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Drug Effects and the Environmental Control of Behavior

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THERE are conditions under which response-dependent termination of either a drug infusion or an associated stimulus will engender and maintain responding. The characteristic fixed-ratio patterns of responding with fixed-ratio schedules of termination of stimuli associated with morphine infusions (24) and the relationship of response rate to schedule parameter and to nalorphine dose are analogous to findings obtained with fixed-ratio schedules of termination of stimuli associated with electric shock. Hoffmeister (7) and Hoffmeister and Wuttke (7, 9) have shown that monkeys not exposed to morphine will reliably terminate stimuli associated with higher doses of nalorphine, although only low rates of responding were maintained under these conditions. The extent to which maintenance of responding by termination of stimuli associated with nalorphine depends on schedule requirements, nalorphine dose, and concurrent or previous exposure to morphine is certainly worthy of further study.

Downs and Woods (5) have shown that responding can also be maintained by termination of naloxone infusions. Characteristic patterns of responding were maintained under a fixed-ratio schedule in which responding terminated either a naloxone infusion or a visual stimulus that preceded an infusion. Furthermore, responding was maintained in both morphine-dependent monkeys, and in monkeys who had never received morphine. The dose of naloxone required for response-maintenance was appproximately 1000 times greater in the nondependent monkey, further emphasizing the importance of dose in determining whether termination of a narcotic antagonist will maintain responding in nondependent animals. It may be significant that lower doses of naloxone (*e.g.*, 0.3 mg/kg per min) seem to maintain higher rates of responding after a monkey had been exposed to a higher dose (1.0 mg/kg per min) than before. We have occasionally noted a similar change in the direct effects of both nalorphine and naloxone on responding maintained in the squirrel monkey under fixed-interval schedules of either stimulus-shock termination or shock presentation; there is frequently a marked shift in the dose-effect curves after the monkeys have been exposed to rather large doses (*e.g.*, 10 or 17 mg/kg).

Downs and Woods (5) also studied responding under fixed-interval schedules of termination of naloxone infusions or of stimuli associated with them. Though some responding was reliably maintained, patterns of responding characteristic of fixed-interval schedules did not develop. Clearly there is a need for further exploration of responding under a variety of schedule types and parameters, and for exploration of optimum conditions for engendering and maintaining performances under various schedules. For example, our experience has been that it can be much more difficult to engender characteristic fixed-interval performances under schedules of stimulus-shock termination than it is under comparable schedules of food presentation. Under schedules of food presentation one can

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abruptly shift from a schedule in which each response produces food to a 5- or 10-min fixed-interval schedule, and typical patterns of positively accelerated responding will develop over time. We have not been as successful in abruptly shifting to similar fixed-interval schedules of termination of a stimulus associated with electric shock; extended exposure to fixed-ratio schedules, and a gradual lengthening of the fixed-interval duration, as well as day to day adjustments in the *t*-parameter (the time between the end of the fixed-interval and the delivery of the first shock) are frequently necessary before responding is well maintained. The same types of manipulations, and others as well, may be necessary for establishing characteristic patterns of responding under fixed-interval schedules of drug-termination.

In agreement with an earlier report by Goldberg *et al.* (6), Downs and Woods (5) have shown not only that responding can be maintained by termination of narcotic-antagonist infusion, but also that there seem to be conditions under which responding can be enhanced in morphine-dependent subjects by the response-dependent infusion of an antagonist. These results are reminiscent of experiments showing that delivery of intense electric shock can, depending on the schedule and on the history of the subject, either maintain responding that terminates it or maintain responding that produces it (11, 14, 20). The conditions under which nalorphine or naloxone injections can maintain responding in morphine-dependent subjects are not well defined as yet. For example, Downs and Woods (5) found that responding was maintained under a second-order fixed-ratio schedule for naloxone injection, but for only limited periods of time. The extent to which durable schedule-controlled performances can be engendered and maintained under a variety of environmental conditions will be an important subject for future experiments. By analogy to experiments on maintenance of responding with electric shock, some conditions should favor maintenance of responding by injections of antagonists, whereas other conditions should favor maintenance of responding by termination of such injections.

Hoffmeister and Wuttke (8, 9) have shown that responding can be maintained when a single response terminates a visual stimulus associated with infusions of either LSD, nalorphine, STP, or chlorpromazine, whereas responding is poorly maintained by termination of stimuli associated with injections of either pentobarbital or imipramine. Their experiments also show that there is no consistent relation between the functioning of a drug as a negative reinforcer and its tendency, at comparable doses, to affect responding under a similar schedule of stimulus-shock termination. Hoffmeister and Wuttke (8, 9) also reported that chlorpromazine functioned as a negative reinforcer whereas impramine did not; this is of particular interest in view of the similar behavioral effects these compounds have in many situations. Further experiments with a wide dose range of both compounds, and perhaps different schedule types and parameters, will be necessary to establish the generality of this apparent difference between two otherwise very similar drugs.

Thus, the experiments reported here, along with previously published work, indicate that behavior can be maintained by the termination of either the infusion, or of stimuli associated with the infusion, of several different classes of drugs. In many cases, no particular pharmacological preconditions seem necessary. In the case of chlorpromazine, however, prolonged exposure to the drug may be necessary, and in the case of the narcotic antagonists, much higher doses seem to be required in subjects who are not dependent on morphine. Delimitation of the conditions under which each of these effects will obtain, and determination of conditions under which these effects may be weak or absent, or even completely reversed, will certainly be worthwhile topics of future work. The pa-

pers in this section of the symposium constitute a firm beginning in this experimental analysis.

Apart from discussion of these particular papers, a few comments seem generally relevant to the experimental analysis of behavior controlled by drug administration. Most of these comments will be based on considerations generally important in the control of behaviors by environmental events.

Although early experiments on behavior maintained by drug injection focused on identification of drugs that could act as reinforcers, more recent work, as the papers in this volume attest, goes considerably beyond mere categorizing of drugs and is directed at answering basic questions about drug injections as consequences of behavior. The question to be answered is not so much "*which* drugs serve as reinforcers?", but rather "what factors determine whether or not *any* drug will serve as a reinforcer." Knowledge both about particular drugs and about generally applicable principles are critical to our understanding of the consequent effects of drugs on behavior. Questions which will continue to be of vital interest include: What are the conditions under which drugs of particular classes serve as reinforcers or punishers, and what are the conditions under which these effects are minimal or absent? What other factors, pharmacological and nonpharmacological, can modulate these effects? Under what conditions can established behavior maintained by drug injections be changed by other environmental events? How similar are drugs to nonpharmacological events that serve as reinforcers or punishers? To what extent are questions about drugs as reinforcers separable from general questions about the process of reinforcement? Although work has begun, the questions will not be answered easily and there is considerable work to be done. Further, since the important effects of drugs are not confined to their effects as consequences of behavior, we need to know much more about the behavioral pharmacology of these drugs, independently of explicit considerations of how the drugs find their way into the organism.

To what extent can the current state of knowledge about behavior controlled by its consequences be useful in the experimental analysis of the effects of drugs as consequences? Some of the determinants of the environmental control of behavior are coming clearly into focus, and it seems certain that their importance would apply as well to the study of drugs as consequences. First, the ways in which environmental events affect behavior are *in*completely predictable from expectations based on the physical nature of the events or knowledge of their effects in other situations (20, 21). Second, the interplay between behavior and its consequences is an evolving, dynamic one. As Morse and Kelleher (21) reminded us some years ago, when behavior is changed by its consequences the consequences that further affect behavior may change too. A corollary is that the conditions optimal for initially engendering a behavior may not be the same as the conditions that ensure its continued maintenance.

Current behaviors, and changes in them as a result of new conditions, are the product of multiple factors including (a) the history of the individual, (b) currently ongoing behaviors, including not only those of direct experimental interest, but also other behaviors in the individual's repertoire, and (c) the exact relation (schedule) between the emission of behaviors and the occurrence of critical environmental events (reinforcing, punishing, discriminative) (20, 21). These factors must be assumed to be of equal importance; over-emphasis on any one to the exclusion of others is likely to lead to restricted conclusions. Consideration of the experimental history of the subject is important, for example, but not to the exclusion of examination of the profound influence of current environmental circumstances. Similarly, concentration on current sched-

ule conditions, influential as these may be, may seriously limit conclusions if previous experience is overlooked. Finally, there must be an appreciation, even when history and current schedule conditions are held constant, that the effects of new experimental interventions (including pharmacological ones) can be profoundly influenced by characteristics of the full range of behaviors currently in the individual's repertoire; that is, by the context in which the behavior occurs.

The questions we ask about behavior are usually considerably influenced by expectations of likely results; that is, we tend to look for the kinds of effects that seem to make "good sense" in terms of our presumptions about the world. For example, by extension from the fact of human opiate use it was expected, and confirmed, that experimental animals would self-administer a variety of morphine-like compounds. From what was known about the pharmacology of narcotic antagonists, we further expected that morphine-dependent subjects would avoid exposure to an antagonist that either diminishes the effects of the opiate or that precipitates acute withdrawal; and so they do—usually. In both cases predictions based on intuitive good sense serve well in that they predict what can be confirmed experimentally. But, valuable as it can be, good sense can be misleading. We may find only what we expect to find, and miss things that we are not especially looking for. We do not, naturally enough, set out to investigate counterintuitive phenomena unless, as it were, "our consciousness has been raised." We have known for some time that morphine *can* serve as a reinforcer, and that there are conditions under which narcotic antagonists *may* act as noxious stimuli, but the logical extension of searching for conditions under which these effects are either absent or reversed in direction has been much more recent. Tradition tells us that organisms seek compounds like morphine or heroin but shun withdrawal-producing drugs like nalorphine, just as they are assumed to strive for pleasure and to avoid pain. Unfortunately, things are more complex than this; the control of behavior by the environment turns out to be as exquisitely complicated as we knew it had to be.

At first glance, behaviors controlled by drug administration might seem to be unusual in that special conditions are often required for demonstrating certain effects. But, this dependence on special conditions is in no way peculiar to pharmacological consequences of behavior. All events that affect behavior, as reinforcers, punishers, or discriminative stimuli, have special conditions under which they are most effective. The effects of environmental events, including drugs, do not inhere in the events themselves, but instead depend critically on such things as the individual's previous experience, characteristics of existing behaviors upon which the new event is superimposed, the schedule under which it is presented, and on characteristics of other behaviors in the individual's repertoire. Thus, it cannot be said that a particular event is a reinforcer or punisher apart from specifying the precise conditions under which these effects are observed (20). Morphine need not be a positive reinforcer, and nalorphine need not be a negative reinforcer or a punisher—they can be, but they need not. The same holds true, of course, for other events that maintain or suppress behavior. Food presentation, for example, may very generally serve as a positive reinforcer, but there are conditions under which it will not maintain behavior, and it is not hard to envision situations in which it could serve as a punisher. Similarly, although presentation of electric shock right after some behavior may decrease its occurrence in the future (punishment), there are conditions in which the same operation results instead in an enhancement and maintenance of behavior (reinforcement).

Some of the effects of electric shock illustrate how the effects of an environmental event can depend on things other than

the physical nature of the event. We have known for some time that electric shock, as the prototype "noxious" stimulus, can have many different effects. The response-eliciting effects of shock are well known, as are its effects in suppressing behavior that produces it (punishment), and in maintaining behavior that terminates or postpones it. All these effects make "good sense," in that they would be expected of any good aversive stimulus. But, as was first shown by Kelleher and Morse (11, 20), these are conditions under which intense electric shock can have a directly opposite effect, *viz.*, its presentation can maintain rather than suppress responding.

In our own experiments with maintenance of behavior by response-produced electric shock (13, 14), squirrel monkeys are first trained under a shock-postponement schedule; then, this shock-postponement, or avoidance, schedule is eliminated and a schedule of response-produced shock is put in effect. The only consequence of responding is then the occasional delivery of an intense electric shock. When a shock is delivered for the first response to occur after a fixed minimum period of time has elapsed (fixed-interval schedule), the pattern of responding—a pause and then a gradual increase—is the same as that seen under similar schedules in which behavior is maintained by events such as food, water, or electrical brain stimulation. When responses no longer produce shocks, responding declines just as it would if responses no longer produced food or any other maintaining event. When shocks are again made available, responding recovers, and the rate of responding is directly related to the intensity of shock. Characteristic patterns of responding are also maintained under a variety of other schedules of shock presentation (2, 12, 15, 16).

Behavior whose only obvious effect is to subject the individual to intense electric shock may seem odd and maladaptive, even as the ultimate consequences of drug-taking may seem to be. But, these behaviors are not "abnormal," since they can be established in any monkey exposed to appropriate experimental conditions. Since the end result is that the individual engages in behaviors that seem counter-adaptive, it is of some interest to determine whether, in the establishement of these behaviors, some basic and irreversible change has taken place in the monkey. Have we created monkeys who now "like" or are "addicted to" narcotic injections or intense electric shocks, or have we simply demonstrated that likes and dislikes are not what it is all about? To what extent is the monkey constrained by his history and to what extent are the changes in behavior a reflection of how that behavior is presently related to consequent changes in the environment (the schedule)?

There is ample evidence that monkeys who repeatedly shock themselves have in no way been permanently altered; when the schedule is changed, all of the "usual" effects of shock can still be observed. What is "usual" and what is "unusual," then, depends on the schedule. For example, when a subject with experience under a schedule of shock presentation is studied under a schedule in which responding instead postpones shock, a stable level of responding will be maintained; subjects will again postpone the same electric shock they previously worked "for." A similar kind of categoric difference in the effects of shock depending on how it is scheduled can be repeatedly observed within an experimental session. For example, in one experiment responding was maintained under a 3-min variable-interval schedule of response-produced shock. During certain segments of the experimental session a change in the color of the lights in the chamber signified that each response would be shocked. Figure 1 shows a cumulative response record for one monkey studied under this multiple schedule of shock presentation. Responding was maintained under the variable-interval schedule, but was suppressed during the periods when each response produced shock. This alternation between maintenance and suppres-

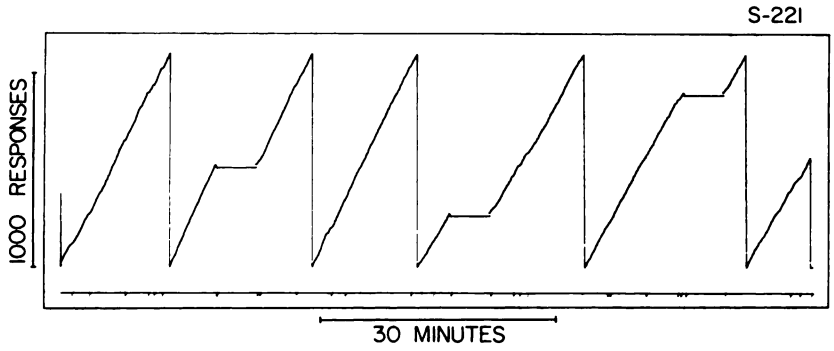

FIG. 1. Maintenance and suppression of responding under a multiple schedule of electric shock presentation (monkey S-221). During the 3-min variable-interval component a response-produced shock (5 mA) was delivered on the average of once per 3 min. During minutes 21-25, 51-55, and 81-85 of each experimental session, the color of the lights in the chamber changed and each response produced a 5 mA shock (1-response fixed-ratio schedule). Electric shocks are denoted by diagonal marks on the event record. During fixed-ratio components, the response pen was offset. This monkey had previous exposure to a shock postponement schedule, and exposure to a variety of schedules of shock presentation. Note that responding was well maintained during variable-interval components, but was suppressed during 1-response fixed-ratio components.

sion was observed reliably over an extended number of experimental sessions. Thus, depending on the schedule under which it was delivered, shock could either maintain or suppress responding (16). I have digressed somewhat to describe these experiments because they illustrate the types of data supporting the general conclusion that the effects of environmental events can be absolutely determined by the details of the conditions under which an individual is exposed to them. One implication is that, just as there are conditions under which a given event will maintain behavior, so also are there likely to be conditions under which this event will not maintain behavior, and yet other conditions under which it may suppress behavior.

By now it is clear that knowledge about the physical properties of events can be of little practical value in predicting when these events will affect behavior, or even the direction of such effects. For example, knowledge of the molecular pharmacology of narcotics is no more likely to tell us when and how these drugs will serve as reinforcers than knowledge of the physical properties of electricity would give us insight into how electric shocks serve as reinforcers or punishers. Reinforcement is a behavioral phenomenon, and is properly studied on this level. As the papers in this symposium attest, we are beginning to be able to specify certain of the conditions under which drugs will serve as reinforcers or punishers. However, we still need to know more about the limitations of these conditions, and more about what determines when these drugs may have opposite effects. We now seem to be in the position of knowing more about the things we already knew something about, but we still have much more to learn in less well-charted areas where our "good sense" is somewhat stretched.

I find it encouraging to observe the growing list of things about behavior that go against the established doctrines of a few years ago, because I think this means that we are doing experiments open-mindedly and looking at results more analytically. We are beginning to regard contradictory results not as theoretically troublesome, but instead as invitations to further experimental analysis. A few examples are in order. Starting outside of behavior pharmacology, we know that rats which work to produce electrical brain stimulation will actually terminate identical stim-

ulation if it is instead freely presented to them (23). As discussed earlier, we also know that, although subjects will postpone or terminate intense electric shocks under certain circumstances, there are also conditions under which the same subjects will reliably produce the shocks. Are these events reinforcers or punishers?

There are many examples from the literature on the direct behavioral effects of drugs. Years ago it was assumed that the behavioral effects of drugs somewhow depended on the motivations and emotions underlying the behaviors. Subsequently, carefully conducted comparisons indicated that the effects of a given drug seemed remarkably independent of the type of event that maintained responding (4, 10). Recent work, however, has shown that the effects of certain drugs do seem to depend on the type of event maintaining responding (1, 17, 18). Another example has to do with the effects of amphetamine on behavior suppressed by electric shock delivery (punishment). Although amphetamines do increase responding in many situations, they do not generally increase punished behavior. Yet, when we studied punished behavior in subjects also exposed, in different portions of the experimental session, to a shock-postponement schedule, there were marked increases in punished responding after amphetamine (19). Thus, the effects of drugs may, but need not, depend on the types of events controlling behavior or whether behavior is maintained or suppressed by these events. We simply cannot make categorical statements about the effects of drugs.

There are many apparent contradictions in the known effects of drugs as consequences of behavior. We know, for example, that animals will self-administer amphetamine (22), but we also know that injection of amphetamine right after exposure to a novel drinking fluid will suppress future intake of that solution (so-called "conditioned taste aversion") (3). In this symposium, Hoffmeister and Wuttke (8) have shown us that monkeys will terminate stimuli associated with injections of LSD, yet we know that it is not uncommon for individuals to seek out and take this drug. What determines which effect will be observed? From work presented here we also know that monkeys will terminate infusions of narcotic antagonists, or stimuli associated with them; this seems very reasonable in view of the intensity of acute withdrawal they produce. But, we are also informed that there are conditions, as yet incompletely defined, under which the behavior of morphine-dependent monkeys may actually be maintained by injections of an antagonist. Are narcotic antagonists positive or negative reinforcers? Given the extent to which "good sense" predictions turn out to be limited, eventually someone may demonstrate conditions under which dependent or postdependent subjects will terminate or postpone injections of opiates. Can anyone say that it would not be worth trying?

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