

P. B. DEWS AWARD LECTURE

Lecture given at Experimental Biology 2008 by the
P. B. Dews Lifetime Achievement Award Recipient

Contributions of Behavioral Pharmacology to Our Understanding of the Etiology, Prevention, and Treatment of Substance Abuse

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I was privileged to meet Dr. Peter B. Dews in the 1950's when I was working for Smith Kline and French. Dr. Leonard Cook, a previous Peter B. Dews Awardee, and I went up to see Dr. Dews at Harvard to get some advice about behavioral procedures that we could use for screening new pharmacological agents for potential use in the treatment of psychiatric disorders. Dr. Dews was very gracious, very helpful, and recommended that I get Dr. Charles B. Ferster as a consultant. Ferster had recently published with B. F. Skinner, a comprehensive collection of behavioral studies in which the scheduling of behavioral consequences was the major factor that influenced behavior (Ferster and Skinner, 1957). Dr. Ferster assisted us for a couple of years during the three years that I worked at Smith Kline and French, and during that time I learned a lot from Dr. Ferster about what became known as the Experimental Analysis of Behavior, or more colloquially, Skinnerian behaviorism. During that time I also learned a lot about pharmacology from my colleagues at SK&F, and through an extension class from the University of Chicago taught by Dr. Francis Oldham Kelsey, a professor there. Of course this was more than a few years ago, and there was no internet. I took the course through what is now called "snail mail," but it seemed to me to be fast paced, at least by the standards of the day. Dr. Kelsey, by the way, while working at the Food and Drug Administration was the one that blew the whistle on the teratogenic effects of thalidomide.

Because I had learned a bit of behavioral psychology and pharmacology, I was happy to be able to attend the Sigma Xi lectures given that year by Dr. Joe Brady, another P. B. Dews Awardee. Dr. Brady's lectures reviewed his experiments on "executive monkeys," and the behavioral conditions inducing ulcers in primates. The lectures were exciting, as they pointed out that the interactions between environment and physiologic response could be quite profound, and substantiated the importance of environmental control that was also pointed out by Ferster with regard to behavior. In talking with Dr. Brady after the lecture, he found out that I knew a little bit about pharmacology and a little bit about behavior, which was a rare combination in those days. Dr. Brady said, "Hey you've got to get your doctorate. Why don't you come down to the University of Maryland. I just got a grant with Sherm Ross, and we're setting up a behavioral pharmacology lab and could sure use you to help us." Such was the formality of graduate school application in those days. So I went back to school to get my doctorate at the University of Maryland.

Well as many are aware, Dr. Brady was not only on the faculty at the University of Maryland as an adjunct professor, but he was a lieutenant colonel in the Army, stationed at Walter Reed Army Institute of Research. In those days, WRAIR was a hot bed of behavioral, pharmacological, physiological, and endocrinological research. Among the people there were a number of behavioral psychologists that were very influential in terms of my career: In addition to Brady, Drs. Murray Sidman, Richard Herrnstein, and Jack Findley were there, and along the way influenced the course of behavioral and behavioral pharmacology research. WRAIR in the late 1950's and early 1960's was indeed quite literally a rare place, and provided me with an incredible intellectual environment.

Among the influential experiences that I had at WRAIR was an opportunity to observe Dr. John Mason, a neuroendocrinologist, surgically implant jugular catheters in rhesus monkeys. Dr. Mason was conducting studies on hormonal responses to stress, necessitating the collection of blood samples. As Heisenberg could tell us, to conduct these studies the sampling of blood itself could not influence Mason's measures – physical restraint for venipuncture just would not do. In order to proceed with these studies, Mason developed a surgical procedure for the placement of chronic indwelling jugular catheters which ran subcutaneously up to a plug mounted on the top of the skull. During studies the monkeys were restrained in chairs which did not allow them to reach the head mounts, and samples could be collected without undue stress.

In observing Mason's experiments, it was obvious that the catheters could transmit material (i.e., drugs) into the vein, maybe even easier than it could transmit material out. Being an operant conditioner, the obvious next step was to do that contingent on a response from the monkey. Before working at SK&F I had aspired to be a jazz musician and had several older musician friends who were shooting up heroin and tragically became hopelessly addicted. I wondered whether the rhesus monkeys would find heroin reinforcing. Times being what they were, I did not think that I could make a normal healthy rhesus monkey self inject drugs – that was psychopathology. At the time psychoanalysis was substantially influential and offered the most prevalent theory of the time about heroin addiction. According to the theory, opiate addiction was a product of latent homosexuality. Homosexual ideation generated by the Id disturbed the conscience, or the Superego, producing a neurotic conflict. That conflict could be alleviated by a drug that decreased sex drive, which was a purported effect of the opiates. In walking around the animal quarters, I didn't see any indication that any of our monkeys would be good candidates to test this theory, so I decided that we were going to have to go in a different direction.

After some explorations, we started in earnest when Travis Thompson joined the lab as a post-doctoral fellow. Both Shirley Spragg and John Nichols previously had success with chimpanzees and rats, respectively, by making their subjects physiologically dependent on morphine before giving them an opportunity to self inject the drug when they were in withdrawal. So we started that way.

We were helped in a substantial way by Jack Findley, who was one of the principal researchers in the laboratory, and in my opinion one of the most brilliant scientists in the history of behavior analysis. His work on multi-operant repertoires was just phenomenal, and we incorporated some of Findley's complex multi-operant procedures into our studies of morphine self administration. In these studies, we surgically implanted venous jugular catheters; made the rhesus monkeys dependent by injecting them with 2 mg/kg of morphine four times a day; and then trained them on a multiple schedule. The multiple schedule was comprised of a fixed-ratio schedule of food reinforcement for 8 min, a 5-min period of shock avoidance, followed by a chained FI, FR schedule in which a response was reinforced with morphine infusion (2 mg/kg). After the injection, the food and shock-avoidance components were repeated, and the complete cycle was repeated four times a day at 6-hr intervals. After some exposure to this schedule, performances were stable and characterized by a progressively increasing rate of response during the FI link of the chain followed by a high sustained response rate up to morphine injection within the FR link of the chain (Fig. 1A). In addition, response rates under the fixed-ratio schedule of food reinforcement averaged close to 30 responses per min, and responses occurred with an average latency of less than 2 sec during the shock avoidance component (Fig. 1B).

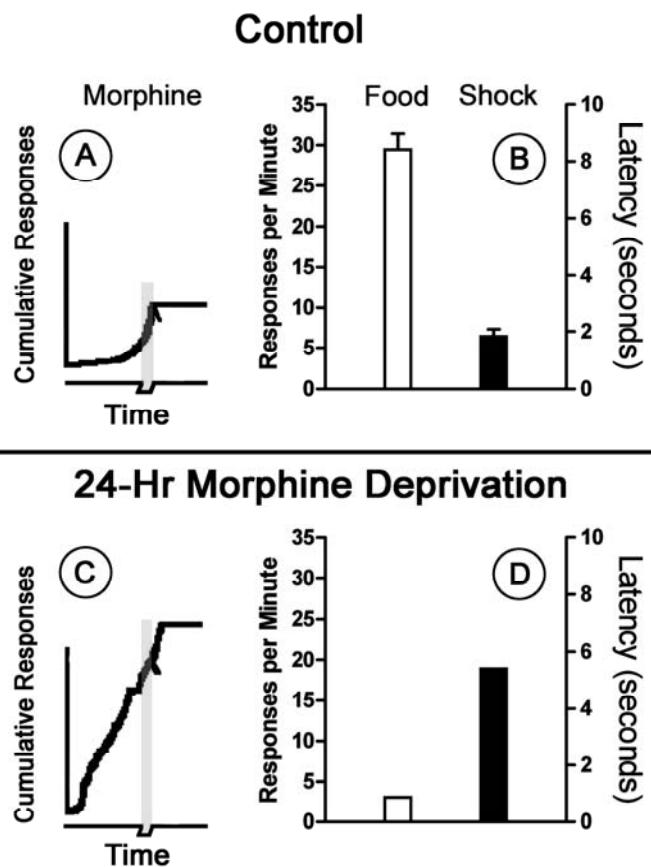


Fig. 1. Effects of morphine deprivation on responding maintained under a complex schedule of morphine injection, food presentation and shock avoidance. Morphine maintained responding under a chained FI, FR schedule, whereas a signaled FR schedule of food presentation and a signaled discrete-trial shock avoidance schedule maintained responding in alternate components. A representative cumulative record of control performance maintained under the chained schedule by morphine is shown in panel A, whereas the representative control performance parameters of food-maintained responding are shown as average response rates, and the latencies maintained by shock avoidance are shown in panel B. For the cumulative records, the x-axis represents time and the y-axis shows cumulative responses. The record starts with the onset of the two-min FI and the deflection of the lower "event" line and corresponding gray portion indicate the FR-link of the chained schedule. The slash mark on the cumulative curve indicates the completion of the FR link with the infusion of morphine. The lower row of graphs (panels C and D) show performances after 24 hours of morphine deprivation. Adapted from Thompson and Schuster, 1964.

After these stable performances were obtained, the effects of a number of different variables were assessed. First, treating subjects with morphine before the food and shock-avoidance components, had no effect on these performances, however, responding maintained by morphine injection under the chained FI, FR component was markedly suppressed. It would be presumptuous to take credit for agonist-maintenance therapy from this study, but it certainly demonstrated its feasibility. The decreases in responding under the chained schedule by the monkeys, and the agonist control of morphine seeking in addicted patients likely are a product of similar mechanisms.

Omitting the chained FI, FR morphine-injection component induced withdrawal in the monkeys, decreased response rates maintained by food, and increased latencies to avoid shock 24 hrs after the last morphine injection (Fig. 1D). When the chained FI, FR schedule of morphine injection was re-introduced, the number of responses in the fixed interval was greatly increased (Fig. 1C). The increase in responding during the FI link of the chain was also obtained with nalorphine injection (the only opioid antagonist available at the time). Nalorphine also markedly disrupted performances during the food and shock-avoidance components similarly to 24 hours of morphine deprivation. The increases in the number of responses in the fixed-interval component, whether with nalorphine injection or morphine deprivation along with the disruptions in responses maintained by food presentation or shock avoidance suggested that withdrawal specifically enhanced the reinforcing efficacy of morphine.

Interestingly, this experience with morphine injections rendered saline transiently effective in restoring to normal patterns the withdrawal-disrupted food-maintained and shock-avoidance behavior. The stimuli associated with both the morphine component, and those associated with morphine infusion had the capacity to temporarily reverse some of the signs of withdrawal. These results were so exciting, and the potential of this line of research so promising, that I spent the next 50 years doing studies on drug self administration in animals and humans.

Getting back to the studies of Spragg and Nichols, it concerned me that we initially made the subjects dependent on opioids to obtain reinforcing effects of morphine. My jazz musician friends were not physically dependent when they first tried heroin, and they used it intermittently and gradually before it became a regular habit. Certainly they were not physically dependent when they first found the drug reinforcing, and if self administration in animals was to be a more complete approach to drug abuse, the issue of whether dependence was a necessary condition for animal studies needed to be addressed.

After moving from the University of Maryland to the University of Michigan I was joined by Dr. James H. Woods, and we initiated a study to address whether dependence was necessary for morphine reinforcement. In that study monkeys were allowed to self inject extremely low doses of morphine – in the range of 10 to 25 $\mu\text{g}/\text{kg}$ per infusion – only three times a week. Under these conditions, morphine was an effective reinforcer, even though the morphine exposure was too low to produce physical dependence as indicated by the absence of withdrawal signs. Thus, morphine served as a positive reinforcer even without physical dependence. However, our earlier study showed that when opioid dependence developed, morphine could function as a negative reinforcer, with subjects escaping from the aversive state of withdrawal. Morphine's reinforcing effects were complex indeed.

Dr. Woods and I also showed that stimuli associated with the infusion of morphine could maintain extremely long chains of behavior even during extinction. And it reminded me of the fact that human drug addicts will spend all day long hustling, and going through long chains of behavior, ultimately being able to obtain the money to be able to buy drugs. And there is no doubt that this behavior is sustained by conditioned reinforcers along the way, which have been associated ultimately with the drug as a reinforcer.

By this time more people were studying drugs as reinforcers, and many of us were marching through the pharmacopeia, determining which drugs would, and which would not, serve as reinforcers in laboratory animals. Two of my colleagues, Drs. Robert Balster and Chris-Ellyn Johanson in the 1970s comprehensively reviewed the accumulated literature and found that by and large the drugs that animals self administered were the drugs that humans abuse. Additionally, drugs that humans find aversive would actually serve as negative reinforcers in animals – responses of animals were reinforced by avoidance of, or escape from these injections. Further, drugs that are neutral in humans were also neutral in animals, they would neither avoid them nor work for them. Finally, the patterns of drug self administration were similar among animals and humans. With opiates animals gradually increased their intake as tolerance developed, and finally stabilized at some high dose, which is essentially what humans do when access to drug is relatively unrestricted. On the other

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hand, psychomotor stimulant drugs were taken in binges both in animals and humans. These similarities across animals and humans render this an animal model with both face validity, predictive validity, and substantial potential for translational research. I can't imagine another model that is more impressive in that regard than is drug self administration.

With that in mind, it is worthwhile to explore some of the ways that self-administration procedures have been used. Clearly one practical application is in assessing new drugs with an eye towards preventing those with abuse liability from ever entering the market, or in doing so only with adequate warning. We are currently in a period of time when prescription drug abuse is rampant. Drug self administration in animals during the process of drug development helps a pharmaceutical company determine whether or not their compound has the potential to be abused – a very practical application. We can also examine new formulations of older drugs, or novel ways of delaying the onset of effects of the drug to decrease its abuse liability.

We are also in the present time looking very intensively for compounds that may be useful medications to treat drug abuse. The drug self-administration procedure typically factors heavily in these attempts, as it should. Given its validity as detailed above, it is natural to assess efficacy by examining whether a compound might in some way alter the propensity to self administer a drug. When coupled with an examination of the effects of the compound on behavior maintained by other reinforcers we can go further to assess the specificity by which the compound may alter drug self administration. And indeed a number of recent papers show selective effects of compounds on behaviors maintained by drugs of abuse compared to behaviors reinforced with food presentation. In our studies with morphine pretreatments described above, we also showed selective effects – food-maintained responding under the fixed-ratio schedule and responding maintained by shock avoidance were not affected, whereas self administration of morphine was virtually eliminated. Certainly many of the more recent attempts to assess efficacy of potential drug abuse treatments are elegant demonstrations of either the success or failure of medicinal chemistry to provide new compounds that might serve as leads. However, I wish that other studies would compare self administration to responding maintained by several other reinforcers, lest we confuse a selective effect on responding maintained by the drug of abuse with a selective lack of effect on responding maintained by the single comparison non-drug reinforcer.

Drugs can serve as important tools for understanding the brain mechanisms that mediate the reinforcing effects of all positive and negative reinforcers, not simply drug reinforcers. The advance of our science into more molecular aspects of reinforcement mechanisms in the brain is exciting, and clearly has great potential for new and important basic information that may also have eventual applications to further the public health. As a former NIH Institute Director I want to caution that we need to keep in mind that the public funds these studies, and we are obligated to give them something for their money, whether it be basic knowledge or new advances in medicine. To do this most effectively our studies will have to be able to predict the behavior of the intact organism in an ever-changing environment. Any scientific approach, whether reductionistic or one dealing with whole animals, needs to be ever mindful of the public trust.

In the process of studying drug self administration, it is important to emphasize that the finding that drugs can serve as reinforcers has allowed us to use all of the principals of the experimental analysis of behavior to better understand the etiology of drug addiction. We have explored and found that most of the same variables that influence behavior maintained by more traditional reinforcers affect drugs as reinforcers in the very same way, indicating a functional equivalence of reinforcing effects. These findings allow us to examine the special circumstances of drug abuse from a more informed perspective.

One important aspect of drug abuse in human beings is that it is very frequently a social enterprise. Because drugs are often self administered in a social context along with the delivery of social reinforcers, the drugs can acquire conditioned reinforcing effects that may augment any primary reinforcing effects. My colleague, Dr. Chris-Ellyn Johanson and her students have demonstrated in studies with human subjects that drugs, originally devoid of reinforcing effects, can be self administered after specific circumstances. Normal human subjects who volunteered for the study were given differently colored capsules on different days; one color was associated with diazepam and the other with placebo. When normal subjects were subsequently given a choice between the two colors of capsules they almost invariably chose the capsule color that was associated with placebo. Under other conditions the subjects were told that they would be participating in a study of the effects of drugs on performance, and were put on a very ambiguous performance task in which it was impossible for them to assess how well they performed. On the days in which they were given diazepam in a colored capsule, the computer program signaled a superior performance and they earned a substantial amount of money. On the

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days in which they were given placebo in a differently colored capsule, the computer program signaled that they did poorly on the task and the subjects earned little money. After four occasions, the subjects were given a choice between the two capsules with no work requirements and no money involved. The experiences resulted in a switch in their preference to the diazepam capsule that had been associated with the monetary reinforcement. So it appears that the previously ineffective diazepam became a conditioned reinforcer due to its association with the reinforcing effects of money. And this change in the effectiveness of a drug as a reinforcer could very well be an important mechanistic factor in the etiology of drug abuse.

Reflecting on this mechanism may provide insight into the reinforcing effects of psychomotor stimulant drugs. These like many other drugs of abuse are very often taken in a social context and have perhaps the capacity to become conditioned reinforcers, as well as having their own intrinsic positive reinforcing effects. In addition, the studies by Ron Hill and several subsequent preclinical studies demonstrate that psychomotor stimulant drugs can enhance the effectiveness of conditioned reinforcers. So it is possible that the psychomotor stimulant drugs may enhance their own conditioned reinforcing effects. Some may label this effect “incentive salience” or formulate some other novel hypothetical construct rendering the phenomenon more enigmatic. With the phenomenon cast in terms of known stimulus functions it may lose some of the enigma, but doing so renders it more amenable to empirical study, which of course is what the scientific enterprise is all about. Moreover, this interpretation helps us understand why psychomotor stimulant drugs are so effective as reinforcers. They have primary reinforcing potential, conditioned reinforcing potential, and the potential to increase their own conditioned reinforcing effects. Together these effects can render them especially effective reinforcing stimuli which combined render them especially addicting.

Some have characterized the especially addicting effects of some drugs as inducing individuals to totally lose control over their behavior. This characterization puts the emphasis in the wrong place. As George Bigelow has noted, circumstances often characterized as a complete loss of control by the individual are better characterized as excessive control over behavior by the drug. Instead of focusing on a failing of the individual, possibly a failing of moral consistency, we focus on aspects of the environment of which the behavior is a function. Experiments in monkeys by Robert Balster and Tom Aigner speak to the issue. In those experiments, rhesus monkeys were given a choice between cocaine and food reinforcement. After a few days under these choice contingencies, Balster and Aigner had to stop the experiment because had they continued, the monkeys would have starved; they just were not choosing food often enough. The National Institute on Drug Abuse, the press coverage, and other groups in the United States responded to this study with sensational claims that “cocaine is so addictive that animals will die in order to get it.” Of course any student of the experimental analysis of choice behavior suspected that those claims were exaggerated. Another one of my students, Bill Woolverton, then having moved to the University of Mississippi, replicated Balster and Aigner’s study, but did so covering more parameters of the reinforcing stimuli. In addition to a choice between simply an injection of cocaine, at its maximally effective dose, and a single pellet of food, Woolverton varied the magnitude of food reinforcement and convincingly demonstrated that it is simply an issue of the relative sizes of the reinforcing stimuli, as my old friend and colleague Dick Herrnstein would have predicted. At sufficiently large magnitudes of food reinforcement the subject switched from predominately choosing cocaine injections to choosing food more often. Not only does Woolverton’s study apply the brakes to inappropriate hyperbole about cocaine abuse, it importantly points to the importance of concurrent contingencies that can be applied to address the problem of drug dependence in people with contingency management. These techniques were successfully applied to alcohol abuse by Nate Azrin, significantly advanced in application with cocaine abusers by Steve Higgins, and brilliantly incorporated into the workplace by Ken Silverman. Powerful concurrent contingencies of non-drug reinforcement can compete with drugs as reinforcers and completely capture the individual’s repertoire of behavior so that s/he just says no to drugs!

Alternative reinforcement can be even more powerful from the standpoint of prevention. Many of the risk factors that exist for the development of a drug addiction can be looked at as a paucity of alternative reinforcers in the individual’s environment, especially those that are incompatible with drug use. That paucity, combined with readily available drugs and peer group contingencies, can render the environment one that makes drug abuse highly likely. A paucity of non-drug reinforcement could be due to their complete absence due to a poverty-stricken environment, or it could be due to an absence of a behavioral repertoire necessary to acquire available reinforcers. Drug abuse starts out easy. You don’t have to be smart; you don’t have to be good-looking; you don’t have to be anything other than willing to take drugs. Absent alternative competing reinforcers, drug addiction is a highly likely outcome.

This conceptualization speaks directly to how we can best bring about the necessary change to prevent drug abuse. Dr.

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Shepherd Kellam at Johns Hopkins University actually started research on prevention at the University of Chicago. Kellam and his colleagues went into a number of different schools in the Woodlawn area of Chicago and intensively studied children throughout their entire first year of school. Kellam found that young males who were disruptive in their first-grade class, aggressive, and shy, had an odds ratio of about 2.5 for using alcohol and cigarettes at age of 13 to 14, and at age 21 had the approximately the same 2.5 odds ratio for using hard drugs. Thirty years later these same individuals had an odds ratio of about two for having used cocaine in the past three months. This astounding predictive power had not been obtained previously in any research along the same lines.

In addition, the finding pointed Kellam to preventative research. After relocating to Johns Hopkins University he bumped into my old mentor, Joe Brady, who pointed him to the “good-behavior game.” The “good-behavior game” had been developed at the University of Kansas by Montrose Wolf (Barrish et al., 1969). The game dictates that a classroom be divided into groups of four individuals with the aggressive boys randomly distributed across the groups. The game arranges reinforcers to be distributed based on the behavior of the group. The behavior reinforced is refraining from speaking out of turn, staying seated, and basically conduct essential for learning to take place in the classroom. Reinforcers are only provided if the entire group follows the rules, which puts peer pressure from classmates on the identified at-risk children. As the game progresses, the length of time during which the reinforcement contingencies are in place increases, so that over the first year of school good classroom behavior is “shaped,” allowing the at-risk children to become better students.

The results of this implementation of the “good behavior game” (Kellam et al., 2008) were astounding. First, there was a decrease in the probability of drug use. Second, there was a decrease in the likelihood of involvement with the criminal justice system. Third, there was a decrease in cigarette smoking. There also was an increased probability of graduating from high school, and a decrease in the utilization of mental health services. In addition, all of these outcomes were obtained in the children who were at the higher end on ratings of aggressiveness and disruptiveness at the beginning of the first grade. This finding also points to an important implication for intervention and prevention: start early. If we wait until adolescence to intervene it will be more difficult, less likely to achieve positive outcome, and more costly to individuals and society. Kellam has identified early behaviors that distinguish children at risk. We need to use that information.

In summing up, it has been about 50 years since I was first introduced to the concepts of behavioral pharmacology, and behavior analysis. I have spent those 50 years putting those principles to test, and to work in understanding drug abuse, drug dependence and drug addiction. It has been extremely exciting and rewarding to have participated in the development of the field of behavioral pharmacology, and to see it contribute mightily to our understanding of the etiology, prevention, and treatment of drug abuse and drug addiction. While we may not completely eradicate the problem of drug addiction, I have no doubt that in the future we can tremendously curtail the multiplicity of problems associated with drug addiction.

Acknowledgments

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