

EFFECTS OF DOSE AND DOSE INTERVAL ON
CONDITIONED HEART RATE TOLERANCE
TO SMOKING

By

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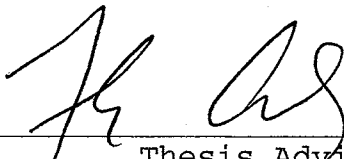
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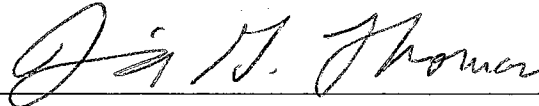
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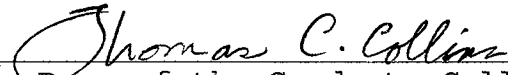
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PREFACE

Dose and dose-interval were jointly manipulated to determine the effects on conditioned cardiovascular tolerance to smoking. Forty smokers were assigned to one of four groups in a 2 (Administration: low dose/long dose-interval or high dose/short dose-interval) x 2 (Environment: repeating or changing context) design. The environment prior to smoking consisted of story segments, each 4 1/2 minutes long, which repeated or changed across five trials. The Repeating context group which received the low dose/long dose-interval, developed conditioned or associative cardiovascular tolerance, while the Changing context group showed no tolerance development. Modifying the context before smoking on a sixth trial did not reverse tolerance. Groups which received the high dose/short dose-interval did not develop tolerance; rather, the Repeating context group demonstrated sensitization. In a second experiment, thirty-six non-smokers, who were exposed to the changing or repeating context without smoking, did not show cardiovascular tolerance development. In conclusion, cardiovascular responses to smoking is subject to conditioning. Cigarette smoking may not be conducive to

nonassociative tolerance development. The role of attention and information processing in the development and disruption of tolerance is discussed.

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Effects of Dose and Dose-Interval on Conditioned Heart Rate Tolerance to Smoking

Tolerance is a central factor in drug addiction. According to the Diagnostic and Statistical Manual of Psychiatric Disorders, Third Edition - Revised (American Psychiatric Association, 1987), the symptoms of psychoactive substance dependence often include marked tolerance (defined as a need for at least a 50% increase in the amount of substance in order to achieve intoxication or the desired effect) or a distinctly decreased effect with repeated use of the same quantity of the substance. The same mechanisms that mediate tolerance may also be responsible in withdrawal and craving (Ternes, 1977), which are also symptoms indicative of dependence.

The development of tolerance to the effects of nicotine and cigarette smoke may be important in the establishment and persistence of smoking behavior (Caggiula, Epstein, & Stiller, 1989; Henningfield, 1984; Jarvik, 1979). Therefore, examining nicotine tolerance and its development is necessary to a full understanding of nicotine dependence (Hinson, 1985; Hinson & Siegel, 1980). Furthermore, the need to examine basic variables such as tolerance to smoking is suggested in light of the typically less than desirable long-term results of most smoking cessation treatment programs (Shiffman, 1993).

The purpose of this study is to add to the existing

knowledge about the development of tolerance to smoking. Of specific interest is the role of conditioning in the development of tolerance. The establishment of conditioned stimuli and responses may be partially responsible in the repetitive use of cigarettes and relapse following a period of abstinence (Henningfield, 1984). In this introduction, the following topics will be discussed: (a) Definitions of tolerance, (b) the Pavlovian model of tolerance, (c) the opponent-process model, (d) the habituation model, (e) the homeostatic model of tolerance, (f) some differences among the presented models, (g) the impact of dose and dose interval on tolerance development, (h) smoking effects and tolerance, and, finally, (i) the hypotheses tested in this study.

Definitions of Tolerance

Drug tolerance generally refers to a decreased drug effect with repeated drug administrations (Baker & Tiffany, 1985; Porchet, Benowitz, & Sheiner, 1988). Tolerance has also been defined as a shift in the dose response curve to the right (Goudie & Griffiths, 1986). As tolerance develops, a greater drug dose is required to achieve the initial drug effect.

Several forms of tolerance have been identified. These include behavioral, contingent, acute, chronic, associative and nonassociative tolerance. Behavioral tolerance has been defined two ways. Descriptively, the term has been used to

refer to tolerance that develops to a specific behavioral effect of a substance. From a more mechanistic viewpoint, behavioral tolerance has also come to mean tolerance that is mediated by behavioral compensation for the initial effects of a drug (Wolgin, 1989). Contingent tolerance is the process of stimulating tolerance development by placing certain demands on a drugged organism (Poulos & Cappell, 1991).

Acute tolerance, or tachyphylaxis, has been specifically defined as a decreased drug effect on the descending, compared to the ascending, portion of the blood-drug concentration curve at the same drug concentration (Kalant, LeBlanc, & Gibbins, 1971). Porchet et al. (1988) demonstrated that acute tolerance is not merely the result of changing distribution or concentration of the drug in the subject. Whereas acute tolerance is also defined as decreased responding to a drug within a single administration, chronic tolerance is defined as decreased responding to a drug across many administrations (Perkins, Epstein, Stiller, Marks, & Jacob, 1989; Porchet et al., 1988). It is believed that chronic and acute tolerance are related, but this relationship is unclear (Hinson, 1985).

The degree of involvement of environmental cues distinguishes nonassociative and associative tolerance. Nonassociative tolerance develops independent of cues, and, therefore, is independent of learning and believed to be

primarily a physiological phenomenon (Poulos & Cappell, 1991). In contrast, associative (or learned, conditioned, or environment-specific) tolerance develops in relation to cues that signal or are present during drug administration (Baker & Tiffany, 1985; Siegel, 1989).

With so many seemingly different forms of tolerance, it is easy to see why it is difficult to study. The development of a unified model of tolerance is beyond the scope of this project. Rather, this study was conducted in an effort to make a contribution to the understanding of tolerance, particularly tolerance to nicotine and smoking, by investigating associative and nonassociative tolerance.

Before the middle 1960's, drug tolerance was the domain of pharmacology and neurobiology. Systemic changes within the organism such as modified receptor sensitivity, neurochemical changes, metabolic changes, and immune system reactions were theorized as being responsible for the development of tolerance (Baker & Tiffany, 1985; Hinson & Siegel, 1980). However, by the 1970's, evidence was mounting that environmental cues were related to the development of tolerance. Most of this evidence came from studies with opiates (Adams, Yeh, Woods, & Mitchell, 1969; Siegel, 1977, 1978). The traditional pharmacological models of tolerance were not sufficient to explain this new evidence. Today, the Pavlovian, opponent-process, habituation, and homeostatic models of tolerance are often

used to account for and to investigate tolerance.

Pavlovian Model of Tolerance

The development of drug tolerance follows the rules of Pavlovian conditioning (Siegel, 1975, 1977, 1989). It is assumed that the drug effect disrupts the homeostasis of the organism. This disruption then elicits a compensatory response in order to restore homeostasis. Hinson and Siegel (1980) suggest that acute tolerance may be the result of such compensatory responding. This compensatory response becomes the conditioned response (CR) in this model of tolerance development. The drug dose is the unconditioned stimulus (UCS) which produces the drug effect, the unconditioned response (UCR). Rather than the conditioned response being in the same direction as the unconditioned response, the conditioned response is opposite in direction to the drug effect. When cues in the environment (conditioned stimuli, CS's) are repeatedly paired with drug administration, those cues come to elicit the conditioned response, which is the compensatory response, in anticipation of the drug administration. After many pairings of the drug administration and environmental cues, the effect of the drug is increasingly canceled.

This model of drug tolerance spurred much research. However, the Pavlovian model of tolerance has since been revised. In the original model, the CR was opposite in direction to the UCR, which was inconsistent with

traditional Pavlovian principles. Siegel (1989) addressed this issue by taking into consideration the site of action of the drug. When the substance has an efferent site of action, the biological disturbance caused by the drug can accurately be identified as the UCS, which then elicits the compensatory response of the central nervous system, the UCR. This same response may become associated with environmental stimuli (CS's) and become the CR. Therefore, when the drug has an efferent site of action, the CR mimics the UCR. He further stated that when the substance has an afferent site of action, the drug that initiates CNS activity is the UCS and the effect of the CNS activity is the UCR. Again, the CR then mimics the UCR. This model is in line with traditional Pavlovian principles and is the current Pavlovian model of tolerance.

Opponent-process Model of Tolerance

The opponent-process theory, like the Pavlovian conditioning model, is also based on the assumption that organisms strive to maintain homeostasis by responding in some compensatory manner when homeostasis is disrupted (Solomon, 1980; Ternes, 1977). Drugs are stimuli (UCS) that disrupt this balance. In the terminology of the opponent-process model, the homeostatic disrupting UCR is called an a-process. An a-process is defined as a "positive excursion from baseline" (Ternes, 1977) and always comes after the stimulus onset. The onset of the a-process elicits a

negative divergence from the baseline which is called the b-process. The purpose of the b-process is to restore homeostasis. Initially, the b-process is weak and sluggish at onset. With repeated exposures, its latency decreases and the intensity and duration increases (Solomon, 1980).

The algebraic sum of the intensities of the two processes determines the state of the organism after administration of the drug. Initially, the a-process intensity is great and the b-process is weak and sluggish. Therefore, the initial effect of the drug is great. The state experienced is mostly the product of the a-process and is called the A-state. After many presentations, the a-process is smaller and the b-process is larger and longer-lasting. The b-process then contributes most to the sum, resulting in a state that is primarily the result of the compensatory b-process. This state is called the B-state. The growth of b-processes results in a decreased drug effect that is typically called tolerance.

Environmental stimuli can be associated with both a- and b-processes (Solomon, 1980; Solomon & Corbit, 1973; Ternes, 1977). If a stimulus (CS) comes to be associated with the onset of the a-process (UCR), that stimulus becomes capable of eliciting a-processes (CR) which are followed by the b-process. However, a stimulus (CS) that has come to be associated with the offset of the UCS (peak b-process) can elicit that b-process (CR) without the a-process ever

occurring. The B-state experienced by the organism is said to be craving (Ternes, 1977).

Habituation Model of Tolerance

Baker and Tiffany (1985) proposed that drug tolerance development is analogous with the characteristics of habituation. Habituation is a process of decreased responding with repeated exposures to a stimulus (Gleitman, 1987). Habituation is used to conceptualize tolerance as decreased responding to repeated drug administrations. Baker and Tiffany (1985) used Wagner's (1976, 1979) model of habituation to pattern their model of tolerance. According to Wagner's model, the magnitude of a response to a stimulus is dependent on the extent to which the properties of that stimulus are already primed in short-term memory. If the stimulus is not expected or primed, the response is great. However, if the properties of the stimulus are primed, the response is diminished, which results in habituation.

There are two ways in which a stimulus comes to be expected or primed. The first is self-generated priming. Self-generated priming occurs when the properties of the stimulus from a prior, recent exposure still exist in the memory register at the time of the next presentation of the same stimulus. When this occurs, the stimulus is not nearly as surprising on subsequent presentations, so there is less stimulus processing and responding.

The second way that priming may occur is through

associational means. If a stimulus is presented that has in the past been consistently paired with the target stimulus, the former stimulus will elicit priming of the target stimulus in the memory register. So when the target stimulus is then presented, less processing is required and responding decreases because the stimulus was expected due to the priming elicited by the stimulus associated with the target stimulus. Both self-generated or nonassociational and associational priming result in habituation.

The central tenant of the habituation model of tolerance "is that drugs have salient stimulus properties and that these may be retained in memory for long periods of time" (Baker & Tiffany, 1985, p. 83). They did not claim that short-term memory, per se, was responsible, but they did propose that a memory-like mechanism retains information and that this register is much like short-term memory, with the exception of having greater temporal parameters than short-term memory.

In order to apply the model of habituation to tolerance development, the following assumptions must be made: (a) Drug exposure creates a representation of the stimulus in memory (self-generated priming) and the magnitude and duration of that representation depends on the drug dose, (b) presenting a cue previously paired with the drug provides for associatively-generated priming of the representation of the drug, (c) decreased neural processing

of the drug stimulus is the result of both self-generated and associatively-generated priming, and (d) this decreased processing and resulting behavioral effect, which constitutes tolerance, is related to the extent of priming at the time of drug administration.

Given those assumptions, if a drug is administered while some of its properties remain in memory, the drug then requires less processing and the resulting response is diminished. This constitutes nonassociative tolerance. If drug administration is repeatedly paired with certain cues, the presentation of those cues primes the representation of the drug properties in memory. So, when the drug is administered, again less processing is required and responding is lessened. This constitutes associative tolerance.

Baker and Tiffany (1985) were not the first to equate tolerance with habituation. Siegel (1977, 1989) briefly discussed the conceptualization of tolerance as habituation. Because the Pavlovian model could not account for a number of tolerance effects such as nonassociative tolerance, Kesner and Cook (1983) proposed a two-process model of tolerance. Classical conditioning remained the explanation for associative tolerance, and habituation was proposed as an explanation for nonassociative tolerance. The habituation process was believed to be mediated by alteration in specific neurotransmitter systems, rather than

through memory processes. Baker and Tiffany (1985) later abandoned the Pavlovian model and the compensatory response.

Homeostatic Model of Tolerance

The fourth model of tolerance, the homeostatic theory, like the Pavlovian and opponent-process models, assumes that the organism is equipped to maintain homeostasis. Drug tolerance is viewed as one such response to regain homeostasis. However, the authors of this model propose that the mere presence of the drug is not sufficient to elicit a compensatory response. Based on studies of contingent tolerance, Poulos and Cappell (1991) assert that in order for the organism to detect a disturbance in its homeostasis, it must interact with its environment in response to environmental demands. In fact, they state that "explicit or implicit behavioral demands placed on physiological systems are required for the biological detection of homeostatic disturbances" (p.391). For example, a rat cannot develop tolerance to the anorectic effect of amphetamine unless food is present. Poulos and Cappell (1991) state that their model applies only to systemic tolerance, and not nonspecific or general tolerance. Systemic tolerance is used to refer to specific adaptations that occur in specific physiological systems, for example, the analgesic system and its response to morphine.

Poulos and Cappell (1991) hypothesize about the

mechanisms underlying the development of nonassociative and associative tolerance. Nonassociative tolerance is assumed to be mediated by the unconditional compensatory adaptation that supposedly perseverates after the disappearance of the drug on subsequent administrations. Associative tolerance is said to be the result of Pavlovian conditioning in this model. Once the unconditional adaptive response is elicited (UCR), this response becomes the basis of the conditioned response when reliable drug cues are available in certain drug-administration regimes. The UCR and CR are isodirectional (Poulos & Cappell, 1991).

Differences Among the Models

One difference among these four models is the extent to which both associative and nonassociative tolerance is addressed. The Pavlovian model is primarily associative. Hinson and Siegel (1980) did not deny the existence of nonassociative factors in some instances of tolerance, but had nothing further to say about nonassociative mechanisms. Ternes (1977) proposed that the opponent process model is primarily non-associative in its explanation of tolerance development. Associative mechanisms come into play, but are not essential for tolerance development. The growth of the b-process and weakening of the a-process mediate nonassociative tolerance. In contrast to these two models, both the habituation and the homeostatic models address nonassociative and associative tolerance.

Perhaps the most distinct difference among these models is the proposed existence and necessity of compensatory responding to the effects of a drug. The Pavlovian, opponent process, and homeostatic models are based on the idea that the organism works to restore homeostasis with some compensatory response that is opposite in direction to the effects of the drug. However, Baker and Tiffany (1985) believe that compensatory responses are not necessary for the development of tolerance. The existence of compensatory responses has been the subject of much debate. Baker and Tiffany (1985) presented evidence that compensatory responses to morphine are often difficult to demonstrate. Poulos and Cappell (1991) recognize the difficulty in revealing these responses, but argue that this is hardly decisive. They cite considerable evidence of compensatory responses to a number of different drugs, such as alcohol, morphine, naloxone, and scopolamine (Poulos & Cappell, 1991). Whether or not compensatory responses exist and mediate tolerance development is beyond the scope of this study.

Dose and Dose-Interval

Other differences among these theories include the ability to account for the effects of certain variables (such as dose, dose-interval, and frequency of exposure) on the development of tolerance. Of particular interest to this study are the effects of dose-interval, drug dose, and

their interactive effects on tolerance development. Generally, the rate and magnitude of tolerance development is an inverse function of the dose-interval and a positive function of drug dose (Seaman, 1985; Tiffany & Maude-Griffin, 1988). When predictable cues are not present, tolerance generally does not develop when relatively small doses are repeatedly administered and the interval between doses is large (Baker & Tiffany, 1985).

According to Pavlovian principles, the strength of conditioning is directly related to the UCS magnitude (Baker & Tiffany, 1985). Given that an increase in the drug dose size increases the homeostatic disturbance (UCS), drug dose can strengthen the conditioning of tolerance.

The authors of the opponent process model recognized the effect of dose-interval on tolerance development (Ternes, 1977). Dose-interval, in this model, is proposed to be one of the parameters that affect the growth of b-processes. B-processes have a critical period or duration of decay. If the dose-interval is longer than the duration of decay of the b-process, then it is predicted that the b-process will not grow and the a-process will remain unopposed (Solomon, 1980). Tolerance then should not occur. The organism will continue to experience an A-state similar to the initial A-state. However, if the dose-interval is shorter than the duration of decay of the b-process, then the b-process will grow through summation.

Two other variables said to affect the growth of the b-process are the intensity and the duration of the UCS (drug dose). If these are increased, the critical decay period will increase, allowing for greater opportunity for a subsequent administration to occur during that period and growth of the b-process by summation (Ternes, 1977).

Authors of the habituation model of tolerance predicted that tolerance development is reduced as the dose-interval is increased and drug dose is decreased. Rather than through the growth of the compensatory response, this effect is accounted for in terms of priming. If a drug is administered while its stimulus properties still exist in the memory register (self-generated priming), less processing is required and responding is decreased. So the dose-interval must be shorter than the duration of the existence of the stimulus properties in the memory register. If the dose-interval is longer than this duration, then the organism is no longer primed and the drug elicits greater processing and responding.

Drug dose is predicted to increase the magnitude and duration of self-generated priming, which would delay the decay of the stimulus properties of the drug in the memory register. Extrapolating from the habituation literature, Baker and Tiffany (1985) assume that "the duration and magnitude of self-generated priming induced by any given drug exposure is a direct function of the drug dose" (p.

84). Data has supported the prediction that tolerance magnitude is positively related to dose level (for example, Kayan, Ferguson, & Mitchell, 1973). Combined, dose-interval and dose level have been found to have an interactive effect on tolerance. Tolerance magnitude has been shown to be a positive function of dose size and a negative function of dose-interval (Seaman, 1985).

Baker and Tiffany (1985), however, went one step further and proposed an interactive effect of dose-interval and dose on the conditioning of tolerance. They stated that "the relative impact of drug-cue contingencies decreases as a negative function of dose and a positive function of dose-interval" (p. 85). High doses and short dose-intervals are conducive to the development of nonassociative tolerance. At very high doses, tolerance develops whether or not cues are present (Baker & Tiffany, 1985). They predicted that self-generated priming should diminish the association of a salient cue with a drug representation, reducing the development of associatively-generated priming. A high drug dose increases the magnitude and duration of self-generated priming. If the drug is again administered within a short dose-interval, the self-generated priming will mediate tolerance development and, at the same time, prevent drug cue-contingencies from exerting any substantial impact. In contrast, long dose-intervals and low doses are likely to be conducive to the development of associative tolerance and

detrimental to the development of nonassociative tolerance, because these conditions mitigate against self-generated priming. According to the habituation model of tolerance, the proportion of tolerance development attributable to drug-cue contingencies generally decreases with an increase in dose and a decrease in the dose-interval.

Authors of the homeostatic model also recognized the impact of drug dose and dose-interval on tolerance development, as well as their interactive effect on the development of associative and nonassociative tolerance. The strength and persistence of the unconditional adaptation is said to be a function of the magnitude of the drug disturbance, which is a direct function of the dose. Nonassociative tolerance is mediated by the perseveration of the unconditional adaptation. It then follows that short dose-intervals and large doses foster the development of nonassociative tolerance.

According to the homeostatic model, the perseveration of the adaptation can interfere with the development of associative tolerance. This is based on the ineffectiveness of a backward conditioning paradigm. No conditioning should occur when the cue is presented in a backward or simultaneous relationship with the UCR (Rescorla & Wagner, 1972). If the CS is presented during the perseveration of the UCR, a backward conditioning trial has occurred. "Consequently, the procedures favorable for the acquisition

of nonassociative tolerance (high doses and short dose-intervals) are incompatible with the development of associative tolerance even when salient drug signaling is ostensibly provided" (Poulos & Cappell, 1991, p. 400).

Smoking

The majority of the research on models of tolerance has been performed with opiates and alcohol. Relative to the research base on these drugs, nicotine tolerance has not been studied as extensively. One reason may be the numerous, varying and sometimes paradoxical effects of smoking. Nicotine produces both stimulant and depressant effects (Henningfield, 1984). Increased heart rate, blood pressure, EEG activity, release of catecholamines, adrenaline output, cortisone secretion, vasopressin output resulting in the antidiuretic effect, respiratory rate, coronary blood flow, cutaneous vasoconstriction, and muscle blood flow are a few of the effects of smoking (Benowitz, 1986; Frankenhaeuser, Myrsten, Post, Johansson, 1971; Hughes, Higgins, & Hatsukami, 1990; Perkins, Epstein, Jennings, & Stiller, 1986; Perkins et al., 1989; Rose, Ananda, & Jarvik, 1983; Russell, 1976; Shiffman & Jarvik, 1984; West & Russell, 1987). Smoking has also been found to produce decreased muscle tension, depression of spinal reflexes, decreased skin temperature, and decreased peripheral blood flow (Frankenhaeuser et al., 1971; Rose et al., 1983; West & Russell, 1987). Additional effects of

smoking include a subjective experience of relaxation (Shiffman & Jarvik, 1984), attenuation of the pain threshold (Epstein, Caggiula, & Stiller, 1989), and anorexia (Caggiula et al., 1989).

Thousands of different compounds are contained in tobacco and tobacco smoke (Dube & Green, 1982; Henningfield, 1984), chief among these are tar, carbon monoxide, and nicotine (Jarvik, 1979). Most of the physiological and some of the psychological effects of smoking have been attributed to nicotine (West & Russell, 1987). Nicotine has been said to be the primary responsible agent for why people smoke (Benowitz, 1986).

Tolerance to a number of the effects of smoking and/or nicotine has been observed in both animals and humans. Acute cardiovascular tolerance to nicotine (Aceto, Tucker, Ferguson, & Hinson, 1986) and chronic tolerance to the cardiovascular effects of nicotine has been clearly demonstrated in animals (Marks, Stitzel, & Collins, 1987). Animals have also been shown to develop tolerance to the depressant effect of nicotine, namely on the spontaneous activity and rearing activity of rats (Keenan & Johnson, 1972; Morrison & Stephenson, 1972; Stolerman, Fink, & Jarvik, 1973). Tolerance to the analgesic and anorectic effects of nicotine have also been demonstrated in rats (Caggiula et al., 1989; Epstein et al., 1989; Levin, Morgan, Galvez, & Ellison, 1987; Mousa, Aloyo, VanLoon,

1988).

Tolerance to the heart rate and blood pressure effects of nicotine have been demonstrated in humans (Benowitz, 1986; Jarvik, 1977; Jones, Farrell, & Herning, 1978). Acute and chronic tolerance to the effect of nicotine on heart rate in humans has been documented (Perkins et al., 1989; Porchet et al., 1988).

Like the research on opiates, the impact of environmental cues on the development of tolerance to some of the effects of nicotine has been demonstrated. Epstein et al. (1989) found that tolerance to the antinociceptive effects of nicotine was associative. Using rats, tolerance was established in a fixed environment. On the test trial, nicotine was administered in a new environment. The rats showed their initial responses to nicotine before developing tolerance on this test, demonstrating a reversal of tolerance.

On a follow-up study, Caggiula et al. (1989) manipulated the temporal cues before administration of nicotine on the test trial by omitting the weighing of the animals. Even though the animals remained in the same environment where tolerance had developed, they showed some loss of tolerance to the anorectic effect of nicotine. Manipulating subtle cues such as temporal patterns affected tolerance, demonstrating that these cues are also associated with tolerance development.

Conditioned or associative tolerance to smoking has also been demonstrated in humans. Epstein, Caggiula, Perkins, McKenzie, and Smith (1991) manipulated the environment by playing 5 five-minute segments of a story on audiotape. One-half of the subjects listened to different or changing segments of the story (a Sherlock Holmes radio show), while the other half of the subjects heard the same segment repeated between trials. Subjects in the repeated group developed tolerance to the heart rate effect of smoking, while subjects in the changing group did not show heart rate tolerance. No differences were found in heart rate during the story segments and prior to smoking.

These results suggest that a changing context can inhibit the development of tolerance to smoking. Epstein et al. (1991) suggested that these results have implications for understanding tolerance to smoking and the behavior of smokers. In many laboratory studies involving humans, the context remains constant, which may maximize the development of tolerance. However, generalization to natural settings is limited where the environmental stimuli may be variable. Epstein et al. (1991) also suggested that smokers may vary their environment (by drinking coffee or moving to a different room, for example) to maximize the effects of smoking by inhibiting tolerance development. Further research on the relationship between dose and environmental effects on humans was recommended (Epstein et al., 1991).

Present Study

The purpose of this study was to replicate and extend the findings of Epstein et al. (1991) by examining the effects of dose and dose-interval on the development of acute tolerance to the effect of smoking on heart rate in humans. The results found by the Epstein et al. (1991) study may vary depending on these two variables, as suggested by the habituation and homeostatic models of tolerance. According to the habituation model of tolerance, high doses increase the duration and intensity of self-generated priming. When the dose-interval is shorter than the duration of this priming, tolerance develops regardless of environmental cues, because the priming inhibits the acquisition of drug-cue contingencies. In contrast, low doses and long dose-intervals permit priming of the drug-cue contingencies, or associative priming, which leads to associative tolerance, and at the same time preventing self-generated priming and nonassociative tolerance (Baker & Tiffany, 1985). In the homeostatic model of tolerance, a low dose plus a long dose-interval results in associative tolerance through Pavlovian conditioning of a compensatory response. However, high doses increase the perseveration of the compensatory response, and when combined with a short dose-interval, establishes a backward conditioning sequence, inhibiting the development of conditioned tolerance. Therefore, high doses and short dose-intervals enhance

nonassociative tolerance development (Poulos & Cappell, 1991)

The present study employed a design similar to the one used by Epstein et al. (1991). The context prior to smoking was varied or held constant. Dose and dose-interval were jointly manipulated. Whereas Epstein and colleagues used five trials, a sixth trial was added to the current study during which a new story segment was presented before smoking to all subjects. If the developed tolerance was associative, then it could be disrupted or at least partly reversed by the introduction of a new story segment.

The following predictions were made: (a) subjects who smoked a low dose with a long dose-interval in a constant environment would develop heart-rate tolerance from Trials 1 to 5, while subjects who also smoked a low dose with a long dose-interval in a changing environment would not develop tolerance, replicating the findings of Epstein et al. (1991); (b) in the high dose plus short dose-interval condition, subjects would develop tolerance regardless of the environmental manipulation, demonstrating nonassociative tolerance to the heart-rate effects of smoking and nicotine; and (c) tolerance would be disrupted in the subjects who smoked a low dose with a long dose-interval in a constant environment when the cue was changed by playing a new story segment. No effects of the manipulation on the sixth trial in the other groups were expected.

Lastly, Epstein et al. (1991) suggested that a group of sham smoking controls "would provide a test for the role of nicotine versus smoking in the conditioning process" (p.17). While true sham smoking was not used, a second study was conducted without smoking to determine if the Epstein et al. (1991) results could be accounted for by habituation to the experimental stimuli.

Method

Experiment 1

Subjects. Forty male subjects (mean age = 26.1 years, S.D. = 9.2) participated. Although no gender differences were expected, males were chosen because the Epstein et al. (1991) were based on male subjects. Each subject had reportedly smoked 15 or more cigarettes per day for at least 6 months, had made no serious attempts to quit (i.e., smoke-free for more than 72 hours) within the last 6 months, had no reported cardiac dysfunction or disease, and had an alveolar carbon monoxide (COa) level of at least 8 ppm at the time of arrival for the experiment. In addition, subjects were required to be within 20% of their ideal weight for their height and at least 18 years of age.

Measures. Expired alveolar carbon monoxide (COa) levels were measured using a Vitalograph BreathCo COa monitor (model 29.000) after the cigarette smoked at the beginning of the adaptation period and after the cigarette smoked on the final trial. COa was used as an indirect

measure to determine the effectiveness to the dose manipulation, since it is an easily obtained and useful measure of recent cigarette smoking. COa has a half life between 2 to 4 hours and is absorbed quickly, which occurs only if the person actually inhales the smoke. Furthermore, peak COa levels can serve as estimates of plasma nicotine levels during smoking (Henningfield, 1984).

Heart rate was measured using a photoelectric plethysmograph that was wrapped around each subject's middle finger. The signal was processed and amplified through a J & J Systems computer program, and then converted to beats per minute (bpm). At the end of the adaptation period, a 15 second baseline recording of each subject's heart rate was taken. Heart rate was then recorded on each trial during the last 2 minutes of the pre-smoking stimulus and during the 2-minute smoking period. All subjects had at least 5 minutes (10 minutes in the low dose/long dose-interval condition) between smoking periods to recover from the heart rate boosting effect of smoking.

Procedure. Each subject participated in one 2-hour session. As compensation for their time, subjects received either extra credit in a psychology course (if the subject was a student) or a \$10 honorarium. Subjects smoked ad lib before the session that day and were tested at various times of the day. While this method had the disadvantage of producing differing levels of exposure to nicotine across

subjects and the risk of reduced heart rate acceleration, since the greatest heart rate boost occurs after the first few cigarettes of the day (Benowitz, 1986), ad lib smoking before the experiment had the advantage of allowing greater generalization to natural smoking behaviors and responses. On arrival, subjects read and signed the consent form, heard the instructions for the experiment, and then had the photoelectric plethysmograph placed on the middle finger of the hand that was not used during smoking. Each subject then smoked one cigarette so that the time from that cigarette to the beginning of the experimental session was constant among subjects. A total of 30 minutes passed to permit the subjects to adapt to the room, during which they were encouraged to relax and browse through some magazines.

Subjects were randomly assigned to one of four groups in the three factor mixed design. The two between factors were the smoking administration condition (high dose/short dose-interval vs. low dose/long dose-interval) and the context prior to smoking (changing vs. repeating pre-smoking stimulus). The within factor was time (Trials 1 - 6).

The procedure for this study is presented in Table 1.

Insert Table 1 about here

Each group was presented with six smoking trials. For the subjects in the low dose/long dose-interval smoking

condition, each smoking period was separated by a 10 minute segment (dose-interval = 10 min), which was divided into two 5-minute blocks -- 5 minutes of silence and 5 minutes of the pre-smoking stimulus (CS). This was the dose-interval used by Epstein et al. (1991). For subjects in the high dose/short dose-interval smoking condition, smoking periods were 5 minutes apart (dose-interval = 5 min); this was the 5 minutes of the pre-smoking stimulus. Only the subjects in the low dose/long dose-interval condition received 5 minutes of silence after each smoking period.

Subjects were presented with a changing pre-smoking stimulus or a repeating pre-smoking stimulus. Segments of a short, fictional mystery by King (1988) on audiotape were used as the pre-smoking stimulus. Approximately the first 4 1/2 minutes of the story were played for subjects in all groups on the first trial. On Trials 2, 3, 4, and 5, subjects in the changing context condition heard the second, third, fourth, and fifth 4 1/2-minute segments, respectively. Subjects in the repeating context were presented with the first segment on Trials 2, 3, 4, and 5. To further assess the extent to which any tolerance was associative or nonassociative, a sixth trial was added to the design used by Epstein et al. (1991). On Trial 6, all subjects were presented with the sixth segment of the story. Thus, the subjects in the changing context received new information with each trial, requiring new processing, while

subjects in the repeating context were exposed to a consistent CS on Trials 1 through 5, and a new stimulus on Trial 6. So until Trial 6, subjects in the repeating context were not required to process new information on each trial. Only the first and sixth 4 1/2-minute segments were presented to subjects in the repeating context condition. The length of time spent listening to a segment was held constant across groups. To ensure that the subjects attended to the stimulus, they were asked to recall as much of the story segment as they could by recording it on a piece of paper during the final 30 seconds of the 5-minute block before smoking. Subjects were informed that their recall sheets may be inspected at the end of the session, however accuracy in recall was not stressed. Visual inspection of the recall sheets indicated that subjects were compliant. At the end of Trial 6, subjects were debriefed and thanked for their participation.

Smoking. Subjects smoked their preferred brand of cigarettes six times. Smoking periods were 2 minutes in length for all groups. In the low dose/long dose-interval condition, subjects received four puffs at 30 second intervals, while subjects in the high dose/short dose-interval condition received six puffs taken at 20 second intervals. To attempt to decrease variability in dosage between each puff and each trial, subjects were asked to use a simple paced-puffing procedure, instructing them when to

inhale and exhale. A new cigarette was used for each trial.

At the start of each smoking period, subjects were instructed to light a new cigarette without inhaling. Five seconds passed while the subject lit the cigarette and waited for the next instruction. When subjects heard the word "ready," they brought the cigarette to their lips. They were then told to inhale, and 4 seconds later, were told to exhale. Visual and auditory cues provided evidence that subjects were compliant with the procedure. Subjects in the high dose/short dose-interval condition exhaled their sixth puff at 107 seconds into the 2-minute period, and subjects in the low dose/long dose-interval exhaled their fourth puff at 97 seconds into the 2-minute period.

Experiment 2

Subjects. Thirty-six male subjects (mean age = 20.6 years, S.D. = 2.7 years) participated. All subjects were nonsmokers, were within 20% of their ideal weight for their height, and were at least 18 years of age. Additionally, each had a COa of less than 2 ppm at the time of the experiment and had no reported cardiac dysfunction or disease.

Measures. COa was measured prior to the initiation of the experimental session to provide confirmation that the subjects were non-smokers.

Heart rate was assessed in the same manner using the same equipment described in Experiment 1. Heart rate was

measured for 15 seconds at the end of the adaptation period. During the final 2 minutes of the stimulus and during the 2-minute inhalation/exhalation period, recordings of heart rate were taken for each trial.

Procedure. As in the first experiment, subjects were seen for one 2-hour session each, at various times of the day. As compensation for their time, each received a \$10 honorarium or, if they were a student, extra credit in their psychology course. First, subjects read and signed the consent form, listened to the instructions, and then had the photoelectric plethysmograph placed on the middle finger of their non-dominant hand. A 30-minute period was provided to allow subjects to adapt to the experimental setting. During this time, subjects browsed through a selection of magazines.

Random assignment to one of the two groups of the two factor mixed design was made. Context (changing vs. repeating stimulus) was the between groups factor, while time (Trials 1-6) was the within factor. As in Experiment 1, each group received six paced-inhalation/exhalation periods (used in place of smoking). Each period was separated by a 10-minute episode, which was divided into two 5-minute blocks. No stimuli were presented during the first 5 minutes. The second 5 minutes contained the 4 1/2-minute pre-inhalation/exhalation stimulus (the same as the pre-smoking stimulus used in Experiment 1). Subjects in the

changing context group heard Segments 1, 2, 3, 4, 5, and 6 on Trials 1-6, respectively. The first segment was presented to subjects in the repeating context group on Trials 1-5, and the sixth segment was presented on Trial 6. In sum, the same procedure that was used with subjects in the low dose/long dose-interval condition in Experiment 1 was used in Experiment 2 (with paced deep breathing instead of smoking). The only difference between these two groups in Experiment 2 is the context prior to the inhalation/exhalation stimulus.

Smoking Substitution. In place of smoking, subjects were asked to simply inhale and exhale using the same procedure described in Experiment 1 to pace puffing. Four deep breaths were coached every 30 seconds within the 2-minute period. Subjects exhaled their fourth deep breath at 97 seconds into the period.

Results

Experiment 1

Manipulation check. COa levels measured at each subjects' arrival were subjected to a 2 x 2 analysis of variance, with Group (constant or changing environment) and Administration (high dose\short dose-interval or low dose\long dose-interval) as the between factors. Significant differences in baseline COa among the four groups were not found. To determine the effectiveness of the manipulation of dose within the two Administration

conditions (high dose\short dose-interval or low dose\long dose-interval), COa levels measured at the end of the experiment were analyzed using a 2 x 2 (Group x Administration) analysis of variance. A significant main effect for Administration was demonstrated, $F(1, 36) = 5.55$, $p < .03$. The two High dose groups were shown to have significantly greater post-experiment COa levels ($M = 33.4$ and 38.0) than the two Low dose groups ($M = 30.5$ and 27.2) in a single factor analysis of variance simple effects test, $F(1, 38) = 5.57$, $p < .02$. Therefore, it can be concluded that the manipulation of dose was successful.

Dependent variable. Baseline heart rate was analyzed using a 2 x 2 analysis of variance, with Group (changing or constant environment) and Administration (high dose\short dose-interval or low dose\long dose-interval) as the between factors. No significant differences in heart rate during the baseline period were found.

Because tolerance is defined as a change in responding across time, change scores for each subject were calculated by subtracting the heart rate during smoking on Trial 1 from heart rate during smoking on all six trials. These change scores represent the departures from the initial response on Trial 1 and are presented in Figures 1 and 2.

Insert Figures 1 and 2 about here

The change scores for Trials 1 through 5 were analyzed first using a 2 x 2 x 5 mixed analysis of variance, where Group (changing or constant environment) and Administration (high dose\short dose- interval or low dose\long dose-interval) were the between factors and Trials was the within factor. A significant Group x Administration x Trials interaction was found, $F(4, 144) = 5.95, p < .0001$.

Because specific predictions were made based on the two combinations of dose and dose-interval, simple effects analyses were conducted holding Administration constant. For the two Low dose\long dose-interval groups, a 2 x 5 mixed analysis of variance (Group x Trials) was employed to analyze the changes in heart rate. A significant Group x Trials interaction was shown, $F(4, 72) = 2.93, p < .02$. Post hoc t -tests were conducted between the two groups at Trials 2 through 5, yielding significant differences at Trial 2 ($p < 0.04$) and Trial 5 ($p < 0.03$). The difference between the two groups approached significance at Trial 4 ($p < .06$).

When Administration was held constant at the high dose\short dose-interval condition, a 2 x 5 mixed analysis of variance (Group x Trials) showed a significant Group x Trials interaction, $F(4, 72) = 5.13, p < .002$. Post hoc t -tests revealed significant differences between the two groups at Trial 2 ($p < .003$), Trial 3 ($p < .04$), Trial 4 ($p < .007$), and Trial 5 ($p < .03$).

To determine the effect of the manipulation at Trial 6, the change scores at Trials 5 and 6 were analyzed using a 2 x 2 x 2 mixed analysis of variance with Group (constant or changing environment) and Administration (high dose/short dose-interval or low dose/long dose-interval) as the between factors and Trials (5 and 6) as the within factor. No significant differences were found.

Additional analyses of heart rate during the audiotape presentation (Figures 3 and 4) before smoking were conducted to determine the effect of the stimulus itself on heart rate. Differences between groups in heart rate during this period may provide some evidence that subjects' responses to the environment could contribute to conditioned drug effects.

Insert Figures 3 and 4 about here

A 2 x 2 x 5 mixed analysis of variance (Groups x Administration x Trials) of heart rate showed no significant effects. To further investigate any possible effects of the environmental manipulation on Trial 6, heart rate during the audiotape presentation on Trials 5 and 6 was analyzed using a 2 x 2 x 2 mixed analysis of variance (Groups x Administration x Trials). Again, no significant effects were found.

Post-experiment ratings. Subjects' ratings of dizziness, light-headedness, and nausea at the end of the experiment were each analyzed employing a 2 x 2 analysis of variance (Group x Administration). There were no significant effects in the dizziness ratings. A significant Administration effect, $F(1, 36) = 4.1, p < .05$, was found in ratings of light-headedness. Post hoc t -tests revealed that subjects in the high dose/short dose-interval condition reported feeling more light-headed at the end of the experiment than subjects in the low dose/long dose-interval condition ($p < .05$). A significant Group x Administration interaction was found in ratings of nausea, $F(1, 36) = 4.95, p < .04$. Post hoc t -tests showed that subjects who received a high dose in the changing environment reported more nausea than subjects who received a low dose in the changing environment ($p < .025$).

Experiment 2

For subjects exposed to the environmental manipulations without smoking, a comparison of baseline heart rate between the two groups (changing or repeating context) was made using a t -test. The two groups did not differ significantly in heart rate at the beginning of the experimental session.

As in Experiment 1, change scores were calculated by subtracting the heart rate during paced-breathing on Trial 1 from the heart rate during paced-breathing in the remaining trials. These change scores represent the departures from

the initial response on Trial 1 (Figure 5). The change scores for Trials 1 through 5 were analyzed using a 2 x 5

Insert Figure 5 about here

mixed analysis of variance, with Groups as the between factor (changing or repeating environment) and Trials as the within factor (1-6). There were no significant effects. To investigate any possible effect of the manipulation on Trial 6, heart rate change on Trials 5 and 6 was analyzed using a 2 x 2 mixed analysis of variance (Groups x Trials). Again, no significant effects were found.

Further analyses were conducted on heart rate during the audiotape presentation to determine the immediate effect of the audiotapes themselves on heart rate. Heart rates during the story segments are presented in Figure 6. Heart

Insert Figure 6 about here

rate during the first five trials was analyzed with a 2 x 5 mixed analysis of variance (Groups x Trials), which revealed a significant main effect of Trials, $F(4, 136) = 5.68, p < .001$. Post hoc t-tests were used to compare heart rate during Trials 2 through 5 to Trial 1 for each of the two groups. In the Changing-environment group, heart rate had significantly decreased during Trial 4 ($p < .004$) and Trial

5 ($p < .005$) . Heart rate during Trials 2 and 3 did not differ from heart rate on Trial 1. No significant differences in heart rate between Trial 1 and Trials 2 through 5 were found in the Repeating-environment group. To investigate any possible effect of the environmental manipulation on Trial 6, heart rate during the audiotape presentation on Trials 5 and 6 was analyzed using a 2 x 2 mixed analysis of variance (Groups x Trials). No significant effects were found.

Discussion

Subjects who received a low dose (four puffs), within a long dose-interval (10 minutes), when the environment was constant (hearing the same story segment each trial), developed tolerance to the heart rate effect of smoking. That is, with repeated trials of smoking, heart rate boost following the four puffs decreased. Subjects who received the same low dose and dose-interval, but in a changing environment (different story segments presented before each trial), did not show similar decreased heart rate boost. These data are consistent with the predictions.

No differences in pre-smoking heart rate across trials were found. This suggests that habituation to the environmental manipulation cannot independently account for the observed effect. If subjects were merely habituating to the repeating story segment rather than developing tolerance, a significant heart rate decline should have

been observed during the pre-smoking periods. This was not found. These results provide a replication of Epstein et al. (1991). Based on similar findings, they concluded that the cardiovascular effects of smoking can be influenced over time by the context in which smoking occurs. These data are similarly consistent with the general literature on the conditioning of drug tolerance (Siegel, 1989; Baker & Tiffany, 1985; Poulos & Cappell, 1991).

Based on the habituation and homeostatic models of tolerance (Baker & Tiffany, 1985; Poulos & Cappell, 1991), subjects who received a high dose (six puffs) within a short dose-interval (5 minutes) were predicted to develop heart-rate tolerance independent of the environmental manipulations. That is, they would develop nonassociative tolerance. However, heart rate tolerance under these conditions was not observed.

Two hypotheses may account for the failure to develop nonassociative tolerance. First, six puffs every 5 minutes may have resulted in a rapid build-up of nicotine, and possibly toxic levels. This administration level may have been too great to allow for the development of heart rate tolerance. Other researchers have found that larger doses do not lead to greater tolerance to nicotine. Stolerman, Bunker, and Jarvik (1974) found that elevated doses of nicotine in rats induced less tolerance than lower doses. They suggested that there may be an optimal dose for

eliciting tolerance to nicotine. Perkins et al. (1989) observed acute tolerance in heart rate in humans during the first 2 minutes following nasal-spray nicotine administration, particularly in the low dose rather than in the high dose condition. Unfortunately, neither of these studies assessed the contribution of the environment. Given that there may be upper limits to the level of nicotine administration for the development of tolerance, it leads one to question if nonassociative tolerance to smoking occurs.

The second possible reason for the inhibition of tolerance development is the novelty of smoking a high dose within a short dose-interval. Subjects who smoked four puffs every 10 minutes may have found that level similar to their typical self-administration pattern (Epstein et al., 1991). However, subjects who smoked six puffs every 5 minutes may have had certain subjective or emotional responses (such as anxiety or discomfort) because it was unlike their usual self-administration or because they experienced unpleasant side-effects. Subjects who received six puffs every 5 minutes reported more light-headedness than those getting four puffs every 10 minutes (no differences in dizziness were found, while mixed results were observed in ratings of nausea). Increased heart rate, inhibiting tolerance development, could have been associated with subjective responses.

Both of these factors (an exceedingly high dose and certain subjective responses) not only appeared to have prevented tolerance development, but they may have contributed to what appeared to be the development of sensitization in subjects who received six puffs every 5 minutes in a repeating environment. Sensitization is defined as an increased response to an initial drug effect over repeated drug administrations (Baker & Tiffany, 1985). Subjects who smoked six puffs every 5 minutes had a greater heart rate boost in response to smoking on Trials 2 through 6 as compared to Trial 1.

Unfortunately, the habituation and the homeostatic models of tolerance are unable to account for sensitization. Baker and Tiffany (1985) stated that tolerance and habituation are analogous. The authors employed the theoretical mechanisms of habituation to explain the development of associative and nonassociative tolerance. These same mechanisms cannot be used to account for sensitization, as it is not similar to habituation. Poulos and Cappell's (1991) homeostatic theory of drug tolerance is based on the assumption that organisms strive to reinstate systemic balance. Because sensitization represents an increase in the departure from baseline, their model could not explain drug sensitization.

In contrast, there exists a Pavlovian conditioning model of sensitization (Siegel, 1989). According to this

model, some drug-conditioned responses mimic the drug effect. The end result is an augmentation of the drug effect over repeated administrations. Siegel (1989) cited examples of drug sensitization that occurred when administration was in a constant environment, as opposed to administration in a varied environment.

Based on this model, it would have been expected to see greater sensitization in the group that received six puffs every 5 minutes in the repeating environment than in the group that received the same amount in a changing environment. These data are consistent with the model. Subjects in the repeating environment showed sensitization (greater heart rate boost on Trials 2 through 5 compared to Trial 1), whereas subjects in the changing environment did not. Differences in COa levels between the two High administration groups were not found, suggesting that differential smoke intake is not responsible for the differences in heart rate.

According to the Pavlovian model, the observed sensitization is a result of a conditioned response that mimics the drug effect. However, in the Low dose/long dose-interval, Repeating environment group, tolerance developed as a result of a conditioned drug-compensatory response, according to this model. Perhaps nicotine produces effects that can lead to conditioned tolerance or sensitization, which depend on the dose and dose-interval.

These data may also be explained by the opponent-process model (Solomon & Corbit, 1973). Over time, the drug effects are diminished by the opposing process, the b-process, producing tolerance. Initially, the b-process has a long latency, leaving the drug effect (a-process) unopposed. With repeated administrations, the intensity and duration of the b-process grows, while the latency decreases. Sensitization may occur when the drug is presented more rapidly than the latency of the b-process. This would not allow the b-process to reach its peak manifestation, resulting in a state that is mostly the result of the a-process. Furthermore, the short dose-interval may have permitted conditioning of the a-process, accounting for the development of sensitization in the Repeating group and not in the Changing group. When the dose-interval was long, the latency of the b-process may have decreased, possibly allowing the b-process to become the conditioned response.

With respect to the hypotheses about tolerance reversal, it was predicted that changing the environment before smoking on the sixth trial, after tolerance had developed, would interfere with further tolerance development or reinstate a heart rate boost. Baker and Tiffany (1985) referred to this phenomenon as dishabituation. They stated that dishabituation occurs when a novel, salient stimulus interferes with the maintenance of

the drug's stimulus properties in memory, or interferes with the retrieval of the stimulus properties from long-term memory storage. A very similar process where tolerance is reversed is called external inhibition (Siegel, 1989). This occurs when the conditioned response is disrupted by the presentation of a novel, extraneous stimulus. This phenomenon was described by Pavlov (1927). According to his observations, any novel stimulus presented before or in conjunction with the conditioned stimulus (CS) would interfere with the expression of the conditioned response (CR), even after further presentations of the CS where the novel stimulus was no longer present. It is this author's understanding that external inhibition does not refer to a modification in the CS, but rather the introduction of a second, independent stimulus. In this study, the CS was modified on the sixth trial, creating a CS that was different from the one associated with the developed CR (decreased heart rate). Even though these phenomena are somewhat different, the same effect was predicted (tolerance would be disrupted).

Unfortunately, current data do not support the prediction. An analysis of heart rate boost during smoking revealed no significant effect from Trials 5 to 6 by modifying the story segment on Trial 6. In the group that had developed tolerance after receiving four puffs every 5 minutes in a repeating environment, a significant reversal

of tolerance was not observed.

One potential explanation for the failure to demonstrate reversal of tolerance may be related to attention and information processing. On the sixth trial, all groups heard approximately 4 1/2 minutes of the story that was near the conclusion. For the subjects in the changing context, there was continuity in the story between trials. However, the subjects in the repeating context heard only the first 4 1/2 minutes of the story. So, the story segment that was played on the sixth trial had little connection with the first 4 1/2 minutes, lacking that continuity experienced by the Changing context group. Therefore, subjects in the repeating group, perhaps already having decreased their level of attention and processing of the tape, may have not attended to and processed the tape on the sixth trial because it did not make sense or fit with the tape that they had repeatedly heard. This attention factor may have inhibited the reversal of tolerance.

Perhaps merely changing environmental cues is not sufficient to inhibit or disrupt tolerance. It may be necessary for subjects to also notice and be able to process the change in the environment. Baker and Tiffany's (1985) model of tolerance relies on the information processing of the subject. According to the authors, a stimulus produces a greater response when that stimulus is "surprising," and requires increased processing. This implies that the

subject plays a somewhat active role in determining its response, rather than a passive role.

In other studies that demonstrated partial or complete reversal of tolerance, the change in environment was distinct and may have required processing on the part of the subject, even in animals. For example, Epstein et al. (1989) administered nicotine to rats in a different room than the one where tolerance had developed. Caggiula et al. (1989) omitted a cue in the sequence of cues that had come to be associated with drug administration. Both of these studies demonstrated a more clear reinstatement of the initial drug response. In a preliminary study (Payne, Etscheidt, & Corrigan, 1990) using a single-subject design, heart rate tolerance was reversed when the subject smoked in a new environment. Puff duration could not account for the effect.

In the case of external inhibition, some have speculated that a novel stimulus disrupts tolerance via an orienting response that interferes with CR expression (Siegel, 1989). This also seems to suggest that the CS should be modified so that it requires an increase in information processing on the part of the subject in order to reverse tolerance. Playing the new segment of the same story on Trial 6 may not have encouraged the attention and processing that might have been needed for more complete dishabituation. Further research is needed to test this

notion.

Subjects who were exposed to either a changing or repeating context without smoking, but using a paced inhalation/exhalation procedure instead (four breaths every 10 minutes, with normal breathing in between coached breaths), demonstrated no differences in heart rate during the paced breathing. This appears to provide some evidence, although not conclusive, that normal habituation to the environmental stimuli can not explain the decreased heart rate boost observed in the group that smoked. The combination of environmental cues and smoking were required to produce the development of heart rate tolerance.

In summary, associative tolerance developed in the group which received a low dose within a long dose-interval in a constant environment that reliably signalled smoking. When the environment varied, tolerance development was inhibited. No differences were found in pre-smoking heart rate, suggesting that the effect is not mostly due to stimulus novelty in the changing environment condition. Also, no differences in heart rate were found during paced breathing in the subjects who did not smoke. With respect to the high dose/short dose-interval condition, tolerance was not observed, however, it appears that some degree of conditioned sensitization was. Tolerance may have been prevented due to the smoking administration level. Possibly, nonassociative heart rate tolerance does not occur

in smoking. Finally, the manipulation used in this study on Trial 6 did not reverse associative heart rate tolerance in subjects who received the low dose and long dose-interval. Clearly, further research is needed to address the previously discussed questions about the development and disruption of tolerance to smoking.

At this time, the relationship between the conditioning of physiological responses to smoking and the persistence of smoking behavior is not clear. Epstein et al. (1991) stated that smokers may change environmental cues, thereby inhibiting or disrupting tolerance, and maximizing the effects of smoking. However, tolerance to some of the effects of smoking may be desired by smokers. Future research may extend the findings of this study by investigating how tolerance development and reversal impact smokers' subjective responses and behavior.

Most models of tolerance propose that tolerance, withdrawal, craving, and dependence are closely related, and may even be mediated by the same mechanisms (Hinson & Siegel, 1980; Poulos & Cappell, 1991; Ternes, 1977). Clinical lore suggests that environmental cues previously associated with smoking can elicit craving and associated physiological responses and increase the probability of smoking. Cessation programs often recommend that smokers who are attempting to quit avoid certain environments likely to evoke these responses (Henningfield, 1984). It would be

premature to make generalizations from the results of this study in designing interventions for smoking cessation. In order to improve smoking cessation interventions, according to Shiffman (1993), "the field needs a rededication to basic research on smoking behavior and on nicotine dependence" (p. 721). Much more research is needed to provide a foundation for the development of improved clinical practice and outcome.

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Table 1

Sequence of events in the procedure for Experiment 1

	Trial					
Context	1	2	3	4	5	6
6 puffs every 5 min						
changing	1 P	2 P	3 P	4 P	5 P	6 P
repeating	1 P	1 P	1 P	1 P	1 P	6 P
4 puffs every 10 min						
changing	Q 1 P	Q 2 P	Q 3 P	Q 4 P	Q 5 P	Q 6 P
repeating	Q 1 P	Q 1 P	Q 1 P	Q 1 P	Q 1 P	Q 6 P

Note: Q = quiet (no stimulus presentation), 1-6 = story segments, P = paced smoking.

Figure Captions

Figure 1. Smokers' heart rate change from Trial 1 during smoking: four puffs every 10 minutes.

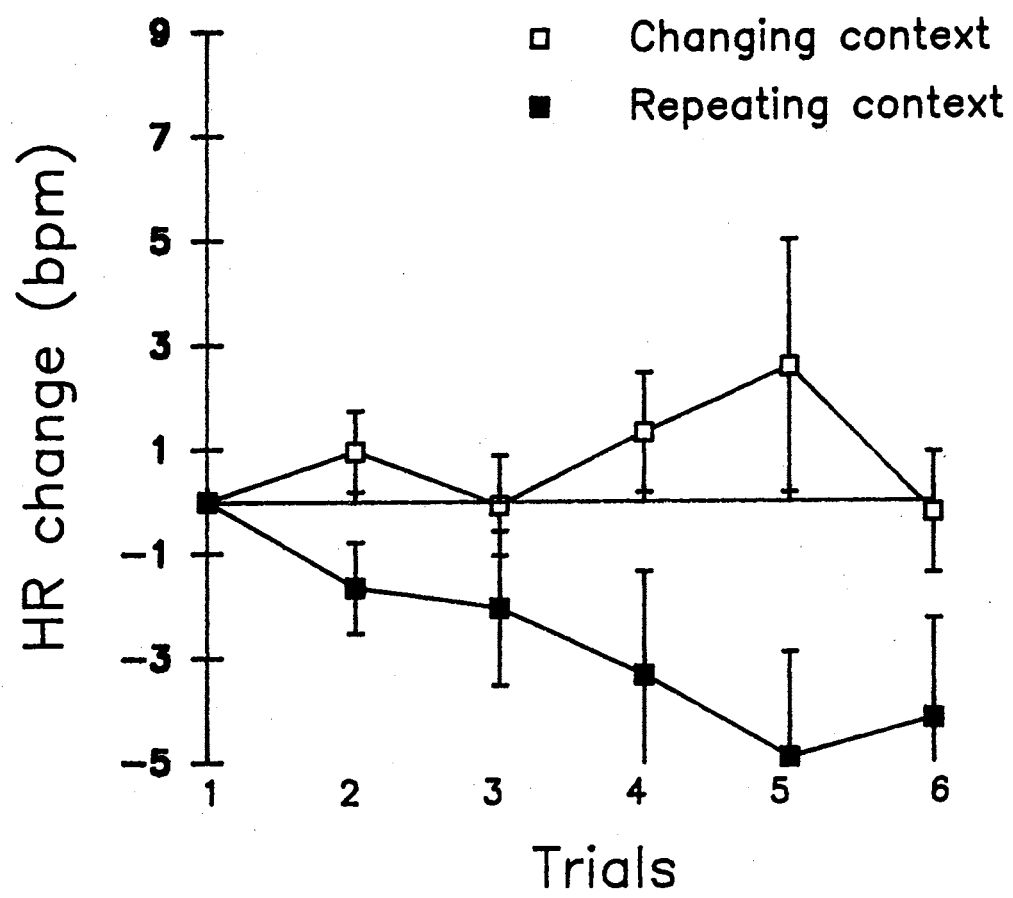
Figure 2. Smokers' heart rate change from Trial 1 during smoking: six puffs every 5 minutes.

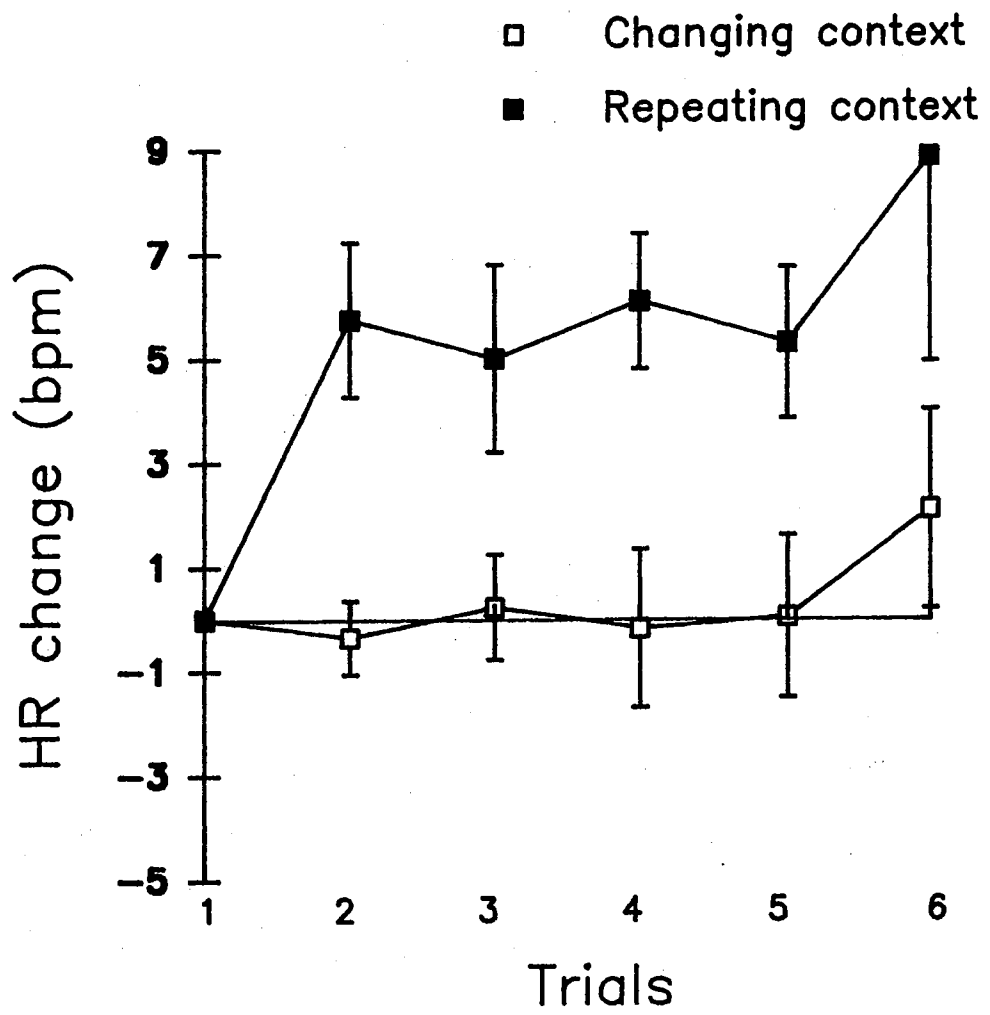
Figure 3. Smokers' heart rate before smoking (during the story segments): four puffs every 10 minutes.

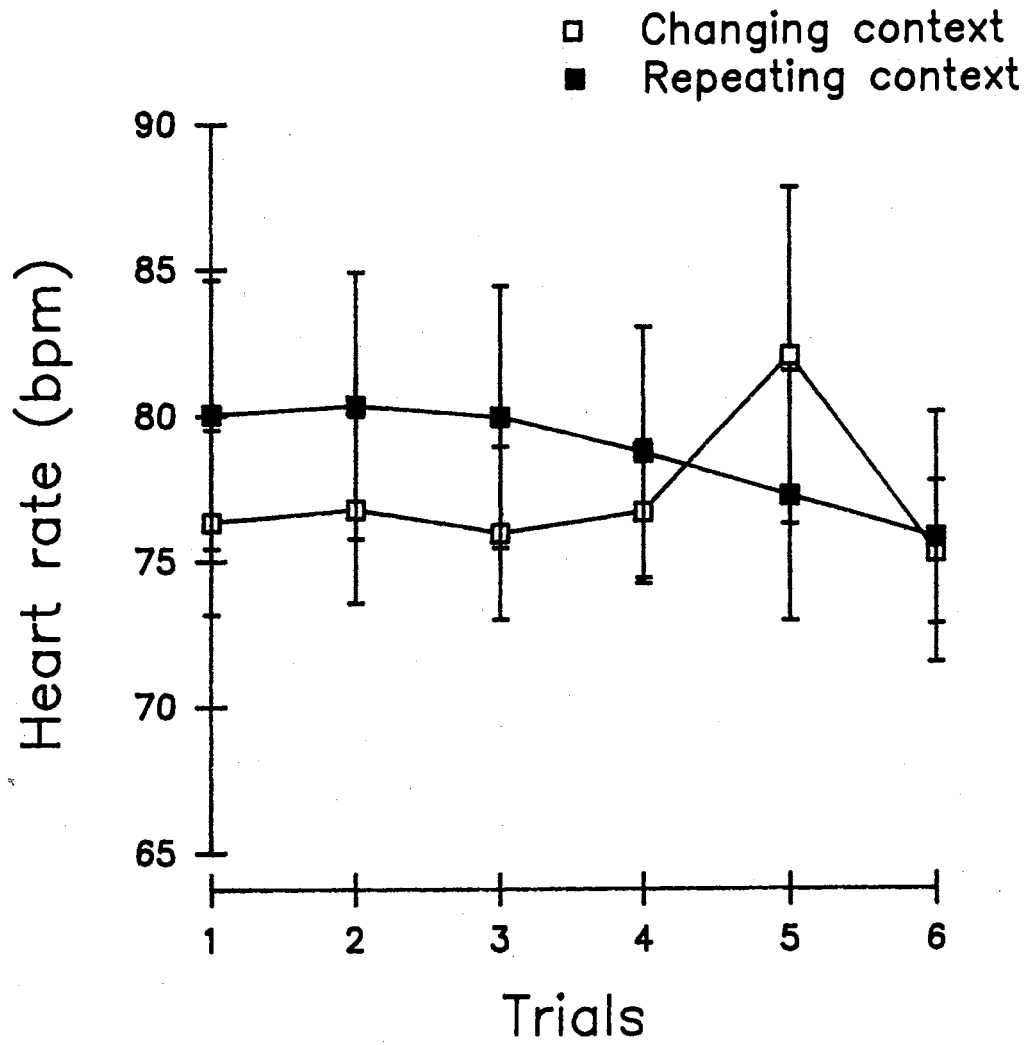
Figure 4. Smokers' heart rate before smoking (during the story segments): six puffs every 5 minutes.

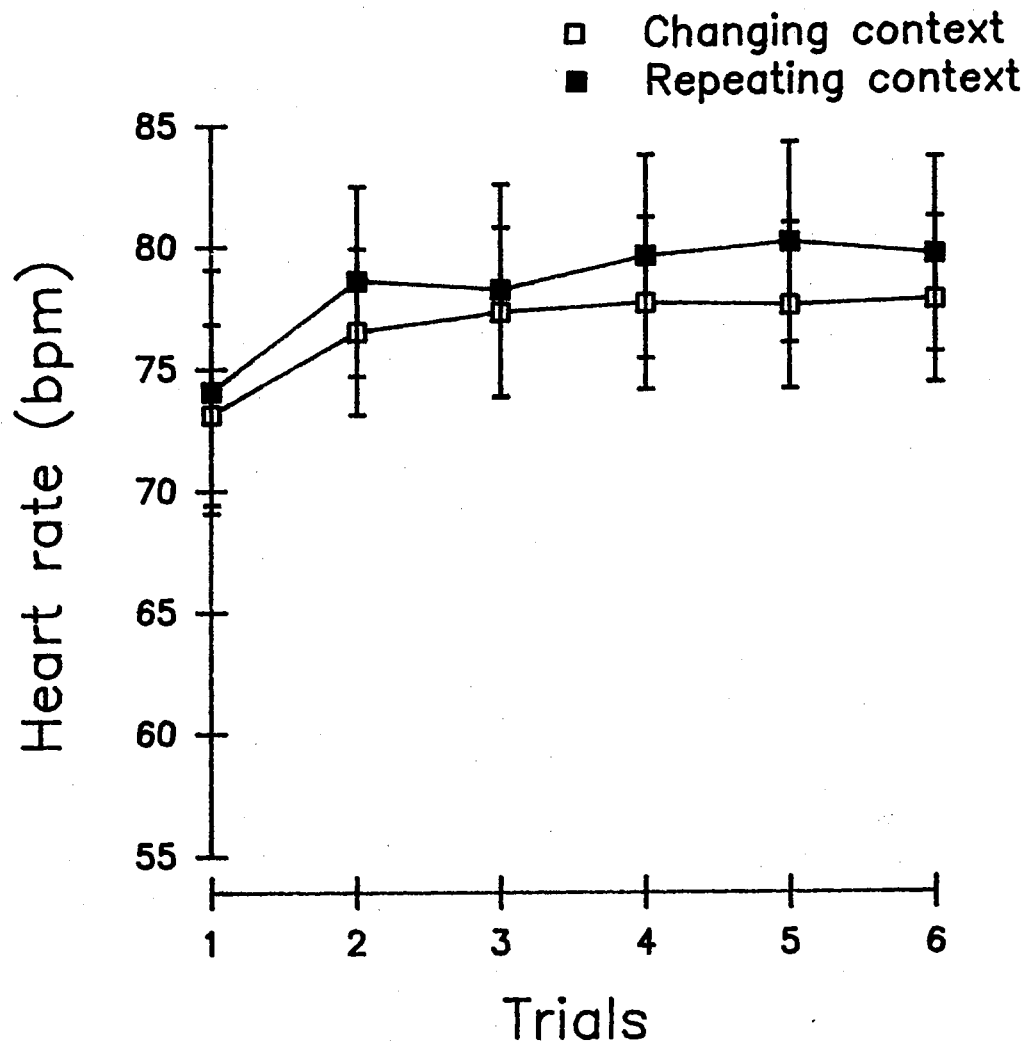
Figure 5. Nonsmokers' heart rate change from Trial 1 during paced-breathing.

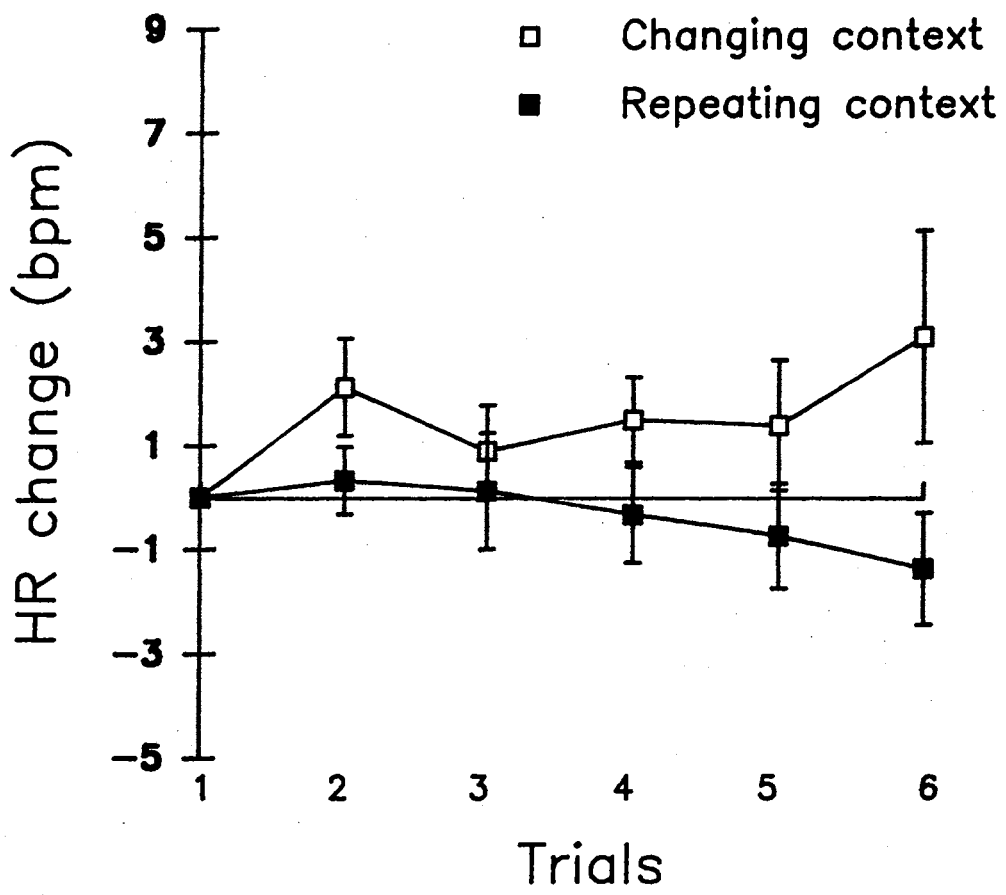
Figure 6. Nonsmokers' heart rate before paced-breathing (during the story segments).

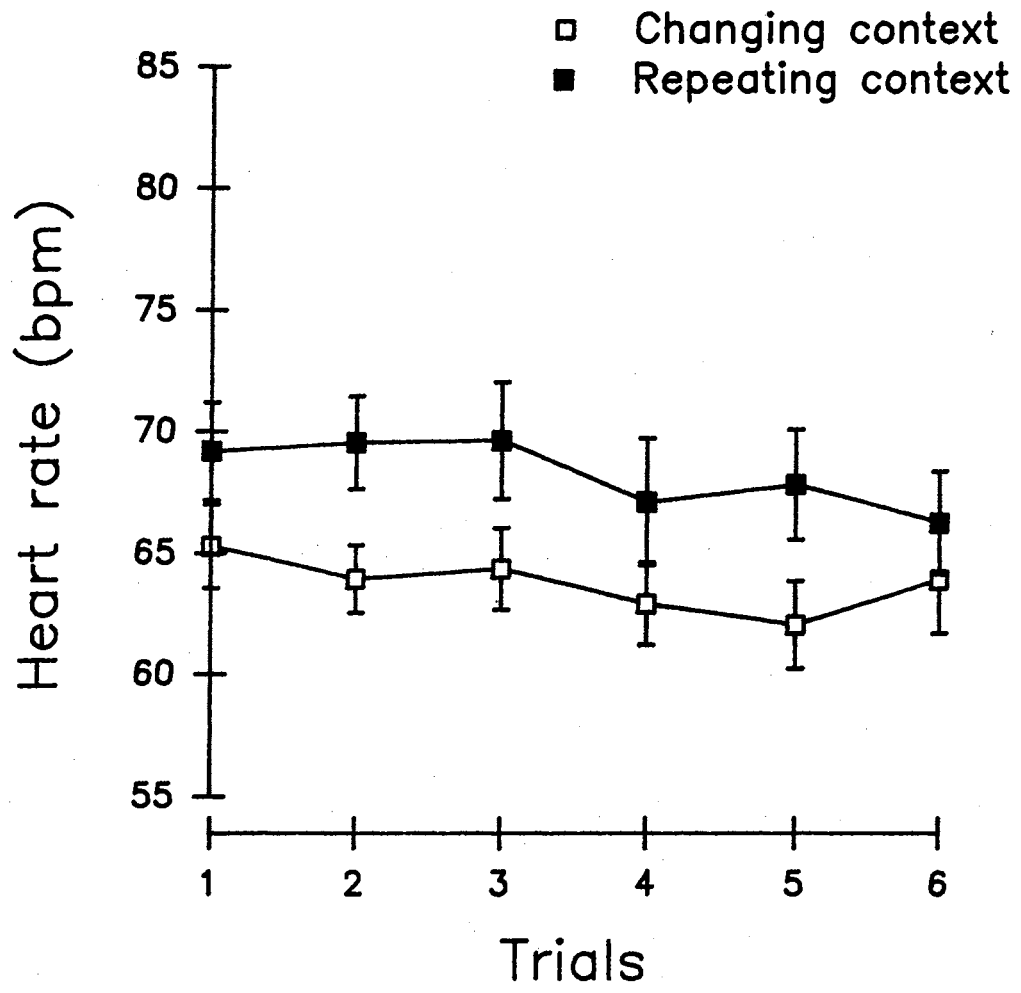












VITA 2

Lisa Christine Goulden

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Doctor of Philosophy

Dissertation: EFFECTS OF DOSE AND DOSE INTERVAL ON
CONDITIONED HEART RATE TOLERANCE TO
SMOKING

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Biographical:

Personal Data: Born in Tulsa, Oklahoma, On December
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Experience: employed as a Graduate Instructor in the
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OKLAHOMA STATE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
FOR HUMAN SUBJECTS RESEARCH

Proposal Title: Effects of Dose and Inter-Dose Interval on Conditioned
Tolerance to Smoking

Principal Investigator: Frank Collins/ Lisa Goulden

Date: 10-31-91 IRB # AS-92-017

This application has been reviewed by the IRB and

Processed as: Exempt Expedite Full Board Review
Renewal or Continuation

Approval Status Recommended by Reviewer(s):

Approved Deferred for Revision
Approved with Provision Disapproved

Approval status subject to review by full Institutional Review Board at
next meeting, 2nd and 4th Thursday of each month.

Comments, Modifications/Conditions for Approval or Reason for Deferral or
Disapproval:

Modifications Received

Signature: *Maria S. Tilley* Date: 6-25-92
Chair of Institutional Review Board