LECTURE

Drug anticipation and drug addiction. The 1998 H. David Archibald Lecture*

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Abstract

Environmental cues associated with drug use become capable of eliciting withdrawal symptoms, craving and relapse to drug self-administration. The phenomenon, although noted almost 150 years ago, has repeatedly been confirmed in epidemiological and experimental studies. Drug tolerance, which is closely correlated with withdrawal symptoms and craving, is also modulated by drug-associated environmental cues. The contribution of predrug cues to withdrawal and tolerance is emphasized in a Pavlovian conditioning analysis of drug administration. Drug-induced disturbances are modulated by homeostatic responses elicited by pharmacological stimulation. According to the conditioning analysis, we learn to anticipate the drug effect; corrective responses (conditional compensatory responses) occur in the presence of situations and events that have been associated with the drug in the past. These conditional responses, seen in anticipation of drugs, importantly contribute to drug tolerance, failures of tolerance (enigmatic overdoses), and withdrawal symptoms. I review evidence indicating that a complete analysis of drug withdrawal and tolerance requires an appreciation of the contribution of Pavlovian conditioning.

Introduction

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. As Macnish stated over 140 years ago, in describing difficulties he encountered in treating alcoholics: "To remove the habit of drunkenness from any one in whom it has been long established, is a task of peculiar difficulty. We have not only to contend against the cravings of the body, but against those of the mind" (Macnich, 1859, p. 145).

Cravings of the mind

According to Macnich, "cravings of the mind" were elicited by cues that had become associated with the drug. For example, the drinker craves alcohol in the context of cues previously associated with alcohol:

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

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of taking his libations (Macnish, 1859, p. 151).

Macnish distinguished "cravings of the mind" from "cravings of the body". Others have distinguished "mental desires" from "physical desires", or "psychological craving" from "physiological craving". The similar terminologies describe a similar phenomenon—the role of environmental cues in relapse. In more recent times, many clinical, epidemiological and experimental reports have confirmed Macnish's observations.

Clinical reports
After the passage of the Harrison Narcotic Act in the United States in 1914, government clinics were established to treat addicts. According to the prevailing view, after the opiate addict had been detoxified in the clinic, he would be relieved of his addiction—he would be "cured". It soon became apparent that this was not the case. Lawrence Kolb was an Assistant Surgeon General of the United States Public Health Service and the first superintendent of the 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. The genesis of this desire is apparently wholly mental" (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. By arousing memory associations this unfavorable environment creates a craving that the unstable cured cases seldom resist for any length of time (Kolb, 1927, pp. 39–40).

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, e.g. returning to an old neighborhood following a prolonged period of incarceration and abstinence (e.g. O'Brien et al., 1976; Kissin, 1983), seeing actors seeming to inject heroin in a movie (Biernacki, 1986, p. 115), seeing the paraphernalia of addiction such as a syringe and tourniquet (e.g. Teasdale, 1973) or discussing drugs with others (e.g. Wikler, 1977).

Epidemiological reports
On the basis of such clinical observations, it might be expected that the likelihood of long-term abstinence should be enhanced if the addict moves away from an environment rich in drug-associated cues. Evidence in support of the salutary effect of protection from drug-associated cues is provided by follow-up studies of returning Vietnam veterans who were addicted to heroin while in Vietnam. A study of a sample of enlisted men departing Vietnam in September, 1971 indicated that approximately 20% of them were addicted to heroin while in Vietnam (Robins, Davis & Goodwin, 1974). Unlike most civilian addicts, following treatment these Vietnam addicts returned to an environment very different than that in which they used drugs. They also evidenced much less relapse than did civilian addicts. In one report, United States narcotic use by returned veterans addicted in Vietnam was compared to that seen in addicts of comparable age treated at the large federal facilities in Lexington, Kentucky and Fort Worth, Texas (Robins, Helzer & Davis, 1975). Those addicted in Vietnam (and returned to a very different environment) were much less likely to relapse than those addicted in the environment to which they subsequently returned—indeed, the veterans evidenced "rates of remission unheard of among narcotics addicts treated in the United States" (Robins et al., 1975, p. 958). Many of Robins' conclusions have been substantially confirmed in other follow-up studies of other populations of returned soldiers who were addicted in Vietnam (e.g. O'Brien et al., 1980).

In addition to the Vietnam veteran findings, there are other epidemiological reports indicating that environmental alteration favors long-term abstinence in treated addicts. Residence relocation has been associated with long-term, post-treatment abstinence in addict populations in Detroit, Michigan (Ross, 1973), San Antonio,
Texas (Maddux & Desmond, 1982) and Sweden (Frykholm, 1979).

Experimental studies
Clinical observations suggesting that drug-associated cues elicit withdrawal distress, and epidemiological evidence that removal of these cues promotes abstinence, are complemented by experimental findings. Results of experiments, both with non-human animals and humans, indicate that drug-associated cues contribute to withdrawal symptoms and relapse.

Experiments with non-human animals. Results of many experiments indicate that rats display more behavioral withdrawal symptoms in a drug-paired environment than in an alternative environment (e.g. Deffner-Rappold, Kelsey, Aranow & Matthews, 1990; Azorlosa & Baker, 1996). Drug-paired cues not only contribute 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 (e.g. Hinson et al., 1986), cocaine (Meil & See, 1996) and ethanol (e.g. Krank, 1989).

Experiments with humans. Several investigators (e.g. O'Brien et al., 1976) have demonstrated that former addicts display physiological signs of narcotic withdrawal when they perform the “cooking up” ritual while being monitored by a polygraph. Other investigators have reported that heroin addicts display craving and withdrawal symptoms when presented with a pictures containing drug-related cues (e.g. Sell Cowen & Robson, 1995; Sideroff & Jarvik, 1980). Similar findings have been reported with respect to other drugs. Thus, alcoholics display alcohol withdrawal symptoms and report craving for alcohol in the presence of alcohol-related cues (e.g. Staiger & White, 1991) and cigarette smokers (who are subsequently given the opportunity to smoke) display more nicotine withdrawal symptoms, cigarette craving and a shorter latency to smoke, following the presentation of cigarette-associated cues than following the presentation of alternative cues (e.g. Droungas et al., 1995).

Macnish’s (1859) observation that “cravings of the mind” are the major impediments to successful drug abuse treatment, and these cravings are often seen in the context of drug-associated stimuli.

A phenomenon closely correlated with drug craving and withdrawal symptoms is drug tolerance—a decreasing effect of a drug over the course of repeated administrations (e.g. see Peper et al., 1987; Koob et al., 1989). William Carpenter, a contemporary of Macnish, described the phenomenon of tolerance in drug-dependent people (Carpenter, 1855, p. 16); indeed, the phenomenon of tolerance probably was recognized in the 17th century (see Kalant, 1998). As noted by Poulos & Cappell (1991), “the fact that a strong relationship exists between the degree of tolerance and the intensity of withdrawal must be taken into consideration in evaluating the kind of basic mechanism involved” (p. 402). There is increasing evidence that the “basic mechanism” is Pavlovian conditioning. The conditioning analysis addresses both “cravings of the mind” and “cravings of the body” in a way that circumvents the dualism apparently inherent in the distinction. I will first summarize the contribution of conditioning to tolerance, and then the relationship between tolerance and withdrawal.

Pavlovian conditioning and drug tolerance
In the Pavlovian conditioning situation (Pavlov, 1927), a contingency is arranged between two stimuli; typically, one stimulus reliably predicts the occurrence of the second stimulus. Using the usual terminology, the second of these paired stimuli is termed the “unconditional stimulus” (UCS). The UCS, as the name implies, is selected because it elicits relevant activities from the outset (i.e. unconditionally), prior to any pairings. The stimulus signaling the presentation of the UCS is “neutral” (i.e. it elicits little relevant activity prior to its pairing with the UCS), and is termed the “conditional stimulus” (CS). The CS, as the name implies, becomes capable of eliciting new responses as a function of (i.e. conditional upon) its pairing with the UCS. Such responses elicited by the CS are termed “conditional responses” (CRs).

Events occurring during drug administration correspond to a Pavlovian conditioning trial. Cues accompanying the drug effect function as
conditional stimuli (CSs), and the direct drug effect constitutes the unconditional stimulus (UCS). Prior to any learning, this UCS elicits responses that compensate for drug-induced disturbances. These responses that compensate for the drug effect are “unconditional responses” (UCRs). After some pairings of the predrug CS and pharmacological UCS, the drug-compensatory responses are elicited as conditional responses (CRs). For example, about 60 years ago Subkow & Zilov reported that after injecting dogs with epinephrine (adrenaline) on a number of occasions, merely placing the dog in the injection stand and administering an inert substance produced bradycardia (compensatory to the tachycardic effect of the hormone): “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” (Subkow & Zilov, 1937, p. 295).

Subsequent research has demonstrated conditional compensatory responses with respect to many effects of a variety of drugs (see Siegel, 1991), including commonly abused drugs such as opiates (e.g. Hinson & Siegel, 1983; Grisel et al., 1994), ethanol (e.g. Siegel, 1987; Larson & Siegel, 1998) and caffeine (e.g. Andrews, Rozin et al., 1984; Blumenthal & Flaten, 1998). When the drug is administered in the context of the usual drug-administration cues, these CRs attenuate the drug effect and contribute to tolerance.

Evidence for the contribution of Pavlovian conditioning to tolerance
The original phenomenon that inspired development of the conditioning model was described in a number of experiments conducted by Clifford Mitchell and colleagues between 1969 and 1972, and has been termed the “Mitchell effect” (see review by Siegel, 1978) or the “situational-specificity of tolerance” (Siegel, 1976).

Situational-specificity of tolerance
In Mitchell’s experiments morphine was administered on several occasions, with the same environmental cues associated with each drug administration. Over the course of repeated administrations rats developed tolerance to the analgesic effect of the drug, but this tolerance was far more pronounced in the presence of cues previously paired with morphine than in the presence of alternative cues.

Many subsequent experiments have confirmed and extended Mitchell’s demonstration of the situational-specificity of tolerance. Situational-specificity of tolerance has been demonstrated in experiments that have explicitly paired cues with a drug effect (e.g. consistently injecting rats with morphine in a distinctive room; see Siegel, 1991), or that have used “opportunistic designs” that rely on the subjects’ extra-experimental conditioning histories. An example of an opportunistic design is that used by Remington, Roberts & Glautier (1997). One group of (human) subjects was given alcohol in a beverage typically associated with alcohol—beer. Subjects in another group consumed the same amount of alcohol in a novel liquid—a blue, peppermint-flavored beverage. Alcohol-induced impairment was less in the beer-drinkers than in the peppermint-drinkers.

Although situational-specificity of tolerance has been studied primarily with opiates and alcohol, the phenomenon is also seen with nicotine (e.g. Epstein, Caggiula & Stiller, 1989), naloxone (Goodison & Siegel, 1995b), benzodiazepines (reviewed by Siegel, 1986), pentobarbital (e.g. Cappell, Roach & Poulos, 1981), phencyclidine (Smith, 1991), immunoenhancing drugs (Dyck et al., 1987), cholecystokinin (Goodison & Siegel, 1995a), carisoprodol (Flaten et al., 1997) and haloperidol (Poulos & Hinson, 1982). It is seen in many species, from snails (Kavaliers & Hirst, 1986) to humans (e.g. Flaten et al., 1997).

The most dramatic demonstrations of the situational-specificity of tolerance concern concern tolerance to the lethal effects of drugs. Following a series of drug administrations, each in the context of the same cues, tolerance develops to the 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, including heroin (Siegel et al., 1982; Siegel, 1984, 1989), morphine (Siegel & Ellsworth, 1986), pentobarbital (Vila, 1989) and alcohol (e.g. Melchior, 1990; but see Tsibulsky & Amit, 1993).

Situational-specificity is expected on the basis of the conditioning analysis of tolerance. That is, drug-associated cues elicit the conditional
compensatory responses that attenuate the drug effect; thus tolerance is greater when tolerance is assessed in the presence of drug-associated cues than when it is assessed elsewhere. In addition, there are many other findings implicating Pavlovian conditioning in drug tolerance.

Parallels between conditioning and tolerance
If conditioning processes contribute to tolerance, it would be expected that non-pharmacological manipulations of the putative CS (cues present at the time of drug administration), known to affect the course of Pavlovian conditioning, should similarly affect the course of conditional compensatory response acquisition and thus tolerance. The results of many such manipulations have been assessed. Because much of these data are extensively reviewed elsewhere (e.g. Siegel, 1989, 1991; Ramsay & Woods, 1997; Siegel & Allan, 1998), they are only summarized briefly here.

Extinction of tolerance. The magnitude of established CRs is decreased by "extinction", i.e. repeated presentations of the CS without the UCS. Similarly, tolerance to a variety of effects of many drugs is attenuated by repeated presentations of predrug cues without the drug. Such extinction has been demonstrated with respect to tolerance to both the lethal (Siegel, Hinson & Krank, 1979) and analgesic (e.g. MacRae and Siegel, 1987) effects of morphine. Furthermore, tolerance to a variety of effects of ethanol, amphetamine, midazolam (a short-acting benzodiazepine), and the synthetic polynucleotide, Poly 1:1, can also be extinguished (see reviews by Siegel, 1989, 1991).

External inhibition of tolerance. Pavlov (1927) noted that presentation of a novel, extraneous stimulus disrupts the elicitation of established CRs. Such "external inhibition" of conditional responding has also been shown to eliminate tolerance to the analgesic effect of morphine (Poulos, Hunt & Cappell, 1988) and the hypothermic (Siegel & Sdao-Jarvie, 1986) and ataxic (Siegel & Larson, 1996; Larson & Siegel, 1998) effects of ethanol. That is, drug experienced rats that normally display tolerance fail to do so when presented with an arbitrary novel stimulus.

Retardation of the development of tolerance. One technique for attenuating the development of a CS–UCS association is to present the CS-alone prior to pairing it with the UCS (the so-called CS-pre-exposure, or "latent inhibition" effect, see Mackintosh, 1974). If Pavlovian conditioning contributes to tolerance, it would be expected that subjects with extensive experience with drug administration cues prior to the time that these cues are paired with the drug should be relatively retarded in the acquisition of tolerance (compared to rats with minimal preexposure to these cues), despite the fact that the groups do not differ with respect to their histories of drug administration. Such an effect of CS pre-exposure has been demonstrated with respect to tolerance to the analgesic effect of morphine, the immunostimulatory effect of Poly:IC and the anorectic effect of cholecystokinin (see Siegel, 1989; Goodison & Siegel, 1995a).

Another procedure for attenuating the development of a CS–UCS association is partial (rather than continuous) reinforcement. That is, if only a portion of the presentations of the CS are paired with the UCS, CR acquisition is retarded (compared to the situation in which all presentations of the CS are paired with the UCS; see Mackintosh, 1974). On the basis of a conditioning analysis of tolerance, it would be expected that such partial reinforcement would retard the development of tolerance; a group in which only a portion of the presentation of drug administration cues are followed by the drug (i.e. a partial reinforcement group) should be slower to acquire tolerance than a group that never has exposure to drug-predictive cues without actually receiving the drug (i.e. a continuous reinforcement group), even when the two groups are equated with respect to all pharmacological parameters. Such findings have been reported with respect to tolerance to several effects of morphine (see Siegel, 1989, 1991).

Glucose administration. In recent years there has been increasing evidence that simple glycemic manipulations, applied immediately after a CS–UCS pairing, modulate learning. For example, injection of glucose after a trial facilitates learning in mice and rats and oral consumption of glucose facilitates learning in humans. The post-training treatments presumably modulate memory storage processes because the effect of glucose on memory is
time-dependent. That is, the effects are maximal if the glycemic manipulations occur immediately after a trial and are minimal to non-existent if the manipulations are delayed, e.g. for 1 hour (for reviews of glycemic manipulations and conditioning see Manning et al., 1997; Okaichi & Okaichi, 1997).

If drug tolerance is due, in part, to an association between drug administration cues and the systemic effect of the drug, the formation of this association, and hence the development of tolerance, should be enhanced in subjects receiving glucose shortly after each drug administration. Consistent with this prediction, we recently demonstrated that the development of tolerance to both the analgesic effect of morphine, and the ataxic effect of ethanol, is enhanced if each administration of the drug is followed by an injection of glucose (120 mg/kg). However, if the injection of glucose is delayed, the glucose does not facilitate the development of tolerance (Siegel, 1999).

Other evidence. In addition to the research described above, results of many other experiments have provided evidence that drug-anticipatory responses contribute to tolerance (see Siegel, 1989, 1991). For example, tolerance to morphine (Siegel, Hinson & Krank, 1981; Fanselow & German, 1982), pentobarbital (Hinson & Siegel, 1986) and scopolamine (Vila & Miranda, 1994) is subject to inhibitory learning. Tolerance can also be manipulated by compound conditioning phenomena, such as “blocking” (Dafters, Hetherington & McCartney, 1983) and “overshadowing” (e.g. Walter & Riccio, 1983).

Pavlovian conditioning and withdrawal symptoms
As noted previously, drug tolerance and withdrawal symptoms are highly correlated. 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 conditioning analysis the relationship between tolerance and withdrawal, and the drug-compensatory characteristics of withdrawal symptoms, are attributable to the fact they are both manifestations of the same drug-compensatory CR.

When the drug is administered in the context of the usual drug-administration cues, compensatory CRs 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 CRs achieve full expression because they do not interact with the drug effect. Such pharmacological CRs, displayed in such circumstances, are termed “withdrawal symptoms”.

There is much experimental (both human and non-human animal) and epidemiological evidence that so-called “withdrawal symptoms”, seen long after the last exposure to a drug, are especially pronounced in the presence of drug-related cues (e.g. Kelsey et al., 1990; Deffenbacher et al., 1996); 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). The powerful effect of drug-related cues is also apparent in many clinical reports (see Siegel, 1988a), e.g.:

After being detoxified and having served their sentence at the U.S. Public Health Service Hospital, the postaddict felt fine and had no craving for heroin or morphine but just before his release, or on his way home, or after arriving in his drug-ridden environment, he felt sick, craved a fix, and then hustled to obtain it. Some postaddicts described the sickness in more detail: running nose, watery eyes, sweating, chills, nausea and vomiting—“like the flu, doc.” One postaddict, a physician, remarked that the sickness resembled heroin abstinence phenomena, but he dismissed that interpretation as preposterous (Wilder, 1977, p. 35).

The symptoms, apparently elicited by stimuli associated with opiates, appear to be opiate-opponent responses. The “running nose, watering eyes” are opposite in direction to the secretory-drying effects of opiates. The “sweating” is evidence of hyperthermia that is opposite to the hypothermic effect of opiates. The “chills” are evidence of peripheral constriction, opposite to the peripheral vasodilatory effects of opiates. The “nausea and vomiting” are evidence of increased peristaltic activity, opposite to opiate-induced decrease in intestinal motility.
On the basis of the conditioning analysis "cravings of the mind" (Macnish, 1859), or "mental desires" for drugs (Kolb, 1927), or "psychological craving" (Kissin, 1983), are all different terms for the conditional responding seen when the usual predrug cues are not followed by the usual pharmacological consequences. These cues elicit conditional compensatory responses. The CRs include the readily observable drug-opposite responses that are interpreted as withdrawal symptoms, and the less-readily observable neurochemical responses that are interpreted as craving.

Cues for drugs
Although studies of the associative basis of drug effects typically have manipulated environmental cues (e.g. the room where the drug is administered), there is evidence that a variety of different stimuli may become associated with a drug and control the display of tolerance. Thus, distinctive ambient temperatures (Kavaliers & Hirst, 1986) or magnetic fields (Kavaliers & Ossenkopp, 1985) may, after being paired with morphine administration, control the display of morphine tolerance. Two types of cues that recently have been studied in our laboratory are pharmacological cues and cues incidental to self-administration.

Pharmacological cues for drugs
There have been various types of experiments concerning pharmacological cues for drugs. In some experiments ("intra-drug conditioning"), a given drug repeatedly is administered before a second, different drug. Other experiments have evaluated the ability of a drug to serve as a cue for itself. In such "intra-drug conditioning" studies, a small dose of a drug is administered prior to a larger dose of the same drug.

Inter-drug associations
There is evidence that inter-drug associations may importantly contribute to tolerance (see Krank & Bennett 1987). For example, Taukulis (1986) described the results of an experiment in which atropine sulfate was routinely injected prior to pentobarbital. Tolerance to the hypothermic effect of the barbiturate was much more pronounced when it was preceded by atropine than when it was presented without the signal provided by the anticholinergic.

As discussed by Siegel (1988b), such pharmacological associations may be manifest as "state-dependent" learning of tolerance. As elaborated by MacQueen & Siegel (1989), inter-drug associations, and the contribution of such associations to the display of tolerance, may be important considerations in treatment schedules that routinely involve sequential presentations of different drugs (e.g. chemotherapy for cancer).

Intra-drug associations
There are reports that a small dose of a drug may serve as a CS, signaling a subsequent, larger dose of the drug (see Greeley & Ryan, 1995). Greeley et al. (1984) provided the first demonstration of such an intra-drug association. In this Greeley et al. (1984) 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 an ethanol-compensatory thermic CR; paired rats, but not unpaired rats, evidenced a hyperthermic CR (opposite to the hypothermic effect of the drug) in response to the low dose of ethanol. There is also 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).

Several investigators have suggested that intra-drug associations may play a hitherto unappreciated role in the effects of repeated drug administrations (Greeley et al., 1984; Cepeda-Benito & Short, 1997). That is, a gradual increase in systemic concentration is an inevitable consequence of many drug administration procedures. Within each administration, drug onset cues reliably precede the later and larger drug effect, thus is the potential for pharmacological associations whenever a drug is administered (see King, Bouton & Musty, 1987; Mackintosh, 1987). Such associations, formed within
each administration, may be termed “intra-
administration” associations.

**Intra-administration associations**

According to the conditioning analysis, signals for the drug elicit conditional compensatory responses. If signaling is inherent within an administration, injection of a smaller dose of the drug to a subject with a history of injections of a larger dose of the drug might be expected to elicit such a CR. That is, the smaller dose should reproduce the early effect of the larger doses previously administered. Such a finding was reported by Krank (1987). Following 10 daily injections of 5 mg/kg morphine, 1 mg/kg elicited hyperalgesia.

More recently, Mucha, Kalant & Birbaumer (1996) also provided evidence that intra-administration associations contribute to tolerance. They evaluated the analgesic effect of morphine, administered either intravenously or intraperitoneally, on a final test session. Prior to the test, some rats received extensive experience with the drug administered by one of the two parenteral routes. Tolerance was maximal when the route on the test corresponded with the route used for pre-test administrations. Mucha et al. (1996) suggested that their findings were “analogous to the specificity of environmental factors of a tolerance treatment situation reported in the literature on classically conditioned tolerance” (p. 371), that is, “interoceptive stimuli produced by morphine acting through a particular route” (p. 371), in common with environmental stimuli, may act as CSs in the control of tolerance.

The fact that an alteration in the route of administration may attenuate tolerance (because such alteration involves a change in pharmacological signal) has important clinical implications. Johnson & Faull (1997) described the case of a patient that was tolerant to the analgesic effect of orally administered morphine. When narcotic analgesia subsequently was induced with a mu-antagonist administered by a different route—transdermal fentanyl—the expected cross-tolerance was not obtained. Rather, the patient suffered opioid toxicity.

**Self-administration and drug effects**

Illicit drug use consists of drug self-administration, yet much psychopharmacological research involves passive administration; the experimenter, not the subject, controls the administration. Although expressed over 30 years ago, many investigators would agree with Nichols’ (1965) assertion that “the physiological effect is the same whether an organism passively receives morphine or actively takes it” (p. 80). However, there is evidence that there are differences in the effects of self-administered and passively-received drugs. Of special relevance are reports that the self-administration enhances both tolerance and withdrawal.

**Effect of self-administration on tolerance**

An especially elegant procedure for 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 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 animals (i.e., tolerance is less pronounced). For example, nicotine does not affect plasma epinephrine and norepinephrine levels in SA rats, but Y rats display markedly elevated levels of these adrenal hormones (Donny et al, 1995). Dworkin, Mirkis & Smith (1995) reported that cocaine-induced mortality is significantly lower in SA than in Y rats.

Mello & 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 than following the programmed condition.

**Effect of self-administration on withdrawal symptoms**

In Mello & Mendelson’s (1970) study they evaluated withdrawal symptoms as well as tolerance. They reported that withdrawal effects were greater in the spontaneous condition (when subjects could ingest alcohol when they wished) than in the programmed condition (when sub-
jects could ingest alcohol only during experimenter-determined intervals).

We (MacRae & Siegel, 1997) reported recently results of an experiment in which rats assigned to a self-administration-of-morphine group (SA-M) could press a lever in an operant chamber to deliver an intravenous infusion of morphine to themselves and to a yoked morphine (Y-M) rat, and an infusion of Ringer's solution to another yoked rat (Y-R). Although rats assigned to SA-M and Y-M groups received the same drug doses at the same time, withdrawal symptoms were much more pronounced in SA-M rats.

Summary of the effects of the self-administration contingency
The effects of drugs are different if they are self-administered than if they are passively received. The effect of the drug is less (i.e. tolerance is more pronounced) and withdrawal symptoms are greater, in self-administering subjects. The results suggest that self-administration may provide internal cues for a drug that function like external signals. That is, interoceptive cues accompanying self-administration, in common with external signals, may elicit anticipatory homeostatic responses. Thus, a variety of cues may become associated with a drug effect, and contribute to the display of tolerance and withdrawal symptoms: environmental cues (e.g. diffuse contextual cues, such as the physical environment of drug administration), pharmacological cues (e.g. early, drug onset cues signaling the later, larger effect within a single administration) and interoceptive cues accompanying self administration.

Conclusions
It has become increasingly apparent that learning contributes to many effects of drugs. The contribution of learning to tolerance is emphasized in the Pavlovian conditioning interpretation of drug administration that emphasizes the development of conditional compensatory responses. There are associative interpretations of tolerance that do not emphasize the contribution of such CRs. The most prominent of these is Baker & Tiffany's (1985) "habitation model". Several investigators have critically evaluated the various models, and discussed the advantages of the conditional compensatory response analysis (e.g. Cepeda-Benito & Siegel, 1989; Poulos & Cappell, 1991; Tiffany, 1996).

Pavlovian conditioning in general, and conditioning-mediated tolerance in particular, serve an important homeostatic function. We have evolved the proclivity to make CRs because it enhances reproductive success (Dworkin, 1993; Siegel & Allan, 1998). For example, as a result of our tendency to associate paired events we can tolerate a high dose of a drug that otherwise would be fatal (e.g. Siegel et al., 1982; Vila, 1989). However, the CRs that mediate such tolerance also are expressed as "withdrawal symptoms" if drug-associated cues are not followed by the usual drug effect. Thus, even after a prolonged drug-free period, reexposure to drug-paired cues may—to use Macnab's (1859, p. 145) terminology—elicit "cravings of the mind", making the treatment of addiction "a task of peculiar difficulty".

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