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Applying Laboratory Research: Drug Anticipation and the Treatment of Drug Addiction

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Basic research concerning drug tolerance and withdrawal may inform clinical practice, and vice versa. Three areas that integrate the work of the laboratory and the clinic are discussed: (a) drug overdose, (b) cue exposure treatment of addiction, and (c) pharmacological treatment of withdrawal symptoms. The areas are related in that they indicate the contribution of drug-paired cues to the effects of addictive drugs and the role of Pavlovian conditioning of drug effects in drug tolerance and withdrawal symptoms.

The concerns of the laboratory researcher often seem esoteric to the clinician. For example, the laboratory scientist might be enthusiastic about a finding that opiate tolerance is correlated with c-Fos expression in the striatum of the rat's brain (Baptista, Siegel, MacQueen, & Young, 1998), but the clinician likely would find little in these results relevant to the treatment of opiate addiction in people. Similarly, the clinician may be intrigued by the case report of a palliative-care patient, tolerant to the analgesic effect of oral morphine, who suffered an overdose when switched to transdermal fentanyl (Johnson & Faull, 1997). This singular observation, however, probably would not appear immediately relevant to the researcher studying fundamental processes of opiate effects in nonhuman animals. The purpose of this article is to indicate the relationship of these, and other, experimental and clinical observations—that is, to emphasize the symbiotic relationship between the researcher and the clinician.

Three Areas of Interrelated Experimental and Clinical Research

In this article we summarize three areas of interrelated research that integrate the work of the laboratory and the clinic: drug overdose, cue exposure treatment of addiction, and pharmacological treatment of withdrawal symptoms.

Drug Overdose

Many addicts die shortly after injecting heroin. Although it has been conventional to attribute such deaths to heroin overdose, it has been clear, since the pioneering work of Brecher (1972), that *overdose* is a misnomer in describing the cause of death in heroin addicts. Most of the deaths are not due to a pharmacological overdose, as the term usually is understood. Brecher summarized the extensive literature that existed 30 years ago: "(1) The deaths *cannot* be due to overdose. (2) There *never has been any evidence* that they are due to overdose. (3) There has long been a plethora of evidence demonstrating they are *not* due to overdose" (p. 102, italics in original). Results of subsequent research confirmed Brecher's conclusions, and it has been suggested that "the term 'overdose' has served to indicate lack of understanding of the true mechanism of deaths in fatalities directly related to opiate use" (Greene, Luke, & DuPont, 1974, p. 175), and "continued utilization of the term 'overdose' to cover all heroin-related fatalities may be counterproductive in developing strategies to reduce the morbidity and mortality associated with heroin" (Darke & Zador, 1996, p. 1770). Despite the likely misuse of the word, we continue to use the generally accepted term *overdose* when referring to these enigmatic fatalities, rather than more cumbersome alternatives such as "an idiosyncratic reaction to an intravenous injection of unspecific material(s) and probably not a true pharmacologic overdose of narcotics" (Cherubin, McCusker, Baden, Kavalier, & Amsel, 1972, p. 11).

Despite the fact that pronounced tolerance develops to the respiratory depressive effects of opiates, the heroin overdose victim typically dies of respiratory depression. Inasmuch as the victims of overdose typically are not novice users (e.g., Darke & Zador, 1996), it would be expected that they would have been very tolerant to heroin and thus would have self-administered a very large dose when they overdosed. However, postmortem examinations of heroin overdose victims often do not reveal very high levels of opiate in their system. For example, Monforte (1977) found that about three quarters of the victims of heroin overdose had blood levels of morphine no higher than those seen in a control group of heroin addicts who died as a result of homicide (rather than heroin overdose): "One must conclude that in the great majority of cases death was not a result of a toxic quantity of morphine in the blood" (p. 720).

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What does account for these deaths? Basic psychopharmacology research, with mice and rats, has elucidated a cause for at least some overdoses that has implications for minimizing death among drug abusers.

Cue Exposure Treatment of Addiction

"It has long been recognized that the processes of 'detoxification' and physical withdrawal are not the major impediments to effective drug-abuse treatment. Rather, the problem is relapse following completion of the withdrawal crisis" (Siegel, 1999a, p. 1113). Early addiction commentators noted that craving and relapse occur in response to cues that, in the past, have been associated with drug use. Over the years, many clinicians have rediscovered the importance of environmental cues to relapse. For example, in *The Anatomy of Drunkenness*, Macnish (1859) noted the following:

> Man is very much the creature of habit. By drinking regularly at certain times he feels the longing for liquor at the stated return of these periods—as after dinner, or immediately before going to bed, or whatever the period may be. He even finds it in certain companies, or in a particular tavern at which he is in the habit of taking his libations. (p. 151)

When the Harrison Narcotics Act was implemented in 1915, and the United States government established addiction treatment facilities for the then newly criminalized addicts, the problem of cue-elicited relapse quickly became apparent. Lawrence Kolb was an Assistant Surgeon General of the United States Public Health Service and the first superintendent of the then newly established Service's hospital for addicts in Lexington, Kentucky. He observed that merely enforcing abstinence during the period of withdrawal distress was not an effective treatment:

> We see this plainly exemplified in the cured tobacco smoker. . . . A cured smoker who usually does not crave tobacco may feel an intense desire resembling hunger when he gazes on a box of cigars or sits in the company of friends who are smoking. (Kolb, 1927, p. 39)

Kolb noted a similar phenomenon in opiate addicts:

> Nearly all of those who have abstained from narcotics for several months report that they have no desire for the drugs unless they see someone else take them or unless they associate with other addicts in situations which they formerly enjoyed. (Kolb, 1927, p. 40)

Subsequently, many other clinicians have described examples of patients who display withdrawal symptoms and crave drugs when confronted with cues that had signaled the drug in the past, for example, seeing the paraphernalia of addiction such as a syringe and tourniquet (e.g., Teasdale, 1973), returning to an old neighborhood following a prolonged period of incarceration and abstinence (e.g., Kissen, 1983; O'Brien, 1976), discussing drugs with others (e.g., Wikler, 1977), or even seeing actors seeming to inject heroin in a movie (Biernacki, 1986, p. 115). As Ludwig, Wikler, and Stark (1974) noted some years ago with respect to alcoholism treatment:

> Any therapeutic approach, whether it be insight, behaviorally or pharmacologically oriented, that does not recognize the powerful evocative effects of interoceptive and exteroceptive stimuli on craving and alcohol acquisition behavior and that neglects to provide techniques for modifying the strength of these effects will likely be destined to failure. (p. 547)

Recognition of the evocative effects of drug-associated stimuli has encouraged the development of treatments that incorporate systematic exposure to these stimuli (see Childress, McLellan, & O'Brien, 1986; Siegel, 1988, 1999a)—so-called cue exposure treatment. Results of laboratory research suggest techniques to improve the efficacy of cue exposure treatment.

Pharmacological Treatment of Withdrawal Symptoms

A defining characteristic of addiction is the appearance of drug withdrawal symptoms when drug use terminates. These symptoms may occur long after the last drug administration and may be one reason for relapse. A drug that ameliorates these symptoms would be a useful addiction treatment tool. Most pharmacotherapies to treat withdrawal symptoms involve drug substitution, such as methadone for the treatment of heroin addiction and nicotine patches for the treatment of smoking. Some pharmacotherapies, however, are designed to decrease withdrawal severity without the complications of continued addictive drug use. For example, both *N*-methyl-D-aspartate antagonists and agonists for specific serotonin receptors have been used in the treatment of alcoholism (Bisaga & Popik, 2000).

Results of recent laboratory research suggest that a class of drugs that function as antagonists of a particular neuropeptide, cholecystokinin-8 (CCK), "might be of value in the treatment and prevention of relapse in opiate addicts" (Lu, Huang, Liu, & Ma, 2000, p. 832). Although there are some studies of the relationship between CCK activity and opioid effects in humans (e.g., McCleane, 1998), the research concerning CCK antagonists as a pharmacotherapy for addiction has been conducted primarily with mice (Rezayat, Azizi, & Zarrindast, 1997) and rats (e.g., Kim & Siegel, 2001; Lu et al., 2000; Roques & Noble, 1996). The potential for treating drug withdrawal symptoms by modulating CCK activity is a very recent area of research that may find application in the treatment of human addicts.

Pavlovian Conditioning—A Framework for Integrating Laboratory and Clinical Findings

One framework for integrating clinical and laboratory work in all three areas described earlier was provided by the insightful comments of a heroin addict. This 36-year-old man, in describing the circumstances in which he experienced withdrawal symptoms, "likened himself to one of Pavlov's dogs" (Biernacki, 1986, p. 115). He appreciated that Pavlovian conditioning contributed to his drug effects. Although this man likely reached his conclusion on the basis of introspection rather than a reading of the scientific literature, there is, in fact, extensive research indicating the

role of conditioning in addiction. We briefly review this work before discussing the application of the findings to drug overdose, cue exposure treatment, and pharmacological treatment of withdrawal symptoms.

What Is Pavlovian Conditioning?

Ivan Petrovich Pavlov won the Nobel Prize for physiology in 1904. He was awarded the prize for his studies of digestive reflexes in dogs, using chronic observational methods (i.e., digestive reflexes were observed in intact, awake dogs). Because he used chronic preparations, Pavlov made some observations that, although not the basis for his Nobel Prize, would be the topic of his research for the remainder of his life.

In his Nobel Prize acceptance speech Pavlov did not discuss the gastrointestinal work that formed the basis of the award. Rather, he presented an address entitled "The First Sure Steps along the Path of a New Investigation." The "new investigation" was the study of what we now call "conditional reflexes." Pavlov, then 55 years old, essentially abandoned his successful study of digestive physiology to devote his full energies to this new topic—one that he considered even more important (see Babkin, 1949).

Pavlov observed that his dogs displayed digestive reflexes (such as gastric secretion), not only in response to stimuli that had reflexively elicited such responses (i.e., stimulation of receptors in the stomach) but also in response to stimuli that, in the past, had signaled such stimulation (e.g., the presence of the person who fed the dog). Pavlov concluded that it would be impossible to understand digestive physiology without understanding the role of these *psychic* reflexes (as they were originally termed), as well as physiological reflexes. He developed procedures and terminology that are used today in the study of Pavlovian conditioning.

The Pavlovian Conditioning Paradigm

Pavlovian conditioning (sometimes termed *respondent*, *classical*, or *Type 1* conditioning) is defined by a set of operations in which a neutral conditional stimulus (CS) is paired with a biologically significant unconditional stimulus (UCS). At the start of conditioning, the UCS reflexively (i.e., unconditionally) elicits some response, termed the *unconditional response* or *unconditional reflex* (UCR). The UCR is the response of the central nervous system to the UCS. As a result of CS–UCS pairings, the CS becomes associated with the UCS. The acquisition of this association is revealed by the emergence of a new response to the previously neutral CS. Because this new response is conditional on CS–UCS pairings, it is termed the *conditional response* or *conditional reflex* (CR). Pavlov realized that salivation was much easier to measure than gastric secretion and that the manipulation of cues such as tones and lights could be much more precise than manipulation of cues such as the sight of the person that normally fed the dogs.

Pavlov's well-known conditioning preparation is schematically illustrated in Figure 1A. Dogs were presented with small amounts of food or dilute acid was injected into their mouth. Such stimulation of receptor cells in the mouth initiates activity along the trigeminal and glossopharyngeal nerves to medullary salivary centers, which results in efferent neural activity, transmitted to salivary glands in the mouth, eliciting salivation—the UCR. The CS was some arbitrary cue (such as a tone of a certain pitch). After some pairings of CS and UCS, a new reflex developed—the tone elicited salivation: "The activity of the salivary gland has thus been called into play by impulses of sound—a stimulus quite alien to food" (Pavlov, 1927, p. 22).

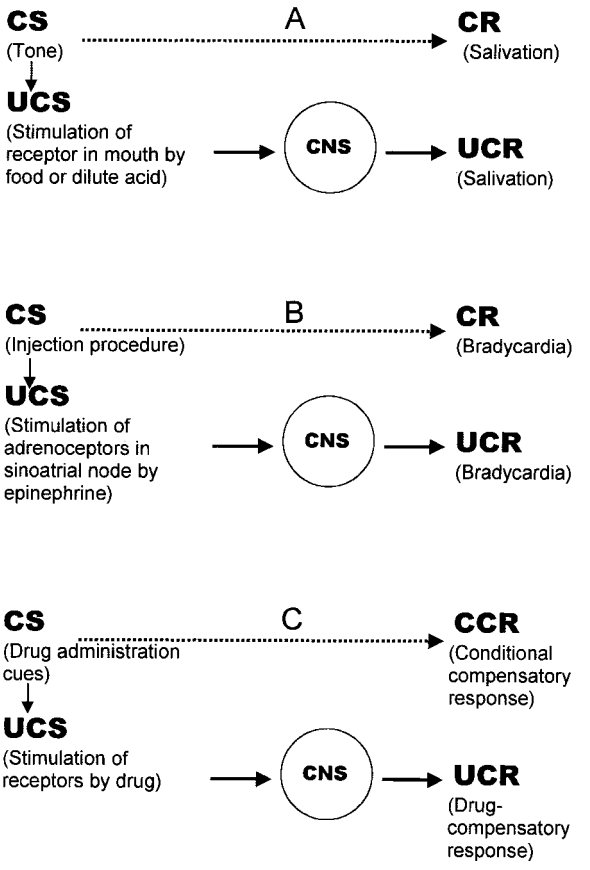

Figure 1. Schematic representation of Pavlovian conditioning of the salivary response (A), conditioning of the cardiac effects of epinephrine by Subkov and Zilov (1937; B), and conditioning compensatory responses to drugs (C).

Drug Administration as a Conditioning Trial

Pavlov (1927, p. 35) suggested that the administration of a drug could be viewed as a conditioning trial; stimulation of receptors sensitive to the drug served as the UCS and the immediately antecedent environmental cues served as CSs. The development of conditional pharmacological responses can be ascertained merely by presenting the CS (predrug cues) without the UCS (the drug), that is, by administering an inert substance in the usual drug-administration environment.

Subkov and Zilov (1937) provided an early demonstration of pharmacological conditioning. Their preparation is schematically illustrated in Figure 1B. Subkov and Zilov injected dogs with epinephrine (adrenaline) on a number of occasions. Epinephrine stimulates β_1 adrenoceptors in the sinoatrial node of the right atrium of the heart (hence increasing blood pressure and heart rate as a result of direct stimulation of the heart). The reflex response to this unconditional stimulation is a compensatory homeostatic response (e.g., increased vagal activity) that decreases heart rate. Subkov and Zilov (1937) noted that, following such a series of epinephrine injections, merely placing the dog in the injection stand and administering an inert substance produced bradycardia:

> It follows that the mere reproduction of the experimental conditions in which the animal is accustomed to receive adrenaline is alone sufficient to set in motion the mechanism, by means of which the animal counteracts the high vascular pressure produced by adrenaline. (Subkov & Zilov, 1937, p. 295)

In fact (as depicted in Figure 1C), many types of pharmacological stimulation elicit UCRs that compensate for the unconditionally elicited, drug-induced disturbances. After some drug administrations, drug-compensatory responses occur in the presence of drug-administration cues. Such learned responses have been termed *conditional compensatory responses*—CCRs (Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). CCRs have been demonstrated with respect to many effects of a variety of drugs, including commonly abused drugs such as opiates (e.g., Kim, Siegel, & Patenall, 1999; Mucha, Volkovsiks, & Kalant, 1981; Raffa & Porreca, 1986), ethanol (e.g., Duncan, Alici, & Woodward, 2000; Larson & Siegel, 1998; Lê, Poulos, & Cappell, 1979), and caffeine (Andrews, Blumenthal, & Flaten, 1998; Rozin, Reff, Mark, & Schull, 1984).

Conditional Compensatory Responses, Drug Tolerance, and the Situational-Specificity of Tolerance

Tolerance is said to occur when the effect of a given dose of a drug decreases over the course of repeated administrations. Pavlovian conditioning contributes to tolerance. When the drug is administered repeatedly in the context of the usual predrug cues, these cues elicit a CCR that attenuates the drug effect. As the drug is administered more and more often, and the CCR grows in strength, the attenuation of the drug effect becomes more pronounced.

The extensive evidence that conditioning contributes to tolerance recently has been reviewed (see Siegel et al., 2000). Briefly, posttrial events that affect memory consolidation similarly affect the rate of tolerance acquisition; thus, electroconvulsive shock or frontal cortical stimulation decreases the rate of acquisition of morphine tolerance, and glucose facilitates the rate of acquisition of morphine tolerance (Siegel, 1999b; Siegel et al., 2000). Furthermore, in common with other conditional responses, the expression of drug tolerance is disrupted by presenting a novel external stimulus (external inhibition) or by altering the putative CS (changing the context for each successive drug administration in an unpredictable manner). The acquisition of tolerance is retarded by partial reinforcement, preexposure to the CS, and inhibitory learning. Like other conditional responses, drug tolerance displays extinction, spontaneous recovery, stimulus generalization, and a flattening of the generalization gradient as a result of extending the interval between acquisition and assessment. Tolerance also displays sensory preconditioning and a variety of compound conditioning effects such as overshadowing and blocking (Siegel et al., 2000). One prediction of the conditioning analysis of tolerance that is especially relevant to clinical issues has been termed the *situational-specificity of tolerance* (Siegel, 1978, p. 345).

Results of many experiments indicate that, following a series of drug administrations, tolerance is more pronounced in the presence of the usual drug-associated cues than it is in the presence of alternative cues (Siegel et al., 2000). For example, Siegel, Hinson, and Krank (1978) demonstrated situational-specificity of tolerance using a paired–unpaired design. Rats were assigned to same-tested or different-tested conditions. For same-tested rats, pretest morphine injections were signaled by an audiovisual cue. Different-tested rats received their pretest drug injections and cue presentations in an unpaired manner. Following the last pretest injection, analgesia was assessed in the presence of the audiovisual cue. Although same- and different-tested rats received the same number of morphine injections, at the same doses and at the same intervals, same-tested rats were more tolerant to morphine-induced analgesia than were different-tested rats.

The fact that tolerance displays situational-specificity is consistent with the conditioning analysis of tolerance. That is, drug-associated cues elicit CCRs that attenuate the drug effect; therefore, tolerance is greater when assessed in the presence of drug-associated cues than when it is assessed elsewhere.

Interoceptive Cues for Drugs

Although experimental studies of the associative basis of tolerance typically have manipulated exteroceptive cues (e.g., the room where the drug is administered), there is evidence that a variety of stimuli may become associated with a drug and control the display of tolerance. For example, distinctive flavors, ambient temperatures, or magnetic fields, after being paired with morphine administration, may influence the display of morphine tolerance (Siegel et al., 2000). Especially relevant to clinical applications are results indicating that two categories of interoceptive cues, pharmacological cues and self-administration cues, may become associated with a drug effect.

Pharmacological Cues

There is considerable evidence that organisms can learn that a stimulus, normally considered to be a UCS, signals the delivery of another UCS (Goddard, 1999); thus, it is not

surprising that organisms can associate two drug effects. There have been various types of experiments concerning pharmacological cues for drugs (see Siegel et al., 2000). Of special relevance are findings that a drug can serve as a cue for itself. For example, Greeley, Lê, Poulos, and Cappell (1984) demonstrated that a small dose of ethanol could serve as a CS for a larger dose of ethanol. In this Greeley et al. study, rats in one group (paired) consistently received a low dose of ethanol (0.8 g/kg) 60 min prior to a high dose of ethanol (2.5 g/kg). Another group of rats (unpaired) received the low and high doses on an unpaired basis. When tested for the tolerance to the hypothermic effect of the high dose following the low dose, paired subjects, but not unpaired subjects, displayed tolerance. Moreover, if the high dose of ethanol was not preceded by the low dose, paired rats failed to display their usual tolerance. This tolerance, dependent on an ethanol–ethanol pairing, was apparently mediated by a thermic CCR; paired rats, but not unpaired rats, evidenced hyperthermia (opposite to the hypothermic effect of the drug) in response to the low dose of ethanol. There also is evidence that a small dose of morphine may serve as a cue for a larger dose of the opiate and control the display of morphine tolerance (Cepeda-Benito & Short, 1997). Kim et al. (1999) have termed such associations, in which a small dose of a drug serves as a cue for a larger dose of the same drug, *intradrug associations*.

Several investigators have suggested that intradrug association findings have important implications for understanding the contribution of conditioning to tolerance. Within each drug administration, drug-onset cues (DOCs) reliably precede the later, larger drug effect; thus, there is the potential for the formation of associations whenever a drug is administered (e.g., Greeley et al., 1984; King, Bouton, & Musty, 1987; Mackintosh, 1987; Tiffany, Petrie, Baker, & Dahl, 1983). Results of several experiments indicate that such *intraadministration* associations do form when a drug is administered, and that DOCs, in common with exteroceptive cues, contribute to drug tolerance (Célèrier, Laulin, Corcuff, Le Moal, & Simonnet, 2001; Grisel, Wiertelak, Watkins, & Maier, 1994; Kim et al., 1999; Mucha, Kalant, & Birbaumer, 1996).

Self-Administration Cues

Typically, humans self-administer the drugs that they use. Such self-administration is a characteristic of both illicit (e.g., cocaine and heroin) and licit (e.g., nicotine and ethanol) drug use. In contrast, in the laboratory most psychopharmacology researchers administer the drug to subjects. Thus, much of what we know about the effects of drugs, such as the development of drug tolerance, is based on results of studies in which the experimenter—not the subject—administered the drug. If drug delivery is contingent on a response, interoceptive response-initiating (or response-produced) cues are paired with the drug effect. Weise-Kelly and Siegel (2001) suggested that these self-administration cues (SACs) function as other CSs—that is, they come to elicit CCRs. If SACs elicit CCRs, it would be expected that self-administered drugs should have a smaller effect than do passively received drugs; that is, the self-administration contingency should enhance the development of tolerance. There are several reports that this is the case.

Mello and Mendelson (1970) provided perhaps the first demonstration of the importance of the self-administration contingency in a drug effect. Alcoholic men were allowed to ingest alcohol in each of two conditions: when they wished (spontaneous condition) or only during experimenter-determined intervals (programmed condition). Tolerance was greater in the same individuals following the spontaneous condition than it was following the programmed condition. More recently, Ehrman, Ternes, O'Brien, and McLellan (1992) evaluated the effects of 4 mg hydromorphone in detoxified opiate abusers under two conditions: when they intravenously self-administered the drug and when the drug was infused by the experimenter. Ehrman et al. reported that several effects of hydromorphone were greater when the drug was passively received than when it was self-administered and concluded that "tolerance was observed when the subjects injected the opiate, but not when the same dose was received by unsignaled intravenous infusion" (p. 218).

An especially elegant procedure for evaluating the role of self-administration in drug effects is the yoked-control design. With this design, each time a subject assigned to a self-administration (SA) group makes a particular response (e.g., presses a lever in an operant chamber), the same amount of drug is administered to that subject and to another, yoked (Y), subject. Thus, both SA and Y subjects receive the same dose of the drug, equally often and at the same intervals. Several investigators have reported that, after some drug experience, the effects of the drug are greater in Y than in SA rats; that is, tolerance is less pronounced in Y animals (Donny, Caggiula, Knopf, & Brown, 1995; Weise-Kelly & Siegel, 2001).

In sum, cues such as SACs and DOCs function as CSs. They become associated with the drug effect and come to elicit CCRs that mediate tolerance. Thus, the fact that tolerance is especially pronounced when the drug effect occurs following the usual DOC (e.g., Kim et al., 1999) or SAC (Weise-Kelly & Siegel, 2001) is but another demonstration of the situational-specificity of tolerance. That is, situational cues that elicit CCRs may be interoceptive, as well as exteroceptive.

Pavlovian Conditioning and Drug Overdose

The most dramatic demonstrations of the situational-specificity of tolerance concern tolerance to the lethal effects of drugs. Following a series of drug administrations involving escalating doses, each in the context of the same cues, tolerance develops to the potentially lethal effect of that drug as long as it is administered in the usual context. Altering the context of drug administration increases the lethality of several drugs (summarized in Siegel, 2001). The findings were originally reported in studies with nonhuman animals, but results of clinical research concerning opiate overdose in humans are consistent with the laboratory findings.

Experiments With Rats and Mice

Although there were procedural differences among the experiments that evaluated the role of predrug cues in drug lethality, they all incorporated groups of rats or mice that were administered a high drug dose in a test session. Prior to this test, some of the subjects were administered lower doses of the drug and received the test infusion in the same environment in which they received the prior infusions (same-tested). Other subjects had the same pretest history of drug administration as same-tested subjects but received the test infusion in a different environment than that previously paired with the drug (different-tested). Finally, subjects in a control group received the drug for the first time in the test session. The results of three experiments that have used this procedure, with three different drugs, are summarized in Figure 2.

Figure 2A summarizes results reported by Melchior (1990). In her experiment, same- and different-tested mice were intraperitoneally injected with 3.5 g/kg ethanol twice per day for 4 days. The mortality in each group resulting from a 5.5 g/kg ethanol injection on the 5th day is depicted in Figure 2A. All same-tested mice survived the high dose of the drug. However, despite the fact that different-tested mice (like same-tested mice) received ethanol for the ninth time in this test session, most of them died as a result of the test-session injection. It would appear that, as expected on the basis of a conditioning analysis of tolerance, altering the context of ethanol administration enhances ethanol-induced lethality: "Conditioned tolerance can provide protection against ethanol lethality" (Melchior, 1990, p. 205).

Figure 2B summarizes results reported by Vila (1989). In this experiment, same- and different-tested rats were intraperitoneally injected with 30 mg/kg pentobarbital on 20 occasions, with each injection of the barbiturate occurring in a distinctive room. In a final test session, all rats were injected with 95 mg/kg pentobarbital. Test-session mortality data reported by Vila and summarized in Figure 2B indicate, again, that the environment of drug-administration affected drug-induced mortality. Same-tested rats were more likely to survive the high dose of pentobarbital than were different-tested rats. Indeed, chi-square analyses of the data summarized in Figure 2B indicated that the mortality in pentobarbital-experienced different-tested rats did not differ from that seen in pentobarbital-naïve control rats: "These results indicate that the probability of pentobarbital-induced lethality is substantially diminished in an environment previously associated with pentobarbital administration" (Vila, 1989, p. 366).

Figure 2C summarizes results reported by Siegel, Hinson, Krank, and McCully (1982). Prior to participation in this experiment, rats were prepared with chronic intravenous cannulae. Same- and different-tested rats then received 15 intravenous infusions of heroin. The dose was gradually increased over the course of the infusions from 1 mg/kg to 8 mg/kg. In a final test session, all rats were infused with 15 mg/kg heroin. Once again, drug-induced mortality was significantly higher in different-tested than in same-tested subjects. Because of the large number of rats that were used in this Siegel et al. (1982) study the experiment was conducted in six replications. In every replication, a greater proportion

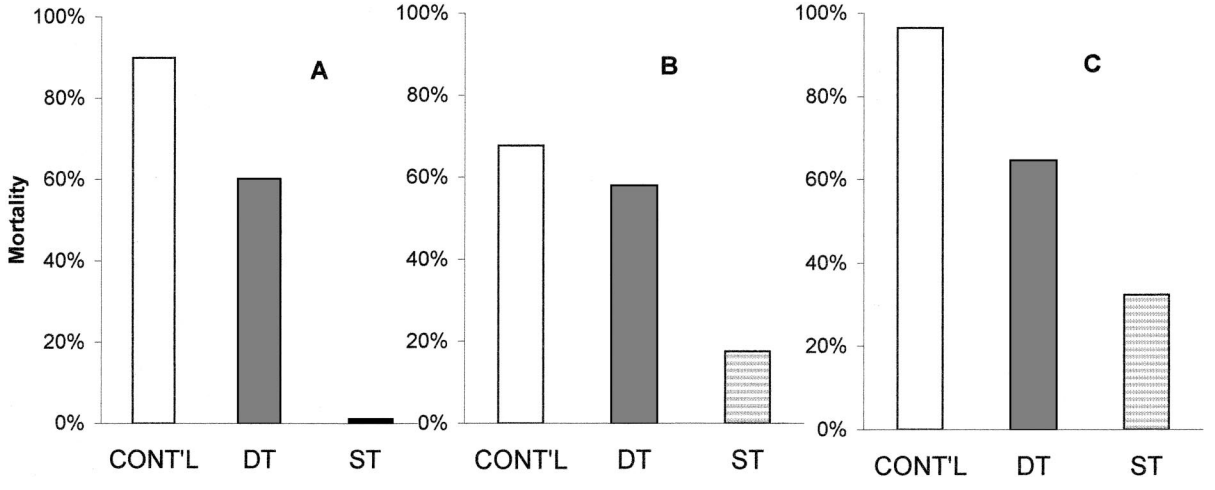

Figure 2. Mean mortality in rodents administered a high dose of a drug on a test session. Prior to this test, some of the animals were administered lower doses of the drug and received the test infusion in the same environment in which they received the prior infusions (same-tested; ST). Other animals had the equivalent pretest history of drug administration as ST subjects but received the test infusion in a different environment than that previously paired with the drug (different-tested; DT). Animals in a third group received the drug for the first time on the test session (control group; CONT'L). Figure 2A summarizes results reported by Melchior (1990) for mice intraperitoneally injected with ethanol. Figure 2B summarizes results reported by Vila (1989) for rats intraperitoneally injected with pentobarbital. Figure 2C summarizes results reported by Siegel, Hinson, Krank, and McCully (1982) for rats intravenously injected with heroin.

of different-tested than same-tested rats died—a statistically significant effect, using the binomial test:

> In conclusion, groups of rats with the same pharmacological history of heroin administration can differ in mortality following administration of a high dose of the drug: rats that received the potentially lethal dose in the context of cues previously associated with sublethal doses were more likely to survive than animals that received the dose in the context of cues not previously associated with the drug. (Siegel et al., 1982, p. 437)

As indicated previously, interoceptive cues, as well as exteroceptive cues, may become associated with a drug effect and mediate tolerance. For example, SACs are important predrug signals; thus, we might expect that a drug administered in the presence of the SACs should be less lethal than the same dose administered without this salient predrug interoceptive CS. Indeed, Johanson and Schuster (1981) reported that experimenter-programmed administration of phencyclidine in monkeys frequently is lethal "at dose levels at or below those self-administered, which animals survived" (p. 280). More recently, Dworkin, Mirkis, and Smith (1995) evaluated the effects of cocaine in SA and Y rats. Mortality was significantly lower in SA rats (that had SACs signaling the drug effect) than in Y rats (that received the drug in the absence of SACs).

Studies of Overdoses in Humans

Obviously, research with humans cannot incorporate experimental manipulation of predrug cues in an attempt to precipitate overdose. Rather, clinical research can only retrospectively evaluate the conditions that prevailed on the occasion of an overdose and compare those conditions with the overdose victim's usual circumstances of drug administration. Results of such studies of human drug addicts and patients that receive medically prescribed opiates for pain relief are consistent with the results obtained from experiments with nonhuman animals—altering the context of drug administration increases the risk of overdose (Siegel, 2001).

Overdoses in Drug Addicts

Siegel (1984) interviewed 10 heroin overdose survivors in an attempt to ascertain whether the overdoses occurred following novel predrug cues. For seven of the overdoses, the drug was administered in an environment not previously associated with drug use. These reports are consistent with the suggestion that administration in the presence of cues not previously associated with heroin is a risk factor for heroin overdose in humans, as it is in rats.

A more thorough evaluation of the contribution of drug-associated cues to heroin overdose was reported by Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, and Camí (1994). These investigators interviewed 76 heroin addicts admitted to the emergency room of a university hospital in Barcelona, Spain: Fifty-four patients were admitted because of heroin overdose, and 22 were seeking urgent medical care for unrelated conditions, but their interview revealed intravenous heroin self-administration 1 hr or less before admission. The results of the Gutiérrez-Cebollada et al. study are summarized in Table 1. As can be seen in Table 1, every one of the patients that recently had used heroin, but had not suffered an overdose, injected the drug in their usual drug-administration environment. In contrast, 52% of the overdose victims administered "in an unusual setting" (Gutiérrez-Cebollada et al., 1994, p. 171). Chi-square analysis of the interaction apparent in Table 1 was statistically significant ($p < .0001$). As summarized by Gutiérrez-Cebollada et al.,

> The association between heroin overdose and unusual drug administration setting confirms the influence of non-pharmacological factors in heroin overdosing. Further studies should be considered to address the role played by self-administration of heroin in an unusual setting in conditioned tolerance. (p. 173)

Evidence in support of the conditioning interpretation of tolerance is provided by studies indicating parallels between Pavlovian conditioning and tolerance. As indicated previously, a variety of nonpharmacological manipulations that are known to affect the magnitude of conditional responding similarly affect drug tolerance. One that may be relevant to overdose in humans is external inhibition. CRs, once established, can be disrupted by the presentation of a novel, extraneous stimulus. The phenomenon was termed *external inhibition* by Pavlov (1927), who described its operation in the salivary conditioning situation:

> The dog and the experimenter would be isolated in the experimental room, all the conditions remaining for a while constant. Suddenly some disturbing factor would arise—a sound would penetrate the room; some quick change in illumination would occur, the sun going behind a cloud; or a draught would get in underneath the door, and maybe bring some odour with it. If any of these extra stimuli happened to be introduced just at the time of application of the conditioned stimulus, it would inevitably bring about a more or less pronounced weakening or even a complete disappearance of the reflex response depending on the strength of the extra stimulus. (p. 44)

There are several demonstrations that, as expected on the basis of a conditioning interpretation of tolerance, the expression of tolerance is disrupted when a subject, displaying a small, tolerant response to a drug, is presented with a novel stimulus, for example, an unexpected noise (Larson &

Table 1
Circumstance of Heroin Administration for 76 Patients Who Recently Had Used Heroin and Were Admitted to a Hospital Emergency Room, Either for a Heroin Overdose or for Other Reasons

Environment of heroin use prior to admission	Reason for admission	
	OD	Non-OD
Usual	48% (26/54)	100% (22/22)
Unusual	52% (28/54)	0% (0/22)

Note. Based on data from Gutiérrez-Cebollada et al. (1994). OD = heroin overdose; Non-OD = other reasons.

Siegel, 1998; Poulos, Hunt, & Cappell, 1988; Siegel & Larson, 1996; Siegel & Sdao-Jarvie, 1986). As discussed by Larson and Siegel (1998),

> The conditioning analysis of tolerance has been shown to be important in understanding drug overdose. . . . Based on findings of external inhibition of tolerance, we would predict that if people consistently administer a drug under one set of circumstances, a novel stimulus presentation or the novel omission of a stimulus should disrupt tolerance and result in an exaggerated drug effect. (p. 141)

Indeed, Siegel (1989) described such a case report in which external inhibition of tolerance may have contributed to a heroin overdose. The victim (E. C.) was a heavy user of heroin for 3 years. She usually self-administered her first, daily dose of heroin in the bathroom of her apartment, where she lived with her mother. Typically, E. C. would awake earlier than her mother, turn on the water in the bathroom (pretending to take a shower), and self-inject without arousing suspicion. However, on the occasion of the overdose, her mother was already awake when E. C. started her injection ritual, and she knocked loudly on the bathroom door telling E. C. to hurry. When E. C. then injected the heroin, she immediately found that she could not breathe. She was unable to call to her mother for help (her mother eventually broke down the bathroom door and rushed E. C. to the hospital, where she was successfully treated for heroin overdose). Obviously, there are any number of reasons why E. C. may have overdosed on this occasion, but it is possible that the novel, external stimulus (mother knocking on bathroom door) disrupted the CCR usually elicited by drug-associated cues.

Overdoses in Patients Receiving Medically Prescribed Opiates

There are case reports of patients that were receiving medically prescribed opiates and, for seemingly inexplicable reasons, suffered an apparent overdose following a particular administration. These reports are consistent with the conditioning analysis of tolerance and the failure of tolerance that occurs when the environment of drug administration is altered.

Siegel and Ellsworth (1986) described a case of an apparent overdose death of a patient receiving morphine for relief of pain from pancreatic cancer. The patient's son, N. E., regularly administered the drug in accordance with the procedures and dosage levels specified by the patient's physician. N. E. was 17 years old when he administered the fatal dose of morphine. Two years later, N. E. was a student in a class in which the Pavlovian conditioning analysis of drug tolerance was discussed. It was only then that N. E. realized the applicability of the model to his father's death and attempted to reconstruct the circumstances of the event. Many details concerning the overdose are not accessible, and some information was forgotten over the period between the death and N. E.'s insight into the potential role of conditioning in the death. Nevertheless, N. E.'s interpretation of the event as another instance of exacerbation of a drug effect by environmental alteration is reasonable.

The patient was being attended at home and received a morphine injection four times per day (at 6-hr intervals). The injections had been given for 4 weeks. The patient's condition was such that he stayed in his bedroom, which was dimly lit and contained much hospital-type apparatus necessary for his care. The morphine had always been injected in this environment. For some reason, on the day that the overdose occurred, the patient dragged himself out of the bedroom to the living room. The living room was brightly lit and different in many ways from the bedroom–sickroom. The patient, discovered in the living room by N. E., appeared to be in considerable pain. Inasmuch as it was time for his father's scheduled morphine injection, N. E. injected the drug while his father was in the living room. He had never administered the morphine in this environment before. N. E. noticed that his father's reaction to this injection was atypical; his pupils became unusually small, and his breathing became very shallow.

Alarmed by his father's reaction to this injection in the living room, N. E. called his father's physician. The physician instructed N. E. to evaluate some indices of his father's status. On the basis of the information supplied by the son, the physician concluded that his father suffered an overdose of morphine. The father died some hours later.

In view of the patient's condition, there was no postmortem examination to ascertain the potential role of morphine in his death. The evidence that he died from an overdose is based on his reaction to the final morphine administration and the physician's interpretation of the symptoms as described in his telephone conversation with N. E. at the time of the event. Of course, there are a variety of possible explanations for this very sick patient's death. However, the symptoms immediately preceding death strongly implicate morphine overdose, and the circumstances of the death are congenial with a Pavlovian conditioning interpretation of this overdose. The patient's shallow breathing and constricted pupils are classic symptoms of opiate overdose. The fact that N. E. stated that he was always assiduous in preparing the morphine (including the preparation on the occasion of the apparent overdose) suggests that there was nothing unusual about the drug dosage on the occasion of the apparent overdose.

As discussed previously, a variety of cues may become associated with a drug effect and control the display of tolerance, including DOCs. Recall that these drug-onset cues are the early drug effects, experienced shortly after each administration, that reliably signal the later, larger drug effect. Johnson and Faull (1997) described a case of an apparent overdose in a patient receiving medically prescribed opiates that Siegel and Kim (2000) suggested may be interpretable by a conditioning analysis of tolerance that incorporated the CS properties of DOCs. Johnson and Faull's patient had been treated for pain with a regimen that included oral morphine for about 3 months. Tolerance to the analgesic effect of the drug developed. The patient opted to change to transdermal fentanyl, and cross-tolerance was expected. Fortuitously, the morphine–fentanyl conversion dose was incorrectly calculated and the patient received one quarter of the manufacturer's recommended conversion

dose. Nevertheless, the patient suffered an opioid overdose. Johnson and Faull concluded that, despite the patient's tolerance to oral morphine, there was apparently no cross-tolerance to fentanyl: "If this man had received the 'correct' dose [of fentanyl] as calculated from the manufacturer's data sheet he would have experienced severe toxicity" (Johnson & Faull, 1997, p. 494).

Although Johnson and Faull (1997) did not offer an explanation for the overdose that they noted, Siegel and Kim (2000) did. Siegel and Kim suggested that this disruption of tolerance seen following a change in route of administration is a further demonstration of the situational-specificity of tolerance. Among the stimuli that comprise the drug-associated cues are those cues inherent within the administration procedure (such as DOCs). As summarized by Siegel and Kim (2000),

> Johnson and Faull's observations concerning a failure of cross-tolerance to occur between two μ-opioid receptor agonists in conjunction with an alteration in administration procedure may represent another demonstration of the situational-specificity of tolerance. The phenomenon has been implicated in unexpected overdose deaths resulting from opiates, alcohol, and pentobarbital, and may also (as Johnson and Faull's observations suggest) be relevant to understanding and preventing enigmatic overdoses in clinical practice. (p. 76)

Drug Overdose: The Researcher and the Clinician

Situational-specificity of tolerance was originally described in many experiments conducted by Clifford Mitchell and colleagues more than 40 years ago (see review by Siegel, 1978). Subsequent laboratory research has established the reliability of the phenomenon with respect to tolerance to many effects of a variety of drugs: opiates, naloxone, ethanol, nicotine, pentobarbital, phencyclidine, immunoenhancing drugs, cholecystokinin, carisoprodol, haloperidol and several benzodiazepines (see Siegel et al., 2000). The relevance of situational-specificity of tolerance to heroin overdose in rodents was first demonstrated in the laboratory approximately 20 years ago (Siegel et al., 1982), and the basic finding subsequently has been replicated with respect to overdose to nonopiate drugs (Melchior, 1990; Vila, 1989). Results of case reports (e.g., Siegel, 1984, 1989) and epidemiological studies (e.g., Gutiérrez-Cebollada et al., 1994) evaluating the circumstances of heroin overdose in humans are consistent with the results of laboratory experiments with mice and rats. Furthermore, the role of environmental cues in tolerance in general, and in failures of tolerance responsible for overdoses in particular, are explicable on the basis of a theoretical account of tolerance (i.e., Pavlovian conditioning) that has considerable empirical support (Siegel et al., 2000). In short, the data and theory implicating drug-paired cues in overdose are overwhelming (Siegel, 2001).

Nevertheless, there does not seem to be widespread dissemination of this information, either among clinicians who treat patients with opiates for pain relief or among clinicians who deal with heroin addicts. For example, Siegel and Kim's (2000) explanation of the overdose seen in a patient switched from oral morphine to transdermal fentanyl (described by Johnson & Faull, 1997) was subjected to peer review by the journal in which both articles appeared, *Palliative Medicine*. One of the anonymous reviewers of the Siegel and Kim submission stated, "the hypothesis that tolerance is situation specific is a completely new one to me—and I suspect to all others actively involved in patient care." Similarly, in a recent summary of the potential mechanisms of heroin overdose, Zador (1999) noted, accurately, that "ingesting heroin in an unusual or unfamiliar setting is not currently publicized as a risk" (p. 976). Communication between researchers and clinicians in this area needs improvement.

Pavlovian Conditioning and Cue Exposure Treatment

Drug withdrawal symptoms and drug tolerance are highly correlated (e.g., Koob, Stinus, Le Moal, & Bloom, 1989; Peper, Grimbergen, Kraal, & Engelbart, 1987). Moreover, withdrawal symptoms are compensatory responses: "As a general pharmacological principle, it can be asserted that withdrawal effects are usually opposite to acute drug effects" (Poulos & Cappell, 1991, p. 402). According to the Pavlovian conditioning analysis, the relationship between tolerance and withdrawal, and the fact that most withdrawal symptoms are drug-compensatory responses, are attributable to the fact they are both manifestations of the same conditioned compensatory drug response.

Pavlovian Conditioning and Drug Withdrawal Symptoms

When the drug is administered in the context of the usual drug-administration cues, CCRs attenuate the drug effect and contribute to tolerance. However, if there is no drug effect (i.e., the usual cues for drug administration are present, but the usual drug is not administered), these CCRs achieve full expression because they are not modulated by a drug effect. Such CCRs, displayed in such circumstances, are termed *withdrawal symptoms*. In discussing the role of CCRs in withdrawal symptoms, it is important to make a distinction between the acute withdrawal reaction seen shortly after the initiation of abstinence (which typically lasts for days or, at most, weeks) and the apparently similar symptoms often noted after detoxification is presumably complete (see Hinson & Siegel, 1982). In the latter case, it is likely that Pavlovian conditioning contributes to the symptoms:

> Consider the situation in which the addict expects a drug, but does not receive it; that is, no drug is available, but the addict is in an environment where he or she has frequently used drugs in the past, or it is the time of day when the drug is typically administered, or any of a variety of drug-associated stimuli occur. Research with animals demonstrates that presentation of cues previously associated with drug administration, but now not followed by the drug, results in the occurrence of drug-compensatory CRs. . . . In the situation in which the drug addict expects but does not receive the drug, it would be expected that drug-compensatory CRs would also

> occur. These CRs normally counter the pharmacological disruption of functioning which occurs when the anticipated drug is administered. However, since the expected drug is not forthcoming, the CRs may achieve expression as overt physiological reactions, e.g., yawning, running nose, watery eyes, sweating . . . or form the basis for the subjective experience of withdrawal sickness and craving. (Hinson & Siegel, 1982, p. 499)

There is much evidence that such withdrawal symptoms, seen long after the last exposure to a drug, are especially pronounced in the presence of drug-related cues (Siegel, 1999a); that is, "it is the anticipation of the drug, rather than the drug itself, that is responsible for these symptoms . . . some drug 'withdrawal symptoms' are, more accurately, drug 'preparation symptoms'" (Siegel, 1991, p. 412). According to the conditioning account of tolerance, as applied to withdrawal symptoms, the CCRs elicited by the usual drug-paired cues, in the absence of the usual drug, include the readily observable drug-compensatory responses and the less readily observable neurochemical responses that are interpreted as craving (Siegel, 1999a).

The results of many studies support clinical observations that predrug cues are powerful elicitors of withdrawal symptoms. The findings have been obtained in both laboratory experiments (with humans and nonhuman animals) and in epidemiological studies. This literature recently has been reviewed (Carter & Tiffany, 1999; Siegel, 1999a). Briefly, rats with a history of drug administration display more behavioral withdrawal symptoms in a drug-paired environment than in an alternative environment. Drug-paired cues contribute not only to withdrawal symptoms in rats but also to relapse. That is, following a withdrawal period, the presence of these cues promotes renewed self-administration of opiates, cocaine, and ethanol. Similarly, former heroin addicts display physiological signs of narcotic withdrawal when they perform the "cooking up" ritual while being monitored by a polygraph or when presented with pictures containing drug-related cues. Alcoholics and cigarette smokers similarly respond to the appropriate drug-associated cues with withdrawal symptoms and craving (see reviews by Carter & Tiffany, 1999; Siegel, 1999a).

Epidemiological studies have evaluated relapse in treated drug users who have relocated to an environment very different than that in which they used drugs (e.g., returning Vietnam veterans who were addicted to heroin while in Vietnam or treated civilian drug addicts who moved to a new environment following treatment). Compared with groups that have returned to environments rich in drug-associated cues, relocated patients generally show far less relapse (see review by Siegel, 1999a).

An implication of the conditioning analysis is that successful treatment of drug addiction should acknowledge the substantial influence of drug-predictive cues. On the basis of this reasoning, abstinence is most likely if the addict (who is not likely to relocate after therapy) is treated with a protocol that incorporates extinction of the association between these cues and the drug: "These treatments reflect a logical extension of classical conditioning theory. If addicts' responses to drug-related stimuli reflect CRs, then extinction of these CRs may be achieved through repeated unreinforced exposure to the CS" (Carter & Tiffany, 1999, p. 329).

Extinction of the Response to Drug-Associated Cues

On the basis of the results of research with rats, we would expect that repeated presentations of predrug cues, in the absence of the drug, should extinguish CCRs. Most research in this area has been designed to evaluate a prediction of the conditioning analysis of tolerance. If tolerance is mediated by these CCRs, procedures that decrease the strength of Pavlovian conditioning should similarly decrease the magnitude of tolerance. The magnitude of established CRs is decreased by *extinction*, that is, repeated presentations of the CS without the UCS. Similarly, tolerance to the analgesic, lethal, and behaviorally sedating effects of morphine are attenuated by repeated presentation of the predrug cues. Similarly, tolerance to a variety of effects of ethanol, amphetamine, midazolam (a short-acting benzodiazepine), and the synthetic polynucleotide, Poly I:C, also can be extinguished (see reviews by Siegel, 1999a; Siegel et al., 2000). These findings, indicating that drug CCRs are attenuated by an extinction procedure, suggest that cue exposure should be an effective addiction treatment strategy.

Krank and Wall (1990) reported the results of three experiments that evaluated such a cue exposure treatment with rats. During the self-administration phase of each experiment, rats pressed a lever in an operant chamber for access to a saccharin–ethanol mixture. They subsequently were denied access to ethanol during an extinction phase. During this period of abstinence, groups of rats differed with respect to the extent of their exposure to ethanol-associated cues. Finally, during a reacquisition test, rats were permitted to again respond for the sweetened ethanol solution to evaluate the effect of the various extinction treatments on relapse to ethanol self-administration. For example, in one experiment (Experiment 2), rats were abstinent from ethanol for 12 days following the self-administration phase. Four independent groups of rats differed in their treatment during this 12-day period. Rats in one group were not exposed to ethanol-associated cues—they stayed in their home cage throughout the abstinence phase of the experiment (the home-cage group). Rats in the remaining three groups differed in the number of ethanol-associated cues presented during the abstinence. Rats assigned to the no-bar group received daily exposure to the operant chamber, but there was no response lever in the chamber. Rats assigned to the no-sacch group received daily sessions in the operant chamber, with the lever in place, but lever presses had no consequence. Rats assigned to the sacch group also received daily sessions in the operant chamber, but lever presses were reinforced with unadulterated saccharin solution (no ethanol).

The results of the reacquisition test session for all groups in the Krank and Wall (1990, Experiment 2) study are summarized in Figure 3. As can be seen in Figure 3 (and as confirmed by the results of inferential statistical analyses), cue exposure during extinction reduced self-administration

for ethanol during reacquisition. Following abstinence, sacch group rats responded less than did no-sacch group rats, who, in turn, responded less than did no-bar group rats. There was no statistically significant difference between the no-bar and home-cage groups.

In sum, in this Krank and Wall (1990) research, relapse to ethanol self-administration was attenuated by exposure to drug-associated cues during abstinence, with the extent of relapse inversely related to the number of such cues presented during the extinction phase: "This suggests that implementing some form of cue exposure to the patient's usual drinking environment during abstinence may be useful therapy" (Krank & Wall, 1990, p. 732).

The Effectiveness of Cue Exposure Treatment for Drug Addiction in Humans

There are several reviews of the literature concerning the effectiveness of cue exposure treatment for excessive use of both licit and illicit drugs by humans: alcohol (e.g., Drummond & Glautier, 1994; Monti et al., 1993), nicotine (e.g., Brandon, Piasecki, Quinn, & Baker, 1995), cocaine (e.g., O'Brien, Childress, McLellan, & Ehrman, 1990), and opiates (e.g., Childress et al., 1986). The various studies have used a variety of outcome measures (latency to relapse, extent of relapse, cue reactivity, self-reports of drug use and urges, and withdrawal symptoms). Although there are reports that cue exposure treatment is effective (e.g., Drummond & Glautier, 1994; Heather & Bradley, 1990; Monti et al., 1993), the findings are mixed. That is, there also are reports that such treatments are ineffective (e.g., Dawe et al., 1993; McLellan, Childress, Ehrman, O'Brien, & Pashko, 1986), effective with some drugs but not others (e.g., Drummond, Tiffany, Glautier, & Remington, 1995), effective only as adjunct to more traditional treatments (e.g., Monti & O'Leary, 1999; Monti & Rohsenow, 1999; Rohsenow, Monti, & Abrams, 1995), and effective with some clients and not with others (e.g., Powell et al., 1993; Rees & Heather, 1995). As recently summarized by Carroll (1999), "while cue exposure approaches have generally been associated with reductions in some conditioned responses, the value of these procedures in producing clinically meaningful reductions in substance use has been met with only modest success to date" (p. 261).

Why Cue Exposure Treatment May Not Be Effective

Findings indicating that cue exposure treatment may not always be an effective treatment strategy are explicable on the basis of laboratory work concerning extinction in general, and extinction of conditional pharmacological responses in particular. The results of this research suggest strategies to maximize the effectiveness of cue exposure treatment.

Interoceptive Drug-Associated Cues

As indicated previously, interoceptive, as well as exteroceptive predrug cues may serve as CSs. Thus, the unconditional effects of a drug may be signaled by at least two CSs: (a) exteroceptive cues present at the time of drug administration, and (b) interoceptive cues provided by the early

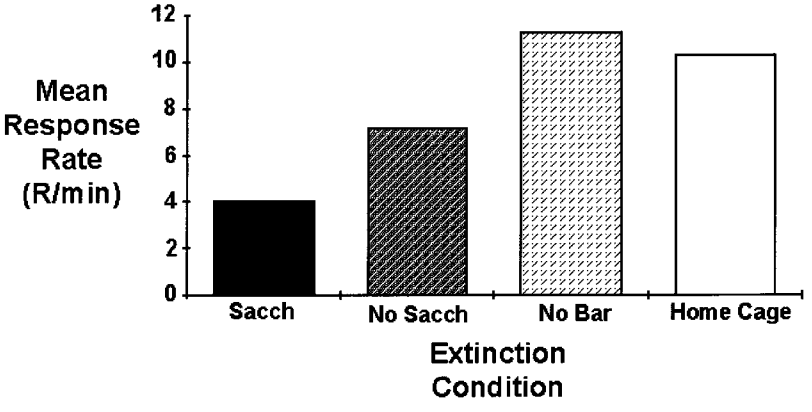

Figure 3. Mean bar pressing for oral saccharin–ethanol reinforcement during the postabstinence reacquisition phase of the Krank and Wall (1990, Experiment 2) study. Prior to this test, rats were trained to respond for the sweetened ethanol mixture. They subsequently were denied access to ethanol. During this abstinence phase, independent groups of rats were not exposed to ethanol associated cues (home-cage group); received daily sessions in which they were placed in the self-administration chamber, but the bar was not available (no-bar group); received daily sessions in the operant chamber with the lever in place, but lever presses had no consequence (no-sacch group); or received daily sessions in the operant chamber with the lever in place and lever presses reinforced with unadulterated saccharin solution (sacch group). From "Cue Exposure During a Period of Abstinence Reduces the Resumption of Operant Behavior for Oral Ethanol Reinforcement," by M. D. Krank and A.-M. Wall, 1990, *Behavioral Neuroscience, 104*, p. 730. Copyright 1990 by the American Psychological Association. Reprinted with permission of the author.

effects of the drug (DOCs) or the act of self-administration (SACs). That is, drug effects may often be signaled by compound predrug cues. There are several compound conditioning phenomena that may be important for understanding the relationship between conditional drug effects and addictive phenomena, but one that is especially relevant is overshadowing.

Overshadowing, first described by Pavlov (1927, pp. 142–143 and 269–270), was extensively investigated by Kamin (1969). Overshadowing is seen if two CSs simultaneously signal a UCS, and one CS is more salient than the other. Other things being equal, a subject trained with a more salient CS will learn more rapidly than a subject trained with a less salient CS. For example, if CS_A and CS_B are both effective CSs, but subjects learn a $CS_A \rightarrow UCS$ association faster than a $CS_B \rightarrow UCS$ association, CS_A is said to be more salient than CS_B. When a compound CS signals a UCS, subjects learn about the more salient CS at the expense of the less salient CS. Consider the situation in which CS_A and CS_B simultaneously signal a UCS. If CS_A is more salient than CS_B, CS_A will become strongly associated with the UCS, and little associative strength will develop between CS_B and the UCS. It is said that CS_A overshadows CS_B.

Overshadowing should be a characteristic of Pavlovian conditioning with pharmacological UCSs, just as it is with nonpharmacological UCSs. Indeed, there is considerable evidence that overshadowing is a feature of learning about drug effects (Dafters & Bach, 1985; Walter & Riccio, 1983). Thus, drug tolerance may be controlled largely by DOCs or SACs (rather than simultaneously present, drug-paired environmental cues) because these interoceptive cues are more salient than the environmental cues (Kim et al., 1999; Sokolowska, Siegel, & Kim, in press; Weise-Kelly & Siegel, 2001).

Drug-onset cues, drug addiction, and cue exposure treatment. It is well established that relapse to drug use sometimes is precipitated by exposure to small drug doses. Although there are various interpretations of such priming effects (Shaham, Rodaros, & Stewart, 1994), it is possible that intraadministration associations may be responsible for some instances of the phenomenon (Siegel et al., 2000). For example, frequently it has been reported that a small dose of alcohol will augment the craving for additional alcohol and enhance subsequent alcohol consumption (see Goddard, 1999; Siegel, 1987). This "loss of control" is incorporated in the doctrine of Alcoholics Anonymous:

> Once he takes any alcohol into his system, something happens, both in the bodily and mental sense, which makes it virtually impossible for him to stop. The experience of any alcoholic will confirm that. . . . We are without defense against the first drink. (Anonymous, 1939, pp. 34–35)

The insalubrious effect of the first drink may be due to the alcoholic's association of that initial effect of alcohol (i.e., DOCs experienced soon after ingestion of alcohol) with subsequent larger amounts of the drug: "The signal value of a small drug dose may make a contribution to 'binge' drinking and drug 'priming' effects in humans" (Goddard, 1999, p. 418).

There is evidence that withdrawal symptoms and craving can be directly elicited by a small dose of the drug to which an individual is addicted. Schachter (1977) reported that some heavy smokers given low-nicotine cigarettes failed to regulate their nicotine intake (i.e., increase the number of cigarettes smoked). These smokers, who repeatedly self-administered lower than normal doses of nicotine, reported extreme withdrawal distress. Other heavy smokers, who increased consumption when given low-nicotine cigarettes, effectively maintaining their normal nicotine intake, reported no withdrawal distress. In experiments with rats, McDonald (2001) demonstrated the contribution of DOCs to withdrawal symptoms. He found that rats with a history of administration of large morphine doses (e.g., 50 mg/kg) displayed behavioral and thermic evidence of morphine withdrawal when administered small doses (e.g., 5 mg/kg) of the opiate.

Cue exposure treatments sometimes may be ineffective because there is no attempt to extinguish these highly salient DOCs. As indicated by Cepeda-Benito and Short (1997), if the early effect of a drug is one cue that elicits CCRs, it is possible that mere exposure to predrug environmental cues may not effectively extinguish the association between predrug cues and the drug effect. Rather, "the inclusion of small drug doses during cue exposure treatments may better reproduce the CSs responsible for craving" (Cepeda-Benito & Short, 1997, p. 239). Indeed, some investigators described successful cue exposure treatment procedures for problem drinking that incorporate priming doses of alcohol (e.g., Sitharthan, Sitharthan, Hough, & Kavanagh, 1997).

Self-administration cues, drug addiction, and cue exposure therapy. Recognition that SACs function as highly salient predrug cues also may have important implications for cue exposure treatments. Typically, cue exposure treatment involves passive exposure of drug-associated environmental cues to patients who have self-administered drugs (e.g., Dawe et al., 1993). If SACs are among the cues that elicit CCRs, it is possible that effective extinction treatments should incorporate opportunities for the patient to engage in the behaviors that previously had culminated in drug administration. Recall that in the Krank and Wall (1990) experiment with rats that had been trained to self-administer ethanol, the effective cue exposure treatments were those that involved components of the self-administration response. That is, treatment was more effective for rats that had experience in making the response that previously resulted in ethanol access but now resulted either in no programmed consequence or access to a dealcoholized solution. Tobeña et al. (1993) similarly suggested that the effectiveness of cue exposure may be enhanced if it incorporated self-administration behaviors:

> It can also be useful to consider the possibility that controlling for the direct consequences of self-administration of drugs (e.g., drinking or injecting), could affect the extinction of the affective states induced by drugs or drug cues . . . treatment should incorporate specific strategies for dealing with the behavioral chains involved in drinking, inhaling, smoking or self-injecting drugs. The corresponding prediction would be that the practice of such behavioral rituals while the patients are exposed to cues (but without actual intake of drugs),

> would lead to faster extinction and loss of the signal value of such behaviors as cues for the drugs. This hypothesis may be worth investigating. (p. 215)

More recently, in discussing cue exposure therapy for cigarette smoking, Brandon et al. (1995) also speculated about a role for incorporating SACs in treatment and indicated that more research is needed: "The benefits of including the self-administration ritual *per se* as part of a cue exposure treatment have not yet been empirically investigated" (p. 219, italics in original).

Images, Memories, and Emotions

Laboratory research relevant to increasing the effectiveness of cue exposure discussed thus far primarily has been concerned with work using nonhuman animals. The findings, however, are relevant to cue exposure therapy with humans. For example, the fact that effective CSs may be "private" (such as DOCs and SACs), as well as "public" (such as the environment of drug administration), although primarily based on the results of research with rats, has important implications for the design of effective extinction-based treatment procedures. However, there are some private predrug cues that can be studied only in humans. These include imagery of drug-paired stimuli and mood states.

Images and memories. Merely thinking about their preferred drug elicits withdrawal distress and craving in cigarette smokers (e.g., Drobes & Tiffany, 1997), alcoholics (e.g., Weinstein, Lingford-Hughes, Martinez-Raga, & Marshall, 1998), and heroin addicts (e.g., Bradley & Moorey, 1988). This imagery-elicited responding may be manifest not only by subjective reports but also by activation of distinctive brain circuits as revealed by positron emission tomography imaging techniques (e.g., Weinstein, Feldtkeller, et al., 1998). As summarized by Greeley and Ryan (1995), "A good case exists, then, for making cognitions *per se* a pivotal concern of conditioning models, allowing the possibility of cognitions as interoceptive cues" (p. 132, italics in original). Research concerning the incorporation of such private stimuli into cue exposure procedures (e.g., Kominars, 1997) will influence in an important way this form of behavioral therapy for addiction.

Emotions. Emotions, especially negative emotions, are frequent elicitors of withdrawal distress and craving. For example, Ludwig and Stark (1974) reported that over 75% of their sample of patients experienced craving for alcohol when "depressed," "nervous," or "under stress." Similarly, Mathew, Claghorn, and Largen (1979) found that about 85% of their patients reported that "non-alcohol-related events of an unpleasant nature" (p. 605) precipitated craving. Similar results have been found with heroin addicts (see summary by Greeley & Ryan, 1995). There are various interpretations of the contribution of negative emotional states to withdrawal distress (Stewart, 2000); however, as discussed by Poulos, Hinson, and Siegel (1981), Pavlovian conditioning may be a factor:

> While one can plausibly relate the psychodynamics of stress and depression to drug use, the conditioning analysis can parsimoniously analyze the situation in terms of an associative process. If stress has been reliably associated with abusive drinking for a particular individual, then stress can function as a conditional stimulus for the elicitation of compensatory responses and craving. . . . The extinction of stress as a conditional cue for drug effects should occur just as the extinction of a distinctive environment for drug effects occurs. (pp. 209–210)

Spontaneous Recovery

When a CR is extinguished, it typically reappears after a period of time. The phenomenon was first noted by Pavlov: "Left to themselves, extinguished conditioned reflexes spontaneously recover their full strength after a longer or shorter interval of time" (Pavlov, 1927, p. 58). Spontaneous recovery of an extinguished response is well established and has been given extensive theoretical treatment (e.g., Brooks & Bouton, 1993; Robbins, 1990).

In common with other CRs, the CCRs that mediate drug tolerance and withdrawal display spontaneous recovery. For example, Brooks, Karamanlian, and Foster (2001) demonstrated that although ethanol tolerance can be extinguished by repeated presentation of drug-associated cues, the tolerant response reappears after a "rest" interval. This spontaneous recovery complicates attempts to effect long-term extinction of these CCRs during cue exposure therapy. With few exceptions (e.g., Corty & Coon, 1995; Hammersley, 1992), however, spontaneous recovery generally has not been recognized as a problem for cue exposure treatment. It would appear that, to be successful, cue exposure treatment should use widely spaced extinction trials (that may minimize the magnitude of spontaneous recovery; see Mackintosh, 1974, pp. 421–422). In addition, the cue exposure protocol should include postextinction sessions in which the spontaneously recovered pharmacological CCR may be repeatedly reextinguished.

Context Effects

The fact that extinguished CRs display spontaneous recovery suggests that extinction does not abolish the ability of a CS to elicit conditional responding. Nevertheless, a view of extinction as unlearning—an eradication of the association formed during acquisition—is pervasive and is implicit in most implementations of cue exposure therapy. Results of research conducted in the past 20 years, however, indicate that extinction does not entail the loss of prior learning. An extensive series of experiments, primarily by Mark Bouton and colleagues (e.g., Bouton, 1994, 2000; Bouton & Swartzentruber, 1991), indicate that, just as something is learned during acquisition (the CS–UCS association), something also is learned during extinction (a CS–*no*-UCS association). During extinction, the association learned during acquisition remains intact, while the new, conflicting association is acquired: "The signal winds up with two available 'meanings.' It is ambiguous . . . its current meaning—or the behavior it currently evokes—is determined by the current context" (Bouton, 2000, p. 57). This view of extinction has profound implications for cue exposure therapy.

Renewal. A phenomenon termed *renewal* (Bouton, 1993) provides evidence for the survival of CRs, even following extensive extinction. Renewal is seen if a CR is established in one context ($Context_{ACQ}$) by repeated CS–UCS pairings and subsequently extinguished in a different context ($Context_{EXT}$) by repeated CS-alone presentations. Despite the fact that following extinction, there is no conditional responding in $Context_{EXT}$, when the subject is presented with the CS in Context $_{ACQ}$ the CS again elicits CRs; that is, conditional responding is renewed. Renewal has been seen in many different types of conditioning preparations, with both nonhuman animals and humans. In experiments with rats, $Context_{ACQ}$ and $Context_{EXT}$ typically consist of experimental chambers that are distinguished by olfactory, visual, and auditory cues but may also consist of different hormonal, drug, or deprivation states. In experiments with humans, contexts may be provided by experimentally induced moods (e.g., Eich, 1995). Although renewal typically has been demonstrated by presenting the CS in $Context_{ACQ}$ following extinction in $Context_{EXT}$, there is evidence, from research with rats, that renewal may be seen when the CS again is presented in a third, neutral context. As summarized by Bouton and Swartzentruber (1991),

> The loss of responding during extinction depends to some extent on the subject learning about, and suppressing performance in, the *extinction* context. One could similarly expect that the positive effects of exposure therapy could be specific to the therapy context. It is as if extinction depends inherently on the subject learning about some version of the idea, 'the CS is safe *here.*' (p. 126, italics in original)

Bouton (2000) provided an example of the potential of the renewal effect to stymie the intentions of the cue exposure therapist. Consider the case of the cigarette smoker who habitually smokes in particular contexts (e.g., at work or under the influence of alcohol). Thus, a variety of exteroceptive and interoceptive cues (including the act of smoking and the effects of nicotine and other tobacco constituents) provide a context in which smoking typically occurs. Following cue exposure in the clinic, this individual may no longer experience substantial withdrawal symptoms or craving when confronted by cigarette-associated stimuli (e.g., the sight of a cigarette or the sight of someone smoking). However, when this individual again returns to $Context_{ACQ}$ (the workplace or the internal state induced by alcohol), cigarette-associated stimuli will again elicit CCRs. Moreover, if renewed smoking occurs in this context (thus reexposing the individual to contextual cues resulting from smoking), the renewal effect is further enhanced:

> In this manner the initial lapse produced by renewal or spontaneous recovery will introduce additional contextual cues that further trap the smoker into smoking again. One begins to envision an ever-expanding set of contextual cues. In this way, a slip or lapse may spiral into relapse. (Bouton, 2000, p. 60)

Implications of the renewal effect for cue exposure therapy. Cue exposure will be successful, in the long term, to the extent that the therapy decreases renewal and promotes retrieval of the extinction learning when the patient returns to $Context_{ACQ}$. On the basis of the results of research with both rats and humans, Bouton (2000) suggested several procedures for enhancing the effectiveness of cue exposure. For example, renewal is reduced if cues present during extinction are presented again on the test of renewal (e.g., Brooks & Bouton, 1994): "The findings begin to suggest that building retrieval cues or retrieval opportunities into the period after therapy—perhaps through reminder cards or reminder telephone calls from the therapist—will help prevent relapse and extend behavior change" (Bouton, 2000, p. 60).

Another procedure to increase the long-term effectiveness of extinction is to conduct extinction, to the extent possible, in $Context_{ACQ}$. For example, Blakey and Baker (1980) described such a cue exposure treatment of a problem drinker. The patient, and one or two therapists, would sit in the pub (where the patient habitually drank) and drink only soft drinks.

Drug use is part of $Context_{ACQ}$, thus extinction therapy may be more effective if it actually incorporated some drug use. Bouton (2000) provided an example of such a procedure that could be used with a cigarette smoker. During cue exposure, the patient not only would be presented with cigarette-associated cues but also would smoke a few cigarettes, thereby increasing the similarity between $Context_{EXT}$ and $Context_{ACQ}$:

> Because those trials would initially reintroduce a contextual cue connected with smoking, they may slow down behavior change in the short run. However, in the long run, because they would allow more effective extinction of some of the cues stimulating relapse, controlled exposures to occasional lapses could theoretically facilitate a more permanent change in behavior. (p. 60)

Finally, there is theoretical and empirical support for the idea that conducting extinction in a variety of different contexts will decrease renewal. By presenting the CS alone not in a single $Context_{EXT}$, but also in many other contexts, the likelihood of shared features between the context of extinction and the context of acquisition is increased (Bouton, 2000). Thus, cue exposure may be more effective if it is conducted in many different contexts (rather than, for example, only in the clinic).

Occasion Setting

Cue exposure treatment is designed to extinguish learned responses elicited by drug-paired cues. However, results of recent Pavlovian conditioning research suggest that repeated presentations of stimuli that had been paired with the UCS do not inevitably lead to extinction. This research has concerned a phenomenon variously termed *facilitation* (Rescorla, 1986), *modulation* (Swartzentruber, 1995), or—the term used here—*occasion setting* (Holland, 1992).

What is occasion setting? Renewal provides one demonstration of the importance of contextual cues in extinction of a CS–UCS association. Another (perhaps related) example is provided by occasion setting. The relationship between a CS and a UCS may be termed a *binary relation* (Domjan, 1998, p. 244). Both humans and nonhuman animals can learn that a third stimulus—an occasion setter—

provides information that a binary relationship will be in effect (Hardwick & Lipp, 2000; Schmajuk & Holland, 1998). This third stimulus is the occasion setter.

Occasion setting is a phenomenon of compound conditioning. As previously discussed, the CS that signals a drug often may be conceptualized as a compound CS consisting of several elements. In the examples given thus far, the various elements of the compound CS (e.g., pharmacological drug-onset cues and environmental cues) occur at approximately the same time. This may be termed a *simultaneous* compound. In contrast, one element of the compound may occur some time before the second element. Using the usual terminology for such serial compounds, the first element is termed the *occasion setter*, and the second element is termed the *target*.

Research using serial compounds indicates that the occasion setter, in contrast with the target, does not enter into a direct association with the UCS—that is, it does not function as a CS. Rather, it acquires unique properties. As discussed by several investigators (e.g., Anagnostaras & Robinson, 1996; Greeley & Ryan, 1995), a complete analysis of the contribution of learning to drug effects should acknowledge the acquisition of occasion-setting properties of drug-paired feature cues, as well as the acquisition of conditional responding by drug-paired target cues.

What is special about occasion setting? Organisms learn about occasion setters, just as they learn about CSs; however, the content of learning about occasion setters is unique. For example, although repeated presentations of a CS by itself (in the absence of the UCS) leads to extinction of conditional responding, such extinction is not characteristic of occasion setting. That is, repeated presentations of an occasion setter by itself does not lead to any diminution in the occasion-setting properties of the stimulus. Following such attempted extinction, the organism still responds to the target CS with conditional responding if this CS is preceded by the occasion setter. Although the nonextinguishability of an occasion setter has been demonstrated primarily with the traditional stimuli used in Pavlovian conditioning (e.g., Holland, 1992; Ross & Holland, 1981), it also has been demonstrated with drugs as UCSs (Ramos, Siegel, & Bueno, in press). As suggested by Ramos et al., the fact that some drug-paired stimuli may function as occasion setters, rather than as CSs, has important implications for cue exposure therapy.

Implications of occasion setting for cue exposure therapy. Sometimes, when cue exposure therapy is ineffective, it is possible that the therapist attempted to extinguish an occasion setter, rather than a CS. As indicated, repeated presentations of an occasion setter by itself does not attenuate its occasion-setting properties. Consider, for example, the sequence of events likely to occur for a heroin addict. Many cues provided by the rituals involved in procuring the drug and injection paraphernalia occur well before the actual heroin injection. It is possible that the cues immediately preceding the central effects of heroin (e.g., piercing the skin with the hypodermic needle, DOCs, SACs) are the functional CSs—the target cues. The more distal cues are occasion setters that signal the binary relationship between these target cues and the drug effect. Attempting to extinguish only the occasion setter (e.g., having the patient repeatedly visualize cues that occur well before drug self-administration) would be fruitless.

Pavlovian Conditioning and Pharmacological Treatment of Withdrawal Symptoms

Cue exposure therapy is designed to decrease the magnitude of abstinence symptoms elicited by drug-associated stimuli. On the basis of a conditioning interpretation, these symptoms are CCRs, and cue exposure is an extinction procedure. An alternative strategy for decreasing the strength of CCRs is to interfere with the biological bases of their expression (see Koob, 2000). Results of some recent research have addressed the intracellular and intercellular processes engaged by cues that have been associated with drug administration (see Siegel et al., 2000).

Conditional Intracellular Alterations

The structural changes in the central nervous system that are responsible for learning and drug effects require gene activation. The gene that encodes a transcription factor, c-*fos*, has been implicated in learning and drug tolerance (Nye & Nestler, 1996; Sotty, Sandner, & Gosselin, 1996). That is, c-Fos (especially striatial c-Fos) mediates the action of many common drugs of abuse (e.g., Hope, Kosofsky, Hyman, & Nestler, 1992; Liu, Nickolenko, & Sharp, 1994), and c-Fos also is important for memory consolidation (Sotty et al., 1996). There is evidence that conditional drug effects are seen in conjunction with conditional c-Fos expression (Baptista et al., 1998; Thiele, Roitman, & Bernstein, 1998). For example, Baptista et al. (1998) used the paired–unpaired situational-specificity design of Siegel et al. (1978), described previously, to simultaneously evaluate both tolerance to the analgesic effect of morphine and striatal c-Fos levels. They reported that rats not only showed behavioral evidence of situational-specificity of tolerance (i.e., paired morphine rats were more tolerant to the analgesic effect of morphine than were unpaired morphine rats) but also demonstrated situational-specificity of c-Fos expression (i.e., paired morphine rats displayed higher striatal c-Fos levels than did unpaired morphine rats). More recently, Schroeder, Holahan, Landry, and Kelly (2000) also demonstrated conditional changes in *fos* expression following training with morphine. In addition, Thiele et al. (1998) reported similar findings with respect to ethanol.

The c-Fos protein combines with other proteins to form an activator protein 1 complex—AP-1 (Angel et al., 1998; Bohmann et al., 1987). This AP-1 complex binds to, and activates, genes. Baptista et al. (1998) demonstrated that AP-1 binding was increased more in the striatum of paired morphine rats than in the striatum of unpaired morphine rats.

In sum, stimuli present at the time of drug administration modify not only the expression of tolerance but also the molecular changes hypothesized to mediate tolerance. Increasing understanding of the molecular bases of condi-

tional pharmacological responses may lead to the development of drugs that modulate these intracellular functions that contribute to drug addiction and relapse.

Conditional Intercellular Alterations

Another strategy for pharmacological treatment of addiction is to use a drug that modulates the conditional changes in neurotransmitter activity that mediate the behavioral expression of CCRs. There recently has been progress delineating such changes with respect to ethanol and opiates. For example, on the basis of results of microdialysis studies, Quertemont, de Neuville, and De Witte (1998) suggested that the CCRs elicited by ethanol-paired cues are mediated by conditional release of the neuromodulator, taurine, in the amygdala.

An especially promising area of research concerns the development of pharmacotherapies for addiction that interfere with neurotransmitter activities that occur in anticipation of opiates. There are findings suggesting that administration of opiates elicits an increase in the production or synthesis of anti-opioid peptides (AOPs). An AOP, as the term indicates, counteracts the effects of opiates and contributes to tolerance and withdrawal symptoms (Wiesenfeld-Hallin, Lucas, Alster, Xu, & Hökfelt, 1999). Increases in AOP activity may occur not only unconditionally (in response to the presence of the drug) but also conditionally (in response to predrug cues); thus, interfering with AOP activity may decrease CCRs elicited by drug-associated stimuli (Kim & Siegel, 2001).

CCK as an AOP

Although several putative AOPs have been proposed, one that has received considerable attention is CCK. There is evidence that CCK attenuates the effect of morphine. For example, if CCK is administered exogenously, it blocks morphine-induced analgesia in a dose-dependent manner (e.g., Han, 1995; Mitchell, Lowe, & Fields, 1998). Cotreatment with a CCK receptor antagonist prevents CCK from attenuating opioid effects (Suh, Kim, Choi, & Song, 1995). Blocking CCK receptors potentiates morphine analgesia in rats (e.g., Zhou, Sun, Zhang, & Han, 1992) and humans (e.g., McCleane, 1998). Moreover, morphine administration accelerates the release of CCK from the central nervous system in a dose-dependent manner (Zhou et al., 1992). Two subtypes of CCK receptors have been identified and termed *CCK_A* and *CCK_B*, in reference to the relative distribution of the receptors in *a*limentary and *b*rain tissue (Saito, Sankaran, Goldine, & Williams, 1980). The availability of highly selective receptor antagonists has demonstrated that the anti-opioid function of CCK is active at the CCK_B, rather than at the CCK_A receptor site (Wiesenfeld-Hallin et al., 1999).

CCK, Tolerance, and Withdrawal Symptoms

If tolerance were mediated by enhanced CCK_B activity, CCK_B antagonists would be expected to attenuate tolerance. Indeed, several investigators have reported that such antagonist treatment prevents the developments of morphine tolerance (e.g., Kellstein & Mayer, 1991) and attenuates the expression of established morphine tolerance (e.g., Hoffmann & Wiesenfeld-Hallin, 1994; Kim & Siegel, 2001). If such enhancement of CCK_B activity is conditionally elicited by morphine-paired cues, the CCR usually elicited by these cues should be attenuated by pretreating rats with a CCK_B antagonist prior to the presentation of these cues. This finding recently has been reported by Kim and Siegel (2001). They demonstrated that, in rats with a history of morphine administration, a hyperalgesic CCR is apparent in rats presented with drug-associated cues (and pretreated with an inert substance), but no such CCR is apparent in rats tested following pretreatment with a CCK_B antagonist.

On the basis of a Pavlovian conditioning interpretation, the CCRs that mediate tolerance (when the drug is administered) are expressed as withdrawal symptoms (when the usual predrug cues are not followed by the usual pharmacological consequences). Thus, it would be expected that these associatively mediated withdrawal symptoms should be attenuated by pretreatment with a CCK_B antagonist. Lu et al. (2000) reported that the expression of withdrawal symptoms in rats with a history of morphine administration was suppressed by pretreatment with a CCK_B antagonist, but these investigators did not evaluate the contribution of predrug cues to these withdrawal symptoms. Further research can determine whether withdrawal symptoms, seen when the long-abstinent organism again is confronted with drug-associated cues (see Carter & Tiffany, 1999; Siegel, 1999a) are attenuated by a CCK_B antagonist (as would be expected if such symptoms are CCRs mediated by CCK_B activity).

Addiction Pharmacotherapy

Inasmuch as there is evidence that the CCRs elicited by predrug cues are mediated by a conditional increase in CCK_B activity (Kim & Siegel, 2001), the compensatory conditioning analysis of tolerance and withdrawal provides a rationale for the use of a CCK_B antagonist as a potential addiction treatment. Many other pharmacotherapies for addiction have been proposed, on the basis of alternative theoretical analyses of addiction, and some have achieved widespread acceptance. There now are a variety of drugs designed to decrease craving to modify the neurochemical bases of substance abuse. In addition, there are drug treatments that use agonists, others that use antagonists, and others that use mixed agonist–antagonists (for a review of addiction pharmacotherapy, see Gottschalk, Jacobsen, & Kosten, 1999). The use of a CCK_B antagonist is but one potential strategy designed to meet a pressing need in opioid addiction treatment: "The main challenge in the management of opioid addiction is to develop a pharmacotherapy to decrease the protracted opioid abstinence syndrome" (Lu et al., 2000, p. 832).

Summary and Conclusions

It has been known for a long time that the effects of a drug are importantly modulated by responses elicited by drug-paired cues. The finding has been reported by clinicians (e.g., Macnish, 1859), epidemiologists (e.g., Frykholm, 1979), and laboratory scientists (e.g., Deffner-Rappold, Azorlosa, & Baker, 1996). It features in narrative reports of addicts (e.g., Biernacki, 1986) and in novels describing opiate effects (see Siegel, 1983). The contribution of drug-anticipatory responses to drug effects is seen in many species, from snails (Kavaliers & Hirst, 1986) to humans (e.g., Remington, Roberts, & Glautier, 1997). These observations have led to the formulation of drug administration as a Pavlovian conditioning trial. Unconditional compensatory responses, elicited by pharmacological stimulation, come to be elicited by drug-paired cues. These cue-elicited CCRs mediate tolerance when the usual predrug cues are followed by the usual drug effect and are expressed as withdrawal symptoms when the usual predrug cues are not followed by the usual drug effect (see reviews by Siegel, 1999a; Siegel et al., 2000). Results of recent research concerning the interaction between pharmacology and conditioning have indicated that private interoceptive cues (e.g., DOCs, SACs, imagery, and moods), as well as public exteroceptive cues, may be associated with the drug effect and elicit CCRs.

The contribution of Pavlovian conditioning to phenomena of addiction provides a focus for appreciating the ways in which laboratory research (frequently conducted with nonhuman animals) and clinical observations are related. In this article we have discussed three areas of interest to both the experimenter and the clinician indicating this relationship: (a) drug overdose, (b) cue exposure therapy, and (c) pharmacological treatment of withdrawal symptoms.

Heroin overdose is a major complication of heroin addiction (Darke & Zador, 1996). In laboratory animals, in heroin addicts, and in patients receiving medically prescribed opiates, an overdose may result when the drug is administered in the absence of the usual predrug cues. In these circumstances, the CCRs that mediate tolerance are not expressed, and overdose may be conceptualized as a failure of tolerance to occur.

Whereas CCRs mediate tolerance when the drug is administered, their expression in the absence of the drug results in uncomfortable symptoms, craving, and an increase in the incentive value of the drug (Hutcheson, Everitt, Robbins, & Dickinson, 2001). Cue exposure therapy is an attempt to extinguish these CCRs. On the basis of results of laboratory research, the effectiveness of cue exposure therapy should be enhanced if the therapist recognizes (a) that interoceptive as well as exteroceptive cues may have become associated with the drug effect; (b) that spontaneous recovery may occur; (c) that renewal of conditional responding may occur when, following cue exposure in a particular context, the patient is confronted with predrug cues in a context other than that in which extinction occurred; and (d) that some predrug cues may function primarily as occasion setters rather than as CSs.

Cue exposure therapy is a behavioral treatment for the attenuation of the drug-compensatory responding. Results of recent research, with rats, suggest a neurochemical basis for such responding: "Conditional compensatory responding elicited by morphine-onset cues is mediated by a conditional enhancement in CCK activity" (Kim & Siegel, 2001, p. 708). Such findings provide a basis for a potential pharmacotherapy for opiate addiction—blocking the effect of such enhanced CCK activity with a CCK antagonist (see Lu et al., 2000).

We have summarized evidence that compensatory responses, unconditionally elicited by a drug, come to conditionally be elicited by a variety of cues paired with the drug, and we have discussed the clinical significance of such CCRs to addiction. It is not always the case, however, that pharmacological stimulation initiates compensatory responses. Depending on the mechanism of drug action, the UCRs to some drugs consist of responses that augment (rather than attenuate) the pharmacological UCS. Although the reasons why some UCRs elicit augmentative (rather than compensatory) responses is debatable (see Dworkin, 1993; Eikelboom & Stewart, 1982; Ramsay & Woods, 1997), such UCRs result in noncompensatory CRs; that is, cues associated with augmentative UCRs will come to elicit conditional augmentative responses (CARs), rather than CCRs. For example, following a series of amphetamine injections, amphetamine-associated cues elicit a CAR of amphetamine-like hyperactivity (e.g., Tilson & Rech, 1973). Although CCRs progressively decrease the drug effect over the course of repeated administrations, CARs progressively increase the drug effect over the course of successive administrations. Such enhancement is termed *reverse tolerance*, or *sensitization*, and CARs contribute to sensitization much as CCRs contribute to tolerance (e.g., Hinson & Poulos,1981; Siegel et al., 2000). Discussion of the contribution of CARs in general, or drug sensitization in particular, to drug addiction is beyond the scope of this review (but see Bardo & Bevins, 2000; Joseph, Young, & Gray, 1996; Robinson & Berridge, 2001; Siegel, 2002; Silverman & Bonate, 1997).

Both researchers and clinicians want to understand addiction and develop effective treatment strategies. Although drug addiction is a major health problem, it also is a fascinating phenomenon. Why do people self-administer fermented fruit, the products of intoxicating plants, or synthetic (and more potent) versions of such chemicals? "Seeking intoxication . . . is paradoxical. It seemingly defies the logic of natural selection" (Courtwright, 2001, p. 91). The paradox has captured the attention of researchers interested in the behavioral, sociological, evolutionary, neurochemical, and molecular–biological bases of addiction (see Siegel & Allan, 1998; Siegel et al., 2000). One would hope that this extensive analysis of addiction would translate into improved treatment outcomes. In this article, we have elaborated a single theoretical framework (Pavlovian conditioning of drug effects resulting in CCRs) and described how data and theory arising from research based on this analysis suggest procedures to decrease drug overdoses and improve cue exposure treatment outcome and to provide a rationale

for a potential pharmacotherapy for opiate addiction. Obviously, there are many ways in which the results of basic research concerning addiction may inform clinical practice (and vice versa). The purpose of this article was not to suggest that conditional compensatory responding is the sine qua non of addiction. In fact, research in this area comprises just a small proportion of addiction research. It does, however, provide an illustration of the ways in which results from even this limited area of research may be of value to clinicians.

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