Pharmacology Biochemistry & Behavior, Vol. 30, pp. 279–294. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Pharmacological Treatment of Tobacco Dependence

MURRAY E. JARVIK*[1] AND JACK E. HENNINGFIELD†

**Veterans Administration Medical Center, Brentwood Division*
and Department of Psychiatry and Biobehavioral Sciences, The Neuropsychiatric Institute
School of Medicine, University of California, Los Angeles
†Biology of Dependence and Abuse Potential Assessment Laboratory
National Institute on Drug Abuse, Addiction Research Center, Baltimore

JARVIK, M. E. AND J. E. HENNINGFIELD. *Pharmacological treatment of tobacco dependence.* PHARMACOL BIOCHEM BEHAV **30**(1) 279–294, 1988.—Pharmacologically based approaches for the treatment of tobacco dependence are reviewed. The rational basis for pharmacologic treatment approaches is that tobacco dependence is partially, and critically, mediated by the actions of tobacco-delivered nicotine to the central nervous system. These actions include direct reinforcing properties of nicotine itself, tolerance and physiologic dependence, possible beneficial effects of nicotine in the alleviation of anxiety and control of weight, and neurohormonal regulation which can become important to the maintenance of emotional well-being and performance at work. Insofar as tobacco abstinence leads to negative consequences, via these biobehavioral mechanisms, pharmacologic intervention should be able to assist in initial tobacco detoxification and help tobacco abstinent persons to avoid subsequent relapse. The purpose of this review is to survey some of the efforts to develop such interventions, as well as to elucidate some of the issues relevant to such development. Four distinct approaches are discussed: (1) Nicotine replacement, in which physiologic dependence is transferred to a safer and more therapeutically manageable nicotine delivering formulation; this category includes nicotine polacrilex gum; (2) Blockade therapy, in which a drug is taken that blocks the reinforcing properties of nicotine should relapse occur; (3) Nonspecific pharmacotherapy, in which the biobehaviorally mediated correlates of tobacco abstinence are treated on a symptomatic basis; (4) Deterrent therapy, in which a drug is taken prior to smoking such that any tobacco use would produce reliable aversive effects.

Tobacco Cigarette smoking Addiction Treatment Chemotherapy Nicotine gum Antagonists Deterrents Drug abuse

CIGARETTE smoking has been implicated as the chief avoidable cause of death and disease in the United States [175]. In fact, the incidence of certain disease states, such as lung cancer, is directly related to cigarette sales, although there appeared to be a latency of approximately two decades for changes in lung cancer mortalities in adult males to reflect changes in cigarette consumption in men [2,173]. Similar findings were observed in response to changes in cigarette smoking by women in the United States: whereas the relative incidence of breast cancer deaths among women has remained stable for several decades, the incidence of lung cancer deaths has steadily risen, approximately two decades behind the increase in cigarette smoking levels; it appears that deaths due to lung cancer, in women, overtook those due to breast cancer in the mid-1980's [174,177]. These figures, and others summarized each year in *Reports from the Surgeon General on the Health Consequences of Cigarette Smoking,* show that tobacco continues to provide the major environmental source of death and disease in the United States; in fact the estimated annual tobacco-related mortalities in the United States of 350,000 is substantially in excess of those related to all other drugs of abuse, traffic accidents, and suicides combined (cf. [131,137]).

Although there is some debate over the degree to which tobacco users understand the extent to which tobacco causes death and disease, as well as all of the specific disease states to which tobacco has been shown to cause, it is clear that the overwhelming majority of cigarette smokers believe that smoking is harmful to their health, express an interest in quitting, and have tried to quit [124]. Yet, approximately 80% of those who attempt to quit fail on their first effort and seven attempts later, more than 60% relapse to cigarette smoking [175]. In fact, even among persons who have undergone major surgery for tobacco-related disease, nearly one-half of these persons resume smoking before or upon discharge from the hospital [13]. Another study showed that only about one-third of those who survived uncomplicated myocardial infarction quit smoking [184]. Thus, although the

[1]Requests for reprints should be addressed to Dr. Murray E. Jarvik, Psychopharmacology Unit, Veterans Administration Medical Center, Brentwood (691/B151D), Los Angeles, CA 90073.

incidence of cigarette smoking among adult males has fallen during the last few decades, nearly one-third of American adults continue to smoke. A critical reason for the persistence of tobacco use is that nicotine, delivered when tobacco products are used as intended by manufacturers, causes behavioral and physiologic dependence [176,178]. Characteristics of nicotine dependence will be further discussed below.

Taken together, the above summarized figures confirm that there is a medical need for treatment of tobacco-dependent persons. It is further clear that there is a substantial existing desire among tobacco-dependent persons for effective ways to quit which do not remove the pleasures and benefits which are at least perceived to result from the use of tobacco. Biomedically-based treatment of tobacco dependence has been further legitimized by the categorization of tobacco use as an organic mental disorder by the American Psychiatric Association [5].

There have been descriptions of various approaches for treating cigarette smoking, as well as data concerning their efficacy (e.g., [123,152]). The main purpose of this paper is to summarize some of the results of attempts to control and/or treat tobacco dependence by pharmacologic intervention. Where it seems reasonable, conceptually, we will group together the various forms of tobacco dependence, although most of the available data regarding addictive aspects of tobacco use involve studies of cigarette smoking. Thus, conclusions regarding the pharmacologic treatment of other forms of tobacco use, including pipe, cigar and smokeless tobacco use, must proceed according to reasonable extensions of available data. The foundation upon which pharmacologic treatment approaches rest, namely our conceptualization of compulsive tobacco use as a behaviorally and pharmacologically controlled behavior, will also be briefly reviewed. It is with this topic that we shall begin.

TOBACCO USE DISORDER

Tobacco use is considered to constitute the Psychoactive Substance-Induced Organic Mental Disorder, Nicotine Dependence, when there is difficulty with quitting [5]. It is exacerbated by the presence of physiologic dependence to nicotine which is marked by the occurrence of nicotine withdrawal following termination of tobacco use (also, cf. [5]). As currently defined by the American Psychiatric Association, nicotine withdrawal is present when (A) there has been daily use of nicotine for at least several weeks, and (B) abrupt cessation of nicotine use, or reduction in the amount of nicotine used is followed within 24 hours by at least four of the following signs:

(1) craving for nicotine,
(2) irritability, frustration, or anger,
(3) anxiety,
(4) difficulty concentrating,
(5) restlessness,
(6) decreased heartrate,
(7) increased appetite or weight gain [5].

Such diagnostic markers are useful insofar as they facilitate the identification of persons with specific psychiatric disorders which may be treated. More broadly, however, nicotine dependence is a form of drug dependence which is indicated by the observation that a drug has come to control a significant portion of the persons' behavior, and by the evidence of tolerance and physiologic dependence to nicotine. With respect to nicotine, demonstration of either index confirms the presence of a substance abuse or drug dependence disorder, the organic cause of which is nicotine ingestion, and for which treatment strategies used for other forms of drug dependence have been extended (e.g., [3, 52, 87]).

The rational basis for pharmacologic treatment approaches rests on commonalities shared by nicotine and other kinds of drug dependence (e.g., opioid dependence, alcoholism, sedative dependence, and psychomotor stimulant abuse). These commonalities have been reviewed in detail elsewhere [84, 88, 92, 145] and will only be briefly summarized here.

Like other drug dependencies, tobacco self-administration results in the delivery of a substance that acts in the central nervous system and is effective in controlling the behavior of animals and humans. Drugs of abuse can modify behavior in a variety of ways depending upon the dose and the conditions of their presentation. In the case of nicotine, depending upon the dose and conditions of presentation, it may function to either strengthen (via reinforcement) or suppress (via punishment) behavior (e.g., [47, 71, 86]). Characteristics of nicotine's effects lend it well to controlling the behavior of its users. For instance, nicotine is well discriminated in animals and humans, and these effects on feeling and mood state are similar in key respects to those of other known addictive drugs [169]. The effects are related to dose, but tolerance occurs; thus, the daily dose levels which most users achieve after several years of use are many times higher than those levels which would have been highly toxic on initial exposure. Even within a single day, a considerable degree of tolerance is lost and gained: for instance tolerance decreases as the smoker sleeps through the night, such that the first cigarettes of the day provide the strongest effects on behavioral and physiological responses; throughout the day of smoking, then, tolerance increases and the smoker may report little effect from the cigarettes (cf. [29, 66, 101]).

As tolerance develops, increased nicotine dose levels may be obtained by increasing the number of cigarettes smoked, or, in the case of smokeless tobacco, switching to brands which deliver larger doses of nicotine. With regard to cigarettes, since nearly all cigarettes actually contain much more nicotine than the smoker routinely extracts, how cigarettes are smoked is a greater determinant of nicotine dose intake than is the nicotine yield which has been determined in machine smoking tests (e.g., Federal Trade Commission Reports) [91]. As implied by the preceding observation, the estimated nicotine yield of a cigarette brand is probably not an important determinant of the initiation of tobacco dependence since the process of dose graduation appears to be readily achieved by the "finger tip control" over dose intake which the smoker can readily learn [7]. Presumably, non-pharmacologic factors such as marketing strategies are determinants of initiation since such factors help determine the social and behavioral consequences of tobacco use in general and of the use of specific tobacco types and brands in particular [25].

With smokeless tobacco use, nicotine absorption is readily accomplished passively once the material is placed in the mouth. Thus, pharmacologic parameters may be specifically manipulated to facilitate the development of an orderly dependence process. For instance, the smokeless tobacco products, termed "starter" products by at least one tobacco product manufacturer, were lower in nicotine concentration and pH, resulting in weaker and more slowly onsetting effects; initial acceptance of the products was further enhanced by flavoring agents that are considered desirable in

their own right. Marketing strategies then utilized the process of brand-fading in the direction of increasing alkalinity and nicotine concentration. The pharmacologic underpinnings of such a marketing approach is that as tolerance develops, higher and quicker onsetting doses may be taken, and may even be necessary to achieve desired effects. This strategy was termed the "graduation process" and appeared to be particularly useful in initiating use among younger (including preadult) individuals. These strategies were based, in part, on the premise "virtually all tobacco usage is based upon 'nicotine,' the 'kick,' (and nicotine-related) satisfaction" which can be controlled, in part, by product design [112].‡

The role of nicotine dose level in determining the nature and degree of the effects of tobacco are well known and have been studied for nearly a century. For instance, when tobacco products are self-administered, compensatory changes in self-administration occur in response to changes in the unit nicotine dose level (e.g., resulting from changes in cigarette nicotine delivery, pretreatment with alternate forms of nicotine, or changing rate of nicotine excretion). That is, amount of cigarette smoking (e.g., number of puffs taken or cigarettes smoked) is inversely related to the total amount of nicotine delivered per cigarette [58]. Such compensatory changes are rarely directly proportional to changes in unit administered dose, with nicotine or any other drugs of abuse, but some compensatory change occurs across a wide variety of conditions [56, 58, 66, 92, 146, 147].

Analogous to the effects of decreases in nicotine dose are the effects produced by the administration of nicotine blockers prior to nicotine administration. The response to a given dose of nicotine may then be an inverse function of the dose of the blocker [172]. Whereas functional behavioral effects are blocked by centrally and peripherally acting antagonists (e.g., mecamylamine), antagonists which do not readily enter the central nervous system (e.g., pentolinium) are not effective modifiers of the centrally mediated behavioral responses to nicotine (e.g., [144,170]).

Tolerance to a variety of physiologic and behavioral responses to nicotine develops when nicotine is repeatedly administered [29, 101, 146]. Acute abstinence from repeated administration of cigarettes, smokeless tobacco or nicotine chewing gum produces a syndrome of withdrawal [63–65, 85, 86], and substitution of nicotine in the form of chewing gum, for inhaled cigarette smoke, alleviates the withdrawal responses [157].

Nicotine also has a variety of effects on neuroendocrine function [133] which may be important in the mediation of many of the so-called "useful" or "therapeutic" effects of nicotine. For instance, nicotine may function as an anxiolytic, an anorectant, a mood enhancer, and a performance enhancer (cf. [42, 43, 133]). Most people who achieve abstinence for even a few weeks relapse (Mark Twain claimed that quitting came easy—he had "done it a thousand times," cf. [1]); more importantly, the patterns of relapse and the situations in which they tend to occur are similar for tobacco, opioids, and alcohol, leading to the development of similar strategies of relapse prevention across these substances [110, 163, 164].

By analogy, and inductive extensions of data, pharmacologic treatment strategies developed for other forms of drug dependence may be applied to tobacco dependence. Pharmacologic treatment of chemical dependence may be typologized as follows: *replacement* or *substitution* therapy (e.g., methadone for opiate dependence), in which a more manageable (and, ideally, less behaviorally addicting) form of the drug is provided according to a prearranged maintenance protocol; *blockade* therapy (e.g., naltrexone for opiate dependence), in which the behavior-controlling effects of the abused drug are blocked by pretreatment with an antagonist; *nonspecific pharmacotherapy*, in which the patient is treated symptomatically (e.g., use of clonidine during opioid detoxification); *deterrent* therapy, in which administration of the treatment drug will result in the occurrence of aversive effects when the abused drug is subsequently taken (e.g., the use of disulfiram to treat alcoholism) [52,90]. All four approaches may have applications in the treatment of cigarette smoking (cf. [67]). We will describe each of these strategies in somewhat more detail below.

NICOTINE REPLACEMENT THERAPY

The general principle of replacement therapy is to provide the patient with a safer and more manageable form of drug that directly alleviates signs and symptoms normally suppressed by the substance upon which the patient is dependent. Ideally, it should also be of lower dependence potential so that its use may be more readily discontinued than use of the original form to which the person was dependent. To serve as a replacement substance, the putative therapeutic agent should produce some degree of cross-tolerance and cross-dependence with the abused substance. The therapeutic agent may be an alternate formulation of the same chemical, or a distinct chemical that is characterized by common effects. Thus, for instance, methadone may be given to the opioid-dependent person, and chlordiazepoxide may be given to stabilize the alcoholic [120,161]. The rational basis for treating tobacco dependence with a non-tobacco nicotine-delivering preparation is the observation of key areas of pharmacologic equivalence of nicotine across route or vehicle of administration (e.g., [146]). This is not to say that each nicotine delivery system is pharmacologically identical; they are not. However, to the extent that non-tobacco nicotine-delivery systems substitute for tobacco-based systems, the ease of substitution-based therapy may be enhanced.

Finding an ideal substitute is also impeded by the contribution of nonpharmacologic factors which vary across individuals and/or situations. For instance, in a male-dominated setting, female-promoted brands of cigarettes (e.g., Virginia Slim®, or Satin®) may be socially unacceptable substitutes for cigarettes which have not been marketed in such a gender-specific fashion (e.g., Marlboro®); even if the tar and

‡This opinion follows from the conclusions of J. E. Henningfield that were based upon review of company documents produced pursuant to an order of a Federal District Court. Those documents included ones detailing a strategy for establishing smokeless tobacco use by the development of a series of products intended to facilitate acquisition of smokeless tobacco self-administration. The documents further described the strategy by which these products were marketed in order of "graduating" nicotine dose administration levels (in the order of increasing nicotine content and pH). Among the documents were two reports of apparently U.S. Tobacco-funded studies in which the pharmacokinetics of nicotine delivery via cigarettes and smokeless tobacco were compared (see plaintiff's exhibits Nos. 3.27—"Pharmacokinetics of Nicotine and its Major Metabolites in Naive and Habituated Snuff Takers," and 3.28—"Results of Comparison of Routes of Nicotine Administration (Snuff vs. Cigarette Smoking)." From *Marsee vs. United States Tobacco Company*, U.S. District Court for the Western District of Oklahoma, No. Civ. -84-2777 R (1986); Oklahoma City, OK 73102.

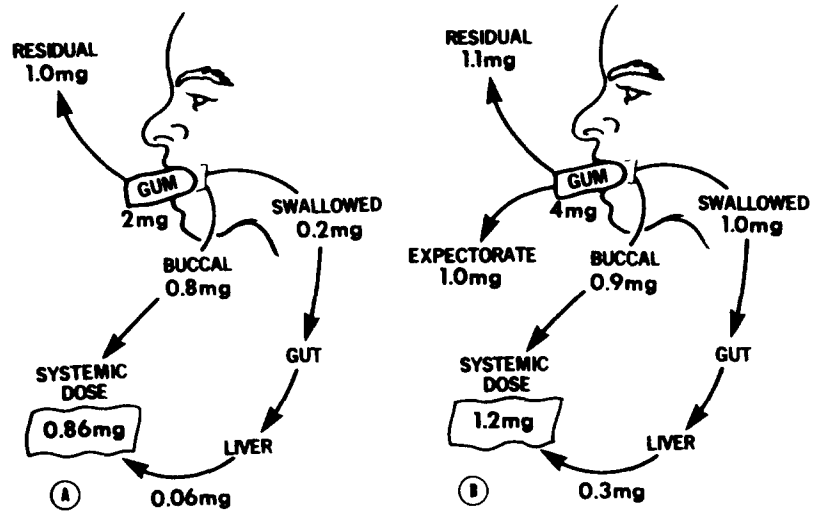

FIG. 1. This schematic diagram shows the disposition of nicotine that follows the chewing of either 2 or 4 mg pieces of nicotine gum. The estimates are based on average values from seven subjects who had been chewing 12 pieces of gum per day. (Reprinted with permission from Benowitz, [11].)

nicotine delivery characteristics are comparable. In fact, Benowitz and his co-workers have shown that, within individuals, nonpreferred cigarette brands are smoked less, and less nicotine is obtained when they are smoked [10], regardless of whether their nicotine yields are rated as being more or less than those of the preferred brand. Low- or non-nicotine-delivering cigarettes may be smoked if regular cigarettes are not available, however, the individuals often experience tobacco withdrawal symptoms [35,48]. The observation that even non-nicotine-delivering cigarettes may be smoked when regular cigarettes are not available [48] has lead to the occasional marketing of such cigarettes (e.g., Bravo® and Free®) as substitutes or as aids for quitting smoking; unfortunately, there are no data published from clinical trials that would indicate that such cigarettes are either acceptable as long-term substitutes or are efficacious in the treatment of cigarette smoking.

The point of these observations is that even when one cigarette is replaced with another, the substitution is less than perfect, since there are both pharmacologic and non-pharmacologic factors which may vary in small but important ways to the individual. These kinds of factors are likely to be of no less importance when non-tobacco nicotine-delivery systems are used as cigarette substitutes. Nonetheless, cigarette smoking can be reduced by pretreating subjects with cigarette smoke [18], or by increasing the amount of tobacco smoke per bout of smoking [32, 57, 105], or by pretreating smokers with nicotine given intravenously, by capsule, or in the form of nicotine gum (see reviews by [58, 66, 92, 146, 147]). In some situations, the desire to smoke can be decreased by increasing the nicotine content of cigarettes smoked or by pretreatment of smokers with nicotine gum [36,115], however, the effect on urge to smoke is not as reliable as are other effects of nicotine administration suggesting that such urges are highly determined by environmental factors (cf. [68,116]).

The most consistent observation across studies is that cigarette smoking is decreased across all tested forms of nicotine administration which may result in elevated plasma nicotine levels [58,66]. For instance, cigarette smoking was decreased by administration of intravenous nicotine [86,107], by oral administration of nicotine in capsule form [91], by buccal administration of nicotine in the form of chewing gum [151], by nasal administration of nicotine in liquid form [95], and a recent study showed that transdermal nicotine administration reduced the preferred concentration of nicotine by smokers [140]. Nicotine has also been introduced at the distal end of the gastrointestinal tract by means of suppositories but these have never successfully entered the armamentarium of therapeutic agents. Absorption from the rectum and distal colon might be expected to be quite efficient and bypass the portal circulation, however, esthetic considerations might militate against their use.

Of the variety of forms of nicotine substitution that might be achieved, only one has been widely tested in clinical trials, approved by the Food and Drug Administration (FDA), and been extensively incorporated into clinical practice. That is the nicotine polacrilex or chewing gum form [4, 34, 156]. Use of the nicotine polacrilex gum has been shown to increase the rates of success of a variety of cigarette smoking treatment programs [53,96]. Under a wide range of conditions, rates of smoking are diminished, and abstinence-associated discomfort ("withdrawal") is lessened; desire to smoke may be lessened too, although this effect is not reliable [116, 156–158]. The above summarized findings constitute much of the empirical basis for using a nicotine replacement approach to treat tobacco dependence.

A commonly used buccal form of nicotine administration is through chewing tobacco or oral snuff [22]. The amount of nicotine administered by this route is comparable to, or may exceed that obtained when cigarettes are smoked [60,148]. In fact, two recently disclosed studies from the tobacco industry showed that nicotine absorption from smokeless tobacco is orderly and controllable, and that such absorption occurs in persons without prior experience using the product; this latter finding was in contrast to data from the same study which showed that nicotine extraction from cigarettes was less effective in persons without experience in smoking.‡ To-

bacco smoke from pipes and cigars is also absorbed largely through the buccal mucosa since its alkaline pH levels, which are higher than those of cigarette smoke, facilitate buccal absorption, while at the same time contribute to harshness which discourages inhalation [6].

Chewing tobacco is also a common component of the mixture that betel-nut users employ. This form of drug self-administration is interesting because it contains two cholinergic-acting substances, a muscarinic agonist (arecholine) as well as nicotine [176]. Systematic studies of behavioral pharmacologic interactions between nicotinic and muscarinic agonists have not been conducted, although studies by Rosecranz and his colleagues indicate that arecholine produces different discriminative effects than does nicotine [143].

Tobacco-based forms of nicotine replacement for cigarette smoking are all casual in the production of characteristic disease states (e.g., smokeless tobacco is a cause of oral cancer). In addition, there is little evidence that these forms of tobacco use are less addictive than are cigarettes, although it would appear to be more common for cigar-only tobacco users to be occasional and/or situation-specific users.

The stability and ready bioavailability of nicotine in various tobacco preparations, combined with its potency, and hydrophilic and lipophilic properties, readily lend nicotine to self-administration via a variety of routes. In fact, American Indians have also administered nicotine from tobacco by nearly every conceivable route not involving modern technology (see [186] for a fascinating discussion). Those nicotine delivery systems which are currently of widespread use in North America are all particularly effective at permitting good control over the administered nicotine dose level, although cultural considerations are also an important determinant of preferred formulation type. For instance, the association of chewing tobacco and the resulting behavior of frequent expectoration with tuberculosis and other diseases sharply curtailed use of such earlier in the twentieth century; this relative decline in use was sharply reversed, producing a "boom" smokeless tobacco industry apparently by sophisticated development of new product formulations and as well as by equally sophisticated new marketing strategies which lead to a change of image associated with smokeless tobacco use in the 1970's and 1980's (see further discussion [176]).

Nicotine can also be administered by the enteral method (i.e., orally or swallowed), however, the high acidity of the stomach inhibits absorption and approximately 70% of the nicotine is metabolized in its first pass through the liver [11, 100, 154]. The fortunate aspect of this pharmacokinetic characteristic is that despite the several potentially lethal doses of nicotine contained in a package of cigarettes, nicotine poisoning deaths in children who have swallowed cigarettes (each of which may contain more than 10 mg of nicotine) [10], or cigars, has been rare; for instance, despite widespread availability of tobacco products, the American Association of Poison Control Centers cited no nicotine poisoning deaths due to tobacco ingestion in 1985 [105].

One putative tobacco substitute that is present in several aids for quitting smoking is lobeline. Lobeline has been described as a weak nicotinic receptor agonist [171], but is of unproven efficacy for the treatment of tobacco dependence [59,159] (see also the review by Sachs [152] for an interesting discussion). Part of the explanation for lobeline's lack of general acceptance may be due to discriminative ("psychoactive") effects of lobeline which differ from those of nicotine; that is, it appears that lobeline does not act via the same receptor sites that appear important in mediating the discriminative effects of nicotine [143]. An additional finding that is consistent with the apparent weak (or absent) efficacy of lobeline [160] is the observation that lobeline is not effective at producing conditioned preferences in animals when tested in an identical fashion as nicotine (which can produce such preferences) [37].

Substitution of psychomotor stimulants for nicotine has also been attempted, but there is little evidence that these approaches are particularly effective in the treatment of tobacco dependence [59,93]. In fact, *d*-amphetamine administration to smokers enhances the pleasure gained by smoking and increases the rate of smoking [73]; caffeine has little consistent direct effect on rate of smoking [17,104].

Another method of nicotine administration, involving inhalation of a nicotine aerosol, appears to more closely resemble that of inhaled cigarette smoke. For instance, nicotine inhalers modeled after the popular medihalers (and, in fact, made by a manufacturer with such experience, viz., Riker Laboratories) were successfully used to investigate various physiological actions of nicotine [28,80]. Jarvik and his colleagues also attempted to use these inhalers as cigarette substitutes in smoking experiments but found what Domino [28] had also reported, namely, that human subjects found nicotine delivery in this fashion so irritating as to limit their use.

A more recent variant on the aerosol procedure appears to provide a significant technological advance that is useful for research, and possibly adaptable for treatment applications. The nasally inhaled aerosol preparation of Perkins and Epstein and their co-workers appears to have the advantages of reasonable subject acceptance, and excellent control over dose as measured by plasma nicotine level, cardiovascular effects, and self-reported responses [127].

A variation on the inhaler technology is the nicotine-delivering rod or "smokeless" cigarette first described by Jacobson and his co-workers [86] and then marketed by Advanced Tobacco Products under the trade name Favor®. Even though the Food and Drug Administration recently decided that this nicotine vapor inhaler fell within its jurisdiction and subject to its regulatory powers, and thus ordered off the market until proven safe and effective, it was initially marketed as a nontherapeutic cigarette substitute. This smokeless cigarette has been studied by Haley and her colleagues at the American Health Foundation [162], by Henningfield and his colleagues at the Addiction Research Center (unpublished data), and by Russell and his colleagues [149]. In the Sepkovic and Haley study, and that by Henningfield *et al.*, puffing on the smokeless cigarette mimicked several effects of nicotine delivered by tobacco, including acute heartrate increase and some of the sensations of tobacco smoke inhalation. In fact, in the Henningfield study, use of the vapor inhaler produced reliable decreases in self-reported desire to smoke cigarettes, although it was not determined whether or not such effects would persist if abstinence from cigarette smoking was prolonged. Interestingly, use of the vapor inhalers in these two studies did not produce detectable elevations in plasma nicotine levels. The Russell *et al.* study found that measurable nicotine plasma levels could be produced by use of the vapor inhaler, but only following extremely active inhalation [149].

These findings with the vapor inhaler suggest the possibility that the vapor inhaler is not a practically effective means of nicotine delivery, and that the apparently nicotinic effects are actually conditioned responses elicited by the pe-

ripheral stimulation provided by the vapor inhaler. To the extent to which such responses persist, such devices could provide useful adjuncts to other forms of replacement therapy and to behaviorally oriented tobacco treatment strategies (cf. [68]). In fact, in what appears to be taking this notion one step further, Rose and Hickman have found that the oral inhalation of a citric acid spray can mimic certain sensory properties of tobacco smoke and reduce self-reported "craving" for cigarettes [138].

Another, not mutually exclusive, explanation of the occurrence of nicotinic effects produced by the vapor inhaler in the absence of measurable plasma nicotine levels is the possibility that nicotine delivery by this route produces effects mediated by the peripheral nervous system. Ginzel has shown that administration of nicotine to lung tissue of animals results in a variety of nicotinic effects often considered to be primarily due to direct central actions of nicotine [43–45].

Peripherally-mediated actions of nicotine could also result from a mode of nicotine delivery in which there was a higher ratio of peripheral to central nicotinic absorption than that obtained when nicotine is delivered via tobacco use. Specifically, nicotine, carried by cigarette smoke, is in the form of a nicotine salt which adheres to the solid and liquid particles which are of an ideal size (about 1 micron in diameter) for deep airway penetration to the alveolar membranes of the lungs; there absorption into the plasma is extremely efficient. In contrast, the vaporous form of nicotine delivered by the smokeless cigarette is a free base, and without the ready availability of particles to which binding may occur. Therefore, this mode of nicotine delivery may result in a higher ratio of upper to lower airway nicotine absorption where systemic absorption may be less efficient. This might account for the rather high degree of ratings of "harshness," and "irritation of the throat," as well as cigarette-like effects produced by use of the nicotine vapor inhaler that were observed in the Henningfield study. Thus, to the extent to which sensory effects of tobacco smoke inhalation are due to nicotine, use of the vapor inhaler would provide a substantial degree of tobacco-like sensations with relatively little central absorption of nicotine. This provides another potential explanation for the greater than predicted efficacy of the nicotine vapor inhalation in simulating cigarette smoke than would be predicted simply on the basis of resultant plasma levels (or lack thereof); namely, upper airway (peripheral) stimulation of sensory receptors could account for some of these actions which might be otherwise interpreted as due to centrally mediated actions of nicotine.

Some of the short-term satisfaction derived from smoking and resulting from upper airway stimulation would at least partially explain the apparent efficacy of the vapor inhaler in reducing desire to smoke when negligible plasma nicotine levels are produced; this is in marked contrast to the negligible effects on desire to smoke which may result from substantial nicotine intake from intravenous or gum delivered nicotine (cf. [79,116]). Whether the effects of the nicotine vapor inhaler are conditioned responses, peripheral nicotinic actions, or both, it remains to be determined if such effects would provide long-term efficacy as a tobacco replacement formulation in the nicotine-tolerant and -dependent tobacco user.

An interesting mode of delivery using sublingual nicotine tablets has been described by Wesnes and Warburton and their colleagues (e.g., [182]). Although not available for therapeutic application, this sublingual-oral mode of delivery has proven quite useful as a research tool. Nicotine is added to buffered dextrose tablets which are then held in the mouth for five minutes, producing fairly efficient and quick nicotine delivery; the tablets are then swallowed and continue to deliver a small but apparently significant amount of nicotine to the plasma (cf. [183]). Nicotine administration via this modality appears to produce significant and dose-related effects on a variety of behavioral and physiologic variables including measures of learning and information processing. The nicotine delivered, and the effects produced, by 1–2 mg given via this modality appear to roughly correspond to the nicotine delivered and effects produced by the smoking of cigarettes with similar dose delivery estimates provided by smoking machine tests.

A novel method of administering nicotine through the skin has recently been reported [140,141]. Transdermal patches have become a common method of administering such drugs as nitroglycerin, scopolamine, and clonidine (cf. [42]). Nicotine is a seemingly ideal candidate for transdermal administration because it is lipophilic and potent. Centrally administered nicotine dose levels may not be as readily controllable by this route of administration, but nicotine's relatively short half-life (about 2 hours), combined with the pharmacodynamic characteristics of rapid initial tolerance to many of its effects, enhance the safety of transdermal nicotine administration, since removal of the patch at the onset of adverse effects should result in an almost immediate decline in plasma levels.

Prominent research problems regarding transdermal nicotine administration which remain to be explored are the following: (1) factors affecting control of the rate and magnitude of nicotine dose administration, (2) possible local irritation resulting from continuous transdermal nicotine application, and (3) the degree to which transdermal nicotine application reduces prominent nicotine-mediated signs and symptoms of tobacco withdrawal (e.g., impairment of mood and performance, weight gain). The potential benefits of such a mode of nicotine delivery justify research into these areas. Three benefits, in particular, seem plausible: (1) persons who are physically unable to obtain adequate amounts of nicotine by chewing the gum (e.g., those with dental or other problems) might be able to use the patch; (2) the possible social stigma sometimes resulting from the frequent administration of a medication which is necessitated by the pharmacokinetic properties of most other formulations would be alleviated by the privacy of administration that such a route would permit; (3) finally, and related to the above, is that patient compliance with the required dosing regimen might be more readily obtainable (a patch could simply be applied once or twice per day, and left in place).

A patch could also be used in conjunction with nicotine gum or with a variety of nicotine free components of the cigarette smoking sequence. These could include the sight and feel of cigarettes, the sight and smell of tobacco smoke or some substitute for it, the taste, and the sensations in the mouth, nose, throat and trachea produced by normal smoking but reproduced with as few components of smoke as possible, or a system such as the previously described citric acid spray [138].

Comments, Caveats and Constraints Regarding Nicotine Replacement

Any nicotine replacement therapy for tobacco dependence faces the issues of efficacy and safety which have as yet

only been met, to the approval of the U.S. Food and Drug Administration, by the nicotine gum formulation (Nicorette®). Experience with other kinds of replacement therapies, and with nicotine gum replacement itself, raises the following specific issues. First, nicotine is a potent, dependence producing drug with potential toxicity and would likely often be accessible by children. To minimize risk to unintended users, the currently available polacrilex (gum) formulation permits little passive exposure. Specifically, release of the nicotine from the gum requires active and proper chewing and swallowing patterns; this level of safety engineering has yet to be achieved with any other marketed or publically tested form of nicotine replacement. At an individual patient level of safety concern, it would appear that any form of nicotine replacement will expose the patient to the general effects of nicotine (e.g., nausea at higher dose levels and contraindications during pregnancy), as well as possible adverse effects which are specific to each route (e.g., skin and throat irritation due to transdermal and inhaled nicotine respectively, and dental problems associated with chronic gum use). Therefore, nicotine replacement approaches should be administered in accordance with the risks and benefits expected for the individual.

The general problem of efficacy is the same as that of any other type of replacement therapy for substance dependence: if the form of replacement does not provide the centrally-mediated pharmacologic and the peripherally-mediated sensory effects of the preferred substance, the level of satisfaction provided to patients may be limited. Specifically, for instance, the "friend" which the patient may claim to have lost upon giving up the substance upon which he was dependent may never be completely replaced by an alternative pharmacologic agent; however, experience with replacement therapies has proven that adequate dosing can better enable the patient to function normally and with minimal discomfort. The crux of the problem is that cigarette smoking, like other forms of drug addiction, is critically but only partially mediated by pharmacologic factors. Therefore, although there is evidence that gum administration enhances efficacy of physician-based programs with minimal intervention [126,148], the nicotine chewing gum is most effectively used in conjunction with an appropriate ancillary treatment program [53].

It should also be noted that not everyone who uses tobacco is physiologically dependent to nicotine and thus nicotine replacement is not indicated for all tobacco users. For instance two recent unpublished surveys (J. E. Henningfield and S. Shiffman) have confirmed earlier findings that approximately 5 to 10 percent of cigarette smokers are "chippers" averaging less than 6 cigarettes per day, and not smoking every day [145]. Consistent with this observation, persons who are most effectively treated with the gum may be selected on the basis of a short questionnaire that provides an index of level of nicotine dependence [35,94].

When nicotine polacrilex is used, the following observations related to dose control should be considered:

(1) Since pharmacokinetic and pharmacodynamic data suggest that one piece of 2-mg nicotine gum (the only formulation commercially available in the United States) is equivalent to about one-half to one cigarette with regard to its nicotine delivery and nicotine-related effects, it may be necessary to prescribe 20 to 30 pieces per day during the initial treatment phase in which the gum is substituted for tobacco.

(2) To provide an approximation of the bolus nicotine effect that may be important to some patients, these patients may need to occasionally chew two or more pieces of the gum simultaneously.

(3) Patients should be instructed that not only must they "chew the nicotine out of the gum," but they must "avoid swallowing the nicotine" before it has time to be absorbed. Therefore, after a bout of active chewing, the patient should avoid swallowing for at least one minute and swallowing should be limited to no more than once every minute during periods of slow chewing.

(4) For some patients it may be most effective to schedule dosing at intervals of one hour or less, following a "loading" phase of several pieces within the first hour of waking. That is to self-administer nicotine prophylactically in a pattern similar to that in which tobacco is smoked.

(5) Nicotine absorption via the buccal mucosa is inversely related to oral pH, therefore, drinking of acidic beverages (e.g., coffee, soft drinks) should be avoided while using the polacrilex.

(6) A practical bioassay for effective nicotine administration is the subjective response of the patient; if nicotine gum administration following, for example, a few hours of deprivation does not produce a discriminated effect, then the dose absorbed was too low (due to inadequate dose administration, chew pattern or swallowing of the saliva); conversely, nausea and/or dizziness are useful indications that too much nicotine was absorbed. Alternatively, the patient may be treated with an adequate dose level, but may expect an effect (e.g., elimination of urge to smoke) that is not reliably produced, and therefore the person may inappropriately conclude that the gum "did not do anything."

NICOTINE BLOCKADE THERAPY

A pharmacologic alternative to replacement therapy is to produce a pharmacologic blockade of receptors which mediate the reinforcing as well as the toxic effects of the abused substance [90]. In the case of opioid agonists such as morphine and heroin, the short-acting antagonist naloxone can be used to reverse the effects of an overdose of the opioid agonist. The longer acting antagonist, naltrexone, can be given on a daily basis to opioid abusers to prevent them from experiencing the reinforcing and toxic effects of opioid agonists. Unfortunately for most opioid abusers, there is poor compliance with a therapeutic regimen which prevents the possibility of experiencing opioid agonist effects, i.e., patients do not reliably take the antagonist. It appears that approximately 5% of opioid abusing patients are willing to comply with such a therapeutic regimen [54]; characteristics of patients lend support to the possibility that a greater percentage of cigarette smokers would be amenable to such treatment. Specifically, the three characteristics that correlate with success in naltrexone treatment are that the patient is (1) highly motivated, (2) well adjusted in society, and (3) has a steady job [54]. It seems likely that a substantially higher percentage of cigarette smokers than opioid dependent persons would meet these criteria (see also [168]).

It has been known for several decades that there were pharmacologic antagonists for nicotine, the administration of which could diminish a variety of responses to nicotine (e.g., [29]). It has also been well documented that those antagonists which act both centrally and peripherally (mecamylamine), but not those which only act peripherally (e.g., pentolinium and hexamethonium), have functional effects on patterns of cigarette smoking in humans and behavioral effects of nicotine (including self-administration) in animals (cf. review [66,168]). Preliminary data suggest the

possibility that mecamylamine could be used as an antagonist to block the nicotine-mediated reinforcing consequences of cigarette smoking.

The following findings seem of particular relevance: (1) Mecamylamine pretreatment produces a dose-related blockade of the ability of animals and humans to discriminate nicotine from placebo [78, 144, 168]; (2) Mecamylamine pretreatment diminishes the reinforcing efficacy of intravenous nicotine administration in animals [47], and possibly in humans (see preliminary data in [71]); (3) Acute mecamylamine pretreatment increases the preference for high nicotine-delivering cigarette smoke (apparently by reducing its nicotinic effects) when subjects are tested using a device which blends smoke from high and low nicotine-delivering cigarettes [142]; (4) Acute mecamylamine pretreatment increases a variety of measures of cigarette smoking behavior and/or tobacco smoke intake when subjects are allowed to freely smoke [118, 134, 170]. Interestingly, results from the Pomerleau *et al.* study also suggested that the toxicity of nicotine exposure was substantially reduced by mecamylamine pretreatment.

In addition, a preliminary clinical trial was conducted by Tennant and his colleagues to determine if mecamylamine could be safely and efficaciously used to treat cigarette smoking [172]. Mecamylamine was given to a population of heavy cigarette smokers in conjunction with counseling to quit smoking. It was found that mecamylamine reduced tobacco craving in 13 of 14 subjects, and half of the subjects quit smoking within 2 weeks of initiation of mecamylamine treatment. The mean dose level of mecamylamine, at the time of quitting, was 26.7 mg per 24-hour day. A rather curious aspect of this application of mecamylamine is that it was not used in an analogous fashion as is naltrexone used for opioid dependence: that is, it was used as an aid to detoxification and as a means to alleviate withdrawal. In theory, a blocker should precipitate withdrawal, and therefore would not be used as a detoxification approach per se. Rather, it would be expected to be used as a means to prevent relapse once acute detoxification had been achieved. Perhaps the apparently beneficial effects of mecamylamine were due to its sedating side effect or some as yet unreported nicotine-mecamylamine interaction. Despite these curiosities and the fact that the trial was not placebo-controlled, the data suggest that this treatment approach would appear to warrant further exploration.

The main obstacles to this treatment approach are as follows: (1) The anticholinergic/antihypertensive effects of mecamylamine constitute a major obstacle to the utilization of such therapy; (2) Therapeutic compliance may be inadequate; (3) the strength of the conditioned and non-nicotine-mediated reinforcers for tobacco use may be powerful enough that even when they are no longer associated with the pharmacologic effects of nicotine, their urge-to-smoke evoking actions may persist indefinitely. On the other hand, if only a few percent of tobacco-dependent persons in the U.S. alone were amenable to such treatment, the absolute numbers would still be considerable and might well warrant the availability of such therapy.

NONSPECIFIC PHARMACOTHERAPY—SYMPTOMATIC TREATMENT

The above summarized pharmacologic intervention approaches are specifically aimed at nicotine receptor-mediated responses, either by agonist administration (e.g., nicotine replacement), or by antagonist administration (e.g., mecamylamine pretreatment). However, as we will discuss in somewhat greater detail in this section, administration and withdrawal from nicotine produces a cascade of effects which involve a variety of neurohormones. It has been hypothesized that certain neurohormonal effects of nicotine enhance the reinforcing efficacy of nicotine by providing therapeutic benefit or useful effect; such effects may vary across individuals [133]. Consequently, it should be possible to achieve some of these same effects using pharmacologic interventions which do not directly involve activation or blockade of nicotinic receptors at the ganglia and central nicotinic receptors. Moreover, it should be possible to target treatment approaches to meet individual needs. For instance, if nicotine's anxiolytic effects (discussed below) are important determinants of its abuse for certain individuals, it should be possible to develop specific pharmacologic and behavioral treatments to replace nicotine (see [133] for a more thorough discussion of these issues).

Whereas certain drug effects are common across classes of dependence producing drugs (e.g., most widely abused drugs produce centrally-mediated discriminative effects), other effects vary as a function of drug class and may even be highly specific to drug type. For instance, amphetamine, heroin, and pentobarbital are all well discriminated, and can elevate mood and serve as positive reinforcers; however, of these three drugs, amphetamine is also a particularly effective psychomotor stimulant, heroin is an effective analgesic, and pentobarbital is most useful as a sedative. Such actions may serve to initiate and/or to strengthen the abuse liability of dependence producing drugs.

The only clinically approved application of nicotine to treat tobacco dependence is Nicorette®. However, as is becoming increasingly clear, nicotine administration produces a variety of beneficial effects which might be considered clinically therapeutic and which probably contribute to the dependence potential of the drug. For instance, it appears likely that some individuals may have specific therapeutic needs which are at least partially treated by their use of nicotine (e.g., anxiety or weight control). In such individuals, prevention of their relapse to tobacco may require specific intervention (pharmacologic or behavioral) for that need. It is in this context that supportive pharmacologic therapies are posed.

Several actions of nicotine which have been claimed to provide specific "reasons for smoking" or beneficial effect have also been shown to produce analogous effects in laboratory studies with both human and animal subjects. Such data do not indicate that these are the main reasons that the dependence to tobacco-delivered nicotine is so strong, but they do support the notion that there is a behavioral and pharmacologic basis for these claimed effects of nicotine administration and deprivation. Three such categories of beneficial effect are prominent. Although they are not necessarily mutually exclusive, they are usefully summarized with regard to the following three categories of effect.

Several effects of nicotine may be regarded anxiolytic effects of nicotine. Laboratory studies with human subjects have shown that nicotine administration can reduce reported distressed responses to stressful stimuli and to enhance mood, and have also demonstrated that stressful situations lead to increased nicotine self-administration (i.e., increased cigarette intake) [40, 41, 49, 139, 153]. In addition, nicotine administration reduces aggressive responses in experimental situations [19]. Conversely, relapse to cigarette smoking often occurs in response to stressful situations [20, 51, 62,

110, 122, 132, 163, 164]. Such observations would suggest the possibility that targeted use of more specific anxiolytics (e.g., benzodiazepines) may be useful for some persons in the maintenance of abstinence.

Nicotine Serves as a Mood Regulator

Nicotine may also be a useful mood regulator, in part by virtue of its stimulation of release of catecholamines, as well as modulation of a variety of other neuroregulatory hormones [40,133]. Catecholamine release both peripherally and centrally is also stimulated by excitement, exercise, sex, antidepressant drugs, and other drugs of abuse, suggesting that cigarette smoking may pharmacologically function to alleviate boredom and stress. Both animal and human data suggest that an elevated ratio of norepinephrine to epinephrine release is associated with pleasureable states of arousal (e.g., sex, cocaine, amphetamine administration, electrical brain self-stimulation), whereas as the reverse (increased epinephrine) is thought to be associated with certain dysphoric mood states such as boredom, stress, electric shock administration (cf. [9, 16, 26, 27, 155, 180, 181]). Interestingly, both animal and human data also suggest that nicotine administration results in an increased ratio of norepinephrine to epinephrine release [23, 50, 185, 187]. These observations suggest that for certain persons, selective use of antidepressants, or even psychomotor stimulants, may be beneficial in preventing relapse.

Nicotine is a Weight Regulator

Smokers weigh less than nonsmokers, although the relation is not simple; moderate smokers weigh the least, light and heavy smokers somewhat more, and nonsmokers weigh the most [85,135]. Among persons who have quit smoking, those treated with nicotine gum gain less weight than those treated with placebo gum, and it appears that the magnitude of the effect is directly related to nicotine intake via the gum [167]. Quitting smoking is associated with some degree of weight gain in at least one half of people studied, although meaningful quantitative data are difficult to acertain since the data are presented in a variety of ways across studies (e.g., one study may report the percentage of persons in which a "significant" change occurred, while another may compare mean changes in groups) [21, 38, 39, 85, 103]. People do tend to eat somewhat more when they quit smoking [24,165], and some may even increase their food intake as an adjunct strategy to quitting smoking [14].

As an anorectant or weight reducer, smoking and/or nicotine itself may function in at least three ways: (1) by increasing resting metabolic rates [24,85]; (2) by specifically reducing the appetite for foods containing simple carbohydrates [61]; (3) by nonspecifically reducing the eating that may occur in times of stress [15], although these relations are complicated by observations in which some smokers eat more than nonsmokers [85].

Taken together, it would have to be concluded that nicotine is a rather robust anorectant. Furthermore, the general effect is attributed by many smokers as an aversive side-effect of quitting smoking [109,114], and others report that "fear of gaining weight" is one factor that keeps them from quitting [179]. Despite the fact that the health benefits of quitting smoking exceed the risks of weight gain for most individuals, the apparent relevance of weight gain as a factor in preventing abstinence attempts and in provoking relapse, must be addressed. Since the control of weight may be as difficult a behavioral problem as is the control of drug abuse, this challenge to the tobacco cessation therapist may be considerable. The possibility should therefore be considered of employing systematic weight control programs as indicated for individual patients. Such programs may also benefit from the use of some of the apparently more selective anorectants (e.g., fenfluramine).

Nicotine Can Reverse Tobacco Deprivation-Induced Decrements in Performance

The findings that nicotine withdrawal can lead to performance impairments on conventional measures of cognitive function, and conversely, that nicotine administration can reverse such deficits has now been well established (cf. reviews by [77,183]). It is also possible that under certain conditions nicotine administration may directly enhance performance independently of alleviation of tobacco withdrawal [30,183]. Since a variety of attentional, motivational, memory, and even mood-related factors can contribute to measured performance, the likely mechanisms by which nicotine prevents performance decrements are not completely defined. Thus, it may be more difficult to selectively mimic these effects of nicotine than those discussed above. For instance, performance deficits may arise secondarily to nicotine withdrawal-induced disturbance of mood, reduction of attention, or even reduced information processing capability (cf. review [183]). Therapeutic approaches to such difficulties may be integral to the prevention of relapse, although the appropriate treatment will have to be individually developed. For some, nicotine replacement may be the treatment of choice.

Supportive Therapy to Treat Tobacco Withdrawal

In one of the few recent scientifically studied approaches to treating tobacco dependence with a supportive form of pharmacotherapy, Glassman and his colleagues compared alprazolam and clonidine to placebo in heavy cigarette smokers on days during which they abstained from tobacco [46]. The subjects were exposed to one of the medication conditions on three separate study days, which were separated by at least three days of normal smoking. Alprazolam, a benzodiazepine-like drug, was included as a "sedative placebo" because of the known sedative effects of clonidine. Both clonidine and alprazolam were more effective than placebo in reducing anxiety, irritability, restlessness, and tension. Only clonidine, however, successfully reduced the craving for a cigarette. Since desire to smoke tended to increase during the day, the difference between clonidine and the other two conditions became more evident as the day progressed.

Despite the preliminary nature of the study, this was an important demonstration of the possible utility of a nonnicotine based pharmacologic treatment strategy. It is also interesting to compare the utility of clonidine in the treatment of tobacco withdrawal to its utility in the treatment of opioid withdrawal. When assessed in an analogous paradigm, clonidine was just as effective as morphine in the reduction of certain physiologic signs of opioid withdrawal [99]; however, in the Jasinski *et al.* study, clonidine did not as effectively reduce the self-reported "discomfort" as did morphine (measures of "desire to use narcotics" or narcotic seeking behavior were not collected), moreover, observation of the subjects suggested to the investigators that clonidine was not as effective as morphine in suppressing the desire to take a narcotic (D. R. Jasinski, personal communication).

Experimental Laboratory Studies of the Effects of Drugs on Cigarette Smoking

As should be evident from the brief review presented above, despite the variety of drugs which have been proposed for their possible utility in the treatment of tobacco dependence, little systematic work has been done that would provide practical clinical information. In fact most of the experimental studies have concentrated on the behavioral pharmacologic effects of drug administration on cigarette smoking. The findings of several of these studies may be summarized as follows: (1) Ethanol pretreatment increases cigarette smoking (e.g., [55, 69, 70, 113]), although the effect may be related to a history of ethanol drinking [70]; (2) Pentobarbital can either increase or decrease cigarette smoking, and like ethanol, there is some evidence that increases are related to histories of pentobarbital abuse [69]; (3) Opioid agonists, heroin and methadone, increase cigarette smoking in opioid abusers [17a,111]; (4) the opioid antagonist, naloxone, may decrease cigarette smoking under certain conditions [102], but the effect is weak at best, and not reliably demonstrated in other studies [119]; (5) *d*-Amphetamine increases cigarette smoking robustly and in non-drug abusers [17,73]; (6) Marijuana has unreliable effects on smoking [111a].

The effects of caffeine on smoking are interesting since caffeine might be expected to either increase smoking by its general stimulant-like effects, or by its anxiogenic effects [136]; it might also be expected to decrease smoking by serving as a substitute for some of nicotine's stimulant-like effects [104]. It has also been widely observed that the incidence of coffee drinking and cigarette smoking are related, and that rates of coffee drinking and cigarette smoking covary [66]. When evaluated in laboratory studies, however, the direct effects of caffeine administration on cigarette smoking are weak and inconsistent. Two studies showed no reliable effect [17,121], another showed weak decreases in smoking [104], and a fourth showed weak increases in smoking following caffeine administration [125].

The outcomes of many of these studies have provoked various hypothetical explanations in accord with the finding of the particular study. For instance, the ethanol-induced increase in smoking has been interpreted as a result of the mutual antagonism of a sedative and a stimulant, and the naloxone-induced decrease in smoking in one study has been interpreted as a consequence of the blockade of endorphins which are presumed to play some role as a determinant of the reinforcing effects of tobacco. As is evident from the diversity of these findings, no simple pharmacologic theory seems to provide a satisfactory explanation, although one interesting observation has been made. That is, that in subjects for whom the pretreatment drug produces an elevated mood state (e.g., increased "euphoriant" scale scores) [98], the drug also produces elevated levels of cigarette smoking; the converse of this observation also seems to hold true [74]. The two notable exceptions to this observation are the two drugs which have been similarly tested but which act directly at the nicotinic receptor. These are nicotine, which elevates mood but suppresses smoking, and mecamylamine, which has more sedative-like effects and increases cigarette smoking.

While these findings and observations do little to suggest which kinds of drugs should be used in supportive therapy, they do suggest some caveats and pitfalls to avoid. Firstly, simply attempting to mimic some action of nicotine with a non-nicotinic drug, e.g., providing stimulation with *d*-amphetamine or relaxation with a sedative, could be counter-productive if the main effect of that substance is to increase tobacco use. Secondly, there are anecdotal observations and some experimental support for the notion that drugs of abuse should be avoided when attempting to quit smoking. Thirdly, that as a function of experience and/or other factors, the effects of a drug on smoking may vary across individuals. Finally, the findings do not rule out an increasingly evident possibility: that is, certain therapeutic drugs could be highly useful in certain subpopulations, even though their possible benefit would not be evident when administered indiscriminately. For instance, situational use of anxiolytics might be of benefit in individuals in whom stressful situations were especially likely to provoke relapse, even through indiscriminate use of benzodiazepines may not appear effective.

PHARMACOLOGIC DETERRENTS

The last category of pharmacologic aids to treat tobacco dependence are the deterrents. The rational basis for the use of pharmacologic deterrents are reports that drug taking can sometimes be reduced or eliminated if the consequences are severe enough (e.g., use of punishment for drug use). There has been relatively little systematic study of the use of such procedures with humans however. A series of studies with ethanol-drinking animal subjects has confirmed the likely potential utility of the approach [128–130]. These studies have shown that when drinking reliably leads to an aversive stimulus (e.g., electric shock) or the loss of reinforcers (e.g., food), that alcohol drinking is suppressed. One practical conclusion is that approaches which result in unreliable consequences, or consequences that are far removed in time, may be of limited efficacy. This is consistent with the observation that even a powerful stimulus, such as the threat of the Sultan of Turkey to remove the heads of tobacco smokers in the 17th century [8] did not eliminate cigarette smoking, nor have warnings of the possibility of lung cancer and other diseases from the Surgeon General eliminated smoking in the U.S.; these consequences, although terribly severe, were/are uncertain and usually far removed in time from development of the dependence. A more systematic, and apparently more effective application of reducing cigarette smoking by means of contingent aversive consequences was demonstrated by Elliott and Tighe in a study in which they found that loss of money, and even simply "threatened" loss of money, substantially reduced expected relapse to cigarette smoking following treatment [31].

Perhaps the best example of a form of drug self-administration in which pharmacologic pretreatment has such a consequence is the treatment of alcoholics by daily administration of disulfiram (Antabuse®). Disulfiram inhibits the further degradation of an ethanol metabolite, acetaldehyde, and, therefore, leads to a toxic accumulation of acetaldehyde [89]. Thus, a rather small amount of alcohol will often produce a rather severe discomfort and acute illness. Of course, parameters such as dose of disulfiram and dose of ethanol, and individual variability, attenuate the effectiveness of the treatment for many. A few observations about the use of disulfiram therapy may illustrate some of the problems and issues which may arise when such approaches are applied to tobacco dependence.

The main difficulty with disulfiram therapy is in maintaining adequate levels of use of the medication itself. It appears to be most effectively employed when circumstances can be

arranged such that the drug is taken when the motivation to drink is relatively low, such as upon daily attendance to a treatment clinic or when patients are under a court order to comply with the therapeutic protocol.§ The same issues would be of likely relevance to the development of effective deterrents for cigarette smoking. That is, they should be able to be administered when the motivation to smoke is relatively low; then the medication can provide a "crutch" for subsequent instances of high motivation to smoke. Unfortunately, a characteristic of nicotine-dependent tobacco users is that one of the most consistent periods of high motivation to smoke is immediately upon awakening after a night of sleep [33]. Therefore, upon waking, the immediate motivation to smoke may preclude the taking of a medication which will facilitate abstinence later in the day. Alternately, very long-acting (at least 24 hours) deterrents might be developed which would permit the person to take them later in the day, perhaps even after "one last cigarette was smoked."

With regard to cigarette smoking, the main analog to a disulfiram treatment is the administration of silver acetate. Variants on this method have been marketed for a number of years. The physiological basis of the approach is that sulfide salts are produced when silver acetate contacts the sulfides in tobacco smoke. The resulting sulfides are extremely distasteful for most people. The approach is, therefore, not specific to nicotine intake, but rather from sulfur containing smoke. Variants on this procedure have been reviewed [160]. Most recently, a gum preparation of silver acetate has been tested as a means to maintain abstinence for tobacco smoke [108]. This is a revival of an older treatment with silver nitrate and has the danger of inducing argyria. Furthermore, it must be taken upon awakening and then repeatedly during the day to assist in abstinence, since a single piece of gum is apparently only effective for a few hours.

In principal, the use of pharmacologic deterrents could provide an important adjunctive therapy for the treatment of tobacco dependence. Those presently available, however, appear deficient in critical respects. What appears to be needed is longer acting deterrents and systematic behavioral programs to ensure compliance with therapeutic protocols. It is also plausible that the tobacco users who may benefit most for such developments would be those for whom emergent symptomology and/or nicotine withdrawal is not significant, but for whom the desire to smoke is strong.

CONCLUSIONS

This paper has briefly summarized the rational basis for the use of pharmacologically-based therapies to help establish and maintain abstinence from tobacco products, as well as reviewed data regarding some specific pharmacologic approaches. In summary, the precedent for such approaches is the use of similar kinds of approaches to treat other substance abuse disorders. That tobacco dependence is partially, but critically mediated by a centrally acting chemical (viz., nicotine), ultimately lead the American Psychiatric Association to identify tobacco use as an Organic Mental and a Substance Use Disorder, when certain diagnostic criteria are fulfilled [5]. Additional findings that there are clinically relevant points of similarity shared by nicotine dependence and other kinds of chemical dependence have provided a strong rational basis for the use of analogous kinds of therapeutic approaches. For example, among dependence producing drugs, similar environmental factors seem prominent in both the control of the drug seeking behavior during periods of active abuse, as well as in the enhancement of the probability of relapse during abstinence.

Some variant on each of the pharmacologic treatment approaches described in this review have been applied to other forms of drug dependence, and with similar limited success as with tobacco. In fact, there has as yet been found no pharmacologic intervention which is readily accepted by drug-dependent persons, and which results in total abstinence from any drug of widespread abuse. Regarding specific pharmacologically-based treatment approaches for tobacco dependence, preliminary data suggest that approaches developed for the treatment of other substance abuse disorders may be rationally applied. Specific approaches may be deliniated in various ways, but it is useful to categorize them according to the following four categories: (1) replacement, (2) blockade, (3) nonspecific pharmacotherapy, and (4) deterrent. It would seem plausible that the diversity of factors which may be relevant to the control and treatment of tobacco use across individuals will require a diversity of treatment approaches.

The prominent role of nicotine itself in the mediation of tobacco dependence suggests that replacement therapies would be of utility to a large proportion of tobacco users. Nicotine polacrilex is the only currently available formulation to provide nicotine replacement on a clinical basis and it has a clearly demonstrable efficacy in both laboratory and clinical settings. Since its efficacy as well as its side effects appear to be related to the rate and efficiency with which nicotine is extracted and absorbed, special instructions to patients and clinicians, regarding the use of the gum, could probably improve its efficacy. In addition, making available a stronger formulation (e.g., 4-mg gum is available outside of the U.S.) would facilitate the provision of adequate dosing to those who require higher dose levels of nicotine, since the physical burden of chewing as many as 20 to 30 pieces (when 2-mg gum is used) per day could be reduced. Use of the polacrilex formulation has not only confirmed that a replacement strategy is of potential therapeutic benefit, but also that alternate replacement formulations are needed for those who cannot use the gum for dental and other reasons. Other nicotine replacement approaches under active development include the transdermal patch, a nasal spray or droplet form, and a nicotine vapor inhaler.

Blockade approaches, have not, historically, been readily accepted by more than a minority of chemically-dependent persons. However, such approaches would still seem important to pursue since the potential absolute numbers of persons who could benefit from such approaches is considerable (e.g., 5% of a conservatively estimated 50 million cigarette-dependent persons is 3 million). Mecamylamine is available at present, but its use will probably be constrained by the possibility of inducing orthostatic hypotension. A blocker that is more analogous to naltrexone for morphine with minimal side effects would seem to be of likely clinical benefit.

§Such programs were apparently implemented with a reasonable degree of success at Baltimore City Hospitals (now Francis Scott Key Medical Center) in the mid 1970's, cf. Dr. M. E. McCaul, Director, Alcoholism Rehabilitation Center, Francis Scott Key Medical Center.

Another approach of potential major impact has not been widely studied; that is, the use of nonspecific pharmacotherapies to use on an individual patient basis in accordance with specific symptomatology. That is, to use available medicinals to treat signs and symptomatology which appear upon termination of tobacco use. Whether the symptoms are part of the short-term withdrawal from nicotine, part of the likely more protracted phase of nicotine withdrawal, or are emergent symptoms which had been suppressed by the chronic use of tobacco, may not be important in clinical practice. What is important is that such symptomology can lead to relapse. In fact, such conditions may have operated to enhance the reinforcing efficacy of nicotine and hence its control over behavior. Fortunately, many of such symptoms (e.g., anxiety, and weight control problems) can occur independently of nicotine dependence and withdrawal, and therapeutic strategies are available. Therefore, it is plausible that medications which are not of clear efficacy when used for groups of smokers (e.g., [160]), may still be appropriately used on an individual case basis. For instance, the use of benzodiazepines and anorectants should not be ruled out simply because such drugs may increase smoking in persons not trying to quit. Similarly, even though there is little evidence for the use of antidepressants to treat tobacco dependence, it is plausible that their use to alleviate emergent affective symptomology could facilitate efforts to maintain abstinence. Such pharmacologic approaches are not incompatible with behavioral treatments and, in most cases, may benefit from the concurrent behavioral treatment.

Deterrent approaches, in principle, could be of enormous potential utility, however, a satisfactory deterrent has yet to be developed and marketed. These approaches are hindered by both developmental and implementational issues. The problem for development is to produce a product which reliably leads to consequences which are both sufficiently severe immediate to discourage smoking, and the product should be without side effects that would act to inhibit its use (e.g., the staining of gums cause by some deterrents). Implementation is hindered by many of the same kinds of issues that hinder quitting in general, namely, achieving compliance with the therapeutic regimen.

As the preceding has shown, there is a strong rational basis, and even some direct evidence, that pharmacologic intervention for the treatment of cigarette smoking can be of therapeutic utility. The efficacy of pharmacologic intervention may be limited by the extent to which the substance seeking behavior, and the derived benefits, have become functionally autonomous from the drug itself. This problem is not unique to tobacco [68]. It is well known that treating opiate users, for instance, involves considerably more than blocking physiologic withdrawal, an entire "life-style" may require change (cf. [12,52]). In the case of tobacco dependence, by the time the dependent smoker attempts to quit, there have probably been 100's of thousands of pairings of various effects of nicotine with the stimuli provided by the use of the tobacco product. These environmental stimuli are certainly not replaced by any pharmacologic agent, and much time may be required until their absence no longer contributes to the discomfort of withdrawal and the precipitation of relapse. Perhaps the most that pharmacologic intervention can provide is a means to alleviate the physiologically-mediated components of withdrawal and their contribution to relapse. The rest will be up to intervention programs and the contingencies set by the individual himself.

REFERENCES

1. Adams, A. K. (Ed.). *The Home Book of Humorous Quotations*. New York: Dodd Mead, 1969, p. 329.
2. American Cancer Society. *Cancer Facts and Figures*. New York: American Cancer Society, Inc., 1984.
3. American College of Physicians, Health and Public Policy Committee. Methods for stopping cigarette smoking. *Ann Intern Med* **105:** 281–291, 1986.
4. American Hospital Formulary Services. *Drug Information*. 12:92 Miscellaneous Autonomic Drugs: Nicotine Polarcrilex. Bethesda, MD: American Society of Hospital Pharmaceuticals, 1987, pp. 657–662.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, revised. Washington, DC: 1987.
6. Armitage, A. K. Some recent observations relating to the absorption of nicotine from tobacco smoke. *Smoking Behavior: Motives and Incentives*. New York: V. H. Winston & Sons, 1973, p. 83.
7. Armitage, A. K., G. H. Hall and C. F. Morrison. Pharmacological basis for the tobacco smoking habit. *Nature* **217:** 331–334, 1968.

7a Austin, G. A. Perspectives on the history of psychoactive substance use, National Institute on Drug Abuse, Research Issues 24. DHEW Pub. No. ADM 79-810. Washington, DC: U.S. Government Printing Office, 1968.

8. Austin, G. A. *Perspectives on the History of Psychoactive Substance Use*. Washington, DC: U.S. Government Printing Office, 1979.
9. Ax, A. The psychological differentiation between fear and anger in humans. *Psychosom Med* **15:** 433–442, 1953.
10. Benowitz, N. L.,S. M. Hall, R. I. Herning, P. Jacob, III, R. T. Jones and A. L. Osman. Smokers of low-yield cigarettes do not consume less nicotine. *N Engl J Med* **390:** 139–142, 1983.
11. Benowitz, N. L., P. Jacob, III and C. Savanapridi. Determinants of nicotine intake while chewing nicotine polacrilex. *Clin Pharmacol Ther* **41:** 467–473, 1987.
12. Bigelow, G. E., M. L. Stitzer and I. A. Liebson. Substance abuse. In: *Pharmacological and Behavioral Treatment: An Integrative Approach*, edited by M. Herson. New York: John Wiley & Sons, 1985, pp. 289–311.
13. Burling, T. A., E. G. Singleton, G. E. Bigelow, W. F. Baile and S. H. Gottlieb. Smoking following myocardial infarction: A critical review of the literature. *Health Psychol* **3:** 83–96, 1986.
14. Burling, T. A., M. L. Stitzer, G. E. Bigelow and N. W. Russ. Techniques used by smokers during contingency motivated smoking reduction. *Addict Behav* **7:** 397–401, 1982.
15. Burse, R. L., G. D. Bynum and K. B. Pandolf. Increased appetite and unchanged metabolism upon cessation of smoking with diet held constant. *Physiologist* **18:** 157, 1975.
16. Carruthers, M. Modification of the noradrenaline related effect of smoking by beta-blockade. *Psychol Med* **6:** 254–256, 1976.
17. Chait, L. D. and R. R. Griffiths. Effects of caffeine on cigarette smoking and subjective response. *Clin Pharmacol Ther* **34:** 612–622, 1983.

17a Chait, L. D. and R. R. Griffiths. Effects of methadone on human cigarette smoking and subjective ratings. *J Pharmacol Exp Ther* **229:** 636–640, 1984.

18. Chait, L. D., N. W. Russ and R. R. Griffiths. Effects of graded smoke inhalation on subsequent cigarette smoking behavior. *Addict Behav* **10:** 273–280, 1985.
19. Cherek, D. R. Effects of smoking different doses of nicotine on human aggressive behavior. *Psychopharmacology (Berlin)* **75:** 339–345, 1981.
20. Cohen, S., T. Kamarck and R. Mermelstein. A global measure of perceived stress. *J Health Soc Behav* **24:** 385–396, 1983.

21. Comstock, G. W. and R. W. Stone. Changes in body weight and subcutaneous fatness related to smoking habits. *Arch Environ Health* **24:** 271, 1972.
22. Connolly, G. N., D. M. Winn, S. S. Hecht, J. E. Henningfield, B. Walker and D. Hossman. The reemergence of smokeless tobacco. *N Engl J Med* **314:** 1020–1027, 1986.
23. Cryer, P. E., M. W. Haymond, J. V. Santiago and S. D. Shah. Norephinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *N Engl J Med* **295:** 573–577, 1976.
24. Dallosso, H. M. and W. P. T. James. The role of smoking in the regulation of energy balance. *Int J Obes* **8:** 365–375, 1984.
25. Davis, R. M. Current trends in cigarette advertising and marketing. *N Engl J Med* **316:** 725–732, 1987.
26. Dimsdale, J. and J. Moss. Plasma catecholamines in stress and exercise. *JAMA* **243:** 340–342, 1980.
27. Dimsdale, J. and J. Moss. Short-term catecholamine response to psychological stress. *Psychosom Med* **42:** 493–497, 1980.
28. Domino, E. F. Neuropsychopharmacology of nicotine and tobacco smoking. In: *Smoking Behavior: Motives and Incentives*. New York: V. H. Winston and Sons, 1973, pp. 5–31.
29. Domino, E. F. Behavioral, electrophysiological, endocrine and skeletal muscle actions of nicotine and tobacco smoking. In: *Electrophysiological Effects of Nicotine*, edited by A. Remond and C. Izard. Amsterdam: Elsevier, 1979, pp. 133–146.
30. Edwards, J. A., K. Wesnes, D. M. Warburton and A. Gale. Evidence of more rapid stimulus evaluation following cigarette smoking. *Addict Behav* **10:** 113–126, 1985.
31. Elliott, R. and T. Tighe. Breaking the cigarette habit: Effects of a technique involving threatened loss of money. *Psychol Rec* **18:** 503–513, 1968.
32. Fagerström, K. O. Effects of a nicotine-enriched cigarette on nicotine titration, daily cigarette consumption and levels of carbon monoxide, cotinine and nicotine. *Psychopharmacology (Berlin)* **77:** 164–167, 1982.
33. Fagerström, K. A comparison of psychological and pharmacological treatment in smoking cessation. *J Behav Med* **5:** 343–351, 1982.
34. Ferno, O. A substitute for tobacco smoking. *Psychopharmacologia* **31:** 201–204, 1974.
35. Finnegan, J. K., P. S. Larsson and H. B. Haag. The role of nicotine in the cigarette habit. *Science* **102:** 94–96, 1945.
36. Frith, C. D. The effect of varying the nicotine content of cigarettes on human smoking behavior. *Psychopharmacologia* **19:** 188–192, 1971.
37. Fudala, P. J. and E. T. Iwamoto. Further studies on nicotine-induced conditioned place preference in the rat. *Pharmacol Biochem Behav* **25:** 1041–1049, 1986.
38. Garrison, R. J., M. Feinleib, W. P. Castelli and P. M. McNamara. Cigarette smoking as a confounder of the relationship between relative weight and long term mortality—the Framingham Heart Study. *JAMA* **249:** 2199, 1983.
39. Garvey, A. J., R. Bosse and C. C. Seltzer. Smoking, weight change and age. *Am J Public Health* **28:** 327, 1974.
40. Gilbert, D. G. Paradoxical tranquilizing and emotion-reducing effect on nicotine. *Psychol Bull* **86:** 643–662, 1979.
41. Gilbert, A. G. and R. Wesler. Emotion, anxiety, and smoking. In: *Smoking and Human Behaviour*, edited by T. Ney and A. Gale. London: John Wiley, 1987.
42. Gilman, A. G., L. S. Goodman, T. W. Rall and F. Murad. Drug addiction and drug abuse. In: *Pharmacological Basis of Therapeutics*. New York: Macmillan, 1985, pp. 532–581.
43. Ginzel, K. H. Introduction to the effects of nicotine on the central nervous system. *Ann NY Acad Sci* **142:** 101–120, 1967.
44. Ginzel, K. H., E. Eldred, S. Watanabe and F. Grover. Drug-induced depression of gamma efferent activity—i. Peripheral reflexogenic effect of nicotine. *Neuropharmacology* **9:** 151–167, 1970.
45. Ginzel, K. H., S. Watanabe and E. Eldred. Drug-induced depression of gamma efferent activity—ii. Central action of nicotine. *Neuropharmacology* **9:** 369–379, 1970.
46. Glassman, A. H., W. K. Jackson, T. Walsh, S. P. Roose and B. Rosenfeld. Cigarette craving, smoking withdrawal, and clonidine. *Science* **226:** 864–866, 1984.
47. Goldberg, S. R., R. D. Spealman, M. E. Risner and J. E. Henningfield. Control of behavior by intravenous nicotine injections in laboratory animals. *Pharmacol Biochem Behav* **19:** 1011–1020, 1983.
48. Goldfarb, T. L., M. E. Jarvik and S. D. Glick. Cigarette nicotine content as a determinant of human smoking behavior. *Psychopharmacologia* **17:** 89–93, 1970.
49. Golding, J. and G. L. Mangan. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation. *Psychophysiology* **19:** 449–456, 1982.
50. Goodman, E. R. Effects of nicotine on distribution and release of ^{14}C-norepinephrine and ^{14}C-dopamine in rat brain striatum and hypothalamus slices. *Neuropharmacology* **13:** 1025–1032, 1974.
51. Gottlieb, N. H. The determination of smoking types: Evidence for a sociological-pharmacological continuum. *Addict Behav* **8:** 47–51, 1983.
52. Grabowski, J., M. L. Stitzer and J. E. Henningfield (Eds.). *Behavioral Intervention Techniques in Drug Abuse Treatment*, National Institute on Drug Abuse Research Monograph Series No. 46. Washington, DC: U.S. Government Printing Office, 1984.
53. Grabowski, J. G. and S. M. Hall (Eds.). *Pharmacological Adjuncts in Smoking Cessation*, National Institute on Drug Abuse Research Monograph, 53. Washington, DC: U.S. Government Printing Office, 1985.
54. Greenstein, R. A., B. D. Evans and A. T. McLellan. Predictors of favorable outcome following naltrexone treatment. *Drug Alcohol Depend* **12:** 173–180, 1983.
55. Griffiths, R. R., G. E. Bigelow and I. Liebson. Facilitation of human tobacco self-administration by ethanol: A behavioral analysis. *J Exp Anal Behav* **25:** 279–292, 1976.
56. Griffiths, R. R., G. E. Bigelow and J. E. Henningfield. Similarities in animal and human drug taking behavior. In: *Advances in Substance Abuse: Behavioral and Biological Research*, edited by N. K. Mello. Greenwich, CT: JAI Press, 1980, pp. 1–90.
57. Griffiths, R. R., J. E. Henningfield and G. E. Bigelow. Human cigarette smoking: Manipulation of number of puffs per bout, interbout interval and nicotine dose. *J Pharmacol Exp Ther* **220:** 256–265, 1981.
58. Gritz, M. E. Smoking behavior and tobacco abuse. In: *Advances in Substance Abuse: Behavioral and Biological Research*, edited by N. K. Mello. Greenwich, CT: JAI Press, 1980, pp. 91–158.
59. Gritz, E. R. and M. E. Jarvik. In: *Proceedings of the Third World Conference—Smoking and Health, Vol II, Pharmacological Aids for the Cessation of Smoking*, edited by J. Steinfeld, W. Griffiths, K. Ball and R. M. Taylor. Washington, DC: U.S. Government Printing Office, 1977.
60. Gritz, E. R., V. Baer-Weiss, N. L. Benowitz, H. Van Vunakis and M. E. Jarvik. Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. *Clin Pharmacol Ther* **30:** 201–209, 1981.
61. Grunberg, N., D. J. Bowen, V. A. Maycock and S. N. Nespor. The importance of sweet taste and caloric content in the effects of nicotine on specific food consumption. *Psychopharmacology (Berlin)* **87:** 198–203, 1985.
62. Gunn, R. C. Reactions to withdrawal symptoms and success in smoking cessation clinics. *Addict Behav* **11:** 49–53, 1986.
63. Hatsukami, D. K., J. R. Hughes and R. W. Pickens. Characterization of tobacco withdrawal: physiological and subjective effects. In: *Pharmacological Adjuncts in Smoking Cessation*, edited by J. Grabowski and S. M. Hall, National Institute on Drug Abuse Research Monograph 53. Washington, DC: U.S. Government Printing Office, 1985, pp. 56–67.
64. Hatsukami, D. K., J. R. Hughes, R. W. Pickens and D. Svikis. Tobacco withdrawal symptoms: An experimental analysis. *Psychopharmacology (Berlin)* **84:** 231–236, 1984.

65. Hatsukami, D. K., S. W. Gust and R. Keenan. Physiological and subjective changes from smokeless tobacco withdrawal. *Clin Pharmacol Ther* **41:** 103–107, 1987.
66. Henningfield, J. E. Behavioral pharmacology of cigarette smoking. In: *Advances in Behavioral Pharmacology*, edited by T. Thompson and P. B. Dews. New York: Academic Press, 1984, pp. 131–210.
67. Henningfield, J. E. Pharmacologic basis and treatment of cigarette smoking. *J Clin Psychiatry* **45:** 24–34, 1984.
68. Henningfield, J. E. and B. S. Brown. Do replacement therapies treat craving? *NIDA Notes 2* **1:** 8–9, 1987.
69. Henningfield, J. E., L. D. Chait and R. R. Griffiths. Cigarette smoking and subjective response in alcoholics: Effects of pentobarbital. *Clin Pharmacol Ther* **33:** 806–812, 1983.
70. Henningfield, J. E., L. D. Chait and R. R. Griffiths. Effects of ethanol on cigarette smoking by volunteers without histories of alcoholism. *Psychopharmacology (Berlin)* **82:** 1–5, 1984.
71. Henningfield, J. E. and S. R. Goldberg. Control of behavior by intravenous nicotine injections in human subjects. *Pharmacol Biochem Behav* **19:** 1021–1026, 1983.
72. Henningfield, J. E. and S. R. Goldberg. Stimulus properties of nicotine in animals and human volunteers: A review. In: *Behavioral Pharmacology: The Current Status*, edited by L. S. Seiden and R. L. Balster. New York: Alan R. Liss, 1984, pp. 433–450.
73. Henningfield, J. E. and R. R. Griffiths. Cigarette smoking and subjective response: Effects of *d*-amphetamine. *Clin Pharmacol Ther* **30:** 497–505, 1981.
74. Henningfield, J. E. and R. R. Griffiths. Relationship between the effects of drugs on cigarette smoking and subjective response. Presented at the Annual Meeting of the American Psychological Association, Toronto, Canada, 1984.
75. Henningfield, J. E., R. R. Griffiths and D. R. Jasinski. Human dependence on tobacco and opioids: Common factors. In: *Behavioral Pharmacology of Human Drug Dependence*, National Institute on Drug Abuse Research Monograph 37, DHHS Pub. No. ADM 81-1137. Washington, DC: U.S. Government Printing Office, 1981.
76. Henningfield, J. E. and D. R. Jasinski. Pharmacological basis for nicotine replacement. In: *Nicotine Replacement: A Critical Evaluation*, edited by O. F. Pomerleau, C. S. Pomerleau, K. O. Fagerstrom, J. E. Henningfield and J. R. Hughes. New York: Alan R. Liss, in press.
77. Henningfield, J. E., E. D. London and J. H. Jaffe. Nicotine reward: studies of abuse liability and physical dependence potential. In: *Brain Reward Systems and Abuse*, edited by J. Engel and L. Oreland. New York: Raven Press, 1987, pp. 147–164.
78. Henningfield, J. E., K. Miyasato, R. E. Johnson and D. J. Jasinski. Rapid physiologic effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. In: *Problems of Drug Dependence, 1982*. NIDA Research Monograph No. 43, edited by L. S. Harris, National Institute on Drug Abuse Research Monograph Series No. 73. Washington, DC: U.S. Government Printing Office, 1982, pp. 259–265.
79. Henningfield, J. E., K. Miyasato and D. R. Jasinski. Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav* **19:** 887–890, 1983.
80. Herxheimer, A., M. B. Lond, R. L. Griffiths, B. Hamilton and M. Wakefield. Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man. *Lancet* **2:** 754–755, 1967.
81. Heyden, S. The workingman's diet. *Nutr Metab* **20:** 381–386, 1976.
82. Hofstetter, A., Y. Schutz, E. Jequier and J. Wahren. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med* **314:** 79–82, 1984.
83. Hughes, J. R. and D. Hatsukami. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* **43:** 289–294, 1986.
84. Hughes, J. R., D. Hatsukami and K. P. Skoog. Physical dependence on nicotine gum: A placebo substitution trial. *JAMA* **255:** 3277–3279, 1986.
85. Jacobs, D. R. and S. Gottenborg. Smoking and weight: The Minnesota Lipid Research Clinic. *Am J Public Health* **71:** 391, 1981.
86. Jacobson, N. L., A. A. Jacobson and J. P. Ray. Noncombustible cigarette: Alternative method nicotine delivery. *Chest* **76:** 355–356, 1979.
87. Jaffe, J. H. and M. E. Jarvik. Tobacco use and tobacco use disorder. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. DiMascio and K. F. Killam. New York: Raven Press, 1978, pp. 1665–1676.
88. Jaffe, J. H. and M. Kanzler. Smoking as an addictive disorder. In: *Cigarette Smoking as a Dependence Process*, edited by N. A. Krasnegor, National Institute on Drug Abuse Research Monograph 23, DHEW Pub. No. ADM 79-800. Washington, DC: U.S. Government Printing Office, 1979, pp. 4–23.
89. Jaffe, J. H. and D. A. Ciraulo. Drugs used in the treatment of alcoholism. In: *The Diagnosis and Treatment of Alcoholism*, edited by J. H. Mendelson and N. K. Mello. New York: McGraw-Hill Book Co., 1984, pp. 355–389.
90. Jaffe, J. H. Drug addiction and drug abuse. In: *Goodman and Gilman's Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan, 1985, pp. 532–581.
91. Jarvik, M. E., S. D. Glick and R. K. Nakamura. Inhibition of cigarette smoking by orally administered nicotine. *Clin Pharmacol Ther* **11:** 574–576, 1970.
92. Jarvik, M. E. Further observations on nicotine as the reinforcing agent in smoking. In: *Smoking Behavior: Motives and Incentives*, edited by W. L. Dunn, Jr. Washington, DC: V. H. Winston and Sons, 1973, pp. 33–49.
93. Jarvik, M. E. Can drug treatment help smokers? In: *Proceedings of the Third World Conference—Smoking and Health*, Vol II, edited by J. Steinfeld, W. Griffiths, K. Ball and R. M. Taylor. Washington, DC: U.S. Government Printing Office, 1977, pp. 509–514.
94. Jarvik, M. E. and N. G. Schneider. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* **141:** 790–791, 1984.
95. Jarvis, M. Nasal nicotine solution: Its potential in smoking cessation and as a research tool. In: *The Pharmacologic Treatment of Tobacco Dependence: Proceedings of the World Congress*, edited by J. K. Ockene. Cambridge, MA: Harvard Institute for the Study of Smoking Behavior and Policy, 1986, pp. 167–173.
96. Jarvis, M. The treatment of cigarette dependence. *Br J Addict* **78:** 125–130, 1983.
97. Jasinski, D. R. and J. E. Henningfield. Conceptual basis of replacement therapies for chemical dependence. In: *Nicotine Replacement: A Critical Evaluation*, edited by O. F. Pomerleau, C. S. Pomerleau, K. O. Fagerstrom, J. E. Henningfield and J. R. Hughes. New York: Alan R. Liss, in press.
98. Jasinski, D. R., R. E. Johnson and J. E. Henningfield. Abuse liability assessment in human subjects. *Trends Pharmacol Sci* **5:** 196–200, 1984.
99. Jasinski, D. R., R. E. Johnson and T. R. Kocher. Clonidine in morphine withdrawal: Differential effects on signs and symptoms. *Arch Gen Psychiatry* **42:** 1063–1066, 1985.
100. Jenner, P., J. W. Gorrod and A. H. Beckett. The absorption of nicotine-1′-N-oxide and its reduction in the gastrointestinal tract in man. *Xenobiotica* **3:** 341–349, 1973.
101. Jones, R. T., T. R. Farrell and R. I. Herning. Tobacco smoking and nicotine tolerance. In: *Self-Administration of Abuse Substances: Methods for Study*, edited by N. A. Krasnegor, National Institute on Drug Abuse Research Monograph 20. Washington, DC: U.S. Government Printing Office, 1978, pp. 202–208.
102. Karras, A. and J. M. Kane. Naloxone reduces cigarette smoking. *Life Sci* **27:** 1441–1445, 1980.
103. Kittel, F., R. M. Rustin and M. Dramai. Psycho-sociobiological correlates of moderate overweight in an industrial population. *J Psychosom Res* **22:** 145–158, 1978.
104. Kozlowski, L. T. Effects of caffeine consumption on nicotine consumption. *Psychopharmacology (Berlin)* **47:** 165–168, 1976.

105. Lichtenstein, E., D. E. Harris, G. R. Birchler, J. M. Wahl and D. P. Schmahl. Comparison of rapid smoking, warm smokey air, and attention placebo in the modification of smoking behavior. *J Consult Clin Psychol* **40:** 92–98, 1973.
106. Litovitz, T. L., S. A. Normann and J. C. Veltri. Annual report of the American Association of Poison Control Centers National Data Collection System/Toxicology. *Am J Emerg Med* **4:** 427–458, 1986.
107. Lucchesi, B. R., C. R. Schuster and G. S. Emley. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. *Clin Pharmacol Ther* **8:** 789–796, 1967.
108. Malcolm, R., B. S. Currey, M. A. Mitchell and J. E. Keil. Silver acetate gum as a deterrent to smoking. *Chest* **10:** 107–111, 1986.
109. Manley, R. and F. Boland. Side-effects and weight gain following smoking cessation program. *Addict Behav* **8:** 375–380, 1983.
110. Marlatt, G. A. and J. R. Gordon. Determinants of relapse: Implications for the maintenance of behavior change. In: *Behavioral Medicine: Changing Health Life Styles*, edited by P. O. Davidsen and S. M. Davidsen. New York: Brunner Mazel, 1980.
111. Mello, N. K., J. H. Mendelson, M. L. Sellers and J. C. Kuehnle. Effects of heroin self-administration on cigarette smoking. *Psychopharmacology (Berlin)* **67:** 45–52, 1980.
111a Mello, N. K., J. H. Mendelson, M. L. Sellers and J. C. Kuehnle. Effect of alcohol and marihuana on tobacco smoking. *Clin Pharmacol Ther* **27:** 202–209, 1980.
112. Mintz, M. The Artful Dodgers. *The Washington Monthly* **October:** 9–16, 1986.
113. Mintz, J., G. Boyd, J. E. Rose, V. C. Charuvastra and M. E. Jarvik. Alcohol increases cigarette smoking: A laboratory demonstration. *Addict Behav* **10:** 203–207, 1985.
114. Murray, A. L., P. Lawrence and L. Scott. Sequelae to smoking cessation: A review. *Clin Psychol Rev* **14:** 143–157, 1984.
115. Nemeth-Coslett, R. and J. E. Henningfield. Effects of nicotine chewing gum on cigarette smoking and subjective physiologic effects. *Clin Pharmacol Ther* **39:** 625–630, 1986.
116. Nemeth-Coslett, R., J. E. Henningfield, M. K. O'Keeffe and R. R. Griffiths. Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. *Psychopharmacology (Berlin)*, in press, 1987.
117. Nemeth-Coslett, R., J. E. Henningfield, M. K. O'Keefe and R. R. Griffiths. Effects of mecamylamine on human cigarette smoking and subjective ratings. *Psychopharmacology (Berlin)* **88:** 420–425, 1986.
118. Nemeth-Coslett, R., J. E. Henningfield, M. K. O'Keefe and R. R. Griffiths. Effects of marijuana on human cigarette smoking and physiologic changes and subjective responses. *Pharmacol Biochem Behav* **25:** 659–665, 1986.
119. Nemeth-Coslett, R. and R. R. Griffiths. Naxolone does not affect cigarette smoking. *Psychopharmacology (Berlin)* **89:** 216–264, 1986.
120. Newsom, J. A. and R. B. Seymour. Benzodiazepines and the treatment of alcohol abuse. *J Psychoactive Drugs* **15:** 97–98, 1983.
121. Nil, R., R. Buzzi and K. Battig. Effects of single doses of alcohol and caffeine on cigarette smoke puffing behavior. *Pharmacol Biochem Behav* **20:** 583–590, 1984.
122. Ockene, J. K., R. C. Benfari, R. L. Nuttall, I. Hurwitz and I. S. Okene. Relationship of psychosocial factors to smoking behavior change in an intervention program. *Prev Med* **11:** 13–28, 1982.
123. Ockene, J. K. *The Pharmacologic Treatment of Tobacco Dependence: Proceedings of the World Congress*. Cambridge, MA: Harvard Institute for the Study of Smoking Behavior and Policy, 1986.
124. Orleans, C. T. Understanding and promoting smoking cessation: Overview and guidelines for physician intervention. *Annu Rev Med* **36:** 51–61, 1985.
125. Ossip, D. J. and L. H. Epstein. Relative effects of nicotine and coffee on cigarette smoking. *Addict Behav* **6:** 35–39, 1981.
126. Oster, G., D. M. Huse, T. E. Delea and G. A. Colditz. Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. *JAMA* **256:** 1315–1318, 1986.
127. Perkins, K. A., L. H. Epstein, R. Stiller, J. R. Jennings, C. Christiansen and T. McCarthy. An aerosol spray alternative to cigarette smoking in the study of the behavioral and physiological effects of nicotine. *Behav Res Methods* **18:** 420–426, 1986.
128. Poling, A. and T. Thompson. Attenuation of ethanol intake by contingent punishment of food-maintained responding. *Pharmacol Biochem Behav* **7:** 393–399, 1977.
129. Poling, A. and T. Thompson. Suppression of ethanol-reinforced lever pressing by delaying food availability. *J Exp Anal Behav* **28:** 271–283, 1977.
130. Poling, A. and T. Thompson. Effects of delaying food availability contingent on ethanol-maintained lever pressing. *Psychopharmacology (Berlin)* **51:** 289–291, 1977.
131. Pollin, W. The role of the addictive process as a key step in causation of all tobacco-related diseases. *JAMA* **252:** 20, 1984.
132. Pomerleau, O., D. Adkins and M. Pertschuk. Predictors of outcome and recidivism in smoking cessation treatment. *Addict Behav* **3:** 65–70, 1978.
133. Pomerleau, O. F. and C. S. Pomerleau. Neuroregulators and the reinforcement of smoking: Towards a biobehavioral explanation. *Neurosci Biobehav Rev* **8:** 503–513, 1984.
134. Pomerleau, C. S., O. F. Pomerleau and M. J. Majchrzak. Mecamylamine pretreatment increases subsequent nicotine self-administration as indicated by changes in plasma nicotine level. *Psychopharmacology (Berlin)* **9:** 391–393, 1987.
135. Rabkin, S. Relationships between weight change and the reduction or cessation of cigarette smoking. *Int J Obes* **8:** 665–673, 1984.
136. Rall, T. W. Central nervous system stimulants: the methylxanthines. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and R. Murad. New York: MacMillan Publishing Company, 1985, pp. 589–603.
137. Ravenholt, R. T. Addiction mortality in the United States, 1980: Tobacco, alcohol, and other substances. *Popul Dev Rev* **10:** 697–724, 1984.
138. Rose, J. E. and C. S. Hickman. Citric acid aerosol as a potential smoking cessation aid. *Chest* **92:** 1005–1008, 1987.
139. Rose, J. E., S. Ananda and M. E. Jarvik. Cigarette smoking during anxiety-provoking and monotonous tasks. *Addict Behav* **8:** 353–359, 1983.
140. Rose, J. E., J. E. Herskovic, Y. Trilling and M. E. Jarvik. Transdermal nicotine reduces cigarette craving and nicotine preference. *Clin Pharmacol Ther* **38:** 450–456, 1986.
141. Rose, J. E., M. E. Jarvik and K. D. Rose. Transdermal administration of nicotine. *Drug Alcohol Depend* **13:** 209–213, 1984.
142. Rose, J. E., A. Sampson and J. E. Henningfield. Blockade of smoking satisfaction with mecamylamine. Paper presented to the American Psychological Association, Los Angeles, CA, August 26, 1985.
143. Rosecrans, J. A. and W. T. Chance. Cholinergic and noncholinergic aspects of the discriminative stimulus properties of nicotine. In: *Discriminative Stimulus Properties of Drugs*, edited by H. Lal. New York: Plenum Publishing, 1977, pp. 155–185.
144. Rosecrans, J. A. and L. T. Meltzer. Central sites and mechanisms of action of nicotine. *Neurosci Biobehav Rev* **5:** 497–501, 1981.
145. Russell, M. A. H. Cigarette smoking: natural history of a dependence disorder. *Br J Med Psychol* **44:** 1–6, 1971.
146. Russell, M. A. H. Tobacco smoking and nicotine dependence. In: *Research Advances in Alcohol and Drug Problems*, edited by R. J. Gibbons, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: Wiley, 1976, pp. 1–46.

147. Russell, M. A. H. Tobacco dependence: Is nicotine rewarding or aversive? In: *Cigarette Smoking as a Dependence Process*, NIDA Research Monograph No. 23, edited by N. Krasnegor. Washington, DC: U.S. Government Printing Office, 1979, pp. 100–122.
148. Russell, M. A. H., M. J. Jarvis, G. Devitt and C. A. Feyerabend. Nicotine intake by snuff users. *Br Med J* **283:** 814–817, 1981.
149. Russell, M. A. H., M. J. Jarvis, G. Sunderland and C. Feyerabend. Nicotine replacement in smoking cessation: Absorption of nicotine vapor from smoke-free cigarettes. *JAMA* **257:** 3262–3265, 1987.
150. Russell, M. A. H., R. Merriman, J. Stapleton and W. Taylor. Effect of nicotine chewing gum as an adjunct to general practitioner's advice against smoking. *Br Med J* **10:** 1782–1785, 1983.
151. Russell, M. A. H., C. Wilson, C. Feyerabend and P. V. Cole. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. *Br Med J* **2:** 391–393, 1976.
152. Sachs, D. P. L. Cigarette smoking health effects and cessation strategies. *Clin Geriatr Med* **2:** 337–362, 1986.
153. Schachter, S. Regulation, withdrawal, and nicotine addiction. In: *Cigarette Smoking as a Dependence Process*, NIDA Monograph No. 23, edited by N. A. Krasnegor. Rockville, MD: National Institute of Drug Abuse, 1979, pp. 123–133.
154. Schievelbein, H. Nicotine, resorption and fate. In: *Nicotine and the Tobacco Smoking Habit*, edited by D. J. K. Balfour. Oxford, England: Pergamon Press, 1984, pp. 1–15.
155. Schildkraut, J. J. and S. S. Kety. Biogenic amines and emotion. *Science* **156:** 21–30, 1967.
156. Schneider, N. G., M. E. Jarvik and A. B. Forsythe. Nicotine gum in smoking cessation: A placebo-controlled, double-blind trial. *Addict Behav* **8:** 253–261, 1983.
157. Schneider, N. G. and M. E. Jarvik. Time course of smoking withdrawal symptoms as a function of nicotine replacement. *Psychopharmacology (Berlin)* **82:** 143–144, 1984.
158. Schneider, N. G. and M. E. Jarvik. Nicotine vs. placebo gum: comparisons of withdrawal symptoms and success rates. In: *Pharmacological Treatments in Smoking Cessation*, NIDA Monograph No. 53, edited by J. Grabowski and S. Hall. Washington, DC: Department of Health and Human Services, 1985, pp. 83–101.
159. Schwartz, J. L. Critical review and evaluation of smoking control methods. *Public Health Rep* **84:** 483–506, 1969.
160. Schwartz, J. L. *Review and Evaluation of Smoking Cessation Methods: The United States and Canada, 1978–1985*, NIH Publication No. 87-2940. Washington, DC: U.S. Government Printing Office, 1987.
161. Sellers, E. M., C. A. Naranjo, M. Harrison, P. Devenyi, C. Roach and K. Sykora. Diazepam loading: Simplified treatment of alcohol withdrawal. *Clin Pharmacol Ther* **34:** 822–826, 1983.
162. Sepkovic, D. W., S. G. Colosimo, C. M. Axelrad, J. D. Adams and N. J. Haley. The delivery and uptake of nicotine from an aerosol rod. *Am J Public Health* **76:** 1343–1344, 1986.
163. Shiffman, S. Relapse following smoking cessation: A situational analysis. *J Consult Clin Psychol* **50:** 71–86, 1982.
164. Shumaker, S. A. and N. E. Grunberg (Eds.). Proceedings of the National Working Conference of Smoking Relapse. *Health Psychol* **5:** Suppl, 1–99, 1986.
165. Stamford, B. A., S. Matter, R. D. Fell and P. Papanek. Effects of smoking cessation on weight gain, metabolic rate, caloric consumption, and blood lipids. *Am J Clin Nutr* **43:** 486–494, 1986.
166. Stitzer, M., J. Morrison and E. F. Domino. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists. *J Pharmacol Exp Ther* **171:** 166–177, 1970.
167. Stitzer, M. L. and J. Gross. Smoking relapse: The role of pharmacological and behavioral dependence. In: *Nicotine Replacement in the Treatment of Smoking: A Critical Evaluation*, edited by O. F. Pomerleau and C. S. Pomerleau. New York: Alan R. Liss, Inc., 1987, pp. 163–184.
168. Stolerman, I. P. Could nicotine antagonists be used in smoking cessation? *Br J Addict* **81:** 47–53, 1986.
169. Stolerman, I. P. Characterization of central nicotinic receptors by studies on the nicotine cue and conditioned taste aversion in rats. *Pharmacol Biochem Behav* **30:** 235–242, 1988.
170. Stolerman, I. P., T. Goldfarb, R. Fink and M. E. Jarvik. Influencing cigarette smoking with nicotine antagonists. *Psychopharmacologia* **28:** 237–259, 1973.
171. Taylor, P. Ganglionic stimulating and blocking agents. In: *The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan, 1985, pp. 215–221.
172. Tennant, F. S., A. L. Tarver and R. A. Rawson. Clinical evaluation of mecamylamine for withdrawal from nicotine dependence. In: *Problems of Drug Dependence, 1983*, edited by L. S. Harris, National Institute on Drug Abuse Research Monograph Series No. 49. Washington, DC: U.S. Government Printing Office, 1984, pp. 239–246.
173. U.S. Department of Agriculture. *Tobacco Outlook and Situation Report*, 1984.
174. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer*, A report of the Surgeon General, DHHS (PHS) Publication No. 82-50179. Washington, DC: U.S. Government Printing Office, 1982.
175. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease*, A report of the Surgeon General, Publication No. DHHS (PHS) 84-50205. Washington, DC: U.S. Government Printing Office, 1984.
176. U.S. Department of Health and Human Services. Nicotine exposure: Pharmacokinetics, addiction and other physiologic effects. In: *The Health Consequences of Using Smokeless Tobacco. A Report of the Advisory Committee to the Surgeon General*, NIH Publication No. 86-2874. Washington, DC: U.S. Government Printing Office, 1986, pp. 137–186.
177. U.S. Department of Health and Human Services Smoking. *Tobacco and Health*, Public Health, Publication No. DHHS (CDC) 87-8397. Washington, DC: U.S. Government Printing Office, 1987.
178. U.S. Public Health Service. *Why People Smoke Cigarettes* (pamphlet), PHS Publication No. (PHS) 83-50195. Washington, DC: U.S. Government Printing Office, 1983.
179. Wakefield, J. (Ed.). U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute. *Adult Use of Tobacco*, 1975.
180. Weideking, C., R. Lake and M. Niegler. Plasma noradrenaline and dopamine-beta-hydroxylase during sexual activity. *Psychosom Med* **39:** 143–148, 1977.
181. Weiss, J. M., E. A. Stone and N. Harrell. Coping behavior and brain norepinephrine level in rats. *J Comp Physiol Psychol* **72:** 153–160, 1979.
182. Wesnes, K. and D. M. Warburton. The effects of cigarette smoking and nicotine tablets upon human attention. In: *Smoking Behaviour: Physiological and Psychological Influences*, edited by R. E. Thornton. London: Churchill-Livingston, 1978, pp. 131–147.
183. Wesnes, K. and D. M. Warburton. Smoking, nicotine and human performance. In: *Nicotine and the Tobacco Smoking Habit*, edited by D. J. K. Balfour. Oxford, England: Pergamon Press, 1984, pp. 133–151.
184. West, R. R. and D. A. Evans. Lifestyle changes in long term survivors of acute myocardial infarction. *J Epidemiol Community Health* **40:** 103–109, 1986.
185. Westfall, T. C. Effect of nicotine and other drugs on the release of ^{3}H-norepinephrine and ^{3}H-dopamine from rat brain slices. *Neuropharmacology* **13:** 693–700, 1974.
186. Wilbert, J. *Tobacco and Shamanism in South America*. New Haven, CT: Yale University Press, 1987.
187. Winternitz, W. W. and D. Quillen. Acute hormonal response to cigarette smoking. *J Clin Pharmacol* **17:** 389–397, 1977.