Drug Anticipation and the Treatment of Dependence

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INTRODUCTION

It has long been recognized that the process of "detoxification" and the crisis of withdrawal are not the major impediments to effective drug abuse treatment. Rather, the major problem is relapse following the completion of the withdrawal crisis. The high relapse rate following apparently "successful" treatment (or prolonged abstinence due to incarceration) has been documented in many studies (Siegel 1983), and the typical scenario has been described by several investigators. For example:

> The patient was a 28-year-old man with a 10-year history of narcotic addiction. He was married and the father of two children. He reported that, while addicted, he was arrested and incarcerated for 6 months. He reported experiencing severe withdrawal during the first 4 or 5 days in custody, but later, he began to feel well. He gained weight, felt like a new man, and decided that he was finished with drugs. He thought about his children and looked forward to returning to his job. On the way home after release from prison, he began thinking of drugs and feeling nauseated. As the subway approached his stop, he began sweating, tearing from his eyes, and gagging. This was an area where he had frequently experienced narcotic withdrawal symptoms while trying to acquire drugs. As he got off the subway, he vomited onto the tracks. He soon bought drugs, and was relieved. The following day he again experienced craving and withdrawal symptoms in his neighborhood, and he again relieved them by injecting

heroin. The cycle repeated itself over the next few days and soon he became readdicted. (O'Brien 1976, p. 533)

PREDRUG CUES AND RELAPSE

Results of recent research indicate that the occurrence of withdrawal distress and relapse, long after detoxification, are not readily predictable from an individual's drug history (e.g., length of addiction, type, and purity of drugs used). Rather, understanding the phenomenon requires an appreciation of drug-predictive environmental signals, as well as pharmacological considerations. This is apparent in both the experimental literature (with animals), and the clinical and epidemiological literature (with humans).

ENVIRONMENTAL CUES AND RELAPSE

Animal Studies

An early demonstration that environmental cues play an important role in relapse was provided by Thompson and Ostlund (1965). In the first phase of their experiment (addiction phase), rats were orally addicted to morphine by having it as their only available fluid for 60 days. They were then withdrawn from morphine by replacing the opiate solution with water for 30 days. Finally, during the readdiction phase of the experiment, the rats were again permitted to drink the morphine solution. For half the rats, readdiction occurred in the same environment as that used during the addiction phase. For the remaining rats, readdiction took place in a very different environment. During readdiction, rats displayed greater avidity for morphine solution when it was presented in the environment where original addiction had occurred than when readdiction occurred in an alternative environment.

More recently, Hinson et al. (1986) confirmed and extended the results of Thompson and Ostlund (1965). In the Hinson et al. (1986) experiment, rats received a series of morphine injections in one environment (the DR, or "distinctive room" environment), and also a series of saline injections in another environment (the HR, or "home room" environment). When subsequently given the opportunity to consume morphine solution in both environments, the rats drank significantly more morphine solution in the morphine-associated DR environment than in the saline-associated HR environment.

Anecdotal evidence of the contribution of environmental cues to relapse is provided by Ternes' (1977) description of the behavior of monkeys that were repeatedly injected with morphine in the presence of an arbitrary auditory cue--tape-recorded music. This music became capable of eliciting withdrawal symptoms and relapse in these monkeys after a considerable period of abstinence:

> After the animal had been weaned from the drug and maintained drug-free for several months, the experimenter again played the tape-recorded music and the animal showed the following signs: he became restless, had piloerection, yawned, became diuretic, showed rhinorrhea, and again sought out the drug injection. (Ternes 1977, pp. 167-168)

Human Studies

There is considerable evidence that relapse in human addicts, like relapse in experimentally addicted animals, is influenced by drug-associated cues. As indicated in the above quote from O'Brien (1976), the physical environment in which drugs had previously been used frequently elicit withdrawal symptoms in the individual who had been drug free for a considerable period of time. Often the association between environmental cues and relapse is noted, but the role of the environment is minimized. Wikler has described a typical instance of this incognizance:

> . . . 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. (Wikler 1977, p. 35)

Not only is relapse in humans related to the presence of drug-associated cues, but successful abstinence is related to the absence of these cues. Evidence in support of the salutary effect of protection

from drug-associated cues is provided by followup studies of returning Vietnam veterans who were addicted to heroin while in Vietnam:

> During the summer and fall of 1971, drug use by United States servicemen in Vietnam had, by all estimates, reached epidemic proportions. (Robins 1973, p. 1)

> The high rates of narcotic use and addiction there were truly unlike anything prior in the American experience. (Robins et al. 1975, p. 960)

A study of a sample of enlisted men departing Vietnam in September 1971 indicated that approximately 20 percent were addicted to heroin while in Vietnam (Robins et al. 1974). Although known heroin users were treated before release, a substantial social problem was anticipated. Since there is a very high relapse rate following all known forms of treatment, it was expected that a new, large population of relapsing heroin addicts would substantially add to the indigenous civilian addict population:

> This will obviously lead to crime and other problems with law enforcement when he (the returning Vietnam heroin user) brings his addiction home . . .. They will be unable to cut off this drug use. (Senate Testimony 1972, p. 481)

Unlike most civilian addicts, following treatment, these Vietnam addicts returned to an environment very different from that in which they used drugs. They also evidenced much less relapse than civilian addicts. In one report, narcotic use in the United States by returned veterans addicted in Vietnam was compared to that seen in addicts of comparable age treated at the large Federal facilities in Lexington, KY, and Fort Worth, TX (Robins et al. 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 a more recent followup study of a different population of returned soldiers who were addicted in Vietnam (O'Brien et al. 1980).

In addition to the Vietnam veteran findings, other data suggest that alteration in the addict's environment promotes long-lasting abstinence. Ross studied 109 opiate addicts in Detroit and noted that

physical relocation was significantly associated with abstinence from illicit drugs:

> It appears that for a large group of a treatment population (almost 40%) cessation of illegal drug use meant moving away physically from an area of high drug use. (Ross 1973, p. 561)

Frykholm evaluated 58 intravenous drug users in Sweden who had been abstinent for 3 years or more. Residence relocation was considered a prime factor in achieving this abstinence:

> When asked what they had done to change their lives in order to give up drugs, a majority of the respondents answered that they had felt it necessary to change residence. (Frykholm 1979, p. 376)

More recently, Maddux and Desmond (1982) studied patterns of abstinence in heroin addicts in San Antonio, TX. They found that frequency of 1-year abstinence was three times higher in relocated respondents than in respondents staying in San Antonio. These and many other reports (see review by Maddux and Desmond (1982)) all indicate that environmental alteration favors long-term drug abstinence.

ENVIRONMENTAL CUES, DRUG TOLERANCE, AND DRUG DEPENDENCE

Findings that environmental cues are important contributors to relapse are accommodated in a model of drug tolerance and dependence that emphasizes learning principles. The model will first be discussed with respect to tolerance, and then the relevance of this analysis of tolerance to dependence will be discussed.

Environmental Specificity of Tolerance

It has become increasingly apparent that the pharmacokinetic or pharmacodynamic principles usually used to explain tolerance are insufficient. Rather, a complete account of tolerance requires an appreciation of environmental influences.

The importance of environmental cues in tolerance is illustrated by the results of a number of studies that have demonstrated that

tolerance is not the inevitable result of repeated drug administration. Rather, the drug-experienced organism may or may not display the hyporesponsivity to the drug that characterizes tolerance, depending on whether the drug is administered in the usual drug administration environment or an alternative environment.

Early studies of the environmental specificity of tolerance evaluated tolerance to the analgesic effect of morphine. A number of experiments by Mitchell and colleagues (e.g., Adams et al. 1969) demonstrated that rats displayed the expected analgesia-tolerant response to the last of a series of morphine injections only if the final injection occurred in the same environment as the prior injections in the series. Results of many subsequent experiments have confirmed and extended Mitchell's observations, in several species (including humans), using a range of morphine doses, a variety of analgesiometric procedures, and various modifications of Mitchell's original design (Siegel and MacRae 1984). Additional research has indicated the environmental specificity of tolerance to the thermic and locomotor effects of morphine, and to the lethal effect of diacetylmorphine hydrochloride (heroin) (Siegel and MacRae 1984). The environmental specificity of tolerance has also been demonstrated with many nonopiate drugs: ethanol, pentobarbital, amphetamine, scopolamine, haloperidol, and a variety of benzodiazepines (see reviews by Siegel (1983), Siegel (1986), and Siegel (1987)). Such findings have inspired analyses of tolerance that emphasize learning principles.

Tolerance and Learning

Several investigators have indicated parallels between tolerance and learning. Both processes frequently exhibit great retention, both are disrupted by electroconvulsive shock and frontal cortical stimulation, both are retarded by inhibitors of protein synthesis, and both are facilitated by antagonists of these metabolic inhibitors (Siegel 1983). Although there are several ways in which learning may contribute to tolerance, a clearly articulated model of tolerance that emphasizes the contribution of learning is based on Pavlovian conditioning principles.

The Pavlovian Conditioning Situation. In the Pavlovian conditioning situation, 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 signalling 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. In Pavlov's (1927) well-known conditioning research, the CS was (for example) a bell, and the UCS was food (which elicited a conveniently monitored salivary response).

Conditioning of Drug Responses. Pavlov (1927) suggested that the usual drug administration situation corresponded to the conditioning paradigm: environmental cues uniquely present at the time of drug administration constitute the CS (e.g., location of injection, or drug administration rituals), with the actual systemic effect of the drug constituting the UCS. Subsequent to Pavlov's original demonstrations, there have been many studies concerned with the conditioning of drug effects (Siegel 1985).

Compensatory Pharmacological Conditional Responses (CRs). The development of an association between the environmental CS and the pharmacological UCS may be seen by administering an inert substance in the presence of the usual drug-signalling cues. The nature of the pharmacological CR observed in these circumstances depends very much on the nature and mechanism of the drug effect (Eikelboom and Stewart 1982). For many effects of many drugs, the CR is an anticipatory compensation: drug-associated environmental cues elicit responses that are opposite to the drug effect. For example, the subject with a history of ethanol administration (and its hypothermic consequences) displays a CR of hyperthermia (Siegel 1987). Similar drug compensatory CRs have been reported with respect to a variety of effects of morphine (analgesia, temperature, locomotor activity, and gastrointestinal transit time), as well as many other drugs (Siegel 1983; Siegel and MacRae 1984).

Although most studies of pharmacological conditioning have been conducted with animals, there is evidence that humans display drug-compensatory CRs too. Most of this human research has been conducted with alcohol, and evidence of alcohol-compensatory conditional responding has been reported by several investigators (see review by Siegel (1987)). A compensatory CR has also been reported with respect to caffeine in humans (Rozin et al. 1984).

Compensatory Pharmacological CRs and Tolerance. As indicated above, organisms with a history of drug administration frequently evidence CRs opposite to the drug effect, as revealed by presentation of the usual predrug cues without the usual pharmacological consequences. When these predrug cues are followed by the usual pharmacological consequences, the compensatory CR would be expected to attenuate the drug effect. As the association between the environmental CS and the pharmacological UCS is strengthened by repeated pairings, the effect of the drug becomes increasingly attenuated. Such a progressively diminished response to a drug over the course of repeated administrations defines tolerance.

Comparison With Nonassociative Interpretations of Tolerance. It should be noted that the analysis of tolerance that emphasizes the importance of environment-drug associations is not an alternative to traditional interpretations. Rather, the conditioning model is complementary to views of tolerance that do not acknowledge a role for learning. Many such nonassociative analyses of tolerance emphasize the role of drug-elicited homeostatic corrections that restore pharmacologically induced physiological disturbances to normal levels. Several investigators have indicated that the potential adaptive advantage of these homeostatic corrections actually antedate the pharmacological insult (e.g., Siegel et al. 1987; Wikler 1973). Pavlov was certainly aware of the importance of such anticipatory responding:

> It is pretty evident that under natural conditions the normal animal must respond not only to stimuli, which themselves bring immediate benefit or harm, but also to other physical or chemical agencies—waves of light and the like—which in themselves only signal the approach of these stimuli. (Pavlov 1927, p. 14)

Pavlovian conditioning provides a mechanism for such anticipatory responding. On the basis of a conditioning model, the systemic alterations that mediate tolerance occur not only in response to pharmacological stimulation, but may also occur in response to reliable environmental signals of this stimulation.

Evidence for the Conditioning Model of Tolerance

A considerable amount of evidence has been published that supports the conditioning analysis of tolerance. Much of these findings have

been reviewed elsewhere (Siegel 1983; Siegel 1986; Siegel 1987) and are only briefly summarized here.

Environmental Specificity of Tolerance. The observation that there often is pronounced environmental specificity to the display of tolerance is readily interpretable by an analysis of tolerance that incorporates Pavlovian conditioning principles. If the repeatedly drugged organism receives the drug in the context of the usual predrug cues, the compensatory CR partially cancels the drug effect; thus, tolerance is observed. On the other hand, if this drug-experienced organism receives the drug in the context of cues not previously associated with the drug, there would be no pharmacological CR cancelling the drug effect, and the tolerance attributable to such a CR would not be observed. An especially dramatic demonstration of the environmental specificity of tolerance concerns tolerance to the lethal effect of opiates.

Environmental Specificity of Tolerance and Opiate Overdose. The conditioning model of tolerance has been elaborated to account for some instances of overdose in human heroin addicts (S. Siegel 1984; Siegel and Ellsworth 1986; Siegel et al. 1982). Although deaths from overdose are prevalent, the mechanisms of many of these deaths are far from clear. Some deaths result from pharmacological overdose (Huber 1974), but often victims die following doses that would not be expected to be fatal for these drug-experienced, and presumably drug-tolerant, individuals (see reviews by Brecher (1972) and Reed (1980)). Indeed, the victims sometimes die following self-administration of a heroin dose that was well tolerated the previous day (Government of Canada 1973). Some fatalities may result from a synergism between the opiate and other drugs concomitantly administered or from adulterants (especially quinine) in the illicit heroin, but many deaths do not result from such drug interactions (Brecher 1972; Government of Canada 1973; Reed 1980). Thus, it has been suggested that "the term 'overdose' has served to indicate lack of understanding of the true mechanism of death in fatalities directly related to opiate abuse" (Greene et al. 1974, p. 175). Some instances of these enigmatic failures of tolerance may be interpretable by the conditioning analysis. According to this analysis, an organism is at risk for overdose when the drug is administered in an environment that has not previously been paired extensively with the drug (and thus does not elicit the compensatory pharmacological CR that attenuates the effect of the drug).

Results of an experiment by Siegel et al. (1982) support the Pavlovian conditioning interpretation of heroin overdose. Rats injected with high doses of heroin in the same environment as that previously associated with the drug were more likely to survive than rats with the identical pharmacological history receiving the final drug administration in an alternative environment.

The role of predrug cues in overdose has also been evaluated by interviewing drug addicts who have survived a heroin overdose. Findings obtained in such retrospective studies are mixed: S. Siegel (1984) reported that novel predrug cues typically accompany such overdoses, but Neumann and Ellis (1986) reported that there is typically nothing unusual about the predrug cues on the occasion of the overdose.

A recent report suggests that Pavlovian conditioning may be relevant to some instances of death from overdose of medically prescribed opiates (Siegel and Ellsworth 1986). A single case is described--a patient receiving morphine for relief of pain from pancreatic cancer. The circumstances of this patient's death from apparent overdose of licitly used morphine are readily interpretable by the Pavlovian conditioning account of tolerance: on the occasion of his final morphine administration, he was in an environment very different from that associated with prior morphine administrations.

Extinction of Tolerance. Following CR acquisition, presentation of the CS without the UCS causes a decrease in the CR strength, i.e., "extinction." If drug tolerance is partially mediated by drug-compensatory CRs, extinction of these CRs should attenuate tolerance. That is, established tolerance should be reversed by placebo administrations. Such extinction has been demonstrated with respect to tolerance to both the analgesic (e.g., Siegel et al. 1980) and lethal (Siegel et al. 1979) effects of morphine, as well as a variety of effects of amphetamine, midazolam (a short-acting benzodiazepine), and the synthetic polynucleotide Poly I:C (see reviews by Siegel (1986) and Siegel (1987)).

Another procedure for extinguishing a CS-UCS association is to continue to present both the CS and the UCS, but in an unpaired manner (Mackintosh 1974). That is, the subject receives both conditioning stimuli, but the CS does not signal the UCS. Rather, the UCS is presented only during intervals between CS presentations. It has been reported that such unpaired presentations attenuate tolerance to the behaviorally sedating effect of morphine in rats

(Fanselow and German 1982). In this experiment, morphine was administered on a number of occasions in the presence of a distinctive environmental cue. When tolerance was established, continued presentation of the drug and cue, but in an explicitly unpaired manner, eliminated tolerance. That is (as expected on the basis of a conditioning analysis of tolerance), despite the fact that morphine-tolerant rats continue to receive morphine, tolerance is reversed if the continued morphine administrations are unpaired with a cue that was initially paired with the drug. Such a finding would appear uninterpretable by any view of tolerance that does not acknowledge the contribution of learning.

Retardation of Tolerance. A variety of nonpharmacological procedures retard the acquisition of CRs. According to the conditioning interpretation of tolerance, similar procedures should retard the development of tolerance. One technique for attenuating the strength of an association is to repeatedly present the CS alone prior to pairing it with the UCS. The deleterious effect of such preconditioning exposure to the CS has been termed "latent inhibition" (Mackintosh 1974). If drug tolerance is mediated, at least in part, by an association between predrug cues and the drug, it would be expected that rats with extensive experience with administration cues prior to the pairing of these cues 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 latent inhibition of tolerance has been reported with respect to the analgesic effect of morphine (Siegel 1977; Tiffany and Baker 1981) and the immunostimulatory effect of Poly I:C (Dyck et al. 1986).

Another procedure for decreasing the strength of a CS-UCS association is partial (as compared to consistent) reinforcement. That is, if only a portion of the presentations of the CS is 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)). This literature has clear implications for a Pavlovian conditioning account of morphine tolerance: a group in which only a portion of the presentations of the drug administration cues is actually followed by morphine (i.e., a partial reinforcement group) should be slower to acquire tolerance than a group that never has exposure to environmental cues signalling the drug without actually receiving it (i.e., a continuous reinforcement group), even when the two groups are equal with respect to all pharmacological parameters.

Such a finding has been reported with respect to tolerance to the analgesic, thermic, and anorexigenic effects of morphine (Krank et al. 1984; Siegel 1977; Siegel 1978).

Other Evidence for the Conditioning Analysis of Tolerance. In addition to the research summarized above, results of many other experiments have provided further evidence that Pavlovian conditioning contributes to tolerance to many drugs. These experiments demonstrate that nonpharmacological manipulations of predrug environmental cues affect both CR acquisition and tolerance in a similar manner. For example, tolerance to both morphine (Fanselow and German 1982; Siegel et al. 1981) and pentobarbital (Hinson and Siegel 1986) is subject to inhibitory learning. Furthermore, morphine tolerance is subject to sensory preconditioning (Dafters et al. 1983) and "external inhibition" (Siegel and Sdao-Jarvie 1986), and can be manipulated by compound conditioning phenomena such as "blocking" (Dafters et al. 1983) and "overshadowing" (Dafters and Bach 1985; Walter and Riccio 1983). A full discussion of these findings is beyond the scope of this review, but it should be emphasized that a variety of additional experiments support the conditioning analysis of tolerance.

Pavlovian Conditioning and Withdrawal Symptoms

According to most current views, tolerance and withdrawal symptoms are both manifestations of homeostatic mechanisms that correct for pharmacological disturbances: the feedback mechanisms that mediate tolerance when the drug is administered are expressed as withdrawal symptoms when the drug is not administered (Siegel et al. 1987). It has become increasingly apparent that, just as feedforward, or anticipation (as well as feedback), contributes to tolerance, it also contributes to withdrawal symptoms. Thus, some "withdrawal symptoms" are due not to alterations in feedback mechanisms induced by past drug administrations, but rather to the anticipation of the next drug administration. That is, some drug "withdrawal symptoms" are, more accurately, drug "preparation symptoms"; they result from drug-compensatory CRs.

In discussing the role of compensatory CRs in so-called 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 (Hinson and Siegel 1982). In the latter case, it is likely

that it is the anticipation of the drug, rather than the drug itself, that is responsible for 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 and Siegel 1982, p. 499)

Actually, the role of environmental cues in the display of withdrawal symptoms and relapse has been known for a long time. The following observation is from *The Anatomy of Drunkenness*, written in 1859:

> 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. (Macnish 1859, p. 151)

More recently, many other investigators have noted that environmental cues affect the display of the symptoms of withdrawal from a variety of drugs.

Observations of Addicts. One way to evaluate the role of environmental cues in withdrawal distress is simply to ask addicts to recall the circumstances in which they suffer such distress. Several investigators have done just this, and have noted that both opiate addicts

and alcoholics report that such distress is especially pronounced in the presence of drug-associated cues (see reviews by Siegel (1983) and Siegel (1987)). Several clinicians have reported that opiate withdrawal symptoms are displayed when, during behavior therapy (even with long detoxified former addicts), drugs are discussed (O'Brien 1976; Wikler 1977) or the paraphernalia of addiction (syringe and tourniquet) are viewed (Teasdale 1973). The appearance of such symptoms in these circumstances can be enigmatic to an observer not acquainted with the phenomenon of pharmacological conditioning, as one of Wikler's recollections demonstrates:

> On two separate occasions, psychiatrists at the U.S. Public Health Service Hospital told me that in group therapy with long detoxified postaddicts, the patients would suddenly begin to blow their noses, wipe their eyes, and yawn incessantly when the subject under discussion turned to dope. The psychiatrists, unaware of this theory of relapse, were puzzled by the reappearance of opioid abstinence phenomena 3 to 6 months after detoxification. (Wikler 1977, p. 35)

One's own personal experience may provide similar evidence of the importance of drug-associated cues in withdrawal distress and craving--environmental cues associated with smoking (or seeing others smoking, or talking about smoking) often elicit craving for a cigarette in individuals addicted to nicotine.

In the case of orally ingested drugs, such as alcohol and tobacco, an especially effective cue for the drug's systemic effects should be the flavor of the drug. It has been reported that cigarette smokers will display nicotine withdrawal symptoms if they experience the taste of the cigarette without the usual accompanying nicotine administration, i.e., they puff on a cigarette containing much less than the usual amount of nicotine (Schachter 1977). It is well known that alcoholics find the taste of alcohol a potent elicitor of craving (e.g., Ludwig and Stark 1974) and have difficulty in refraining from drinking if they sample an alcoholic beverage (Hodgson and Rankin 1976). This "loss of control" is apparently elicited by the taste cue since, if the taste of the alcoholic beverage is masked, a sip does not elicit such craving (Merry 1966).

Drug-associated olfactory cues can apparently also elicit withdrawal sickness and craving. Teasdale (1973) noted that several heroin

addicts who had usually injected themselves in public lavatories reported that a lavatory smell elicited craving.

Many other anecdotal reports of environmentally elicited withdrawal symptoms and craving are reported by Biernacki in his study of recovery from heroin addiction:

> Those in the study who were able to isolate the source of their cravings to use drugs again usually pointed to some olfactory or visual cue that they associated in their past experience with obtaining the drug and/or using it. Being in an area where they once had obtained the drug, seeing old addict associates, or (especially) witnessing another person using drugs were the most frequent reported events that engendered craving to use opiates. One man, who had been addicted for five years prior to his being interviewed, recalled how drug cravings were prompted when he saw a group of actors seem to inject heroin in a movie that he was watching on television. (Biernacki 1986, pp. 107-108)

Another of Biernacki's respondent's displayed remarkable insight. He "likened himself to one of Pavlov's dogs when he felt the nausea accompanying a craving. He explained: 'I had the objectivity to even see my own behavior for what it was and that was like getting nauseous whenever I'd even think about fixing. Like one of Pavlov's dogs'" (Biernacki 1986, p. 115).

Experiments Concerning Environmental Elicitation of Withdrawal Distress. There are several laboratory demonstrations of the ability of drug-associated cues to elicit withdrawal distress. For example, it has been noted that former addicts display physiological signs of narcotic withdrawal when they performed the "cooking up" ritual while being monitored by a polygraph (O'Brien et al. 1976). Teasdale (1973) showed addicts slides of both opiate-related material, e.g., inserting a syringe into a vein, and non-opiate-related material, e.g., a hand holding a cup of coffee. On the basis of a variety of psychometric measures, Teasdale (1973) concluded that the opiate-related slides induced more emotional responding and evidence of withdrawal distress than the non-drug-related slides. Sideroff and Jarvik (1980) also reported that drug-associated cues elicit symptoms of withdrawal. They presented a videotape depicting scenes of heroin preparation and administration to groups of both heroin addict patients and nonaddicts. They found that the videotape elicited evidence of withdrawal (changes in heart rate and galvanic skin

response, and subjective ratings of anxiety and craving) in only the addict group.

Similar findings have been reported with respect to alcohol. Ludwig and colleagues (Ludwig et al. 1974; Ludwig et al. 1977) have presented results of experiments demonstrating that alcoholics, in the presence of laboratory-reconstructed alcohol-associated cues (e.g., a mock barroom or the odor of bourbon) display withdrawal sickness, subjective reports of alcohol craving, and (if liquor is available) relapse to drinking.

IMPLICATIONS FOR TREATMENT

According to the conditioning model, those drug-compensatory CRs which contribute to tolerance when the anticipated drug is administered contribute to withdrawal symptoms when the anticipated drug is not administered. It follows that treatment techniques should address the crucial contribution of environment-drug associations to dependence (Poulos et al. 1981).

As described previously, when treatment consists primarily of a period of "detoxification" in an insulated treatment environment, and the released patient is returned to the original addiction environment, treatment success is poor: the vast majority of the treated addicts quickly relapse following reexposure to predrug cues. The conditioning analysis suggests several factors which should be considered in a treatment program to minimize such relapse.

Environmental Change and Treatment Effectiveness

As discussed previously, transfer of an addict to an environment not associated with drug use should promote recovery. This is what happened with soldiers addicted while in Vietnam (e.g., Robins 1973) and with experimentally addicted rats (e.g., Hinson et al. 1986; Thompson and Ostlund 1965). As discussed in the beginning of this chapter, results of several epidemiological studies suggest that environmental change is frequently associated with long-lasting abstinence.

Of course, environmental change may be a good prescription, but it is not one that can readily be implemented. Since such changes usually do not occur, a function of treatment might be the extinction of the pharmacological associations that are responsible for relapse, and/or the teaching of other, overriding behaviors in response to drug CSs.

Extinction of Responses to Drug-Associated Cues

The primary treatment implication of the conditioning analysis of withdrawal is that the usual predrug cues must be subjected to extinction. There are reports of the effectiveness of extinction-like procedure in eliminating the ability of predrug cues to elicit craving and withdrawal distress (Siegel 1983). The study by Blakey and Baker (1980) provides an example of how extinction procedure may be used with alcoholics. One of the cases they described (W.R., case 1) illustrates the procedure. The drinking history of the patient was first analyzed in terms of the events which "triggered" craving for alcohol and relapse to consumption. For this patient, these stimuli included "tiredness after long hours of work, boredom, smell of drink on customers, bouts of illness, travelling home past a particular pub at night, and the taste, smell, and sight of alcohol" (Blakey and Baker 1980, p. 320). Treatment involved extinction of the capacity of these usual predrug cues to elicit craving by presenting the cue and not allowing drinking. At first, presentation of one of the usual predrug cues elicited strong craving, trembling, and feelings of depression. With repeated presentations of the cue not followed by the drug, these symptoms diminished. When the capacity of one cue to elicit craving had been extinguished, another predrug cue was introduced and subjected to the same extinction procedure. The extinction procedure continued until most of the "trigger" stimuli had undergone extinction, after which the patient apparently successfully gave up drinking.

Blakey and Baker (1980) report other cases involving the same general procedure for eliminating the capacity of the usual predrug cues to elicit craving: Identification of the usual predrug cues for the individual patient and systematic exposure to each of the cues while not allowing alcohol consumption until the capacity of that cue to elicit craving is diminished. In some cases, it was necessary that the extinction program be conducted outside the institutional setting. For example, treatment for one patient who reported that being in a pub in the company of friends was the most powerful elicitor of craving involved sitting in the pub with one or two therapists while he and they drank soft drinks. Later sessions included being in the presence of people drinking alcohol, going into a well-known pub, and going into a pub alone.

Ronald Siegel (1984) has reported the use of extinction therapy to treat cocaine dependence. Patients being treated for cocaine addiction were provided with vials that contained a chemical that

duplicated the odor of "street" cocaine. They could sniff the vapors *ad libitum*. Such exposure to a cocaine odor was an effective adjunct to treatment for the majority of the users who participated in the study:

> Repeated sniffing of the aroma unaccompanied by cocaine itself appears to result in some 'extinction' of the cocaine craving itself. (R.K. Siegel 1984, p. 61)

"Extinction therapy" has also been used to treat opiate addiction (O'Brien and Ng 1979). Although dramatic successes have not been reported, a problem in implementing this procedure with these patients is the difficulty in reconstructing predrug environmental cues. As indicated by O'Brien and Ng (1979), "for optimal effectiveness it might be necessary for patients to be desensitized in situations that clearly resemble their own neighborhoods" (O'Brien and Ng 1979, p. 196). Obviously, such realistic presentation of drug-associated cues may present special problems, although it has been used in some cases, such as Kraft's (1970) procedure of having amphetamine-barbiturate (Dexamyl, or "purple hearts") abusers go to areas of the city where they usually obtain the drug and refrain from buying it.

A promising extinction procedure has the patient actually self-inject the opiate in an environment similar to that in which heroin is usually self-administered, but the effects are blocked by a long-lasting narcotic antagonist such as cyclazocine or naltrexone (Meyer and Mirin 1979).

SUMMARY AND CONCLUSIONS

Results of much research demonstrate that tolerance is not the inevitable consequence of repeated drug exposure: the drug-experienced organism often demonstrates tolerance when the drug is administered in the context of the usual predrug cues, but not in the context of alternative cues. Such findings raise the importance of learning factors above that of the purely physiological factors in substance abuse. Incorporated in a model of tolerance that emphasizes the Pavlovian conditioning of an association between predrug cues and the systemic effect of the drug are findings that learned tolerance leads to death by overdose. A history of association results in drug-compensatory conditional responses, and these conditional pharmacological responses may be displayed as "withdrawal symptoms" and craving when the organism with a history of drug

administration is confronted with the usual predrug cues without the usual pharmacological consequences.

An implication of the conditioning analysis is that successful treatment of drug addiction should acknowledge not only pharmacodynamic and pharmacokinetic principles, but also the powerful evocative effects of drug-predictive environmental cues. Permanent abstinence is most likely if the treated addict is either protected from reexposure to these predrug cues (for example, by residence relocation), or treated with a protocol which incorporates extinction of the association between these cues and the drug. As Hamlet suggested to his mother (Act III, Scene 4):

> Assume a virtue if you have it not
> . . . refrain tonight;
> And that shall lend a kind of easiness
> To the next abstinence: the next more easy;
> For use almost can change the stamp of nature
> And master ev'n the devil or throw him out
> With wondrous potency.

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