The Ghost in the Addict: Drug Anticipation and Drug Addiction

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ABSTRACT

People who stop drinking or smoking or using other drugs, for weeks and even years, report that cravings reappear. As described by Cocteau, “the dead drug leaves a ghost behind. At certain hours it haunts the house.” The “ghost” is summoned by the memory of the drug, typically elicited by places, times, or circumstances that have been associated with the drug in the past. The study of associations is the study of Pavlovian conditioning, and recent research concerning Pavlovian conditioning of drug-elicited responses reveals the relationship between drug anticipation and drug addiction.

Until the early part of the 20th Century there was very little in the way of restrictive legislation concerning drug use in North America. There certainly were concerns about excessive drug (primarily alcohol) use, but all manner of addictive substances, and paraphernalia for administering them, were widely available in drug stores and general stores. Preparations of opium (laudanum and paregoric), cocaine-containing beverages, and hypodermic syringes were freely available by mail order from the Sears-Roebuck catalogue as recently as 1897. In many places in the Canada, the United States, and Great Britain per-capita consumption of highly addictive drugs was far in excess of any current levels. Although some expressed alarm about the baneful effects of drugs, the users generally were considered to be people with an annoying and unwholesome habit. There were temperance movements that advocated control of alcohol availability, and even prohibition, but they were generally seen as extremist organizations. There were few attempts to make the use of drugs other than alcohol illegal (Siegel, 1986).

The way we thought about drugs and drug-users changed dramatically at the start of the twentieth century. Politicians in North America were seized by a prohibitionist frenzy. In Canada the Opium and Drug Act of 1911 prohibited the nonmedical use of controlled drugs. In the United States the Harrison Narcotics Act (passed in 1914, implemented in 1915, and strengthened as a result subsequent legislation and judicial decision) had a similar effect. What had been lawful activity for perhaps a quarter of a million drug addicts was now illegal. Legislators did not realize that they were dealing with remarkably tenacious behavior. The general view was that some drug users might have moderately uncomfortable withdrawal symptoms when drugs no longer were available, but these would pass in about a week or so and they would be as good as new.

It soon became clear that the cessation of drug use was not something that could be imposed simply by legislative fiat. It was noted that even after protracted periods of abstinence “detoxified” addicts would, with few exceptions, return to drug use. Merely waiting out the withdrawal symptoms was not sufficient to overcome addiction – Enforced abstinence, in a treatment facility or in prison, was, in the vast majority of cases, followed by relapse to drug use.

Clearly, merely refraining from drug use for a protracted period of time was not sufficient treatment for addiction. Why? The answer became apparent to Lawrence Kolb, an Assistant Surgeon General of the United States Public Health Service and the first superintendent of the then newly-established “Narcotics Treatment Farm” in Lexington, Kentucky. He noted that
treated addicts, when confronted with situations that had been paired with drug use, experienced drug withdrawal symptoms and craving: “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, pp. 39-40)

Subsequently, other clinicians have similarly noted that the, when confronted with cues that had been paired with drug use, former addicts displayed withdrawal symptoms and relapsed. Benjamin Kissin studied heroin addicts that were confined to Sing Sing, the Federal penitentiary in Ossining, New York (about 50 kilometers from New York City): “Heroin addicts returning from Ossining to New York by train, after 5 years of incarceration and abstinence, experience acute withdrawal symptomatology as the train passes their old neighborhoods” (Kissin, 1983, p. 113). The sociologist, Patrick Biernacki, interviewed heroin addicts about the circumstances of their relapse:

“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 experiences 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 use drugs were the most frequent reported events that engendered craving to use opiates. One man, who had been addicted over a period of 12 years and not 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 ... the cravings are related to things associated in the past, either with using the drug or with its immediate effect” (Biernacki, 1986, p. 115).

O’Brien (1976) described an example of a narcotic addict in Philadelphia who was imprisoned and drug-free for six months: “He gained weight, felt like a new man, and decided that he was finished with drugs” (p. 533). However, when he was released from prison, “as the subway approached his stop be began sweating, tearing from his eyes, and gagging ... As he got off the subway, he vomited on to the tracks. He soon bought drugs and was relieved” (p. 533). Many others have provided examples of patients who display withdrawal symptoms and crave drugs when confronted with cues that had signaled the drug in the past, e.g., seeing the paraphernalia of addiction such as a syringe and tourniquet (Teasdale, 1973), or discussing drugs with others (Wikler, 1977).

Some clinicians have noted that many long-term heroin addicts have achieved abstinence only after moving to a new environment (Bammer & Weekes, 1994). 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 to groups that have returned to environments rich in drug-associated cues, relocated patients generally show far less relapse (see review by Siegel, 1999).

The results of many experiments (with humans and non-human animals) support clinical observations and epidemiological reports that predrug cues are powerfulelicitors of withdrawal
symptoms. 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 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, 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 a picture 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, 1999; Siegel & Ramos, 2002).

In summary, when confronted with cues that have been paired with the drug in the past, withdrawal symptoms are displayed. That is, drug users respond in anticipation of drugs (“sight of cigars,” hypodermic syringe, etc.) with these symptoms. The study of such anticipatory responding to biologically significant effects is the study of Pavlovian conditioning.

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 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 the sight of the person that normally fed the dogs. In Pavlov’s well-known work, the dogs were presented with small amounts of dry food. The dry mouth was the UCS. The UCR was salivation – a reflex
response that attenuated the dry mouth, and 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. In this example, the tone elicited salivation.

**Drug Administration as a Conditioning Trial**

Pavlov (1927, pp. 35ff) suggested that the administration of a drug could be viewed as a conditioning trial; the drug effect served as the UCS and the immediately antecedent environmental cues served as CSs. Prior to any learning, many types of pharmacological stimulation elicit UCRs that compensate for the drug-induced disturbances. After some pairings of the pre-drug CS and pharmacological UCS, a drug-compensatory response is elicited as a conditional response. These conditional compensatory responses (CCRs) mediate the development of tolerance by counteracting the drug effect.

The development of conditional pharmacological responses can be ascertained merely by presenting the CS (predrug cues) without the UCS (the drug), i.e., administer an inert substance in the usual drug-administration environment. Results of many experiments using this procedure have demonstrated that the drug-experienced organism typically responds to the CS with CCRs. For example, about 65 years ago Subkov and 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 tachycardiac 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” (Subkov & Zilov, 1937, p. 295).

Subsequent research has demonstrated CCRs with respect to many effects of a variety of drugs, including commonly abused drugs such as opiates, ethanol, and caffeine (see reviews by Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000; Siegel & Ramos, 2002). For example, in rats with a history of morphine injections (each injection eliciting hypoalgesia, decreased activity, and decreased intestinal transit time), administration of an inert substance elicits hyperalgesia, increased activity, and increased intestinal transit time. Similarly, in rats with a history of ethanol injections (each injection eliciting hyperthermia, decreased spontaneous locomotor activity, and ataxia), administration of an inert substance elicits hyperthermia, increased locomotor activity, and hypertaxia (enhanced ability to maintain balance on a tilted surface).

**Pavlovian Conditioning and Drug Tolerance**

To understand the role of drug-associated cues in drug addiction we first must understand the role of these cues in drug 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.

There is extensive evidence that Pavlovian CCRs contribute to tolerance, and this evidence has been extensively reviewed (Siegel et al., 2000). The original phenomenon that inspired development of the conditioning model has been termed the “situational-specificity of tolerance” (Siegel, 1976). Situational-specificity of tolerance is readily demonstrated. An
organism is administered a drug in a particular environment on a number of occasions – sufficient for tolerance to be apparent (i.e., the magnitude of the drug-elicited response is less than it was originally). If the drug is administered again, but in an environment that had nor previously been paired with drug administration, tolerance is attenuated. Environmental-specificity of tolerance is very general. It has been seen with respect to tolerance to a variety of effects of various drugs, and in many species, from snails to humans, suggesting that such specificity “may be a general phenomenon having an early evolutionary development and broad phylogenetic continuity” (Kavaliers & Hirst, 1986, p. 1201).

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 non-human-animals, but results of clinical and epidemiological; research concerning opiate overdose in humans are consistent with the laboratory findings. For example, Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, and Camí (1994) interviewed 76 heroin addicts admitted to the emergency room of a university hospital in Barcelona, Spain: 54 patients because of heroin overdose, and 22 seeking urgent medical care for unrelated conditions for whom the interview revealed intravenous heroin self-administration one hour 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 had recently 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 the drug “in an unusual setting” (Gutiérrez-Cebollada et al., 1994, p. 171). Chi-square analysis of the interaction apparent in Table 1 was statistically significant. 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” (p. 173).

Table 1
Circumstance of heroine administration (usual environment or unusual environment) for 76 patients who had recently used heroin and were admitted to a hospital emergency room, either for a heroin overdose or for other reasons (OD or Non OD, respectively) (data) from Gutiérrez-Cebollada et al., 1994)

<table>
<thead>
<tr>
<th>Environment of Heroin Use Prior to Admission</th>
<th>Reason for Admission</th>
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<tr>
<td></td>
<td>OD</td>
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<tr>
<td>Usual Environment</td>
<td>48% (26/54)</td>
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<tr>
<td>Unusual Environment</td>
<td>52% (25/54)</td>
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Pavlovian Conditioning and Drug Withdrawal Symptoms
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 CCRs.

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 CRs achieve full expression because they do not interact with the drug effect. Such CCRs, 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., Deffner-Rappold, Azorlosa, & Baker, 1996; Kelsey, Aranow & Matthews, 1990); 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, 1988). As noted earlier, the first serious reports of addiction treatment and relapse following the passage of anti-drug legislation noted the important role of drug-associated stimuli. A prominent researcher in Lexington, Kentucky facility was Abraham Wikler. A physician and scientist, he quickly came to the conclusion that understanding drug addiction required far more than simply an understanding of pharmacology. He summed up his observations in a paper published in 1977 – “The search for the psyche in drug dependence: A 35-year retrospective study.” He described a typical scenario:

“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).

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 vasoconstriction, 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.

**Interoceptive Cues for Drugs**

Although experimental studies of the associative basis of tolerance and withdrawal symptoms 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. There are many interoceptive stimuli that signal a drug effect (Siegel & Ramos, 2002).
One type of interoceptive cue is provided by the cognitive and proprioceptive stimuli resulting from the act of self-administration. That is, 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. If drug delivery is contingent on a response, interoceptive response-initiating (or response-produced) cues are paired with the drug effect. There is considerable evidence that these self-administration cues function as other CSs—that is, they come to elicit CCRs. These self-administration cues importantly contribute to tolerance (e.g., Weise-Kelly & Siegel, 2001) and withdrawal symptoms (e.g., MacRae & Siegel, 1997).

Another category of interoceptive cues that has received considerable attention is drug-onset cues. That is, following each drug administration, early drug-onset cues may be detectable some time before that later, larger drug effect is experienced. These drug-onset cues may be considered the CS, and the subsequent larger drug effect the UCS. An association between the small drug effect and the later, larger drug effect has been termed an “intra-administration association” (Kim, Siegel & Patenall, 1999). There is extensive evidence that intra-administration associations contribute to drug tolerance and withdrawal symptoms.

**Drug-Onset Cues and Conditional Compensatory Responding**

There are several ways to demonstrate that drug-onset cues serve as CSs; that is, as the drug is repeatedly administered early drug effects become associated with later drug effects (see Sokolowska, Siegel, & Kim, 2002). For example, following a number of gradual intravenous infusions of morphine, rats become tolerant to the analgesic effect of the drug. If these rats are now administered a brief infusion of a small dose of the opiate (to simulate the early effect of the prior infusions, but now there is no subsequent later, larger effect), a CCR of hyperalgesia is obtained. That is, in these rats a small dose of an analgesic drug actually elicits heightened sensitivity to nociceptive stimulation (because it had served as a CS for a larger dose of the analgesic drug).

**Drug-Onset Cues and Withdrawal Symptoms**

On the basis of the conditioning analysis, withdrawal symptoms— a manifestation of a pharmacological CR— should be elicited not only by drug-associated environmental cues, but also by drug-associated pharmacological cues. If an intra-administration association was formed during a series of morphine administrations, presenting a small dose of the opiate might be expected to reproduce the early effect of the drug—an effect that had become associated with the subsequent, larger effect.

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 reported extreme withdrawal distress. The small dose of the drug functions as a drug-onset cue in these smokers—it conditionally elicits the pharmacological CRs that constitute withdrawal symptoms. In experiments with rats, McDonald and Siegel (submitted) demonstrated the contribution of drug-onset cues to withdrawal symptoms. They found that rats with a history of administration of large morphine doses (50 mg/kg) displayed behavioral and thermic evidence of morphine withdrawal when administered small (5 mg/kg) doses of the opiate. Such a finding would be expected if, during administrations of the large dose of morphine, the rats had formed an association between drug-onset cues and the subsequent larger drug effect. Alternative interpretations, such as sensitization, have been excluded on the basis of additional experiments (see McDonald & Siegel, submitted; Sokolowska et al., 2002).
Drug-Onset Cues and Relapse

It is well established that relapse to drug use sometimes is precipitated by exposure to small drug doses. For example, a small dose of alcohol may augment the craving for additional alcohol and enhance subsequent alcohol consumption. 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). Although there are various interpretations of such “priming” effects, it is possible that intra-administration associations may be responsible for some instances of the phenomenon (see Siegel et al., 2000; Sokolowska & Siegel, 2002). The effect of “the first drink” may be due to the alcoholic’s association of that initial effect of alcohol with subsequent larger amounts of the drug (Goddard, 1999).

Other Interoceptive Cues

Interoceptive cues discussed thus far, such as drug-onset cues and self-administration cues, have been extensively studied in experiments with humans and non-human animals (see reviews by Ramos & Siegel, 2002; Siegel et al., 2000). However, there are some interoceptive predrug cues that can be studied only in humans. These include memory of drug-paired stimuli and mood states.

Memories. Merely thinking about their preferred drug elicits withdrawal distress and craving in cigarette smokers, alcoholics, and heroin addicts. 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 (see Ramos & Siegel, 2002): “A good case exists, then, for making cognitions per se a pivotal concern of conditioning models, allowing the possibility of cognitions as interoceptive cues” (Greeley & Ryan, 1995, p. 133).

Emotions. Emotions, especially negative emotions, are frequent elicitors of withdrawal distress and craving. (see Greeley & Ryan, 1995; Ramos & Siegel, 2002). As discussed by Poulos, Hinson, and Siegel (1981), these interoceptive emotional cues may become associated with a drug, much like other cues:

“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” (pp. 209-210).

The Ghost in the Addict

Drug addicts, and people who treat drug addicts, and scientists who study addiction, all agree on one thing. The real problem in treating addiction is relapse following treatment. It’s not really an overwhelming problem to get people to stop using drugs for a time. To paraphrase W. C. Fields, “it’s easy to stop drinking – I’ve done it many times.” However, people who stop drinking or smoking or using other drugs, for weeks and even years, report that cravings reappear. The former addict is bedeviled by some remnant of his prior drug experiences. As Jean
Cocteau described in his confession, *Opium*, “the dead drug leaves a ghost behind. At certain hours it haunts the house” (Cocteau, 1958, p. 60).

The “ghost” is the CCR elicited by drug-associated cues. It “haunts the house” when the addict is confronted with CSs that have been paired with drug use. These CSs may be exteroceptive cues that have been paired with the drug in the past; cues such as the time the drug is usually taken, the people usually present when the drug is administered, the places where the drug is used and tastes or odors present at the time the drug is used. More importantly, the CCR may be elicited by highly salient interoceptive cues that have been associated with the drug; cues such as drug-onset cues, thoughts about drugs, and emotional states paired with drug use. Understanding addiction requires an appreciation of the mechanisms whereby this ghost appears. Effective treatment requires an understanding of how it may be exorcised. Such treatment should be based on the application of conditioning principles (Siegel & Ramos, 2002).
References


