PARAMETERS OF NICOTINE TITRATION IN ADDICTED AND NON-ADDICTED CIGARETTE SMOKERS

by

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(ABSTRACT)

Nicotine titration was studied in cigarette smokers not interested in cutting down or quitting smoking. Forty smokers were classified as high nicotine dependent (n=20) and low nicotine dependent (n=20) using a validated tolerance questionnaire. Subjects were randomized into baseline (n=10) or nicotine fade conditions (n=10) within their dependency group. Subjects in the baseline conditions smoked their preferred brand of cigarette throughout the experiment. Smokers in the fade conditions switched to a reduced nicotine brand in the latter half of the procedure.

Multiple in vivo and in vitro measures of smoking rate and topography were collected over a four day period. Based on analyses of these data, it was concluded that no compensatory changes in smoking behavior occured that were clearly attributable to nicotine titration. It was found that smokers classified as high nicotine dependent smoked more intensively that low dependent smokers.

The implications of these findings given the design and experimental controls employed in this experiment are discussed, and directions for future research explored.

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Overview

Statement of the Problem

The health consequences of cigarette smoking have been well established and documented after years of research (USPHS, 1979; 1981). Smoking has been shown to be related to increased risks of chronic conditions such as bronchitis, emphysema and arteriosclerotic cardiovascular disease and increased risk of mortality due to coronary artery disease, lung and other cancers and obstructive lung disease (USPHS, 1979, 1982, 1983, 1984).

In the United States, it has been recently estimated that 170,000 coronary heart disease, 125,000 cancer and 62,000 obstructive lung disease death occur annually as a function of smoking (Fielding, 1985). Recent data from the well known Framingham study (Kannel, McGee & Castelli, 1984) indicate that for middle-aged Americans smoking: (a) doubles the risk of myocardial infarction and occlusive peripheral vascular diseases, (b) doubles the risk of premature stroke in men, (c) doubles the risk of heart failure in women, and (d) increases risk of sudden cardiac death by a factor of 5 in women and a factor of 10 in men. Data from recent hypertension treatment trials in Great Britain show a frequency of coronary events 5 times greater in smokers than

in non-smokers. Further, rates of stroke were about double in smokers compared to non-smokers (Cruickshank, 1985).

Cigarette smoking appears to interact with hypertension compounding the cardiovascular risk of each factor (Castelli, 1984). Smoking and hypertension also interact to increase the risk of malignant hypertension (Tuomilelto, Elo & Nissinen, 1982). Smoking appears to interact in a synergistic fashion with elevated serum cholesterol levels, a third major cardiovascular risk factor (Perkins, 1985).

Data from British hypertension trials indicate that smoking may cancel beneficial effects of beta-adrenergic blocking agents (MRC, 1985). In this recently reported Medical Research Council trial in mild hypertension the difference in cardiovascular event rate between smokers and non-smokers was greater than the effect of antihypertensive drug treatment (MRC, 1985). Finally, Kannel and collegues (Kannel, McGee & Castelli, 1984) have concluded that the benefits of quitting smoking are on par with beneficial effects of cardiovascular drugs and cardiac surgery.

Response to the Problem

A multitude of strategies have been developed to address the problem of cigarette smoking. The U.S. Public Health Service and the U.S. Surgeon General consistently and continually inform the American public of the health risks

associated with smoking.' Further, these agencies make ongoing research and legislative recommendations related to a more cogent delineation of the health risks associated with smoking (USPHS 1979; 1981). Apparently, these efforts have had some impact to the extent that: (a) the percentage of persons smoking in the United States has declined since 1964, (b) smokers have increased their use of lower tar and nicotine cigarettes since 1966, and (c) tobacco and cigarette manufacturers are continually marketing "safer" (i.e., lower tar and nicotine) cigarettes.'

Another response to the problem of smoking has been the development, implementation and empirical evaluation of a multitude of psychologically based treatment strategies aimed at getting cigarette smokers to stop smoking. Despite years of reseach and study into the best approaches to use to initiate and maintain smoking cessation, quit or success rates have been poor (Bernstein, 1970; Hunt, Barnett & Branch, 1974; Hunt & Bespalec,, 1974; Lichtenstein, 1982; USPHS, 1979). Typically, a given treatment strategy will meet with initial success only to show high rates of recidivism beginning at 3-4 months post treatment. A one year abstinence rate of 30-40% seems to be the absolute best that one can expect from current "state of the art" smoking treatment strategies. This is true even when self-referred "motivated" smokers are studied. This dismal success rate

holds for single and multicomponent treatments, treatments with added maintenance phases and treatments that focus specifically on relapse prevention.

Controlled Smoking

In the mid-1970's a new treatment strategy began to be researched. Controlled smoking is directed at the modification of smoking risk rather that a modification of smoking per se (Frederiksen, 1979; Frederiksen, Peterson & Murphy, 1976). The rationale for this approach rested on the notion that smoking risk is dose related, varying with the degree of exposure to the harmful constituents of cigarette smoke (USPHS, 1975, 1977). In turn the dosage of harmful substances is a function of an interaction between the tobacco substance used (e.g., brand of cigarette), and the rate and topography of tobacco consumption (Frederiksen, Peterson & Miller, 1977; Frederiksen & Martin, 1979; Frederiksen & Simon, 1979; USPHS, 1979). It is through the assessment and modification of these three classes of variables that smoking risk is reduced.

A potentially promising treatment approach has recently been developed within the controlled smoking model. This approach involves a modification of smoking risk through cigarette brand changes. This may be an isolated, voluntary event undertaken as an alternative to abstinence as has been

suggested (Cf. Gori, 1976; Gori & Lynch, 1978, Hoffmann, Tso & Gori, 1980; Prue, Scott, Martin & Lomax, 1983; Ross, 1976). On the other hand, the brand change could be part of a systematic brand or nicotine fading treatment program which has abstinence as an ultimate goal (Foxx & Axelroth, 1983; Foxx & Brown, 1979; Foxx, Brown & Katz, 1981; Jaffee, Kanzler, Cohen & Kaplan, 1978; Prue, Davis, Martin & Moss, 1983; Prue, Krapfl & Martin, 1981).

There has been a great deal of controversy over whether or not controlled smoking accomplishes its purpose of reducing the health risks of smoking. There is evidence that smoking low tar and nicotine cigarettes reduces the relative risks of and gross mortality rates from certain diseases (USPHS, 1981). However, these data do not reflect the smoking behaviors of individual smokers or the clinical implications of reductions in relative risk and gross mortality rates. Further, the interaction of behavioral and pharmacological factors in smoking may greatly attenuate any benefit of a brand change or some other controlled smoking strategy.

The Complexity of Smoking Behavior

The initiation, maintenance and cessation of a cigarette smoking habit is a complex behavioral, psychological and physiological process. As smoking

cessation research has indicated, the smoking habit or process is quite resistant to change. Logically, there are some factors operating to maintain smoking behavior despite the best efforts of clinicians and researchers of various backgrounds. It is safe to assume that neither a purely behavioral or a purely biological model of smoking initiation and maintenance can adequately conceptualize the problem.

Within the past 15-20 years the role of nicotine in cigarette smoking has come under a great deal of experimental scrutiny. Much research has been done on the interaction between nicotine and smoking behavior, and there is wide agreement that nicotine plays a major role in the maintenance of cigarette smoking and its recalcitrance to treatment. Before reviewing the data on the interaction between nicotine and cigarette smoking behavior, data on nicotine and its role in smoking behavior will be examined further.

The Role of Nicotine in Smoking Behavior

Nicotine which is liberated from the burning of tobacco may be rapidly absorbed through the lungs, gastrointestinal tract and the mucosa of the mouth nose and throat (Travell, 1960). In the case of cigarettes, the dosage of nicotine liberated and subsequently absorbed is typically large

enough to produce a myriad of psychopharmacological effects, both centrally and peripherally (Domino, 1973; Gilbert, 1979; Russell, 1976; Stephens, 1977; USPHS, 1979, 1981).

Research has indicated that nicotine effects heart rate and stroke volume (Luchessi, Shuster & Emely, 1967; Elliot, 1968; Hill & Wynder, 1974; Sarin, 1974), blood pressure (Lucchesi, et al., 1967; Frankenhauser, Mystren, Wasnak, Neri & Post, 1968; Hill & Wynder, 1974), blood flow and skin temperature (Ague, 1973; Herxheimer, Griffiths, Hamilton & Wakefield, 1967; Simon & Iglauer, 1967), and autonomic nervous system arousal and affective/emotional states (Cf. Gilbert, 1979). Nicotine also affects central and peripheral neurochemical transmitters. Russell (1976) has observed that nicotine can produced stimulation at cholinergic receptor sites, and may also cause the release of catecholamines such as norepinephrine, serotonin and dopamine. Increases in the release of epinephrine and corticotrophic hormones from the adrenal glands have also been shown to follow smoking (Kershbaum, Pappajohn, Bellet, Hirabayashi & Shafiika, 1968; Frankenhauser, Mystren, Post & Johansson, 1971; Hill & Wynder, 1974; Jarvik, 1970). In a recent review, Russell (1980) has noted that the catecholamines release affected by nicotine, may effect the hypothalamic reward system.

Numerous investigators have noted that it is difficult to determine whether the aforementioned actions of nicotine

are a direct function of nicotine or are mediated (indirect) effects (Domino, 1973; Gilbert, 1979; Meyers, Jawetz & Goldfien, 1974; Russell, 1976; Stephens, 1977; USPHS, 1979). Regardless of the specific underlying mecanisms, it is clear that a substantial number of pharmacological effects result from varying dosages of nicotine. The central and peripheral events which result from nicotine intake are primarily manifest as excitation and stimulation. These excitatory effect may come to be subjectively pleasant or rewarding to certain smokers (Stephens, 1977; USPHS, 1979; Russell, 1980). Under these circumstances nicotine can take on reinforcing properties and may become an important variable in the maintenance of smoking behavior.

Nicotine Addiction

In addition to possessing reinforcing properties, there is evidence that the use of nicotine (e.g., cigarette smoking) produces physical dependency. Physical dependency is differentiated from a "psychological" dependence by the presence of tolerance (to the substance in question) and a physical withdrawal syndrome (Russell, 1976; USPHS, 1979). Tolerance to the effects of nicotine has been found in rats (Stolerman, Fink & Jarvik, 1973) and in human subjects (Russell, 1976; Fagerstrom, 1978). Evidence of a physical withdrawal syndrome has also been found. Subjectively,

cravings and feelings of tension and irritability have been associated with nicotine withdrawal. More objective measures have shown decreases in blood pressure and heart rate as well as sleep disturbances as a function of cigarette deprivation (Jaffe & Jarvik, 1978; Knapp, Bliss & Wells, 1963; Russell, 1971; Shiffman & Jarvik, 1976).

The Nicotine Titration Effect

Given the pleasant, reinforcing effects of nicotine, the potential for the development of nicotine addiction and the aversiveness of any subsequent nicotine withdrawal, any procedure which involves a reduction in nicotine intake (e.g., decrease in cigarette nicotine content) may have profound effects on smoking behavior. Russell (1976) in fact, has noted a "nicotine titration effect" (NTE). Proponents of this phenomenon hold that smokers smoke so as to maintain a fairly constant blood plasma nicotine level. Compensatory changes in smoking rate and/or topography which occur when a smoker's usual per cigarette dose of nicotine is altered constitute the NTE. Dependent on the direction of the nicotine content change (i.e., increase or decrease) either "upward" or "downward" nicotine titration may occur.

Assuming the existence of the NTE, a reduction in the nicotine content of a smoker's cigarette may cause him/her to smoke in a more pathological manner. That is, while

seeking to maintain a constant plasma nicotine level, exposure to other constituents of tobacco smoke and the health risks associated with these substances are being maintained or increased.

Empirical Evidence on Nicotine Titration

Experimental investigations of nicotine titration have manipulated nicotine in a number of ways: (a) providing/administering an alternative source of nicotine, (b) changing brands of cigarettes, (c) diluting smoke through the use of a filter system and (d) using "shortened" cigarettes. Other techniques have been used to manipulate nicotine in experiments and these will be considered as well.

Administration of Nicotine

In studies providing alternative sources of nicotine, the nicotine is typically administered to smokers before or during an episode of smoking. This has been accomplished in a number of ways. First, nicotine has been administered intravenously, producing small but significant differences in smoking rate in some cases (Johnson, 1942; Lucchesi, Shuster & Emely, 1967), and showing no effects in other studies (Kumar, Cooke, Lader & Russell, 1977)

Second, cigarette smoke itself has been used to administer nicotine before an experimental procedure (Gritz, Rose & Jarvik, 1983; Herman, 1974; Kozlowski, Jarvik & Gritz, 1975). Results of these studies generally show increases in inter-cigarette-intervals and decreases in puffing as a function of the nicotine pre-loads. Alternately, other studies, involving very similar experimental procedures, have found only minimal effects of smoke "pre-loads" (Chait, Russ & Griffiths, 1985).

Finally, nicotine containing chewing gum has been utilized both as an experimental "pre-load" and more recently as a smoking cessation strategy. Kozlowski et al. (1975) found that at certain dosages nicotine gum decreased puffing. Conversely, Jarvik, Glick & Nakamura (1970) found that orally administered nicotine had minimal effects on smoking rate. Russell, Wilson, Feyerabend & Cole (1976) found that when the pH of the gum was such that buccal absorption occurred, smoking rate was significantly reduced. More recently, a nicotine containing gum, Nicorette, was approved by the U. S. Food and Drug Administration for use as a smoking cessation aid. A series of clinical trials have been undertaken since the introduction of the gum and indicate that the gum is effective in obtaining abstinence. This was the case even in double blind placebo studies (British Thoracic Society, 1983; Fagerstrom, 1982, in press;

Fee & Stewart, 1982; Hall & Killen, in press; Jarvik & Schneider, 1984; Killen, Maccoby & Taylor, 1984; Malcolm, Sillett, Turner & Ball, 1980; Puska, Bjorkqvist & Koskela, 1979; Russell, Merriman, Stapleton & Taylor, 1983; Schelegel & Manske, in press; Schneider, Jarvik & Forsythe, 1984; Schneider, Jarvik, Forsythe, Read, Elliot & Schweiger, 1983). In general, the above studies indicate that at sufficient dosages, the administration of nicotine via chewing gum produces changes in smoking consistent with the NTE.

Brand Changes

A series of studies over the past 15 years has found evidence of the NTE when cigarette nicotine content was altered via brand changes. Nicotine titration has been found via assessment of nicotine or its metabolites (e.g., cotinine) after smoking cigarettes of varying nicotine contents (Ashton, Stepney & Thompson, 1979; Benowitz, Hall, Herning, Jacob, Jones & Osman, 1985; Goldfarb, Gritz, Jarvik & Stolerman, 1976; Haley, Sepkovic, Hoffmann & Wynder, 1985; Herning, Jones, Benowitz, & Mines, 1983; Hill & Marquardt, 1980; Jaffe, Kanzler, Friedman, Stunkard & Verebey, 1981; Rickert & Robinson, 1981; Russell, Jarvis, Iyer & Feyerabend, 1980; Sepkovic, Parker, Axelrad, Haley & Wynder, 1984).

Nicotine titration has also been observed through compensatory changes in smoking behavior (rate and topography). Compensation has been found in: (a) smoking rate (Ashton, Stepney & Thompson, 1979; Frith, 1971; Russell, Wilson, Patel, Cole & Feyerabend, 1973; Schachter, 1977; Turner, Sillett & Ball, 1974), (b) puff rate and frequency (Ashton, Stepney & Thompson, 1979; Ashton & Watson, 1971; Epstein, Ossip, Coleman, Hughes & Wiist, 1981; Feyerabend, Cole & Russell, 1978; Gust & Pickens, 1982), (c) cigarette duration (Ashton & Watson, 1970; Epstein, et al., 1981; Frith, 1970), (d) amount of tobacco burned (Russell, et al., 1973), (e) puff duration (Epstein, et al., 1981; Gust & Pickens, 1982) and (f) puff volume (Creighton & Lewis, 1978; Epstein, et al., 1981; Gust & Pickens, 1982; Herning, Jones, Bachman & Mines, 1981; Kumar, Cooke & Lader 1978; Rawbone, Martin, Tate & Kane, 1978; Tobin & Sackner, 1982).

However, other investigators using similar procedures and measures have found only very slight or negligible compensation (Cf. Beaver, Brown & Lichtenstein, 1981; Burling, Lovett, Richter & Frederiksen, Note 1; Forbes, Robinson, Hanley and Colburn, 1976; Foxx & Axelroth, 1982; Foxx & Brown, 1979; Prue, Kraphl & Martin, 1981; Russell, Wilson, Patel, Feyerabend & Cole, 1975; Sepkovik, Haley, Axelrad & Wynder, 1983). Further, one group of researchers

(Sepkovic, et al., 1983, 1984) has obtained data indicating that when smokers are exposed to higher than usual per cigarette doses of nicotine they adapt to higher plasma nicotine baseline levels rather than compensate with some type of downward titration. It is also important to note the role cigarette draw resistance has been shown to play in studies where it was controlled. Dunn and Freiesleben (1978) found that when draw resistance was held constant, changes in cigarette nicotine content produced no changes in puff parameters. In another study, changes in puff parameters were found when nicotine content was held constant and draw resistance was varied (Dunn, 1978).

Dilution of Smoke

In another series of studies, filter systems have been used to decrease (dilute) the tar and nicotine concentrations of cigarette smoke. Schindler, West, Gordon & Fantino (Note 2) found no evidence of nicotine titration through changes in smoking rate when using a four stage graduated filter system. Sutton, Feyerabend, Cole & Russell (1978) have evaluated the effects of the first two filters of a four stage filter system on smoking behavior. In this experiment, a filter which reduced tar and nicotine by 20% produced no changes in smoking topography. A second filter, reducing nicotine concentrations by 60% produced partial

compensation in topography. Martin, Prue, Collins & Thames (1981) have found reductions in smoking rate, alveolar carbon monoxide levels, carbon monoxide "boost", and an absence of compensation in topography when using a four stage filter system. On the other hand, Henningfield & Griffiths (1980) found statistically significant compensation in rate and frequency of puffing when using a four stage filter system. Smoking rate, however, did not change as a function of the dilution of tobacco smoke.

Shortened Cigarettes

Shortening cigarettes serves to decrease the dose of smoke available from a cigarette without diluting the smoke. A number of investigations have found such a procedure to produce compensatory changes in smoking topography (i.e., rate, puff frequency, puff volume) and in levels of nicotine and/or its metabolites in the body (Ashton, Stepney & Thompson, 1978; Chait & Griffiths, 1982; Gritz, Baer-Weiss & Jarvik, 1976; Jarvik, Popek, Schneider, Baer-Weiss & Gritz, 1978; Russell, Sutton, Feyerabend & Saloojee, 1980; Stepney & Thompson, 1977). Conversely, Goldfarb & Jarvik (1972) found no indication of changes in smoking behavior as a function of shortened cigarettes.

Nicotine Enriched Cigarettes

Fagerstrom (1982) has evaluated the effects of nicotine enriched cigarettes on smoking behavior. He found a trend toward decreased rate with the highest nicotine cigarettes, but no significant changes. On the other hand, nicotine and cotinine levels remained constant across cigarettes indicating that some compensation did occur. Dunn & Freiesleben (1978) found relative decreases in CO levels when nicotine enhanced cigarettes were smoked. However, as noted above, it is possible for smokers to adapt to a higher baseline nicotine level rather than compensate for any increase in nicotine availability (Sepkovic, et al., 1983, 1984).

Cigarette Deprivation

Several laboratory studies have been done in which smokers were deprived of nicotine for some period of time and subequent ad libitum smoking was measured. In these studies, smokers tend to smoke more cigarettes, take more puffs per cigarette and have a shorter latency to smoke the longer the deprivation interval (Griffiths, Henningfield & Bigelow, 1982; Henningfield & Griffiths, 1979; Zacny & Stitzer, 1985). In a more controlled deprivation study, Epstein et al. (1981) found smoking topography to be stable at the end of a 120 minute laboratory session whether smokers had been deprived of cigarettes during this time or

had smoked 4 cigarettes at 30 minute intervals. In a separate experiment within the Epstein et al. (1981) study, topography was also found to remain stable when smokers quit smoking via gradual rate reductions over the course of four weeks.

Miscellaneous Manipulations

Freedman & Fletcher (1976) have altered nicotine delivery by replacing 30% of the tobacco in cigarettes with a specially developed cellulose substitute. When smokers switch to these cigarettes, no changes in smoking rate or estimated nicotine intake were found. These results were taken to indicate that smokers adapted to the decrease in nicotine. Unfortunately no topography measures were obtained in this experiment.

Stolerman, Goldfarb, Fink & Jarvik (1970) compared smoking rates when subjects were smoking their preferred brand and lettuce containing cigarettes to which varying amounts of nicotine had been added. No changes in smoking rates were found across three levels of nicotine in the experimental cigarettes. However, the possibility that taste factors confounded the results of this experiment has been suggested (Frith, 1971).

One study has been done to show that certain nicotine antagonists can produce some changes in cigarette rate and

puff frequency when administered at certain dosages (Stolerman, Goldfarb, Fink & Jarvik, 1973)

Schachter (1977) has summarized data indicating that nicotine excretion (in urine) is affected by the pH of urine. Specifically, excretion increases as alkalinity decreases. It logically follows that if smokers are seeking to maintain a certain plasma nicotine level, increased excretion of nicotine should affect smoking behavior in some way. Schachter, Kozlowski & Silverstein (1977) administered two different acidifying agents and a placebo to smokers to evaluate effects on smoking rate. Significant increases in daily rate were found with both acidifying agents as compared to the placebo. Unfortunately, no topographical data were available. Schachter has also found that stress decreases urinary pH, leading to increased nicotine excretion (Schacter, Kozlowski & Silverstein, 1977; Schachter, Silverstein, Kozlowski, Herman & Liebling, 1977). In a test of the effects of stress on smoking behavior, Schacter, Silverstein & Perlick (1977) found that under stressful conditions smokers urinary pH decreased (presumably mediating an increase in nicotine excretion) and number of cigarettes and puff frequency increased.

In a rather novel approach to the issue of factors maintaining/affecting smoke intake, Sutton, Russell, Iyer, Feyerabend & Saloojee (1982) have found evidence of tar

compensation. Puff volumes increased when tar was decreased and nicotine was held constant. When tar was held constant and nicotine was reduced, no changes in puff volume were noted. Although the authors note the limitations of their data, there is evidence of tar compensation over and above any compensatory changes attributable to nicotine.

Based on all the data presented and reviewed, it is clear that the evidence on the NTE is mixed (inconclusive). Two recent reviews of the nicotine titration/nicotine regulation data (McMorrow & Foxx, 1983; Moss & Prue, 1982) have pointed out that definitive conclusions are lacking in this area due to problems in the design and conduct of many of the nicotine regulation studies. These problems seem to lie in three major areas: (a) methodological and design problems, (b) measurement problems, and (c) possible artifacts in the data.

In more basic research, many studies have relied soley on relatively short laboratory sessions/ manipulations, ignoring smoking in the natural environment. Second, these investigations typically focus on acute reactions to a nicotine manipulation, failing to assess intermediate and longer term reactions to the change. Third, baseline smoking behaviors have often been ignored. Fourth, group measures have been heavily relied upon, and control or comparison

groups have not been used where appropriate or needed. Further, individual smoker/subject characteristics have generally been ignored. Fifth, these studies have typically not comprehensively assessed smoking topography. Sixth, many of the nicotine manipulations used have had little practical significance (e.g., nicotine injections; shortened cigarettes) or have not taken baseline nicotine levels or exposure into account.

In more applied studies, laboratory measures of smoking have often been ignored. Thus topographical measures are scarce and measures of rate have been relied upon too heavily. Further, applied studies have generally been treatment studies and may be subject to extraneous, uncontrolled sources of variability (e.g., individual smoker's motivation to cut down or quit). Applied studies have also tended to ignore subject characteristics. Additionally, a number of applied studies have used rather questionable measures such as tar and nicotine intake calculations. Group measures predominate in these studies and control/comparison groups are generally not used.

Both basic and applied research endeavors in this area have failed to produce conclusive results. Many basic studies are seemingly too controlled and artificial in many ways. The manner in which these studies are conducted may eliminate or ignore a number of factors related to nicotine

regulation and therefore be limited in generality. Applied studies have generally not been set up to comprehensively assess smoking behavior. Further, a treatment situation is often uncontrolled in many respects.

As noted above, the equivocal nature of the data on the NTE is very likely due to the methodological and other problems discussed above. There may also be artifacts in the data (e.g., spurious effects due to high baseline variability within and between smokers) or effects due to measurement procedures alone which obscure more conclusive findings.

Clearly, what is needed are studies to address both basic and applied issues surrounding the NTE. Perhaps the first step is to design a study which minimizes the problems and confounds which have characterized other studies to date. The present experiment was designed to: (a) utilize _in vitro_ and _in vivo_ measures, (b) employ multiple behavioral measures, (c) take baseline smoking behavior into consideration, (d) utilize a nicotine manipulation (brand change) which has practical significance and which was standardized by taking the nicotine level of each smokers preferred brand of cigarette into account, (e) employ controls for effects due to measurement alone or effects due to group classification alone, (f) evaluate acute and intermediate reactions to the nicotine manipulation, and (g)

assess the subject characteristic of dependency to nicotine which may have important implications for the NTE.

Method

Subjects

Subjects were 40 cigarette smokers recruited from a general university student population. All subjects received a 48 hour supply of cigarettes, and either course credit or a small monetary incentive ($2.00) for participating in the experiment. Selection criteria were that smokers: (a) were free from any smoking related illnesses, (b) had smoked at least 1 cigarette per day for no less than 1 year, (c) used tobacco in the form of cigarettes exclusively, (d) had no expressed interest in changing their smoking behavior (i.e., cutting down or quitting) and (e) were willing to comply with the experimental procedure.

Forty-six smokers signed up to participate in the experiment, with six smokers never returning for an initial briefing. No subjects declined to participate or dropped out once an in person contact with the experimenter had been made. Of the 40 subjects randomized into the experimental procedure, 55% were male, 45% were female. The mean age of the subjects was
18.87 years (range 17-32 sd=2.39)

Smokers were classified as either high (n=20) or low (n=20) in physical dependence to nicotine on the basis of

Fagerstrom's (1978) Tolerance Questionnaire (see Measures section). Subjects from each nicotine dependency group were randomly assigned to either an experimental or a control nicotine manipulation, referred to as fade and baseline conditions, respectively. The four groups of 10 subjects each were referred to as: (a) High-Baseline, (b) High-Fade, (c) Low-Baseline and (d) Low-Fade, where High and Low refer to nicotine dependency and Fade and Baseline refer to the nicotine content of the cigarettes smoked during part of the experimental procedure. The demographic make-up of each group was: (a) High-Baseline: 6 males, 4 females; mean age 20.6 years (SD=4.16), (b) High- Fade: 5 males, 5 females; mean age 19.0 years (SD=0.82), (c) Low-Baseline: 5 males, 5 females; mean age 17.7 years (SD=0.67), (d) Low-Fade: 6 males, 4 females; mean age 18.2 years (SD=0.92).

Procedure

The experimental procedure consisted of four phases involving 2 distinct conditions: (a) Natural Environment Assessment, and (b) Laboratory Assessment. These conditions differed in the extent to which smoking behavior was controlled and in the measurement/assessment procedures which were utilized within the condition (see Measures section). Each of these conditions was presented on two separate occasions in an A-B-A-B fashion.

The experimental conditions were presented as follows: Natural Environment Assessment 1: Subjects in all groups smoked their preferred brand of cigarette, and self-monitored their consumption for a 48 hour period (see Measures section). This condition also involved initial contact with subjects in which they were briefed on the experimental procedure, administered all forms and questionnaires, classified as to dependency to nicotine and randomly assigned to an experimental or control group. Laboratory Assessment 1: In this condition, all subjects were required to smoke 2 cigarettes with a 30 minutes inter-cigarette-interval. Smokers in the Baseline conditions (High-Baseline and Low-Baseline) smoked their preferred brand of cigarette at the beginning of the session and after the 30 minute break. Smokers in the Fade conditions (High-Fade and Low-Fade) smoked their preferred brand of cigarette initially, but switched to a brand with a nicotine content 60% less than that of their preferred brand for the second cigarette smoked during this assessment. Natural Environment Assessment 2: This condition was similar to the first natural environment assessment. All smokers continued to self-monitor their cigarette consumption for a second 48-hour period. Smokers in the Baseline conditions continued to smoke their preferred brand of cigarette, with smokers in the Fade conditions continuing to smoke the

reduced nicotine brand first introduced in Laboratory Assessment 1.

Laboratory Assessment 2: This condition was similar to the first laboratory assessment. However, only one cigarette was smoked by each subject in this session. Here, smokers in the Baseline conditions smoked one of their preferred brand of cigarette and those in the Fade conditions smoked one cigarette of the reduced nicotine brand.

Measures

The aforementioned Tolerance Questionnaire (Fagerstrom, 1978) was used to classify smokers as to high and low dependency on nicotine. The Tolerance Questionnaire (see Appendix A) is an eight item inventory designed to assess behavioral characteristics of smokers which are logically related to nicotine addiction. These characteristics are quantified on a 0-11 scale with higher numbers indicating greater dependency (see Appendix B). A median split of this 12 point scale was used to classify low and high dependent smokers. The Tolerance Questionnaire has been validated against tolerance and withdrawal responses (Fagerstrom, 1978), and has been shown to predict differential nicotine titration in low and high dependent smokers (Fagerstrom & Bates, 1981). The data presented suggest that this behaviorally based instrument is more valid than earlier

attempts to classify smokers into various "typologies" (e.g., Ikard, Green & Horn, 1969; Tompkins, 1966, 1968) which have been shown to be poor predictors of smoking behavior (Adesso & Glad, 1978; Leventhal & Avis, 1978). To date, analyses of the Tolerance Questionnaire have not been conducted to reflect the variance in the total score accounted for by individual items. Most importantly, it may be that the items of daily rate and/or cigarette nicotine content may be so highly correlated with the Tolerance Questionnaire to be equally predictive of titration. In this sample of smokers the Tolerance Questionnaire was significantly correlated with baseline smoking rate ($r = +.584$, $p < .01$), but not with cigarette nicotine content ($r = +.168$ $p > .05$). Thus this measures seems to reflect more than just baseline smoking behaviors even considering that rate accounts for 34% of the variance in the measure.

As noted above, all subjects self-monitored their cigarette consumption during the Natural Environment Assessment conditions. Smokers recorded the time each cigarette was smoked on small cards designed to slip inside the cellaphane wrapper on a cigarette package. This "continuous" type of self-monitoring has been shown to be highly reliable and relatively non-reactive (Frederiksen, Epstein & Kosevsky, 1975). Two measures were taken from these self-report data: (a) Daily Cigarette Rate was

expressed as the number of cigarettes smoked in each of the four 24 hour periods, and (b) Inter-Cigarette-Interval which represents the time elapsed from the lighting of the previous cigarette and the lighting of the current cigarette. This value was expressed as a mean across all inter-cigarette-intervals occuring during a given 24 hour period.

During Natural Environment Assessment 2, smokers were provided with cigarettes to smoke, and were required to return empty cigarette packages and un-smoked cigarettes at the end of the experiment. This allowed for reliability of the self-report data to be confirmed. Reliability was expressed as a percentage of agreement by the following equation: (Actual Daily Rate - Reported Daily Rate)/(Actual Daily Rate x 100). Self-monitoring data which was not within 75% agreement was excluded from data analysis.

During the Laboratory Assessment conditions, subjects were videotaped while smoking all cigarettes. Subjects smoked alone in a small room and were provided with newspapers and magazines to read while smoking. Prior to being taped, subjects were instructed to "smoke in their usual manner." During the standard 30 minute inter-cigarette-interval, subjects were instructed to not smoke and remain relatively sedentary.

The following topographical measures (Frederiksen, Peterson & Miller, 1977) were taken from the videotape: (a) Cigarette Duration: time elapsed from the lighting to the extinguishing of a single cigarette, (b) Puff Frequency: the number of times (per cigarette) that the cigarette touches the smokers lips and "flares", (c) Puff Duration: total time that the cigarette is touching the smokers lips and flaring. This value was expressed as a mean across all puffs, (d) Inter-Puff-Interval: the time elapsed from the termination of one puff to the intitiation of the following puff. This value was expressed as a mean across all inter-puff-intervals for the cigarette, and (e) Percent of Time Spent Puffing was expressed a cumulative puff time/cigarette duration. This measure was computed in order to provide a measure of puff intensity.

Data were scored from videotapes by a rater who was blind to group classification. A random sample of 30% of all cigarettes scored was selected for reliability scoring. Reliability was expressed as Pearson Product Moment Correlation Coefficients for cigarette duration and cumulative puff time. Reliability for puff frequency was expressed as a percentage of agreement by the formula: agreements/ agreements + disagreements x 100.

Results

Reliability

Self-monitored cigarette consumption was found to be in 92.25% agreement with actual consumption. Pearson product moment correlation coefficients for cigarette duration and cumulative puff time were +0.99 and +0.90, respectively. The percent agreeement for puff frequency was 97.11%. It was not necessary to eliminate any data due to poor reliability. It may have been possible for subjects to have deceived the experimenter in reporting rate data. It was not felt that this was a significant problem and if deception did occur it likely occurred with equal frequency in all groups.

Data Analysis

On a preliminary consideration of the rate and topography measures, there appeared to be differences in the baseline values. To evaluate these differences, baseline values of all rate and topography variables were subjected to a one-way ANOVA to evaluate the significance of the apparent baseline differences. The results of these ANOVAs are shown in Table 1. The differences between groups on all variables except cigarette duration at least approached significance. Based on these findings, the data

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Insert Table 1 about here

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were subjected to 3 factor, repeated measures Analyses of Covariance (ANCOVA) with baseline differences used as the covariate. When the assumption of homogeniety of regression could not be satisfied, the data were analyzed with three factor mixed model repeated measures ANOVA's.

Main effects in both ANOVAs and ANCOVAs were dependency to nicotine (Addiction), nicotine manipulation condition (Nicotine) and the repeated measures factors of cigarettes (for topography variables) or days (for rate and inter-cigarette- interval). When significant main effects were found, the locus of the effect was evaluated with Dunn's test for multiple comparisons (Keppel, 1973). When significant interactions were found, F-tests for simple effects were conducted to more precisely define the interaction. The results of these analyses are discussed below by variable.

Cigarette Rate

The means and standard deviations for daily cigarette rate for all groups are shown in Table 2. The corrected means from the ANCOVA are shown in Table 3. The relationship

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Insert Table 2 about here

Insert Table 3 about here

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among the four groups is depicted in Figure 1. The ANCOVA (see Table 4) shows no significant main effects or interactions. The differences in the groups seen in Figure 1 were apparently due to baseline differences occuring with randomization, and were eliminated when baseline differences were used as the covariant in the ANCOVA.

Insert Figure 1 about here

Insert Table 4 about here

Interval-Cigarette-Interval

Insert Table 5 about here

Insert Figure 2 about here

The means and standard deviations for inter-cigarette-interval are shown in Table 5, with the relationship among groups illustrated in Figure 2. The ANOVA summary table (see Table 6) shows a significant main effect for Addiction ($F_{1,36}=8.03$ $p < .01$), with no other main effects or interactions being significant. Dunn multiple comparisons

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Insert Table 6 about here

(see Appendix C) show that on all cigarettes, smokers in the High-Fade and High-Baseline groups have significantly shorter inter-cigarette-intervals than smokers in the Low-Fade and Low-Baseline groups (Critical $Range_{Dunn}$ $p < .05=330.8$; $p < .01=392$). Thus independent of nicotine

manipulation condition, High dependent smokers had shorter inter-cigarette-intervals than Low dependent smokers.

Cigarette Duration

Insert Table 7 about here

Insert Figure 3 about here

Means and standard deviations for all groups on the variable of cigarette duration are shown in Table 7. Figure 3 illustrates the relationships among the groups. The ANOVA (see Table 8) reveals a significant main effect for Cigarettes ($F_{2,72}=8.39$, $p < .001$) and a significant

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Insert Table 8 about here

Cigarette x Nicotine interaction ($F_{2,72}=9.24$, $p < .001$). F-tests for simple effects (see Appendix D) indicate no

significant effect of Nicotine manipulation at Cigarette 1 ($F_{1,72}=2.87$ $p < .10$). However, the nicotine manipulation did produce significant effects at Cigarette 2 ($F_{1,72}=11.32$ $p < .01$) and Cigarette 3 ($F_{1,72}=14.85$ $p < .001$). Here, there is a significant difference between the duration of the "fade" cigarettes as compared to the baseline cigarettes for both High and Low Fade groups.

Although, these cigarettes may have been smoked faster due to a lack of nicotine satiation, it is documented that many lower tar/nicotine cigarettes have faster burn times as a function of how they are manufactured (Jenkins, Quincy & Guerin, 1979).

Puff Frequency

The means and standard deviations for the number of puffs taken per cigarettte are shown in Table 9. The corrected means from the ANCOVA are shown in Table 10. The relationship between groups on the variable of puff

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Insert Table 9 about here

Insert Table 10 about here

Insert Figure 4 about here

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frequency is shown in Figure 4. The ANCOVA Summary Table (see Table 11) shows no significant main effects. There was a significant Addiction x Cigarette interaction ($F_{1,36}=6.97$ $p<.025$). F-tests for simple effects show a significant effect of addiction on Cigarette 2 ($F_{1,36}=19.75$ $p<.001$),

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Insert Table 11 about here

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but not on Cigarette 3 ($F_{1,36}=0.48$ $p>.05$) (see Appendix E). Here smokers in the Low dependency conditions took fewer puffs per cigarette than did smokers in the High dependency groups on Cigarette 2, but not on Cigarette 3.

Mean Puff Duration

Table 12 shows the means and standard deviations for mean puff duration. The corrected means for this variable are shown in Table 13. The relationship among the four

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Insert Table 12 about here

Insert Table 13 about here

Insert Figure 5 about here

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experimental groups are shown in Figure 5. The ANCOVA (see Table 14) shows a significant Main Effect for Addiction ($F_{1,35}=7.36$, $p < .025$) and Cigarettes

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Insert Table 14 about here

Dunn multiple comparisons for the Addiction Main Effect (see Appendix F) indicate that High-Fade and High-Baseline smokers have significantly longer mean puff durations than Low-Fade and Low-Baseline smokers on both Cigarettes 2 and 3 (Critical $Range_{Dunn}=0.06$, $p < .05$; 0.08, $p < .01$). Multiple

comparisons for the Cigarettes Main Effect (see Appendix G) show that for all groups the mean puff duration for Cigarette 2 was greater than the mean puff duration for Cigarette 3. This analysis indicates that high nicotine dependent smokers take longer puffs than low dependent smokers. This would seem to be independent of cigarette nicotine content as the fade condition had no significant effects here. Further, puff duration decreased across trials for all groups which may reflect some habituation to the experiment per se in addition to any habituation to the new cigarette for the fade groups.

Inter-Puff-Interval

Insert Table 15 about here

Insert Figure 6 about here

Means and standard deviations for inter-puff- interval are shown in Table 15, and the relationship among groups on this variable are shown in Figure 6. The ANOVA Summary Table

(see Table 16) shows significant main effects for Nicotine ($F=7.79$, $p < .01$) and Cigarettes ($F= 3.76$, $p < .05$). There was also a significant Addiction x Cigarette Interaction ($F_{2,72}=3.93$ $p < .025$). Dunn multiple comparisons (see Appendix H) for the main effect of Nicotine show that only on Cigarette 1 was there a significant difference in inter-puff-interval. Here, the High-Fade group had a significantly higher inter-puff-interval than the Low-Baseline group. The difference between the High-

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Insert Table 16 about here

Fade and High-Baseline groups only approached significance (Critical $Range_{Dunn}=171.17$, $p < .05$; 202.82, $p < .01$). F-tests for simple effects of the Addiction x Cigarette interaction (see Appendix I) showed a significant effect of Addiction on Cigarette 1 ($F_{1,72}=8.61$, $p < .01$), but not on Cigarettes 2 or 3. It is very difficult to interpret these findings given these results. It was on this variable that significant differences existed between the groups at baseline, but the assumption of homogeneity of variance could not be satisfied to allow for an ANCOVA.It appears that the High-Fade group

data was discrepant enough from the other groups to account for the observed effects.

Percent Time Spent Puffing

The means and standard deviations for the time puffing measure are shown in Table 17, with the corrected mean shown in Table 18. Figure 7 depicts the relationship among groups on this variable. The ANCOVA

Insert Table 17 about here

Insert Table 18 about here

Insert Figure 7 about here

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summary table (see Table 19) reveals a significant Main effect for Addiction ($F_{1,35}=9.28$, $p < .01$). No other main

effects or interactions were significant for this variable. In the evaluation of this Main effect, Dunn multiple

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Insert Table 19 about here

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comparisons (see Appendix J) reveal that the High-Baseline group had significantly higher percent time puffing measures than both Low-Fade and Low-Baseline groups on both Cigarettes 2 and 3. The difference in percent time puffing between the High-Fade group and the Low-Baseline group only approached significance on Cigarette 3. All other comparisons between the High-Fade and the two low dependency groups were not significant (Critical $Range_{Dunn}$=10.86, $p < .05$; 13.08, $p < .01$).

Discussion

The data from this relatively well controlled experimental procedure do not demonstrate any compensatory changes in smoking behavior clearly attributable to nicotine titration or nicotine regulation. Nicotine titration would have been evidenced by significant Nicotine x Cigarette interactions indicating significant changes in smoking behavior associated with the brand changes in the fade conditions. The other possibility was to have found significant Addiction x Nicotine x Cigarette interactions. Significant three way interactions would have demonstrated that nicotine dependency classification differentially predicted responses to the nicotine fading manipulation. However, in this study, no Addiction x Nicotine x Cigarette interactions approached significance. The only significant Nicotine x Cigarette interaction was on the variable Cigarette Duration. It is quite probable that much of this effect is a function of the faster burn times of most lower tar and nicotine cigarettes.

The only other variable in which there appeared to be some indication of nicotine regulation was inter-puff-interval (Figure 6). This was a variable on which significant differences were found between groups at baseline, but the data could not be appropriately analyzed

with an ANCOVA. Although it appears that the fade groups decrease their inter-puff-intervals as a function of the fade manipulation, there is too much variability in data to draw any firm conclusions.

Thus the demonstration of nicotine titration/regulation in this study was questionable at best. This is, however, an important result given the nature of the study. This experiment assessed the effects of a nicotine manipulation which: (a) had practical significance, and (b) was standardized to the nicotine rating of the smokers's preferred brand of cigarette. Second, smokers who had no expressed interest in cutting down or quitting smoking were used in a procedure collecting in vivo and in vitro measures over the course of a 4 day period. Further, the smokers who were divided on the basis of dependency to nicotine were paired with dependency matched control groups. Finally, baseline variability in smokers was statistically controlled for to as great an extent as possible.

As was noted in the introduction, definitive findings in the area of nicotine regulation are dependent on improvement in the methodology and measurement strategies employed. Here, we defined a number of methodological and measurement problems and either controlled them and/or considered their limitations in designing and conducting an experiment and interpreting the results of the study. Given

these circumstances, no clear evidence of nicotine titration was shown through compensatory changes in smoking behavior.

These findings must be interpreted in light of the limitations of the technology available when this study was conducted. First, it was not possible to directly assess nicotine levels in serum or other body fluids. Second, we were not able to assess puff volume via current pressure tranductions methods. Finally, an equipment break-down early into the data collection process prevented the collection of expired air carbon monoxide samples. However, these limitations do not discount the importance of the improved design features and experimental control built into this study.

The manner in which the experiment was designed and conducted may have implications for the generality of these findings. First, the subjects were younger than other groups that have been studied. It may be that smokers with longer pack year histories would have been more sensitive to the nicotine fade manipulation.
Second, smokers were self-referred to the experiment and this may have biased the sample studied. For instance, perhaps very high dependent smokers did not volunteer to participate out of fear of being asked to change their smoking in some subjectively aversive manner. Additionally, the generality of these findings may be limited due to

inadequacies in the measurement capabilities of this study. Finally, although control groups were utilized, effects due to measurement alone, lack of compliance with the experimental procedures, deception on the part of fade subjects in making brand changes may have spuriously affected the results.

In looking beyond the group data to individual smokers in the fade conditions it was noted that of 20 smokers exposed to the nicotine fade condition, seven smokers showed clear evidence of nicotine titration. Nine smokers showed no indication of nicotine titration and four smokers showed questionable changes in rate and topography measures. In an effort to discern some differences between the subjects that did and did not appear to regulate their nicotine some comparisons were made. The smokers who appeared to follow the nicotine titration hypothesis were 57% female and 43% male. 43% of this group were scored as high-dependent with 57% scored as low dependent. Smokers not showing compensation were 66% female and 34% male. High dependent smokers accounted for 55% of this group, with 45% of the smokers scoring in the low dependent range. Comparisons between these groups were also done with t-tests on the variables of baseline rate, cigarette tar and nicotine content, cigarette draw resistance and Tolerance Questionnaire score. Means, standard deviations and t-scores

are shown in Table 20 and indicate no significant differences between these two groups on these variables.

Insert Table 20 about here

Predicting nicotine titration/regulation or statistical discrimination of smokers that do and do not regulate nicotine may be possible and potentially valuable. Superficial examination of these small samples did not, however, elucidate any discriminative variables or characteristics.

An interesting and unexpected finding in this study has to do with the differences between Addicted and Non-Addicted smokers. On several variables, Addicted smoker's smoking behavior was significantly different that than of Non-Addicted smokers under the same conditions. In general, Addicted smokers spaced their cigarettes more closely together temporally, took more puffs per cigarette, had longer mean puff durations and spent a greater percent of time puffing on each cigarette smoked than did those scored as Low-Addicted. These effects were largely independent of the nicotine manipulation in the experiment.

The logical implications of this are clear. As a result of their smoking topography, highly addicted smokers should have a higher exposure to the harmful constituents of cigarette smoke. Consequently, the health risks of smoking for smokers more highly addicted to nicotine should be greater than the risks for low addicted smokers. This relationship will be maintained at least across a 60% reduction in the rated nicotine content of a brand of cigarette as was seen in this study. The ultimate clinical implications of this tendency or the relative risk for larger groups of smokers is not known. It may be that the highly nicotine dependent smoker has adapted to a higher baseline serum nicotine level than the low dependent smoker and has developed a pattern of smoking which maintains this level.

From a treatment standpoint, addicted smokers may experience more physiological withdrawal when attempting to become abstinent. Assessment of serum nicotine levels in addicted and non-addicted smokers is the next logical step to pursue these findings.

In conclusion, this experiment has shown a lack of compensatory changes in smoking behavior in response to a nicotine reduction manipulation. These findings held across a four day period using two nicotine dependency groups and in vivo and in vitro measures. Analysis of data at an

individual level revealed that a small subgroup of smokers from the nicotine fade conditions did appear to regulate or titrate nicotine in response to the fade. It was, however, not possible to distinguish or characterize this group from smokers not reacting to the fade in a logical or simple statisical manner. It was also demonstrated that smokers classified as High-Dependent smoked more intensively than did Low-Dependent smokers.

The major question in the area of nicotine regulation and nicotine titration has been whether the phenomenon occurred. This experiment has shown that under these cicumstances nicotine regulation/ titration cannot be inferred from compensatory changes in smoking behavior. There would seem to be two major issues in continued research into nicotine regulation. First, as this study has done, it is extremely important to refine research and measurement methodologies to eliminate all possible confounds and/or sources of extraneous variance. Second, it seems important to research nicotine regulation in a more fine grained manner. Current research has focused too much on the issue of whether nicotine regulation occurs or not. It may be possible to more cogently delineate the variables which produce and perhaps preclude the nicotine titration effect. It may also be possible to discriminate which smokers will and will not react to a manipulation of their

per cigarette dose of nicotine. Once the parameters of the phenomenon are established nicotine regulation and titration can be studied with greater precision. Further, and perhaps most importantly, understanding how to reduce nicotine exposure and hold compensation to a minimal level will have great clinical appplication.

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Table 1.

F-Ratios and Significance levels from One-Way ANOVA's on Baseline Values of Dependent Variable Across Groups.

VARIABLE	F-RATIO	PROBABILITY
DAILY CIGARETTE RATE	$F_{3,39}=7.35$	$p < .001$
INTER-CIGARETTE-INTERVAL	$F_{3,39}=2.50$	$p < .10$
CIGARETTE DURATION	$F_{3,39}=0.28$	$p > .25$
PUFF FREQUENCY	$F_{3,39}=4.58$	$p < .01$
MEAN PUFF DURATION	$F_{3,39}=2.66$	$p < .10$
INTER-PUFF-INTERVAL	$F_{3,39}=7.69$	$p < .001$
PERCENT TIME PUFFING	$F_{3,39}=2.37$	$p < .10$

Table 2

Daily Cigarette Rate Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
DAY 1	M=21.26 SD 6.27	M=23.10 SD 7.85	M=9.40 SD 5.16	M=15.10 SD 7.87
DAY 2	M=23.80 SD 8.81	M=23.30 SD 11.33	M=9.70 SD 6.19	M=13.70 SD 5.64
DAY 3	M=21.80 SD 7.64	M=20.90 SD 9.67	M=11.00 SD 8.39	M=15.80 SD 10.40
DAY 4	M=18.30 SD 6.72	M=23.20 SD 9.82	M=9.30 SD 6.78	M=12.80 SD 6.32

Table 3

Daily Cigarette Rate Corrected Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
DAY 2	M=20.39 SD 9.28	M=18.27 SD 11.94	M=16.34 SD 6.53	M=15.48 SD 5.64
DAY 3	M=18.39 SD 7.64	M=15.87 SD 10.17	M=17.64 SD 8.84	M=17.58 SD 10.40
DAY 4	M=14.89 SD 6.72	M=18.17 SD 10.34	M=15.94 SD 7.14	M=14.58 SD 6.66

Table 4.

ANCOVA Summary Table for Daily Cigarette Rate.

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	38.9	1	38.9	0.55
Nicotine	10.1	1	10.1	0.14
Addict x Nic	0.7	1	0.7	0.01
$ERROR_b$	2473.6	35	70.7	----
WITHIN				
Days	69.5	2	34.7	1.43
Days x Addict	76.3	2	38.2	1.58
Days x Nic	37.0	2	18.5	0.76
Days x Add x Nic	72.2	2	36.1	1.49
$ERROR_w$	1742.9	72	24.2	----

*p <.05, **P <.025, ***p <.01

Table 5.

Inter-Cigarette-Interval (Minutes)
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
DAY 1	M=47.46 SD 15.13	M=47.97 SD 16.12	M=100.16 SD 74.06	M=81.31 SD 61.20
DAY 2	M=44.57 SD 19.97	M=50.56 SD 27.35	M=99.86 SD 91.63	M=86.04 SD 56.31
DAY 3	M=44.97 SD 13.97	M=43.07 SD 15.32	M=97.87 SD 82.51	M=80.85 SD 48.25
DAY 4	M=50.12 SD 14.94	M=42.06 SD 10.13	M=94.20 SD 85.90	M=81.37 SD 48.90

Table 6.

ANOVA Summary Table for Inter-Cigarette-Interval.

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	76948.4	1	76948.4	8.03**
Nicotine	2721.8	1	2721.8	0.28
Addict x Nic	2179.9	1	2179.9	0.23
$ERROR_b$	345031.4	36	9584.2	----
WITHIN				
Days	365.8	3	121.9	0.17
Days x Addict	99.2	3	33.0	0.04
Days x Nic	259.7	3	86.6	0.12
Days x Add x Nic	366.7	3	122.2	0.17
$ERROR_w$	75915.1	108	702.9	----

*p <.05, **P <.025, ***p <.01

Table 7.

Cigarette Duration (Seconds)
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 1	M=405.4 SD 111.6	M=378.0 SD 81.24	M=392.4 SD 86.07	M=367.3 SD 92.68
CIG 2	M=331.0 SD 92.76	M=357.9 SD 81.54	M=319.0 SD 32.61	M=396.2 SD 102.2
CIG 3	M=314.9 SD 91.67	M=368.1 SD 82.07	M=312.0 SD 52.68	M=378.0 SD 78.66

Table 8.

ANOVA Summary Table for Cigarette Duration

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	76.8	1	76.8	0.004
Nicotine	24310.5	1	24310.5	1.28
Addict x Nic	3564.3	1	3564.3	1.19
ERROR$_b$	683827.7	36	18995.2	----
WITHIN				
Cigarettes	41018.5	2	20509.2	8.39****
Cigs x Addict	3179.2	2	1589.6	0.65
Cigs x Nic	45193.7	2	22596.8	9.24****
Cigs x Add x Nic	3183.8	2	1591.9	0.65
ERROR$_w$	175965.5	72	2243.9	----

*p <.05, **P <.025, ***p <.01, ****p <.001

Table 9.

Puff Frequency (Puffs per Cigarette)
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 1	M=10.5 SD 3.35	M=15.80 SD 4.71	M=13.30 SD 2.97	M=17.30 SD 5.25
CIG 2	M=10.10 SD 3.01	M=16.00 SD 5.64	M=10.80 SD 3.46	M=16.30 SD 7.17
CIG 3	M=10.80 SD 3.06	M=15.20 SD 4.66	M=11.70 SD 2.32	M=17.80 SD 5.96

Table 10.

Puff Frequency (Puffs per Cigarette)
Corrected Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 2	M=14.40 SD 3.19	M=14.47 SD 5.94	M=11.69 SD 3.64	M=13.02 SD 7.17
CIG 3	M=14.40 SD 3.22	M=13.67 SD 4.91	M=12.59 SD 2.45	M=14.82 SD 6.28

Table 11.

ANCOVA Summary Table for Puff Frequency.

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	27.3	1	27.3	2.52
Nicotine	8.0	1	8.0	0.74
Addict x Nic	22.1	1	22.1	2.05
$ERROR_b$	337.2	35	10.7	----
WITHIN				
Cigarettes	4.5	1	4.5	2.06
Cigs x Addict	15.3	1	15.3	6.97***
Cigs x Nic	0.01	1	0.01	0.005
Cigs x Add x Nic	3.6	1	3.6	1.64
$ERROR_w$	79.0	36	2.19	----

*p <.05, **P <.025, ***p <.01, ****p <.001

Table 12.

Mean Puff Duration (Seconds)
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 1	M=1.62 SD 0.52	M=1.54 SD 0.43	M=1.51 SD 0.27	M=1.15 SD 0.26
CIG 2	M=1.62 SD 0.49	M=1.62 SD 0.41	M=1.42 SD 0.29	M=1.21 SD 0.33
CIG 3	M=1.55 SD 0.41	M=1.62 SD 0.38	M= 1.34 SD 0.24	M=1.05 SD 0.26

Table 13.

Mean Puff Duration (Seconds)
Corrected Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 2	M=1.49 SD 0.51	M=1.55 SD 0.43	M=1.37 SD 0.31	M=1.45 SD 0.35
CIG 3	M=1.42 SD 0.43	M=1.54 SD 0.40	M= 1.45 SD 0.35	M=1.29 SD 0.27

Table 14.

ANCOVA Summary Table for Mean Puff Duration

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	0.42	1	0.42	7.36***
Nicotine	0.09	1	0.09	1.53
Addict x Nic	0.01	1	0.01	0.18
$ERROR_b$	1.9	35	0.57	----
WITHIN				
Cigarettes	0.12	1	0.12	4.57*
Cigs x Addict	0.03	1	0.03	1.16
Cigs x Nic	0.00	1	0.00	0.00
Cigs x Add x Nic	0.02	1	0.02	0.96
$ERROR_w$	0.97	36	0.03	----

*p <.05, **P <.025, ***p <.01, ****p <.001

Table 15.

Inter-Puff-Interval (Seconds)
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 1	M=42.86 SD 11.97	M=26.45 SD 9.28	M=32.34 SD 8.83	M=22.84 SD 7.09
CIG 2	M=36.52 SD 10.78	M=25.46 SD 10.24	M=35.34 SD 13.12	M=32.16 SD 18.87
CIG 3	M=32.12 SD 9.90	M=24.94 SD 7.85	M=29.69 SD 10.24	M=24.53 SD 10.33

Table 16.

ANOVA Summary Table for Inter-Puff-Interval

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	111.1	1	111.1	0.38
Nicotine	2287.7	1	2287.7	7.79***
Addict x Nic	238.4	1	238.4	0.81
$ERROR_b$	10559.9	36	293.3	----
WITHIN				
Cigarettes	441.2	2	220.6	3.76*
Cigs x Addict	491.1	2	245.6	4.19**
Cigs x Nic	266.0	2	133.0	2.26
Cigs x Add x Nic	49.9	2	24.9	0.42
$ERROR_w$	4221.1	72	58.62	----

*p <.05, **p <.025, ***p <.01, ****p <.001

Table 17.

Percent Time Puffed
Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 1	M=4.31 SD 1.59	M=6.69 SD 2.59	M=5.25 SD 1.62	M=5.49 SD 1.64
CIG 2	M=5.04 SD 3.17	M=7.42 SD 4.05	M=4.81 SD 1.69	M=4.82 SD 2.50
CIG 3	M=5.37 SD 1.52	M=7.44 SD 3.28	M=5.12 SD 1.56	M=4.99 SD 1.72

Table 18.

Percent Time Puffed
Corrected Means and Standard Deviations

	HIGH-FADE	HIGH-BASELINE	LOW-FADE	LOW-BASELINE
CIG 2	M=5.64 SD 1.92	M=6.74 SD 2.12	M=4.91 SD 1.79	M=4.78 SD 2.63
CIG 3	M=5.97 SD 1.60	M=6.75 SD 3.45	M=5.21 SD 1.64	M=4.96 SD 1.81

Table 19.

ANCOVA Summary Table for Percent Time Puffed

SOURCE	SS	df	MS	F
BETWEEN				
Addiction	34.3	1	34.4	9.28***
Nicotine	2.5	1	2.5	0.68
Addict x Nic	5.9	1	5.9	1.59
$ERROR_b$	129.4	35	3.7	----
WITHIN				
Cigarettes	0.85	1	0.85	0.22
Cigs x Addict	0.02	1	0.02	0.006
Cigs x Nic	0.26	1	0.26	0.07
Cig x Add x Nic	0.04	1	0.04	0.012
$ERROR_w$	135.4	36	3.67	----

*p <.05, **P <.025, ***p <.01, ****p <.001

Table 20.

Demographic and Baseline Smoking Characteristics of Smokers Showing and Not Showing Nicotine Titration

VARIABLE	POSITIVE TITRATION	NEGATIVE TITRATION
SEX	F 57% M 43%	F 66% M 34%
NICOTINE DEPENDENCE	HIGH 43% LOW 57%	HIGH 55% LOW 45%
RATE	M=12.7 SD 6.9	M=16.6 SD 8.5
	t= .962*	
NICOTINE CONTENT	M=0.86 SD=0.27	M=0.81 SD=0.09
	t= .540*	
TAR CONTENT	M=13.7 SD=5.97	M=13.5 SD=3.25
	t= .111*	
DRAW RESISTANCE	M=112 SD=25.16	M=123.2 SD=10.26
	t= 1.22*	
TOL. QUEST. SCORE	M=5.14 SD=2.48	M=5.78 SD=2.10
	t= .553*	
AGE	M=18.6 SD=.78	M=18.4 SD=.1.13
	t= .252*	

* p > .05

Figure Captions

Figure 1. Mean daily cigarette smoking rate.

Figure 2. Mean daily inter-cigarette-interval.

Figure 3. Mean cigarette duration.

Figure 4. Mean puff frequency (puff per cigarette).

Figure 5. Group mean of mean puff duration.

Figure 6. Mean inter-puff-interval.

Figure 7. Mean percent time spent puffing per cigarette.

Figure 1

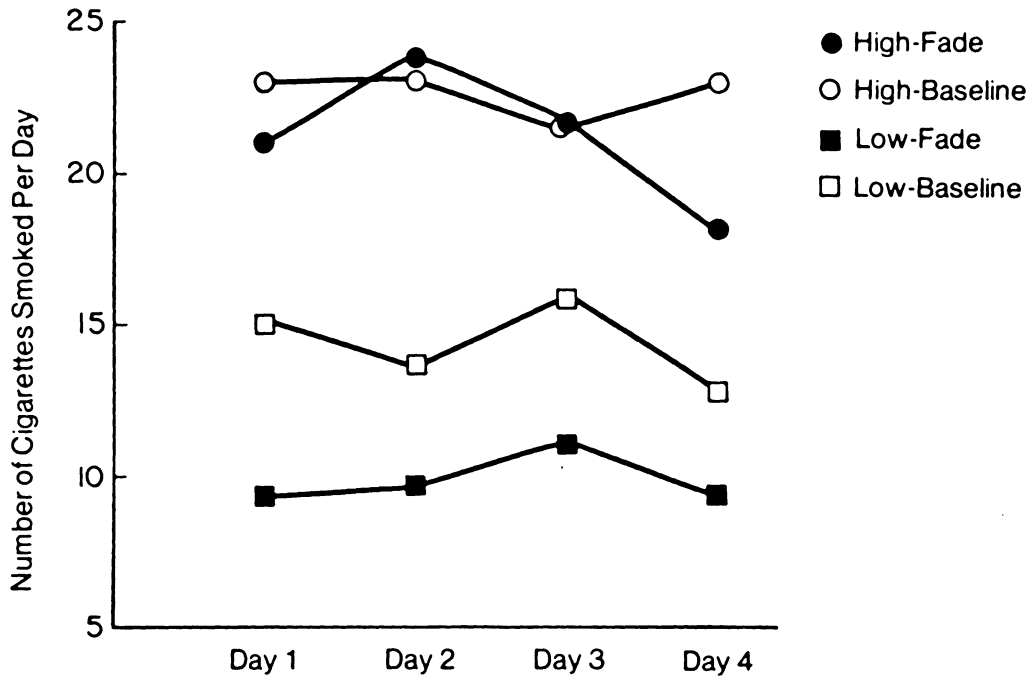

25
20
15
10
5
Number of Cigarettes Smoked Per Day
Day 1
Day 2
Day 3
Day 4
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Figure 2

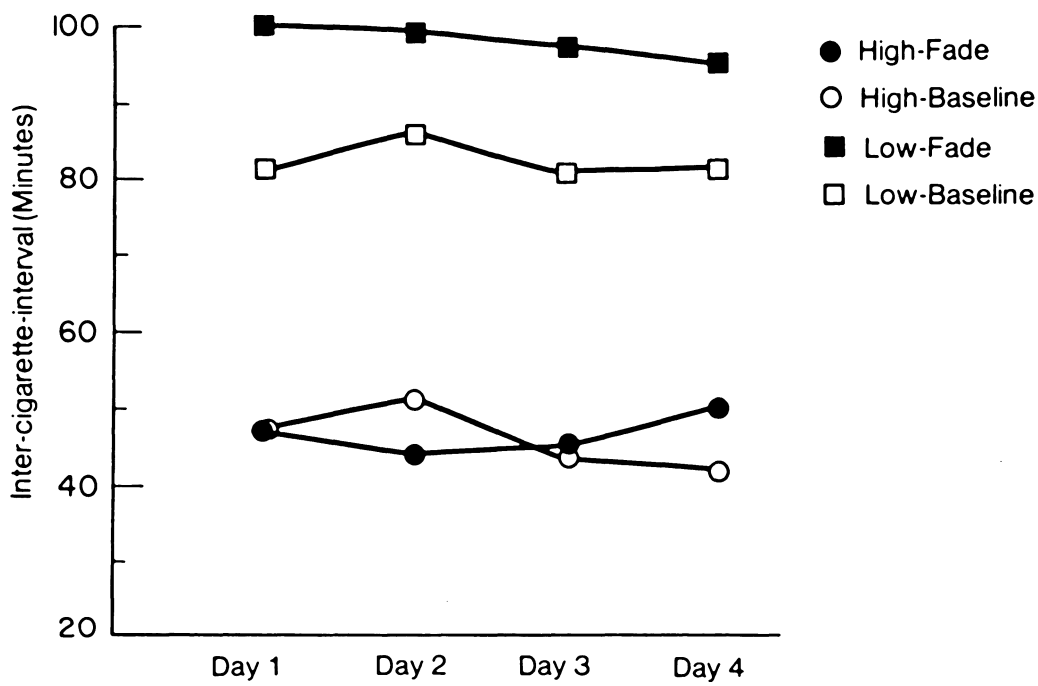

100
80
60
40
20
Inter-cigarette-interval (Minutes)
Day 1
Day 2
Day 3
Day 4
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Figure 3

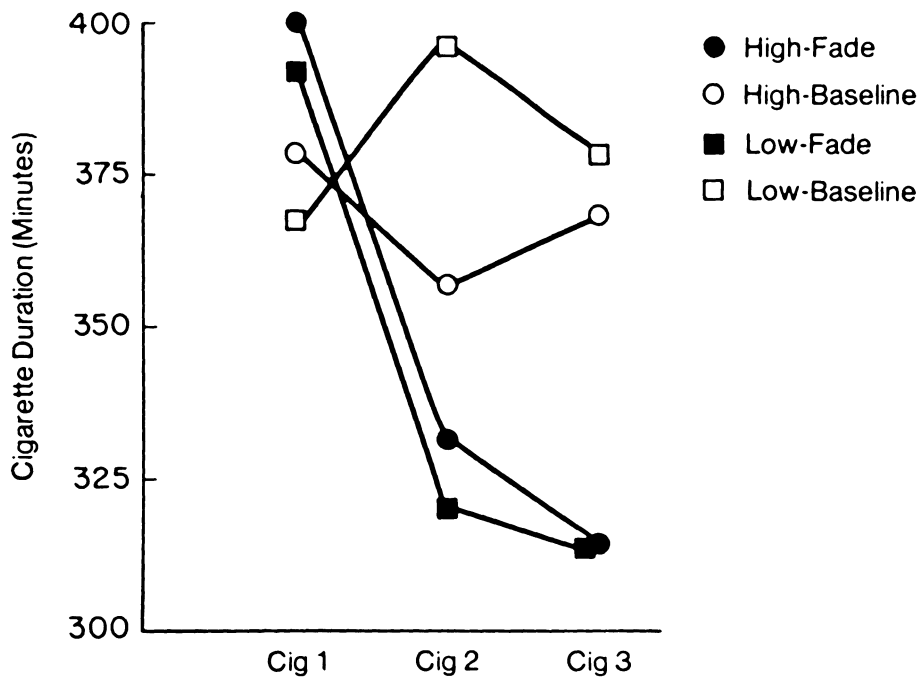

400
375
350
325
300
Cigarette Duration (Minutes)
Cig 1
Cig 2
Cig 3
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Figure 4

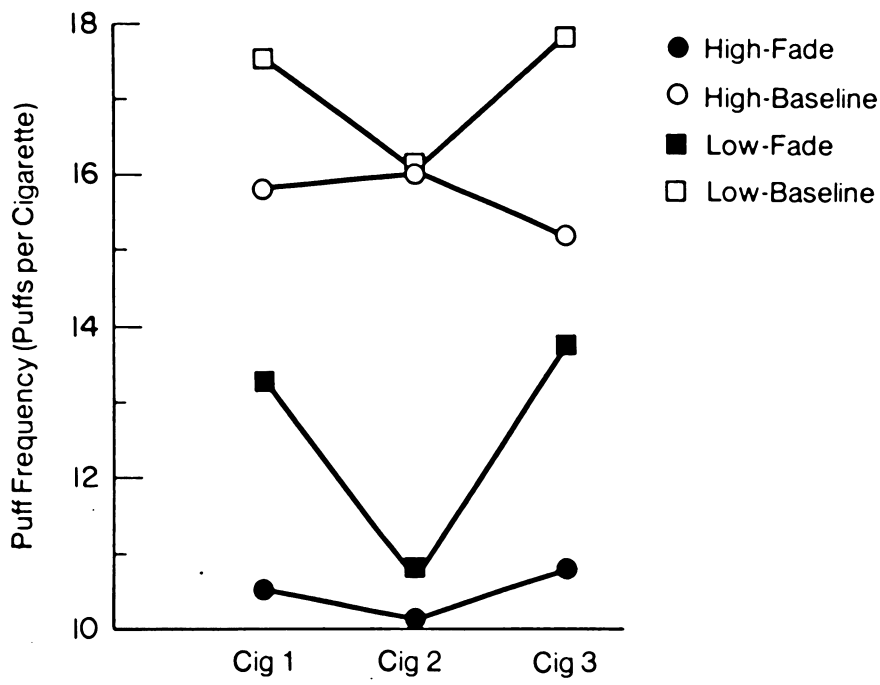

Puff Frequency (Puffs per Cigarette)
18
16
14
12
10
Cig 1
Cig 2
Cig 3
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Figure 5

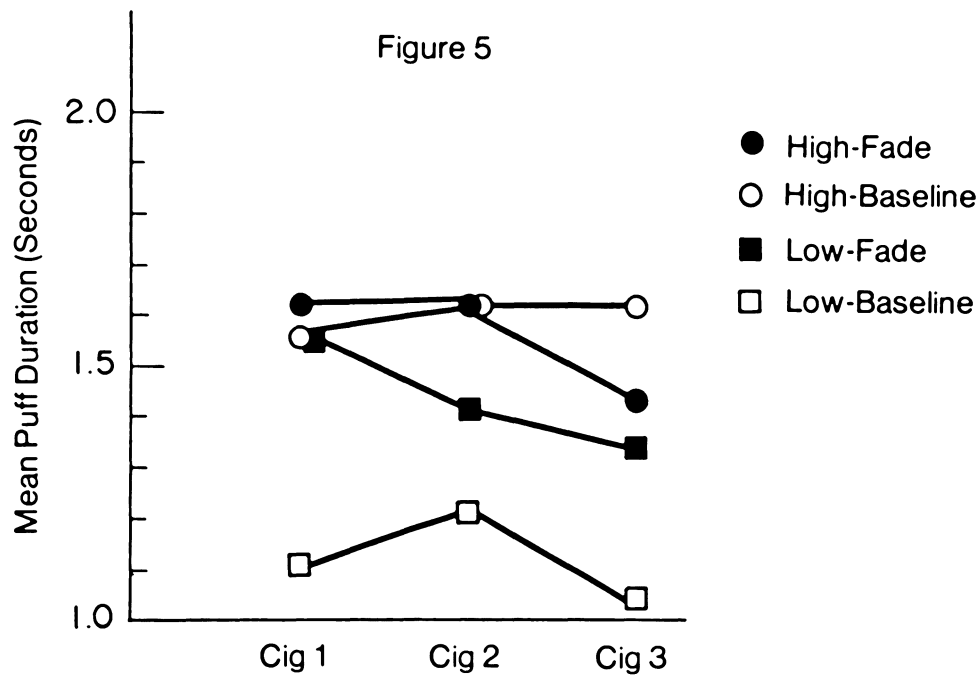

Mean Puff Duration (Seconds)
2.0
1.5
1.0
Cig 1
Cig 2
Cig 3
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Figure 6

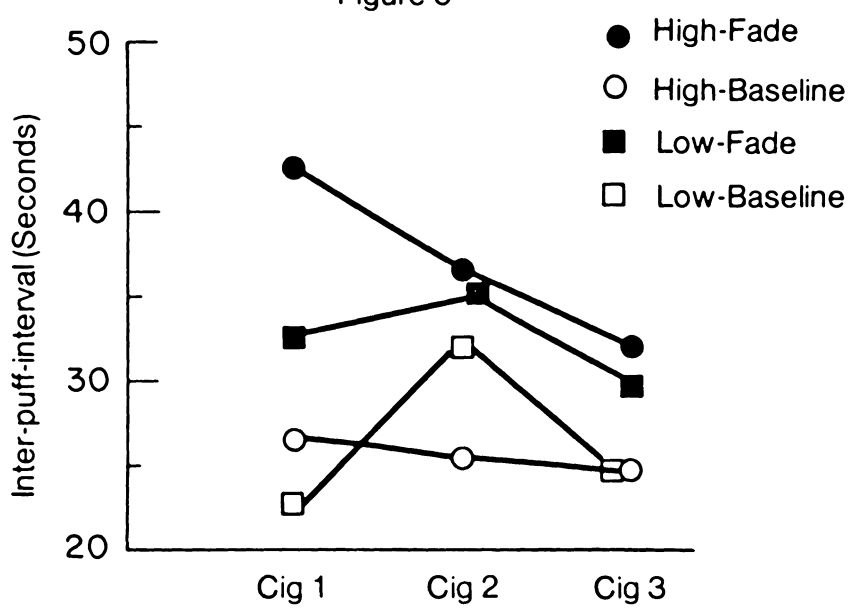
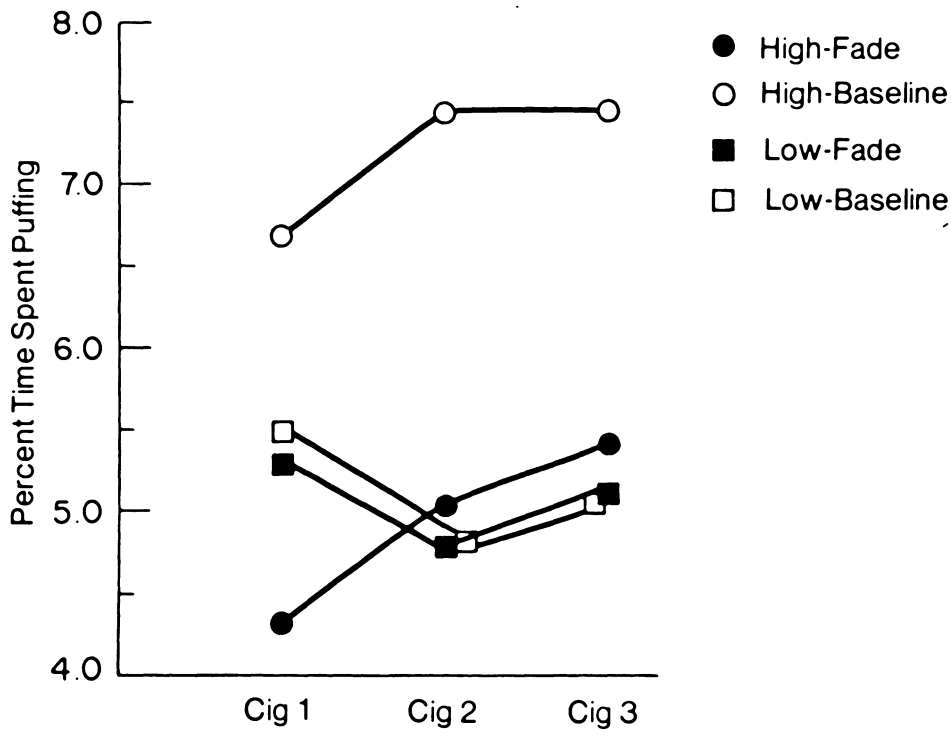

High-Fade
High-Baseline
Low-Fade
Low-Baseline
Inter-puff-interval (Seconds)
50
40
30
20
Cig 1
Cig 2
Cig 3

Figure 7


8.0
7.0
6.0
5.0
4.0
Percent Time Spent Puffing
Cig 1
Cig 2
Cig 3
High-Fade
High-Baseline
Low-Fade
Low-Baseline

Appendix A

The Tolerance Questionnaire

1. How many cigarettes a day do you smoke? _____

2. What brand do you smoke?_____

3. Do you inhale? (circle one) Always Sometimes Never

4. Do you smoke more in the morning than during the rest of the day? (circle one) yes no

5. How soon after you wake up do you smoke your first cigarette? _____

6. Which cigarette would you hate to give up? _____

7. Do you find it difficult to refrain from smoking in places where it is forbidden (church, library, movie)? (circle one) yes no

8. Do you smoke if you are so ill that you are in bed most of the day? (circle one) yes no

Appendix B

Scoring the Tolerance Questionnaire

The questionnaire has a range of 0-11 points with 0 and 11 indicating lowest and highest physical dependency to nicotine, respectively. For this study the 12 point scale will be split so that scores of 0-5 will reflect low nicotine dependency and 6-11 high nicotine dependency.

SCORING:

1. 0-15 cigarettes----0
   16-25 cigarettes---1
   >25 cigarettes-----2

2. 0.05-0.6 mg nicotine-----0
   0.7-1.0 mg nicotine------1
   1.1-1.8 mg nicotine------2

3. Never-------0
   Sometimes---1
   Always------2

4. No----0
   Yes---1

5. If within 30 minutes---1

6. If 1st cigarette in morning---1

7. No----0
   Yes---1

8. No----0
   Yes---1

Appendix C.

Dunn Multiple Comparisons for Main Effect of Addiction in the Variable Inter-Cigarette-Interval.

Difference in Treatment Cell Sums

	HIGH FADE1	HIGH FADE2	HIGH FADE 3	HIGH FADE4
LOW FADE 1	526.8**			
LOW FADE 2		552.9**		
LOW FADE 3			528.96**	
LOW FADE 4				440.7**

	HIGH B.L.1	HIGH B.L.2	HIGH B.L.3	HIGH B.L.4
LOW B.L. 1	333.4*			
LOW B.L. 2		354.8*		
LOW B.L. 3			377.8**	
LOW B.L. 4				393.0**

*p <.05, **p <.01

$d_{8,108}$ (p <.05)=2.79
(p <.01)=3.31

Critical Range$_{Dunn}$ (p <.05)=330.8
(p <.01)=392.4

Appendix D.

Summary Tables for F-tests for Simple Effects for the Nicotine x Cigarette Interaction for the Variable Cigarette Duration.

Table of Treatment Cell Sums

	FADE	BASELINE	SUMS
CIG 1	7978	7453	15431
CIG 2	6500	7541	14041
CIG 3	6269	7461	13730

	SS	df	MS	F
EFFECT AT CIG 1:	6890.7	1	6890.7	2.87
EFFECT AT CIG 2:	27092.0	1	27092.0	11.32**
EFFECT AT CIG 3:	35521.6	1	35521.6	14.85**

MSerror=2392.6
**p <.01

Appendix E.

Summary Tables for F-tests for Simple Effects for the Addiction x Cigarette Interaction for the Variable Puff Frequency.

Table of Treatment Cell Sums

	HIGH	LOW	SUMS
CIG 2	288.7	247.1	535.8
CIG 3	280.7	274.1	554.8

	SS	df	MS	F
EFFECT AT CIG 2:	43.26	1	43.26	19.75**
EFFECT AT CIG 3:	1.09	1	1.09	0.49

$MS_{error} = 2.19$

**p <.01

Appendix F.

Dunn Multiple Comparisons for the Main Effect of Addiction in the Variable Mean Puff Duration.

Difference in Treatment Cell Sums

	HIGH B.L. 2	HIGH B.L. 3
LOW B.L. 2	1.00**	
LOW B.L. 3		2.50**

*p <.05, **p <.01

$d_{4,36}$ (p <.05)=2.62
(p <.01)=3.23

$Critical\ Range_{Dunn}$ (p <.05)=0.06
(p <.01)=0.08

Appendix G.

Dunn Multiple Comparisons for the Main Effect of Cigarettes in the Variable Mean Puff Duration.

Difference in Treatment Cell Sums

	HIGH FADE 2		HIGH B.L. 2
HIGH FADE 3	0.70**	HIGH B.L. 3	0.10**
	LOW FADE 2		LOW B.L. 2
LOW FADE 3	0.90**	LOW B.L. 3	1.60**

*p <.05, **p <.01

$d_{4,36}$ (p <.05)=2.62
(p <.01)=3.23

$Critical\ Range_{Dunn}$ (p <.05)=0.06
(p <.01)=0.08

Appendix H.

Dunn Multiple Comparisons for the Main Effect of Nicotine in the Variable of Inter-Puff-Interval.

Difference in Treatment Cell Sums

	HIGH FADE1	HIGH FADE2	HIGH FADE3
HIGH B.L.1	164.15		
HIGH B.L.2		110.60	
HIGH B.L.3			71.76
LOW B.L.1	200.20*		
LOW B.L.2		43.70	
LOW B.L.3			75.83

Difference in Treatment Cell Sums

	LOW FADE1	LOW FADE2	LOW FADE3
LOW B.L. 1	93.99		
LOW B.L. 2		31.89	
LOW B.L. 3			51.53
HIGH B.L.1	57.94		
HIGH B.L.2		98.85	
HIGH B.L.3			47.00

*p <.05, **p <.01

$d_{12,72}$ (p <.05)=2.92
(p <.01)=3.46

Critical Range$_{Dunn}$ (p <.05)=171.17
(p <.01)=202.82

Appendix I.

Summary Tables for F-tests for Simple Effects for the Addiction x Cigarette Interaction for the Variable Inter-Puff-Interval.

Table of Treatment Cell Sums

	HIGH	LOW	SUMS
CIG 1	693.1	550.9	1224
CIG 2	619.8	675.0	1295
CIG 3	570.6	542.2	1113

	SS	df	MS	F
EFFECT AT CIG 1:	505.95	1	505.95	8.61**
EFFECT AT CIG 2:	76.12	1	76.12	1.29
EFFECT AT CIG 3:	20.12	1	20.12	0.34

MSerror=58.62
**p <.01

Appendix J.

Dunn Multiple Comparisons for the Main Effect of Addiction in the Variable Percent of Time Spent Puffing.

Difference in Treatment Cell Sums

	HIGH FADE2	HIGH FADE3
LOW FADE 2	7.30	
LOW FADE 3		7.60
LOW B.L.2	8.60	
LOW B.L.3		10.00

Difference in Treatment Cell Sums

	HIGH B.L.2	HIGH B.L.3
LOW FADE 2	18.30**	
LOW FADE 3		15.40**
LOW B.L.2	19.60**	
LOW B.L.3		17.90**

*p <.05, **p <.01

$d_{8,36}$ (p <.05)=2.89
(p <.01)=3.48

$Critical\ Range_{Dunn}$ (p <.05)=10.86
(p <.01)=13.08

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