Behavioral and Pharmacological Determinants of Pharmacological Plasticity

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Introduction

Behavioral pharmacology has generally been defined as the experimental study of the effects of drugs on behavior and of the ways in which behavior affects drug action. The first part of this definition is reasonably straightforward and appears to occupy the predominant focus of many currently engaged in behavioral pharmacology research. The latter portion of this definition, however, has been frequently overlooked as well as underappreciated. Yet, evaluating the ways in which behavioral antecedents and consequences affect drug action broadens the spectrum and dimensions of pharmacology and also contributes significantly to our understanding and appreciation of the contribution of behavior to determining the pharmacological effects of drugs. Since the initial experiments conducted by P.B. Dews demonstrating that the behavioral effects of a drug depended on the schedule of reinforcement, behavioral pharmacologists steeped in the tradition of the experimental analysis of behavior have been profoundly influenced and intrigued by the powerful effects of environmental variables that control behavior and on the manner in which those variables may modulate drug action.

In his initial landmark study (Dews, 1955) which established the foundation for the discipline of behavioral pharmacology, pentobarbital increased the rate of key peck responding of pigeons under a fixed-ratio schedule of food reinforcement at doses that markedly reduced responding maintained under a fixed-interval schedule of reinforcement. Surprisingly, the effects of pentobarbital on these behaviors were not uniform — as might have been expected — but depended on the schedule of reinforcement that maintained responding. Although Dews discussed the sensitivity of behavior to the effects of pentobarbital, he emphasized use of the “techniques” of schedules of reinforcement to detect the behavioral effects of drugs. This emphasis on schedule-controlled behavior as a determinant of the effects of drugs is a theme that runs throughout much of Dews’s subsequent work on drugs whether he was discussing the specific effects of drugs under many different experimental conditions or whether he was elucidating more global concepts such as addiction (Dews, 1973), analgesia (Dews, 1974), or neurotransmitters (Dews, 1975). His penetrating insight, together with his expansive and often poetic description of the principles and concepts underlying the contribution of schedule-controlled behavior to pharmacology, have been inspirational to many and were posited with a perspective that foreshadowed many findings that were to be supported experimentally in the years to follow. Thus, it is appropriate that this article summarizes a considerable amount of research on the behavioral effects of drugs that has embraced Dews’s emphasis on the importance of schedule-controlled behavior and on the role of the environment in contributing to those effects. Concepts such as the environmental context in which behavior is occurring, along with an examination of prior behavioral and pharmacological experience, have been studied and seen to greatly influence drug effects. In what are now multiple instances, these conditions have been demonstrated to completely reverse the “typical” actions of many drugs, particularly those that are abused. These findings have implications for a more thorough understanding of variables affecting drug abuse and also for arriving at a more detailed understanding of behavioral influences on neuropharmacological and epigenetic mechanisms contributing to those effects. The results of studies summarized here provide a strong recognition and appreciation of Dews’s emphasis on the remarkable contribution of behavior as a determinant of drug action, an emphasis that leads to the general conclusion that not only is behavior malleable or modifiable (i.e., “plastic”) but, perhaps somewhat unexpectedly, so are the effects of drugs.

Schedules of Reinforcement Using Noxious Stimuli

Advances in science and the elucidation of certain principles are frequently made following the introduction of a new technique or the introduction of a new technology. This was the case following the introduction and emphasis on schedules of reinforcement as a means to establish and maintain behavioral performances that provided objective methods for analyzing many complex processes (Ferster and Skinner, 1957). This was also the case when it was demonstrated that the effect of a behavioral consequence such as the delivery of a response-produced electric shock does not uniformly result in a suppression of responding (i.e., punishment) but can, under some conditions, actually maintain high levels of responding that result only with its presentation. Convenient dichotomies sometimes allow for a certain orderliness and regularity but, on occasion, may neglect or mask certain fundamental principles about the relationships between behavior and the environment. For example, it seems quite reasonable that food should maintain or increase behavior when it follows a response and that a noxious electric shock that follows a response should result in a decrease in responding. However, Kelleher and Morse (1968a) and McKearney (1968) demonstrated in a striking set of experiments conducted with squirrel monkeys that the noxious stimulus of electric shock could function as a reinforcer, maintaining behavior in much the same way as other reinforcing events. Byrd (1969) conducted similar experiments with comparable outcomes in cats. Several studies that followed these initial experiments demonstrated that the same electric shock can maintain behavior that results in its presentation, serving as a reinforcer, while, in the same animal under a different component of a multiple schedule, can suppress behavior, functioning as a punisher (Barrett and Glowa, 1977; Kelleher and Morse, 1968a). Similarly, the same event—electric shock in one experiment (Barrett and Spealman, 1978) and cocaine in another (Spealman, 1979)—has been shown to maintain
behavior that terminates its presentation while also serving simultaneously under a different stimulus condition to maintain responding. Under some conditions, it has been possible to demonstrate that two different responses of squirrel monkeys can be simultaneously maintained with one response (a chain pulling response) terminating the delivery of electric shock while a second response (a lever press) is maintained by the presentation of the very same shocks terminated by the first response (Barrett and Stanley, 1980a).

These several experiments which focused primarily on schedules of reinforcement using noxious stimuli, while seemingly enigmatic, provided compelling data that broadened the interpretation of the nature and scope of reinforcement, focused attention on the importance of the behavioral history of the subject, and further emphasized the powerful contribution of schedules of reinforcement to the shaping and maintenance of behavioral performances. They also opened new avenues to develop complex behavioral performances to explore the importance of these variables in the field of behavioral pharmacology and to expand the focus on topics such as the nature of the reinforcing event, the influence of the context in which behavior occurred and the role of behavioral history.

Environmental Events and Behavioral Consequences

Early experiments using squirrel monkeys demonstrated that the nature of the event controlling behavior did not appear to be as significant as the schedule of reinforcement in determining the effects of certain drugs such as amphetamine and chlorpromazine (Kelleher and Morse, 1964). These results were surprising to some because it seemed that the effects of a drug might differ depending on whether responding was maintained by food or, alternatively, by the termination of a noxious electric shock. Nevertheless, the study by Kelleher and Morse reaffirmed the importance of schedule-controlled behavior to drug action that was first described by Dews (1955). Many of the early studies pointing to the importance of schedules of reinforcement as well as to other determinants of drug action were summarized in a now classic publication by Kelleher and Morse (1968b) that remains to this day an important contribution to the literature in behavioral pharmacology.

Subsequent studies with squirrel monkeys responding under fixed-interval schedules of food- or shock-presentation examined the effects of a wider range of drugs such as morphine, alcohol and chlordiazepoxide, (Barrett, 1976; McKearney, 1974). These experiments demonstrated differential drug effects depending on whether food or shock was the consequent event. Under these conditions, alcohol and chlordiazepoxide increased food-maintained responding but decreased comparable rates and patterns of responding maintained by shock (see Figure 1 for the effects of chlordiazepoxide). Morphine, however, increased responding maintained by shock presentation while decreasing food-maintained responding (McKearney, 1974). Cocaine and amphetamine, as might have been expected based on the earlier study by Kelleher and Morse (1964), increased responding regardless of whether it was maintained by shock or by food (Barrett, 1976; McKearney, 1974), and chlorpromazine decreased responding under both conditions (McKearney, 1974). Thus, it appears that some drugs do indeed produce different effects depending on the specific consequence that maintains responding (Barrett and Katz, 1981). Based on these studies, it appears that anxiolytic and sedative-hypnotic drugs decrease responding maintained by the delivery of a noxious shock, whereas these drugs appear to increase responding maintained by the delivery of food; in contrast, the μ opioid receptor agonist morphine produces the opposite effects, increasing responding maintained by shock while decreasing food-maintained responding. Psychomotor stimulants, on the other hand, appear to produce increases in responding maintained by either event, whereas drugs such as chlorpromazine reduce responding under both conditions.

There are a number of striking aspects to these studies. One noteworthy point is that these experiments studied squirrel monkeys responding under a multiple schedule of food and shock reinforcement. Under this schedule, the two maintenance events were occurring within the same experimental session under different stimulus conditions and both events maintained comparable rates and patterns of responding (see Figure 1). This latter point is another feature emanating from Dew’s work emphasizing the schedule-controlled rate and temporal pattern of responding as an important feature contributing to the behavioral effects of drugs (e.g., Dews and Wenger, 1977). Because Dews demonstrated the dependency of drug effects on reinforcement schedules with a single reinforcer, for any valid comparison of the effects of drugs on responding maintained by different consequent events, it is critical that those different events maintain comparable rates and patterns of responding. This was the case in the original publication by Kelleher and Morse (1964) and was also the case in the experiments just described. A second point is that the majority of these results were obtained when responding was maintained solely under fixed-interval schedules and the effects differ under other schedules of reinforcement. For example, when responding was maintained under fixed-ratio schedules of food or stimulus-shock termination, the effects of ethanol, pentobarbital, and chlordiazepoxide were similar under both of these maintenance conditions (Katz and Barrett, 1978). Therefore,
it may be the case that responding under fixed-interval schedules is more sensitive to drug effects that depend on the type of maintaining event than is the case with other schedules. In another experiment with responding of squirrel monkeys maintained under second-order schedules of intramuscular cocaine injection or food presentation, cocaine, chloridiazepoxide, and chlorpromazine did not affect responding differently depending on the maintaining event (Valentine et al., 1983). The use of second-order schedules of reinforcement in these studies was unique in that the event maintaining responding—either cocaine or food presentation—was delivered only at the end of the experimental session where it was paired with a visual stimulus; responses throughout the session produced the stimulus according to a schedule, and responding was maintained throughout by the visual stimulus that only occurred at the end of the session with the administration of cocaine or food. Thus, taken as a whole, these studies indicate that, under certain schedules of reinforcement, the type of event that maintains responding can play an important role in determining the effect a particular drug will have on behavior. However, the schedule of reinforcement is also a significant factor in the determination of those effects as these differences were primarily demonstrated under fixed-interval schedules.

In many respects, the outcomes of studies described in this section are not unreasonable nor should they be surprising. They would appear to be consistent with Dew’s perspective of the importance of the environment and of behavioral consequences and the role they play in behavioral pharmacology. In addition, it would indeed be surprising if a particular drug had effects that were uniform across a wide range of behaviors and consequent events. Selectivity of drug effects is important under a wide range of conditions and can be crucial under others. For example, it is important that drugs targeting anxiety, depression, schizophrenia, or drug abuse be relatively devoid of effects on behaviors other than those targeted for treatment. This has often been a formidable challenge for the development of drugs in the area of neuropsychopharmacology where the effort has been on targeting key symptoms while not affecting other behaviors that are a critical part of the behavioral repertoire.

**Environmental Context**

Behavior, more often than not, occurs in a complex environment where multiple factors may be converging and where both proximal and remote influences can play an important role in governing that behavior. The environmental context in which behavior is occurring can also exert a powerful influence on the behavioral effects of a drug. In one experiment (Mc Kearney and Barrett, 1975) responding of squirrel monkeys was maintained by food presentation in one component of a multiple schedule, whereas in the alternate component, associated with a different visual stimulus, there were no scheduled consequences for responding (extinction). Subsequently, responding maintained by food was suppressed by the delivery of electric shock (punishment); responding in the extinction component was not affected by this change in the schedule. Under these conditions, d-amphetamine only decreased punished responding (Figure 2, triangles), a result that has been replicated repeatedly in a number of species and experimental situations. In addition, there were no effects on responding during the extinction component (data not shown). Subsequently, an avoidance schedule was introduced during the component in which responding previously had no consequences. After rates of responding stabilized, d-amphetamine now produced substantial increases in punished responding in the other schedule component (Figure 2, filled circles) and also increased responding maintained by the avoidance schedule (Figure 2, open circles). Thus, under one experimental condition or context, d-amphetamine had no effect on punished responding but when the context in which that behavior alternated with avoidance behavior, dramatic increases occurred in punished responding.

Similar rate-increasing effects of d-amphetamine on punished responding were obtained in a study in which responding of squirrel monkeys was maintained under a multiple schedule. In one component, responding was maintained under a fixed-interval schedule of shock presentation and, in the alternate component, food-maintained responding was suppressed (punishment) by the same shock that maintained responding in the other component (Barrett, 1977). The effects of d-amphetamine on punished responding under these schedule conditions could reflect induction from the rate-increasing effects on shock-maintained responding that would reflect an interaction between the two components of the schedule. Such contextual interactions where changes in the schedule of reinforcement in one component of a multiple schedule produce changes in behavior in the alternate component where the conditions have not changed have been reported often in the behavioral literature (e.g., ‘behavioral contrast’) by a number of investigators (Reynolds, 1961a, b; Spealman, 1976). Rarely, however, have these been seen in the behavioral pharmacology literature (but see Barrett and Stanley, 1980b). Nonetheless, these findings indicate that the behavioral effects of drugs can be significantly influenced not only by the more immediate consequences of behavior, as suggested by Dew, but also by more remote influences such as those occurring in a different environmental context.

Recent studies examining the social context of drug self-administration in non-human primates have the potential to extend our understanding of the role of social factors in drug...
Behavioral History

Analyses of the determinants of the behavioral effects of drugs, as summarized above, have generally focused on those more immediate factors governing behavior such as the schedule of reinforcement and the environmental context in which behavior is occurring. However, there are a number of instances in which historical factors have been shown experimentally to contribute to current behavior and to the effects of drugs. Studies in both rodents and humans have shown that a history of responding under one schedule of reinforcement can produce enduring effects on responding subsequently maintained under a different schedule (e.g., Wanchisen et al., 1989; Weiner, 1964). A number of studies using rats and pigeons also have demonstrated that reinforcement history can alter the effects of drugs such as methadone and d-amphetamine (Egli and Thompson, 1989; Nader and Thompson, 1987; 1989; Poling et al, 1980; Urbain et al., 1978). Although some of these studies examined drug effects when rates of responding were different, possibly contributing to the outcome due to rate-dependent effects, the finding that there are potential historical influences on behavior and on drug effects was significant in expanding the number of variables experimentally demonstrated to contribute to the behavioral effects of drugs (see Nader et al., 1992).

Historical influences on drug effects in squirrel monkeys were obtained (Barrett, 1977) in an experiment similar to the one described above where the introduction of an avoidance schedule in one component of a multiple schedule changed the effects of d-amphetamine on punished responding (McKearney and Barrett, 1975). In this study, responding of squirrel monkeys was initially established under a punishment schedule in which food-maintained responding was suppressed by the delivery of shock. The effects of d-amphetamine were as expected, i.e., responding was either not affected or was decreased (Figure 3, left panel). The punishment schedule was then removed and an avoidance schedule was introduced. Under this condition, as in the McKearney and Barrett (1975) study, responding was established and maintained by the postponement of electric shock delivery. After several weeks of avoidance training, the avoidance schedule was removed and the punishment schedule was reintroduced; punished responding was allowed to stabilize under the punishment condition for several weeks. At this point, punished responding was now substantially increased with d-amphetamine (Figure 3, right panel). The increases in punished responding in monkeys with a history of shock avoidance are clear in the cumulative response records of performances shown in Figure 4. Following exposure to the avoidance schedule, increasing doses of d-amphetamine now produced large increases in punished responding with subject MS-12 (left panel). The same doses of d-amphetamine only decreased punished responding in subject MS-21 with no history of responding under the avoidance schedule (right panel). Thus, a temporally distant history of responding under the avoidance schedule was sufficient to substantially alter the effects of d-amphetamine, producing a qualitatively different effect of this drug on punished responding. These effects of prior and ongoing experience as determinants of the effects of d-amphetamine on punished behavior were confirmed and extended by Bacotti and McKearney (1979).
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Subsequent studies indicated that the effects of drugs other than d-amphetamine could also be reversed by behavioral history. For example, a history of responding under a fixed-interval schedule of shock presentation reversed the rate-decreasing effects of morphine on avoidance responding (Barrett and Stanley, 1983, Figure 5); these effects of morphine also occurred when responding was concurrently maintained by the schedules of response-produced shock and shock avoidance (not shown). In addition, the rate-decreasing effects of clonidine on responding maintained by electric shock can be reversed in monkeys with a history of punished responding (Figure 6). That the effects of drugs such as cocaine (see below), d-amphetamine, morphine, and clonidine can produce different outcomes depending on behavioral history is of interest, for it suggests that the behavioral effects of these drugs which are often abused can depend quite critically on prior consequences of behavior.

Several experiments were conducted to further examine the conditions potentially contributing to the effects of behavioral history. In one experiment (Barrett and Witkin, 1986), the role of the avoidance schedule was examined by first determining the effects of d-amphetamine on punished responding. One monkey of a pair was then exposed to an avoidance schedule where responding postponed the delivery of shock. A second monkey was "yoked" to this monkey. The yoked monkey received the same shocks that were not avoided by the "lead" monkey. Thus, the yoked monkey received the same intensity and temporal distribution of shocks but had no control over their delivery. When the punishment schedule was reintroduced, d-amphetamine increased responding in those monkeys with an avoidance history (Figure 6, filled circles) but had no effect or only decreased responding in the yoked subjects (Figure 7, filled squares). Thus, the avoidance schedule and the contingencies arranged by that procedure are the significant factors in contributing to the behavioral history.

Further studies were conducted to determine whether the response that was trained under the avoidance schedule had to be the same as that under the punishment schedule. The question was whether the avoidance response could be trained using one response manipulandum with punished responding maintained using a different manipulandum. One way of looking at this question was whether it was sufficient to have a behavioral history of shock avoidance even with a response that differed from that which was subsequently punished. To examine this question, squirrel monkeys were trained under a shock avoidance schedule using a chain-pulling response. Lever pressing was established with food as a

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subsequently trained under the multiple schedule, increases in punished responding occurred and again paralleled exposure to a drug and a specific schedule under a punishment procedure even though the history of avoidance responding was established using a chain-pulling response. Thus, these results indicate that the history of shock avoidance, even though established with a different behavioral response, still has a substantial effect in diametrically changing the effects of a drug from decreases to increases in the likelihood of a response.

In a further effort to evaluate the role of the shock postponement or avoidance schedule, responding of squirrel monkeys was initially maintained under a differential-reinforcement of low-rate schedule (DRL) where responding within a certain period of time postpones the delivery of food (Tatham and Barrett, 1993). The rationale behind this study was that perhaps the behavior of postponing a consequent event may alter the pharmacology of cocaine. Following training under the DRL schedule, monkeys were then exposed to the punishment procedure and the effects of cocaine were determined. Under those conditions, cocaine did not produce increases in punished responding. However, when those animals were subsequently training under the avoidance schedule and cocaine effects were re-determined, increases in punished responding occurred. Thus, this study provides another example, in addition to that of Barrett and Witkin (1986) and Tatham et al. (1993), where the avoidance schedule appears to be critical in establishing this particular pharmacological plasticity of drug effects on punished responding related to behavioral history.

**Drug-Behavior Interactions and Pharmacological History**

There are now a number of instances where the administration of a drug under a particular set of experimental conditions produces a behavioral effect that is opposite that typically obtained. In most instances, these effects have been shown to persist even when those initial conditions are removed. These experiments provide further examples of the ‘plasticity’ of the pharmacological effects of drugs on behavior and add a further dimension to our understanding of the many determinants of drug action. As one example of this drug-behavior interaction, Brady and Barrett (1986) studied the effects of morphine on squirrel monkeys responding under a multiple fixed-interval schedule where responding in each of the two components terminated a visual stimulus in the presence of which shocks could occur. During one of these components, every 30th response also produced shock and responding was suppressed (punishment). In contrast to the previous literature on the effects of morphine on punished responding, this drug produced large increases in punished responding under the multiple schedule, effects that persisted when the effects of morphine were examined under the single schedule of punished responding alone (Figure 8). Morphine was then examined in another set of subjects under the punishment schedule alone and did not increase punished responding (Brady and Barrett, 1986). However, when subjects were subsequently trained under the multiple schedule and administered morphine, increases in punished responding occurred and again persisted when its effects were re-examined under the punishment condition alone (data not shown). These and similar studies suggest that the combined exposure to a drug and a specific behavioral experience can produce dramatic differences in drug effects that persist even when the original conditions that induced those effects are removed.

Although these experiments on drug-behavior interaction history are similar in many respects to those discussed previously as contextual determinants, there are other instances in which the effects of pharmacological history alone have been shown to affect the actions of a drug. In one set of experiments, Glowa and Barrett (1983) showed that the effects on pentobarbital on punished responding of squirrel monkeys maintained under a schedule of stimulus-shock termination depended on whether those monkeys had previously received morphine under these schedule conditions. In monkeys without prior exposure to morphine, pentobarbital increased responding, whereas in monkeys with prior morphine experience pentobarbital produced decreases in responding. These findings suggest that the behavioral effects of drugs may depend on previous experience with other drugs, even when those drugs are from a different pharmacological class.

![Figure 8. Dose-response curves for two squirrel monkeys under multiple- and single-schedule conditions in which responding was maintained under a fixed-interval stimulus-shock termination schedule; the first response after five minutes terminated a visual stimulus in the presence of which shocks could occur. During one component of the multiple schedule, every 30th response produced a shock which suppressed responding during that component (punishment). The effects of morphine were studied under the multiple schedule and subsequently under the single schedule of punishment alone. In contrast to the effects of morphine on punished responding in the presence of shocks, morphine increased punished responding. Thus contextual or historical factors can dramatically affect morphine’s effects on behavior. (Brady and Barrett, 1986, used with permission.)](image-url)
The importance and impact of pharmacological history has also been seen in drug discrimination experiments in which prior drug history has been shown to enhance or diminish the discriminative stimulus effects of drugs that have multiple neuropharmacological actions. Findings from drug discrimination studies indicate that prior pharmacological experience appears to be capable of "biasing" the subjective effects of drugs, thereby enhancing or diminishing the discriminative stimulus effects of drugs with multiple pharmacological effects (Barrett and Olmstead, 1989). Studies in humans also have reported a relationship between prior drug experience and later use and/or addiction (Haertzen et al., 1983). Other studies have examined the role of drug history in self-administration experiments and have demonstrated that pharmacological history can affect the potential for a drug to be self-administered (e.g., Bergman and Johanson, 1985; Falk and Tang, 1989; Panlilio et al., 2013; Shinday et al., 2013; Young et al., 1981). For example, Hiranta et al. (2013) have shown that rats that previously self-administered cocaine will also self-administer sigma1 receptor agonists (σ1Rs). However, without that history, σ1R agonists were not self-administered. Of interest, is the additional finding in this study that the reinforcing effects of the σ1R agonists were not mediated by dopamine receptor systems; dopamine receptor antagonists, which blocked cocaine self-administration, did not block the self-administration of the σ1R compounds. In addition, there were no changes in dopamine levels in the nucleus accumbens shell at doses of the σ1R agonists that were self-administered. These studies taken as a whole provide a compelling perspective on the powerful effects of prior behavioral experience and pharmacological history on the effects of abused drugs. As Falk (1983) once commented, "Pharmacological structure does not imply motivational destiny" (p. 320).

**Summary and Conclusions**

Peter Dews has had a significant and enduring influence on the field of behavioral pharmacology. This influence is based not only on his establishing its origins, blending the two disciplines of the experimental analysis of behavior and pharmacology, but also on how that field developed following his initial studies and how it has matured throughout the past near 60 years. Many of the themes and implications regarding the role and importance of the environment and of the influence of schedule-controlled rates and patterns of responding on drug action have served to guide research for many years, allowing the field to develop following the principles of an experimental and quantitative discipline closely and beneficially aligned with both pharmacology and the experimental analysis of behavior. This article serves as a reminder of how prescient Dews was in his framing of the scope and importance of behavioral pharmacology and how far the current emphasis seems to have drifted from those early concepts which addressed intriguing and fundamentally important questions about the behavioral determinants of drug action that remain unresolved to this day.

The collective findings summarized in this manuscript, representing the contributions of many individuals, may have certain implications not only for formulating issues fundamental to an analysis of the behavioral effects of drugs but also to increasing our understanding of drugs of abuse and abuse liability. One striking aspect of the many studies summarized in this manuscript is the observed "pharmacological plasticity," that is, the multiple ways in which drugs can affect behavior. This plasticity is intimately linked to the schedule of reinforcement, to behavioral consequences, to the environmental context and to behavioral and pharmacological history. It is important to appreciate that all these factors contribute eventually to historical influences on behavior and on the effects of drugs. An experimental or an environmental context in which events occur and produce behavioral consequences becomes part of that individual's repertoire and governs future behavior. As we have seen here, these influences can play an overwhelming role in the effects of drugs.

The effects summarized here have been seen predominantly with a wide variety of abused drugs from different pharmacological classes. If certain drugs are abused due to their effects on behavior, and those behavioral effects are related to past behavioral experience or to experience with a particular drug, then such historical factors become exceedingly important in our understanding of the etiology of substance abuse and in the development of various approaches undertaken for treatment and prevention strategies. A better understanding of those behavioral and pharmacological factors may generate novel approaches for 'immunizing' individuals against the effects of drugs having abuse liability and for the development of potential pharmacological interventions. Although seemingly remote at the present time, it remains quite clear that both behavioral and pharmacological variables can influence the effects of abused drugs in striking and significant ways as suggested throughout this paper.

A related point has evolved from the studies demonstrating the importance of behavioral history in determining the effects of abused drugs. In the majority of the studies described in this manuscript, the behavioral performances were comparable prior to and following the interpolated procedure that was responsible for modifying drug effects. Thus, although the ongoing rate and pattern of responding can be an important influence on the effects a drug will have on behavior, it is not all determining. A number of abused drugs can reveal "sequestered" or residual influences on behavior that are not otherwise evident in ongoing behavior. Prior behavioral experience can leave residual effects that are not manifested in ongoing behavior and are observed only following the administration of a particular drug. The nature of those residual influences remains unclear at the present time and in need of clarification.

It is becoming increasingly possible to probe more deeply into "structural plasticity" associated with exposure to drugs of abuse that may yield further insight into changes occurring at the molecular and epigenetic level. For example, Robinson and Kolb (2004) have demonstrated that exposure of rats to amphetamine, morphine, cocaine, or nicotine produces persistent alterations in dendritic structure and on dendritic spines on cells in brain regions such as the nucleus accumbens. These authors suggest that this plasticity in CNS structure following exposure to abused drugs may be responsible for some of the factors related to addiction and may also be related to behaviorally-driven influences as well. Similarly, Nader et al. (2006) have demonstrated long-term decreases in dopamine D2 receptor availability in rhesus monkeys following a one-year period of cocaine self-administration suggesting that the plasticity induced by these changes in CNS activity are long lasting. Finally,
Damez-Werno et al. (2012) have reported that repeated exposure to cocaine produces epigenetic modifications in chromatin that can be viewed as "epigenetic scars" suggesting another approach to addressing and clarifying some of the issues related to both the pharmacological and behavioral factors that may provide new insights into the molecular neurobiology of drug addiction.

It is quite clear that the marriage of the experimental analysis of behavior and pharmacology has been an active and vibrant field, only a portion of which is summarized in this manuscript. The field of behavioral pharmacology has frequently been criticized for its emphasis on overt schedule-controlled behavior to the exclusion of other variables and hypothetical mechanisms. However, knowledge of the pharmacology and neuropharmacological mechanisms and molecular biology of abused drugs, while of unquestionable importance, does not provide a complete account of the behavioral effects of drugs of abuse. As Dews once said, "A drug is obviously essential for drug addiction, as are Mycobacteria for tuberculosis ...[but] ...knowledge of the pharmacology of abused drugs will not tell us all we need to know about addiction" (Dews 1973, p. 37). The point is that behavioral analyses continue to demand far more attention than has been the case in recent years. Indeed, the enduring legacy to Dews's many contributions will be in a continued analysis of, and appreciation for, the importance of environmental influences on the effects of drugs on behavior and of the importance of behavioral pharmacology to the broader discipline of pharmacology.

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**Celebrating the Life of Peter Dews**

Please join us to celebrate the life of Peter Dews (1922-2012), whose life and work contributed greatly to the development of behavioral pharmacology as a discipline.

**Tuesday, April 23, 2013**

Harvard Club (Bartlett Room), 374 Commonwealth Avenue, Boston, MA

6:30 - 9:00 p.m.

RSVP is required. If you would like to attend, please email Danielle Jordan at djordan@aspet.org.