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Alcohol, Alcoholism, and the Autonomic Nervous System: A Critical Account

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Much of the current human experimental research on alcohol and the autonomic nervous system is driven by theoretical interests that were not apparent at the time of earlier reviews (e.g., Jones, et al., 1976; Naitoh, 1971; Wallgren and Barry, 1970). Among these theoretical concerns are expectancy and the balanced placebo design, cue reactivity and craving, priming, risk factors, and conditioned tolerance. These issues are important not only because of their theoretical significance but also because of their practical implications for treatment and treatment choice: abstinence versus controlled drinking. In this chapter we review some of these issues as they are reflected in studies using measures of the autonomic nervous system (ANS).

Experimental research and related theory in these areas might be enhanced if they were integrated more closely with theory and research in traditional areas of psychophysiology, especially those concerned with the organismic orienting reflex (OR), (Kimmel et al., 1979; Maltzman, 1990; Sokolov, 1960, 1963a,b; Sokolov and Vinogradova, 1975). The OR serves as an integrative framework, as well as a focus for our critical evaluation of much of the recent experimental research on alcohol and the ANS.

General Considerations

Some of the most important, obvious, but often uncontrolled variables in experiments in the field of alcohol and alcoholism are characteristics of the subject population.

Smoking and Other Drug Use

A subject variable that is often overlooked by investigators is whether the participant in an experiment is a smoker or nonsmoker. Smoking tends to be more common among alcoholics than nonalcoholics (Istvan and Matarazzo, 1984; Walton, 1972). It may have complex interactions with alcohol and other drug use, which may confound the effects of ethanol. For example, while performing in a psychophysical experiment, smokers who still smoked had consisistently higher heart rates (HRs) than abstaining smokers and nonsmokers whether they received high, low, or no dose of alcohol (Mello and Mendelson, 1986). In terms of electrodermal measures, smokers may attain the level of responsivity of nonsmokers immediately after smoking. However, smokers who abstain for a few hours will show lesser skin conductance responses (SCRs) than nonsmokers. These effects may interact with the kind of responses to novel or significant signal stimuli and may be modulated further by the stress of the unfamiliar psychophysiological laboratory (Lyvers et al., 1988).

Changing policies of hospitals concerning the permissibility of smoking make it more difficult to compare current and future studies with earlier experiments, making it all the more important to describe explicitly the smoking history of subjects, and where possible, to use the number of cigarettes smoked per day as a co-variate.

Controlling for illicit drug use is also essential, especially since polydrug use seems increasingly common among younger alcoholics. Interactions between alcohol and narcotics are likely to be reflected in autonomic measures. For example, Foltin and Fischman (1988) reported that a combination of ethanol and cocaine resulted in a higher heart rate (HR) than the use of either drug alone. Prescription medication and psychotropic drug use must be assessed and taken into account, since they may directly affect ANS measures.

Head Injuries

A history of head injuries is usually overlooked in studies using alcoholics or problem drinkers as subjects. Since alcoholics are more likely to have suffered head injuries than nonalcoholic control subjects, it is important to obtain a history from all subjects.

Chandler and co-workers (1975) demonstrated that possible brain injury, as indicated by self-reports of alcoholics, had an attenuating effect on autonomic measures, particularly phasic skin conductance (SC). Including patients with possible brain injury in the same group with patients with negligible injury reduced the overall difference in SC-ORs between patients and control groups in a psychophysical task situation.

Gender and Ethnicity

By far the majority of studies of alcohol and alcoholism are restricted to male subjects. Ethanol's effects on women are therefore much less understood. Examining

gender differences will sharpen the precision of the statistical analyses, increase the generality of the results, and provide an opportunity to isolate possible differences between women and men on variables of importance. Except for cardiovascular differences between men of Asian and European ancestry in response to an alcohol challenge, ethnic differences also have been neglected (Newlin, 1989b).

ANS, Specific and Nonspecific Responses, and Functional Systems

Despite anatomical and functional differences, the CNS and ANS act in synchrony and interact on numerous levels. Although the ANS has a certain degree of autonomy (hence the term "autonomic") in its control over the internal physiological milieu, its function is also highly influenced by the CNS. Ethanol's effects on ANS function are many and by no means simple. To maintain an optimal physiological state, the ANS operates with complex and interdependent sequences of negative and positive feedback. Any simplified generalization about the effects of alcohol on the ANS is virtually impossible.

Unlike many drugs (e.g., morphine and cocaine) alcohol, lacking specific receptors, exerts nonspecific effects on the cell membrane. Alcohol's effects on a wide array of cell activities (such as neuronal excitability, enzyme functions, and receptor sensitivity, seem to indirectly involve the "fluidization" changes of the membrane.

Effects of alcohol on the ANS cannot be studied in isolation without considering endocrine changes since the two coordinating systems are closely related and interdependent, as reflected by the adrenal medulla as the hormonal component of the ANS. Adrenomedullary activity, as activated by the sympathetic nervous system (SNS), has been reported to increase in response to the administration of alcohol, excreting noradrenaline and adrenaline (Marks, 1980).

Peripheral responses are relatively nonspecific. An increase in HR or electrodermal activity may be a component in different functional physiological systems and be induced by a variety of stimulus events. These functional systems include the appetitive, sex, fear, pain, and orienting systems. They involve integrated central and peripheral, somatic, autonomic, hormonal, and behavioral specific consummatory responses, as well as approach, avoidance, or indifference to environmental events. In our area of concern, an autonomic response often reflects an interaction between one or more functional systems, usually fear and/or orienting and the pharmacological effects of alcohol as they are modulated by higher cortical processes.

Further compounding the difficulties of interpreting the effects of alcohol upon the most commonly employed ANS measures—HR and SC—is the complexity of the response measures and the different neural circuits that may be involved in their regulation

Cardiovascular Measures (Heart Rate and Blood Pressure)

Using an EKG, HR is measured in terms of the interbeat interval (IBI), but is also frequently expressed in terms of pulse rate, the number of beat per minute. Heart rate is not controlled by a simple mechanism that indicates the state of the

originating physiological system in a straightforward manner, but rather by a complex interaction between the sympathetic and parasympathetic branches of the ANS as modulated by hormones of adrenocortical, gonadal, and thyroidal origin (Larsen et al., 1986). Postganglionic sympathetic fibers increase the HR by releasing noradrenalin in the proximity of the sinoatrial and atrioventricular nodes. The adrenal medulla increases sympathetic tone and consequently the HR by releasing adrenaline and noradrenaline. In contrast, the parasympathetic branch of the ANS exerts a direct deceleratory influence on IBIs of the heart via the cholinergic vagal nerve, as well as, indirectly by an inhibitory vagal influence on terminal sympathetic neurons. Thus, an increase in HR does not necessarily indicate an increase in sympathetic tone; it could also mean a decrease in parasympathetic input or reflect the interaction of the sympathetic and parasympathetic branches of the ANS. Heart rate changes do not occur independently of other organismic events. Influences of respiratory rhythm can be seen in heart rate records as respiratory sinus arrhythmia. The heart rate reflects inspirations and expirations as it co-varies with vagal tone. There seems to be a cardiac-somatic coupling so that increases and decreases in somatic activity are accompanied by corresponding changes in the HR (Obrist et al., 1974).

Heart rate acceleration has been demonstrated repeatedly when alcohol is given to nonalcoholics (Dafters and Anderson, 1982; Grassi et al., 1989; Kilpatrick et al., 1980; Sayette and Wilson, 1991; Sutker et al., 1982; Tong et al., 1974). The effect is proportional to the given dose (Kilpatrick et al., 1980; Tong et al., 1974). Moreover, abstaining alcoholics are characterized by faster HRs than normal controls (Chotlos and Goldstein, 1967) in response to innocuous stimuli, and their HRs increase more after a drink relative to normal controls (Kaplan et al., 1983; Lehrer and Taylor, 1974; Schandler et al., 1988). However, alcoholics showed a reduced range of HR acceleration in response to loud tones when sober (Knott and Bulmer, 1984) and intoxicated (Lehrer and Taylor, 1974).

Numerous studies have reported an increase in blood pressure, both systolic and diastolic, as a result of alcohol consumption (Grassi et al., 1989). Sympathetic innervation of skeletal arteries controls the degree of peripheral vasoconstriction, although the actual blood pressure is a result of a complex interaction among noradrenaline, a potent peptide angiotensin II, HR and contractility, and fluid volume, etc. (Larsen et al., 1986). Direct recordings of postganglionic sympathetic nerve activity in a study by Grassi et al. (1989) indicate the acute inebriation results in elevated blood pressure, which is closely related to increases in sympathetic activity. Increases in plasma catecholamines after a moderate dose of alcohol also suggest sympathetic involvement resulting in elevated blood pressure (Ireland et al., 1984). Chronic alcohol use is accompanied by heightened blood pressure in both genders (Criqui et al., 1981).

Skin Conductance Responses and the Orienting Reflex (SCR-OR)

Tonic skin conductance levels (SCL) and phasic response changes from those levels (SCRS), are determined primarily by the sympathetic nervous system (SNS)

in contrast to HR and most other peripheral autonomic responses, which are innervated by both parasympathetic and sympathetic branches of the ANS.

Changes in skin conductance to the passage of a weak constant current are attributed to activity of the eccrine sweat glands, which are found most often on the palmar and plantar surfaces. Although supplied by cholinergic fibers, activity of the eccrine sweat glands is controlled by the SNS branch (Fowles, 1986).

Some investigators have reported smaller SCR-ORs under the influence of alcohol (Kilpatrick et al., 1980; McGonnell and Beach, 1968). In contrast, other studies have reported that alcohol intake increases nonspecific SCR-ORs (Lyvers and Maltzman, 1991a; Pishkin et al., 1988; Richter et al., 1977;) as well as the SCR-ORs evoked by signal stimuli (Lyvers and Maltzman, 1991b). Variations in results of the above sort may be a consequence of the alcohol dose, the type of task, and whether voluntary or involuntary SCR-ORs are induced by significant or nonsignificant stimuli (Lyvers and Maltzman, 1991a; Maltzman, 1979a, 1979b).

Skin conductance changes seem to be the most sensitive and reliable measures of the OR system (Voronin and Sokolov, 1960) in response to novel innocuous stimulus changes. The OR is assumed to be a relatively nonspecific organismic response. Among its antecedent conditions are relative and absolute novelty of stimulation. Any increase or decrease or any qualitative, quantitative, or temporal change in stimulation may give rise to a generalized phasic or tonic nonspecific OR. It is conditionable and may also be elicited by unlearned biologically significant stimuli (Razran, 1961). It is considered an organismic OR because it includes generalized ANS, CNS, and neurohumoral changes. It involves activation of the ascending reticular activating system and, especially in novel biologically significant situations, the hypothalamic-pituitary-adrenal (H-P-A) axis (Hennessy and Levine, 1979; Levine & Wiener, 1989), as well as ascending dopaminergic pathways (Wise, 1988). It may also involve the release of endogenous opioids having analgesic effects that are reversible at least in part by naltrexone (Siegfried et al., 1987). Its assumed functional properties are that it habituates relatively quickly to innocuous nonsignificant stimuli, but shows varying degrees of resistance to habituation as a function of the significance of stimuli. Since Pavlov, it has been assumed that the important functional role of the OR is to facilitate perception and learning.

Sokolov's (1963a,b) neuronal model, comparator, or match/mismatch theory of incongruency between past and present stimulation is the most generally accepted interpretation of the effects of stimulus change. Habituation—decreases in measures of responsivity—occurs relatively rapidly with repeated occurrences of the same innocuous stimulus change. As the neuronal model of the new stimulus situation is formed, there is increasing congruency between past and present stimulation and its context and therefore a decrease in the conditions giving rise to the OR. Imparting significance or signal value to stimuli enhances resistance to habituation (Maltzman, 1979a,b, 1990; Sokolov, 1963a,b).

Another important consideration determining the kind and extent of the OR is the momentary state of the individual (Maltzman, 1990). Reactions to the unknown, the new, may vary as a function of the physiological state, developmental stage, and the context, including the presence of a significant other (Reznick, 1989). Many years of research by Gantt and his associates has demonstrated the profound impact that presence of one person may have upon the physiological state of another, thereby modulating the influence of such variables as pain, stress, alcohol and the like (Gantt et al., 1966/1991). Momentary states of the organism, both learned and unlearned, that affect the magnitude and resistance to habituation of orienting, will vary with individual differences (Kagan, 1989) and the environmental context. As Lacey (1959) has emphasized, autonomic responses are part of the total behavior of the individual that must be considered within the social context of the moment. They are transactions, not simple measures of a unitary dimension of arousal or anxiety.

There may be consistent individual differences in the organismic OR to biologically significant novelty (Reznick, 1989). These individual differences correspond to differences in introversion-extraversion (Kagan, 1989) and are pertinent to a variety of theories of personality differences in reaction to alcohol (Jones et al., 1978; Zuckerman, 1991). Theories of personality differences and their physiological correlates have also been related to personality types at risk for different kinds of alcoholism (Cloninger, 1987).

The above considerations are particularly important in considerations of set (the biobehavioral disposition at the moment) and setting (the physical and social environment at the moment). Although interactions between set and setting and the effects of illicit drugs have been recognized for years, studies have characteristically been descriptive in nature (Weil, 1972; Zinberg, 1984). Independent measures of physiological states underlying set and setting effects and demand characteristics would do much to clarify and establish a sound biopsychosocial basis for the interaction of the effects of instructions and social interactions in the laboratory with the effects of alcohol and other drugs. An effect obtained with alcohol is a consequence of the physiological state of the individual at the moment and its interaction with environmental factors. A different state of the individual, which differs as the result of instructions, social relationship to the experiment and experimenter, familiarity, and lack of fear of the physical and social environment, may interact with alcohol and influence the obtained effects of alcohol. In turn, the effects of alcohol on the physiological state of the individual influence other reactions and behavior in the social environment.

However, only a limited understanding of the effects of alcohol on the central dynamics of the OR can be obtained using slow peripheral autonomic measures, such as SCR. Measures of central activity as reflected in the EEG and its derivative, event-related potentials (ERPs), complement peripheral autonomic measures inasmuch as they have better temporospatial resolution, are less affected by homeostatic mechanisms, and can help discern the cortical generators of different phases and kinds of orienting behavior. A persistent problem has been the determination of the relationship between these two functionally different measures and the concomitant influence of alcohol.

Marinkovic (1993) has measured ERPs and SCRs concurrently in a within-subject balanced placebo design using moderately low alcohol doses (highest blood alcohol level (BAL) = 0.045). Measures were obtained during an auditory odd ball paradigm consisting of frequent tones, rare signal tones, and rare, unique novel tones. Subjects were instructed to count and press a button in response to rare signal tones and to disregard the frequent and novel tones. To investigate the manner in which the changes in activity of one system relate to changes in the other, the SCR-OR was used as a grouping criterion. The ERPs evoked by each stimulus type were averaged separately, depending on whether there was a measurable SCR-OR on a particular trial (SCR+ waveform) or not (SCR− waveform). Visual inspection of the waveforms in Figure 7-1b reveals a dramatic difference in the late positivity between SCR+ and SCR− waveforms evoked by novel tones in the placebo conditions. Whereas a large P3a peaking at about 280 msec was evoked on trials accompanied by a measurable SCR-OR, there was no such deflection on trials without an OR. In contrast, only a P3b with a latency of 300 msec was evoked on trials with no phasic SCR-ORs. Although a slightly biomodal late positive complex can be observed in the grand average waveform (Figure 7.1a), with bifurcated peaks corresponding in latency to the P3a and P3b as defined above, the measure of autonomic arousal clearly reveals the apparent connection between the P3a deflection and the phasic SCR-OR that appears 1 second later. Mild alcohol intoxication selectively abolished the P3a component evoked by novel tones. No reliable P3a was evoked by rare signal tones in any of the conditions, and the ERPs were not differentially affected by alcohol on SCR+ and SCR− trials. This evidence suggests that task-relevant signal tones and equally probable novel tones may be processed in a different manner by different sets of generating structures that are differentially affected by low alcohol doses. Intracerebral recordings in humans obtained during comparable tasks indicate that large P3a potentials can be observed in all frontal areas, with prominent inversions in orbitofrontal and anterior cingulate cortices indicating local generation (Baudena et al., in press).

Habituation

Habituation of an autonomic response—a decrement in some measure of responsivity, such as amplitude, with repeated presentations of the evoking stimulus—is a function of nonspecific and specific effects. Specific effects are dependent upon occurrence of a particular evoking stimulus and are ordinarily confounded with nonspecific effects of stress produced by novelty, unfamiliarity with the experimental situation itself, and lack of initial predictability of the experimental regime (Hennessy and Levine, 1979). The confounding of specific and nonspecific effects occurs within a given session, especially during the first experimental session and between repeated sessions (Lindsley, 1951; Lyvers et al., 1988; Maltzman et al., 1971b). Decreases in novelty-induced stress with repeated exposure to an innocuous predictable experimental regime result in decreases in autonomic responsivity. Repeated presentations of an innocuous nonsignificant stimulus produces stimulus-specific habituation quite aside from the nonspecific effects. Possible individual differences in habituation to novelty-induced stress arousal or familiarity with the experimental situation may further complicate the confounding effects of specific and nonspecific contributions to habituation of autonomic activity and moderate the effects of alcohol reflected by nonspecific autonomic responses.

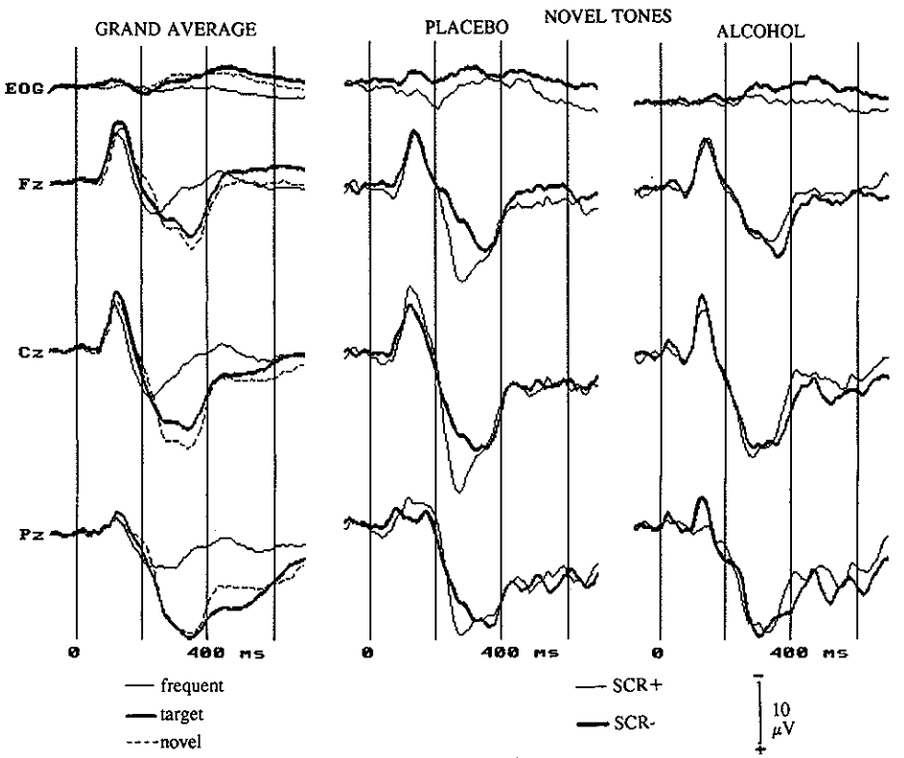

Fig. 7-1 A. ERP grand average for all subjects across all sessions. Waveforms obtained during the first 700 msec after stimulus onset on frequent, target, and novel trials are superimposed. Tone duration is 50 msec. Negative is up. **B.** Grand average SCR+ and SCR- waveforms to novel tones in "given placebo" condition. A large P3a deflection (280 msec latency) is accompanied by a SCR-OR one second later. In contrast, on trials with no measureable SCR-ORs, novel tones evoked P3b only. **C.** Grand average SCR+ and SCR- waveforms to novel tones in "Given Alcohol" condition. Moderately low alcohol intoxication selectively abolished the P3a deflection evoked by novel tones when only placebo was ingested. In contrast to a large difference in the Placebo condition, no difference in ERPs between the trials with and without SCR-ORs was detected in the Alcohol condition.

The value of familiarizing subjects with experimental procedures is indicated in an experiment by Marinkovic (1993). She used 1-minute intervals of resting

electrodermal activity as a measure of a general arousal state (Burch and Greiner, 1960; Silverman et al., 1959). Measures were taken during four within-subject sessions of a balanced placebo design. In addition, the same measures were obtained during the introductory visit to the laboratory. Repeated measures of ANOVA revealed no effect of the beverage or instructions on the SCRs. However, a significant effect of the session order for the number of nonspecific skin conductance responses (NS.SCRs), as well as for the average amplitude of the NS.SCRs generated within 1-minute intervals, was observed. As apparent in Figure 7-2, these measures declined significantly after the nonexperimental introductory session and remained rather constant throughout subsequent experimental sessions. Thus, the OR to novelty habituated after the first visit to the laboratory, resulting in stable arousal levels during the experiment and controlling for potential interactions of situation-induced arousal and alcohol.

Studies of Alcoholics

We now review some experimental studies of alcoholics that are related to theories of alcoholism and its treatment. Some of the clinical consequences of chronic alcoholism are then presented.

Priming, Craving, and Loss of Control

According to traditional theory (Jellinek, 1952, 1960; Keller, 1972), alcoholics are differentiated from problem drinkers by the syndrome of withdrawal symptoms, tolerance, craving, and loss of control. This syndrome is characterized by the inability to consistently refrain from drinking when the opportunity is present and to consistently stop drinking before a state of inebriation is reached. If loss of control is the critical behavioral marker of alcoholism, the implication for a treatment goal is obvious: abstinence.

Research-oriented opponents of the loss of control conception have examined the hypothesis in analogue laboratory studies. The best known of such studies is the experiment by Marlatt et al. (1973). It popularized use of the balanced placebo design for investigating the effects of alcohol in the laboratory and was instrumental in promoting an expectancy interpretation of the behavior of alcoholics, as well as the apparent effects of alcohol in social drinkers. Although Marlatt et al. (1973) did not use measures of autonomic activity, their experiment stimulated other studies that have employed such measures.

In that study, a double-balanced placebo factorial design was employed where half the subjects received an alcoholic beverage and half received a nonalcoholic tonic. Half the subjects in each of these two conditions were instructed that they received alcohol, whereas half were instructed that they received tonic. Two different groups of subjects each received these four treatments: given alcohol/told alcohol, given alcohol/told tonic, given tonic/told tonic, and given tonic/told alcohol. One group consisted of social drinkers, and the second group were non-

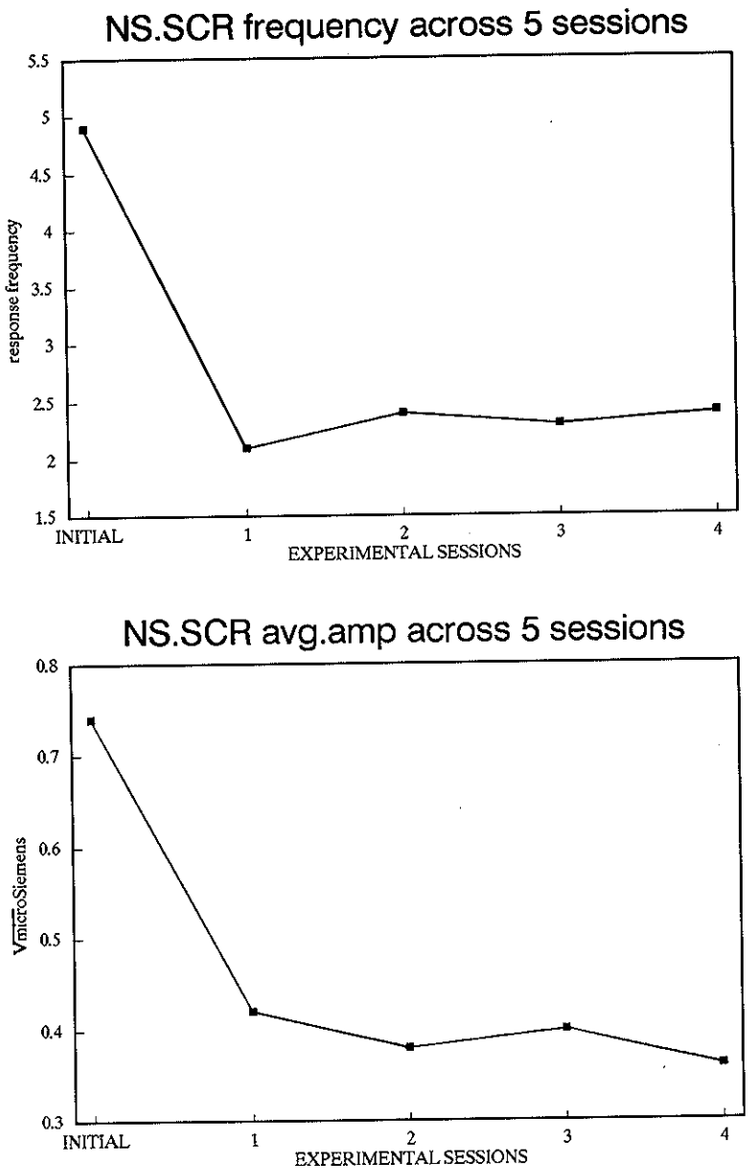

Fig. 7-2 Frequency and amplitude measures of nonspecific SCRs obtained by recording 1-minute intervals during the initial nonexperimental session and the four experimental sessions of the balanced placebo design.

abstinent "alcoholics," as defined by such criteria as having received treatment for alcoholism, membership in Alcoholics Anonymous, repeated arrests for drunk and disorderly conduct, etc. A priming dose was administered to the subjects before a beverage taste-rating task. Subjects receiving alcohol in the taste-rating task received a priming dose of vodka and tonic, whereas subjects receiving the nonalcoholic beverage in the taste rating task received tonic as a primer. Priming doses were administered approximately 20 minutes before the taste-rating task.

Results indicated that "alcoholics" and social drinkers drank more during the test if they were told that they were drinking alcohol whether or not they received alcohol. The interpretation offered was that the expectancy for alcohol or tonic determined the amount consumed and not the actual beverage administered. Corresponding effects were obtained in "alcoholics" and social drinkers. Furthermore, there was no evidence of loss of control or significantly more drinking by "alcoholics" who received alcohol than those who received the tonic placebo. "Alcoholics" drank more than social drinkers under both treatment conditions.

There are several serious shortcomings in this study that generally have been overlooked. One difficulty is that there was no independent measure of the severity of dependence. Loss of control is a behavioral characteristic of alcoholics who have had repeated and severe withdrawal experiences and not of problem drinkers, who have not displayed such symptoms of physical dependence. If subjects are not severely dependent upon alcohol, they would not experience craving and loss of control and therefore would not drink more with a priming dose than without one. In addition, the investigators conflate instructions, an experimental variable, with expectancy, a theoretical conception. An alternative interpretation of the effects of instructions is available and supported by experimental studies: the instructions employed induced demand characteristics (Knight et al., 1986; Korytnyk and Perkins, 1983). Additional shortcomings in the study have been discussed elsewhere (Maltzman, 1987, 1991, 1994).

According to the demand characteristics interpretation (Orne, 1962) the difference in status between the experimenter and subject induces a tendency in the subject to please the experimenter. The subject tries to produce the results desired by the experimenter. Hence, the effects of instructions are peculiar to the social psychology of the laboratory situation and have no generality beyond the laboratory. Korytnyk and Perkins (1983) have provided evidence in support of a demand characteristic interpretation of the effects of instructions in a balanced placebo experiment that is contrary to expectancy theory, evidence that generally has been ignored. In their study, in the absence of the experimenter—therefore in the absence of the demand induced by the usual experimental situation—more graffitti was produced by participants administered alcohol than tonic regardless of the instructions concerning drink content. Additional shortcomings in the balanced placebo design, its use, and its interpretation have been discussed in some detail elsewhere (Bradlyn and Young, 1983; Lyvers and Maltzman, 1991b; Martin and Sayette, 1993; Martin et al., 1990; Ross and Pihl, 1989; Sayette et al., 1994).

Rankin et al. (1979) designed a study to provide a valid and reliable biobehavioral measure of craving. Outpatients diagnosed as severely dependent and drinking heavily were visited by the experimenters in their homes, a setting and related set quite different than that found in the usual experiment. On different days participants were asked to remain abstinent for one half-hour or 3 hours. The speed of drinking two glasses of vodka and tonic was significantly faster in the higher-craving, 3-hours abstinent condition than the low-craving condition. Increased speed of alcohol consumption in the group abstaining for 3 hours was accompanied by several correlated behaviors, such as a self-rated increased desire to drink, difficulty in resisting a drink and anxiety, as well as physiological measures, e.g., increased body temperature, hand tremor.

In another study, severity of dependence and the effects of a priming dose were studied using the speed of drinking measure of craving along with self-ratings of the desire to drink, pulse rate, and blood alcohol level (Hodgson et al., 1979). Subjects were classified as severely or moderately dependent on the basis of the frequency and severity of their reported withdrawal symptoms. Each subject participated in each of the three different treatments: no priming dose, a low priming dose (15 mL vodka in tonic), and a high priming dose (150 mL vodka in tonic). Priming doses were administered in the morning. Three hours later participants received the behavioral test of craving, the time required to consume at least one vodka and tonic. Severely dependent alcoholics showed an appetizer effect on the behavioral test. The larger the priming dose in the morning, the greater the speed of consumption of the vodka and tonic 3 hours later. In contrast, the moderately dependent alcoholics or problem drinkers showed a satiation effect. The larger the priming dose in the morning, the slower the rate of consumption of the vodka and tonic 3 hours later.

The above results are important for several reasons: they suggest that the Marlatt et al. (1973) double-balanced placebo design employing "alcoholics" who were not independently assessed for their severity of dependence did not meet the boundary conditions necessary for an adequate test of the conception of loss of control. Since loss of control is behavior that differentiates alcoholics from problem drinkers, it is essential to classify the subjects independently to ensure that physically dependent alcoholics rather than problem drinkers are being tested. These results indicate that there is a qualitative difference between alcoholics and problem drinkers in accord with Jellinek's (1960) formulation. Social drinkers, problem drinkers, and alcoholics are not on a continuum defined solely by the amount of alcohol consumed, as argued by some (Heather and Robertson, 1983; Marlatt, 1979).

A craving and loss of control analogue experiment by Stockwell et al. (1982) provides further evidence that contradicts the continuity hypothesis and the notion that the behavior of alcoholics is determined by expectancies. A within-subject balanced placebo design was employed for priming doses where each subject participated in all four treatments. The behavioral test for craving—the speed of consumption of a vodka and tonic—was given 1 hour after ingesting the priming

dose, which was 60 mL of vodka mixed in a soft drink. The pulse rate was elevated 60 minutes later in those given alcohol compared to those given soft drinks, regardless of the instructions received. Self-reports of desire to drink were not influenced by alcohol content in either group.

The time taken to consume the first drink was significantly shorter with an alcohol priming dose regardless of instructions in the severely dependent alcoholics, whereas instructions but not the type of beverage produced a significant decrease in consumption time among problem drinkers. These results suggest that demand characteristics may influence the social and problem drinker in the typical experimental situation with the usual status difference between experimenter and subject. However, demand characteristics are not powerful enough to override the disposition to drink in severely dependent alcoholics under the conditions established in this experiment.

An apparently different outcome is reported for a double-balanced placebo within-subject design by Berg et al. (1981). Male patients in an alcoholism treatment center, the severity of their dependence unspecified, and social drinkers participated in this study. Social drinkers constituting the control group were apparently associates and friends of the investigators. Subject triads from each group participated in a social situation, the hospital lounge, where they watched a soccer game on television.

An overall larger increase in systolic blood pressure (SBP) among patients than social drinkers was the only significant physiological effect obtained. Results for the principal dependent behavioral measure, the amount of alcohol consumed, showed that instructions had an effect upon patients but not upon social drinkers, whereas the type of beverage tended to have an effect upon the social drinkers and not the patients.

No adequate explanation for the different results obtained in the two groups and for the difference in results obtained in this and the Marlatt et al. (1973) study has been offered. We suggest that the comparable results obtained with ''alcoholics'' in the two experiments reflect the comparable influence of demand characteristics. Demand characteristics would also be present in the Marlatt et al. (1973) experiment for the social drinkers in a laboratory setting who were not associates of the experimenters. Demand characteristics of an experiment and the status differences between experimenter and subject were absent only for the control group in the Berg et al. (1981) study. Therefore, an exeriment is needed in which demand characteristics are varied systematically for patients explicitly classified in keeping with DSM-IV criteria, manifesting alcohol dependence and abuse, and a control group of social drinkers.

Laberg (1986) met some of the above conditions in a study in which severely dependent, moderately dependent, and social drinker control subjects, all males, were studied in a balanced placebo within-subject design. Unfortunately, Laberg used the time to the first sip and time engaged in drinking instead of the measure used by Stockwell et al. (1982)—the time required to consume the first glass of vodka and tonic. No priming effect was obtained either as a function of the

beverage or instructions. However, there was a significant increase in HR, as well as in the number of spontaneous SCRs in the alcohol as compared to the placebo conditions in all groups. Basal SCL was significantly higher in the severely dependent patients than in the remaining two groups in all treatment conditions.

It is claimed that analogue studies of loss of control using the balanced placebo design refute the disease concept of alcoholism and its critical behavioral marker of loss of control (Heather and Robertson, 1983; Marlatt, 1983). On the contrary, our review indicates that these experiments suffer from major methodological shortcomings. When severity of dependence, priming dose, and length of abstinence are considered, evidence supporting the conception of loss of control is obtained, and the continuity hypothesis—there is no difference between alcoholics and problem drinkers other than the amount of alcohol consumed—is contradicted (Hodgson et al., 1979; Stockwell et al., 1982).

There is also growing recognition that the requirements of the balanced placebo design cannot be fulfilled, particularly the inability to establish an ''antiplacebo'' treatment, which requires deceiving subjects into believing that they are drinking tonic when they are given a moderate amount of alcohol (Glautier et al., 1992; Lapp, et al., 1994; Lyvers and Maltzman, 1991b; Martin and Sayette, 1993; Martin et al., 1990; Ross and Pihl, 1989; Sayette et al., 1994).

Craving, Cue Reactivity, and Response Prevention

Mello (1972) noted some years ago that the term ''craving'' was ambiguous and of questionable scientific value. Since then, attempts to obtain objective measures of the increased disposition to drink—craving—have taken three directions. One uses instrumental behavior; a second employs physiological, usually ANS, measures; and the third relies on various forms of verbal report. One variation of the instrumental approach is to obtain a sample of the behavior in question—alcohol seeking—as a function of antecedent conditions of hours of abstinence from alcohol, priming, and severity of dependence. As previously described, speed of drinking has been utilized in this manner (Hodgson et al., 1979; Rankin et al., 1979). Although craving can be defined operationally in terms of the antecedent conditions of deprivation and independently assessed severity, with a dependent measure of speed of drinking, evidence on lawful relationships of speed of drinking to physiological measures and self-reports is limited. Another potentially promising instrumental behavior measure that has been occasionally utilized is choice behavior, allowing the subject to choose to work for alcohol or some other incentive (Funderburk and Allen, 1977; Kaplan et al., 1983; Ludwig et al., 1974).

A second approach to the analysis of craving based upon classical conditioning (Ludwig and Wikler, 1974; Wikler, 1980) asserts that craving may be defined explicitly as the cognitive-symbolic correlate of classically conditioned subclinical withdrawal symptoms. Objective measures of craving are therefore verbal reports of craving or the desire to drink, as well as the elicitation of physiological responses that are presumably components of the withdrawal syndrome that become

conditioned because withdrawal may be followed by the reinforcement—the ingestion of alcohol. Another conditioning hypothesis is that appetitive physiological changes are conditioned (Wise, 1988). Positive rather than negative reinforcement is the basis for craving and reactivity to cues associated with alcohol ingestion. More recent research demonstrates the important role of neurotransmitters in determining verbal reports of craving and the behavioral loss of control over alcohol ingestion. O'Malley et al. (1992) and Volpicelli et al. (1992) have reported encouraging preliminary treatment outcomes with naltrexone, an opioid antagonistic, in preventing relapse and reducing reported craving. Modell et al. (1993) demonstrated that haloperidol, a dopamine antagonist, increased alcoholics' behavioral control over alcohol ingestion and decreased their reported craving for alcohol after a priming dose of alcohol. Some evidence that a serotonin reuptake blocker may reduce alcohol consumption and ratings of craving in alcoholics has also been reported (Gorelick and Paredes, 1992).

Neurobiological research suggests that craving and excessive alcohol consumption may be reactions to subnormal levels of one or more neurotransmitters: the neuropeptides, serotonin, dopamine, and GABA (Blum and Payne, 1991; McBride et al., 1990; Volpicelli, 1987).

Although an operational definition of craving is possible in terms of physiological responses—that is, their differential elicitation in the presence of cues associated with alcohol—or in terms of self-rating procedures, the problem of craving is not definitional, a statement of the rule governing usage of a term. Rather, it is that the objective measures proposed as its indices do not co-vary with great consistency, are not lawfully related and, are not integrated into a larger set of biobehavioral principles. Furthermore, few studies employ multiple indices from the three different response domains, incuding CNS and ANS measures. As a consequence their lawful interrelationships have not been assessed adequately.

Each of the measures utilized has difficulties. Autonomic measures commonly employed as dependent variables in the operationalization of craving are nonspecific, may be evoked as components of a variety of functional systems, and are not necessarily involved in withdrawal or unique to the positive reinforcement stemming from the ingestion of alcohol. The veracity of verbal reports depends upon the cooperativeness of participants, their ability to differentiate internal states, normal neuropsychological functioning of the participants, and the absence of demand characteristics. Few of these criteria are met in the typical experiment on craving and related phenomena. As a consequence, principles of craving have not developed appreciably beyond the state characterized some years ago by Mello (1972).

Interest in cue exposure and response prevention research stems largely from their apparent applicability to treatment. It is assumed that the extinction of classically conditioned components of withdrawal or positive reinforcement by their repeated elicitation and nonreward will result in a decrease in craving and therefore a decreased tendency to relapse when the subject is confronted with cues for alcohol. Response prevention is a natural extension of cue exposure. The latter

may be combined with a priming dose of alcohol to increase craving, the internal cues for alcohol consumption, in the extended presence of the sight and smell of the subject's favorite alcoholic beverage. Such extended exposure to cues with the prevention of the target responses is a useful treatment for obsessive-compulsive disorders (OCD; Jenike et al., 1990).

In perhaps the first study of alcoholics' craving and cue reactivity, Ludwig et al. (1974) attempted to vary cue reactivity by administering different doses of alcohol or a placebo to veterans in an alcoholism treatment unit either in the presence of a bottle (cue) of their favorite alcoholic beverage or not. There were significant increases in reported craving in the cue group under low-dose conditions. After a priming dose, there was a significantly higher frequency of conversions to alcohol acquisition behavior in the cue than the noncue group and a significant increase in HR, respiratory rate (RR), EEG alpha activity, and latency of the peak contingent negative variation (CNV). Priming dose did not affect spontaneous or evoked skin potential responses (SPRs). Given the large number of uncorrected statistical tests generated in the study, the above results must be accepted with caution.

Ludwig and Stark (1974) found that alcoholics most frequently report that they crave alcohol when in a dysphoric state, possibly as a consequence of its similarity to the withdrawal state. They rarely reported craving while in a busy or happy state. Ludwig et al. (1977) attempted to vary emotional states by varying success and failure experiences induced in a laboratory outfitted to resemble a bar room versus laboratory situation. Binge and steady drinkers were the participants since it was hypothesized that steady drinkers were more likely to develop conditioned withdrawal symptoms than binge drinkers.

There were no significant differences in any of the physiological measures as a function of set, success or failure, or setting. However, steady drinkers worked more for alcohol, reported greater craving, higher HR diastolic blood pressure, SC, and RR, but lowered systolic blood pressure. The type of drinker also tended to interact with situation. Greater differences between types occurred in the simulated bar than the laboratory.

The absence of significant main effects as a consequence of set, failure versus success, and situation, bar room versus laboratory, may be a consequence of the failure to adequately establish these set and setting conditions. Failure in the problem task, which was the interpretations of proverbs, does not seem to be an overpowering failure experience to alcoholic patients nor do correct interpretations strike them as a joyous occasion. Although a laboratory is outfitted with trappings of a bar—with neon signs, bottles, and the like—it is still known to be a laboratory where an experiment is being conducted.

Litt et al. (1990) attempted to vary set by hypnosis, but failed to find different physiological effects in a cue reactivity test. Corty et al. (1988), in the second of their two experiments, induced seemingly appropriate sets by means of videotapings of TV commercials. Because only three carefully selected subjects were employed in this demonstration of differentially greater salivation to an alcoholic

beverage than a soft drink, the study needs to be replicated on a larger scale. Turkkan et al. (1989) obtained reliable increases in HR, SC, and skin temperature (ST) in a cue reactivity test in a simulated bar. However, they did not use a control setting, and their procedures differed in details from other experiments so that the positive results cannot be attributed specifically to the setting because it is confounded with other procedural changes. Further research on the problem of set and setting is needed, but not necessarily in the direction of better simulated bars.

Rubonis et al. (1994) attempted to induce different moods that might affect cue reactivity. A drinking triggers interview was first employed where subjects were asked for retrospective descriptions of the four drinking situations that were associated with the strongest urge to drink. The situation with the highest rating was used to induce a mood. Subjects, both women and men, all had a diagnosis of alcohol abuse or dependence. Unfortunately, a single order of presentation was used: water cues, alcohol cues, mood induction, followed by alcohol cues. Salivary responding was measured along with ratings of craving. No significant mood effect was found for salivation. Using only negative moods and only those who were "urge reactors," the investigators claim that there was a significant gender effect as reflected by a gender × trials effect for self-ratings. Contrary to the investigators' claim, their crossover interaction only indicates that the difference between the gender differences is different on the two trials. No evidence is provided showing that women reported significantly greater craving than men after a negative mood induction.

Kaplan et al. (1983) recorded HR, SCL, and ST in abstinent male alcoholics and social drinkers in a cue reactivity test comparing responsivity to beer and nonalcohol beer after holding, smelling, thinking about, and then drinking the beverage. Significant differential responsivity was obtained only with ST.

A shortcoming in this study was the failure to equate the alcohol and nonalcohol beer for taste. The problem of equating stimuli is exacerbated when an alcohol beverage and cedar chips, with no control over sniffing, are used in a cue reactivity test as in the study by Pomerleau et al. (1983). They recorded electromyographic (EMG) activity induced by swallowing as an estimate of salivation along with HR and SCR. Males in treatment for alcoholism and a social drinker control group sniffed cedar chips and then alcohol. Patients manifested greater swallowing and self-reports of craving then the control group in response to alcohol than cedar. There was no differential responsivity in HR and SCR.

Among other problems, this study suffers from the same shortcoming as that of Monti et al. (1987) and the other studies by this group of investigators. It capitalizes on an order effect by presenting the test trial for the control stimulus first, followed by the test trial for alcohol. Greater novelty-induced stress on the first trial will tend to inhibit salivation. Some habituation of the response to novelty by the second trial will permit an increase in salivation. It is essential that repeated test trials are presented in counterbalanced orders in order to habituate nonspecific effects that may interact with the dependent variable and with alcohol. It must also be noted that, even with an order effect in the alcohol trial following

the control trial, Monti et al. (1987) did not obtain a significant main effect for drink or a group × drink interaction where patients as compared to controls salivated differentially to alcohol.

Cooney et al. (1987) report positive evidence of craving by recording salivation from men in alcoholism treatment. Subjects sniffed cedar chips and alcohol on a single trial. Significant partial correlations among several self-ratings, such as a desire to drink and saliva, corrected for salivation to cedar chips, were obtained. However, given the small number of subjects employed and the absence of a control group of nonproblem drinkers these results must be viewed with caution. In addition, the stimuli were not equated for pleasantness and intensity of odor, nor was sniffing controlled, a variable that may affect both the intensity of the olfactory experience and the amount of saliva secreted (Feather and Wells, 1966).

Further inconsistency of findings with swallowing and salivation as measures in cue reactivity studies is indicated by the results obtained by Kaplan et al. (1985). This study with a larger number of subjects of both genders contradicts the results of Pomerleau et al. (1983) in at least two important findings: there was no evidence that swallowing differentiated inpatients from controls, and there was no increase in reported craving after exposure to alcohol as compared to cedar chips.

In addition to methodological flaws, many studies reviewed above also suffer from the failure to obtain reliable measures of severity of dependence from the patients. The participants usually are a heterogeneous group differing considerably in the severity of their dependence and as a consequence are likely to respond markedly differently to alcohol cues, i.e., the less dependent patients would be no different from control subjects. Heterogeneity is suggested by the Kaplan et al. (1985) finding that only patients above the median in drinking history showed a significant partial correlation between SCL and self-reported desire to drink.

More recent studies have improved their methodology in some areas, for example by controlling sniffing and by using broad and explicit exclusionary criteria, including medications that inhibit salivation (e.g., Monti et al., 1993a,b). However, most studies still fail to use severity of dependence as a grouping factor, despite its demonstrated importance as a determiner of verbal and instrumental measures of craving (Hodgson et al., 1979; Rankin et al., 1979).

There have been some recent exceptions, and a few studies have explored the effects of drinking history and severity of dependence on craving and cue reactivity. For example, Greeley et al. (1993) examined the effects of the amount of alcohol consumption on cue reactivity in social drinkers who had not been diagnosed as physically dependent upon alcohol. A group of heavy male drinkers consuming more than 28 standard drinks per week were contrasted with a group of males drinking less than 28 drinks per week. Subjects were exposed to their favorite alcoholic beverage and a "pungent" lemon drink in counterbalanced order and were permitted to taste as well as see and smell the drinks. Heart rate, SCL, and self-ratings of craving for alcohol were continuously obtained. Blood pressure and ratings of stress and arousal were obtained before and after presen-

tation of each cue. Relatively weak effects were obtained with the physiological measures. There were significant interactions between groups and order of presentation in HR and a tendency for heavy drinkers to show a lower SCL than light drinkers. Self-ratings of craving by the heavy drinkers appeared consistently higher than the reports of the lighter drinkers, showing an increasing trend in craving for alcohol, regardless of its order of presentation.

Glautier and Drummond (1994) have published a multivariate examination of the relationship between severity of alcohol dependence and cue reactivity. Subjects were men who were severely dependent on alcohol who were participants in a controlled trial of cue exposure and response prevention treatment (Drummond and Glautier, 1994). Alcohol dependence was measured in terms of five subscales of the Severity of Alcohol Dependence questionnaire (Stockwell et al., 1979). Different subscales describe symptoms of physical withdrawal, affective withdrawal, craving, relief drinking, and relapse after a period of abstinence. Physiological measures employed included SCL, cardiac interbeat interval (IBI), finger pulse volume (FPV), and forearm EMG. Self-ratings of how tense (TENSE) they were and how much they wanted (WANT) a drink were also obtained from the subjects. Preferred alcoholic beverage and nonalcoholic beverage were the cues presented to each subject. Difference scores were obtained by subtracting the magnitude of the response to the neutral cue from those to the alcohol cue for each of the physiological measures and self-ratings. The largest differences were obtained with SCL and the TENSE and WANT ratings. Difference scores were factor analyzed and a single principal component of responsivity (RESP) extracted. Affective withdrawal was the subscale of the SADQ that showed the highest correlations with the multivariate measures of responsivity.

Among the variety of possible shortcomings in early studies of cue reactivity and craving, some of the most obvious have been the failure to equate target and control stimuli for such characteristics as pleasantness of taste and smell, intensity, palatability and consumability, and the somatic activity involved in sniffing. Staiger and White (1991) demonstrated that subjects having a diagnosis of alcohol dependence showed greater responsivity in absolute HR to the sight and smell of their favorite drink as compared to a different brand of the same beverage or a different kind of beverage. Only the magnitude of response to the sight and smell of their favorite brand of alcoholic beverage as compared to a neutral stimulus was significant. These results indicate that subjects should be matched with their favorite drink in order to optimize responsivity. Sight plus smell of their favorite drink produced a larger absolute HR change than sight of the drink alone. Since frequency and extent of sniffing induced by the two beverages were not controlled, the amount of somatic activity induced by the two drinks might differ. A greater amount of somatic activity elicited by alcohol could therefore be the basis for the response of a greater HR to alcohol than lemonade according to the cardiac-somatic coupling hypothesis (Obrist et al., 1974).

Staiger and White (1991) also report a result that may be related to cardiac-somatic coupling and requires further investigation. Sixteen subjects participated

in the specificity phase of their experiment. Six showed an increase in HR in response to the sight and smell of their favorite drink, whereas ten subjects showed a decrease in HR. Absolute change was taken as the response measure. If directional change had been averaged, no effect would have been apparent. Unfortunately, no information is given concerning the reliability of these individual differences across phases of the study. So they might not be consistent individual differences. Rather, they might be a function of whether somatic activity increased or decreased during the exposure of the beverage. Staiger and White's results nevertheless call into question the notion of a particular HR change as a conditioned component of withdrawal or as an appetitive response to alcohol ingestion and suggest the influence of the law of initial value (see below; LIV) and/or cardiac-somatic coupling.

However, in a study using HR and finger ST, Payne et al. (1992) report that all HR cue reaction baseline changes were positive, whereas no effects were evident for ST. They used a between-subject design with male veterans in a 28-day inpatient treatment program. Four different groups were employed in a 2×2 design, receiving either lemonade or their favorite alcoholic beverage and imagining either high- or low-risk situations for drinking lapses. After a baseline period, subjects were exposed to one of the two beverages for 2 minutes and then, while still in the presence of the beverage, imagined a situation that would put them at high or low risk for a drinking lapse. Recording of HR and finger ST continued during a 2-minute recovery phase after removal of the stimuli. In each of the phases of the experiment, self-ratings were also obtained for the desire to drink, mood, and anticipated taste. Regression analysis was used to adjust mean scores for initial baseline values. A significant main effect for beverage was obtained with HR but not ST. Significantly greater responsivity was evident to alcohol than lemonade. Analysis of covariance was used to study responsivity induced by imagery, with rated clarity of imagery as a covariate. No significant effects or interactions were obtained. However, significant effects were obtained during the recovery phase after removal of the cues and cessation of imagined drinking situations. Subjects imagining high-risk situations for lapsing while exposed to lemonade were significantly more responsive than low-risk imaging subjects exposed to lemonade. Alcohol low-risk imaging subjects were also more responsive than lemonade low-risk subjects. High-risk imaging subjects exposed to alcohol were not significantly different from the other subjects, suggesting the influence of a ceiling effect and LIV and/or cardiac-somatic coupling.

Newlin et al. (1989) also examined the effects of different kinds of control stimuli employed with the preferred alcohol stimulus. They used a desirable and consumable nonalcoholic beverage as a liquid stimulus and a sweet roll, which is also desirable and consumable, as well as water. Unfortunately, in order to conform to Monti et al. (1987), they also used a constant order of stimulus presentation: water, preferred nonalcoholic beverage, preferred alcoholic beverage, sweet roll. Physiological measures were HR, pulse transit time (PTT), SC, finger and cheek temperature, and salivation. Self-reports of craving were also obtained after

presentation of each stimulus. There were two groups of subjects: male inpatients in an alcoholism treatment program who met criteria for alcohol dependence and male social drinkers. Results indicated that the alcoholics salivated significantly more to water and to alcohol than the social drinkers. Unfortunately, the groups × stimulus interaction was not examined. Neither was evidence presented indicating whether the alcoholics showed differentially greater reactivity to alcohol than the nonalcoholics. Cheek temperature was the only other physiological measure that yielded a significant effect, with the social drinkers showing greater reactivity to water and to alcohol than the alcoholics. Among alcoholics, salivation was positively correlated with the craving to drink alcohol after exposure to alcohol and to the sweet roll, whereas these correlations were negative among social drinkers. There was no significant difference in the severity of craving reported by alcoholics and social drinkers.

Monti et al. (1993a) investigated the relationship between cue reactivity as measured by salivation and self-ratings of craving as a function of the stage of detoxification. Groups of subjects in a detoxification facility experiencing unmedicated withdrawal were studied 2, 4, and 6 days and 4 weeks after their BAL returned to 0. A comparison group of subjects receiving librium during detoxification because of more severe withdrawal symptoms was also studied. Cue reactivity was assessed in the usual manner by this group of investigators; they elicited salivary responses and self-ratings of craving and other variables to water and to the subject's favorite drink, in that order. Salivation to alcohol partially correlated with the severity of dependence while controlling for salivation to water. It is also interesting that self-ratings of anxiety and craving to drink had a correlation of 0.61. There were no significant group × beverage interactions, indicating that reactivity to alcohol did not vary with time since detoxification. The overall reactivity to water and to alcohol for alcoholics after 1 week of detoxification was greater than for alcoholics assessed 4 weeks after detoxification. Alcoholics in the librium group did not differ from the other groups.

Turkkan et al. (1988) introduced several worthwhile innovations in their study of cue reactivity, including 12 repeated experimental sessions and screening for illicit drug use. Male participants were recruited through newspaper advertisements. Half had self-reported histories of alcohol abuse ("alcoholics"), and half were social drinker controls. Heart rate, ST, and BAC showed significant dose main effects, whereas systolic and diastolic blood pressure and salivation did not. Results obtained for salivation were not in keeping with previous studies (Kaplan et al., 1985; Pomerleau et al., 1983). Alcoholics showed the greatest increase in salivation after ingestion of the placebo. Ethanol seemed to decrease salivation below baseline levels in alcoholics and in social drinkers.

McCaul et al. (1989a) investigated the role of stimulus intensity by presenting alcohol, pepper juice rated equally intense as alcohol, and water with variable intertrial intervals. Both groups, men with reported histories of alcohol abuse and moderate social drinkers, rated alcohol and pepper similar in intensity and more intense than water. HR decreased significantly over sessions for both groups.

There was no evidence of differential tolerance to alcohol as indicated by a sessions × drink interaction or greater tolerance to alcohol in one group rather than another such as a group × sessions × drink interaction. The two groups did not differ on any of the measures: HR, SC, or self-reports of craving.

In a similar study, Turkkan et al. (1989) used actively drinking male alcoholic volunteers who met DSM-III-R criteria for alcohol dependence. In five daily sessions, subjects underwent trials in which they were exposed to the taste and smell of water, hot pepper juice, and bourbon. Each daily session ended with a compound stimulus trial in which the participant was permitted to consume a shot glass of the bourbon. The study was conducted in a simulated bar, and subjects were instructed that sometime during each session they would receive an alcohol drink. Each trial consisted of the taste and smell of bourbon poured by the participant into a shot glass and a visible display of the bottle.

Results showed that the HR, SC, and ST increases induced by alcohol differed significantly from the pepper juice stimulus, as well as from water. An observation with important implications for tolerance theory is that SC and ST to all three stimuli declined in magnitude over days. There was no differential decline in responsivity to alcohol versus nonalcohol cues. These results suggest that the decline was due to habituation of the OR to novelty, a nonspecific effect, rather than tolerance to alcohol. A corresponding effect was found in an earlier experiment over 12 sessions (Turkkan et al., 1988).

Differential responsivity to alcohol cues in the Turkkan experiment as compared to the lack thereof in the previous study by this group (McCaul et al., 1989a) could be a consequence of one or more of several different variables: the different state induced by the simulated bar as compared to a laboratory complex; instructions indicating the possibility of a drink at the conclusion of each session; and the variable intertrial interval and varying number of trials each day, which increased uncertainty and maintained responsivity. Several subject variables may also have influenced the different outcome of the Turkkan study. For example, participants in the experiment may have had a greater severity of alcohol dependence than participants in the previous experiment, and they were deprived of alcohol for a longer period of time before the start of the experimental sessions.

Laberg and Ellertsen (1987) examined the effects of a priming dose of alcohol versus no alcohol and attempted to determine whether availability of alcohol during cue exposure and response prevention would facilitate extinction as compared to the presence of symbolic alcohol cues. An immediate difficulty in this between-group study is evident upon examination of the drinking histories of the different groups. Patients in the critical subgroup receiving the alcohol priming dose and cue exposure with alcohol (P+/C+) consumed considerably more alcohol per week and reported considerably more years of problem drinking than the patients in the remaining three subgroups. This group reported significantly more craving than the three remaining groups on the first day. The groups also differed in self-reports of craving, although not significantly, before the first cue exposure.

Mean SCL and number of nonspecific SCRs increased and then declined over trials within sessions. Mean HR showed an interaction between days and treatments. The highest HR group, P+/C+, decreased slightly for the first 3 days and then increased. The interaction is not readily interpretable and provides no clear evidence of extinction, as seen by a decreased HR, as a consequence of priming or cue exposure with alcohol, contrary to the interpretation by Laberg and Ellertsen.

Habituation of the organismic OR to the novelty of the situation is confounded in this and other studies. There is spontaneous recovery from the previous session and habituation within a session because of the predictability of the sequence of events within a session, but not between sessions. For evidence that cue exposure and priming produce extinction of physiological indices of craving, there must be persistence of the extinction effect between sessions. There is no such evidence in this experiment nor in any of the other experiments reviewed.

In view of the above serious shortcomings in their study and the absence of any follow-up to the experimental treatment, Laberg and Ellertsen's (1987, p. 1347) conclusions are surprising: "since it is possible to demonstrate that craving is reduced in one experimental situation it is reasonable to assume that this also holds relevance in real life situations. These results lend strong support to findings by others that cue exposure and response prevention is an effective treatment method for severely dependent alcoholics."

In addition to its pharmacological and possible conditioned effects, consumption of alcohol in the experimental situation assists in establishing a set and setting as nonthreatening, less stressful, and less like an experiment. It helps change the physiological state of the subject. However, set or physiological state can be changed without alcohol consumption, as indicated by the differential reactivity to alcohol obtained by Kennedy (1971).

Stormark et al. (1993) attempted a novel variation in studies of cue reactivity. They presented a single slide depicting different alcoholic beverages and a control slide showing a page of the telephone directory to patients in an alcoholism treatment facility and to social drinkers. Seven presentations of the two slides in two prearranged orders were administered while recording SCR and SCL. Alcoholics had significantly larger magnitude SCRs to both kinds of stimuli, but there was no groups × stimulus interaction. Both groups showed habituation. Further research is warranted on this interesting problem. The failure to obtain differential responsivity to the alcohol slide may be due to several possible shortcomings in the study design. As Staiger and White (1991) and others have demonstrated, differential reactivity to alcohol as compared to nonalcohol cues is enhanced if the favorite alcoholic beverage of the subject is presented. A larger number of different slides of alcohol and of different control stimuli also need to be employed in order to avoid habituation. Differential SCRs to significant slides of activities depicting favorite recreational interests have been demonstrated (Wingard and Maltzman, 1980). A similar methodology may need to be employed to study cue activity in alcoholics. If slides of preferred recreational interests can elicit differential activity, one would think that a consuming interest, such as alcohol for an alcoholic, would elicit differential responsivity as well. A corresponding study using verbal scripts describing alcoholic and nonalcoholic activities would be of value as well.

Cue Reactivity as a Predictor of Treatment Outcome and Cue Exposure and Response Prevention as Treatment

Kennedy (1971) conducted the first study we know of that used an autonomic response, pupillary dilation, as a measure of progress in alcoholism rehabilitation and a predictor of post-treatment outcome. His approach was based upon the earlier work of Hess (1965) demonstrating that pupillary dilation, an index of the OR, may serve as a measure of interests and attitudes.

Kennedy studied 35 subjects who completed an alcoholism rehabilitation program and were followed up 3 months after discharge. Pupillary dilations were recorded in response to a test tube presentation of water and their favorite alcoholic beverage, in that order, every 2 weeks until completion of the 16-week program. The principal dependent variable was dilation to the alcohol during the last three measurements prior to completion of the program. Criterion of abstinence on follow-up was sobriety for 3 months. Large dilations—thus, larger ORs to alcohol—were related significantly more often to relapse than no dilations. Kennedy also reported that dilations declined during treatment, indicating habituation of the OR.

Decreases in pupillary dilation during the course of the treatment and repeated testings could be a consequence of any one or more of three variables: (1) a nonspecific reflection of the progress of treatment, (2) nonspecific habituation to the test situation, or (3) repeated test situations that resulted in extinction of conditioned pupillary dilation. Contributions of these possible variables to the outcome cannot be determined in the absence of control groups that did not receive repeated testings or treatment. If, as Kennedy suggests, the decline in pupillary dilation was a function of a declining interest in alcohol, it seems that relatively nonspecific treatment effects were at work. It may be unnecessary to directly extinguish responses elicited to cues of alcohol. Semantic, mediated, extinction may occur as a consequence of talking about drinking alcohol and not imbibing, the sort of activity that occurs in group treatment and self-help groups.

Rohsenow et al. (1994) used cue reactivity measures in an attempt to predict the 3-month post-treatment drinking status of the alcoholics who received nonmedicated treatment for withdrawal in the study by Monti et al. (1993a). A regression analysis of craving ratings obtained in the post-treatment environment, with craving and salivation induced by alcohol as the independent variable and reactivity to water as the covariates, was not significant. Nor was a similar regression analysis with total abstinence as the dependent variable. Separate regression analyses of days to the first drink, with craving and salivation as independent variables, likewise were not significant. However, regression analyses of

percentage of days abstinent were significant, with salivation contributing a small but significant amount of the variance, indicating that greater salivation to alcohol than water was related to fewer abstinent days.

Rohsenow et al. (1994) interpret their significant effect for salivation but not self-ratings of craving as indicating that salivation is an automatic process and is related to the initiation of drug use. There are serious difficulties with this interpretation, in addition to the questionable reliability of the effect, given that another study by this group of investigators failed to find that differential salivation predicted post-treatment status (Monti et al., 1993b). The status of "automatic" processes within cognitive theory is also questionable (Pashler, 1994). The concept "automatic" is poorly defined and of doubful generality. Assuming that automatic processes are involuntary is also questionable, particularly in the case of salivation, which can be readily influenced by the respondent (White, 1978).

Monti et al. (1993b) integrated cue exposure and urge (craving) coping skills training (CET) with standard treatment and contrasted it to a second condition (CC) of daily assessments and standard treatment. Drinking status was assessed 3 and 6 months after treatment. Participants all met the criteria for alcohol dependence and were randomly assigned to one of the two groups. Subjects in the CET group received extended exposure to their favorite alcohol beverage in each cue reactivity session and were given practice in using skills to reduce the urge to drink in the presence of the alcoholic beverage and in imaginal exposures. Six such treatment and assessment sessions were administered within a 2-week period of standard hospital treatment. Subjects in the CC condition received only the assessments and standard hospital treatment. Cue reactivity tests at the outset of treatment and at post-treatment showed an overall significant decline in salivation. There was no significant interactions with groups or beverages. Similar effects were obtained with self-ratings of craving. Post-treatment assessment of drinking status found no significant group differences for the first 3 months. However, during the 3 to 6 month period there were significantly fewer drinkers in the CET than the CC group: 50% versus 80%. Using self-ratings of craving to water as a covariate, craving for alcohol during the first cue reactivity test showed a significant partial correlation with the percentage of abstinent days in the 3- to 6-month follow-up. Craving in the post-treatment reactivity assessment did not predict any measure of post-treatment drinking status. Salivary responding at neither pre- nor post-treatment cue reactivity tests predicted post-treatment status.

Drummond and Glautier (1994), in a carefully designed study, report that cue exposure and response prevention produced significantly better outcome 6 months post-treatment than did relaxation training with a group of subjects meeting the criteria for severe alcohol dependence. Coping skills training was not administered. They also report prediction of post-treatment drinking outcome by physiological measures of cue reactivity obtained on the last day of the 10-day treatment program. Measures included SCL, IBI, FPV, and forearm EMG. Approximately 26% of the variance in latency to morning drinking and withdrawal was accounted for by SCL, and approximately 20% of the variance in these symptoms was accounted for by FPV. A variety of other interesting results are reported concerning treatment outcome in relation to demographic and personal history variables.

Evaluation of Research on Cue Reactivity and Response Prevention. In the absence of reliable, long-term follow-up evidence that cue reactivity training is effective as a treatment or an adjunct to treatment and is more effective than alternative approaches, the outspoken and enthusiastic support for this treatment (Rosenberg and Hodge, 1990) is premature. Enthusiasm for research on cue reactivity as a component of relapse prevention and treatment (Heather and Bradley, 1990; Marlatt, 1990; Niaura et al., 1988) overlooks the serious shortcoming in the relevant research literature. A more tempered view is warranted (Drummond et al., 1990). Research on alcohol cue reactivity and response prevention needs to be integrated into treatment programs as it has in some treatments of heroin addiction (O'Brien et al., 1990). Such integration seems to be the most effective way to study the possible role of cue reactivity in treatment and relapse prevention.

More recent studies of cue reactivity and response prevention have improved methodology. However, restricting research to peripheral ANS measures severely limits research efforts to explain the behavior under consideration and to advance the treatment of alcoholism because of the generalized and nonspecific nature of such measures. Research increasingly suggests that there are basic commonalities in obsessive-compulsive disorders (OCD) and alcoholism with respect to the neurobiological basis of craving, the inability to inhibit target behaviors, and risk factors (Baxter et al., 1992; Modell et al., 1990, 1992, 1993; Rauch et al., 1994). Pre- and post-treatment PET scans after pharmacotherapy or behavior therapy using cue exposure and response prevention indicate that successful treatment by either method resulted in similar changes in serotonergic circuits. What sort of results would be obtained with PET scans before and after corresponding treatments of alcoholics? Other studies of OCD have recorded PET scans during cue exposure and response prevention, again obtaining evidence of basic involvement of serotonergic circuits during such exposures (Rauch et al., 1994). Corresponding studies are needed of alcoholics, studies that include autonomic measures along with PET scans. Perhaps then research results and theory will belie Mello's (1972) pessimistic evaluation of the concept of craving.

Risk for Relapse. Several studies have attempted to predict the risk for relapse on the basis of the patient's autonomic responses to alcohol. However, few studies have obtained physiological measures with the subject at rest after detoxification in order to predict post-treatment outcome and or have used a control group to evaluate possible risk factors. Bauer (1994) has conducted such a study employing an EEG and several measures of cardiovascular activity: HR, respiratory sinus arrhythmia (RSA) as a measure of vagal tone, and carotid pulse amplitude and velocity. Seventeen patients hospitalized for alcohol detoxification and inpatient treatment were tested, as well as 14 nonhospitalized control subjects. Treatment outcome for the 17 inpatients was assessed as either relapse prone (n=11) if any

alcohol was consumed within 3 months of treatment discharge or abstinent prone (n=6) if no alcohol was consumed within the first 3 months after treatment. The groups differed significantly in carotid pulse amplitude and EEG beta power at the vertex lead. Relapse-prone subjects were significantly higher on both measures than the abstinent-prone patients and control subjects; the latter two groups did not differ from each other. However, the two inpatient groups had similar family and personality risk factors.

Bauer's (1994) study is interesting for several reasons. His results encourage the use of a variety of physiological measures to differentiate between patients who will or will not relapse. Use of a control group of nonpatients provides valuable information indicating that the abstinent group did not differ from nonpatients on the physiological measures obtained. Despite the lack of the study's power due to the small number of subjects participating in it, significant physiological differences between inpatient groups were obtained, but not personality or family risk factors. Additional research employing a larger number of subjects and longer post-treatment periods is needed.

Effects of Chronic Alcoholism

The Pupillary Light Reflex

Pupillary constriction evoked by light increases is based upon parasympathetic innervation of the sympathetically controlled pupillary dilators (Appenzeller, 1990). In contrast to the fast and reflexive pupillary constriction in response to a light flash that seems to be controlled by parasympathetic input, adaptation to the darkness is a much slower process resulting from relaxation of the pupillary sphincter.

Pupillary dilation and changes in the pupillary light reflex are rarely used in research on alcohol effects and alcoholism. One study by Rubin et al. (1977) has demonstrated that alcoholics show attenuated pupillary reflexes to both light and darkness. Compared to normal controls, the alcoholics also showed less pupillary dilation in response to a cold stressor. When apparently the same data were reanalyzed in more detail (Rubin, 1980; Rubin et al., 1978), a difference emerged between the alcoholics who chose to drink during the treatment and those who volunteered to abstain. No drinking was allowed during the last week before testing. The dilation response to darkness of the "abstainers" was midway between the normal controls and the "drinkers," who showed the most attenuated response. There was no difference between drinkers and abstainers in the pupillary constriction measure (light reflex), although their responses were attenuated overall when compared to the controls. During a cold stressor task, the abstainers displayed the same degree of pupil dilation as the normals, whereas the response of the drinkers was markedly smaller. These data do not warrant any definite conclusions regarding the selective impairment of the two ANS branches in alcoholics, although Rubin et al. (1978) suggest that the alcoholics who chose to drink had decreased sympathetic activity and supranuclear inhibition.

Bender (1933) has measured pupillary constriction in response to a light flash in nonalcoholic subjects under the influence of alcohol. His results suggest that alcohol ingestion produces increased pupillary diameter, indicating increased sympathetic activity.

Alcohol and Sexuality

It is a commonly accepted belief that alcohol intoxification leads to heightened sexual desire and arousal. People experiencing doubts and insecurities about their sexual functioning are more likely to drink in potentially sexual situations in an attempt to increase their chances of "better performance," especially if they believe that alcohol decreases nervousness (Leigh, 1990).

Most of the experimental evidence on this subject, however, which comes from studies of men, contradicts this widely accepted common knowledge of the beneficial effects of alcohol on sexuality. In a study of acute effects of alcohol given to male nonalcoholics, Briddell and Wilson (1976) reported a decrease in sexual arousal proportional to the increase in the BAL, as measured by penile tumescence evoked by an erotic film. Similarly, Malatesta et al. (1979) obtained a negative correlation between BAL and sexual arousal, degree of pleasure, and orgasm latency. Farkas and Rosen (1976) replicated those results with the exception that at the lowest BAL, 0.025%, which was lower than in the Briddell and Wilson study, there was an increase in penile tumescence. In addition, studies of sexual arousal in male subjects and dogs as measured by nocturnal penile tumescence have confirmed the lack of any positive effect of alcohol intake on different parameters of arousal (Morlet et al., 1990).

Numerous studies have documented the deleterious effects of chronic alcohol consumption on sexual responsiveness as assessed at the time of hospitalization (Jensen, 1984; Whalley, 1978), as well as 9 months after alcohol dependence treatment (Fahrner, 1987).

Different aspects of the sexual response are subserved either by predominantly sympathetic or by predominantly parasympathetic branches of the ANS. Parasympathetic activity during the excitement phase results in arterial dilation and increased blood supply to the surface of the body and thus subserves the erection and vulvar swelling. The sympathetic branch contributes to the erection by constricting the venous valves. The SNS is primarily responsible for increases in tachycardia, blood pressure and hyperventilation, leading to the short period of arterial constriction during ejaculatory activity (Masters and Johnson, 1966; Miller and Gold, 1988).

Central mechanisms of the sexual response in humans are not well understood. Cox (1979) reported that stimulation of the septal region in humans produced strong sensations of sexual pleasure. However, sexual activity is by no means purely reflexive in nature. A prominent and perhaps determining influence of imagination and fantasy on sexual responsivity, as measured by penile tumescence, indicates an input from the cerebral cortex into centers regulating auto-

nomic activity. A capacity to control sexual arousal voluntarily has been observed in many studies contrary to the widely held opinion that penile erection is an involuntary response (Henson and Rubin, 1971; Quinsey and Carrigan, 1978). Moreover, Smith and Over (1987) have noted that men with the greatest capacity to form vivid images while fantasizing achieved the greatest voluntary control over their sexual arousal. Ability to voluntarily suppress sexual arousal while viewing sexually explicit materials was also noted in persons convicted of rape (Wormith et al., 1988).

Studies using the balanced placebo design with nonalcoholic subjects seem to indicate no positive effect of alcohol on sexual arousal, but a strong effect of instructional set such that the greatest arousal was shown by male subjects tricked into believing that they were receiving alcohol (Briddell et al., 1978; Crowe and George, 1989; Hull and Bond, 1986; Wilson and Lawson, 1976b). In view of the above evidence it comes as no surprise that sexual arousal is primarily under voluntary control and verbal regulation and the effects of alcohol are detrimental to sexuality.

Chronic alcohol abuse often results in sexual dysfunction. Possible mechanisms of this widely cited effect are still unknown. In addition to impotence and a lack of sexual desire, heavy drinking in men may result in endocrine syndromes of hypogonadism (Bannister and Lowosky, 1987) and hyperestrogenization (Van Thiel and Lester, 1979), which are thought to be caused by direct toxic effects of alcohol on testicular activity, as well as a decreased gonadotropin output by the hypothalamus-pituitary axis (Van Thiel and Lester, 1974). Chronic alcohol abuse results in sexual dysfunction in both genders, as indicated by erectile dysfunction, impaired female reproductive functions, and reduced sexual arousal and interest (Snyder and Karacan, 1981; Van Thiel and Lester, 1979). Finally, it is known that chronic alcoholism interferes with numerous neurochemical mechanisms in a highly complex manner, and it is possible that disturbances in these mechanisms (e.g., cholingeric, serotonergic, GABAenergic) indirectly contribute to sexual dysfunction (Hoffman and Tabakoff, 1985).

Since alcoholism is a highly complex biopsychosocial disease, the causes of sexual dysfunction cannot be attributed only to the physiological effects of alcohol. Different aspects of psychosocial functioning, such as anxiety, adequacy in personal and professional function, and personality factors and their physiological correlates, interact with physiological states in an intricate and interdependent manner to determine sexual functioning in the alcoholic.

Acute and chronic effects of alcohol on female sexuality have not been given the attention they merit. Although some studies report results paralleling alcohol effects on male sexuality—more specifically, a negative correlation between BAL and physiological measures of sexual arousal in women (Wilson and Lawson, 1976a)—other findings emphasize gender differences (Wilson and Lawson, 1976b). In their balanced placebo study, Wilson and Lawson (1978) replicated their earlier findings of decreased physiological sexual arousal in women after acute alcohol intake. However, in contrast to men, women did not manifest the

expectancy effect, failing to show arousal by the mere instruction to expect alcohol. Chronic effects of alcohol intake seem to result in sexual dysfunction in women as indicated by reduced sexual arousal, altered senses, and sterility, thus broadly paralleling the deficits observed in men (Van Thiel and Lester, 1979). More work is needed to elucidate the complex interactions among effects of alcohol, instructional set, hormonal and social contexts and personality variables on sexual arousal in women and men.

ANS Susceptibility to Chronic Effects of Alcohol

Several studies have endeavored to assess the susceptibility of the ANS to pathological changes caused by chronic exposure to alcohol. Matikainen et al. (1986) examined alcoholic patients free of overt neurological symptoms and observed subclinical abnormalities in the ANS, particularly in the functioning of its parasympathetic branch. In a group of chronic alcoholics diagnosed with peripheral neuropathy, Low et al. (1975) observed reduced sweating, higher resting arterial pressure, and a smaller reduction of arterial pressure in response to trinitroglycerin. Patients did not exhibit symptoms of postural hypotension, thus distinguishing the effects of chronic alcohol abuse from those of Wernicke's encephalopathy and diabetic neuropathy. In a postmortem study, Appenzeller and Richardson (1966) observed abnormal degenerating neurons in sympathetic ganglia in a subset of patients with clinical symptoms of polyneuropathy. Novak and Victor (1974) performed a postmortem examination of four patients with severe neuropathy caused by excessive alcohol consumption. They observed sympathetic nerve degeneration, as well as vagus demyelination and degeneration. These pathological changes in peripheral nerves might be partially responsible for several impairments. For example, reduced conduction velocity or even a complete block of nerve conduction might be caused by axonal degeneration and demyelination (Mawdsley and Mayer, 1965). Causes of the abnormalities are not understood, although it has been suggested that they may be a result of the direct toxic effects of alcohol, liver failure, metabolic dysfunction, or thiamine deficiency (Mayer and Khurana, 1982).

Withdrawal

In a unique study, Isbell et al. (1955) demonstrated the full spectrum of dramatic effects resulting from the sudden cessation of chronic exposure to large amounts of alcohol. Most commonly reported withdrawal symptoms are tremors, nausea and vomiting, and a variety of sympathetic responses: hypertension, sweating, tachycardia, elevated body temperature, pupil dilation, and insomnia (Adinoff et al., 1988). Occasionally, the autonomic-motor excitation is accompanied by hallucinations, seizures, and delirium tremens (Kanzow, 1986). In addition to those symptoms, sympathetic hyperarousal during withdrawal has been indicated by increased levels of noradrenaline metabolites in the cerebrospinal fluid (Linnoila

et al., 1987). Measures taken 10 days later in the same patients indicated a significant reduction in noradrenaline turnover, which was correlated with the disappearance of withdrawal symptoms. Administration of agonists to alpha-2-receptors, a major noradrenaline receptor, results in reversal of withdrawal symptoms (Gold et al., 1979).

In addition to increased noradrenaline release, withdrawal alters the activity of other neurotransmitter systems. Deficiency in GABA activity has been noted (Cowan and Nutt, 1982), further increasing CNS activity due to its "disinhibition" and probably contributing to seizure occurrence. Comparing medicated and unmedicated groups of alcoholics undergoing withdrawal, Wang (1986) has observed increased sympathetic arousal in the unmedicated alcoholics as assessed by electrodermal responsivity. This group exhibited larger SCR-ORs to aversive stimuli and failed to show habituation. In contrast to commonly observed tolerance effects after prolonged exposure to alcohol, withdrawal episodes tend to occur after increasingly shorter time intervals, indicating the "sensitization" of autonomic symptoms. Ballenger and Post (1978) suggested that the gradual increase in neural reactivity apparent from the increasingly severe withdrawal symptoms is due to a kindling effect.

Studies of Nonalcoholics

Theoretical concerns increasingly dominate research on the effects of alcohol on nonalcoholics that uses ANS measures of such effects. This section reviews some of this research in three interrelated problem areas: tolerance, risk factors related to alcoholism, and the tension reduction and stress dampening hypothesis.

Tolerance

Tolerance, like habituation, which it resembles, is a descriptive term referring to a decline in responsivity to a stimulus—in this case, the drug alcohol—with repeated ingestions. To maintain the same level of responsivity or effect with repeated ingestions, the amount ingested must increase. Various theories have been proposed to account for the development of tolerance. Recent reviews describe current theories of behavioral augmentation of tolerance, reinforcement density, classical conditioning theories, current neurobiological research, and systemic effects (e.g., Goudie and Demellweek, 1986; Lê and Kalant, 1990). The most extensively studied theory in recent years in human research and research examining effects on the ANS has been the classically conditioned compensatory response (CCR) theory of tolerance (Siegel, 1979, 1987; Siegel and Sdao-Jarvie, 1986).

According to CCR theory, the environmental context in which a drug is administered serves as a conditioning stimulus (CS) that elicits for many drugs a compensatory response opposite to the drug effect. Alcohol tolerance is therefore a consequence of the growth of CCRs with repeated pairings of the environmental CS-CCR association. Experimental manipulations that influence CRs should have

comparable effects upon CCRs and hence influence alcohol tolerance (Siegel and Sdao-Jarvie, 1986).

Consideration of set and setting in terms of the physiological state and the organismic OR of the individual interacting with the environment, and consequently interacting with the drug alcohol, may provide a basis for an interpretation of apparent tolerance that fundamentally differs from the CCR theory. We propose that apparent nonsystemic tolerance to alcohol seems to be specific to a particular situation not because of the conditioning of a compensatory response to the context in which alcohol was ingested, but because of the physiological state induced by the novelty of the laboratory test situation interacting with the drug. Our hypothesis is that the evidence for the role of CCRs in determining tolerance is produced in the test situation—it is an artifact. Some of the strongest evidence for our hypothesis is the occurrence of an apparent CCR in a novel test situation where a placebo was substituted for alcohol but in the absence of the prior development of apparent tolerance to alcohol (McCaul et al., 1989b; Newlin, 1986).

There are at least two reasons for the failure to recognize the confounding that has given rise to the apparent evidence for a CCR, one methodological and the other theoretical. A major reason for failing to grasp the importance of the novel test situation is that studies have used incomplete factorial designs. This shortcoming may become apparent when we turn to an examination of a specific experiment. The second reason is the failure to realize that the OR to novelty is a manifestation of a nonspecific organismic response, as previously noted. In most laboratory experiments a mismatch or discordance between a neuronal model of past and present stimulation induced the organismic response to exteroceptive stimuli. Neuronal models may be assumed to develop to discriminably different internal states as well. Conditions for arousal of an OR occur when an individual has repeatedly experienced an internal state induced by a drug and then experiences a discordance between that neuronal model and the state induced by a placebo—or vice versa. A discordance, hence an OR, may occur by shifting from a placebo to a drug. However, the OR need not be of the same magnitude as in shifting from a drug to a placebo. The ORs would not be symmetrical because the OR is a function of intensity of the stimulus to which the change occurs, as well as the amount of change (Maltzman et al., 1971b).

In the usual experiment conducted with human subjects, upon entrance into a new situation, such as a laboratory, the individual is in a state of heightened arousal due to the stress induced by the situation's unfamiliarity and unpredictability. Activation of the ANS, especially its sympathetic branch as it prepares the organism for a potential alert, summates with activation initially induced by alcohol. Initial effects of alcohol and novelty produce a "high" level of arousal via the activation of the H-P-A axis, which is especially reinforcing. As nonspecific arousal habituates with increasing familiarity and loss of novelty of the situation, the effects of alcohol seem to habituate, and tolerance is said to have occurred. Habituation of nonspecific arousal effects due to increasing familiarity is specific to the situation. Apparent decreased responsivity to alcohol is not tol-

erance produced by the acquisition of a CCR, but rather habituation of the organismic OR to the novel stimulus context due to the development of a neuronal model with repeated concordance between past and present interoceptive as well as exteroceptive stimulation.

A study by Peris and Cunningham (1986) is relevant to our hypothesis. They demonstrated interactive effects of alcohol and stress that have important implications for human as well as animal studies of tolerance. In one treatment they used ambulatory and telemetered recording of HR and rectal temperature, thereby avoiding the stress of manual recording of temperature in rats receiving injections of alcohol or saline (1). The usual manual recording of temperature was used in a second treatment (2).

Alcohol in the absence of handling stress produced significant tachycardia and hypothermia (3). Handling stress in the absence of alcohol produced significant tachycardia and hyperthermia (4). Handling stress and alcohol combined produced heightened tachycardia greater than that produced by stress or alcohol alone. They also produced greater hypothermia than in the alcohol no-stress treatment, rather than reduced hypothermia or even hyperthermia reflecting competing physiological processes. Blood alcohol levels did not vary with the different handling treatments.

The obtained results suggest that repeated exposure to stress and alcohol, which permits stress to habituate, would result in a decline in tachycardia and body temperature, regardless of the changing tolerance to alcohol. These changes seem to be specific to the environmental context.

These results suggest an alternative to the CCR interpretation of apparent tolerance. An experiment on tolerance usually starts with conditions 3 and 4 above, with stress and alcohol producing heightened tachycardia and hypothermia. After repeated trials in the same context, stress habituates due to increased familiarity. Habituation of stress results in a state resembling condition 1 in Peres and Cunningham's experiment; alcohol alone produces tachycardia and hypothermia, but less than in the combined conditions 3 and 4 that characterized the start of the experiment. Tolerance would seem to have occurred, but it is in fact the consequence of habituation of stress. A placebo test in which alcohol is omitted is similar to condition 2 in Peres and Cunningham's experiment. Stress is induced as a consequence of novelty and in the absence of alcohol results in tachycardia and hyperthermia. The latter is taken as a CCR uncovered by the placebo, but it is not an opponent process or compensatory response that was increasing throughout the tolerance trials. It appears in the test situation as a response to novelty stress.

Dafters and Anderson (1982) conducted one of the first and most extensive attempts to demonstrate conditioned tolerance in human subjects. They investigated tolerance in the tachycardia response to ethanol in male undergraduate students considered to be moderate social drinkers. Electrodes were attached to subjects, and baseline recordings were obtained in a neutral room. Two distinctly different rooms were employed for the experimental sessions. There were 10 days

of habituation or tolerance acquisition. On half the days subjects received the alcohol in room A, and on the remaining days they received the placebo in room B. On day 11 all participants received alcohol for the first time in their placebo room (A or B as the case may be), and on day 12 they all received alcohol once again in their alcohol room.

Results indicated the habituation of tachycardia to alcohol, interpreted as growing tolerance, over the course of the 5 alcohol administration days. A significant increase in tachycardia in response to alcohol in the novel room occurred in the first test session, day 11, as compared to the last previous day of alcohol administration in the usual alcohol room. On day 12 there was a significant decrease in HR as compared to the response on the previous day and no difference from the response on the last day subjects received alcohol in their alcohol room. Results of the test days were taken as evidence that tolerance is due to a competing CCR that is conditioned to particular environmental stimuli, a specific distinctive room. When alcohol is received in a different room, the CCR is not elicited, and the original HR change is once more evoked.

After the tolerance-acquisition period in which alcohol is repeatedly administered in one and the placebo in another context, four test situations are necessary to separate the contributions of context-novelty versus alcohol to the resulting apparent tolerance. These test situations include (1) alcohol administered in the context associated with alcohol during the tolerance acquisition period, (2) placebo given in the context associated with placebo, (3) placebo given in the context previously associated with alcohol, and (4) alcohol given in the context previously associated with the placebo. As the current test for conditioned tolerance was conducted, the change in room in which alcohol was received is confounded with novelty—receiving alcohol in a new situation for the first time. Novelty evokes widespread physiological changes involving an increase in overall arousal, including tachycardia. If a placebo were given for the first time in the alcohol room, tachycardia should be evoked due to novelty according to our hypothesis. The last two groups should both show significant increases in tachycardia according to a novelty OR interpretation. A conditioned tolerance theory would predict that only the treatment employed by Dafters and Anderson—alcohol in the novel placebo room—would show increased tachycardia.

A similar analysis may be applied to a study by Staiger and White (1988) with the additional assumption that the state induced by the room—novel or familiar—has a primacy effect (Maltzman et al., 1971a) in its interaction with the beverage subsequently received. Primacy and novelty would determine whether the CR is isodirectional or drug-opposite response (Eikelboom and Stewart, 1982), in contrast to the interpretation offered by Staiger and White (1988).

Shapiro and Nathan (1986) conducted an experiment attempting to demonstrate tolerance and CCRs using measures of performance, as well as autonomic measures. The autonomic measures were analyzed using difference scores between initial baseline and each of the three postconsumption recording periods, a procedure that does not adequately adjust for LIV. During the tolerance development phase, alcohol

as compared to tonic consumption resulted in significantly greater increases in HR and finger pulse amplitude (FPA) and greater decreases in body temperature (BT), but only within a given session. Since persistence of decrements in responsivity between sessions was lacking, there was no reliable evidence of the development of tolerance across sessions in any of the physiological measures. Likewise, there were no significant physiological effects on the test days. Therefore, the suggested evidence of tolerance in performance measures may be seriously questioned.

Additional studies of tolerance in humans suffer from a variety of procedural difficulties. Failure to equate for pleasantness and other dimensions of the placebo and nonplacebo drinks leaves interpretations moot and does not support CCR theory, contrary to the investigators' claims (e.g., McCusker and Brown, 1990; Newlin, 1985a).

Furthermore, CCR theory has unreasonable implications for human behavior outside the laboratory context, as well as within it. It implies that individuals with varying degrees of tolerance as a consequence of past drinking history will show no tolerance in a laboratory when offered an alcoholic beverage since the environment is so very different from their usual drinking context. It is unfortunate that various studies of tolerance utilizing autonomic measures or studies that have administered alcohol to the heterogeneous sample have not obtained detailed drinking histories as an estimate of tolerance. However, such an experiment has been conducted using somatosensory evoked potentials (SEPs). Seales et al. (1978) found that the effect of alcohol on late components of the SEP varied inversely with the drinking history of participants. Contrary to CCR theory, tolerance as a function of drinking history was demonstrated in the context of a laboratory, which should not evoke CCRs. Earlier laboratory research described by Wallgren and Barry (1970) also demonstrates tolerance as a function of drinking history with a variety of response measures.

Interest in tolerance in large part stems from the assumption that the reinforcing effects of alcohol decrease with the repeated ingestion of alcohol. As a consequence, an individual must increase the amount ingested to obtain the same level of reinforcement as obtained initially. Ingestion of increasing amounts of alcohol to obtain reinforcement can result ultimately in physical dependence on alcohol and a myriad of social and personal problems, as well as biomedical complications. None of the studies considered addresses this essential characteristic of tolerance, the assumed decline in reinforcing effects.

Risk Factors

Studies have employed autonomic measures under several different experimental arrangements in order to assess individual differences in the risk for alcoholism. The attempt is to differentiate among individuals in terms of the heightened probability or risk for problem drinking or dependence prior to any signs of excessive alcohol consumption. Two categories of risk factors have been studied: familial and personality.

A reasonable research question is to determine whether or not individuals who may be at increased risk differ in autonomic responsivity under a variety of conditions, when challenged by alcohol as well as in its absence. However, differences in autonomic responsivity in the offspring of alcoholics as compared to nonalcoholics do not necessarily mean that these differences are genetically determined effects or that they reflect an increased probability of developing alcoholism. Differences may be entirely environmentally determined, a result of an interaction of environment and genetic factors, or a function of nonspecific factors related to a dysfunctional family, rather than be specific to alcoholism.

We know of no studies employing autonomic measures that have used an essential control group: offspring who come from dysfunctional but nonpsychiatric and nonalcoholic families, e.g., families where the father is paraplegic because of injury so that family roles change, etc. Sociopathy, depression, attention deficit disorder and stress stemming from being raised in a dysfunctional family may all influence autonomic responsivity quite aside from the presence of familial alcoholism. Use of such measures as the Family Environment Scale (Moos and Moos, 1981), especially the Cohesion subscale (Maltzman and Schweiger, 1991) might differentiate a specific family history of alcoholism from nonspecific familial factors.

Another important consideration is whether or not the risk factor is relatively specific or nonspecific. Does the apparent risk factor limit its effects to an increase in the risk of alcohol abuse/dependence or to an array of disorders, dependence upon other drugs, antisocial personality, attentional deficit disorder, depression, and juvenile and adult delinquency, all conditions that may be related to deviant autonomic responsivity? These considerations suggest that studies of risk factors for alcoholism need to be multivariate investigations in which a broad range of psychosocial, personality, and family environment factors serve as independent variables. Multiple dependent variables—autonomic, electrophysiological, and neuropsychological tests—are also needed since they may vary in their sensitivity as measures of risk. Finally, because of the many variables usually employed in risk studies, they need to apply appropriate statistical precautions, e.g., correction for Type I error rates.

Risk Factors and Cue Reactivity and Tolerance. Several different methods have been used to subjects with a positive history of alcoholism in the family (FH+) and those with no history of alcoholism among their biological relatives of varying degree (FH−). Investigators have attempted to induce differences between groups by having them ingest alcohol, administering cue reactivity tests, and then observing tolerance and stress response dampening.

Studies using alcohol challenge and differential cue reactivity with various physiological measures have failed to find reliable differences between FH+ and FH− men, which may or may not be due to the method of selecting subjects at risk. McCaul et al. (1990, 1991a, 1991b) used DSM-III-R criteria for alcohol dependence as reported by college students for their father. Walitzer and Sher

(1990) used the short version of the Michigan Alcoholism Screening Test (SMAST). McCaul et al. (1990, 1991a, b) challenged subjects with varying doses of alcohol and secobarbital and found no group differences between FH+ and FH− in any of their performance or physiological measures: HR, ST, and SCL. The only difference was self-reports of more hangovers in the FH+ than FH− men. Walitzer and Sher (1990) reported two cue reactivity studies in which they found no differential group effects where FH+ as compared to FH− was significantly more responsive on the measures of salivation, ST, SCL, HR, and frontalis EMG to a priming dose of preferred beer.

Newlin and Thompson (1991) used cue reactivity to investigate the development of tolerance versus sensitization in FH+ and FH− college men selected on the basis of their completion of a Michigan Alcoholism Screening Test (MAST) on their biological father. There were no changes in FH+ men for ST and SC, whereas FH− men showed tolerance in these measures. Their conclusions that sensitization developed in FH+ and tolerance in FH− participants are based in part upon an analysis of difference scores that mainly show positive slopes of changes within sessions for FH+ and negative slopes for FH− subjects. Newlin and Thompson's analysis of their results is unconvincing, because it only shows changes occurring within sessions. Sensitization and tolerance are generally assumed to be relatively persistent phenomena, whether or not they are classically conditioned, and therefore their effects should be apparent as significant changes between sessions. There should be a significant groups × sessions effect, which was not obtained. Furthermore, no significant between-group differences were obtained in the placebo test session on any of the physiological measures, a result that contradicts Newlin and Thompson's interpretation of the prior changes occurring within sessions with alcohol challenges.

Risk and Classical Conditioning. We know of only one study of family risk factors in classical conditioning of autonomic measures (Finn, et al., 1994). Density of risk was studied in that high-risk (FH+) subjects had an alcoholic father and at least one additional first- or second-degree alcoholic relative. Low-risk (FH−) subjects had no identifiable first- or second-degree alcoholic relatives. There were 16 FH+ and 16 FH− male subjects. Prospective subjects were excluded if they met DSM-III-R criteria for current alcohol abuse or dependence. There were no differences between the groups on the Sensation Seeking Scale, Socialization Scale, MacAndrew Alcoholism Scale or trait anxiety. Significantly higher MAST scores were obtained by the FH+ than FH− group. Delayed conditioning with a short CS-US interval was used. A high tone served as the CS+, and a low tone served as the CS− interspersed among conditioning trials pairing the CS+ with an electric shock. Test trials in which the CS+ was presented in the absence of the US were used to assess the development of discriminative conditioning—responsivity to the CS+ as compared to the CS−. An extinction session followed conditioning without interruption where CS+ and CS− were presented in the absence of the US until a criterion of three successive trials with no response was attained. After a 10-minute rest period ten more tones were presented for a test of spontaneous recovery of the SCR to the CS+ and CS−.

Bilateral recording of the SCR was the dependent variable along with finger pulse amplitude (FPA). Results with the latter measure are only briefly reported. The FH group showed significantly greater FPA to CS+ than CS−. They therefore showed discriminative conditioning. The FH− group also showed greater responsivity on the first trial of the spontaneous recovery phase than FH+. Discriminative conditioning did not differ significantly as a function of family risk.

There were no differences in basal skin conductance during any of the phases of the experiment. Acquisition as measured by mean responsivity to the CS+ test trial as compared to CS− indicated that the FH− group showed greater responsivity than FH+ to the CS+ test trial tones, but no difference in responsivity to the CS− control tones. Only the FH− group showed conditioning in terms of significantly greater mean responsivity to CS+ than CS−. The difference reflected slower habituation of the SCR to CS+ than to CS− during the course of acquisition. There was no significant group × stimulus interaction. The UCRs of the two groups did not differ significantly. Extinction was more rapid in the FH+ than the FH− group. Less spontaneous recovery for the FH+ than the FH− group was apparent on the first two trials of this phase. When a correction for Type I errors was employed, there was no significant relationship between responsivity to CS+ or discriminative responding to the test and control stimuli and any of the paper and pencil tests.

Conditioning results suggest a modest relationship between high-density family risk and discriminative conditioning and responsivity to the CS+. There were no significant correlations between conditionability and measures of antisocial personality or disinhibition. These latter results therefore provide little support for the notion that propelled the study, Gray's (1975) biobehavioral interpretation of disinhibited behavior. According to this interpretation a behavioral inhibition system (BIS) mediates responses to stimuli for punishment, extinction, and novelty. Deficits in behavioral inhibition should therefore result in poorer discriminative conditioning with a noxious US; specifically, less responsivity to the CS+. Individuals with a FH+ should also show a variety of forms of disinhibited personality characteristics, including poor responsivity to signals for punishment.

At best, a weak conditioning effect was obtained, providing a "basement" effect for showing poorer conditioning in subjects at risk. Finn et al. (1994) assume a particular theory of classical conditioning, which has serious limitations. First, it overgeneralizes from the fact that a noxious US was used. It is possible that FH+ subjects would manifest poor conditioning in the absence of a noxious US. An adequate test of the BIS theory would require conditioning with an innocuous US, such as in the forewarned reaction time procedure (Maltzman, 1979a), and demonstrating with such a paradigm that FH+ subjects would condition as well as FH− subjects and more poorly when a noxious US was employed. Another serious methodological problem with the study is the failure to obtain measures of verbalization of the CS-US contingency. The most important

source of variance in laboratory classical conditioning of SCR is the verbalization of the CS-US contingency (Maltzman, 1979a, 1987). Averaging results over verbalizers and nonverbalizers presents a very misleading picture of what occurred in the experiment. Difficulties of interpretation of the results are compounded by the use of test trials, rather than a long CS-US interval. The latter procedure would permit assessment of the magnitude of the CR and the UCR on each trial. Absence of an initial phase in which SCR-OR is habituated to the tones further confounds the acquisition phase. The reasons given for the failure to employ these more commonly used procedures are unconvincing. Additional research on family risk factors and classical conditioning of SCR is needed, but different experimental procedures than the ones used by Finn et al. (1994) need to be employed.

Risk and Stress Response Dampening

The most extensive investigations of risk factors and with some apparent positive findings have been conducted in the context of stress response dampening (SRD); (Finn and Pihl, 1987, 1988; Finn et al., 1990; Levenson et al., 1980, 1987; Peterson et al., 1993; Sher and Levenson, 1982). The term "stress response dampening" was coined by Levenson et al. (1980) to refer to the possible attenuating influence of alcohol upon the effects of stress. This effect and its converse, the disinhibiting effect that stressors may have upon the depressant effect of alcohol, have a long history of research (Wallgren and Barry, 1970). However, the emphasis upon SRD is derived from the tension reduction hypothesis (TRH), which suggests that alcoholism is reinforcing because it reduces tension or drive (Conger, 1951, 1956). Research on SRD by Levenson and others has evolved into the study of individual differences in SRD or tension reduction as a strategy for approaching the problem of risk in terms of individual differences in the reinforcement value of alcohol. The underlying assumption is that individuals who derive greater reinforcement from alcohol than the average person—for example because it is more tension or stress reducing for them for whatever reason—are at greater than average risk for increasingly seeking and consuming alcohol.

Two general methodological problems persist. First, there is no independent criterion of what constitutes stress or stressors as an independent variable nor is there an agreed-upon independent criterion of tension. Second, tension or drive reduction is no longer a viable general theory of reinforcement for alcohol or any other incentive. Drive or tension reduction theories of reinforcement have repeatedly been refuted in behavioral studies (e.g., Sheffield and Roby, 1950; Sheffield et al., 1951), studies of exploratory and manipulatory behavior (Harlow et al., 1950) and neurobiological studies beginning with brain stimulation (Olds and Milner, 1954). These and other studies have shown that different kinds of stimulation, rather than the reduction of stimulation, are reinforcing.

In the light of behavioral and neurobiological research, continued research on tension reduction as the basis for the reinforcing effects of alcohol is an anachronism. Extensive research on stress and alcohol in animals that assesses the temporal relationships between stress and alcohol consumption (Volpicelli, 1987) suggests that stress depletes one or more neurotransmitters and alcohol consumption temporarily compensates for the depleted stores either by directly or indirectly binding with one or more receptors. Individual differences resulting in lower levels of neurotransmitters either as the result of genetic influences or stress may be compensated for by ingestion of alcohol (Blum and Payne, 1991; McBride et al., 1990). Although the possibility remains that alcohol, in addition to having a positive reinforcing effect, also has a direct negative reinforcing effect—it serves to reduce anxiety by activating the same anatomical mechanisms serving opiates—there is no clear animal evidence that such is the case (Wise, 1988).

Another reason why studies of SRD cannot shed light upon the basis for alcohol's assumed reinforcing effect is analogous to our criticism of tolerance studies: studies of SRD and TRH do not examine the function in question. None of the studies of SRD as investigations of tension reduction actually studies whether learning takes place whenever SRD occurs and does not take place in the absence of SRD produced by alcohol. They examine whether or not physiological responses induced by stressors decrease as a consequence of the ingestion of alcohol and not whether learning may or may not occur as a consequence of the assumed reinforcement indexed by the physiological change.

In addition to the limited information forthcoming from SRD as a means of providing a basis for alcohol's reinforcing effects, these studies may nevertheless shed some light upon risk factors, although not necessarily for the theoretical reason proposed by the investigators conducting the studies, and on the interaction between different physiological states.

Levenson et al. (1980) examined the relationship between stress and alcohol using a relatively high dose of alcohol (1 g/kg) in a double-balanced placebo design with two kinds of stress-inducing situations: (1) electric shock and (2) social anxiety, produced by giving an improvised talk on what the participants like and dislike about their body and appearance. A count-down procedure was used to introduce a stressor, whether the shock or improvised talk.

Analysis of the precountdown phase revealed that subjects consuming alcohol showed significantly faster HR, lower HR variability, high SCL, longer finger-pulse transit time (PTT), and lower self-reported anxiety. There were significant alcohol effects, but no significant instruction effect and no interaction. There was no evidence that might be interpreted in terms of expectancy. Effects of the specific stressor, shock or social anxiety, were similar. There was increased HR, increased somatic activity, increased SCL, decreased ear-PTT, and increased self-ratings of anxiety.

Beverage instructions had no effect upon the magnitude of the response to stress. Consumption of alcohol as compared to the tonic had a significant, apparent attenuating effect on cardiovascular measures. It was followed by a smaller HR increase and a smaller decrease in ear-PTT. Alcohol did not have a significant attenuating affect upon SCL induced by the specific stressors.

Sher and Levenson (1982) reported two experiments in which the same experimental paradigm was employed as in Levenson et al. (1980), with the addition of a personality risk factor. In the first study subjects were categorized on the basis of high and low scores on the MacAndrew (MAC) alcoholism scale because of its success in differentiating between college men who in later years entered treatment for alcoholism as compared to a cohort who presumably did not (Hoffmann et al., 1974). MAC scores interacted with the relationship between alcohol and physiological responses to stressors. There was a significant attenuation of the response to stress under the influence of alcohol in the high- but not the low-risk men as measured by HR and ear-PTT. There was no SRD effect in low-risk men.

A second experiment used MAC scores in combination with scores from Gough's (1960) Socialization (So) Scale, which has repeatedly been found to correlate with alcohol and drug use (e.g., Maltzman and Schweiger, 1991). Subjects were categorized as high and low risk on the basis of their scores on each test separately and in combination. As in the previous experiments, alcohol affected responsivity of some of the physiological measures in the precountdown phase. Personality measures did not interact with alcohol during this phase. Alcohol had a significant attenuating effect on peak responses to stressors in low So (high-risk) men and in high-risk men with corresponding combined MAC and So scores, but not with high-risk MAC subjects alone. Results with MAC scores did not replicate the apparent attenuating effect of stress obtained in the first experiment. Unfortunately, the correlation between MAC and So scores was not reported nor were their means and SDs.

The lack of reported mean So scores and SDs is not a trivial point because of the anomalous results obtained with low So subjects. Fairly extensive research on the psychophysiology of sociopathy has indicated rather consistently that sociopaths—and low So scores have been used as a criterion of sociopathy—are less responsive in SCR but more responsive in HR to noxious stimuli and the threat of noxious stimuli in a countdown procedure (e.g., Hare, 1978). Physiological results obtained by Levenson et al. (1980) in low So subjects in the absence of alcohol are not readily reconciled with the independent body of research on sociopathy in the absence of additional information concerning personality scores.

Levenson et al. (1987) conducted another experiment investigating risk factors and SRD with several useful innovations. Both women and men participated in each of the groups, and personality, as assessed by MAC and So scores, and familial history risk factors were examined along with a low-risk group. Evidence for both factors attenuating the stressor was reported. There was no additivity of familial and personality risk factors when they did occur.

Sher and Walitzer (1986), in a modified countdown procedure using social anxiety as a stressor, employed a moderate and a high dose of alcohol. Personality risk factors based upon MAC and So scores were again employed, as well as a third personality factor, the HK/MBD scale of self-reports of symptoms of hyperactivity before the age of 13 (Tarter et al., 1977). No SRD effects on HR could

be attributed to personality factors, so the study failed to confirm previous findings by Sher and Levenson (1982) and by Levenson et al. (1987). However, Sher and Walitzer reported an SRD effect as a function of moderate and high doses of alcohol. They found this effect after adjusting HR during the precountdown and during the stress interaction for prestress base levels. They concluded that the attenuating effect of alcohol must be the consequence of alcohol reducing centrally mediated anxiety, rather than a consequence of the law of initial values (LIV). A difficulty with their interpretation is that using the prestress base level as a covariate is satisfactory for the immediately following precountdown phase, but not for the stressor phase, which is initiated from the levels of the immediately preceding precountdown phase.

Evidence for an SRD effect of alcohol seems to have been obtained repeatedly for cardiovascular measures but not for SCL. Findings of this sort are susceptible to an interpretation in terms of the law of initial values (LIV; Lacey, 1956; Stern et al., 1980; Wilder, 1967). This "law" refers to the relationship between the size of a phasic response and the tonic level from which it arises (Wilder, 1967). Characteristically, although not always, the relationship is a negative one. The higher the tonic level of activity, the smaller the size of the phasic response arising from that level. In some cases it may even reverse in direction. It is generally agreed that the physiological basis for LIV is negative feedback, which tends to maintain a homeostasis of balance between the sympathetic and parasympathetic ANS (Lacey, 1956; Stern et al., 1980). Presence of the law is most apparent in measures of HR and respiration. It is not apparent in skin temperature, which is complexly determined nor in electrodermal activity measured in terms of skin conductance. The latter is relatively independent of tonic level and may even show a slight positive feedback, with higher tonic levels resulting in larger phasic SCRs (Hord et al., 1964). Several different factors may contribute to the LIV effect, which is part of the general problem of how to measure change. Several different interpretations and methods of dealing with the problem have been proposed (Berntson et al., 1994; Jamieson, 1994; Jamieson and Howk, 1992; Jin, 1992). Jamieson (1994), employing computer simulations, concludes that using change scores, difference scores, or repeated measures analyses, which are all different forms of the same procedure, is superior to regression analyses, such as analysis of covariance, when there is a significant correlation with a third variable; for example familial risk. Regardless of the method used, regression or difference scores, the problem remains of choosing from where to measure the change. The implication of LIV as a physiological phenomenon and not simply a psychometric one is that the base level score should be the point of initiation of the target response.

If appropriate adjustments for preresponse levels were made and SRD effects were obtained, two problems would still remain: (1) why no dampening effect is obtained with SCL, which is not affected by the LIV (Hord et al., 1964) and is not somatically coupled (Roberts and Young, 1971); and (2) is the attenuating effect limited to responses to stress or does it occur to stimuli that cannot be

reasonably considered stressors? If the latter is the case, then the hypothesis that alcohol is a stress dampener per se is undermined.

An experiment by Finn, Zeitouni, and Pihl (1990) employed a control condition lacking in the previously described SRD studies: presentation of an innocuous tone in a simple habituation situation. It was the third in a series of experiments (Finn and Pihl, 1987, 1988) designed to increase the homogeneity of subgroups of men at risk. In addition to the countdown procedure for electric shock with avoidable as well as unavoidable shock, all subjects received ten presentations of an innocuous tone that they were instructed to ignore. Only SC results were recorded for this task.

Under no alcohol the SCR-OR to the first tone was significantly larger in the FH+ than FH− group, with correspondingly slower habituation in the former. There was a significant difference in the response to alcohol, with a larger decrement in the SCR-OR in the FH+ than FH− groups to the first tone and an increased rate of habituation. These changes cannot be considered stress dampening because the tones were innocuous. However, the differential change in habituation may also be considered a form of the LIV (Germana, 1968). Examination of the results indicate a basement effect in operation for the FH− group. They were less responsive than FH+ under no alcohol. Ingestion of the relatively large dose of alcohol had an inhibitory effect but since the FH− group already habituated quickly under no alcohol, there was little room to increase its rate of habituation. In contrast, the FH+ group was considerably more responsive under no alcohol and therefore had room to show an accelerated rate of habituation under alcohol. The only unambiguous result obtained with SCR-OR to innocuous tones was the demonstration that FH+ men were significantly more responsive to innocuous tones than FH− men under no alcohol conditions, a result contrary to BIS theory (Gray, 1975).

The apparent effect of alcohol on SCR to innocuous tones suggests that the corresponding effect obtained with electric shock stressors likewise cannot be considered SRD, in this case resulting in greater tension reduction in FH+ than FH− subjects. It is important to note that no significant effects were obtained for SC in the shock stressor phase of the experiment in accord with the results repeatedly reported by Levenson and his colleagues. Significant groups × drink effects were obtained for HR, digital block volume (DV), and muscle tension in the stressor phase of the experiment.

If these studies claiming to demonstrate SRD on cardiovascular responses turn out to be manifestations of LIV or other mediating variables, such as somatic activity, as we believe they are, it does not follow that alcohol and stressor effects do not interact. There is extensive evidence from a variety of measures other than peripheral ANS indices that indicates that stressors may moderate the effects of alcohol and vice versa (Brick and Poherecky, 1983; Frankenhouser et al., 1974; Myrsten, 1977; Pohorecky, 1990, 1991; Wallgren and Barry, 1970).

Sayette (1993a) reviewed an extensive series of studies of the effects of alcohol upon stress in social drinkers and suggests that there is a primacy effect present

such that there tends to be a greater SRD effect when alcohol is presented before the stressor than after. He offers a cognitively oriented interpretation of this primacy effect—alcohol interferes with the cognitive appraisal of the stressor, thereby indirectly reducing the amount of stress. Given the inconsistency among response measures employed in these studies and the many negative results regardless of the order of stressor and alcohol, there is little consistently obtained evidence of stress response dampening that is likely to support any specific kind of theory, particularly one that relies upon poorly specified cognitive constructs. It is unlikely that an effective theory can be established before consistent reliable evidence of effects are obtained, and the methodological shortcomings and lack of consistent findings with various measures of stress and stress reduction are elucidated. Furthermore, all stress response dampening theories fail to come to grips with animal research demonstrating that stress induces alcohol consumption and not that alcohol reduces stress (Casey, 1960; Volpicelli et al., 1986).

A review of the HR results found in many of the SRD studies leads Sayette (1993b) to the conclusion that inconsistent results and differences in HR results as a function of primacy or order of stress and alcohol may be a consequence of LIV. We agree. It may well be that order could come out of the current disorder if multiple measures of somatic activity were employed when HR reactivity is used as a dependent variable. Extensive research indicates that there is close cardiac-somatic coupling. Changes in HR are closely related to changes in somatic activity (Elliott, 1974; Obrist et al., 1974; Roberts and Young, 1971; Roberts et al., 1974). SCR, which ordinarily does not show an SRD effect, is relatively insensitive to LIV and independent of somatic activity (Roberts and Young, 1971; Roberts et al., 1974).

We question the importance Sayette (1993b) attaches to results purporting to demonstrate an antagonistic placebo response (e.g., Newlin, 1985a, b, 1986, 1987, 1989a). There is no independent measure or delineation of the specific response that purportedly is interfering with the CR to alcohol. An oddball SCR experiment by Lyvers and Maltzman (1991a) employed a placebo group, given tonic and told it was alcohol, which should have produced an antagonistic placebo response. That is, this placebo group should have displayed decreased responsivity, it should have shown smaller SCRs than subjects given tonic and informed that it was tonic. Such was not the case. These two groups did not differ. Lyvers and Maltzman (1991a) also employed a no-beverage control group, which is needed in order to begin to adequately interpret results taken as indicating an antagonistic placebo response in such studies. They employed a control for the mere ingestion of a beverage. The no-beverage control group gave significantly more spontaneous SCRs than the group given tonic and told it was alcohol—the group that should have manifested an antagonistic placebo response—and the group given tonic and told it was tonic. The no-beverage group did not differ from the group given alcohol. Alcohol ingestion maintained the level of spontaneous responses; it retarded habituation as compared to subjects given tonic. A similar effect was obtained with the initial SC-OR to a tone. Why consuming an innocuous beverage

would result physiologically in decreased SCR responsivity is unclear. It may be related to the drinking of a fairly large amount of tonic water, which some subjects report produces discomfort. Whether a similar effect would obtain with HR reactivity is unknown and needs to be investigated (Sher et al., 1994).

Conclusion

In this chapter we have been able to sample only some of the problems that have been investigated in connection with alcohol, alcoholism, and the ANS. Such a selection is arbitrary, and the classifications of problems employed, including the ANS, are conventions constructed largely for convenience. It must always be remembered that "there is one nervous system . . . not two, not three. We speak of specific centers as 'one function' centers, but we do recognize that this is an artefact of our focus and methodology. The somatic and autonomic systems are controlled simultaneously from interacting components of one brain and cord" (Brooks, 1983, pp. 202–203).

We tend to forget in our need to simplify and bring a study within maneageable limits that we select out only one or two physiological measures from a sea of continuous change. Variables tend to become further disembodied and abstract as they enter into theoretical formulations. There has been an unfortunate trend in some areas of experimental research to resort to cognitive conceptions that are far removed from their physiological and behavioral referrants and are inherently ambiguous. Reification of such concepts is no substitute for critical theory and thinking about biobehavioral problems of import as they relate to alcohol, alcoholism, and the autonomic nervous system.

Claude Bernard (1957), the founder of modern physiology and experimental medicine, called research attention to the internal environment and the theory of its constancy. Our area of concern is an intimate part of both disciplines and more. Its approach to science could profit much by emulating Bernard. We must recognize in our research and theory that there is a continuous interaction between the internal and external environments. Nowhere is this more apparent than in drug taking, including alcohol consumption. Constancy of the internal environment is maintained by a dialectical relationship with the external environment, social as well as physical.

The potential of our research area can be best realized by utilizing modern experimental and statistical techniques not available to Bernard in order to approach a fundamental understanding of alcohol, alcoholism, and the ANS. But we must,

> remember that the one unchangeable scientific principle, in medicine as well as in the other experimental sciences, is the absolute determinism of phenomena . . . When search for the causes determining phenomena is once posited as the fundamental principle of the experimental method, materialism, spiritualism, inert matter and living matter cease to exist; only phenomena are left, whose conditions we must determine, i.e., the conditions which play the part of immediate cause. Scientific determinism ceases here; there are only words beyond, which are of course necessary but which may delude us if we are not constantly on guard against the traps which our minds perpetually set for themselves (Bernard, 1957, p. 219).

References

Adinoff, B., Bone, G.H.A., and Linnoila, M. (1988). Acute ethanol poisoning and the ethanol withdrawal syndrome. *Med. Toxicol. Adverse Drug Exp.* **3:**172–196.

Appenzeller, O. (1990). *The Autonomic Nervous System: An Introduction to Basic and Clinical Concepts.* Amsterdam: Elsevier.

Appenzeller, O., and Richardson, E.P. (1966). The sympathetic chain in patients with diabetic and alcoholic polyneuropathy. *Neurology* **16:**1205–1209.

Ballenger, J.C., and Post, R.M. (1978). Kindling as a model for the alcohol withdrawal syndromes. *Br. J. Psychiatr.* **133:**1–14.

Bannister, P., and Lowosky, M.S. (1987). Ethanol and hypogonadism. *Alcohol Alcoholism* **22:**213–217.

Baudena, P., Halgren, E., Heit, G., & Clark, J.M. (in press). Potentials evoked in the human frontal cortex by rare target and distractor auditory and visual stimuli. *J. Physiol.*

Bauer, L.O. (1994). Electroencephalographic and autonomic predictors of relapse in alcohol-dependent patients. *Alcoholism: Clin. Exp. Res.* **18:**755–760.

Baxter, L.R., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Fering, H-K., Munford, P., and Phelps, M.E. (1992). Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch. Gen. Psychiatr.* **49:**681–689.

Bender, W.R.G. (1933). The effect of pain and emotional stimuli and alcohol on pupillary reflex activity. *Psychol. Monog.* **44:**1–32.

Berg, G., Laberg, J.C., Skutle, A., and Ohman, A. (1981). Instructed versus pharmacological effects of alcohol in alcoholics and social drinkers. *Behav. Res. Ther.* **19:**55–66.

Bernard, C. (1957). *An Introduction to the Study of Experimental Medicine* (trans. by H.C. Greene). New York: Dover.

Berntson, G.G., Uchino, B.N., and Cacioppo, T. (1994). Origins of baseline variance and the law of initial values. *Psychophysiology* **31:**204–210.

Blum, K., and Payne, J.E. (1991). *Alcohol and the Addictive Brain.* New York: The Free Press.

Bradlyn, A.S., and Young, L.D. (1983). Parameters influencing the effectiveness of the balanced placebo design in alcohol research. In Stress and Alcohol Use, L.A. Pohorecky and J. Brick, eds. New York: Elsevier, pp. 88–93.

Brick, J., and Pohorecky, L.A. (1983). The neuroendocrine response to stress and the effect of ethanol. In Stress and Alcohol Use, L.A. Pohorecky and J. Brick, eds. New York: Elsevier, pp. 389–427.

Briddell, D.W., and Wilson, G.T. (1976). The effects of alcohol and expectancy set on male sexual arousal. *J. Abnorm. Psychol.* **85:**225–234.

Briddell, D.W., Rimm, D.C., Caddy, G.R., Krawitz, G., Sholis, D., and Wunderlin, R.J. (1978). Effects of alcohol and cognitive set on sexual arousal to deviant stimuli. *J. Abnorm. Psychol.* **87:**418–430.

Brooks, C.McC. (1983). Newer concepts of the autonomic system's role derived from reductionist and behavioral studies of various animal species. *J. Auton. Nerv. Syst.* **7:**199–212.

Bruch, N.R., and Greiner, T.H. (1960). A biolectric scale of human alertness: Concurrent recordings of the EEG and GSR. *Psychiatr. Res. Rep. Am. Psychol. Assoc.* **12:** 183–193.

Casey, A. (1960). The effect of stress on the consumption of alcohol and reserpine. *Q. J. Stud. Alcohol* **21:**208–216.

Chandler, B.C., Parson, O.A., and Vega, A. (1975). Autonomic functioning in alcoholics: A study of heart rate and skin conductance. *Q. J. Stud. Alcohol* **36:**566–577.

Chotlos, J.W., and Goldstein, G. (1967). Psychophysiological responses to meaningful sounds. *J. Nerv. Ment. Dis.* **145:**314–325.

Cloninger, C.R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science* **236:** 410–416.

Conger, J.J. (1951). The effects of alcohol on conflict behavior in the albino rat. *Q. J. Stud. Alcohol* **12:**1–29.

Conger, J.J. (1956). Reinforcement theory and the dynamics of alcoholism. *Q. J. Stud. Alcohol* **17:**296–305.

Cooney, N.L., Gillespie, R.A., Baker, L.H., and Kaplan, R.F. (1987). Cognitive changes after alcohol cue exposure. *J. Consult. Clin. Psychol.* **55:**150–155.

Corty, E., O'Brien, C.P., and Mann, S. (1988). Reactivity to alcohol stimuli in alcoholics: Is there a role for temptation? *Drug Alcohol Depend.* **21:**29–36.

Cowen, P.J., and Nutt, D.J. (1982). Abstinence symptoms after withdrawal of tranquilizing drugs: Is there a common neurochemical mechanism. *Lancet* **2:**360–362.

Cox, C.W. (1979). Control of "sex centers" in the brain (Letter to the editor). *Med. Asp. Hum. Sexual.* **13:**113.

Criqui, M.H., Wallace, R.B., Mishkel, M., Connor, E.G., and Heiss, G. (1981). Alcohol consumption and blood pressure: The lipid research clinics prevalence study. *Hypertension* **3:**557–565.

Crowe, L.C., and George, W.H. (1989). Alcohol and human sexuality: Review and integration. *Psychol. Bull.* **105:**374–386.

Dafters, R., and Anderson, G. (1982). Conditioned tolerance to the tachycardia effect of ethanol in humans. *Psychopharmacology* **78:**365–367.

Drummond, D.C., and Glautier, S. (1994). A controlled trial of cue exposure treatment in alcohol dependence. *J. Consult. Clin. Psychol.* **62:**809–817.

Drummond, D.C., Cooper, T., and Glautier, S.P. (1990). Conditioned learning in alcohol dependence: implications for cue exposure treatment. *Br. J. Addict.* **85:**725–743.

Eikelboom, R., and Stewart, J. (1982). Conditioning of drug-induced physiological responses. *Psychol. Rev.* **89:**507–528.

Elliott, R. (1974). The motivational significance of heart rate. In Cardiovascular Psychophysiology, P.A. Obrist, A.H. Black, J. Brener, and L.V. DiCara, eds. Chicago: Aldine, pp. 505–537.

Fahrner, E.M. (1987). Sexual dysfunction in male alcoholic addicts: Prevalence and treatment. *Arch. Sex. Behav.* **16:**247–257.

Farkas, G., and Rosen, R.C. (1976). The effects of ethanol on male sexual arousal. *J. Stud. Alcohol* **37:**265–272.

Feather, B.W., and Wells, D.T. (1966). Effects of concurrent motor activity on the unconditioned salivary reflex. *Psychophysiology* **2:**338–343.

Finn, P.R., and Pihl, R.O. (1987). Men at high risk for alcoholism: The effect of alcohol on cardiovascular response to unavoidable shock. *J. Abnorm. Psychol.* **96:**230–236.

Finn, P.R., and Pihl, R.O. (1988). Risk for alcoholism: A comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. *Alcoholism: Clin. Exp. Res.* **12:**742–747.

Finn, P.R., Kessler, D.N., and Hussong, A.M. (1994). Risk for alcoholism and classical conditioning to signals for punishment: Evidence for a weak behavioral inhibition system? *J. Abnorm. Psychol.* **103:**293–301.

Finn, P.R., Zeitouni, N.C., and Pihl, R.O. (1990). Effects of alcohol on psychophysiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. *J. Abnorm. Psychol.* **99:**79–85.

Foltin, R.W., and Fischman, M.W. (1988). Ethanol and cocaine interactions in humans: Cardiovascular consequences. *Pharmacol. Biochem. Behav.* **31:**877–883.

Fowles, D.C. (1986). The eccrine system and electrodermal activity. In *Psychophysiology: Systems, Processes and Applications* M.G.H. Coles, E. Donchin, and S.W. Porges, eds. New York: Guilford Press, pp. 51–96.

Frankenhaeuser, M., Dunne, E., Bjurstrom, H., and Lundberg, U. (1974). Counteracting depressant effects of alcohol by psychological stress. *Psychopharmacologia* **38:** 271–278.

Funderburk, F.R., and Allen, R.P. (1977). Alcoholics' disposition to drink. Effects of abstinence and heavy drinking. *J. Stud. Alcohol* **38:**410–425.

Gantt, W.H., Newton, J.E.O., Royer, F.L., and Stephens, J.H. (1966/1991). Effect of person. *Integ. Physiol. Behav. Sci.* **26:**146–160.

Germana, J. (1968). Rate of habituation and the law of initial values. *Psychophysiology* **5:** 31–36.

Glautier, S., and Drummond, D.C. (1994). Alcohol dependence and cue reactivity. *J. Stud. Alcohol* **55:**224–229.

Glautier, S., Taylor, C., and Remington, B. (1992). A method for producing alcohol placebos. *Br. J. Addict.* **87:**303–308.

Gold, M.S., Redmond, D.E., Jr., and Kleber, H.D. (1979). Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am. J. Psychiatr.* **136:**100–102.

Gorelick, D.A., and Paredes, A. (1992). Effect of fluoxetine on alcohol consumption in male alcoholics. *Alcoholism: Clin. Exp. Res.* **16:**261–265.

Goudie, A.J., and Demellweek, C. (1986). Conditioning factors in drug tolerance. In Behavioral Analysis of Drug Dependence, S.R. Goldberg and I.P. Stolerman, eds. Orlando: Academic Press, pp. 225–285.

Gough, H.G. (1960). Theory and measurement of socialization. *J. Consult. Clin. Psychol.* **24:**23–30.

Grassi, G.M., Somers, V.K., Renk, W.S., Abboud, F.M., and Mark, A.L. (1989). Effects of alcohol intake on blood pressure and sympathetic nerve activity in normotensive humans: A preliminary report. *J. Hypertens.* **7**(suppl 6):S20–S21.

Gray, J.A. (1975). *Elements of a Two-Process Theory of Learning.* San Diego: Academic Press.

Greeley, J.D., Swift, W., Prescott, J., and Heather, N. (1993). Reactivity to alcohol-related cues in heavy and light drinkers. *J. Stud. Alcohol* **54:**359–368.

Hare, R.D. (1978). Electrodermal and cardiovascular correlates of psychopathy. In Psychopathic Behaviour: Approaches to Research, R.D. Hare and D. Schalling, eds. Chichester: John Wiley & Sons, pp. 107–143.

Harlow, H.F., Harlow, M.K., and Meyer, D.R. (1950). Learning motivated by a manipulation drive. *J. Exp. Psychol.* **40:**228–234.

Heather, N., and Bradley, B.P. (1990). Cue exposure as a practical treatment for addictive disorders: Why are we waiting? *Addict. behav.* **15:**335–337.

Heather, N., and Robertson, I. (1983). *Controlled Drinking*, rev. ed. London: Methuen.

Hennessy, J.W., and Levine, S. (1979). Stress, arousal, and the pituitary-adrenal system: A psychoendocrine hypothesis. In *Progress in Psychobiology and Physiological Psychology*, J.M. Sprague and A.N. Epstein, eds. New York: Academic Press, pp. 133–178.

Henson, D.E., and Rubin, H.B. (1971). Voluntary control of eroticism. *J. Appl. Behav. Anal.* **4:**37–44.

Hess, E.H. (1965). Attitude and pupil size. *Sci. Am.* **212:**46–54.

Hodgson, R., Rankin, H., and Stockwell, T. (1979). Alcohol dependence and the priming effect. *Behav. Res. Ther.* **17:**379–387.

Hoffman, P.L., and Tabakoff, B. (1985). ethanol's action on brain biochemistry. In Alcohol and the Brain: Chronic Effects, R.E. Tarter and D.H. Van Thiel, eds. New York: Plenum Press, pp. 19–68.

Hoffmann, H., Loper, R.G., and Kammeier, M.L. (1974). Identifying future alcoholics with MMPI scales. *Q. J. Stud. Alcohol* **35:**490–498.

Hord, D.J., Johnson, L.C., and Lubin, A. (1964). Differential effect of the law of initial value (LIV) on autonomic variables. *Psychophysiology* **1:**79–87.

Hull, J.G., and Bond, C.F. (1986). Social and behavioral consequences of alcohol consumption and expectancy: A meta-analysis. *Psychol. Bull.* **99:**347–360.

Ireland, M.A., Vandongen, R., Davidson, L., Beilin, L.J., and Rouse, I.L. (1984). Acute effects of moderate alcohol consumption on blood pressure and plasma catecholamines. *Clin. Sci.* **66:**643–648.

Isbell, H., Fraser, H.G., Wikler, A., Belleville, R.E., and Eisenman, A.J. (1955). An experimental study of the etiology of "rum fits" and delirium tremens. *Q. J. Stud. Alcohol* **16:**1–13.

Istvan, J., and Matarazzo, J.D. (1984). Tobacco, alcohol, and caffeine use: A review of their interrelationships. *Psychol. Bull.* **95:**301–326.

Jamieson, J. (1994). Correlates of reactivity: Problems with regression based methods. *Int. J. Psychophysiol.* **17:**65–72.

Jamieson, J., and Howk, S. (1992). The law of initial values: A four factor theory. *Int. J. Psychophysiol.* **12:**53–61.

Jellinek, E.M. (1952). Phases of alcohol addiction. *Q. J. Stud. Alcohol* **13:**673–684.

Jellinek, E.M. (1960). *The Disease Concept of Alcoholism.* New Brunswick, NJ: Hillhouse Press.

Jenike, M.A., Baer, L., Minichiello, W.E., eds. (1990). *Obsessive-Compulsive Disorders: Theory and Management*, 2nd ed. Chicago: Year Book Medical Publishers.

Jin, P. (1992). Toward a reconceptualization of the Law of Initial Value. *Psychol. Bull.* **111:**176–184.

Jensen, S.B. (1984). Sexual function and dysfunction in younger married alcoholics. Acta *Psychiatr. Scand.* **69:**543–549.

Jones, B.M., Parson, O.A., and Rundell, O.P.H. (1976). Psychophysiological correlates of alcoholism. In *Alcoholism: Interdisciplinary Approaches to an Enduring Problem*, R.E. Tarter and A.A. Sugerman, eds. Reading, MA: Addison-Wesley, pp. 435–477.

Jones, B.M., Hatcher, E., Jones, M.K., and Farris, J.J. (1978). The relationship of extraversion and neuroticism to the effects of alcohol on cognitive performance in male and female social drinkers. In *Currents in Alcohol. Vol. IV. Psychiatric, Psychological, Social, and Epidemiological Studies*, F.A. Seixas, ed. New York: Grune & Stratton, pp. 243–264.

Kagan, J. (1989). The concept of behavioral inhibition to the unfamiliar. In *Perspectives on Behavioral Inhibition*, J.S. Reznick, ed. Chicago: University of Chicago Press, pp 1–23.

Kanzow, W.T. (1986). The clinical stages of alcoholic delirium and their therapeutic significance. *Acta Psychiatr. Scand.* **329**(suppl):124–128.

Kaplan, R.F., Meyer, R.E., and Stroebel, C.F. (1983). Alcohol dependence and responsivity to an ethanol stimulus as predictors of alcohol consumption. *Br. J. Addict.* **78:** 259–267.

Kaplan, R.F., Meyer, R.E., and Virgilio, L.M. (1984). Physiological reactivity to alcohol cues and the awareness of an alcohol effect in a double-blind placebo design. *Br. J. Addict.* **79:**439–442.

Kaplan, R.F., Cooney, N.L., Baker, L.H., Gillespie, R.A., Meyer, R.E., and Pomerleau, O.F. (1985). Reactivity to alcohol-related cues: Physiological and subjective responses in alcoholics and nonproblem drinkers. *J. Stud. Alcohol* **46:**267–272.

Keller, M. (1972). On the loss-of-control phenomenon in alcoholism. *Br. J. Addict.* **67:** 153–166.

Kennedy O.A. (1971). Pupillometrics as an aid in the assessment of motivation, impact of treatment, and prognosis of chronic alcoholics. Ph.D. dissertation, University of Utah. Dissertation Abstracts International, 1971,32,1214-1215B. University Microfilms No. 71-21, 691. Ann Arbor: University Microfilms.

Kilpatrick, D.G., Sutker, P.B., Best, C.L., and Allain, A.N. (1980). Acute alcohol intoxication and vicarious emotional responsiveness. *Addict. Behav.* **5:**191–198.

Kimmel, H.D., van Olst, E.H., and Orlebeke, J.F., eds. (1979). *The Orienting Reflex in Humans.* Hillsdale, NJ: Erlbaum.

Knight, L.J., Barbaree, H.E., and Boland, F.J. (1986). Alcohol and the balanced-placebo design: The role of experimenter demands in expectancy. *J. Abnorm. Psychol.* **95:** 382–385.

Knott, V.J., and Bulmer, D.R. (1984). Heart rate responsivity to a high intensity auditory stimulus: A comparison of male alcoholics and normal controls. *Addict. Behav.* **9:** 201–205.

Korytnyk, N.X., and Perkins, D.V. (1983). Effects of alcohol versus expectancy for alcohol on the incidence of graffiti following an experimental task. *J. Abnorm. Psychol.* **92:**335–340.

Laberg, J.C. (1986). Alcohol and expectancy: Subjective, psychophysiological and behavioral responses to alcohol stimuli in severely, moderately and non-dependent drinkers. *Br. J. Addict.* **81:**797–808.

Laberg, J.C., and Ellertsen, B. (1987). Psychophysiological indicators of craving in alcoholics: Effects of cue exposure. *Br. J. Addict.* **82:**1341–1348.

Lacey, J.L. (1956). The evaluation of autonomic responses: Toward a general solution. *Ann. NY Acad. Sci.* **6:**125–162.

Lacey, J.L. (1959). Psychophysiological approaches to the evaluation of psychotherapeutic process and outcome. In *Research in Psychotherapy.* E.A. Rubenstein and M.B. Parloff, eds. Washington, DC: American Psychological Association.

Lapp, W.M., Collins, R.L., Zywiak, W.H., and Izzo, C.V. (1994). Psychopharmacological effects of alcohol on time perception: The extended balanced placebo design. *J. Stud. Alcohol* **55:**96–112.

Larson, P.B., Schneiderman, N., and DeCarlo, P.S. (1986). Physiological basis of cardiovascular psychophysiology. In *Psychophysiology: Systems, Processes and Applications,* M.G.H. Coles, E. Donchin, and S.W. Porges, eds. New York: Guilford Press, pp. 122–165.

Lê, A.D., and Kalant, H. (1990). Learning as a factor in ethanol tolerance. In *Neurobiology of Drug Abuse: Learning and Memory,* L. Erinoff, ed. NIDA Research Monograph No. 97. DHHS Publication No. (ADM) 90-1677, pp. 193–297.

Lehrer, P.M., and Taylor, H.A. (1974). Effects of alcohol on cardiac reactivity in alcoholics and nonalcoholics. *Q. J. Stud. Alcohol* **35:**1044–1052.

Leigh, B.C. (1990). The relationship of sex-related alcohol expectancies to alcohol consumption and sexual behavior. *Br. J. Addict.* **85:**919–928.

Levenson, R.W., Sher, K.J., Grossman, L.M., Newman, J., & Newlin, D.B. (1980). Alcohol and stress response dampening: Pharmacological effects, expectancy, and tension reduction. *J. Abnorm. Psychol.* **89:**528–538.

Levenson, R.W., Oyama, O.N., and Meek, P.S. (1987). Greater reinforcement from alcohol for those at risk: Parental risk, personality risk, and sex. *J. Abnorm. Psychol.* **96:** 242–253.

Levine, S., and Wiener, S.G. (1989). Coping with uncertainty: A paradox. In *Coping with Uncertainty: Behavioral and Developmental Perspectives,* D.S. Palermo, ed. Hillsdale, NJ: Erlbaum, pp. 1–16.

Lindsley, D. (1951). Emotion. In *Handbook of Experimental Psychology,* S.S. Stevens, ed. New York: John Wiley & Sons, pp. 473–516.

Linnoila, M., Mefford, I., Nutt, D., and Adinoff, B. (1987). Alcohol withdrawal and noradrenergic function. *Ann. Intern. Med.* **107:**875–889.

Litt, M.D., Cooney, N.L., Kadden, R.M., and Gaupp, L. (1990). Reactivity to alcohol cues and induced moods in alcoholics. *Addict. Behav.* **15:**137–146.

Low, P.A., Walsh, J.C., Huang, C.Y., and McLeod, J.G. (1975). The sympathetic nervous system in alcoholic neuropathy: A clinical and pathological study. *Brain* **98:**357–364.

Ludwig, A.M., and Stark, L.H. (1974). Alcohol craving: Subjective and situational aspects. *Q. J. Stud. Alcohol* **35:**899–905.

Ludwig, A.M., and Wikler, A. (1974). "Craving" and relapse to drink. *Q. J. Stud. Alcohol* **35:**108–130.

Ludwig, A.M., Wikler, A., and Stark, L.H. (1974). The first drink: Psychobiological aspects of craving. *Arch. Gen. Psychiatr.* **30:**539–547.

Ludwig, A.M., Cain, R.B., Wikler, A., Taylor, R.M., and Bendfeldt, F. (1977). Physiologic and situational determinants of drinking behavior. *Adv. Exp. Med. Biol.* **85A-85B:** 589–600.

Lyvers, M.F., and Maltzman, I. (1991a). Selective effects of alcohol on electrodermal indices of orienting reflexes to signal and nonsignal stimuli. *Psychophysiology* **28:** 569–579.

Lyvers, M.F., and Maltzman, I. (1991b). The balanced placebo design: Effects of alcohol and beverage instructions cannot be independently assessed. *Int. J. Addict.* **26:** 963–972.

Lyvers, M., Boyd, G., and Maltzman, I. (1988). Effects of cigarette smoking on bilateral electrodermal measures of the orienting reflex. *Psychophysiology* **25:**408–417.

Majchrowicz, E. (1985). Biologic properties of ethanol and the biphasic nature of ethanol withdrawal syndrome. In *Alcohol and the Brain: Chronic Effects,* R.E. Tarter and D.H. Van Thiel, eds. New York: Plenum, pp. 315–338.

Malatesta, V., Pollack, R.H., Wilbanks, W.A., and Adams, H.E. (1979). Alcohol effects on the orgasmic-ejaculatory response in human males. *J. Sex. Res.* **15:**101–107.

Maltzman, I. (1979a). Orienting reflexes and classical conditioning in humans. In *The Orienting Reflex in Humans,* H.D. Kimmel, E.H. Van Olst, and J.F. Orlebeke, eds. New York: Erlbaum, pp. 323–351.

Maltzman, I. (1979b). Orienting reflexes and significance: A reply to O'Gorman. *Psychophysiology* **16:**274–283.

Maltzman, I. (1987). A neo-Pavlovian interpretation of the OR and classical conditioning in humans: With comments on alcoholism and the poverty of cognitive psychology. In *Cognitive Processes and Pavlovian Conditioning in Humans,* G. Davey, ed. Chichester: John Wiley & Sons, pp. 211–249.

Maltzman, I. (1990). The OR and significance. *Pavlov. J. Biol. Sci.* **25:**111–122.

Maltzman, I. (1991). Is alcoholism a disease? A critical review of a controversy. *Integ. Physiol. Behav. Sci.* **26:**200–210.

Maltzman, I. (1994). Why alcoholism is a disease. *J. Psychoactive Drugs* **26:**13–31.

Maltzman, I., and Schweiger, A. (1991). Individual and family characteristics of middle-class adolescents hospitalized for alcohol and drug abuse. *Br. J. Addict.* **86:**1435–1447.

Maltzman, I., Harris, L., Ingram, E., and Wolff, C. (1971a). A primacy effect in the orienting reflex to stimulus change. *J. Exp. Psychol.* **87:**202–206.

Maltzman, I., Smith, M.J., Kantor, W., and Mandell, M.P. (1971b). Effect of stress on habituation of the orienting reflex. *J. Exp. Psychol.* **87:**207–214.

Marinkovic, K. (1993). Effects of alcohol on event-related potentials and skin conductance in two discrimination tasks. Unpublished Ph.D. Dissertation, University of California, Los Angeles.

Marks, V. (1980). The effects of ethanol on the endocrine system. In *Addiction and Brain Damage,* D. Richter, ed. London: Croom Helm, pp. 153–167.

Marlatt, G.A. (1979). Alcohol use and problem drinking: A cognitive-behavior analysis. In *Cognitive-Behavioral Interventions: Theory, Research, and Procedures,* P.C. Kendall and S.D. Hollen, eds. New York: Academic Press, pp. 319–355.

Marlatt, G.A. (1983). The controlled-drinking controversy: A commentary. *Am. Psychol.* **38:**1097–1110.

Marlatt, G.A. (1990). Cue exposure and relapse prevention in the treatment of addictive behaviors. *Addict. Behav.* **15:**395–399.

Marlatt, G.A., Demming, B., and Reid, J.B. (1973). Loss of control drinking in alcoholics: An experimental analogue. *J. Abnorm. Psychol.* **81:**233–241.

Martin, C.S., and Sayette, M.A. (1993). Experimental design in alcohol administration research: Limitations and alternatives in the manipulation of dosage-set. *J. Stud. Alcohol* **54:**750–761.

Martin, C., Earlywine, M., Finn, P., and Young, R. (1990). Some boundary conditions for effective use of alcohol placebos. *J. Stud. Alcohol* **51:**500–505.

Masters, W.H., and Johnson, V.E. (1966). *Human Sexual Response.* Boston: Little, Brown & Co.

Matikainen, E., Juntunen, J., and Salmi, T. (1986). Autonomic dysfunction in longstanding alcoholism. *Alcohol Alcoholism* **21:**69–73.

Mawdsley, C., and Mayer, R. (1965). Nerve conduction in alcoholic polyneuropathy. *Brain* **88:**335–356.

Mayer, R.F., and Khurana, R.K. (1982). Peripheral and autonomic nervous system. In *Encyclopedic Handbook of Alcoholism.* E.M. Pattison and E. Kaufman, eds. New York: Gardner Press, pp. 194–203.

McBride, W.J., Murphy, J.M., Lumeng, L., and Li, T-K. (1990). Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats. *Alcohol* **7:**199–205.

McCaul, M.E., Turkkan, J.S., and Stitzer, M.L. (1989a). Psychophysiological effects of alcohol-related stimuli: I. The role of stimulus intensity. *Alcoholism: Clin. Exp. Res.* **13:**386–391.

McCaul, M.E., Turkkan, J.S., and Stitzer, M.L. (1989b). Conditioned opponent responses: Effects of placebo challenge in alcoholic subjects. *Alcoholism: Clin. Exp. Res.* **13:** 631–635.

McCaul, M.E., Turkkan, J.S., Svikis, D.S., and Bigelow, G.E. (1990). Alcohol and secobarbital effects as a function of familial alcoholism: Acute psychophysiological effects. *Alcoholism: Clin. Exp. Res.* **14:**704–712.

McCaul, M.E., Turkkan, J.S., Svikis, D.S., and Bigelow, G.E. (1991a). Alcohol and secobarbital effects as a function of familial alcoholism: Extended intoxication and increased withdrawal effects. *Alcoholism: Clin. Exp. Res.* **15:**94–101.

McCaul, M.E., Turkkan, J.S., Svikis, D.S., and Bigelow, G.E. (1991b). Familial density of alcoholism: Effects on psychophysiological responses to ethanol. *Alcohol* **8:**219–222.

McCusker, C.G., and Brown, K. (1990). Alcohol-predictive cues enhance tolerance to and precipitate "craving" for alcohol in social drinkers. *J. Stud. Alcohol* **5:**494–499.

McGonnell, P.C., and Beach, H.D. (1968). The effects of ethanol on the acquisition of a conditioned GSR. *Q. J. Stud. Alcohol* **29:**845–855.

Mello, N.K. (1972). Behavioral studies of alcoholism. In *The Biology of Alcoholism, Vol. 2. Physiology and Behavior*, B. Kissin and H. Begleiter, eds. New York: Plenum, pp. 219–291.

Mello, N.K., and Mendelson, J.H. (1986). Cigarette smoking: Interactions with alcohol, opiates and marijuana. In Strategies for research on the interactions of drugs of abuse, M.C. Braude, and H.M. Ginzburg, eds. NIDA Research Monograph No. 68. DHHS Publication No. 86-1453, pp. 154–180.

Miller, N.S., and Gold, M.S. (1988). The human sexual response and alcohol and drugs. *J. Subst. Abuse Treatment* **5:**171–177.

Miller, N.S., Dackis, C.A., and Gold, M.S. (1987). The relationship of addiction, tolerance, and dependence to alcohol and drugs: a neurochemical approach. *J. Subst. Abuse Treatment* **4:**197–207.

Modell, J.G., Mountz, J.M., and Beresford, T.P. (1990). Basal ganglia/limbic striatal and thalamocortical involvement in craving and loss of control in alcoholism. *J. Neuropsychiatr. Clin. Neurosci.* **2:**123–144.

Modell, J.G., Glaser, F.B., Cyr, L., and Mountz, J.M. (1992). Obsessive and compulsive characteristics of craving for alcohol in alcohol abuse and dependence. *Alcoholism: Clin. Exp. Res.* **16:**272–274.

Modell, J.G., Mountz, J.M., Glaser, F.B., and Lee, J.Y. (1993). Effect of haloperidol on measures of craving and impaired control in alcoholic subjects. *Alcoholism: Clin. Exp. Res.* **17:**234–240.

Monti, P.M., Binkoff, J.A., Zwick, W.R., Abrams, D.B., Nirenberg, T.D., and Liepman, M.R. (1987). Reactivity of alcoholics and nonalcoholics to drinking cues. *J. Abnorm. Psychol.* **96:**122–126.

Monti, P.M., Rohsenow, D.J., Rubonis, A.V., Niaura, R.S., Sirota, A.D., Colby, S.M., and Abrams, D.B. (1993a). Alcohol cue reactivity: Effects of detoxification and extended exposure. *J. Stud. Alcohol* **54:**235–245.

Monti, P.M., Rohsenow, D.J., Rubonis, A.V., Niaura, R.S., Sirota, A.D., Colby, S.M., Goddard, P., and Abrams, D.B. (1993b). Cue exposure with coping skills treatment for male alcoholics: A preliminary investigation. *J. Consult. Clin. Psychol.* **61:** 1011–1019.

Moos, R.H., and Moos, B.S. (1981). *Family Environment Scale Manual.* Palo Alto, CA: Consulting Psychologists Press.

Morlet, A., Watter, G.R., Dunn, J., Keogh, E.J., Creed, K.E., Tulloch, B.G., Lord, D.J., and Earle, C.M. (1990). Effects of acute alcohol on penile tumescence in normal young men and dogs. *Urology* **35:**399–404.

Myrsten, A.-L. (1977). Interaction of alcohol with psychological stress. *Adv. Exp. Med. Biol.* **85A–85B:**319–331.

Naitoh, P. (1971). The effects of alcohol on the autonomic nervous system of humans: psychophysiological approach. In *The Biology of Alcoholism, Vol. 2. Physiology and Behavior*, B. Kissin and H. Begleiter, eds. New York: Plenum, pp. 367–433.

Newlin, D.B. (1985a). The antagonistic placebo response to alcohol cues. *Alcohol: Clin. Exp. Res.* **9:**411–416.

Newlin, D.B. (1985b). Offspring of alcoholics have enhanced antagonistic placebo response. *J. Stud. Alcohol* **46:**490–495.

Newlin, D.B. (1986). Conditioned compensatory response to alcohol placebo in humans. *Psychopharmacology* **88:**247–254.

Newlin, D.B. (1987). Alcohol expectancy and conditioning in sons of alcoholics. *Adv. Alcohol Subs. Abuse* **6:**33–57.

Newlin, D.B. (1989a). Placebo responding in the same direction as alcohol in women. *Alcoholism: Clin. Exp. Res.* **13:**36–39.

Newlin, D.B. (1989b). The skin-flushing response: Autonomic, self-report, and conditioned responses to repeated administrations of alcohol in Asian men. *J. Abnorm. Psychol.* **98:**421–425.

Newlin, D.B., and Thomson, J.B. (1991). Chronic tolerance and sensitization to alcohol in sons of alcoholics. *Alcoholism: Clin. Exp. Res.* **15:**399–405.

Newlin, D.B., Hotchkiss, B., Cox, W.M., Rauscher, F., and Li, T.-K. (1989). Autonomic and subjective responses to alcohol stimuli with appropriate control stimuli. *Addict. Behav.* **14:**625–630.

Niaura, R.S., Rohsenow, D.J., Binkoff, J.A., Monti, P.M., Pedraza, M., and Abrams, D.B. (1988). Relevance of cue reactivity to understanding alcohol and smoking relapse. *J. Abnorm. Psychol.* **97:**133–152.

Novak, D.J., and Victor, M. (1974). The vagus and sympathetic nerves in alcoholic polyneuropathy. *Arch. Neurol.* **30:**273–284.

O'Brien, C.P., Childress, A.R., McLellan, T., and Ehrman, R. (1990). Integrating systematic cue exposure with standard treatment in recovering drug dependent patients. *Addict. Behav.* **15:**355–365.

Obrist, P.A., Howard, J.L., Lawler, J.E., Galosy, R.A., Meyers, K.A., and Gaebelein, C.J. (1974). The cardiac-somatic interaction. In Cardiovascular Psychophysiology P.A. Obrist, A.H. Black, J. Brener, and L.V. DiCara, eds. Chicago: Aldine, pp. 136–162.

Olds, J., and Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Psychol. Psychol.* **47:**419–427.

O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., and Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence. *Arch. Gen. Psychiatr.* **49:**881–887.

Orne, M. T. (1962). On the social psychology of the psychological experiment: With particular reference to demand characteristics and their implications. *Am. Psychol.* **17:**776–783.

Pashler, H. (1994). Dual-task interference in simple tasks: Data and theory. *Psychol. Bull.* **116:**220–244.

Payne, T.J., Rychtarik, R.G., Rappaport, N.B., Smith, P.O., Etscheidt, M., Brown, T.A., and Johnson, C.A. (1992). Reactivity to alcohol-relevant beverage and imaginal cues in alcoholics. *Addict. Behav.* **17:**209–217.

Peris, J., and Cunningham, C.L. (1986). Handling-induced enhancement of alcohol's acute physiological effects. *Life Sci.* **38:**273–279.

Peterson, J.B., Pihl, R.O., Séguin, J.R., Finn, P.R., and Stewart, S.H. (1993). Heart-rate reactivity and alcohol consumption among sons of male alcoholics and sons of nonalcoholics. *J Psychiatr. Neurosci.* **18:**190–198.

Pishkin, V., Lawrence, B.E., and Bourne, L.E. (1983). Cognitive and electrophysiological parameters during ascending and descending limbs of the blood alcohol curve. *Alcoholism: Clin. Exp. Res.* **7:**76–82.

Pohorecky, L.A. (1990). Interaction of alcohol and stress at the cardiovascular level. *Alcohol* **7:**537–546.

Pohorecky, L.A. (1991). Stress and alcohol interaction: An update of human research. *Alcoholism: Clin. Exp. Res.* **15:**438–459.

Pomerlerau, O.F., Fertig, J., Baler, L., and Cooney, N. (1983). Reactivity to alcohol cues in alcoholics and non-alcoholics: Implications for a stimulus control analysis of drinking. *Addict. Behav.* **8:**1–10.

Quinsey, V.L., and Carrigan, W.F. (1978). Penile responses to visual stimuli: instructional control with and without auditory sexual fantasy correlates. *Crim. Justice Behav.* **5:**333–341.

Rankin, H., Hodgson, R., and Stockwell, T. (1979). The concept of craving and its measurement. *Behav. Res. Ther.* **17:**389–396.

Rauch, S.L., Jenike, M.A., Alpert, N.M., Baer, L., Breiter, H.C.R., Savage, C.R., and Fischman, A.J. (1994). Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch. Gen. Psychiatr.* **51:**62–70.

Razran, G. (1961). The observable unconscious and the inferable conscious in current Soviet psychophysiology: Interoceptive conditioning, semantic conditioning, and the orienting reflex. *Psychol. Rev.* **68:**81–147.

Reznick, J.S. (Ed.) (1969). *Perspectives on Behavioral Inhibition.* Chicago: University of Chicago Press.

Richter, R., Kielholz, P., Hobi, V., Ladewig, D., Miest, P.C., Reggiani, G., Schwarz, E., and Goldberg, L. (1977). Biphasic time-course of alcohol-induced changes in electrodermal activation parameters. *Blutalkohol* **14:**279–291.

Roberts, L.E., and Young, R. (1971) Electrodermal responses are independent of movement during aversive conditioning in rats, but heart rate is not. *J. Comp. Physiol. Psychol.* **77:**495–512.

Roberts, L.E., Lacroix, J.M., and Wright, M. (1974). Comparative studies of operant electrodermal and heart rate conditioning in curarized rats. In Cardiovascular Psychophysiology, P.A. Obrist, A.H. Black, J. Brener, and L.V. DiCara, eds. Chicago: Aldine, pp. 332–352.

Rohsenow, D.J., Monti, P.M., Rubonis, A.V., Sirota, A.D., Niaura, R.S., Colby, S.M., Wunschel, S.M., and Abrams, D.B. (1994). Cue reactivity as a predictor of drinking among male alcoholics. *J. Consult. Clin. Psychol.* **62:**620–626.

Rosenberg, H., and Hodge, J.E. (1990). Cue exposure and addiction: Some comments on Hodgson's (1989) paper. *Br. J. Addict.* **85:**1351–1354.

Ross, D.F., and Pihl, R.O. (1989). Modification of the balanced placebo design for use at high blood alcohol levels. *Addict. Behav.* **14:**91–97.

Rubin, L.S. (1980). Pupillometric studies of alcoholism. *Int. J. Neurosci.* **11:**301–308.

Rubin, L.S., Gottheil, E., Roberts, A., Alterman, A.E., and Hostine, J. (1977). Effects of stress on autonomic reactivity in alcoholics: Pupillometric studies. I. *J. Stud. Alcohol* **38:**2036–2048.

Rubin, L.S., Gottheil, E., Roberts, A., Alterman, A.I., and Holstein, J. (1978). Autonomic nervous system concomitants of short-term abstinence in alcoholics: Pupillometric studies. II. *J. Stud. Alcohol* **39:**1895–1907.

Rubonis, A.V., Colby, S.M., Monti, P.M., Rohsenow, D.J., Gulliver, S.B., and Sirota, A.D. (1994). Alcohol cue reactivity and mood induction in male and female alcoholics. *J. Stud. Alcohol* **55:**487–494.

Sanders, M.G. (1969). Alcoholic cardiomyopathy: A critical review. *Q. J. Stud. Alcohol* **31:**324–368.

Sayette, M.A. (1993a). An appraisal-disruption model of alcohol's effects on stress responses in social drinkers. *Psychol. Bull.* **114:**459–476.

Sayette, M.A. (1993b). Heart rate as an index of stress response in alcohol administration research: A critical review. *Alcoholism: Clin. Exp. Res.* **17:**802–809.

Sayette, M.A., and Wilson, G.T. (1991). Intoxication and exposure to stress: Effects of temporal patterning. *J. Abnorm. Psychol.* **100:**56–62.

Sayette, M.A., Breslin, F.C., Wilson, G.T., and Rosenblum, G.D. (1994). *Addict. Behav.* **19:**333–342.

Schandler, S.L., Cohen, M.J., McArthur, D.L., Naliboff, B.D., and Hassell, A. (1988). Activation peaking in intoxicated and detoxified alcoholics during visuospatial learning. *J. Stud. Alcohol* **49:**126–130.

Seales, D.M., Naitoh, P., Johnson, L.C., and Schuckit, M.A. (1978). Somatosensory evoked potential as a measure of tolerance to ethanol. In *Multidisciplinary Perspectives in*

Event-Related Brain Potential Research, D.A. Otto, ed. Washington, DC: U.S. Environmental Protection Agency. Office of Research and Development, pp. 392–396.

Selzer, M.L. (1971). The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *Am. J. Psychiat.* **127:**1653–1658.

Sereny, G. (1971). Effects of alcohol on the electrocardiogram. *Circulation* **44:**558–564.

Shapiro, A.P., and Nathan, P.E. (1986). Human tolerance to alcohol: The role of Pavlovian conditioning processes. *Psychopharmacology* **88:**90–95.

Sheffield, F.D., and Roby, T.B. (1950). Reward value of a non-nutritive sweet taste. *J. Comp. Physiol. Psychol.* **43:**471–481.

Sheffield, F.D., Wulff, J.J., and Backer, R. (1951). Reward value of copulation without sex drive reduction. *J. Comp. Physiol. Psychol.* **43:**471–48.

Sher, K.J., and Levenson, R.W. (1982). Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. *J. Abnorm. Psychol.* **91:**350–367.

Sher, K.J., and Walitzer, K.S. (1986). Individual differences in the stress-response-dampening effect of alcohol: A dose-response study. *J. Abnorm. Psychol.* **95:**159–167.

Sher, K.J., Bylund, D.B., Walitzer, K.S., Hartmann, J., and Ray-Prenger, C. (1994). Platelet monoamine oxidase (MAO) activity: Personality, substance use, and the stress-response-dampening effect of alcohol. *Exp. Clin. Psychopharmacol.* **2:**53–81.

Siegel, S. (1979). The role of conditioning in drug tolerance and addiction. In *Psychopathology in Animals: Research and Clinical Implications*, J.D. Keehn, ed. New York: Academic Press, pp. 143–168.

Siegel, S. (1987). Pavlovian conditioning and ethanol tolerance. *Alcohol Alcoholism.* Suppl. **1:**25–36.

Siegel, S., and Sdao-Jarvie, K. (1986). Attenuation of ethanol tolerance by a novel stimulus. *Psychopharmacology* **88:**258–261.

Siegfried, B., Netto, C.A., and Izquierdo, I. (1987). Exposure to novelty induces naltrexone-reversible analgesia in rats. *Behav. Neurosci.* **101:**436–438.

Silverman, A.J., Cohen, S.I., and Shmavonian, B.M. (1959). Investigation of psychophysiological relationships with skin resistance measures. *J. Psychosom. Res.* **4:**65–87.

Smith, S., and Over, R. (1987). Male sexual arousal as a function of the content and the vividness of erotic fantasy. *Psychophysiology* **24:**334–339.

Snyder, S., and Karacan, I. (1981). Effects of chronic alcoholism on nocturnal penile tumescence in the chronic alcoholic. *Biol. Psychiatr.* **16:**399–406.

Sokolov, E.N. (1960). Neuronal models and the orienting reflex. In *The Central Nervous System and Behavior*, M.A.B. Brazier, ed. New York: Josiah Macy Jr. Foundation, pp. 187–276.

Sokolov, E.N. (1963a). Higher nervous functions: The orienting reflex. *Ann. Rev. Physiol.* **25:**545–580.

Sokolov. E.N. (1963b). *Perception and the Conditioned Reflex.* New York: Macmillan.

Sokolov, E.N., and Vinogradova, O.S. (1975). *Neuronal Mechanisms of the Orienting Reflex.* Hillsdale, NJ: Erlbaum.

Staiger, P.K., and White, J.M. (1988). Conditioned alcohol-like and alcohol-opposite responses in humans. *Psychopharmacology* **95:**87–91.

Staiger, P.K., and White, J.M. (1991). Cue reactivity in alcohol abusers: Stimulus specificity and extinction of the responses. *Addict. Behav.* **16:**211–221.

Stern, R.M., Ray, W.J., and Davis, C.M. (1980). *Psychophysiological Recording.* New York: Oxford University Press.

Stockwell, T., Hodgson, R., Edwards, G., Taylor, C., and Rankin, H. (1979). The development of a questionnaire to measure severity of alcohol dependence. *Br. J. Addict.* **74:**79–87.

Stockwell, T.R., Hodgson, R., Rankin, H.J., and Taylor, C. (1982). Alcohol dependence, beliefs and the priming effect. *Behav. Res. Ther.* **20:**513–522.

Stormark, K.M., Laberg, J.C., and Bjerland, T. (1993). Habituation of electrodermal reactivity to visual alcohol stimuli in alcoholics. *Addict. Behav.* **18:**437–443.

Sutker, P.B., Allain, A.M., Brantley, P.J., and Randall, C.L. (1982). Acute alcohol intoxication, negative affect, and autonomic arousal in women and men. *Addict. Behav.* **7:**17–25.

Tarter, R.E., McBride, H., Buonpane, N., and Schneider, D.U. (1977). Differentiation of alcoholics. *Arch. Gen. Psychiatr.* **34:**761–768.

Tong, J.E., Knott, J.V., McGrawy, D.J., and Leigh, G. (1974). Alcohol, visual discrimination and heart rate: Effects of dose, activation and tobacco. *Q. J. Stud. Alcohol* **35:**1003–1022.

Turkkan, J.S., Stitzer, M.L., and McCaul, M.E. (1988). Psychophysiological effects of oral ethanol in alcoholics and social drinkers. *Alcohol: Clin. Exp. Res.* **12:**30–38.

Turkkan, J.S., McCaul, M.E., and Stitzer, M.L. (1989). Psychophysiological effects of alcohol-related stimuli: II. Enhancement with alcohol availability. *Alcoholism: Clin. Exp. Res.* **13:**392–398.

Van Thiel, D.H., and Lester, R. (1974). Sex and alcohol. *N. Engl. J. Med.* **291:**251–253.

Van Thiel, D.H., and Lester, R. (1979). The effect of chronic alcohol abuse on sexual function. *Clin. Endocrinol. Metab.* **8:**499–510.

Volpicelli, J.R. (1987). Uncontrollable events and alcohol drinking. *Br. J. Addict.* **82:**381–392.

Volpicelli, J.R., Davis, M.A., and Olgin, J.E. (1986). Naltrexone blocks the post-shock increase of ethanol consumption. *Life Sci.* **38:**841–847.

Volpicelli, J.R., Alterman, A.I., Hayashida, M., and O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Arch. Gen. Psychiatr.* **49:**876–880.

Voronin, L.G., and Sokolov, E.N. (1960). Cortical mechanisms of the orienting reflex and its relation to the conditional reflex. In *The Moscow Colloquium on Electroencephalography of Higher Nervous Activity*, H.H. Jasper and G.D. Smirnov, eds. Montreal: The EEG Journal, pp. 335–346.

Walitzer, K.S., and Sher, K.J. (1990). Alcohol cue reactivity and ad lib drinking in young men at risk for alcoholism. *Addict. Behav.* **15:**29–46.

Wallgren, H., and Barry, H. III. (1970). *Actions of Alcohol.* Vol. 1. Amsterdam: Elsevier.

Walton, R.G. (1972). Smoking and alcoholism; A brief report. *Am. J. Psychiatr.* **128:** 1455–1456.

Wang, M. (1986). Changes in psychophysiological and conditioning variables during chlormethiazole-medicated and unmedicated ethanol withdrawal: Preliminary report. *Acta Psychiatr. Scand.* **329**(suppl):146–152.

Weil, A. (1972). *The Natural Mind.* Boston: Houghton-Mifflin.

Whalley, L.J. (1978). Sexual adjustment of male alcoholics. *Acta Psychiatr. Scand.* **58:** 281–298.

White, K.D. (1978). Salivation: The significance of imagery in its voluntary control *Psychophysiology* **15:**196–203.

Wilder, J. (1967). *Stimulus and Response: the Law of Initial Value.* Bristol: John Wright and Sons.

Wikler, A. (1980). *Opioid Dependence: Mechanisms and Treatment.* New York: Plenum.
Wilson, G.T., and Lawson, D.M. (1976a). The effects of alcohol on sexual arousal in women. *J. Abnorm. Psychol.* **85**:489–497.
Wilson, G.T., and Lawson, D.M. (1976b). Expectancies, alcohol, and sexual arousal in male social drinkers. *J. Abnorm. Psychol.* **85**:587–594.
Wilson, G.T., and Lawson, D.M. (1978). Expectancies, alcohol, and sexual arousal in women. *J. Abnorm. Psychol.* **7**:358–367.
Wingard, J.A., and Maltzman, I. (1980). Interest as a predeterminer of the GSR index of the orienting reflex. *Acta Psychol.* **46**:153–160.
Wise, R.A. (1988). The neurobiology of craving: Implications for the understanding and treatment of addiction. *J. Abnorm. Psychol.* **97**:118–132.
Wormith, J.S., Bradford, J.M.W., Pawlak, A., Borzecki, M., and Zohar, A. (1988). The assessment of deviant sexual arousal as a function of intelligence, instructional set and alcohol ingestion. *Can. J. Psychiatr.* **33**:800–808.
Zinberg, N.E. (1984). *Drug, Set, and Setting.* New Haven: Yale University Press.
Zuckerman, M. (1991). *Psychobiology of Personality.* Cambridge: Cambridge University Press.

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