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BEHAVIORAL DETERMINANTS OF DRUG ACTION: THE CONTRIBUTIONS OF PETER B. DEWS

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Peter B. Dews played a significant role in shaping the distinctive characteristics and defining the underlying principles of the discipline of behavioral pharmacology. His early and sophisticated use of schedules of reinforcement in the 1950s, incorporated from research in the experimental analysis of behavior and integrated into the discipline of pharmacology, provided tremendous insight, inspiration, and impetus to the newly emerging field of behavioral pharmacology. The experimental findings generated by Dews' research, blending the sophisticated use of behavior and pharmacological principles together with the elegant manner of their presentation and far-reaching implications, provided the force and momentum to establish and direct behavioral pharmacology for several decades. This article attempts to capture some of Dews' research that integrated and inspired the blending of sophisticated behavioral work with that of pharmacology.

Key words: P.B. Dews, behavioral pharmacology, schedules of reinforcement, fixed-interval schedules, pigeons

A large portion of scientific inquiry consists of the clarification and elaboration of certain central themes that have been initiated by an individual or a small group of investigators. The initiation of new, profound and enduring scientific movements is indeed rare. Typically, the momentum behind a worthwhile novel approach or a new beneficial avenue of scientific inquiry builds gradually by yielding significant insights into a particular problem, developing alternative means of approaching a problem through technological developments, or through a combination of these factors. As the interest in or the significance of these endeavors becomes more widely apparent, the field attracts students and other investigators who then establish academic or industrial laboratories and begin to aid in the development of a lineage and corpus of work that eventually places that field on firm footing for subsequent generations. Such is the recurring and magnificent theme of science and such is the case with the scientific line of research initiated by Peter B. Dews.

The emergence of the discipline of behavioral pharmacology and, indeed, many of its defining characteristics and most fundamental findings, rests to a large extent on a line of studies launched by Dews in the early 1950s. As in many emerging fields of scientific creativity, Peter did not single-handedly create or establish the field of behavioral pharmacology; he and others have acknowledged the efforts of many, particularly those of his colleagues W. H. Morse and R. T. Kelleher in the Psychobiology Laboratory at Harvard during a four-decade period of tremendous research innovation and productivity (Barrett, 2002; Branch, 2006; Zeiler, 2006). However, it was largely Peter's scientific leadership, his identification and elucidation of the power of behavioral variables, and his elegant poetic approach that inspired countless researchers and students and, consequently, provided the legacy for this field that is embodied in the discipline of behavioral pharmacology. In 1981, in a tribute to B. F. Skinner and I. P. Pavlov, as well as more generally to the creators of modern biological science, Peter wrote the following:

> Most men who have assisted profoundly the development of science have required four types of skills. First, the ability to recognize and to define important problems susceptible to scientific elucidation and to define them clearly; that is, to see distant goals clearly and to formulate strategy. Second, the tactical ability to conceive and conduct experiments

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> sufficiently limited in scope to be rigorous, but advancing science according to the general strategy. Third, the innovative ingenuity and technical skills needed for the actual conduct of elegant experiments. Fourth, the ability to see how the results of experiments contribute to understanding and to use the results to guide tactics of future experiments. (Dews, 1981, p. 246)

Although written to acknowledge the contributions of two preeminent behavioral researchers, these comments also clearly apply to Peter. Furthermore, we could easily add a fifth dimension to these characteristics, that of inspirational leadership. Though trained as a pharmacologist, having also a degree in medicine, Peter espoused one recurring and unwavering theme that served as the rallying cry for innumerable young researchers—the power of behavior and of behavioral variables to determine the effects of drugs. That perspective, together with the supporting data he and others generated, elevated both behavioral research and pharmacology to new levels and had a profound effect in shaping the field. The finding that provided the impetus for much of the initial direction of behavioral pharmacology, described in more detail below, that the action of a drug could be determined by the distinctive features of ongoing behavior, provided added credibility to the experimental utility of behavioral control by schedules of reinforcement and incorporated the study of drugs as another variable to be explored within the realm of the experimental analysis of behavior.

HISTORICAL CONTEXT AND SETTING

An understanding of the emergence of behavioral pharmacology as a formal scientific discipline is perhaps best viewed from a historical context. The period of the 1950s has been termed the Golden Age of Psychopharmacology because, during this decade, the first therapeutics were identified that treated the debilitating diseases of schizophrenia, depression, and anxiety. Indeed, the first major conference on the use of new pharmaceuticals in the field of psychiatric disorders heralded two of these drugs—chlorpromazine and reserpine—as ''harbingers of a new era'' such that a ''new door had been opened on the treatment of mental disease'' (Kline, 1956). The introduction of these compounds, along with the antidepressant imipramine at about the same time, followed shortly by the discovery of the anti-anxiety drugs from the benzodiazepine series in the latter portion of the 1950s, provided the tools for the beginning of a theoretical debate about the effects of these drugs on emotional states and on the appropriate manner in which experimentation with animal subjects could be used to assess those effects (McMillan & Katz, 2002). Very little was known about the mechanisms underlying the effects of these compounds (or, for that matter, about the presumed emotional states on which it was believed they worked), and it was to be some time before the emergence of the dopamine and biogenic-amine hypotheses of schizophrenia and depression, respectively, were to emerge (Carlsson, 1988; Schildkraut, 1965). Neurotransmitters in the brain were hypothesized to exist and play a role in pharmacology and in emotional states, but only two such substances—acetylcholine and 5-hydroxytryptamine—were believed to meet the criteria for central neurotransmission, and positive experimental evidence even for these was still lacking. Writing in 1962, Peter stated:

> It has been postulated that there are several different neurohumoral transmitters in the brain with differing effects on the postsynaptic membrane. It has been further postulated that the primary site of action of exogenous drugs in the brain, as in the peripheral nervous system, is at synapses. If drugs affecting the brain were to have differential effects which depended upon the chemical nature of the synapse and perhaps also upon the anatomical characteristics of the synapse, then a relatively small number of transmitters and anatomical types of synapses could account, by combinations of varying complexity, for the wide variety of drug effects on the central nervous system. (Dews, 1962a, p. 425)

Perhaps the lack of detailed biochemical information related to the pharmacological effects of drugs in the brain helped to direct Dews' focus on behavioral variables; behavior was easily measurable, readily quantifiable, and also was sensitive to a wide range of variables. In the absence of accessible neurochemical influences, behavior could be differentially reflective of drug action while also yielding important information about the nonpharmacological (i.e., behavioral) factors

that contributed to those effects. Although clearly acknowledging actions of drugs at other levels of analysis, the lack of a clear understanding of receptors, neurochemical pathways, and mechanisms of action was not a deterrent for an evolving focus on behavioral determinants of drug action.

The emergence of behavioral pharmacology and psychopharmacology coincided also with the rapid advances being made in the experimental analysis of behavior. B. F. Skinner, together with his students, had embarked on a series of systematic studies, primarily with pigeons as experimental subjects, that resulted in the publication of the book *Schedules of Reinforcement* (Ferster & Skinner, 1957). A group of individuals then went on to establish the *Journal of the Experimental Analysis of Behavior*, first published in 1958. This journal served as the vehicle for many of the early publications that combined behavior analysis with pharmacology. A retrospective summary of the behavioral work conducted during this period, written by many of those who participated, is provided in ''A tribute to the Harvard Pigeon Lab'' published in the May 2002 issue, Volume 77, Number 3 of the *Journal of the Experimental Analysis of Behavior* (Lattal, 2002). The technical advances made possible by the use of programming equipment enabled experimenters a degree of control over behavior that was extraordinarily powerful, necessarily objective and unobtrusive, and was capable of a dynamic range often found in traditional physiological systems. Thus, it was possible to produce a near-infinite range of behaviors, reproducible across species, stable in their maintenance, manipulable over a wide range, and capable of being brought under rigorous stimulus control—ideal conditions for examining the effects of drugs on behavior. The excitement and vigor surrounding the coalescence of these many opportunities is difficult to reconstruct but is amply and forcefully embodied in Peter's writings as this field emerged as a separate discipline. The exquisite tools contributed by the experimental analysis of behavior coupled with the exciting effects of drugs discovered by pharmacological science provided a wealth of possibilities for this emerging discipline that I hope are captured in descriptions that follow.

INITIAL STUDIES IN BEHAVIORAL PHARMACOLOGY

The theme of the importance of behavior in determining the actions of drugs is seen in one of the first studies Peter published after moving to the Department of Pharmacology at Harvard Medical School. Peter was hired by the eminent pharmacologist Otto Krayer (Anderson, 2005) who suggested that he contact B. F. Skinner who was doing some interesting work with pigeons in the Psychology Department. The manuscript that was generated by these initial interactions (Dews, 1955a) was entitled: ''Studies on Behavior. I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward.'' It was to be one of a series of publications focusing on behavior and the effects of various drugs, with this initial article, perhaps, being most influential in the emergence of the field of behavioral pharmacology. This article described the results of an experiment in which the key peck responding of pigeons was maintained under either a fixed interval (FI) 15-min or a fixed ratio (FR) 50-response schedule. Characteristically, the FI schedule maintained a low response rate during the initial portion of the interval, accelerating to a much higher rate towards the end of the 15-min period; overall, the average response rates under the FI were 24 pecks per min. In contrast, response rates under the FR schedule were constant and averaged approximately 104 responses per min. Pentobarbital was administered to the pigeons prior to certain sessions and, as shown in Figure 1, the effects were striking: pentobarbital had a much greater effect on responding maintained under the FI schedule than it did on responding maintained by the FR schedule. Doses of pentobarbital that produced a marked reduction of FI responding (1 and 2 mg/kg) produced an increase in responding under the FR schedule. Thus, under these conditions, a drug frequently characterized as a ''CNS depressant'' was shown to have either stimulant- or depressant-like effects depending on the schedule of reinforcement. Dews suggested that the greater sensitivity to modification of performance on the 15-min FI by small doses of pentobarbital was due to factors that influence the control rate of response under these schedules.

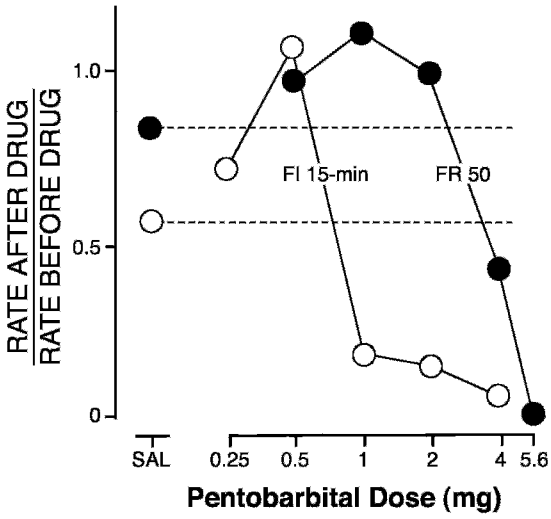

Fig. 1. Effects of pentobarbital on key pecking of pigeons responding under either a FI 15-min (open circles) or a FR 50 (filled circles) schedule of food reinforcement. Control (nondrug) response rates are shown on the left above SAL (Saline). The drug effect is expressed as the ratio of the mean response rate after the drug to the mean response rate before the drug on the same day. The ratios were averaged across the four pigeons. Each point represents the arithmetic mean of the ratios for the same 4 pigeons at each dosage level on each schedule. For the Control points, the mean of the ratios represents sessions in which saline was injected and compared to the noninjection response rates. Note that pentobarbital produced increases in responding under the FR schedule at doses (1.0 and 2.0 mg/kg) that reduced responding under the FI schedule. Modified from Dews, 1955a.

This work was followed by other papers in the series that involved discriminative stimulus control and which also expanded the range of drugs to include scopolamine and methamphetamine (Dews, 1955b, 1957, 1958a; Wurtman, Frank, Morse, & Dews, 1959). In the introduction to the next paper in the series, Peter stated explicitly that in the initial study ''the schedule of reward was thus shown to be a relevant environmental variable in determining the behavioral effect of pentobarbital'' (Dews, 1955b, p. 380). This statement essentially laid the foundation for much of that which followed both in Dews's laboratory as well as more broadly within the field. It provided added credibility to the emerging focus on the importance of behavior, opened avenues for the integration of behavior and pharmacology, and drew attention to certain unsuspected variables of potential import to drug action.

The finding that the behavioral effect of a drug could depend on the ways in which that behavior was and had been controlled by its consequences was to emerge as a dominant theme in much of the work emanating from the Harvard laboratories and other academic centers over the next several years. The capacity of behavioral variables to exert an overwhelming influence on drug action assumed significant proportions. Behavioral variables such as the conditions existing at the time the drug is administered, the environmental context in which that behavior occurred, the type of event maintaining behavior, and even the previous behavioral history of the animal would eventually be shown to direct the outcome of drug action in dramatic ways (Barrett, 1977, 1986, 1987; Barrett & Katz, 1981; Barrett & Witkin, 1986; Kelleher & Morse, 1968; McKearney, 1979; McKearney & Barrett, 1978; Morse, McKearney, & Kelleher, 1977). The findings by Dews that launched this work had tremendous impact in shaping this field by forcing attention not only to the exquisite sensitivity of behavior to drug effects but also to the significant contribution of the controlling variables of behavior as a dynamic influence on the magnitude and direction of those effects.

THE PIGEON

The pigeon was a unique choice in pharmacological studies but was a direct result of the influence of Ferster and Skinner, as well as of the availability of suitable equipment. Dews (1956) addressed the use of the pigeon in pharmacological studies and its utility in general, providing an interesting insight into the more widespread incorporation of this species into pharmacological studies:

> Pigeons have some advantages for this type of work. They stay adult and in their prime for many years without apparent change. … Perhaps the most important advantage is the relative 'pureness' of the behavioral 'response' used; that is, the peck. The pigeon can operate the key only with its beak, and although the precise topography of the peck undoubtedly varies from time to time, the variation is necessarily within fairly narrow limits. This is not always true for most other species and it is

> perhaps the main reason why, by and large, experiments on pigeons seem to progress faster than those performed with other species—a by no means unimportant consideration in a new branch of science. The main disadvantage of the use of pigeons is the great phylogenetic gap between birds and humans. All that one can say is that the general laws of operant behavior seem to show remarkable constancy from species to species, and that so far we have not found drug effects in pigeons that outrageously contradict the known effects of the same drugs in humans. (pp. 268–269)

In response to some concerns and criticisms surrounding the selection of the pigeon and the focus on an ''isolated'' operant response such as the key peck, Dews (1956) had the following comments:

> The … criticism … is that the dependent variable, the rate of pecking, is only a tiny fragment of the total behavior of the animal. Whatever validity this criticism may have from the immediately practical standpoint of discovering new drugs, it seems to be quite invalid from the standpoint of basic research. We do not accuse the biochemists of triviality when they attempt to isolate a pure enzyme system, although any one such system is only a tiny fragment of the total biochemical machinery of the cell. A detailed analysis is a prerequisite of a worthwhile scientific synthesis. (p. 281)

Thus, the species was selected and the foundation in place for a number of pioneering studies that elaborated on the fundamental principle of the influence of behavioral variables in determining the effects of drugs. In parallel to these publications from Dews, there were other studies whose publication complemented and greatly expanded upon the themes arising from Dews's work. These came from a close collaborator and colleague—William H. Morse—who also was to be a pivotal force associated with the Laboratory of Psychobiology for many years to come and whose contributions to the experimental analysis of behavior also are described in this issue by Zeiler (2006). These studies by Morse represented an insightful use and application of the nuances of schedule-controlled behavior to the study of drug action, thereby adding both substance and depth to the emerging field of behavioral pharmacology (Dews & Morse, 1961; Herrnstein & Morse, 1956; Morse & Herrnstein, 1956). Roger T. Kelleher, who also was to become a cornerstone in the developing discipline of behavioral pharmacology, eventually joined Dews and, with Morse, contributed significantly to the study of behavior controlled by noxious stimuli and the effects of drugs (Bergman, Katz, & Miczek, 2002; Branch, 2006; Morse & Kelleher, 1977). The research and emergent themes that emanated from this trio of individual scientists and their students and postdoctoral fellows truly dominated the field of behavioral pharmacology throughout the 1950s to the 1990s (Barrett, 2002).

EXPANSION AND ELABORATION OF PRINCIPLES

Dews moved rapidly into the exploration of other schedules of reinforcement as a basis for examining the effects of drugs, continuing to demonstrate and elaborate on the power and influence of the schedule of reinforcement in determining drug effects. For example, he studied the effects of pentobarbital and methamphetamine in pigeons responding under a multiple FI FR schedule, examining the time course of drug action and the effects of large doses, including recovery of performance in the different components of the schedule (Dews, 1956). The exquisite sensitivity of behavior in the different components of the multiple schedule was again striking. For example, following a large (30 mg, i.m.) dose of pentobarbital, the recovery of responding occurred completely under the FR schedule within 24 hours but responding under the FI schedule was still substantially affected at this time, not recovering fully until 48 hours had passed since the initial injection. Methamphetamine, in contrast, produced its greatest effects under the FI schedule with large increases in responding occurring in that component, with little effect on FR responding.

The striking aspect of these findings was that these experiments were within-subject evaluations of the effects of methamphetamine and pentobarbital using multiple schedules of reinforcement in which the different components, each associated with different visual stimuli, alternated throughout a single experimental session. The concentrations of the drug in the brain, actions at any receptor target or transporter, systemic bioavailability, or any other pharmacological aspects of the

drug were relatively constant when assessed, but the effects were determined completely by the prevailing schedule of reinforcement. It was as though the schedule was a pharmacological ''switch'' that both qualitatively and quantitatively gated and directed drug effects. The ability to enhance or reduce responding by a drug simply by alternating the schedule and associated stimuli was simply stunning and gave tremendous momentum to the youthful field of behavioral pharmacology which was still struggling for a foothold and an identity within the separate fields of experimental psychology and pharmacology. Experimental psychology was heavily imbued with theoretical constructs and ''explanations'' of behavior related to emotional states. Pharmacology, however, was seen as a relatively more mature science, focusing on isolated organ systems where control and precision of measurement was a prominent feature. Interestingly, and in retrospect, both behavior and pharmacology were to become much more reductionistic over the next decades.

The effects of drugs on behavior observed by Dews led to his posing a fundamental question: ''How may the behavioral effects of these drugs be analyzed?'' (Dews, 1956, p. 274). He then proceeded to provide a framework for the behavioral analysis of drug action with the reply to his own question best captured by a direct quotation:

> Traditionally, behavioral effects of drugs are attributed to effects of the drugs on emotions such as fear and anxiety, and on ambitions, inhibitions, drives, and other hypothetical or arbitrarily defined 'states.' The system of experimentation under discussion leads logically to a different approach; it leads to an analysis in operationally defined terms. The pecking performance of the pigeons in these experiments in the absence of a drug depends on a number of explicitly defined variables, many of which are under direct experimental control. The state of food deprivation of the animal can be changed by simply changing the amount of food given. The size of the ratio and the length of the interval are under direct experimental control. The presentation of colored lights, correlated with schedule, comes to have an important effect on performance, and these stimuli can be changed. … These are examples of some of the independent variables under the control of the experimenter that influence the dependent variable; that is, the rate of pecking. In analyzing the effects of a drug, the logical first step is to search for simple interactions between such factors and the effects of the drug; in other words, to determine to what extent the drug effects are 'like' in the sense of having the same effect on behavior, the effect of change of level of deprivation, the change of size of ratio, extinction, and so on. Needless to say, this will only be the *first* step in the analysis of the effect of the drug. (Dews, 1956, p. 274)

The questions raised in this paper, some of which were addressed by Dews in the same manuscript (e.g., effects of extinction, potential loss of stimulus control, changes in the parameters of the schedule), focused on controlling variables and were to serve as some of the main emphases of behavioral research for decades to come. Furthermore, in this publication, Dews also conducted some analyses under FI schedules comparing several drugs such as chlorpromazine, methyprylon, pipradol, and methylphenidylacetate, in an attempt to determine how their effects differed under this schedule. He was able to demonstrate both qualitative and quantitative differences amongst them, thereby providing a concept that was a harbinger of subsequent behavioral ''screening procedures'' used commonly in industrial settings; this analysis demonstrated ''considerable power to discriminate between different kinds of drugs affecting the central nervous system'' (Dews, 1956, p. 281). This suggestion and approach may not be terribly surprising in light of the fact that before Dews went to Harvard he worked at the Wellcome Pharmaceutical Research Laboratories to develop screening methods for the evaluation of various compounds in mice (Dews, 1953), approaches that have continued to evolve in the pharmaceutical industry to examine CNS-active drugs (Sanger, Willner, & Bergman, 2003). These principles and behavioral approaches were expanded significantly in pharmaceutical companies to profile and develop the benzodiazepines and antipsychotic drugs and other compounds with potential activity in a variety of psychiatric disorders (Cook & Kelleher, 1963; Geller, 1964; Geller, Kulak, & Seifter, 1962; Geller & Seifter, 1960).

The potential contribution of operant approaches to the investigation of the actions of these newly emerging drugs, the area of research that became known as psychophar-

macology, is captured in a number of reviews written by Dews and his colleagues during this time (e.g., Dews, 1958b, 1962a; Dews & Morse, 1961). In 1958 Dews wrote that ''the great interest in psychopharmacology during the last few years has not been due to the formulations of new theories or the impact of cogent arguments … but due mainly to the remarkable success which experimental pharmacologists and observant clinicians have had in discovering new drugs with hitherto unsuspected effects on behavior. This success has made it extremely important that a basic science of psychopharmacology develop as fast as possible'' (Dews, 1958b, p. 1024).

THE MATURATION AND DEVELOPMENT OF BEHAVIORAL PHARMACOLOGY

The thrust of the integration of operant approaches to behavioral analysis with those of pharmacology began to take hold in the late 1950s and early 1960s and is manifested in statements such as ''the extraordinary power of the free-operant technique results from the fact that it permits performances to be 'tailor-made' in order to obtain optimum circumstances for manifestation of any specific aspect of a drug effect on which one wishes to focus attention'' (Dews, 1956, p. 279). One of the fundamental principles underlying Peter's approach was to establish rigorous control over the behavior under study—the reproducible patterns of behavior, generated by strong behavioral consequences, were essential to examining the behavioral effects of drugs. Clearly, the ability to control behavior precisely, minimize variability, and isolate controlling variables were of critical import to Dews and to individuals seeking to understand drug action and to apply these techniques to drug discovery. Dews cautioned against certain approaches within the emerging field of psychopharmacology, one of which was on the use of the ablation technique to evaluate the influence of certain brain regions for their contribution to the effects of drugs. For him, this technique raised certain concerns, again stated eloquently, with force, and some humor at this early stage of the field:

> The concept is emerging that the brain is a number of systems of neurons acting on one another through the liberation of an unknown number of humoral transmitters, with the different regions of the brain differing in the relative concentrations and preponderances of the different types of cells. If true … then it is clear that ablation studies will be unprofitable to understanding brain function. If we are interested in trade activities of, say Western Europe with the rest of the world, we would learn little from studying the effects of ablation of Italy; the place of Fiats in the ships leaving Europe would be filled rapidly by Renaults and Volkswagens and that of chianti by claret. (Dews, 1962a, p. 435)

RATE DEPENDENT EFFECTS OF DRUGS AND STIMULUS CONTROL

Other principles in addition to that of the importance of the schedule of reinforcement were to emerge in rather rapid succession in Dews's work. One of the main additional themes was that of ''rate-dependent drug effects.'' This effect is based on the quantitative and proportional relationship observed between the control rate of responding in the absence of a drug and the effects on response rate following its administration. Dews first examined this principle in the context of investigating the effects of the barbiturate amobarbital on ''inhibitory'' behavior (Dews, 1964a). It had been suggested that the paradoxical increases in responding seen with barbiturate sedative hypnotics were due to a release of inhibition. Thus, with the responding of pigeons maintained under a FI 500-s schedule, Dews periodically superimposed a visual stimulus that was correlated with the absence of reinforcement (S^{Δ} or extinction). When present, as would be expected, this stimulus produced a reduction or cessation of responding. For analytical purposes, the fixed interval was divided into segments that permitted the analysis of response rates throughout the interval, including those very low response rates separately occurring during the ''inhibitory'' stimulus. Amobarbital produced substantial increases in the low rates of responding during the inhibitory stimulus compared to the effects on responding during other portions of the schedule; when plotted on a log-log scale, however, it was evident that there was a direct relationship between the control (nondrug) rate of responding and the increases in response rate: high rates of responding were increased less or were de-

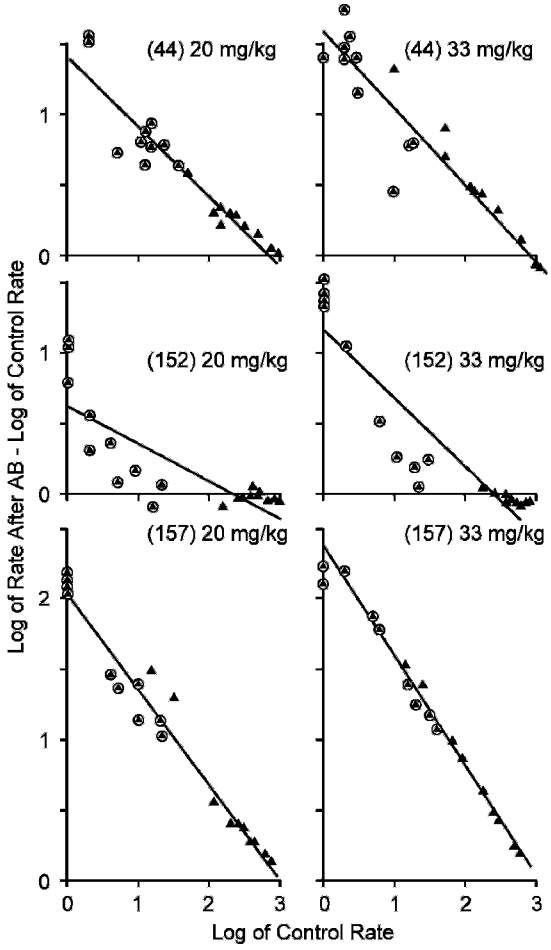

Fig. 2. The relationship between mean rates of responding in individual 25-s periods under control conditions and following administration of amobarbital. X-axis: log of the rate of responding as responses per session (the fixed interval was 500 s, divided into 25-s periods; the 20 periods within each FI were cumulated over the course of the session); Y-axis: change in log response rate following amobarbital. There are 20 points on each graph, 10 representing periods when the houselight was present (shown as circled triangles), and 10 representing periods when the houselight was not present (shown as triangles). The numbers in parentheses represent the pigeon number. Note the inverse relationship between control response rate and the effects of amobarbital with the lower response rates in the stimulus associated with nonreinforcement (i.e., houselight present, circled triangles) showing larger increases following amobarbital. After Dews, 1964a.

creased relative to the lower response rates which were increased markedly (Figure 2).

The apparent specificity of the effects of amobarbital on inhibitory behavior vanished under this analysis. Dews related the dependence of the drug effect on control rate more generally to the biological principle of the Law of Initial Values. The general principle that the effects of drugs were influenced by behavioral variables was emerging clearly and is captured by this quotation (Dews, 1964a):

> It is becoming increasingly clear that the behavioral effects of barbiturates—and other drugs—are to be understood in terms of the changes in the parameter values of functional relationships between sequential environmental events and the dynamic dependent behavior, just as the effects of drugs on blood pressure are to be understood as changes in parameters of cardiovascular functions. They will not be understandable in terms of specific effects on hypothesized psychological entities such as inhibitions and anxieties. Behavioral responding is dependent on temporal relationships between responses and reinforcing stimuli, and is modulated by discriminative stimuli; … it is these dependencies that are modified by drugs. (p. 305)

The principle of rate-dependent drug effects was to assume a prominent position in the field of behavioral pharmacology and was used to account for the effects of many different drugs on diverse behaviors (Kelleher & Morse, 1968). Indeed, the contributions of response rate as a determinant of the behavioral effects of drugs were believed to be so strong that comparisons of drug effects on different behaviors or on behaviors maintained by different types of events (e.g., drug- versus food-maintained responding, appetitive versus aversive events) could not be conducted unless the control (nondrug) response rates were equivalent. Again, the emphasis and attention was drawn to the importance of the behavior and of the variables controlling behavior as a significant factor in determining the outcome of drug effects.

ANALYSIS OF FIXED-INTERVAL SCHEDULES

Although Peter's principal research as described thus far focused mainly on the analysis of the behavioral effects of drugs, his frequent use of fixed-interval schedules to study the effects of drugs also generated an interest in the behavioral analysis and theory of responding under fixed-interval schedules. The im-

pressive and ubiquitous ''scalloped'' appearance of responding maintained under fixed interval schedules generated a number of concepts in an effort to account for this pattern. These concepts included theories such as ''chained responding,'' ''mediating behavior,'' and/or a learned temporal discrimination which may be related to either or both of these concepts. According to the chained responding concept, a chain of responses is a sequence in which each response serves as a discriminative stimulus that changes the probability of occurrence of a further response. Mediating behavior was defined as a sequence of responses between two events that serves to transmit the behavioral influence of one event to that of the other. Accordingly, if the overall positively accelerated scalloped pattern of fixed-interval responding was organized and maintained by the chaining together of responses that in some way mediates responding throughout the interval, then it should be possible to perturb this orderly progression by disrupting responding at certain points throughout the interval. Dews did this in his first manuscript in this area (Dews, 1962b) by periodically arranging S^{Δ} periods throughout the interval that disrupted responding; the delivery of food never occurred in the presence of S^{Δ}. Despite the disruption of the continuous, coherent pattern of positively accelerated responding (i.e., that which was presumed to be chained and/or mediated responding) typically maintained under fixed-interval schedules, the interpolated S^{Δ} periods did not disrupt the general pattern of fixed interval responding. In eliminating the chaining of responses along with an account based on mediating behavior as a means of accounting for fixed interval patterns, Dews posited the possibility that the progressive increase in the rate of responding throughout the interval might be based on a ''declining retroactive rate-enhancing effect of the reinforcing stimuli'' that occurred upon completion of the fixed interval (Dews, 1962b, p. 373). It should be noted that this approach of using interpolated S^{Δ} periods throughout the fixed interval to control different rates of responding subsequently was used to study the inhibitory effects of amobarbital, mentioned earlier (Dews, 1964b).

This theory, together with attempts to demonstrate the lack of feasibility of the chained mediating behavior hypothesis, was pursued further in a broad series of experiments that focused on species typicality, with results similar to those obtained in pigeons also demonstrated in nonhuman primates (Dews, 1965a). Further studies examined multiple, irregular disruptions in the interval, variations in the length of the interval, with fixed interval schedules up to 27.75 hours, and variations in the duration of the S^{Δ} period for as long as 2.75 hours (Dews, 1965b). Subsequent research focused on an analysis of interresponse times at the moment of reinforcement (Dews, 1969), with this particular study reaffirming Dews' view that the effects of the reinforcer extend over much longer time periods than just the last interresponse time. These efforts to analyze responding maintained under fixed-interval schedules were summarized in 1970 (Dews, 1970) in a chapter that provides the most comprehensive analysis of variables contributing to the emergence and maintenance of responding under fixed-interval schedules to date (see, also, Dews, 1978a). Moreover, this body of behavioral work demonstrates the same degree of rigor and the same sophisticated understanding of the interactions of behavior with its environment that is so characteristic of Dews' research in studying the behavioral effects of drugs.

OTHER DIRECTIONS

In addition to the efforts of Dews and his colleagues to study the effects of drugs on carefully controlled behavior, Peter also expanded the study of behavioral control and the effects of drugs to the investigation of cardiovascular function (e.g., Dews & Herd, 1974; Knowler & Dews, 1975). Using a combination of techniques that required monkeys to exert force by pulling or holding a T-bar device, it was possible to examine the effects of behavioral activities on cardiovascular function. These experiments provided an extension of the basic approach, expanding the study of behavioral control and drug effects to different physiological parameters and to different species.

Peter also expanded his research efforts to incorporate the mouse, a direction that preceded the more recent intense efforts, stemming from genetic manipulations, to study this

species more widely using a variety of behavioral preparations (Wenger, 1979). Again, the rigor of these analyses, the insight into the behavioral variables, and the foresight displayed were all characteristic of Dews' commitment to the pursuit of behavioral variables contributing to drug action.

SUMMARY AND CONCLUSIONS

Behavioral pharmacology emerged initially as a relatively independent discipline, somewhat apart from the mainstream of pharmacology and psychology. Perhaps this was necessary to ensure a firm footing, the development of a substantive body of experimental literature, and a well-defined focus. Peter wrote and spoke infrequently about his impetus in launching the field of behavioral pharmacology (1978b) but, in referring to the origins of behavioral pharmacology in 1985, he wrote the following:

> Behavioral pharmacology is the offspring of pharmacology and psychology, with the paternal genes of pharmacology predominating. Behavioral pharmacology has tended to be judged by its molecular relevance, which has been, and still is, modest to say the least. Psychology has been an even more unsympathetic parent. Living in the halls of ornate theory, psychology has asked what behavioral pharmacology had to offer in the way of additional embellishment. Behavioral pharmacology is close to earthy reality, so the answer has been, again, precious little. Indeed, heavy-footed behavioral pharmacology has caused tremors that have jeopardized the whole filmy fabric of the theories. (Dews, 1985, p. 4)

The discipline of behavioral pharmacology has emerged significantly over the past 50 years. New journals have been founded (e.g., *Behavioural Pharmacology, Experimental and Clinical Psychopharmacology*), the American Society for Pharmacology and Experimental Therapeutics (ASPET) now has a Division of Behavioral Pharmacology, and the genome project together with academic research laboratories and the pharmaceutical industry have invigorated the need for suitably trained individuals with skills not only in behavior and pharmacology but also with the needed expertise at the more molecular level. This is as it should be in an evolving field.

Peter's emphasis was appropriately on behavior and on the variables of which it was a function as these contributed to and clarified our understanding of the behavioral effects of drugs. His appreciation of and emphasis on behavior as more than a passive transmitter of drug action was crucial to the evolution of the field and, unquestionably, helped to place it on a firm foundation. His sophisticated understanding of both behavioral processes and of pharmacological principles, coupled with the forcefulness and inspirational aspects of his writings, has helped to bring the field of behavioral pharmacology to its current status. Although the analytical basis of drug effects on behavior was at the level of response rate resulting from the closure of switches that produced reinforcement according to some schedule, the beauty of Dews' work was in its implications and in its enhancement of our appreciation for and understanding of behavior:

> The selectivity [of the drug effect on behavior] was related to the schedule … the schedule is, as it were, the score of the symphony. Drugs given to the orchestral organism affect the tempi of the themes and the relative predominance of different sections of the orchestra. These changes are sufficient to change the music profoundly, making slow themes into fast and soft interludes into loud, even though the drugs do not affect the symphony or the quality of the instruments. (Dews, 1964b, p. 477)

The work initiated by Peter Dews triggered a cascade of vibrant experimental research that culminated in the creation of the field of behavioral pharmacology. Dews was the first to recognize and then emphasize that the same dose of a drug can exert an array of effects on behavior depending on how that behavior was controlled by its environmental consequences. Such dramatic qualitative modifications of the behavioral effects of drugs indicated that the mechanisms by which these effects are produced are quite powerful; the range of conditions under which such effects occur suggests that the environmental determinants of the behavioral effects of drugs are not trivial nor of limited generality. Drug effects on behavior are clearly a reflection of how that behavior is and has been controlled by its environment. Whatever momentary changes may be taking place at a more molecular level

remains somewhat of an enigma. However, it is clear that whatever those changes may be, they also are under the influence of the environment and of the contingencies controlling behavior. It is for future work to blend the discipline of behavioral pharmacology with other disciplines to arrive at a more complete understanding of how these dramatic effects occur.

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