METHODS FOR STUDYING THE BEHAVIORAL EFFECTS OF DRUGS[1,2,3]

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Man has exploited the behavioral effects of drugs for uncounted generations. Rauwolfia and opium have a classic history in the relief of distress, cannabis contributed unpleasantly but dramatically to politics in the Middle East in the eleventh century, and peyote and kindred materials have played their roles in religion, to mention but a few instances. Alcohol, of course, has served as a social lubricant since the beginnings of human history, to make life less dull if not less brutish and short. And the distinguished botanist, Edgar Anderson, has commented that all known sources of caffeine were discovered by primitive man and that even the prehominids probably made special use of fatigue-relieving plants (1).

Such prescientific screening for psychological activity tended to emphasize compounds that calmed undue excitement, stimulated individuals into intensified participation in events, or produced transcendental experiences; accidental discovery was the rule. Modern trends remain much the same: we still emphasize tranquilizers, energizers, and hallucinogens; happy accident continues as a major source of new psychoactive compounds.

The emphasis in this review will be on animal behavioral methods that have been used widely enough to have accumulated a reasonable body of background data to facilitate interpretation. The effects of drugs on human behavior have been covered in a recent review (2).

General Methods

Experiments going beyond the standard studies of activity and sedation emphasize conditioning, learning, and motivation. Scientific comparison of the effects of drugs on innate action patterns of a variety of species (using ethological techniques) has lagged somewhat but is increasing. Influenced by psychiatric interest in tranquilization, animal studies have emphasized effects of drugs on behavior that is under the control of aversive stimulation. This is stimulation the onset of which is punishing and the termination rewarding (e.g., electric shock), as contrasted with appetitive stimula-

[1] The survey of the literature pertaining to this review was concluded in June, 1960.

[2] Prepared during the author's tenure as a Fellow, Center for Advanced Study in the Behavioral Sciences, Stanford, California.

[3] Abbreviations used in this chapter include: CS (conditioned stimulus); UCS (unconditioned stimulus); CER (conditioned emotional response); DRL (differential reinforcement of low rates); LSD-25 (*N,N*-diethyl-D-lysergamide).

tion in which the onset is rewarding and the termination possibly negative in effect (e.g., food or water reinforcement) (3, 4, 5). Most workers recognize that a substance will be unlikely to influence emotional behavior significantly without influencing other kinds as well and that the behavior of an organism—including pathological behavior—is a totality that does not readily permit easy fractionation to produce specific effects without some risks of generalized consequences. Accordingly, studies of largely nonemotional behavior, as well as of emotional behavior, have been quite common, not only to get information on behavioral effects of drugs in general but also to permit an assessment of "behavioral toxicity"—the general psychological cost in adaptation and performance that a substance may exact for producing some desired, specific effect (6, 7). Further, important new findings about behavior itself are beginning to emerge from attempts to develop test methods sensitive to behavioral effects that familiar drugs are thought to have.

Experimental Neuroses

The production of experimental neuroses in animals is an appealing technique for investigating effects of drugs and other therapies on complex, emotionally toned behavior. These persistent, maladaptive behavior patterns can be produced almost at will under controlled laboratory conditions, and the symptomatology resembles that found among human beings with emotional-motivational disorders (8). Russell's survey noted increased irritability, increases or decreases in spontaneous motor activity, phobic behaviors ("irrational fears"), regression and loss of learned adjustive habits, posturing and tic-like movements, abortive occurrence of conditioned responses at inappropriate times (hallucinations?), changes in social behavior toward increased aggressiveness or toward a withdrawn and submissive pattern, plus effects presumably of autonomic origin such as altered respiration, rapid and irregular pulse, and hypersensitivity to stimuli as characteristic symptoms (9). In Pavlov's original experiments (10) and in later studies by Liddell & Bayne (11) and others (see 12, 13), such behavior was thought to develop when the animal was forced to make discriminations beyond its capacities. Subsequent work has revealed that other demands and constraints on the animal can produce breakdown: restraint of voluntary movement, unavailability of alternative possibilities for response, insoluble problems with punishment for failure, demands for protracted inhibition, forced alteration in patterns already learned, strong painful stimulation, and conflict situations in which the animal is forced to experience an unpleasant stimulus in order to get an earned reward (9).

Liddell and his colleagues (14, 15), and Anderson & Parmenter (16), working largely with sheep, goats, and dogs, have added self-imposed restraint and monotony to this list. Initially, they employed the Pavlovian harness to restrain the animal and conditioned leg flexion to the sound of a metronome with reinforcement by unavoidable shock to the leg as the unconditioned stimulus; more recently, they have allowed the animal free

movement in the experimental room and have supplemented each leg shock with 10 seconds of prior darkness. The rigid temporal schedule of stimulation and conditioning trials they considered a critical condition for development of neurotic behavior, with the daily pattern of anxiety-producing monotony consisting of a series of 20 conditioned signals for darkness (and shocks) spaced exactly two minutes apart. Liddell has argued that the sheep or goat in training eventually substitutes a self-imposed restraint for the external restraint ordinarily imposed by the laboratory harness. The animal thereby becomes "emotionally muscle-bound" and in a "psychical straightjacket of anxious foreboding" so that it can no longer cope with the vicissitudes of daily living, in or out of the laboratory (15, p. 103), in a manner reminiscent of the human patient incapacitated by excessively rigid self-imposed restraints on thought and behavior.

Both Russell and Masserman emphasize the importance of conflict. Russell (9) argues that conflict in some form is to be found in all neurotogenic situations and that all limit the animal's possibilities for escape from a conflictful situation that generates competition between incompatible response tendencies. Masserman and his colleagues have elaborated conflict techniques to produce neuroses in the cat and monkey, as part of a program of basic research in psychiatry (17, 18). In addition to observation and rating of spontaneous individual and social behavior, Masserman's methods include two- to eight-months training until the animal has learned to respond efficiently to specific visual, auditory, olfactory, or temporal stimuli by pressing one of two available levers a required number of times to secure a reward such as food, warmth, liquid, sexual gratification, etc. The data from observation and training, supplemented by continued observation of the subject in and out of the apparatus, provide baselines for evaluating learning, what the subject's normal behavior is like, and a picture of its adaptive patterns and their variation under "normal" laboratory stress. Neurotic breakdown is then induced by presenting the animal with an aversive stimulus (e.g., a shock or air blast for the cat, a toy snake or loss of a companion for the monkey) just as it is getting its reward for the learned behavior. From three to 40 or 50 repetitions of this experience produce dramatic departures from normal behavior and a loss of learned adaptations (see 19).

Recently, Masserman has summarized over 20 years of this work to show that experimental neuroses respond favorably to treatment with psychoactive drugs, as well as to other treatment (20, 21). Though alcohol adversely affects learned adaptive skills, particularly the most complex and recently acquired, it also disorganizes the complex neurotic behavior to allow simpler, learned adaptive patterns that have been disrupted by the neurotic symptoms to re-emerge, with beneficial net effects on over-all behavior. Morphine and barbiturates also relieve experimental neurosis, somewhat more effectively and with fewer side-effects than reserpine, chlorpromazine, meprobamate, and other tranquilizing drugs.

However sensitive they may be, grossly, to drug effects and however useful as rough screens for psychological activity or as demonstrations, experimental neuroses are usually difficult to use with real precision as a tool of analysis. The behavior iself is complex. The conditions necessary and sufficient to produce it are in dispute, and, as listed, cover quite a range of experimental possibilities. That an experimental neurosis is alleviated by a drug tells little, by itself, about the specific actions of the substance—it might be altering any one of a complex chain of interdependent events to produce the dramatic effect. Further, theories about human personality and psychopathology, given their present confused state, in the face of difficulties imposed by interspecies differences, help little if at all in the scientific understanding of experimental neuroses.

Wolpe (13) has argued persuasively that the situation can be simplified, contending that production of these neuroses depends only on the presence of one of two factors—(*a*) noxious stimulation or (*b*) "ambivalent" stimulation—acting in the presence of (*c*) confinement. Noxious and confinement have their usual meanings, but here "ambivalent" is more complex and refers to a stimulus situation that tends to evoke opposing responses simultaneously in approximately equal strength. Though this appears to resemble "conflict," the meaning is closer to "ambiguous." For example, if a dog is conditioned positively to salivate to the conditioned stimulus of a circle and negatively to inhibit salivation to an ellipse with semi-axes in the ratio of, say, 2:1, presentation of an ellipse of intermediate oblateness, with semi-axes in the ratio of 9 :8, will evoke, simultaneously, both a tendency to salivate (by generalization from the circle) and a tendency to inhibit salivation (by generalization from the 2:1 ellipse). If the opposed tendencies are approximately equal in strength and if the animal must cope with this stimulation repeatedly under conditions of confinement, Wolpe believes neurotic breakdown should ensue. This view resembles Pavlov's original emphasis, except that Wolpe rejects Pavlov's idea that the clash between excitation and inhibition necessarily produces a physical change in cortical neurones. Rather, along with most other workers, he considers that neuroses are learned and can be altered by new learning (see also 22).

"Ambivalent" stimulation would thus explain those experiments in which breakdown developed out of difficult discriminations, threshold stimulation, prolonged inhibition or delay of reinforcement, and rapid alternation of positive and negative stimuli. In most "conflict" experiments, however, the animal's incompatible and opposed response tendencies arise from the requirement that it take an unpleasant stimulus (which established escape and avoidance) in order to gain a valued reward (which has reinforced approach). These, as well as the Liddell experiments in which the conditioned reflexes were reinforced by shocks, Wolpe would consider as instances of noxious stimulation. Here, the conditioned stimuli introduced by the experimenter, plus stimulus aspects of the experimental situation, have been paired directly or indirectly with painful stimulation to acquire,

through conditioning, the power to evoke emotional disturbances as conditioned responses. This view coincides with that expressed by a number of investigators concerned with conditioned fear and anxiety (e.g., 23, 24, 25)

Wolpe handles monotony as a neurotogenic factor in the Liddell experiments by pointing out that monotony alone, unaccompanied by traumatic stimulation, rarely if ever produces breakdown among animals in other contexts. Neurosis probably developed more easily under rigidly scheduled stimulation (even when all positive) simply because the waiting-time interval between trials became a conditioned stimulus for emotional response; the interval, too, always preceded and, thus, always was paired with the shocks so that the animal was continuously subjected to conditioned aversive stimulation. [That time intervals can become effective conditioned stimuli is, of course, well known (26.] This observation contains an important caveat for all behavioral experimentation: the subject, animal or human, does not necessarily learn just what the experimenter intends, nor is conditioning necessarily confined to only those stimuli deliberately presented!

The necessary conditions for producing animal neurosis probably can and should be reduced still further. First, Wolpe's notion of "ambivalence" as a primary neurotogenic factor may have a technical weakness. Generalized conditioned responses, both positive and inhibitory, grow sharply weaker as the evoking test stimuli diverge from the values employed in the original training. If the original training and differentiation has been well established, the strength of the opposed positive and inhibitory response tendencies could be expected to be at rather low levels in the case of intermediate (and thus "ambivalent") stimuli—perhaps at too low a level for the clash between them, as such and by itself, to make a really substantial contribution to total behavior. Second, the behaviorial potency of these situations may stem not from their "ambivalent" character but from their aversive properties. Indeed, Hearst & Sidman (27) have presented data showing that escape from concurrent positive and negative stimulation is rewarding, indicating that such situations have noxious (aversive) properties. Thus, only two factors may be critical: noxious stimulation (to reinforce the conditioning of emotional responses to whatever stimuli are present in the situation) and confinement (to keep the subject in the situation so that the unpleasant stimulation can have its full conditioning and other behavioral effects).

Conditioning and Learning Techniques

Conditioning and learning techniques that allow isolation and control of critical components of behavior probably offer greater promise as analytic tools than more diffuse methods, at our present stage of development. The words isolation and components here do not imply testing a restrained animal that can move only a single limb or sense through only one modality. Far from it; the total behavior of the unrestrained organism is probably most sensitive to experimental effects. Rather, these goals are accomplished

through procedures that permit the investigator to determine what actually happened and of what it was a function, both within a single experiment and across experiments made comparable by appropriate controls (28).

The simplest of these techniques is not far removed from naturalistic observation. A neutral signal (the CS) is simply paired repeatedly with an aversive unconditioned stimulus (UCS), usually an electric shock, until the CS acquires the power to evoke a conditioned response, which usually is of emotional character with escape components. Watson & Raynor (23) followed this procedure in conditioning a child to fear furry objects by associating them with a loud sound; later investigators have employed the method in studies on the effects of drugs and other variables (29 to 32). In fact, Wolpe found this the more effective of his two neurotogenic methods and produced, in cats, strong conditioned emotional disturbances that became evocable by a wide variety of stimuli, including the experimenter and the laboratory situation (13). Such conditioned emotional responses (CERs), if strong, appear as a pattern of behavior, easily identified by the experienced observer, that is characteristic of the species, e.g., inhibition of gill movements in goldfish (33), urination and defecation, immobility, cowering in remote parts of the experimental chamber, running or jumping (34), vocalization, attempts to escape or attack. This kind of CER conditioning is quick and cheap, and the learning is durable in the sense that the conditioned response can be evoked by the CS long afterward without any intervening training or practice. Several studies have found that chlorpromazine interferes with acquisition of the simplest form of the CER in the mouse and rat, with amount of interference somewhat dependent upon dosage, though the data do not agree on whether the drug facilitates, retards, or has no significant effect upon experimental extinction (25, 34, 35, 36).

Without substantial modification in method, such simple conditioning has insufficient sensitivity and reliability for precise work. Conditioned emotional responses (as, indeed, all responses) must be considered to appear as and to be defined by a change in the quantity or kind of behavior being emitted intercurrently by the subject, or both. For CERs so weak that the characteristic gross patterns of emotional reaction do not emerge, the conditioned response may appear only as a slight slowing in eating or reduction in exploratory movement (or whatever else the animal is doing in the apparatus), and its occurrence may be missed. Similarly, small differences in the intensity of the response are hard to discriminate, particularly if the responses are weak. Quantitation of the ongoing behavior interrupted by the CER can offset these difficulties to some extent by objectifying and bringing out small deviations indicative of the conditioned response (37). Unless this ongoing behavior is under precise experimental control, however, incidental changes in it produced by general effects of a drug or other factors can obscure the conditioned response or alter its threshold and thus alter the sensitivity of the test.

Superimposition of this aversive conditioning upon some other control-

lable learned behavior, as reported in a number of investigations (25, 29, 30, 31, 37 to 42) objectifies the reaction, provides a means of adjusting sensitivity, and permits a monotonic (though probably not linear) measure of its intensity. Typically, in these studies instrumental lever pressing for a food or water reward was first established; then, CER conditioning was superimposed upon the regular output of lever responses by three- to five-minute presentations of the CS terminated by shocks to the feet during lever-pressing runs. After a few such pairings, presentation of the CS reduces or stops the output of lever responses, even though no lever response has ever been punished directly by a shock. Decrease in output during the CS relative to output of lever responses during an equivalent prior interval indexes the occurrence and intensity of the CER or "conditioned suppression" (40, 43).

In the earliest application of this technique to studies of drug effects, Wickler *et al.* (44) and Hill *et al.* (45, 46) showed that morphine weakened the CER in the rat, indicating the beneficial effect of this substance on the relief of anxiety associated with the anticipation of pain (see also 47, 48). Subsequent studies on the same species have showed that meprobamate (37) and reserpine (41) tended to weaken a CER established under non-drug conditions, with reserpine having by far the greater effect. In fact, reserpine also abolished the usual rise in plasma steroids normally found with evocation of the CER, as the CER was weakened by the drug (49, 50). Chlorpromazine also weakened a CER superimposed upon an instrumental habit in which the rat ran from one end of an experimental chamber to the other to get a water reward (51). In this study, Heistad also was able to show that chlorpromazine had the opposite effect—increased the strength of the CER—if that conditioned response had first been weakened by electroconvulsive shock. Though this latter effect of chlorpromazine was small, it was clear-cut and contrasted in an interesting fashion with other experimental data indicating that meprobamate further weakened a CER previously attenuated by electroconvulsive shock (52).

Though CER conditioning superimposed on lever pressing produces rather similar effects in organisms as diverse as the rat, cat, and monkey (42, 53), species differences requiring further analysis have emerged. For example, Valenstein (54) has reported that the guinea pig shows only a moderate decrease in lever pressing but omits to collect the water rewards during presentation of the CS in CER conditioning with shock intensities that render the rat completely immobile. More important, reserpine appears to have quite different effects on the CER in the two species. In the rat, this drug normally weakens the CER, decreasing the suppressant effect of the CS to increase lever pressing to almost normal rates for that run during presentation of the CS. In the guinea pig (which is more sensitive to that drug than the rat) the effect is the reverse: the suppressant effect of the CS (and the intensity of the CER, as indexed) is increased as compared with placebo runs.

Initially, the CER seemed almost ideally suited for the study of drug effects on emotional behavior. The basic conditioning appeared to be of the simplest kind—just pairing of signal and shocks—with the strength of the CR easily manipulable through variations in number and distribution of the pairing and in the intensity of the shocks. Similarly, the variations in the amount and frequency of food or water reward and in the level of prior deprivation influence the strength of the "competing" lever response to permit control over the sensitivity of the test. Finally, the indicator was not only objective, but also could be used to demonstrate the selectivity of drug effects when the CER was altered while the lever pressing remained essentially intact.

Though the technique has proved useful, the peculiar nature of the "competition" between the lever response and its suppression by the CER has complicated both measurement and interpretation, with a clear resolution of all difficulties not yet in view. For example, the speed with which suppression is acquired in CER conditioning is uncorrelated with rate of lever pressing, as such (55). However, the relative frequency (proportion) of lever responses rewarded distinctly influences both speed of acquisition (56) and speed of extinction (57), with the CER harder to establish and easier to extinguish the larger the proportion of lever responses rewarded. The competition appears to be between reward and emotional disturbance (between two motivational systems?). Stein *et al.* (58) have presented data to indicate that the extent of the suppression is influenced decisively by the degree to which it reduces the rat's opportunities to get the reward for pressing (rewards that could be earned, and received, if the rat pressed the lever, but which are "missed" when the animal does not press during the CS). Other workers have suggested additional complications related to the rat's abilities to discriminate changes in the relative frequency of reward (59). Geller (60) has demonstrated that the speed of acquisition and extinction of the CER depends in part upon the character of the reward for lever pressing, with the suppression developing more slowly and extinguishing more rapidly if sweetened milk rather than water rewards the lever response. Also, suppression does not appear if the lever response is maintained by brain stimulation as the reinforcer (61). Further, Halasz & Hunt (62) have reported that when the CER was overtrained (by giving the rat 100 conditioning trials, as compared with the usual two or three to 20 or so), the CS lost its control over the suppression and no longer produced it. Apparently, the suppression was disseminated to appear fractionally and sporadically throughout the entire run, whether the CS was on or off. Paradoxically, these overtrained CERs, that had been reinforced many times by shocks, extinguished extremely rapidly, as compared with CERs based on five or six pairings of CS and shock. That the CS had retained psychological significance through all this overtraining—had not "adapted out"—was indicated by the fact that nonoccurrence of the CS at the regular time in a lever-pressing run tended to restore discriminated suppression on the

next trial. Finally, Sidman's recent, elegant review (63) summarizes studies in which interactions between the CER and other aversively controlled behavior decisively influenced the dynamics of both, even whether any suppression at all occurred. Among other things, these studies show that the simultaneous use of two different behaviors may complicate the analytic situation as much as the simultaneous use of two different drugs (see also 64).

Instrumental Avoidance Conditioning

Instrumental avoidance conditioning has been one of the most widely used aversively controlled behaviors for drug studies. Here, in the presence of a signal indicating the imminence of a shock or other noxious stimulus, the animal learns to make some specified response, first to escape the shock and, later, to forestall it. The response required may be climbing a rope, jumping up on a "safe" platform or piece of hardware cloth inclined at a steep angle to the floor, leaving a to-be-charged chamber of an apparatus for another section, turning a wheel, pressing a lever, or whatever is appropriate to the species and to the expected motor and psychological effects of the drug (see 65 to 68). The noxious properties of the shock motivate escape, and termination of the pain reinforces this response, but the avoidance response that grows out of the escape behavior and which eventually comes to anticipate the shock and prevent its occurrence is probably not conditioned as a reflex to the CS by virtue of the simultaneous occurrence of escape and the conditioned stimulus. In fact, an animal initially given pairings of CS and shock in a situation permitting no escape can later acquire an avoidance response if reinforced only by termination of the CS (and other stimuli associated with the situation in which shock was given), without further shocks (24, 69). The CS, through pairing with shock in what is essentially CER conditioning, acquires psychological properties that disturb the animal and that make termination of the CS rewarding. At the higher levels of apologetics in behavior theory, views differ as to the full explanation of avoidance conditioning. Some workers (e.g., 24, 70, 71, 72) contend that the response of "fear" or "anxiety" that the CS has acquired the power to evoke also has drive or motivational properties—that the avoidance response is reinforced by a reduction in this "learned drive" as the animal gets out of the stimulus situation that evokes it (i.e., makes the avoidance response). Others (e.g., 4, 73, 74) consider that the CS has acquired aversive properties through conditioning so that its termination reinforces avoidance. Other intermediate views and alternative positions have been proposed (75, 76). For many experiments, these varying opinions make no difference and can be disregarded. For others, however, they can pose critical empirical and inferential problems, particularly if the experimenter wishes to argue that the drug effect on avoidance is mediated through a change in motivation or drive. To make such an argument firm requires additional observations (77).

Miller *et al.*, in an excellent study (78), contrasted avoidance and escape to show the weakening effects of chlorpromazine on avoidance. All drug tests for effects on avoidance came during extinction, after conditioning had been completed. Two experimental situations provided for the contrast: a double-grill box, for avoidance, and a long alley with a continuously electrified floor that the rat had to traverse to escape the shock, to control for motor effects of the drug and for responsiveness to pain during the drug tests. The data show that chlorpromazine clearly reduced the number of avoidance responses obtained during extinction, with a clear dose-effect relation. These investigators controlled for motility by first determining the effect of 1.25 mg./kg. chlorpromazine on running time in the alley and then determining that dose of phenobarbital which would produce equivalent slowing in the running of other trained rats. Then, trained rats under each of these drugs, in doses of equal potency with respect to effect on alley performance, were tested in the avoidance situation where chlorpromazine clearly weakened avoidance while the "equivalent" dose of phenobarbital had little effect. With similar care (and a similar design), these authors (79) also investigated the persistence of the effects of chlorpromazine on experimental extinction (effects of a single dose had been found to be reversible, while several consecutive doses appeared to have more durable effects). With controls for cumulative effects, as such, of the drug and for varied intervals between training and testing, they found that chlorpromazine potentiated experimental extinction and that such extinction under the drug was as permanent as extinction under placebo.

Other investigators have compared escape and avoidance, with both responses having the same topography (i.e., physical characteristics) to show stimulating effects of drugs or to show that a drug such as chlorpromazine weakened or eliminated the avoidance reaction, though the animal still could feel the shock stimulus and still retained sufficient motor function to make the physical response (80 to 83). Verhave *et al.* (84), using an avoidance and an escape response in which the rat rotates a wheel to terminate the CS and to avert or terminate the shocks, proposed a comparison of percentage loss of avoidance with percentage loss of escape behavior to distinguish, in a continuous test, between general depressant effects of tranquilizing and sedative drugs on both responses and specific effects on avoidance. More recently, Weiss & Laties (85, 86) have described a most elegant and precise method for titrating avoidance and escape behavior, based on the observation that rats will press a lever to produce small decrements in the intensity of electric shock to the feet. In testing escape behavior, if the lever is not pressed, the shock periodically increases in intensity, whereas regular and diligent performance can keep it at a minimum. In testing avoidance behavior, the shock is administered intermittently in bursts of increasing intensity if lever responses are not made; lever responses in the intervals between bursts, however, are rewarded by a reduction in the next shock from its last previous value. Comparable behavior, in different subjects, with the important gen-

erating parameters subject to precise control, can be produced as a function of a shock that is present or as a function of a shock to come. Further, this test, like Verhave's, is continuous rather than episodic, as are so many avoidance tests, and permits the time course of a drug effect to be plotted quite exactly.

The use of avoidance conditioning in combination with behaviors controlled by appetitive reward allows analysis of differential effects of drugs on different kinds of habits. For example, John *et al.* (87, 88), in a study of the effects of intraventricular and intramuscular injections of reserpine and other drugs in the cat, employed three different behavioral indicators: running on an elevated pathway and crossing a hurdle to get food, a two-choice discrimination problem with food reward, and avoidance in a double-grill box. They found reserpine via both pathways weakened avoidance but left runway approach behavior relatively untouched; in small doses, this drug interfered with avoidance to a visual but not to an auditory signal. Hughes & Halasz (89), using a technique in which cats were trained intercurrently in the same apparatus to press a lever for milk reward and to deflect a pendulum (on signal) to avoid a shock, found that amphetamine disrupted the appetitive lever response but left avoidance untouched. Halasz (90), in the same situation, found that chlorpromazine weakened avoidance but did not influence lever pressing for milk. Ray & Stein (91) have presented preliminary data for the rat (using a situation in which the animal pressed one lever, on signal, for milk and another lever, on a different signal, to avoid shock) to indicate that reserpine, chlorpromazine, LSD-25, and meprobamate selectively weakened avoidance, while amphetamine selectively eliminated lever pressing for milk. Wenzel (92), in a similar situation, found reserpine weakened avoidance in cats.

Miller and his co-workers (e.g. 93 to 96) have used compound test situations ingeniously for many years in the study of conflict and the effects of various procedures upon it. Miller pits an approach habit (e.g., running down an alley to get food) against avoidance tendencies set up by aversive stimulation (e.g., shock) given at or on the way to the goal. Conflict appears as vacillation between approach and avoidance tendencies, increased running time, and the like. Strength of approach and avoidance tendencies (and thus strength of motivation) were inferred from running speed, strength of pull on a harness, or some other suitable score. With proper controls and computations, selective effects of drugs on the components of the conflict, including motivation, can be analyzed. Miller and his group have been very productive in developing variants of this basic situation and adapting it to experimentation on drugs. His recent, forceful reviews cover this program (97, 98, 99) and new aspects of his theoretical views (100) in detail.

One of the most serious problems to be solved in all experimentation using compound tests is to make sure that the different behaviors to be compared are approximately equal in strength prior to introduction of drugs, or to provide some correction for inequality. Otherwise differential effects

of a drug on the several habits may reflect only differences in their relative strengths, rather than real selectivity of effect, as desired. In many experiments employing different sustaining motivations for behaviors in different experimental settings which require different physical responses, such equality is hard to estimate, let alone establish firmly. The solution of conditioning several habits intercurrently in the same apparatus and requiring similar or identical responses for each may be helpful but is not entirely satisfactory. Such habits appear to interact, and probably in proportion as the physical responses for each approach topographical identity. Finally, what aspect of strength is to be equalized? The word and concept appear ubiquitously in discussions about behavior, yet the standard indicators of strength such as latency, rate, amplitude (intensity), and resistance to extinction tap different aspects of a habit and, thus, do not always agree.

In an exciting series of experiments, John & Killam (101) have explored electrophysiological correlates of the process of simple avoidance conditioning. Recording electrodes were implanted in a number of loci in the brain of the cat, including cortex, midbrain tegmentum, lateral geniculate body, superior colliculus, fornix, septum, amygdala, hippocampus, and nucleus ventralis anterior of the thalamus, with placement confirmed histologically at the end of the experiments. After postoperative recovery, the cats next received adaptation ("familiarization") trials in the double-grill box, with bursts of 10/sec. flickering light introduced to allow a determination of baseline electrophysiological response on all leads to that stimulus. Then, the cats were subjected to avoidance conditioning, with the 10/sec. flickering light serving as the CS and intermittent shocks as the UCS and with the apparatus illuminated by steady light of equal intensity between trials. The flickering CS provided a tracer frequency that could be recovered electrophysiologically from the various brain structures during adaptation and subsequent avoidance conditioning. Such "labelled" electrical responses appeared during adaptation in the visual and auditory cortex, lateral geniculate, superior colliculus, amygdala, and hippocampus, but soon disappeared. They reappeared, except in the hippocampus and amygdala, with the first pairing of CS and shock in conditioning. As training progressed, the labelled frequencies first left the classical visual system to appear in the extralemniscal ascending system and then went back to the visual pathways and centers again toward the end of training. When the cats had achieved perfect performance, 40/sec. bursts appeared in the amygdala and multiples of the 10/sec. CS frequency were found in the cortex. As reserpine blocked the avoidance behavior, the electrophysiological picture regressed to that found in early and intermediate stages in training; as the cats recovered from reserpine, the electrical picture at any given performance level resembled that seen at the equivalent performance level during training. A variety of generalization experiments in most instances confirmed the specificity of the electrophysiological findings to the overt behavior data. These experiments,

with extensions now in progress, signal real progress indeed in an important field of inquiry.

Operant Conditioning and Nondiscriminated Avoidance Conditioning

The operant conditioning methods of Skinner (3, 4, 5) and nondiscriminated avoidance conditioning, developed within the operant framework by Sidman (and justly called "Sidman avoidance") (63, 102, 103, 104), have contributed most fruitfully to the investigation of both behavior and drug effects. Recent reviews and summaries (43, 105 to 110) cover major contributions and considerations of philosophy and technique in detail, making extensive discussion here unnecessary.

Operant behavior is controlled by its consequences; the governing reinforcement is correlated with the response (hence, Type-R conditioning). Any response so controllable, that can be made to occur at a convenient rate, and that, when completed, leaves the subject in a state and position where it is free to respond again and again can be used as an operant (e.g., lever pressing for food reward) (111). The other important category is respondent behavior, established by Type-S conditioning in which the reinforcement (UCS) is correlated with a stimulus (CS) (e.g., the CER, established simply by pairing a CS with shocks).

Operant investigations on drug effects uniquely exploit special schedules of reinforcement, particularly when behaviors under appetitive control are involved. The conditioning apparatus can be set to reward each lever response (continuous reinforcement) or to yield intermittent reward in accordance with an automatically controlled schedule. The schedules may be arranged to make reinforcement available (if the subject presses the lever) (*a*) only after the lapse of a constant or variable interval of time (fixed and variable interval schedules), (*b*) only after the subject has made a specified number—constant or variable—of responses (fixed and variable ratio schedules), (*c*) only as the subject holds its output down to some predetermined low rate [differential reinforcement of low rates (DRL)], and so on. In DRL, only those responses that follow the last preceding response by some predetermined interval (say, 10 or 20 seconds) are rewarded. Operant behavior extinguishes, of course, if reinforcement is continuously withheld.

Different schedules produce characteristically different output curves, defined in terms of rate and distribution of responses in time. Different kinds of schedules can be combined, almost on a prescription basis, to create a behavioral situation with the desired psychological features and spectrum of outputs (e.g. 106, 107, 112, 113). Different kinds of output can be placed under stimulus control by giving one signal (e.g., a light) when one schedule is in force, and another (e.g., a sound), when another schedule is in force, and so on, so that each signal becomes the occasion for the occurrence of the appropriate output. Sequential presentation of several different

schedules (with signals) within a single run tests for differential effects of a drug on several different kinds of behavior, with selective effects demonstrated if one kind is spared while another is disrupted. Alternatively, different schedules may be combined sequentially in this way, but without any previous association with exteroceptive signals, to produce different kinds of output during a single test. Here, in place of special lights or sounds, the subject must depend upon stimuli from his own behavior and its consequences for the signals as to which schedule prevails, to make what Dews has found to be a most sensitive test for drug effects (e.g., 106, 114, 115, 116).

Inferences as to what it is the subject is discriminating as a signal or as to what behavior is being reinforced or blocked, and by what, plays a critical (though insufficiently emphasized) role in the analysis of drug effects on operant behavior. For example, with DRL schedules, elapsed time since the last previous response must be discriminated if the rat is to delay his next response long enough to get a reward. With DRL, Sidman (117, 118) found that amphetamine increased the rat's output but broke up the timing discrimination, while alcohol reduced output but left the timing discrimination intact. Blough (119) trained pigeons to remain still in one place by making the probability of getting a reward from the food magazine increase as the bird stood still for longer intervals. Chlorpromazine increased the ability of the subjects to sustain this continuous response, and pentobarbital weakened the response and made them more active. Presumably, chlorpromazine tended to counteract emotional disturbance generated by the active inhibition the response demands, to improve performance.

In nondiscriminated (Sidman) avoidance, the subject learns to press a lever (or make some other suitable response) to postpone a shock for a response-shock interval of, say, 10 seconds. If the lever is not pressed within a specified interval after a shock, again 10 seconds, the subject receives a shock. This shock-shock interval and the response-shock interval, are the major parameters governing the behavior with some contribution from shock intensity (120).

Opinions differ as to how, exactly, avoidance lever pressing should be explained (63, 121); the technique, however, has both stimulated discussion and revision in behavior theory and opened the door to more efficient investigation of drug effects on aversively controlled behavior. Here, the indicator behavior can be controlled with precision and adjusted in sensitivity. The technique can yield more data per unit of running time than traditional avoidance methods requiring that the subject be returned either to a starting position for the next trial or to an intertrial waiting period. Further, it can be combined with appetitively controlled behavior as one of a sequence of schedules presented during a single run to bring out selective drug effects. As an example of its sensitivity and subtlety, Sidman found that 0.1 mg./kg. reserpine sharply reduced avoidance lever pressing if the rat was given only about 20 per cent of the shocks it should have gotten for

failing to press diligently and regularly enough to forestall them, but the effect disappeared if the rat received all the shocks it "earned" (122). And Verhave (123) has used the Sidman technique to show that amphetamine increased rate of avoidance responding but that this increase was not attributable solely to increases in general activity.

Recently, Brady (124) has described what is probably the most systematic application of complex multiple schedules in assessment of drug effects on the behavior of the rat and monkey. In his "drug-behavior profiling program," he maintains panels of trained subjects of each species receiving daily four-hour test runs which consist of a fixed sequence of four different reinforcement schedules under the control of external signals. Performance of these trained subjects on each schedule under nondrug conditions provides baseline data for each kind of behavior, including Sidman avoidance; departures from these baselines under drugs can indicate selective or generalized effects, depending upon which components are affected, and how. Brady's detailed analysis of the behavioral changes produced by scopolamine and pentothal not only brings out the sensitivity of the indicators and the selective effects of the drugs but also illustrates something of the complexities encountered in interpretation of operant data.

At least some of the behavior of most animal species can be brought under operant control, though ethological peculiarities in some instances pose difficult problems [see (125) for an engaging account of attempts to condition the octopus]. Operant methods have been applied to the study of depth of sleep (126), stuttering (127), human-observing and signal-monitoring behavior (128, 129), child development and behavior (130, 131, 132), and human psychosis (133, 134), among other diverse problems (5). Many different kinds of stimuli have reinforcing properties, including vibration (135) and tactile stimulation (136), onset of illumination (137), attention (131, 138), noise (139), the sight of new or interesting objects outside the apparatus (140), and electrical stimulation of the brain (141, 142), to mention but a few.

Olds and his co-workers have made self-stimulation of the brain (both electrical and chemical) the basis for an extensive program of investigation of drug effects on behavior. Here, operant lever pressing is acquired and maintained in the rat by reinforcement with electrical stimulation through microelectrodes implanted in various hypothalamic or limbic system locations. Presumably, this stimulation activates hypothetical reward ("pleasure") systems in the brain (or, in other locations, "pain" systems with unpleasant or ambivalent effects leading to fluctuations in output of lever responses). Some of the experiments are complex and an adequate picture of the program can be gained only by careful reading of the recent articles and summaries which cover the details (143 to 147). These workers have accumulated considerable evidence, however, to indicate that the two systems respond differentially to drugs and that the method is powerful and productive. For example, some drugs, (e.g., meprobamate, pentobarbital, and

morphine) inhibit operation of the "pain" system but leave the reinforcing function of stimulation of the "pleasure" system relatively intact, while chlorpromazine has the reverse effect.

What identity these "pleasure" and "pain" systems have with well-known CNS functions defined by more traditional physiological and anatomical methods is uncertain. Similarly, the behavior maintained by intracranial self-stimulation may not turn out to be entirely identical with an operant maintained by giving the deprived animal food or water rewards. Here, as is so common in the science of behavior, the empirical findings may indeed have outrun our capacities for explanation. Such an outcome could be a stimulating challenge leading to healthy developments in psychology, pharmacology, and physiology, however disconcerting it might be momentarily.

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