diminished function of the respiratory epithelium and possible depression of taste and smell (Kittel 1970).

The phenomenon of tolerance to tobacco and particularly to nicotine is reviewed by Larson and Silvette (1961, 1968, 1971, 1975) in their four volumes on tobacco. There is a fair sized literature indicating that tolerance to nicotine can be developed in invertebrates, fish, frogs and birds. It has also been demonstrated in mice, rats, dogs and in one donkey forced to inhale smoke through a nasal catheter. In the latter study a donkey initially exposed to the smoke from 20 cigarettes daily showed marked impairment of bronchio-trachial transport of radioactive iron oxide particles for several months. However, by the end of eight months of exposure compensation had occurred and transport was quite normal. Westfall and Brase (1969, 1971) showed in rats that the tolerance to nicotine-induced elevations of urinary catecholamines is due to increased enzymatic metabolism of these amines. Both monamine oxidase and catechol-o-methyl transferase activity of the liver were increased but nicotine oxidases were unchanged.

Schechter and Rosecrans (1972) demonstrated behavioral tolerance to the effects of nicotine in the rat. Nicotine (0.4 mg/kg) was used as the discriminative stimulus in a T-maze. After a criterion of eight out of ten correct responses was attained, the animals were given four daily injections of nicotine for five days. The authors found that tolerance occurred, because discrimination became much more difficult as time proceeded.

Tolerance to the effects of cigarette smoke was noted in dogs given cigarette smoke via tracheostomy (Hammond et al. 1970). In our laboratory Stolennan et al. (1973) showed the development of both acute and chronic tolerance in rats. Nicotine administered intraperitoneally to experimentally naive rats depressed activity in a Y-shaped runway in a dose-related manner. After a single intraperitoneal dose of nicotine, acute tolerance to the depressant action of a second dose developed with a definite time course, becoming maximal after two hours and wearing off after about eight hours. Repeated intraperitoneal doses of nicotine (3 times daily for 8 days) elicited chronic tolerance, which persisted for at least 90 days after the end of regular treatment with the drug. Tolerance was also produced when nicotine was administered in rats' drinking water and through reservoirs implanted subcutaneously. It appears, then, that tolerance to nicotine in rats can develop quickly, may be measured easily, and persists for prolonged periods after withdrawal. In these experiments rapid withdrawal of nicotine did not produce the signs of illness which morphine withdrawal regularly produced. The existence of prolonged tolerance to nicotine in rats suggested that the same phenomenon might exist in man just as it does for opioids. If prolonged tolerance occurred in exsmokers, then it might facilitate relapse, became such individuals would be more resistant to the negative effects of cigarettes.

Stolerman et al. (1974) examined the interaction between pairs of injections of nicotine, which varied both in dose and in interval. Two measures of spontaneous locomotor activity of rats in a T-maze were taken: rears and entries. After a single treatment with nicotine acute tolerance developed as indicated by a shift of the dose response curve. The dose of nicotine required to produce a given decrement in activity was multiplied by a factor of about 2.4 when a delay of two hours was taken between the two injections. When the initial dose was varied, it was found that there was an optimal level for producing tolerance. Higher doses were less effective. An explanation for the relative ineffectiveness of the higher doses in producing tolerance is not available. A general debilitating effect of pretreatment with large doses doesn't seem to explain it, since rats given a saline challenge exhibited normal motor activity. Perhaps the debilitating effects of a large pretreatment dose and a challenge somehow summate.

QUESTIONS FOR FURTHER RESEARCH

The phenomenon of tolerance to the effects of tobacco products has been clearly demonstrated both in humans and in animals. Naturally enough, most of the emphasis has focussed upon nicotine, but carbon monoxide and tar components also play an important role. As with all other drugs, tolerance varies with subjects and functions. Certain invertebrate forms which feed on the tobacco plant have a high genetically determined tolerance. It is reasonable to assume that even in humans some of the variance in response to tobacco is innately determined and may account for some of the high concordance in smoking behavior seen in identical twins. Other forms of tolerance are clearly the result of experience and develop after exposure to tobacco products. Much more research needs to be done to determine the degree of tolerance which develops in different physiological and psychological functions after tobacco use. For example, it is evident that even in heavy smokers of long duration the heart rate speeds up after each cigarette. On the other hand, at least nausea and vomiting diminish and disappear with continuing moderate use of cigarettes. It would be very informative indeed to know what changes take place at the putative sites of action of nicotine with chronic use. Do nicotinic synapses at ganglia change in the same way as nicotinic synapses in the brain? Do carbon monoxide and tar constituents have any action on these components or on enzyme systems elsewhere in the body? Answers to these questions will enable us to understand better the physiological basis of the smoking habit.

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Chapter 13

The Tobacco Withdrawal Syndrome

Saul M. Shiffman, M.A., C.Phil.

Characterizing tobacco use as a dependence process necessarily raises the issue of tobacco withdrawal, as the presence of an abstinence syndrome is crucial to the definition of drug dependence. Indeed, some of the initial reluctance to label tobacco as a dependence-producing substance rested on doubts concerning the existence of a tobacco withdrawal syndrome. This was the position taken by the Surgeon General in 1964, when first alerting the country to the dangers of tobacco, Since then, there has been an accumulation of studies which suggest that withdrawal from tobacco does produce a variety of signs and symptoms which can be characterized as a tobacco withdrawal syndrome. Although the syndrome is variable and is only roughly described and understood, its existence is no longer a matter of great controversy. The focus has shifted from the somewhat semantic question of categorizing tobacco use to exploration of the particulars of tobacco dependence and withdrawal. This paper reviews the findings on tobacco withdrawal syndrome, focusing initially on a description of the syndrome, and then on factors affecting its severity and course. Finally, noting methodological issues which need to be considered, goals and directions for further research are discussed.

SYMPTOMS OF TOBACCO WITHDRAWAL

A number of physiological changes have been observed on withdrawal from tobacco. Decreases in heart rate and diastolic blood pressure are observed as early as six hours after withdrawal (Murphee and Schultz 1968). These changes persist for at least three days and perhaps for thirty (Weybrew and Stark 1967; Glauser et al. 1970). Decreased excretion of both adrenaline and norepinephrine and various metabolic changes have also been observed (Myrsten et al. 1977; Glauser et al. 1970). These indications of decreased arousal have been supported by EEG studies showing a decrease in the peak alpha frequency and increases in low frequency activity (Knott and Venables 1977; Ulett and Itil 1969). Increases in sleeplike activity have been observed in the EEG records of deprived smokers (Itil et al. 1971). It has also been demonstrated that, in sleep,

deprived smokers show decreases in REM latency and increases in REM time (Kales et al. 1970). In contrast, however, Knott and Venables (1978) report that deprived smokers showed hypersensitivity to low intensity stimuli, as indicated by increased amplitude and decreased latency in the evoked response. Thus, while withdrawal from tobacco appears to produce physiological changes suggestive of decreased arousal, this is not a uniform or easily characterized pattern.

Another documented physical change resulting from abstinence is weight gain. Wilhemsen (1968) observed a weight gain of 2.4 kg in two months of abstinence, while Glauser et al. (1970) documented an increase of 3.2 kg in one month. In Fletcher and Doll's (1969) retrospective study of British physicians, the respondents reported gaining as much as 5.3 kg on the average. Although the weight gain itself is thus well documented, it is controversial whether it results from increased appetite and consumption or from metabolic changes (Glauser et al. 1970). It has been demonstrated that withdrawal impairs the performance of smokers on psychomotor tasks requiring vigilance and/or tracking (Heimstra 1973). Not surprisingly, deprived smokers do poorly in a driving simulation task (Heimstra et al. 1967). The effects of tobacco deprivation on verbal learning are complex, with indications of both facilitation and impairment. Kleinman, Vaughn and Christ (1973) found that 24-hour deprivation facilitated learning of easy paired associates, but impaired performance with hard pairs. They interpret this as an indication of hyperarousal, while Andersson (1975) reports mixed facilitation and impairment and interprets this as indicating shifting arousal. Myrsten et al. (1977) found verbal learning essentially unaffected over five days of abstinence. Thus, while psychomotor performance is reliably impaired by abstinence, little can be said about its effects on verbal learning.

Accompanying these objective changes in physiology and performance are subjectively reported changes in physical symptoms, arousal, and mood. These have been reported in studies of smokers sampled while actually undergoing withdrawal, as well as in retrospective studies of exsmokers up to 14 years after cessation. Although the specific symptoms reported differ, as does the percentage of abstinent smokers reporting each symptom, a consistent pattern of symptoms can still be discerned. Common among the physical symptoms reported are nausea, headache, constipation, diarrhea, and increased appetite. Also reported are disturbances of arousal, including drowsiness and fatigue, as well as insomnia and other sleep disturbances (e.g., Guilford 1966). Inability to concentrate is a common complaint and is consistent with objective assessments of the concentration of smokers in abstinence (Perlick 1977; Heimstra 1973). Thus, the objective changes reviewed above appear to be reflected in the subjective experience and self-reports of deprived smokers.

Changes in mood or affective tone are prominent among the symptoms reported in withdrawal from tobacco. Increased irritability and hostility are common sequelae of abstinence from tobacco (Friedman 1972; Mausner 1970). Increases in aggressive behavior and its correlates have also been observed in abstinence (Schechter and Rand

1974; Hutchinson and Emley 1973). Increased anxiety is another affective change which is both reported and observed (Friedman 1972; Nesbitt 1973). In addition to reports of these symptoms under neutral conditions, several studies suggest that deprived smokers are more likely to respond with anxiety and irritability when stressed (Myrsten et al. 1972; Frankenhaeuser et al. 1971). This may only be true compared to nondeprived smokers, however, with smokers showing decreased vulnerability to these dysphoric reactions to stress (Heimstra 1973). In summary, withdrawal from smoking shifts the smoker's affective tone toward dysphoria, and increases anxiety and irritability.

By far the most common and clinically most important symptom appearing following withdrawal from tobacco is craving for tobacco. The best estimates indicate that 90 percent of all smokers in withdrawal will crave (Guilford 1966). Moreover, among smokers who have been abstinent for five to nine years, one out of five report that they continue to have at least occasional craving for tobacco [Fletcher and Doll 1969). The importance of craving lies not in its universality or persistence, but in its relation to the clinical goal of modifying smoking behavior. Indeed, the importance of the tobacco withdrawal syndrome in its entirety is based on its provocative role in causing relapse among abstinent smokers.

SMOKING CESSATION, RELAPSE, AND MAINTENANCE

Since tobacco use--particularly cigarette smoking--was identified as a major cause of "preventable" morbidity and mortality, concerted attempts have been made to apply behavioral technology to the problem of smoking cessation, and, indeed, have become very successful in producing cessation. At least one method--rapid smoking--is claimed to produce cessation in more than 90 percent of clinic patients (Lichtenstein and Danaher 1976). Unfortunately, very little headway has been made in producing long term maintenance of nonsmoking. It has been estimated that, on the average, only about 25 percent of those who successfully quit smoking will remain abstinent for more than six months (Hunt and Matarazzo 1973). The focus of clinical efforts in the treatment of smoking thus needs to shift from producing cessation to encouraging maintenance and preventing relapse.

It is self-evident that craving for cigarettes is a major cause of relapse. The urge to smoke, when it becomes stronger than the ex-smoker's determination to quit, leads to relapse. In a retrospective study of treated smokers 18 months after treatment, Peterson et al. (1968) found that over half of those who had relapsed cited craving specifically as the cause.

Other withdrawal symptoms also play a role in relapse. In Peterson et al.'s study, 35 percent of the recidivists cited anxiety as the cause of relapse, while 12 percent cited weight gain. In my analysis of questionnaire data collected by C. Hammen (personal conmmication 1973), I have found that 61 percent of smokers who were applying for treatment cited either anxiety or craving as the cause

for relapse in previous attempts. This is in line with estimates by Guilford (1966) and Burns (1969). By providing immediate aversive consequences for smoking cessation, withdrawal symptoms thus make continued abstinence difficult, and relapse probable.

FACTORS AFFECTING THE ABSTINENCE SYNDROME

Thus far, the emphasis has been on the uniformity of reports concerning the tobacco abstinence syndrome. The impression might be drawn that every smoker, upon withdrawal from tobacco, becomes irritable and anxious and is unable to think, work, sleep, drive, or carry on normal social discourse for want of a cigarette. Fortunately, this is not the case. The tobacco withdrawal syndrome is apparently quite variable in character, severity, and duration. An examination of various studies reveals large differences in the frequency with which particular symptoms are reported. Where Trahair (1967), for example, reports that sleep disturbance was experienced by only ten percent of exsmokers, Guilford (1966) reports that 31 percent of her subjects suffered from insomnia. Similar examples of variability are commonly reported in the literature on smoking withdrawal. About 23 percent of abstinent smokers report no symptoms at all (Myrsten et al. 1977; Pederson and Lefcoe 1976; Wynder, Kaufman and Lesser 1967). While this has led some to conclude that there is no abstinence syndrome (e.g. USDHEW 1964), this conclusion is contradicted by a mass of data, some of which has been cited above. A simpler conclusion is that the abstinence syndrome is quite variable. This impels us to tease out the causes of this variability. Research on the factors which affect the tobacco withdrawal syndrome is the major focus in the remainder of this paper.

Recent work in our laboratory at UCLA has focused on factors which may affect the tobacco withdrawal syndrome. We have developed a 25 item questionnaire which measures the five symptom clusters which comprise the syndrome: physical symptoms, psychological symptoms, arousal, appetite, and craving for cigarettes. (Our appetite scale subsequently proved to be unreliable and therefore does not figure in our analysis.) Subscales assessing each of the symptom clusters were created using factor analytic methods. The questionnaire was then used to study sources of variance in the tobacco withdrawal syndrome in 40 smokers who were attempting to quit smoking. These subjects completed the questionnaire at the beginning of cessation and then four times daily thereafter. (Most of the data reported here are from a study published in part as Shiffman and Jarvik 1976.)

Baseline Cigarette Consumption

It is characteristic of withdrawal syndromes that their severity is dose dependent (Jaffe 1971). Therefore, it is expected that heavy smokers would report more severe withdrawal symptoms than light smokers. A comparison of subjects smoking a pack or more ($x=26.6$) per day with those smoking less than a pack ($x=15.7$) per day, however, revealed no overall differences in the severity of their symptoms.[1] This replicates our previous finding that light and heavy

smokers do not differ in craving when deprived for 48 hours (Gritz and Jarvik 1973). In work currently under way on the effects of brief deprivation (e.g., a two hour lecture), we have found same dose-related effects on craving (Gritz 1978).

The inconsistency of this effect in our studies parallels the state of the literature. Studies by Myrsten et al. (1977) and by Mausner (1970) also report finding no differences between light and heavy

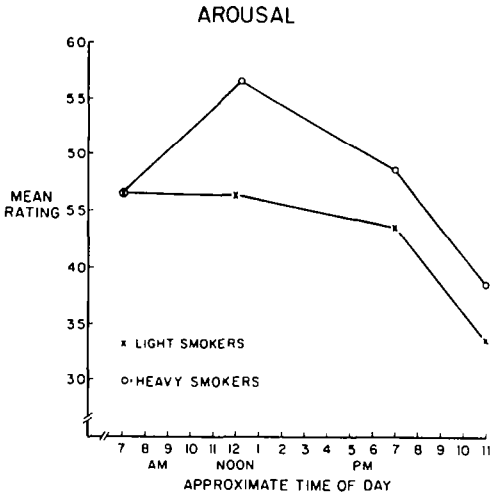
In contrast, Burns (1969) reports that subjects who reported withdrawal symptoms had smoked an average of 6.9 cigarettes/day more than asymptomatic subjects ($p<.01$). Since this is smaller than the mean difference between the light and heavy smoker groups in our study (11.1), this discrepancy is puzzling. Wynder, Kaufman and Lesser (1967) report that the proportion of abstinent smokers reporting more than one withdrawal symptom increases with baseline consumption. A chi squared analysis performed on their data reveals that this association is highly significant ($x^2=15.81$, $df=2$, $p<.001$). Perhaps these discrepancies can be explained by the fact that Burns and Wynder et al. studied the number of symptoms, while we studied the severity of each symptom separately.

Another possible confound is that, because smokers can vary their smoking consumption in other ways -- depth of inhalation, number of puffs, etc. -- cigarette consumption may actually be a very poor measure of dose. Also, differences in nicotine metabolism introduce variability in dose even among those who consume similar amounts of nicotine. Thus, estimating a smoker's dose may require measuring serum levels of nicotine or its metabolites. In the one study which has approached this, Zeidenberg et a1. (1977) found a high and significant correlation between serum cotinine levels before treatment and self-reported "degree of difficulty" in smoking cessation. This result held for men only, however, perhaps because of additional variability in the cotinine levels or the self-reports of the female subjects . There is some indication that the severity of the abstinence syndrome is dose-dependent, but much ambiguity remains. Because dose dependency is so characteristic of withdrawal syndromes from other substances, establishing this effect for tobacco would be an important step towards an understanding of tobacco dependency. Further research into the relationship should probably proceed along the lines of Zeidenberg et al., using serum cotinine levels rather than cigarette consumption as the independent variable. Dependent measures should include more refined instruments than Zeidenberg et al's estimates of "difficulty" and should explore both the number of withdrawal symptoms and their severity.

Diurnal Variations in Symptoms

Since our subjects were providing reports of symptoms at regular intervals throughout the day, we were able to study diurnal variations in symptoms. One puzzling finding which emerged was that, while light and heavy smokers reported the same average level of arousal, they differed significantly in the diurnal pattern of arousal.

FIGURE 1

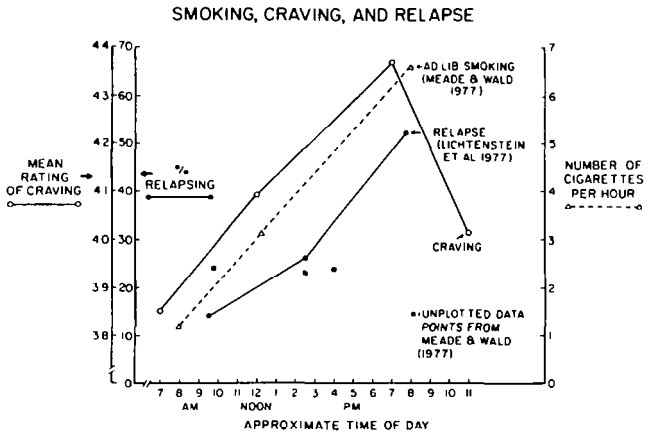


Mean arousal ratings of light and heavy smokers for four times of day. Ratings are based on the average of four questionnaire items relating to arousal or alertness (e.g., "Do you.feel unusually tired?"). Each data point represents an average of 12 days' ratings. The curves for the two groups differ significantly in linear and quadratic trends.

Figure 1 plots arousal by time of day for the two groups, with data points at 7 AM, noon, 7 PM, and 11 FM, approximately. The figure shows that the two groups report the same level of arousal upon awakening. Whereas the heavy smokers then increase in arousal during the course of the day, the light smokers maintain this minimal level of arousal throughout the day. Both groups show a drop in arousal at bedtime, with the light smokers continuing to report lower arousal. This result is difficult to interpret, particularly because this scale does not have a clear evaluative dimension. It is not clear, for example, whether the heavy smokers are hyperaroused during the day, or the light smokers underaroused. At bedtime, it appears that the heavy smokers may be suffering insomnia, since they are reporting nearly as much arousal as they do upon awakening in the morning. This cannot be determined definitively from the data, however, and this effect remains to be explored.

The other symptom cluster which shows significant diurnal variation is craving. Craving is at its lowest point when the subject wakes up, gradually rising to a peak in the evening, then falling again at bedtime.

FIGURE 2



Smoking, craving, and relapse as a function of time of day. Ratings are based on the average of seven questionnaire items relating to craving for cigarettes (e.g., "Do you have an urge to smoke a cigarette right now?"), Note similarities among these functions, all of which peak in the evening. Data on relapse from retrospective interviews (Lichtenstein et al. 1977). Data on smoking from observation of clerical personnel (Meade and Wald 7977). Data on craving from our questionnaire study of smokers in withdrawal.

Figure 2 shows this diurnal variation in craving. Plotted on the same axis is data collected by Meade and Wald (1977) on the cigarette consumption of British office workers at similar times of day. The figure shows that craving in abstinent smokers and ad lib smoking have the same diurnal function. A third function plotted on the same axis draws on data reported by Lichtenstein, Antonuccio, and Rainwater (1977), who surveyed a group of smokers who relapsed following a period of abstinence. The curve shows the percentages of recidivists who said they had first relapsed in the morning, afternoon, and evening. This function parallels the diurnal functions of ad lib smoking and craving in withdrawal. Thus, there is a consistent function which describes three different stages of the habit and its control (unrestricted smoking, ab-

stinence, and relapse). The meaning of the underlying function has not been determined. Two different types of explanation are plausible. One focuses on diurnal variation in the internal environment of the smoker, suggesting the influence of some metabolic factor with diurnal variation[2]. The other explanation focuses on the diurnal variation in the social environment: e.g., the timing of work, meals, social contact, recreation, and so on, which affects craving for tobacco. Research which accurately measures craving and relates it to environmental stimulus events and circadian variations in the internal environment could decide between these explanations. A more comprehensive understanding of how craving varies with stimulus events and with time of day might prove helpful in designing interventions which help prepare the smoker to cope with his/her craving.

Time Course and Duration

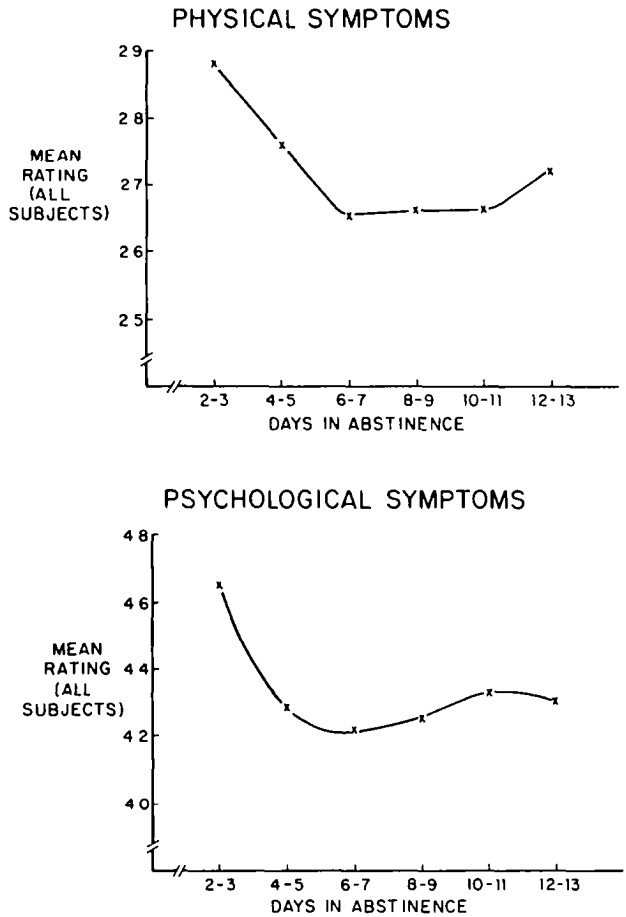
While the time course of the abstinence syndrome following abrupt withdrawal from other dependence-producing substances has been systematically studied (Jaffe 1971), assessment of the course of the tobacco withdrawal syndrome is made difficult by the subtlety and variability of the symptoms (USDEW, 1964).

The onset of the syndrome appears to be rapid, with changes in mood (Schechter and Rand 1974) and performance (Myrsten et al. 1972) evident as early as two hours after withdrawal. However, these early effects are not easily distinguishable from the absence of nicotine effects or the effects of simple frustration. Our research focused on the course of withdrawal symptoms over the first two weeks of abstinence. Figures 3 - 6 show the progression of the four symptom categories -- craving, arousal, physical symptoms, and psychological symptoms -- over a twelve-day period.

(These curves are for all subjects and therefore obscure some important group differences which are discussed below.) Note that these symptoms all decrease at first and then either level off or rise again in the second week of abstinence. (The quadratic curvature of each curve is statistically significant.)

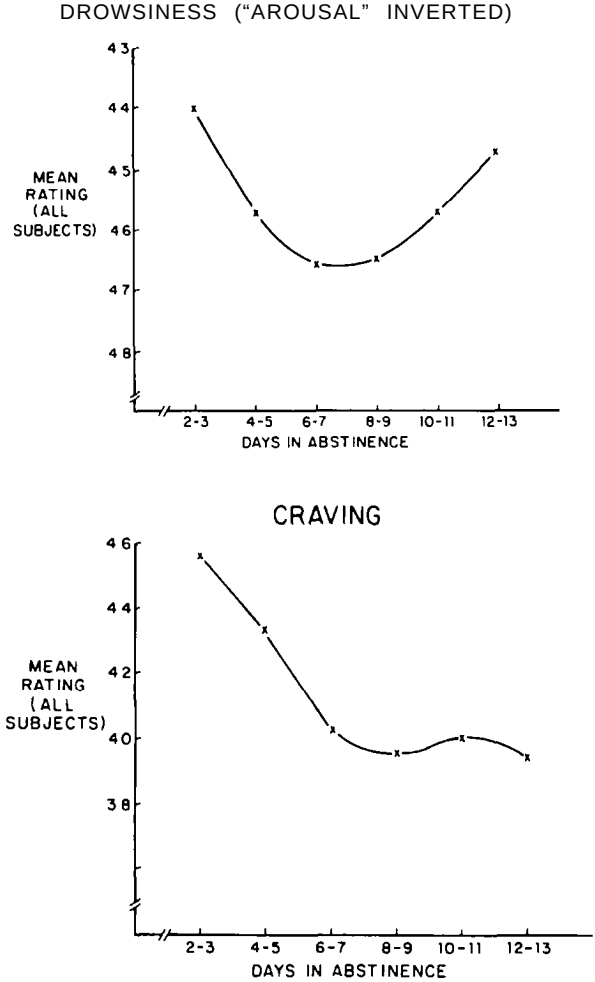
This initial pattern of symptoms is consistent with Herold's (1967) findings concerning the percentage of deprived smokers reporting craving, irritation, tiredness, and headache in the first five days following abrupt withdrawal. Each symptom shows a sharp decline during this period, and all show signs of leveling off by day ten. Other studies also report data suggesting a similar decrease in symptoms over time. (Lichtenstein, Antonuccio and Rainwater, personal communication 1978; Guilford 1966).

FIGURES 3 and 4



Mean reported severity of physical and psychotogical symptoms over 12 days of withdrawal. After an initial decrease, these symptoms level off. Ratings are based on the average of three items relating to physical symptoms and four items renting to psychological discomfort, respectively (e.g., "Is your heart beating faster than usual?"; "Are you more nervous than usual?"). Days have been paired on ordinate in order to smooth the curves. Note small magnitude of changes in ordinate scales.

FIGURES 5 and 6



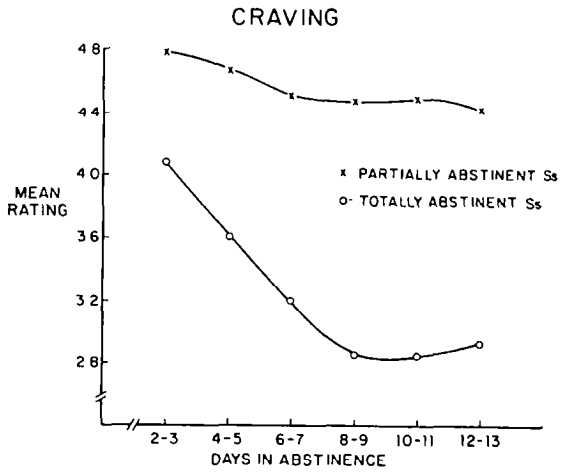
Mean drowsiness and craving ratings after 12 days of withdrawal. Note initial drop and subsequent leveling off (Fig. 6) or rise (Fig. 5). Drowsiness scale is simply an inversion of arousal ratings. Days have been paired in order to smooth the curves. Note small magnitude of changes in ordinate scales.

Thus, after a marked decline in the first week, the tobacco withdrawal syndrome becomes increasingly less yielding. Indeed, figures 3-6 suggest that an aggravation of symptoms occurs after the second week of abstinence, and leaves open the question of the syndrome's subsequent course. Estimates of the tobacco withdrawal syndrome's duration have been made in retrospective studies which ask exsmokers to recall how long their discomfort or "difficulty" lasted. However, these studies produce contradictory findings. Burns (1969) reports a range from one to twelve weeks, and Wynder, Kaufman, and Lesser (1967) report that most symptoms were gone after four weeks. In contrast, Mausner (1970 reports that, of the exsmokers who ventured an estimate, fully two-thirds stated that their difficulty had lasted between one month and five years! In another retrospective study, 21 percent of the sample of exsmokers reported at least intermittent craving for cigarettes five to nine years after cessation (Fletcher and Doll 1969). Thus, the duration of the tobacco withdrawal syndrome appears to be extremely variable, and no definitive estimate is yet available.

Degree of Deprivation

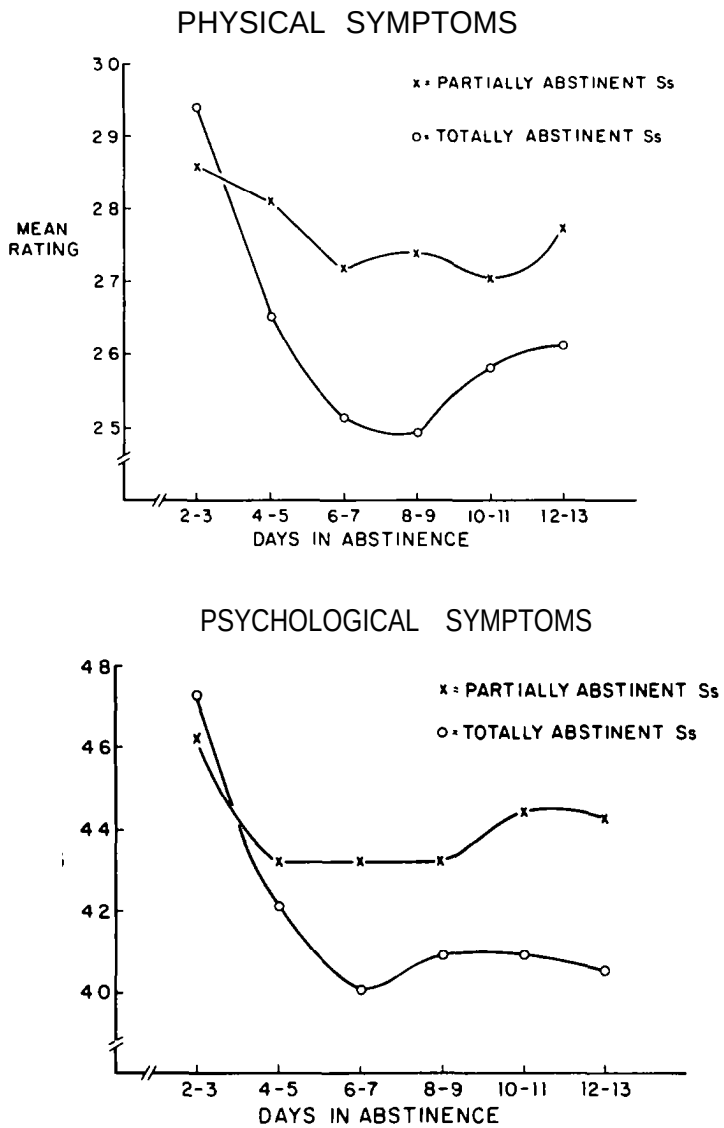
Even with continued use, reduction in the dose of a dependence-producing substance typically results in the emergence of a withdrawal syndrome (Jaffe 1971). It has been shown that smokers changed to low-nicotine cigarettes often report the gamut of withdrawal symptoms described above (Schachter 1977; Finnegan, Larson, and Haag 1945). In order to study the withdrawal syndrome in partially deprived smokers, we divided our sample into two groups: one was composed of totally abstinent smokers who quit "cold turkey" and remained abstinent for the entire period of the study; the second group consisted of partially abstinent smokers who reduced their cigarette consumption by an average of 60 percent. With the exception of the craving scores--which were lower in the cold turkey subjects--we found no overall differences in the severity of the reported symptoms. We found that the two groups did differ in the course of the withdrawal syndrome. Figures 7-9 show the progression of physical symptoms, craving, and psychological symptoms as abstinence proceeded. In each case, the totally abstinent subjects show a greater reduction of symptoms early in the abstinence period.

FIGURE 7



Mean craving scores for partially and totally abstinent smokers over 12 days of abstinence. Note the sharp decline of craving in subjects who quit "cold turkey" and remained abstinent. Days have been paired in order to smooth the curve

FIGURES 8 and 9



Mean reported severity of physical and psychological symptoms for partially and totally abstinent smokers over 12 days of abstinence. Note the sharp decline in symptom severity reported by the totally abstinent subjects, who initially report more severe symptoms. Note small magnitude of changes in ordinate scale.

Notice that early in abstinence the two groups are reporting similar levels of discomfort, but that four days later the completely abstinent group is reporting less craving and fewer physical and psychological symptoms. Thus, abrupt and total withdrawal from tobacco is associated with a withdrawal syndrome that is no worse than that seen in partial abstinence, and which subsides more quickly.

One might speculate that continued smoking results in a prolongation of the abstinence syndrome, while complete abstinence results in a relatively rapid decrease in symptoms. Such causal Interpretations of our data must be made with great caution, of course, because our groups of partially and totally abstinent subjects were formed post hoc. Therefore, it may be that the course of the withdrawal syndrome is determined by some other factor, and the degree of abstinence is in turn determined by some combination of these factors. Nevertheless, there are findings in our study and others which at least suggest that the degree of abstinence does Indeed control the course of the withdrawal syndrome. As figures 7-9 show, the two groups typically begin abstinence with very similar levels of discomfort, and only diverge after a few days of abstinence. Moreover, informal analysis of our data suggests that craving rises when a subject has been abstinent and then begins to smoke again. More systematic observation of this phenomenon was made by Lichtenstein, Antonuccio, and Rainwater (personal communication 1978) in a retrospective study of relapsed smokers. They found that 53 percent of their subjects reported that their craving decreased with time, as long as they were abstinent. In contrast, 42 percent reported that their craving was increased the day after a relapse episode (only 18 percent reported decreased craving). Similar phenomena are well known in other dependency disorders; the alcoholic's proverbial "one drink" is an example. Thus, craving leads to smoking and smoking leads to craving in a cycle of dependence.

Gradual Reduction and Chronic Withdrawal

This has important implications for methods of smoking cessation. Despite the usefulness of gradual withdrawal in other dependency disorders, and despite the congruence of this method with sound behavioral principles, there is considerable evidence suggesting that gradual withdrawal from tobacco is associated with treatment failure (Guilford 1966; USDHEW 1975; Mausner 1970). Our findings suggest an explanation for this discrepancy. Partial abstinence from smoking leads to more, rather than less, discomfort in withdrawal, since the withdrawal syndrome experienced by those who "cut down" on smoking (by 60 percent) is as severe as that in an abrupt cessation group and lasts longer. The result is that a partially abstinent smoker is in a chronic state of withdrawal. That such a condition is possible is confirmed by Perlick (1977) who observed "restrained smokers" who were keeping their cigarette consumption chronically at about

50 percent of their normal intake. These smokers were compared to unrestrained smokers while smoking high and low nicotine cigarettes and no cigarettes. Perlick found that, even when allowed to smoke high nicotine cigarettes, the restrained smokers showed as much irritability as normal smokers deprived of cigarettes. Moreover, they also showed impairments of concentration that were even greater than those observed in heavy smokers. In other words, the showed signs of a severe abstinence syndrome even while smoking "ad lib". Thus, the cigarettes indulged in by smokers who attempt to "cut down" may serve only to prolong their withdrawal by intermittently reinforcing their symptoms and smoking behavior. Typically, this chronic state of withdrawal leads to relapse and return to baseline rates of smoking.

Although this explanation is plausible and fits the data available, it must be treated with caution pending further research. Since all of the research relies on smokers who have chosen whether to quit cold turkey or by gradual reduction, there is still the possibility that smokers in some way predisposed to experience a protracted withdrawal syndrome disproportionately choose the gradual reduction method. What is needed is experimental research in which smokers are randomly assigned to cold turkey or gradual reduction groups, and the effects on the course of the abstinence syndrome evaluated.

Another direction for new research might be to determine the threshold for the onset of the abstinence syndrome in gradual reduction. Perhaps there is some rate or degree of reduction which would not precipitate withdrawal, so that a smoker could be weaned from tobacco. In addition to a "rate of reduction" parameter, the onset of severe withdrawal may also be controlled by the absolute dose, as well. It has been reported that in gradual reduction programs, smokers tend to meet plateaus or "stuck points" at certain levels of consumption, even when the rate of reduction is slow and controlled by the smoker. Levinson et al (1971) report that the most difficult "stuck point" was at 12 cigarettes per day, and that most of the premature terminations of treatment occurred at this level, An intriguing possibility is that this constitutes some minimum dose below which withdrawal is precipitated. In any case, the relationship between degree of tobacco deprivation and the emergence of withdrawal symptoms deserves further study.

Other Factors Which May Affect the Abstinence Syndrome

In addition to the factors already cited, the tobacco withdrawal syndrome may be affected by a number of other variables whose influence remains to be determined. One could speculate, for example, on differences between types of smokers in the severity, pattern and/or course of abstinence. A study by Ikard and Tomkins (1973) suggests rather tautologically that "addictive smokers" experience more severe craving. The smokers in this study were only deprived of tobacco for three hours, however,

so that the effects of this typology on the clinical abstinence syndrome are still essentially unknown and deserving of study. Other individual difference variables also deserve study. A smoker's smoking history, for example, may affect the withdrawal syndrome, especially considering such variables as previous attempts to quit and the reason for failure. Since the symptoms of withdrawal are relatively ill-defined, the smoker's expectations and set are probably related to his/her experience of abstinence, as is his/her motivation to quit (cf. Barefoot and Girodo 1972).

There is another major. factor whose relationship is potentially important but unexpected: Fragmentary evidence suggests that the abstinence syndrome is more severe in women than in men. Unfortunately, relevant data are too seldom analyzed for this sex difference. For example, Guilford (1966) reports data separately by sex, but does not submit it to statistical analysis of the sex difference. Yet, of 18 major symptoms reported by her subjects in the first four days of abstinence, 15 show some sex difference. Among these 15, 13 are more frequently reported by women. This difference is statistically significant (sign test, N=l5, r=2, $p<.005$). Moreover, a chi square analysis of retrospective data collected by Hammen (1973 personal communication) shows a trend ($p<.10$) for women to report more frequently than men that their past relapses were due to anxiety or craving. Data reported in a number of other studies line up in the same direction, though the effect fails to reach significance in the individual studies (Trahair 1967; Peterson et al. 1968; Wynder, Lesser, and Kaufman 1967). It seems likely, then, that women suffer from a more severe abstinence syndrome than men. The importance of this finding lies in its possible relation to another sex difference in smoking cessation: it is well established that women are more likely to fail in smoking cessation efforts (Gritz 1978). Guilford (1966) has also presented data suggesting that the relationship between withdrawal symptoms and failure in smoking cessation is stronger for women than for men. Thus, women experience more discomfort in withdrawal and are more affected by it in their attempts to quit smoking. It seems likely that this is at least partly responsible for their reduced rates of successful cessation.

Nor are organismic variables the only variables relevant here. The method used to achieve cessation may well have an effect on the subsequent withdrawal syndrome. Environmental factors, such as the smoker's social environment, are potentially powerful deteminants of the smoker's experience of withdrawal. Many smokers cite a stressful event or situation, rather than an internal feeling, as the precipitant of relaspse (Hammen, personal communication 1973). These and other events, such as social drinking, may produce conditioned craving and are to be considered high risk situations for relapse (Lichtenstein, Antonuccio, and Rainwater 1977). Thus, in addition to the few factors whose influence on the tobacco withdrawal syndrome is known, there are many other potentially important variables whose effects remain to be determined.

METH0DOLOGICAL ISSUES

The influence of the factors discussed above on the tobacco withdrawal syndrome also touches on methodological issues. Since these variables represent significant sources of variance in the withdrawal syndrome, they must be taken into account when withdrawal effects are assessed. Research in this area must distinguish between partial and total abstinence, for example, if the results are to be consistent. This distinction is blurred in many studies, making the results difficult to interpret or compare. Similarly, data should be reported separately for men and women and for light and heavy smokers. Since some symptoms vary with tune of day and probably with stimulus events, they should, where possible, be measured repeatedly and at fixed times during the day.

Other methodological issues in research on the tobacco withdrawal syndrome involve the measuring process or operation itself. Because there is no accepted standard, no two studies in the literature use the same assessment device, making the results impossible to compare across studies. Some studies use ratings of symptom severity, where others simply use a present/absent symptom checklist method and still others an open-ended query. Consequently, results may be reported as mean ratings or as percentage of subjects reporting a given symptom. Often, no distinction at all is made among various symptoms, and subjects are simply asked whether they experienced <u>any</u> symptoms, or, even more globally, whether they experienced "difficulty" in giving up tobacco. This is a major factor contributing to the variability of estimates of the prevalence and duration of the withdrawal syndrome. Much more clarity would result if the assessment instruments were made homgeneous . A rating scale which taps several symptom clusters, such as the one we have used in our studies, would probably meet the requirements of most investigators.

Some measurement difficulties which arise in the study of withdrawal symptoms are kin to the difficulties inherent in measurement and operationalization of psychological constructs. Take, for example, the mood changes that are reported in withdrawal. Colloquial terms such as "nervous" and "irritable" are most natural and are therefore useful in obtaining self-reports. Unfortunate1y they are also quite ambiguous. It is unclear, for example, whether they refer to tonic, baseline states or to predispositions to overreact to certain stimuli. Does a smoker in withdrawal show higher overall levels of anxiety or a proneness to react with greater anxiety when stressed? These two interpretations imply different measurement operations, and measurements of both varieties appear in the tobacco withdrawal literature as measurements of "anxiety" or "irritability," with different findings resulting.

In order to avoid the ambiguity of colloquial language, one can turn away from self-report methods, which require its use, to observational studies which rely on more defined measurement operations. Behavioral correlates of anxiety can be observed,

for example. As one moves further away from colloquial self-description, however, the interpretation of the data becomes increasingly problematic. Physiological measures such as galvanic skin response are far removed from the affective state, "anxiety," and furthermore do not correlate well with other measures of "anxiety." A tradeoff is inevitable. The more operational the measurement device, the less related it seems to the underlying psychological construct, especially when the latter is a subjective state.

Differences in approach to this dilemma have resulted in different conclusions about the tobacco withdrawal syndrome. In a number of studies reported by Heimstra (1973), deprived smokers performed presumably stressful tasks and rated their mood before and after the task. Results showed that deprived smokers responded much the way nonsmokers did, but that undeprived smokers showed significantly less response to the stressor. This suggests that smoking protects against stress-induced mood changes, but that withdrawal has no effect on mood. In contrast are a series of studies in the Schachter laboratory (Nesbitt 1973; Silverstein 1976; Schachter 1978) which use the number of shocks that a subject will tolerate as a measure of his/her response to stress. In these studies, undeprived smokers behave like nonsmokers and deprived smokers show increased vulnerability to stress. This suggests that smoking per se has no effect on reactions to stress, but that withdrawal resultant over-responsiveness to stress. Thus, self-report and indirect objective measurement of withdrawal symptoms sometimes produce inconsistent and even directly contradictory results.[3] This reflects a general problem in psychological assessment which will not be easily solved. However, investigators studying the withdrawal syndrome should be aware of the dilemma, and perhaps try to obtain measurements at both ends of the spectrum wherever possible.

The cited studies by the Heimstra and Schachter groups also touch on another issue of methodology: control groups. Data from deprived smokers are most interpretable when they can be compared to data from smokers in an undeprived state and from nonsmokers. Ideally, this allows one to tease out the effects of smoking per se, the effects of abstinence, and the effects of smoker/nonsmoker differences. An interesting and novel idea would be to introduce a deprived nonsmoker group which is frustrated in sane way. This would control for the effects of simple frustration, which is conceptually distinct from a withdrawal syndrome, but has some similar effects on mood.

Quite often, the comparison between nondeprived and deprived smokers is made within subjects. This requires that baseline data be collected while the subject smokes normally. This is difficult to achieve in clinical settings, where smokers often begin to modify their smoking behavior before formally beginning treatment. In these cases, baseline measurements should begin as early as possible while instructing the subject to maintain

usual smoking behavior. Where several staggered changes in smoking behavior take place -- as in gradual reduction programs -- multiple baselines should be considered. In a truly ideal world, one would also compare a smoker's responses in withdrawal to the presmoking baseline. As this is impossible, one cannot currently distinguish between the effects of simple return to baseline upon discontinuation of nicotine and true withdrawal effects, which involve an overshoot of predrug baseline. If one assumes that smokers and nonsmokers were similar prior to tobacco use (a tenuous assumption), then the nonsmoker group provides a between group comparison with predrug baseline.

Most of the research on withdrawal symptoms in long term abstinence from smoking consists of retrospective questionnaire studies in which successful exsmokers are queried about their experiences. Almost all of the studies which have a more controlled methodology are confined to short periods of deprivation in the laboratory, and therefore have limited generalizability. The retrospective studies, while more relevant to the experience of a real life user giving up tobacco, suffer from the failings of retrospective and post hoc correlational designs. For example, while such studies show that successful abstainers report fewer withdrawal symptoms than do their relapsed colleagues, this may be an artifact of the retrospective viewpoint. Exsmokers may simply "recall" finding withdrawal easier, whereas recidivists justify their relapse with recollections of serious discomfort. The risk of such bias, while present, is not nearly as great when self-reports are collected during the actual period when the subject is undergoing withdrawal. More such prospective, real time studies of long term abstinence in clinical settings are needed. Such data could readily be collected as part of any clinical or experimental smoking cessation study. Investigators in the field of smoking cessation should document the effects that withdrawal from tobacco has on their subjects. In this manner, a great deal could be learned about the tobacco withdrawal syndrome at very little cost.

DIRECTIONS FOR RESEARCH ON THE TOBACCO WITHDRAWAL SYNDROME

The relationship between withdrawal symptoms and smoking cessation efforts is what lends importance to research on the tobacco withdrawal syndrome. To the extent that avoidance of withdrawal symptoms motivates continued smoking, the problem of smoking control becomes one of understanding and controlling the withdrawal syndrome. Especially as our clinical goals shift away from smoking cessation per se to the prevention of relapse, the withdrawal syndrome will have to become a major focus of our efforts. And it is this clinical public health goal which should, in turn, determine the direction of research on the tobacco withdrawal syndrome. The major foci of such research should be (1) to clarify the relation between the withdrawal syndrome and the outcome of smoking cessation efforts; (2) identify risk factors relevant to the withdrawal syndrome; and (3) formu-

late interventions which affect the withdrawal syndrome, with a view toward encouraging maintenance of abstinence.

Although the association between withdrawal symptoms and failure in abstinence from smoking is well established in retrospective studies, this relationship deserves further exploration. Data on withdrawal symptoms should be collected during the period of initial withdrawal and then analyzed retrospectively for differences between eventual successes and failures. Parameters which modify the association between symptoms and outcome should also be identified. A symptom might have differing predictive power among different subpopulations, for example. The Guilford (1966) study is a model for this type of investigation, but more of the same type are needed in order to understand how the tobacco withdrawal syndrome affects smoking cessation.

Research should continue to study those factors which have already been tentatively identified as determinants of the severity of the tobacco withdrawal syndrome. Besides leading to a better understanding of the process underlying dependence on tobacco, this would identify populations at risk for severe withdrawal symptoms. The influence of factors such as sex, for example, needs to be better documented and explored, Since the smoking behavior of man and women differs in a number of important respects--e.g., dose, age at initiation, etc. (USDHEW 1975)--studies are needed to analyze whether the sex difference is reducible to these other variables.

More generally, the search for other factors affecting the withdrawal syndrome needs to be expanded. One strategy for such a preliminary search would be to analyze data retrospectively, observing the severity of the syndrome, and then attempting to account for it by multiple regression on other variables. Among the other variables whose influence warrants examination is the method of smoking withdrawal. The differences between "cold turkey" and gradual withdrawal should be studied in randomized experiments. The effects of different antismoking therapies should also be explored. This could be easily accomplished if investigators and clinicians in this field agreed to measure and report withdrawal symptoms on a standard instrument. A quasi-experimental comparison among methods would then grow naturally out of the accumulated literature.

The influence of environmental factors on withdrawal and relapse also warrants investigation. One area of investigation that has already been suggested involves explanations of diurnal variations in craving in terms of stimulus events occurring at different times of day. More broadly, the influence of environmental stimuli in producing conditioned withdrawal symptoms--e.g., Wikler (1965)--should be explored with a view toward identifying high risk situations. This has particular relevance to the clinical problem of preventing relapse. If high risk relapse situations are identified, they would provide

natural targets for interventions. Some high risk situations might be entirely avoidable, and methods might be devised for reducing the risk of relapse in others.

Thus, a better understanding of the tobacco withdrawal syndrome could be applied to increasing the probability of success in smoking cessation efforts. Knowledge about individual differences in risk for severe withdrawal symptoms, for example, might be used to screen patients for treatment, with high risk patients receiving additional attention. If more is learned about the influence of cessation methods as well, perhaps matching of treatment methods and patient populations could be used to increase treatment success or cost efficiency. The treatment of choice might depend on the patient's withdrawal syndrome risk factors.

Interventions which directly attack withdrawal symptoms need to be developed and evaluated. Manipulation of patients' expectations or attributions of withdrawal symptoms might be one way in which to reduce their severity and affect relapse (cf. Barefoot and Girodo 1972). If withdrawal symptoms are indeed aggravated by conditioned responses to particular stimuli, it might be possible to decondition or counter-condition these responses as part of the therapy. Patients might also be provided with coping skills to deal with unavoidable withdrawal symptoms. Smokers who suffer from inability to concentrate might be taught to enhance their concentration, for example. Also, progressive relaxation training or other anxiety and affect management techniques might prove useful to those who suffer from anxiety or irritability in withdrawal.

For those smokers for whom weight gain is a major concern, weight control measures might be incorporated into a smoking control program, with the aim of improving maintenance of nonsmoking. Controlling the withdrawal syndrome may be the key to controlling relapse.

SUMMARY AND CONCLUSION

There is an identifiable syndrome which occurs on withdrawal drawal from tobacco. The tobacco withdrawal syndrome is characterized objectively by changes in the EEG and cardiovascular function, by decrements in psychomotor performance, and by weight gain. Subjective symptoms of irritability, anxiety, Inability to concentrate, and disturbances of arousal are characteristic of tobacco users in withdrawal, and intense craving for tobacco is almost universally reported. Although reports vary regarding the prevalence, severity, and course of these symptoms, there is nevertheless sufficient consensus to justify the conclusion that a withdrawal syndrome occurs in habitual tobacco users.

Among the factors which affect the severity of the tobacco withdrawal syndrome are the smoker's sex and habitual dose. Other factors, such as motivation for smoking and motivation for

quitting, remain to be Investigated. At least one symptom -- craving for tobacco -- shows diurnal variation. The early course of the withdrawal syndrome depends on the smoker's degree of deprivation. Totally abstinent smokers show a marked decrease in all symptoms in the first week of abstinence, with subsequent leveling off or increase in symptoms. Smoking among partially abstinent smokers appears to prevent this early drop and to maintain symptoms at their high initial levels, prolonging the withdrawal symptoms. This may explain the ineffectiveness of gradual withdrawal as a method of smoking cessation.

More research on, the tobacco withdrawal syndrome is warranted because of the relation between withdrawal symptoms and relapse in smoking cessation. Research in this area must consider a number of methodological issues, including awareness of sources of variability in symptoms. Standardized assessment of symptoms would be a boon to research on the abstinence syndrome, making results more comparable across studies. Much could be gained from simply assessing and reporting withdrawal symptoms in smoking cessation studies. Most studies in the literature are based on retrospective self-reports of exsmokers, with all the limitations attending to such data. More prospective, randomized experiments using control groups and multiple measures are needed.

Ultimately, the goal of research on the tobacco withdrawal syndrome should be the development of applications in clinical technology for smoking control. Currently, three out of four smokers who succeed in stopping smoking will relapse, most of them because of withdrawal symptoms. A better understanding of tobacco withdrawal phenomena may help us to identify high risk populations of smokers and match them to maximally efficient treatments. A major focus for research should be on developing effective treatments which specifically attack tobacco withdrawal symptoms and thereby discourage relapse. The health of millions of people depends on it.

FOOTNOTES

[1]We did find a rather puzzling difference between these two groups in their diurnal pattern of arousal, with some suggestion that heavy smokers may be more prone to insomnia. See the section on diurnal variations.

[2]Schachter, Silverstein and Perlick (1977) present such an explanation of smoking rates based on urinary pH, which affects the excretion of nicotine. Their explanation, however, leads them to predict that smoking rates will be higher in the morning, and they present data suggesting this is the case. Meade and Wald's (1977) data are probably more reliable in estimating ad lib smoking rates, as they are based on a larger sample and more systematically study the effects of time of day.

[3]Although they do illustrate the point here, these two sets of studies are not entirely contradictory. In the Heimstra (1973)

studies, the smokers perform like the nonsmokers on psychomotor tasks, with the deprived smokers showing impairment, suggesting a withdrawal effect but no effect of smoking per se. Also, the study by Perlick (1977) in the Schachter laboratory, shows a similar pattern of results with self-report ratings of response to a stressor.

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Part IV

Implications and Directions for Future Research

Chapter 14

Implications and Directions for Future Research

Norman A. Krasnegor, Ph.D.

A new Surgeon General's Report on Smoking and Health, which was issued in January 1979, carefully documents the scientific data on the health risks associated with cigarette smoking. A major addition to that document is a series of five chapters on the behavioral aspects of smoking. While much new information on this latter topic is presented, one is struck by the imbalance between what is known about the consequences of smoking and the behavior itself. more specifically, it is clear that research on factors involved in the establishment, maintenance, and cessation of cigarette smoking is only in its formative stages.

Due to the implications of cigarette smoking behavior for the public health and the view that smoking is the prototypical dependence process, the National Institute on Drug Abuse has established a high priority initiative designed to acquire new knowledge on the behavioral, biological, and psychosocial aspects of this type of substance abuse, The Institute's programmatic goal is focused upon the systematic compilation of basic and applied scientific data on variables which are causally related to the acquisition of the behavior and the observed chronic usage patterns. Such information can serve as a basis for designing feasible and effective treatment strategies and enhance our understanding of dependence associated with substance use.

A RESEARCH AGENDA

On the basis of the papers presented in this monograph and my involvement in the preparation of NIDA's contribution to the Surgeon General's Report, I should like to provide a selected research agenda composed of topics which the National Institute on Drug Abuse views as programmatic priorities. One caveat should be noted, however. The list developed below is meant to be a guide for researchers . It is not intended to be all-inclusive or exhaustive. The order of presentation does not imply a rank order among priorities. In general, the NIDA research program is focused upon cigarette smoking behavior and the dependence process associated with it. We

have interest in each stage of the behavior's natural history (experimentation, establishment, maintenance, cessation, and relapse). We view the problem area broadly and are desirous of supporting a multidisciplinary approach to undertaking investigations in this research domain. Accordingly, we would encourage investigators from the biological, behavioral, and social sciences to apply their methodologies to the field of smoking behavior research in order that a comprehensive and balanced understanding can be achieved.

RESEARCH PRIORITIES

1. Peer Pressure

One of the most often cited reasons that people, particularly adolescents, begin smoking is that friends and acquaintances influence those not smoking to take up the behavior and conform to group norms. Peer pressure has been identified by Kandel as a psychosocial variable involved in experimentation with and use of marihuana. Other researchers have emphasized peer pressure as a causative factor in other health-risk behaviors (such as reckless driving, excessive drinking, etc.).

Studies which undertake prospective investigations of peer pressure as this construct relates to cigarette smoking should be initiated. Both laboratory and field experiments should be carried out to determine the contribution of peer pressure to the initiation and maintenance of smoking behavior.

2. The Role of Nicotine

One of the central questions in the field of smoking behavior is the role played by nicotine. Do people smoke cigarettes to maintain a certain level of the drug?

What we know at present is that nicotine can be discriminated by animals, it is intravenously self-administered by rats, it has a central nervous system effect, and has been demonstrated to be titrated by smokers. In addition, the work of Abood and Lowy suggests the existence of a specific nicotine receptor.

The methodologies of Hanson et al. and Abood and Lowy offer exciting possibilities for studying the reinforcing effects of nicotine within the context of both an experimental analysis of behavior and neuropsychopharmacology. We would encourage more research along similar lines.

In the area of self-administration, we have particular interest in developing animal models which employ the inhalation route of administration. This is the case because nicotine passes most rapidly into the brain via the lungs, and it may be that the reinforcing efficacy of nicotine is enhanced when administered via this route.

Studies which explore the central site of action of nicotine and drugs which block its effect are of high programmatic interest to

the Institute. Such research could help to elucidate the neuropsychological and biochemical bases for the reinforcing effects of the drug.

3. Withdrawal

Another important area of research is the characterization of symptoms associated with cessation of smoking, Dr. Shiffman has provided an excellent overview of the literature and a summary of his own research. In general, our interest in withdrawal stems from the anecdotal observation that smokers who relapse often claim that they take up smoking after cessation because they cannot cope with the withdrawal. Many questions need to be addressed. For example, is there a characteristic withdrawal pattern associated with cessation? How does this vary with number of years that one has smoked prior to cessation? How does withdrawal vary with the strength of the cigarettes that were smoked? Is there an acute withdrawal pattern?

4. Behavioral Pharmacology of Smoking

Our interest in this topic stems from the view that collecting descriptive and quantitative information on the smoking act itself can be useful in designing effective treatment. While there are some data on topography of smoking (Dr. Lee Frederiksen), relatively few experiments have been conducted to determine the rate of puffing, volume of puffing, inter-puff interval, etc. We would encourage studies on the relationship of such parameters to smoking history, nicotine content of cigarettes, stimulus control, etc.

5. Prolonging Abstinence

At present, there are a variety of methods (e.g., rapid smoking, warm air, etc.) which can be employed to produce cessation. In general, those smokers who finish such treatment do stop. The problem is that the relapse rate is extremely high. Between 70-80 percent of those who stop are likely to take up smoking again within a year. Thus, we would encourage research designed to discover procedures which will lead to a lengthening of abstinence.

6. Objective Methods for Validating Self-Reports

There are many reports in the literature on incidence and prevalence of cigarette use and on the evaluation of treatment efficacy. Unfortunately, the analysis and conclusions are often based on self-reports only. While some studies do use significant others to corroborate self-reports, few have employed biological assays to validate such subjective data. Work on biological assays such as analysis of breath for CO content and blood for thiocyanate levels is just getting under way. We would encourage more research on these two biological assays and development of others to help supplement self-reports with objective measures.

7. Longitudinal Studies of Smokers

Many of the research findings which appear in the literature are based upon short term studies of smoking. While there are some exceptions, the general picture suggests that followup in treatment studies is conducted for up to one year. Yet more recent experiments show that a minimum of two years of followup is necessary to evaluate treatment efficacy for smoking cessation programs. We would encourage researchers to employ long term followup designs when evaluating efficacy of modalities for cessation. In addition, longitudinal studies should be designed to investigate the natural history of spontaneous quitters. Thus, there are reports that 4 to 5 million smokers each year stop using cigarettes on their own. We know virtually nothing about such people or their success at achieving and maintaining abstinence.

8. Treatment Research

While there have been many different techniques to help people stop smoking, the literature generally shows that the best that can be achieved is a 40-50 percent abstinence rate at the end of two years. This result represents a 10-20 percent improvement over the general finding of a 30 percent success rate. New and innovative techniques, particularly in the context of well-designed-multi-modal treatment approaches, should be carried out. Such research should include within the design appropriate control groups, random assignment, objective measures of cigarette use (CO, thiocyanate, etc.), and longitudinal followup.

9. Drug/Cigarette Smoking, Interactions

Anecdotal observations suggest that alcoholics and heroin addicts smoke at a high rate, particularly during periods of abstinence. Experiments designed to study the interaction of cigarette smoking with alcohol drinking reveal that the rate of consumption of both substances increases when both are used together, compared to the situation when each is used independently. Whether this is an interaction based on pharmacological or behavioral mechanisms is not currently known. However, we would encourage investigators to study the interaction of cigarette smoking with the self-administration of a variety of drugs. Such work would help to elucidate the role that cigarette smoking may play in the maintenance of other drug use.

We hope that this brief listing of selected research topics will aid scientists who are interested in the field to focus their investigations. Further information pertaining to the programs on cigarette smoking may be obtained by contacting the National Institute on Drug Abuse, Division of Research, 5600 Fishers Lane, Rockville, Maryland 20857.

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