

**“Nobody knows more about what really happens
in addiction than Shepard Siegel.”**

Angela Duckworth, cofounder of Character Lab, author of *Grit*,
and Professor of Psychology at the University of Pennsylvania

The Ghost in the Addict

SHEPARD SIEGEL

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Shepard Siegel

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To Laura and Jeffrey and Marcia

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Preface and Acknowledgments

Over half a century ago I first started my research on the Pavlovian conditioning of drug effects in rats. In 1972 the drug I used was insulin, and the effect of interest was blood-sugar level. Insulin lowers blood sugar—a hypoglycemic response. After a number of daily insulin injections, each following a distinctive drug administration ritual, the rat was injected with an inert substance, physiological saline, following the usual drug-administration ritual. This physiological saline injection produced an elevation in blood-sugar levels—a hyperglycemic response. The anticipation of hypoglycemia induced hyperglycemia.¹ A few years later it occurred to me that an anticipatory response that attenuates the drug effect might be a mechanism of drug tolerance—that is, the decreasing effect of a drug over the course of successive administrations—a hypothesis that I was able to confirm.²

What about the situation in which expected tolerance seems insufficient? Often an experienced heroin addict dies from an apparent overdose of the drug. A well-written article about ostensible heroin overdose that I read in the *New York Times* in 1972 made a lasting impression on me. It was written by a science journalist, Edward Brecher, and was titled “So

Why Do Heroin Addicts Drop Dead?"³ Brecher's insights into heroin overdose were extraordinary. He summarized a mass of data indicating that the so-called overdose victims died following self-administration of a dose of heroin that would not be expected to kill these drug-experienced, and therefore drug-tolerant, individuals. Although the profundity of his contribution was not immediately recognized, 44 years later a well-known addiction researcher, Shane Darke, stated, "in one chapter, Brecher laid the foundations for all subsequent overdose research."⁴ Some of that subsequent research was conducted in my laboratory. We hypothesized that tolerance would fail to occur if the anticipatory response responsible for tolerance failed to occur. The anticipatory response would fail to occur if the drug was not taken following the usual drug administration ritual, but rather it was taken in a novel environment not previously paired with the drug. Our hypothesis was confirmed.⁵

The anticipatory drug response is adaptive. It can save the addict's life. In that same year, 1982, we considered circumstances in which the occurrence of the anticipatory drug response was problematic. What if the addict is in the presence of the usual drug-paired cues but there's no drug to administer? That is, the individual 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 typically is administered, or any of a variety of drug-paired stimuli are present. In the situation in which the addict has learned to expect the drug but does not receive the drug, drug anticipatory responses would achieve full expression because they are not countered by any drug effect. The learned anticipatory responses exhibited in such circumstances typically are not recognized or labeled as a drug-anticipatory learned responses. Rather, they

are (mis-)labeled drug “withdrawal symptoms”: “There is, in fact, much evidence suggesting that stimuli normally associated with drug administration elicit so-called withdrawal symptoms . . . Many addicts report that these symptoms are strong motivators for the resumption of drug taking.”⁶ Most addicts are unaware that the drug anticipatory response is elicited by drug-paired stimuli. Rather, they just experience drug-preparatory responses from time to time. The drug preparation/withdrawal set of symptoms elicited by drug-paired stimuli is the ghost that haunts the addict.

Much of my research in subsequent years, usually with talented collaborators, has elaborated on the role of the drug-anticipatory response in addiction. It is now clear that the anticipatory response is a basic mechanism of adaptation. The drug has profound physiological effects that can actually threaten the survival of the drug-taker. The addict’s preparation for the drug in the presence of drug-paired cues minimizes the detrimental effect of the drug. The ghost that haunts the addict can be a compassionate ghost. It potentially saves the addict’s life.

There is the widespread view that addiction is evidence of a pathology wherein withdrawal is a symptom. In fact, the addict has a healthy and adaptive response to the bodily changes caused by the drug. He or she has learned to prepare for the drug in anticipation of the physiological upheaval induced by the drug. These preparatory responses (mistakenly considered as drug-withdrawal symptoms) have wrongly been thought to be due to the baneful effects of the previous drug administrations, rather than the preparatory response for the next drug administration.

There is increasing concern that terms such as “addict” and “drug abuser” are stigmatizing. According to the head of the National Institute on Drug Abuse, Nora Volkow, these

terms neglect to emphasize that people who continually self-administer drugs are suffering from a disorder. She and her colleagues suggest a more person-centered language, e.g., replacing “addict” with “a person having a substance use disorder”⁷ This approach to terminology is problematic. A largely historical analysis of the literature of excessive drug and alcohol use would have to change terms that have been in use for many years. For example, rather than “Alcoholics Anonymous,” we’d have “Persons with an Alcohol Abuse Disorder Anonymous”; in addition, many scientific journals maintain the use of “addiction” in their title: *Addiction*, *Addiction Biology*, *Addictive Behaviors*, *Journal of Addictive Medicine*, *Psychology of Addictive Behaviors*, *American Journal of Addiction*, and many more. More importantly, use of the new terminology would suggest agreement with the National Institute on Drug Abuse’s commitment to a brain disorder view of excessive drug use. It has taken me 50 years to realize that drug addiction is not a “disorder.” It is not an indication of a diseased brain, but rather, it is a manifestation of homeostasis. To use the terminology of Walter Cannon, it’s an expression of “the wisdom of the body.”⁸

The research that has led to that realization was funded primarily by the U.S. National Institute on Drug Abuse and the National Research Council of Canada. This drug-conditioning research has been done in conjunction with the work of many others. For over 30 years the research was facilitated by the diligence and creativity of Doreen Mitchell, my research technician and collaborator. Over the years I have benefited enormously from discussions with my colleague Lorraine Allan. My discussions with Barry Dworkin have done much to clarify my thinking about Pavlovian conditioning in general, and the Pavlovian conditioning of drug responses in particular.

Many graduate students contributed to the drug-conditioning research and have provided insights into the role of learning in drug tolerance: Marco Baptista, Tom Eissenberg, Tina Goodison, Riley Hinson, Joseph Kim, Marvin Krank, Susan Larson, Glenda MacQueen, James MacRae, Robert McDonald, Barbara Ramos, Marta Sokolowska, and Lori Weise-Kelly. Finally, I am indebted to Marcia Frank for her critical reading of various drafts of the book, and for so much more, for the past 35 years.

1 The Haunting of the Addict

The dead drug leaves a ghost behind. At certain hours it haunts the house.

—Jean Cocteau, *Opium: The Diary of a Cure*, translated by M. Crosland and S. Road (New York: Grove Press, 1958 [1930]), 60

People who have a drug addiction, clinicians who treat these people, and scientists who study addictive behavior all agree on one thing: the real problem in treating addiction is relapse following treatment. It's not an overwhelming problem to get people to stop using drugs for a time. To paraphrase an observation variously attributed to W. C. Fields, Mark Twain, and others: "It's easy to stop drinking—I've done it a thousand times." However, people who stop drinking or smoking or using other drugs, for weeks and even years, report that withdrawal symptoms and cravings spontaneously reappear. Former addicts are bedeviled by some tenacious remnant of their prior drug experience.

The persistent residue of addiction was described by the poet Barbara Greenberg. Her addiction was to nicotine, not opium, but she, too, used spectral imagery. Long after her last cigarette, she was (like Jean Cocteau) still pursued by a ghost:

How long has it been since I smoked? Four years? Five?
My father died—and then there were changes right and left
in my life. I moved. I broke with friends. I had my hair cut short,
and I quit smoking. “That’s it, motherweed,” I announced; I quit
cold turkey! Ah, but I am no more rid of it than the faith
I was born into, or the dear ones from whom I am now
estranged, or any blue ghost . . . ¹

Barbara Greenberg was haunted by a “blue ghost,” the residual effects of her previous smoking history, years after she stopped smoking. Opiate users similarly display withdrawal symptoms long after their last drug administration,² as do alcohol users.³ What summons this ghost? Why does the former drug user, abstinent for days, weeks, months, or years, still experience craving and withdrawal distress from time to time? It seems as if the cravings spontaneously occur. The individual may be doing fine and drug-free for a considerable period of time. Suddenly they are overcome by withdrawal distress—a persistent craving for the drug, and frequently relapse to drug use. As noted by the sociologist Patrick Biernacki, “the tendency of some people to relapse, and become readdicted, often after long periods of abstinence, is a perplexing aspect to addiction and a feature that should be addressed in any theory attempting to explain it.”⁴

In fact, perceptive observers realized for a long time that the ghost’s appearance was not arbitrary. Rather, the ghost appears when the individual that has used drugs is in the presence of stimuli that have been associated with the drug—places, times, thoughts, and circumstances that, in the past, had been paired with drug use. These drug-paired stimuli might be internal as well as external. For example, stress, anxiety, or depression may have been experienced prior to each drug use. When these external or internal stimuli are present, the risk of relapse is especially pronounced. The individual may not be aware

that the ghost appears when drug-paired stimuli occur. He or she may simply experience withdrawal distress from time to time but not recognize the relationship between drug-paired stimuli and the reappearance of motivation to use the drug. Nevertheless, the importance of drug-associated situations in relapse was known to some of those concerned about the most common form of drug abuse in colonial America—alcohol.

Many inhabitants of colonial America subscribed to the 1673 opinion of the Puritan clergyman, Increase Mather: “Drink is in itself a creature of God, and to be received with thankfulness.”⁵ However, concerns did develop about excessive drinking in pre-Revolutionary America, especially after the distilling industry became well established. The first commercial distillery opened in Boston. Boston, New Haven, Philadelphia, and Providence became centers for this very profitable business, and by 1770 there were over 140 distilleries.⁶ Many in America developed a taste for the rum (and later grain spirits) that now were widely available and inexpensive. The Continental army was a huge whiskey consumer; a substantial daily liquor ration was provided to American Revolutionary soldiers.

Benjamin Rush was a colonial physician who cautioned about the health problems of excessive alcohol consumption. Rush was the most eminent American physician at the time of the Revolutionary War. He was surgeon general with the Continental Army (until he became critical of George Washington’s leadership and resigned). Dr. Rush was a member of the Continental Congress and a signer of the Declaration of Independence. He wrote the first chemistry and psychiatry textbooks in the United States. He actively promoted a variety of social causes, and also was concerned about the problem of alcoholism in the early days of the republic. He noted an important feature of alcoholism—the “operation of the human mind which obliges it to associate ideas, accidentally

or otherwise combined."⁷ Alcohol is one such idea, and the alcoholic is obliged to associate certain places and times with alcohol. Rush observed that it is in these alcohol-associated situations that withdrawal distress and craving for drink is pronounced, and avoiding these situations facilitates abstinence:

Some men drink only in the morning, some at noon, and some at night. Some men drink only on a market day, some at one tavern only, and some only in one kind of company. Now by finding a new and interesting employment, or subject of conversation for drunkards at the usual times in when they have been accustomed to drink, and by restraining them by the same means from those places and companions, which suggested to them the idea of ardent spirits, their habits of intemperance may be completely destroyed.⁸

The more we learn about addiction, the more we realize the profundity of Dr. Rush's observations. The importance of context in drug use—the time, the place, the company present at the time of use—is the key to understanding addiction. The idea that relapse is often seen in the presence of stimuli that have been paired with drug use has constantly been rediscovered by successive generations of researchers, and repeatedly presented as a new and innovative insight into the addictive mind. It was not until a century after Rush died that tools for the study of associations between paired events were developed, and another century passed before the importance of our obligation "to associate ideas" (including the idea of a drug) with prevailing context was well established.

By understanding the role of drug-paired cues in addiction we can understand why people become addicted and why treatment is difficult, and determine ways we can focus our energy and resources in dealing with drug use. This understanding, unfortunately, was lacking by the policymakers who promoted anti-drug legislation in the early years of the twentieth century.

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