Rational Basis for Chemotherapy
of Tobacco Dependence

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The forms of tobacco use are many, and it is likely that their number is matched by equally varied controlling variables. All the usual forms of tobacco use, however, share at least one commonality: nicotine is extracted from the tobacco and ingested in a manner that permits its distribution to the central nervous system. The tobacco cigarette is the prevalent means of nicotine self-administration in Western society, and cigarette smoking is the primary form of tobacco use addressed by legislative, research, and treatment efforts.

In 1983, the United States Public Health Service categorized cigarette smoking as a form of drug dependence in which nicotine was held to be the critical substance (USPHS 1983). Consistent with the drug dependence model of cigarette smoking, in 1984 a pharmacotherapeutic aid (nicotine gum) for the treatment of tobacco dependence was approved by the Food and Drug Administration. This paper will briefly review nicotine dependence and its implications for the use of chemotherapy in the treatment of tobacco dependence with respect to cigarette smoking.

TOBACCO DEPENDENCE: A DECEPTIVELY COMPLEX PHENOMENON

At first brush, tobacco dependence would seem readily amenable to study. In the form of cigarette smoking, the behavior is public, practiced by many, and appears to involve a simple act with a simple product. However, cigarette smoking has resisted many attempts at quantitative study, and studies have yielded data which often appears contradictory at the most elemental levels. For instance, the role of dose in the control of cigarette smoking has remained unclear despite decades of study. Since dose-response relations are arguably the most critical quantitative relations to be assessed in pharmacologic studies, the absence of consensual agreement as to the nature of dose-response relations has undoubtedly hindered the understanding and treatment of cigarette smoking.

There are specific reasons for some of the ambiguity concerning the role of dose in cigarette smoking. Table 1 provides a partial list of factors which obscure quantitation of dose-response functions.
These factors and others have been more thoroughly discussed elsewhere (cf. Benowitz, 1983; Henningfield, 1983, 1984; Koziowski, Rickert, Robinson and Grunberg, 1980). In brief, compared to most other forms of drug self-administration, cigarette smoking involves a wider variety of confounding factors. In alcohol studies, for instance, ounces of ethanol ingested can be specified with great reliability, and resulting blood ethanol levels are related in some orderly fashion to these values. Similarly, in studies of sedatives, stimulants and opioids, the number of milligrams of actual drug which is swallowed or injected may be readily specified. In the case of cigarette smoking there is often disagreement as to which parameter to specify and the means of specification. One consequence of these difficulties was to delay the positive classification of cigarette smoking as a form of drug dependence. The next two sections will provide the evidence for this classification.

### TABLE 1. Obstacles to the quantitation of dose-response functions in studies of cigarette smoking.

- Many reports do not include any quantitative measure of dose.
- Multiple dose parameters (e.g., nicotine, tar and CO) are frequently confounded.
- Substances of possible functional significance (e.g., tar, CO, CO2) are especially difficult to specify since they are not even present in an unlit cigarette.
- Federal Trade Commission dose level estimates are not necessarily related to either cigarette content or yield by the smoker.
- The behavior of cigarette smoking varies across smokers and even across puffs within a single cigarette.
- A variety of factors may affect absorption of smoke constituents (e.g., smoke pH, inhalation depth).

### COMMONALITIES AMONG CIGARETTE SMOKING AND DRUG ABUSE

For centuries, a variety of parallels have been drawn between tobacco use and the use of opiates, alcohol and other substances. It seemed obvious to many observers of social behavior and physiologic effect that these substances were different from other substances of ingestion, such as food. Indeed, the American Indians knew that as other vegetables were "food for the stomach," "tobacco provided food for the spirit." Beyond these general observations, a variety of points common to cigarette smoking and classically studied forms of drug dependence (e.g., narcotic addiction and alcoholism) have been identified. The various commonalities have been described in greater detail elsewhere (Henningfield, Griffiths and Jasinski; 1981; Jaffe and Kanzler, 1979) and are summarized in Table 2.
TABLE 2. Common factors in tobacco use and drug dependence.

- Spread is socially mediated and is persistent.
- Patterns of relapse are similar following treatment.
- Use persists in face of damage (individual & social).
- Personality types overlap.
- Centrally (CNS) acting substance (drug) is delivered.
- The drug is a reinforcer for animals.
- Deprivation increases drug seeking behavior.
- Tolerance develops with repeated use.
- "Therapeutic effects" may be produced.
- Patterns of self-administration and dose-response functions are orderly.

These commonalities among various forms of drug dependence and tobacco use provide a rational basis for the theory that tobacco use may occur as a form of drug dependence. In brief, tobacco use, particularly in the form of cigarette smoking, is an orderly behavior that is lawfully controlled by the same behavioral and pharmacologic variables as are more commonly studied forms of drug dependence. The commonalities also suggest that treatment strategies which have proven effective in drug dependence may be applied to the treatment of cigarette smokers.

NICOTINE AS A DEPENDENCE-PRODUCING DRUG

While any substance may, under some conditions, be compulsively used, substances characterized by a certain constellation of features are likely to be compulsively used and abused under a much broader range of conditions, including those which lead to damage. In brief, the compound must be psychoactive (produce centrally mediated effects on mood and feeling states), must have euphoriant qualities similar to those of reference drugs (e.g., morphine, amphetamine, ethanol), and must serve as a biologic reinforcer (be voluntarily self-administered). Other qualities such as the ability to produce tolerance and physiologic dependence are interesting and may be of functional significance but are neither necessary nor sufficient determinants of drug dependence.

Two lines of study involving human subjects were undertaken by the Addiction Research Center of the National Institute on Drug Abuse. The first involved pharmacodynamic analyses which assessed the psychoactivity of nicotine and its possible qualities as a euphoriant. A variety of parameters were assessed when nicotine was given in the form of tobacco smoke and intravenous injections. The second line of study assessed the reinforcing properties of intravenous nicotine in cigarette smokers. The intravenous studies were critical in determining whether nicotine, in the absence of the usual confluence of stimuli involving the cigarettes themselves
Psychoactivity and Euphoriant Properties of Nicotine

The initial study showed that nicotine was psychoactive and produced orderly effects on measures of psychoactivity (Henningfield et al. 1985). Following either smoke inhalation or i.v. administration, nicotine was discriminated from placebo, and dose strength estimates were directly related to nicotine dose. These self-reported effects peaked within about 1 minute and dissipated within 3 to 5 minutes. Certain physiologic responses were also dose-related and showed similar temporal patterns of onset and offset: heart rate, pupil diameter, electroencephalographic response (Lukas and Henningfield 1983). A subsequent study showed that the ganglionic blocker, mecamylamine, attenuated physiologic and self-reported effects of nicotine (Henningfield et al. 1983). Variability of response on self-report measures was lower when nicotine was given intravenously than when it was given in the form of tobacco smoke, suggesting that the stimuli provided by cigarette smoking confound discrimination of the effects of nicotine.

Euphoria is objectively defined by the observation that administration of the drug, under controlled experimental conditions, produces dose-related increases in scores on the Liking scale of the Single-Dose Questionnaire, and scores on the Morphine Benzedrine Group (MBG or Euphoria) scale of the Addiction Research Center Inventory (ARCI) (Jasinski et al. 1984). In this study, nicotine, like drugs known to be abused, produced significant dose-related increases in scores on both the Liking and MBG scales (Henningfield and Jasinski 1982; Jasinski et al. 1984). Additionally, intravenous injections of nicotine were most commonly identified as a prototypic euphoriant drug (cocaine) by subjects with extensive drug abuse histories.

These studies confirmed that nicotine produced critical functional effects of tobacco smoke and that nicotine is a psychoactive drug with properties of an euphoriant. These findings are consistent with those obtained in animal drug discrimination studies in which it has been shown that nicotine is readily discriminated and that its discriminative properties are more stimulant-like than depressant-like (cf. review by Henningfield and Goldberg 1984).

Reinforcing Properties of Intravenous Nicotine

The ultimate test of whether nicotine is a dependence-producing drug is, in the abstract, a very simple test: namely, to determine if nicotine injections serve as positive reinforcers and thereby strengthen behavior leading to their administration. Practically, however, there are many difficulties in the safe and ethical conduct of such a study, and the initial study was only completed about 2 years ago (Henningfield et al. 1983). The critical finding of this study was that intravenously available nicotine was self-administered by each of the subjects tested. Furthermore,
patterns of self-administration were similar to those of humans smoking cigarettes or of animals self-injecting cocaine in analogous experimental preparations (Griffiths et al. 1980).

When saline was substituted for nicotine, patterns of injection were irregular and total number of injections generally was lower. In a subject who stated that he disliked taking injections of any kind, the pattern of acquisition was similar to that of animals which are given access to intravenous nicotine for the first time (see Goldberg et al. 1982): Number of injections gradually increased across sessions; then, when saline was substituted for nicotine, the number of injections rapidly declined across sessions. Subsequent studies showed that nicotine was preferred to saline when both substances were concurrently available (Henningfield and Goldberg 1983a); that mecamylamine pretreatment attenuated the nicotine preference (Henningfield 1983); and that the lever was pressed as many as 1600 times per nicotine injection (study in progress).

The human self-administration study findings are consistent with animal studies in which nicotine has been shown to serve as a positive reinforcer in a variety of species including primates and nonprimates, and under a variety of experimental conditions (cf. review by Henningfield and Goldberg 1983b). It is noteworthy that establishment of nicotine as a reinforcer in animals eluded many investigators until effective confluences of parameters were discovered. Such initial difficulty was not unique to nicotine but also characterized initial efforts to determine whether or not ethanol would serve as a reinforcer in animals (Melsch 1977).

**Cigarette Smoking as a Form of Drug Dependence: Summary and Implications for Nicotine-Based Chemotherapy**

Nicotine is a prototypic drug of abuse, and many cigarette smokers are likely to be dependent. Strong, albeit circumstantial, evidence was provided by observations of the many critical commonalities between cigarette smoking and more commonly studied forms of drug dependence. Direct evidence was that the drug itself (nicotine, in isolation from tobacco smoke) was characterized by a profile of pharmacologic effects typical of that of known drugs of abuse such as opiates, stimulants, and alcohol. These data indicate that the role of nicotine in cigarette smoking is similar to the role of other constituent drugs of abused substances. That is, despite the apparently lower biologic reinforcing efficacy of nicotine than some of the more commonly studied drugs of abuse (Henningfield and Goldberg 1983b), the functional role of nicotine in tobacco smoke is similar to the role of cocaine in coca leaf use, to the role of morphine in opium poppy use, to the role of tetrahydrocannabinol (THC) in marijuana use, and to the role of ethanol in alcoholic beverage consumption.

The perspective that cigarette smoking often occurs as a form of drug dependence has specific implications for chemotherapeutic treatment strategies. A variety of nonspecific chemotherapeutic approaches to the treatment of cigarette smokers has been
reported. Most provide little documented efficacy; they have been reviewed elsewhere (Grabowski and Hall, this volume; Gritz and Jarvik 1977; Jarvik 1977).

One specific chemotherapeutic approach for drug dependence is to substitute a safer and more manageable form of the drug for the substance of abuse. The ultimate goal of such an approach is subsequently to withdraw the patient from the substituted drug. The currently available substitution pharmaceutical is the nicotine resin complex or nicotine chewing gum (American Hospital Formulary Service 1984). Use of nicotine gum in treatment of cigarette smoking is the subject of other chapters in this monograph and will not be discussed in detail here. Rather, a few observations will be made, following directly from the above-presented data, which show that cigarette smoking is a form of drug dependence. In addition, some preliminary data which bear on these observations will be presented.

Effective chemotherapy of other kinds of drug dependence is complex and involves systematic application of a variety of pharmacologic and behavioral strategies (cf. Grabowski et al. 1983). A major pharmacologic factor concerns the dose level of the chemotherapeutic drug. Table 3 summarizes a few of these dose-related issues.

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<th>Dose-related issues in chemotherapy of drug dependence</th>
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<td>o Dose must be sufficient to provide relief of withdrawal or deprivation effects.</td>
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<td>o The rate of drug entry to the CNS is critical and may determine whether the particular route of administration used provides an acceptable substitute.</td>
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<tr>
<td>o Patient compliance in taking the therapeutic agent may vary as a function of dose.</td>
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<tr>
<td>o The degree to which nontherapeutic drug taking is suppressed may vary as a function of dose.</td>
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The importance of control over dose suggested the need for further study of such relations regarding the nicotine-delivering chewing gum. Two issues were of interest. The first was the possible functional effects of the rate at which individual pieces of gum were chewed. Since the nicotine in the gum is bound to an ion-exchange resin, chewing is required for its release; thus, rate of chewing should be one determinant of the rate at which nicotine is extracted from the gum. Results from a preliminary study of the effects of chewing rate are described below. The second issue concerned the fact that only one dose level of the gum is commercially available. In preliminary studies we found that rates of voluntary smoking were not affected by scheduled administration of either placebo or 2 mg gum but were suppressed when subjects were given 4 mg gum (Jasinski et al. 1984; Nemeth-Coslett and Henningfield 1985). Furthermore, in a subpopulation of
heavy-smoking male polydrug abusers, little subjective or physiologic response was observed following administration of either 2 mg or 4 mg gum. This observation suggested that, as is the case with other therapeutic drugs, there is a wide range of individual variability in response to a given dose, and that doses which are not tolerated by some patients may be safe and even necessary for others. Results from a preliminary study are also presented below in which such subjects were given either two or four pieces of 4 mg gum to chew.

PRELIMINARY STUDY: EFFECTS OF CHEWING RATE RESPONSE TO NICOTINE GUM

Four male subjects (average age = 34 years, range = 20-50) participated while residing on a pharmacology research ward. Their average weight was 75 kg (range = 67-100 kg), and they smoked an average of 30 cigarettes per day (range 20 to 40 cigarettes, each delivering 1.1 mg nicotine). Mean scores on the Fagerstrom Tolerance Questionaire (Fagerstrom 1978) were 10.0 (range = 9-11). During predesignated days, each subject was cigarette deprived for 8 hours, after which time a 1-hour test session was begun. Physiologic and self-report measures were collected during the initial 10 minutes of the test session. Subjects were then provided with one 4 mg piece of nicotine gum (Nicorette) which they were instructed to chew at a fixed rate for the next 10 minutes. Rates were set at one chew every 1, 2, 4, or 8 seconds, and compliance was assured by a nurse who observed that the subject was chewing in response to a timed "beep" which had been pretaped on a recorder. Each subject was exposed to the four different chew rates using a 4 x 4 Latin Square design. Most physiologic and self-reported responses were measured at 5-minute intervals. Visual line analog scores of positive ("pleasurable") and negative ("unpleasurable") were collected at 15-second intervals for the first 240 seconds after gum chewing and then at 5-minute intervals for the remainder of the test session. Additionally, measures of expired air carbon monoxide level were collected immediately before and after each session.

Preliminary analysis of the data suggests that chewing rate altered magnitude and duration of self-reported effects of the gum. Figure 1 shows the total visual line analog score (sum of negative and positive responses) at each observation for subject CO. Variability across subjects was considerable, however, and precluded meaningful lumping together of the data. No chewing rate produced significant increases on scales of the Addiction Research Center Inventory or the Single-Dose Questionnaire (Jasinski et al. 1984).
MINUTES POST-GUM

This study suggests that chewing rate does make a difference in the response to gum-delivered nicotine. It also raises several additional issues, some of which are being addressed in an ongoing study in which the amount of nicotine extracted from the gum and nicotine plasma levels will be assessed. An immediate implication is that the same kinds of difficulties in quantification of dose-response relations which occur when subjects are given cigarettes to smoke under uncontrolled conditions may arise when subjects are given gum to chew with no specification of the rate at which it is to be chewed.

PRELIMINARY STUDY: HIGH DOSES OF NICOTINE GUM

This study assessed the safety and effects of nicotine in subjects who were known to be relatively insensitive to 2 mg gum. The average age of the subjects was 33 years (range = 23-53). and they had smoked an average of 13 years (range = 9-17). Their mean score on the Fagerstrom Tolerance Questionnaire was 9.7 (range = 8-11). Subjects chewed either two or four pieces of 4 mg gum (total nicotine dose either 8 mg or 16 mg). Each piece of gum was chewed at a rate of 1 chew every 2 seconds for 10 minutes. Two subjects were tested at each of the dose levels twice a day for 2 days while two other subjects received one dose a day for 2 days. Immediately following gum chewing, subjects were asked to report verbally any side effects, their liking for the gum, and to rate the strength of the gum. Additionally, a staff nurse was required to record any observable signs or symptoms displayed by the subject.
The most common signs reported by the staff nurse were belching and hiccups, which showed a slight increase following exposure to 16 mg when compared to 8 mg. Other signs included restlessness, watery eyes, and irritability. However, for the six observations collected at each of the two doses, no observable effect was noted on four of the occasions following 8 mg chewing, and no effect was noted on two occasions following 16 mg chewing.

Subjects reported nausea and throat irritation more than any other symptoms. One subject reported no effect at either the 8 mg or 16 mg dose. Other complaints included nervousness, dizziness, headache, and heartburn. There was little increase at the 16 mg dose when compared to the 8 mg dose. Two subjects reported a dose-related increase in magnitude of effects between 8 mg and 16 mg, and three of the four subjects said that they would not voluntarily chew four pieces again but would chew two pieces. Two of these three subjects reported effects similar to those produced when marijuana was smoked ("high") at both doses and reported liking the feeling. The fourth subject reported no effects at either dose and identified the drug as placebo ("blank").

This study showed that high doses of nicotine-delivering chewing gum can be safely given. It is not clear what specific subject characteristics determine the tolerable dose level. For example, both body weight and level of nicotine intake would be factors of suspected importance. It is also remains to be determined whether high doses are of greater therapeutic efficacy for this population of cigarette smokers. The high doses produced some effects characteristic of those produced by drugs of abuse ("high"), but did not elevate scores on objective scales used to quantitate abuse liability.

DISCUSSION

A variety of theoretical, social, and treatment implications result from the identification of cigarette smoking as a form of drug dependence which is functionally similar to other forms of drug dependence. One implication related to nicotine-based chemotherapy is the role of dose, whether altered by chewing rate or by amount of nicotine-containing gum that is chewed. The results of the preliminary studies which were described raised more questions than they answered. However, some tentative conclusions may be drawn. First, rate of chewing may have functional consequences with regard to the effects produced by the gum. Second, subjects can tolerate higher chew rates and gum dosage levels than are typically employed in current treatment approaches (e.g., Hughes and Miller 1984).

The observation that manipulations which affect the effective dose of a chemotherapeutic agent may have functional consequences is not surprising. Dose is a critical factor in other kinds of chemotherapy, and studies with nicotine in human and animal subjects show that nicotine's effects are dose related. Additionally, clinical observations (e.g., one patient's description of how he used the nicotine gum: "I chew quick till I get the taste, then I"
taper off") suggest that some patients have discovered on their own that chewing rate makes a difference in the effects of the gum. What is surprising is the lack of attention paid to dose in many studies of the behavioral pharmacology of the gum and of its treatment efficacy.

The finding that cigarette smoking may occur as a form of drug dependence offers exciting possibilities, burdens, and hope: Possibilities of applying chemotherapeutic treatment strategies to the treatment of cigarette smoking; the burdens of closely examining existing cigarette treatment programs and applying fundamental principles from drug dependence and alcoholism programs; and hope that these efforts will improve on the past rather dismal treatment programs. As shown by Hall and Killen elsewhere in this monograph, treatment approaches which apply both behavioral and pharmacologic treatment strategies are more effective that those which address only the pharmacologic or the behavioral aspects of tobacco dependence.

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