BEHAVIORAL PHARMACOLOGY[1,2,3]

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It is the purpose of this review to present an integrated, selective, and constructively critical summary of major current trends in behavioral pharmacology. This rather formidable task has been accomplished in at least two relatively recent reviews by Dews & Morse in 1961 (1) and Cook & Kelleher in 1963 (2). The excellence of these contributions lightens the literature-survey burden prior to these dates. Our coverage of major trends, involving the effects of specific classes of drugs upon behavior, pharmacological analysis of biochemical-behavioral interrelations, and drug-behavior interactions, will emphasize developments in these areas as they have emerged since the prior reviews in this series.

Specifically, the present review has been organized around three major topics reflecting both current research emphasis in behavioral pharmacology and the interests and competences of the reviewers. The first major area focuses upon the extensive literature dealing with the effects of specific classes of drugs (e.g., tranquilizers, stimulants) upon behavior. The second includes a somewhat more limited review of recent trends involving psychopharmacological approaches to biochemical-behavioral interrelations. A third major section calls specific attention to the analysis of behavioral processes in relationship to the activity of pharmacologic agents and emphasizes critical drug-behavior interaction problems involving behavior control and environmental contingencies. Finally, a brief concluding section discusses recent methodological developments in behavioral pharmacology.

Of necessity, the coverage of a voluminous research literature in behavioral pharmacology has been fiercely selective and, in some cases, arbitrarily so. Although there may be legitimate questions concerning the appropriate-

[1] The survey of the literature pertaining to this review was concluded in June, 1964.

[2] The following abbreviations will be used: CDP (chlordiazepoxide); CER (conditioned emotional response); CNS (central nervous system); CPZ (chlorpromazine); DOPA (β-3,4-dihydroxyphenyl-L-alanine); DRL (differential reinforcement of spaced responses); EKG (electrocardiogram); FI (fixed interval schedule); FR (fixed ratio schedule); LSD (lysergic acid); SMA (spontaneous motor activity); and VI (variable interval).

[3] Preparation of this review was supported by Research Grant MH-01604 from the National Institute of Mental Health, National Institutes of Health, U. S. Public Health Service.

[4] The authors gratefully acknowledge prepublication copies of papers by Drs. L. Cook & A. C. Catania, R. T. Kelleher & W. H. Morse, L. Stein, and B. Weiss & V. G. Laties.

ness of some of the papers included as well as many that have been omitted, we have emphasized experimental studies with infrahuman species and investigative efforts focusing upon conditioned behavior in controlled laboratory settings. Where the evidence seemed to justify such generalizations, we have attempted critical integrations of the present state of knowledge in specific areas. In many instances, however, our integrative efforts have been limited by both the lack of available data and confidence in our grasp of critical relationships. In any event, the material to be reviewed will hopefully provide some realistic basis for assessing the present status, current trends, and future perspectives of a most rapidly developing investigative field.

EFFECTS OF DRUGS UPON BEHAVIOR

Behavioral Effects of Tranquilizers

Despite exhaustive coverage of the compounds in this general category by both the recent reviews in this series [reserpine, chlorpromazine (CPZ), and related compounds by Dews & Morse (1), and chlordiazepoxide (CDP) and meprobamate (MPB) by Cook & Kelleher (2)], the few intervening years have witnessed the emergence of an extensive literature on the behavioral effects of the tranquilizers. The sample we have chosen as generally representative of the more recent research contributions in this area can be considered in terms of effects upon unconditioned behavior, effects upon conditioned behavior maintained by aversive control (e.g., avoidance behavior), and effects upon conditioned behavior maintained by positive reinforcement.

Unconditioned behavior.—Previous reviews have emphasized the essentially unanimous conclusion that CPZ, reserpine, CDP, and MPB decrease spontaneous motor activity (SMA) in such situations as "jiggle cages," rotating drums, and photocell chambers. In a recent paper, however, Watzman, Barry & Kinnard (3) have reported that CPZ (1 to 4 mg per kg) also decreases the activity of grouped mice, a finding with rather important implications for the antagonistic action of CPZ in relationship to the amphetamine aggregate-toxicity effect. Under certain conditions, an acute dose of reserpine has also been reported to increase activity (4) in mice. Age is an important parameter in producing this effect with the most pronounced changes occurring in 25-day-old mice tested with a 5 mg per kg dose. Fighting behavior among animals has also been used as a measure of the activity of these agents, and a number of research reports in this area have recently appeared (5–8). In an extensive study, Chen, Bohner & Bratton (7) compared the ED_{50}'s of MPB with those of several barbiturates and other depressants and found that for all drugs the antifighting activity was proportional to the maximum-sedative dose. They concluded that "suppression of the fighting episodes of mice may be due to a similar sedative action of these drugs."

Conditioned behavior maintained by aversive control.—The observation that tranquilizers block avoidance responses at doses lower than those at which

escape responses are impaired has been documented in many reviews (1, 2, 9, 10). Although most experimenters accept this result as being related in some analogous fashion to the clinical situation (i.e., fear is lessened but pain-motivated responses are left intact), alternative interpretations of these data have been made. Dews & Morse (1) have proposed that CPZ and reserpine may weaken the "stimulus control" of behavior, rather than produce specific effects on "fear." That is to say, the control of behavior by exteroceptive and interoceptive environmental stimuli may be disrupted with the result that such agents would interfere with positively reinforced (rewarded) behavior as well as aversively controlled behavior. Therefore, in addition to the continued study of the tranquilizer-type drugs on the accepted escape and avoidance schedules, there has developed great interest in comparing tranquilizer effects on behavior under these procedures with effects on positively reinforced behavior.

Several comprehensive avoidance studies have recently been reported. Domino, Karoly & Walker (11) studied leg flexion as an avoidance response using a discrete trial procedure: a tone preceded the aversive shock stimulus with responses in the presence of the tone avoiding the shock and terminating the tone. If no response occurred, the shock was administered and could be terminated by a response; if a response did not occur within 5 sec, the intensity of shock increased gradually from an initial level of 0.7 mA to 7 mA. In this way, shock escape was not defined as an all-or-none event but could be correlated with the shock intensity necessary to evoke it. Avoidance responses failed to occur with increasing doses of CPZ (1 to 8 mg per kg), and escape responses also stopped at the lower but not at the higher shock levels. Reserpine (0.1 mg per kg) had similar effects, as did pentobarbital. A different avoidance procedure was used by Heise & Boff (12) in a comprehensive study of many different classes of drugs. They used a modification of the continuous avoidance situation introduced by Sidman (13, 14). Each response (a bar press) postponed the delivery of a brief electric shock by a fixed period of time; in the absence of avoidance responses, shocks occurred periodically. In this modified procedure (14), the string of shocks was terminated by a response on another lever (escape response). This technique has proven stable, versatile, and sensitive to drugs and, at least in the hands of Heise & Boff (12), has been used successfully to differentiate among several classes of depressants. These authors defined a measure of dose-range ratio in terms of the different doses of a drug necessary to produce a change in responding on the avoidance lever compared to the dose necessary to change the escape response. In terms of this measure, CDP and diazepam are high, hypnotics and primary muscle relaxants are low, and the phenothiazines and reserpine-type drugs are intermediate. This technique apparently avoided the previously reported (cf. 2) paradoxical increases in avoidance rate. Heise & McConnell (15) also reported on a "trace" conditioning avoidance procedure in which a stimulus ("noise") was presented for 5 sec and then followed by 5 sec silence (gap) before administration of a shock if no

response occurred during the total 10 sec interval. They found three types of effects with the drugs tested on this procedure. Phenobarbital (40 to 160 mg per kg), CDP (7.5 to 60 mg per kg), and MPB (50 to 200 mg per kg) increased the response latency, so that more and more responses were made in the "gap." Chlorpromazine (0.5 to 4 mg per kg) led to greater and greater avoidance response failure without increasing gap responses. Finally, pentobarbital (10 to 40 mg per kg) produced avoidance response failure, but unlike CPZ, also produced escape response failure. Heise & McConnell (15) point out that these results differ from Maffii's (16) results with the pole-climb avoidance response, where responses were also available in the absence of the pre-aversive stimulus and in its presence. Maffii (16) found that the responses in the silent period were affected differently under CPZ and pentobarbital. Many methodological differences between the behavioral analysis techniques utilized in these two experiments can be discerned, however, and serve to focus attention upon the importance of subtle environmental contingencies in determining the effects of drugs upon behavior.

Another popular procedure involving aversive control of behavior provides for the same response to produce both a positive reinforcement (e.g., food) and an aversive stimulus. These consequences can follow every response or can occur intermittently. Although there has been a tendency to refer to such techniques as "conflict" procedures, the use of such a single title would imply a unity of experimental outcomes which has not always been the case. One technique developed by Barry & Miller (17) is the "telescope alley." In this procedure, rats are reinforced with food after running down an alley of variable length. On some groups of trials, the rat is shocked when it reaches the food, and the intensity of the shock is proportional to the distance run. Shock trials are given consecutively, as are nonshock trials, and the data in terms of running speed are treated separately, Trials without shock are presumed to occur only under fear, while trials in which shock is administered aretermed "pain-plus-fear." In addition, in one stimulus condition (with the food nearest) no shock was ever given. They found that CPZ (2 to 4 mg per kg) did not have consistent effects on the running speed, although alcohol (1.2 mg per kg) and amobarbital (20 mg per kg) did increase running speed. Grossman & Miller (18) also found that CPZ (2 mg per kg) did not affect the speed of running on fear trials, and, unexpectedly, in fact, had a larger effect on trials in which shocks were delivered. Unfortunately, these studies have most often used only one dose of a drug; also, although the effects are statistically significant, they are quantitatively small.

Other situations have been developed with lever-pressing behavior in rats and monkeys which are analyzed in terms similar to the "telescope alley," but which have produced different drug effects. Grossman (19) and Barry, Wagner & Miller (20) studied the behavior of rats that were reinforced with food for lever pressing and, in the presence of a tone, punished with a shock of increasing intensity. In both studies, low doses of CPZ (2 mg per kg) led to an increased rate of responding in the tone. Geller and co-workers have comprehensively investigated the effects of many drugs with a similar discrimi-

nated punishment (conflict) procedure. Lever presses were reinforced intermittently in a silent period, and, in the presence of a tone, every response was both reinforced positively and also punished with electric shock. The relevant measure under these conditions was a change in the response rate during tone when lever presses were simultaneously punished and reinforced. A number of reports have documented rate increases during the tone with MPB (21, 22, 23), CDP and reserpine (22, 24), and mono-urethans and di-urethans (23). CPZ and promazine, however, had no such effect (22, 23). Dinsmoor & Lyon (25) have reported on work with a very similar technique, different mainly in that responses were reinforced only intermittently in both "punishment" and "safe" periods. They found that the rate of responding in the punishment period, relative to that in the safe period, increased under CPZ (2 to 4 mg per kg). This increase was due to the lower safe rate produced under CPZ, and no discernible increase in punished responses was found. Miller (26) studied the extinction of lever-pressing responses that had previously been reinforced and punished. A larger percentage of rats treated with CPZ (2 mg per kg) bar pressed than did those treated with saline. Hanson, Witoslawski & Campbell (27) recently reported a comprehensive study on monkeys, exposed to several different procedures. In one of the procedures, each tenth response was reinforced with food, and one out of 15 responses was punished. They found that pentobarbital, CPD, and MPB increased the rate of responding under these conditions, but CPZ did not. It is also interesting to note that one schedule in this experiment was the presentation of a stimulus in the presence of which responses were neither punished or reinforced. The same three drugs increased response in this S^{Δ} stimulus.

The rather striking inconsistencies in the reported effects of CPZ, in relationship to these many apparently similar conflict situations, represent but one of the unresolved problems which continue to plague the behavioral pharmacology area. Clearly, however, a detailed analysis of the many methodological differences (schedules of food reinforcement, shock parameters, performance measures) which characterize the different behavioral procedures utilized in these studies would seem to call into serious question the parsimony of indiscriminately assigning unitary labels like "conflict" to behavioral processes which interact differentially with similar drug manipulations. Better studies, with more reliable baseline performances (e.g., 21–25) and a more thorough exploration of drug dose are called for.

One of the behavioral-conditioning procedures involving aversive control which received early attention in behavioral parmacology and which continues to find some applications is the conditioned suppression [conditioned emotional response, conditioned anxiety, (CER)] technique first described by Estes & Skinner (28, 29). With this procedure, lever responding is maintained by positive reinforcement; and, occasionally, a stimulus is presented which, independent of behavior, ends simultaneously with a shock. With appropriate selection of stimulus parameters, the response rate in the stimulus is suppressed, an effect which has led to the reference—conditioned emotional response. Kelleher & Morse (30) have recently reviewed relevant studies

and analyzed this procedure and its relation to the effects of drugs. Early reports of reserpine effects, involving alleviation of the response suppression, have not been uniformly replicated {e.g., with doses of 0.2 to 0.6 mg per kg reserpine [see (31, 32)] for 0.5 and 1 mg per kg reserpine (33)}. The importance of such environmental contingencies as reinforcement schedule, duration, and frequency of presentation of stimuli and shock intensity, all of which determine degree of suppression, has been emphasized (30). The obvious dependence of such effects upon the conditions of the maintaining environment calls attention again to the central role of the drug-behavior interaction problem.

In addition to the extensive application of aversive behavioral control techniques in the evaluation of the more conventional tranquilizing agents, some recent experimental attention has been directed toward an investigation of the effects of amobarbital in the avoidance and conflict procedures.

Although barbiturates have long been used as "control" drugs against which the tranquilizing effects of CPZ and other agents have been evaluated (34), Miller and co-workers (26) have recently reported a series of studies on the "tranquilizing" effects of sodium amobarbital. Barry & Miller (17) have demonstrated faster running in rats, both shocked and food reinforced, under amobarbital. Miller (26) reported that under amobarbital rats made more responses which had previously been both rewarded and shocked, and Miller (26), Barry, Wagner & Miller (35), and Wagner (36) have shown that effects typically produced by nonreward ("extinction") were attenuated by amobarbital (cf. 37). Although Miller has considered the possibility that these effects are due to motivational (cf. 38) or discriminative effects, rather than to the emotional or motivating properties of the drug, he interprets control experiments as arguing against these alternative explanations. The problem of what procedure is the appropriate control for motivational effects is indeed complex and will require further examination. In a related series of experiments, however, Davis & Miller (39) have recently shown that rats subjected to unavoidable shocks will self-administer amobarbital although this effect tends to dissipate after three days.

Conditioned behavior maintained by positive reinforcement.—Possibly by inference from their widespread use in clinical settings, tranquilizers have not been studied as extensively in situations with positive reinforcement as with aversive control. This occurs despite the fact that sizable changes in behavior, maintained by positive reinforcement have been found (1, 2). In this section, we will review several recent studies with tranquilizers and discuss two general aspects of the use of these drugs: effects on the stimulus control of behavior and explicit comparisons between effects on positively and aversively maintained behavior.

Richelle and co-workers (40, 41, 42) have reported that CDP (0.5 to 40 mg per kg) increased response on both a DRL schedule of reinforcement (where responses must be spaced by a minimum time interval to be reinforced) and on a fixed interval (FI) schedule, where the first response after a

given period of time is reinforced and all other responses are without effect. Weiss & Laties (43) have reported that CPZ increased the output of pigeons on FI. Kelleher and co-workers (44, 45) studied the effects of CPZ and other phenothiazines on "observing responses", i.e., responses that serve to clarify the stimulus conditions but do not change the underlying contingencies of reinforcement. They found that CPZ, promazine, trifluopromazine, and prochlorperazine increased the frequency of observing responses, whereas trifluoperazine did not. This surprising qualitative distinction deserves further study. They note (45) that potency, in terms of the ED_{50} to inhibit an avoidance response, places these drugs on a continuum, with trifluoperazine as the most potent. Thompson (37) showed that both CPZ and thioridazine limited the rate increase ordinarily found when a rat's behavior is first extinguished. Hanson, Witoslawski & Campbell (27) found that low doses of CDP (2 to 30 mg per kg) and MPB (30 to 180 mg per kg) in monkeys increased response rates on a variable interval schedule where responses are reinforced after irregular periods in time, whereas CPZ (0.312 to 2.5 mg per kg) decreased response rates at all doses. Waller (46) found increased responding in dogs treated with CPZ at low doses on both FI and fixed ratio (FR) schedules which require emission of a fixed number of responses to produce reinforcement.

Dews & Morse (1) have accounted for the effects of CPZ in the discriminated avoidance situation with the alternative suggestion rather than that the drug weakens the stimulus control of behavior as by the usual motivational analysis of such findings. And indeed, an examination of some of the recent experimental literature on the effects of CPZ and other tranquilizers on discrimination procedures may provide some data relevant to the evaluation of this suggestion. Scheckel (47) examined the effects of CPZ (0.003 to 1 mg per kg) and CDP (0.156 to 40 mg per kg) on a delayed-matching procedure. The subject (monkey) was first shown one color (red or green) and then after 1 to 105 sec was shown both colors. Responses to the color previously shown were reinforced. An "adjusting" schedule was used in which the delay between presentation of the color stimuli increased after correct responses and decreased after incorrect responses. With both drugs, low doses tended to increase the maximum limit at which correct responses could be maintained, and larger doses decreased the limit below control levels. In a similar matching procedure, without the adjusting feature, Berryman, Jarvik & Nevin (48) found variable results with CPZ administered to pigeons. Weiss & Laties (43) attempted to analyze the effects of CPZ on FI schedules by comparing the usual FI with a schedule in which the passage of time was marked by a series of geometrical forms projected on the response key. They reported that CPZ had greater effects on FI without this 'clock' and that the time course of action of CPZ on the two types of schedules differed. In other words, the source of stimulus control, exteroceptive or presumably internal, appears to interact with the drug effect. Terrace (49) reported that CPZ (1 to 17 mg) produced very large increases in pigeons' responding in a stimulus in which responses had previously been extin-

guished. Key (50) reported a lack of effect of CPZ (5 mg per kg) on auditory-generalization functions in cats.

In other studies with animals, disruptions of stimulus control by tranquilizers have been reported recently by Waller [(46) CPZ in dogs], Doty & Doty [(51) CPZ on avoidance extinction in rats], and Hughes & Kopman (52) who found that both discimination and avoidance responses were affected in functionally similar ways by CPZ. Finally with humans, Shurtleff, Mostofsky & Di Mascio (53) found that CPZ impaired auditory discriminations. Clearly, then, these results would seem to support the contention that CPZ and other tranquilizers disrupt the stimulus control of behavior, although a thorough functional analysis of such effects has not been satisfactorily accomplished.

With respect to the problem of explicit comparisons between the effects of drugs upon positively and aversively controlled performances, two behavioral approaches are noteworthy. First, attempts have been made to establish similar performances in animals under both a positive-reinforcement schedule and an escape or avoidance schedule. For example, Waller & Waller (54) reinforced panel pushing in dogs either with food, on VI (variable interval), or with shock avoidance, on a continuous avoidance procedure. Similar rates of response were established with the two procedures. They found that CPZ produced similar decreases in response rate on both the food- and shock-avoidance schedules. On the other hand, in a study with rats, Ray (55) found that with CPZ (as well as MPB and reserpine) the latencies of a shock-avoidance response increased more than latencies of a food-reinforced response. Besides the species difference in these two studies, however, the schedules of food and avoidance responding also differed. In another study, Hecht (56) compared the effects of CPZ, reserpine, and ethylcrotyl-barbiturate on a food-reinforced and shock-avoidance response. He found that CPZ affected both the latency and the stimulus control of the avoidance response, without affecting the food-reinforced response, whereas reserpine (0.1 mg per kg, s.c.) affected the food response without affecting avoidance.

Dews & Morse (1) have emphasized that the exact relation between the response and the environmental consequence was usually different in experiments that compare positive reward and avoidance situations and that even minor changes in schedule often have profound effects on behavior. Recently, Cook & Catania (57) and Kelleher & Morse (30) have compared the effects of CPZ on fixed-interval schedules which, for some animals end in food reinforcement, and for others, in shock escape. Although the procedures differed slightly, the dose-effect relationships obtained with CPZ were quite similar in the two studies, for both types of schedules. Such findings suggest that, when schedule contingencies are held constant, little or no difference between avoidance-produced behavior and reward-produced behavior is to be expected with respect to the effects of tranquilizing drugs. Such studies as these (30, 57) provide an important beginning to specifying the mutual effects of drugs on schedule contingencies and motivational type.

Behavioral Effects of Stimulants

The experimental analysis of behavioral effects related to the stimulants has continued to focus attention upon the amphetamines, doubtless because of their readily demonstrable activity in this area. Again, a survey of recent research efforts concerned with psychopharmacologic evaluation of the amphetamines and related stimulant compounds can be viewed in terms of effects upon both unconditioned and conditioned behavior as well as upon conditioned behavior maintained aversively or by positive reinforcement. Although emphasis in the present review will be confined almost exclusively to the latter two categories, one significant development to the unconditioned behavioral effect of amphetamine in producing increased lethality in aggregated, as compared to isolated, mice requires at least brief comment. Since the detailed review of this topic by Dews & Morse (1), pyrexia has been implicated as a major variable in amphetamine toxicity. Askew (58) found a distinct dichotomy at about 42°C body temperature, which if exceeded led to death. If, on the other hand, body temperature was maintained at a level below 42°C, recovery from the lethal amphetamine dose occurred regardless of the grouping condition and environmental temperature. Other studies have shown the importance of environmental temperature (59, 60) variables that lead to mutual exposure and contact among grouped animals (60, 61) and to activity (59). In addition, experiments on antagonizing the lethality effect have indicated that tranquilizing drugs (62) and phenoxybenzamine (62, 63) markedly decrease the toxicity of amphetamine.

Conditioned behavior maintained by aversive control.—Many studies have indicated that the amphetamines tend to augment the effects of aversive control techniques. Teitelbaum & Derks (64) reported a series of experiments which showed that, under certain doses of amphetamine, shock avoidance responding (electronically-monitored water drinking) increased if rapid licking was required, but it would occur at a low rate when slow licking was required. They interpret this result as partly attributable to "increased emotionality" induced by amphetamine. In addition to changes in response rate, they reported that visual inspection of the animals showed "wild" licking and sustained responding, even when the experiment and its associated stimuli were terminated. Moreover, a host of other studies have also shown this increased-avoidance responding effect of amphetamine (12, 65–69), Hearst & Walen (70) have analyzed this finding in some detail. These authors demonstrated that, in a discriminated-avoidance situation, *d*-amphetamine (3 mg per kg) increased the number of shocks avoided. They also noted that the general topography of the animals' behavior was affected by the drug (e.g., it crouched less and was, therefore, more likely to come into contact with the lever). These same authors have argued, further, that since many studies have failed to show improved avoidance performance with increased shock intensities, the augmenting effect of amphetamine upon avoidance responding is probably not a function of the drug increasing the aversiveness of the shock (64).

The effects of amphetamine have also been examined in punishment and

conflict situations. Brady (71) found that responding during a stimulus paired with shock decreased under 2 mg per kg amphetamine. Teitelbaum & Derks (64), also using the conditioned emotional response with rats, found that the effect of *d*-amphetamine varied with dosage. A dose of 0.5 mg per kg increased response rates in the absence of the shock-paired stimulus, but suppression in the stimulus continued. With a higher dose, 1 mg per kg, the animal responsed continuously at high rates, both in the presence and absence of the stimulus. The animals seemed to be less controlled by external stimuli. Some studies (22, 72) have also shown lower rates of response when behavior was punished as well as reinforced, although other reports have failed to confirm such effects (17, 20 27). Apparently, the effects of amphetamine on punishment procedures are considerably less well established than is the case with respect to avoidance behavior. Although there are theoretical reasons to expect similar results under both conditions, procedural differences between experimental situations utilized in such studies are too gross to identify the relevant variables.

Attempts to control such procedural differences, however, have produced some provocative experimental findings. Kelleher & Morse (30), using shock-escape schedules with similar contingencies to food reinforcement schedules, showed that *d*-amphetamine (0.01 to 1 mg per kg) produced essentially similar effects upon response rate, whether food or shock escape was programmed. Interestingly, however, the direction of the drug-induced behavioral change varied as a function of the reinforcement schedule maintaining the behavior. When fixed-ratio contingencies were programmed, high doses of amphetamine decreased the response rate while fixed interval responding was accelerated.

Conditioned behavior maintained by positive reinforcement.—The effects of amphetamine on behavior maintained by positive reinforcement appear to depend not only on the dose of amphetamine but also on the parameters of the reinforcement schedule. The most recent and representative studies to confirm such relationships can be conveniently considered: first, in terms of the more conventional food- and water-reinforcement schedules, and, second, in terms of variations in the reinforcement per se (e.g., heat, light, brain stimulation). In addition, certain special problems (anorexic effects, tolerance), related especially, although not exclusively, to the technical aspects of experimental work with the amphetamines, would seem to require at least limited attention in the context of this review.

Both increases and decreases in response rate on fixed ratio (FR) schedules of food and water reinforcement have been reported with amphetamine administration primarily as a function of the schedule parameter. When every response is reinforced (FR 1, or continuous reinforcement), amphetamine has been found to increase response rate (73, 74) while methylphenidate (8 mg per kg) decreased response rate on such a schedule (75). With fixed ratio schedules of intermediate size (FR 20 to FR 50), amphetamines increase the pause before responding and decrease response rate (76).

When the baseline performance is not well maintained, however, either because the ratio requirement is large (77, 78) or because of interspersed punishments (79), moderate doses of amphetamine increase responding. Under such conditions, pipradrol (77) has also been reported to increase fixed ratio responding.

With respect to positively conditioned behavior maintained by interval schedules of reinforcement, the effects of amphetamine have been found to be a function both of drug dose and the temporal parameters of the schedule. Moderate doses of amphetamine increase and higher doses appear to decrease responding on FI (30, 77), although the required high dose has not been unambiguously defined (cf. 80) and may depend upon the duration of the interval. This effect has not been explicitly studied. Although it is generally reported that higher doses of amphetamine decrease responding on VI reinforcement (77), low doses have been found both to increase (64, 81) and decrease (82) such response rates. Further comparative experiments are needed to clarify these effects. When the schedule of reinforcement requires temporal spacing of responding as in the case of DRL or differential reinforcement of low response rate performance, amphetamine has been reported to produce general increases in response rate with both lower organisms (80, 83) and man (84). Dews (85) has also found that the effect of methamphetamine on a delay of reinforcement schedule (reinforcement presented 10 to 100 sec after a response) depends upon the length of the delay. Little effect was observed with delays of 10 or 30 sec, but a sizable increase in response rate occurred with the 100 sec delay. Weiss & Laties (43) have reported similar effects with a stochastic reinforcement of waiting schedule, in which the probability of reinforcement increased continuously with the time since the last response.

An overview of even this small sample of studies would seem to justify at least some tentative generalizations regarding the effects of the amphetamines upon positively-reinforced conditioned behavior. Increases in response rate are generally found when the control response rate is low (DRL, some FRs, early in FI schedules). Although it may be tempting to attribute such increases to a general stimulation of behavior, numerous reports fail to substantiate this overall stimulant effect, even in those instances where the response rate could hardly be regarded as having approached physiological limits (some FR and FI schedules, VI schedules). Weiss & Laties (43) suggest that some interference in stimulus control may be involved (cf. 86), but this effect appears quite complex. These authors found that the temporal course of the amphetamine effect upon FI performance under external stimulus control differed from the time course of the effect upon FI behavior not controlled by such an external stimulus. Clearly, further experimental elucidation of such critical differential effects is needed.

The effects of amphetamine on behavior maintained by reinforcers other than food and water have only recently received any substantial experimental attention. In most such studies, schedules of reinforcement have not been

varied to any great extent, although some manipulation of this parameter has been attempted. Weiss & Laties (87), for example, have investigated the effects of amphetamine, as well as CPZ, and pentobarbital on behavior reinforced by turning on a heat lamp. They found that low doses (1 to 2 mg per kg) of amphetamine increased the rate at which the rat worked for heat with a corresponding increase in skin temperature above normal. Fox (88) has also reported that monkeys responded more frequently to turn on a light for 0.5 sec in an otherwise dark box, following administration of 3 mg per kg amphetamine. Extinction of this light-reinforced response was also found to be prolonged under the drug condition. Stein (89) and Olds & Olds (90) found that amphetamine increased the rate at which a rat pressed a lever to produce brief electric shocks in certain subcortical areas of the brain. Using a procedure in which responses on one lever successively increased brain-shock intensity until intensity was decreased by a response on a second lever, Stein & Ray (91)found that 0.75 mg per kg amphetamine decreased the "threshold" electric current for which the rat would work. Stein (92) has also shown that shorter stimulus durations are maintained under methamphetamine (1.5 mg per kg). Stein interprets these data in terms of a neural and biochemical theory of reinforcement (89, 93), hypothesizing that amphetamine acts on a neural "go" mechanism, increasing the effectiveness of at least these brain stimulation reinforcers.

It would seem appropriate to mention at this point that the literature on the enhancement of human performance by amphetamine and caffeine has been reviewed by Weiss & Laties (94). On the basis of this review, the authors have concluded that performance can be enhanced by amphetamine with little cost, and they propose that more studies investigate the "basic parameters of drug action and performance", including control of such variables as task complexity, control rate of response, and tolerance.

Several recent research reports have called attention to two enduring problems of special significance for the psychopharmacological analysis of stimulant compounds like the amphetamines. Studies in this area of behavioral pharmacology can possibly be affected by anorexic effects as well as by tolerance to repeated administrations of a drug. Although a variety of food-reinforcement scheduling techniques are now available for such psychopharmacological analysis, anorexic effects can complicate the investigative effort. Some reports of experiments involving food reinforcement have noted instances wherein the animal does not consume the proferred food (64, 95, 96), although Weissman has reported (97) that food was always consumed in his experiments with *d*-amphetamine (0.25 to 4 mg per kg). Obviously, the critical variables determining these differential effects have not yet been clearly defined. Several investigators have explored the conjecture by Brobeck, Larsson & Reyes (98) that amphetamine stimulates the medial hypothalamus, identified as a "satiety" center (99) and thus produces the decreased food intake. This hypothesis has been tested directly by examining the effects of amphetamine on rats (100–102), cats (103), and mice (104)

made hyperphagic by electrolytic or goldthioglucose destruction of the ventromedial portion of the hypothalamus. Except in the case of the mice which had passed the "dynamic" hyperphagic stage, amphetamine had an exaggerated anorexic effect. In addition, similar anorexic properties have been reported for methamphetamine, methylphenidate, and pipradrol (105), and chlorphentermine (104). Epinephrine has also been found to have extended anorexic properties in dogs (106) but not in rats (101).

The second critical problem in this area, tolerance, defined operationally as the reduced effect of the same dose of drug on repeated administrations, has been studied specifically with respect to the behavioral effects of amphetamine. Schuster & Zimmerman (83) found tolerance to the effects of repeated doses of 0.75 to 1.5 mg per kg amphetamine on responding under a DRL schedule. Locomotor activity, measured separately in the same rats, was not found to decrease with repeated doses. Zimmerman & Schuster (107) confirmed this effect in two DRL schedules of different value which were presented successively to the rat. The animal responded differently to the two schedules but showed tolerance to the rate-increasing effects of amphetamine in both schedules. Recently, Schuster (108) has followed up the observation that tolerance may be shown in only certain aspects of an animal's behavior. Lever pressing was reinforced under either a DRL 30 sec schedule or an FI 30 sec. The schedules were presented alternately in time, with different stimuli correlated with the presentation of each schedule. Administration of 0.5 mg. per kg amphetamine increased response rates in both schedules, but reinforcements were affected only on the DRL schedule where faster responding was not reinforced. After 15 daily administrations, the rate on DRL schedule had returned to the original baseline level, whereas the rate on the fixed interval remained elevated. This schedule-dependent tolerance indicates that tolerance may not be accounted for completely in terms of physiological processes alone, but rather that interactions between the drug-produced behavioral changes and consequences for reinforcement must be considered in the equation. Experimental interest has also been emerging in the development of tolerance to the behavioral effects of LSD (109–111). As has been found with amphetamine, tolerance does not develop uniformly or at the same rate under all behavioral conditions. Freedman et al. (111) summarize this phenomenon by concluding that, "Apparently, patterns of tolerance to LSD-25 depend upon the interaction of a number of factors such as the particular response measured, multiple behavioral variables, the quantity of drug administered and schedule of dosage."

PSYCHOPHARMACOLOGICAL INTERACTIONS AND THE BIOCHEMISTRY OF BEHAVIOR

Of fundamental importance to behavioral pharmacology is an emphasis of growing significance upon investigations of behavioral processes in relationship to the biochemical status of the nervous system. Both empirical and theoretical contributions in this area have been based upon the application

of sophisticated behavioral, pharmacological, and biochemical techniques, and a thorough coverage would require more space and technical breadth than is presently available to the authors of this review. Some brief overview of the more recent representative studies in the area, however, would seem a necessity in evaluating the present status and current trends in behavioral pharmacology.

The continued prominence of the biogenic amines is reflected in the relatively recent appearance of extensive reviews covering their pharmacological, biochemical, and physiological properties (112–114). The relations of brain amines and behavior have been investigated by using amine-depleting drugs (e.g., reserpine and α-methyl-meta tyrosine) in combination with amine precursors (e.g., 5-hydroxytryptophane and l-DOPA) or monoamineoxidase inhibitors (e.g., iproniazid). Correlations are then made between amine levels and behavioral measures. In studies on SMA, for example, most investigations have implicated the catecholamines, rather than serotonin, as a critical mediator of the behavioral changes (115–121). Studies involving conditioned behavior, on the other hand, have shown less agreement in this regard. Aprison and his colleagues have found closer correlations between behavioral changes and serotonin levels with pigeons in a conditioning situation (122–125), while other investigations implicate the catecholamines (e.g., 126–129). In several studies with rats reinforced by subcortical brain stimulation, Stein and his colleagues find evidence for indirect action of amphetamine in central stimulation (89, 131, but see 130), and they have hypothesized that amphetamine acts indirectly on a central reward mechanism (89, 93).

Carlton (132) has recently summarized behavioral studies on the effects of cholinergic agents. In most studies, cholinergic blocking agents. such as scopolamine and atropine, increase response rates in extinction or in the presence of stimuli correlated with extinction (69). This type of result is interpreted in terms of a central cholinergic inhibitory center, complimentary to Stein's adrenergic facilitatory center. Other findings involving cholinesterase inhibition have been reported (133, 134). and central cholinergic systems related to water intake appear to have been identified (135–137). Although it is tempting to speculate about the closeness of a truly adequate understanding of the biochemical basis of behavior, optimism must be tempered by the realization that, as Dews (138) has observed, "merely plausible theories in behavioral pharmacology have a low probability of being right", and with "serial compounding of two or more plausible inferences, then, the conclusion has an infinitesimal chance of being right."

In addition to these more direct psychopharmacological approaches to the behavioral biochemistry problem, other studies involving interactions among drugs in relation to their behavioral effects may be seen to bear, at least indirectly, upon the problem of biochemical correlates. The analysis of CPZ antagonism of the amphetamine aggregate toxicity effect (139) has been extended by a report of CPZ antagonism of an amphetamine-produced decrease in a food reinforced response rate (140). In addition, Stein (130) has

indicated the intimate dependence of such effects upon the relative dosage values of amphetamine and CPZ. And several investigators have reported interactions between barbiturates and the amphetamines in relation to motor activity (141) and positively reinforced behavior (142, 143).

PSYCHOPHARMACOLOGICAL ANALYSIS OF BEHAVIORAL PROCESSES

Drugs and Learning

Interest has increased over the last several years in drugs that influence the acquisition and extinction of learned behavior. Considering the many empirical and theoretical complexities involved in the study of learning (144), it would seem important for purposes of such a psychopharmacological analysis to distinguish between the procedural aspects of behavior acquisition and the "learning process" more broadly conceived. Acquisition procedures can be clearly specified and the effects of drugs defined with some precision. The extent to which such effects can be generalized to an inferential learning process, which has not and can not be observed directly (145), is a matter which requires cautious handling. Admittedly, certain experimental designs (144) would seem to warrant broader generalizations than others, but such elaborate factorial efforts have seldom appeared in the experimental literature concerned with the effects of drugs on behavior acquisition and extinction procedures. Clearly, many ambiguities continue to cloud conceptual formulations of the "drugs and learning" area, and the added complication of hypothetical neurophysiological mediators without empirical validation has done little to alleviate the continuing confusion. For the purpose of reviewing the research literature in this important area, then, an attempt will be made to refer to the terms "acquisition" and "learning" in an operational or procedural sense, as experimental conditions in which the state of some specified behavior is changed by the procedures of conditioning.

CNS stimulants.—Some recent work by McGaugh, his colleagues, and others (146–150), addressed to the long-standing issue of CNS (Central Nervous System) stimulant effects in facilitating the acquisition of behavior, provides an appropriate focus for considering the many complexities of this psychopharmacological problem. Many years ago, Lashley referred to the facilitating effect of strychnine upon the acquisition of responses required in a learning situation, and McGaugh and others have recently reported similar effects (146–149). Despite the consistency of these findings, the interpretation that strychnine affects the learning process, rather than the acquisition procedure used in these experiments has been challenged by Cooper & Krass (150). These latter investigators studied the effects of simply drugging rats with 1.25 mg per kg strychnine sulfate, without any acquisition trials, then waiting 24 or 72 hr before conducting the learning sessions. Since the rats had received no acquisition trials before the strychnine injections, no 'facilitation' (in the sense that this term is usually used in referring to such

experiments) was possible. Yet, they found that at both pretreatment times the strychnine subjects made fewer errors than controls in reaching the learning criterion. In developing the implications of these findings for interpretation of the previous studies showing strychnine facilitation, they point out that injections given after daily trials in these earlier experiments did, of course, occur before the trials of the next day. Despite the parsimonious implications of this apparently straightforward analysis, it must be pointed out that these findings are not in complete agreement with results obtained by McGaugh, Thompson & Westbrook (147) in studying the time course of the strychnine effect. The rat subjects in these latter experiments were trained, one trial per day, in a maze with different groups given strychnine (1.0 mg per kg) at different times in relation to the maze trial (from 6 min before the trial to 90 min afterwards). The maximum effect of strychnine in improving acquisition was found for the group drugged 1 min after the trial, with the group drugged 30 min after the trial showing the least facilitation. As with the many other studies in this series, however, complex interactions involving strain and sex differences were apparent, and in this particular study, females made more errors under each of the temporal conditions investigated. Further studies must be done to confirm the generality of this effect before hypothetical processes are discussed.

Cholinergic drugs.—Several studies (151–154) have indicated that atropine and scopolamine, given before conditioning trials, retard acquisition of various avoidance responses. In some cases (151, 152), the effect was very labile, in that if two 1 min conditioning trials were performed, rather than just one, atropine interference was not found. In another study (155), post-trial injections of physostigmine improved speed of acquisition in an eight-unit maze. An interaction with rat strain (maze "bright" and maze "dull" rats were used) was also reported.

Barbiturates and tranquilizers.—Doty & Doty (156) found that CPZ (2 mg per kg) given 10 sec after avoidance trials reduced the number of avoidance responses by rats of ages 30 to 600 days. The effects of other dosage intervals depended on the age of the subjects. Denenberg, Ross & Ellsworth (157), on the other hand, failed to find significant differences in running or jumping in response to a tone paired with shock as a function of CPZ (1.5 to 4.5 mg per kg). But Doty & Doty (158) found a delayed effect of doses of CPZ (2 mg per kg) given daily to rats at ages 3 to 56 days. When the rats were then trained in a discrimination-avoidance situation, they made fewer responses and more errors than saline controls. Block & Silva (159) found that rats dosed with MPB (30 mg per kg) and pentobarbital (15 mg per kg) during initial nonrewarded exposures to a maze actually performed less effectively during subsequent food-reinforced trials.

A most comprehensive analysis of the effects of drugs upon the acquisition of a lever-press avoidance response has been reported by Stone using four compounds (160). Pipradrol was found to increase and thiopropazate to decrease the number of avoidance responses compared to nondrug controls. Thiopropazate-treated animals required a significantly greater number of

trials to reach a criterion of successful escape or avoidance responses, while the effects of pipradrol tended (nonsignificantly) to decrease this number. Stone has analyzed these differences in terms of the behavior of the drugged animals when shocked, compared to controls, based upon his observations during the actual performance. Rats treated with benactyzine tended to explore the box most and never developed well-controlled avoidance behavior; pipradrol-treated rats attacked the grids and lever, behaviors which seemed to facilitate the development of good avoidance performances; thiopropazate-treated animals appeared tetanized by the shock and showed little tendency to hit the lever accidentally and escape. These careful observations provide a substantive basis for the distinctions drawn earlier in this section between the effects of drugs on specific acquisition behaviors and effects upon some more general learning process. Clearly, as Stone concludes (160), "The effects of the four drugs used in this experiment upon the acquisition of escape and avoidance habits can thus be partially explained as arising from the systematic alteration of the probabilities of occurrence of several classes of events."

RNA and related agents.—The role of ribonucleic acid (RNA) in a theoretical analysis of memory has been reviewed by Landauer (161). This summary indicates that most of the early work on this problem has focused upon lower organisms (planaria), although Cook et al. (162) have recently shown that supplementary feeding with RNA for extended periods before training can lead to faster acquisition and slower extinction of a pole-climbing avoidance response with rats. Gerard, Chamberlain & Rothschild (163) and Chamberlain, Rothschild & Gerard (164) have also demonstrated some behavioral effects of administering drugs that alter RNA metabolism. These investigators reported a decrease in the latency and an increase in the number of avoidance responses following administration of a nucleic acid stimulator, although an antimetabolite had no effect, and neither agent affected maze learning. Comparisons with other data, however, indicate that some modification may be required in the interpretation of these apparent learning effects by the analysis of as yet unidentified parameters (165). In a related series of studies, Woolley & van der Hoeven (166–168) and other investigators (169, 170) have reported on the effects of experimentally produced phenylketonuria in mice and rats. Unfortunately, however, there are a number of inconsistencies in the findings of these several studies with respect particularly to acquisition changes, and the task of clarifying the role of such biochemical processes in the mediation of behavioral performances would seem to depend upon future investigative efforts.

Clearly, an overview of this hopefully representative recent literature related to the problem of drugs and learning indicates that a definitive analysis of the effects of pharmacologic agents on the acquisition of behavior is, as yet, far from a reality. While the effects of some drugs on acquisition appear consistent under different laboratory conditions and in different test situations, others are not. The extent to which these effects are related to the precise behavioral parameters of the situation has not been determined, and the

interpretive significance of such acquisition effects is far from clear. Although direct effects on the physiological substrates of learning would provide exciting discoveries, a convincing finding in this regard would seem to require more than a simple demonstration of behavioral differences on an acquisition procedure. Nondrug transfer trials are certainly important, but the results of such tests may be confounded by "dissociation" between the drugged and nondrugged state. In addition, such results must always be evaluated in terms of subtle but real drug-behavior interactions. Under the influence of a drug, an animal's performance may be modified, and some behavior may be acquired. In later sessions, the appearance of this behavior in attenuated form may not necessarily be interpreted as indicating that it has not been as well learned as the behavior acquired by a control animal. Only a convergent series of experiments in which such "biases" can be ruled out by a balancing of response choices and behavioral contingencies will provide answers to critical questions about the effects of drugs on learning.

Drug-Behavior Interactions

At several points in previous sections of this review, reference has been made to the well-documented finding that the effects of drugs on psychological processes are profoundly dependent upon the environmental conditions which determine the behavior under examination. Such reference has usually served to indicate that "paradoxical" drug effects may not be quite so puzzling, when environmental conditions and other critical experimental details are carefully specified and considered. The importance of the drug-behavior interaction concept, however, goes beyond simply accounting for inconsistencies in the psychopharmacological literature. First, it would seem to limit the extent to which drug effects are specifiable under the rubric of such broad pharmacological classes as "stimulants," "depressants," "tranquilizers," and the like, despite the apparent justification for such classifications on clinical or even physiological grounds. Second, a considered evaluation of the drug-behavior interaction concept would seem to raise serious questions concerning the efficacy of psychopharmacological approaches which emphasize a search for drugs expected to have selective effects upon such inadequately specified psychological processes as "fear," "anxiety," "conflict," and the like. To the extent that such terms fail to specify operationally unified behavioral processes and depend for definition upon a broad range of environmental and physiological measurement conditions (171), no simple psychopharmacological relationships are likely to be found.

Clearly, of course, a host of biological conditions can be expected to contribute significantly to the effects a drug will have upon behavior. The age of an experimental subject has been shown to be a relevant factor in determining activity increments following acute injections of reserpine (4). The species, sex, and strain of the experimental subject are also obvious determining factors in the evaluation of psychopharmacological relationships, as has been clearly demonstrated with respect to strain differences in the lethal effect of amphetamine on aggregated mice (172). And tolerance and sensiti-

zation effects have received attention in other sections of this review. Within the purview of the indicated emphasis upon drug-behavior interactions, however, recent research literature, calling particular attention to the broad range of environmental variables determining drug effects upon behavior, should most appropriately provide the focus for the representative material to be surveyed in the present section.

Schedule of reinforcement.—In addition to the accepted broad categories of positive reinforcement and aversive control, the specific parameters of the response-reinforcement relationship (i.e., the schedule of reinforcement) has been shown to play a significant role in determining the effects of drugs on behavior. Cook & Kelleher (173) have reported some representative experiments in which different schedules of positive reinforcement are differentially sensitive to several drugs in both quantitative and qualitative result. Dews (174) has also demonstrated grossly different dose-effect curves with pentobarbital on a key-pecking response in pigeons maintained by fixed ratio (FR 50) and fixed interval (FI 15 min) schedules of reinforcement. Doses of 1 and 2 mg increased the output on FR but decreased the output on FI. A similar dependence of response output on schedule of reinforcement has been shown for methamphetamine and pentobarbital (77). In addition, Kelleher et al. (175) have shown the differential effects of *d*-amphetamine (0.75 to 3 mg per kg) significantly increasing response rates on performances maintained by a modified DRL schedule and significantly decreasing response rates on FR 50. Boren (176, 177) found that benactyzine increased rates on fixed-interval and decreased rates on variable-interval schedules of reinforcement. A common feature of all these studies would seem to be the finding that gross changes in behavior under a variety of drug treatments depend not only on dose and type of drug but also on the type of reinforcement schedule which maintains the behavior.

Even within a single class of schedules, however, changes in parameter values may be seen to affect drug response. Dews (77), for example, found differential effects of pentobarbital and methamphetamine on two fixed-ratio schedules (FR 50 and FR 900). Somewhat different findings with other reinforcement schedules were reported by Morse (178). In a situation involving delayed reinforcement, where a specified time elapsed between the occurrence of the response and the delivery of food, both pentobarbital and methamphetamine had qualitatively different effects on response output, as a function of the delay interval (85). Bernstein & Cancro (179), in a related study, exposed different groups of rats to continuous avoidance schedules in which each response postponed shock by different periods of time (10, 20, and 40 sec). Response rate under CDP decreased most in the group with a 40 sec interval, while pipradrol produced the largest rate increase with the same 40 sec group. Significantly, these studies indicate that behavioral parameters will determine not only whether a drug effect can be demonstrated but also the nature and relative magnitude of the effect.

Response strength.—Another relevant behavioral parameter to be considered in evaluating the immediate effects of drug administration is the rate

or probability of a response (response strength) under a given set of environmental conditions. Waller & Morse (180), for example, have reported a comprehensive study of drug effects on behavior reinforced on a fixed ratio schedule (FR 30). They found that the dose producing the maximum increase in responding depended on the control rate of responding. Clark & Steele (181) have also shown that CPZ will produce an increase in avoidance responding if the rats have developed a tendency to respond rapidly after each shock. When these post-shock bursts were eliminated by punishment, CPZ produced a decrease in response rate. And Bindra & Mendelson (75, 182) have shown that training level, determined by the number of training sessions, as well as deprivation level can determine the extent to which water-reinforced bar pressing is affected by CPZ. Apparently, the many variables that affect response strength under the influence of drugs may be a direct function of the ongoing rate of responding, as Dews (77) has suggested, or they may be mediated more indirectly. Indeed, the drug effects influenced by different schedules of reinforcement may well be mediated in such a direct fashion. Schedules, such as ratio schedules with large response requirements, typically generate extended time periods during which the organism does not respond, and increases in overall response rates following drug administration can frequently be accounted for by the occurrence of responding in these intervals. To describe such primary drug effects in terms of the removal of inhibition or similar hypothetical constructs would seem to add considerably less to our understanding of such psychopharmacological relationships than would a continued comprehensive experimental analysis of the problem.

Stimulus conditions.—An impressive body of experimental evidence has firmly established the powerful influence of both exteroceptive- and interoceptive-environmental stimuli, experientially associated with the conditions of reinforcement in the control of behavior. The manner in which drug effects upon behavior are mediated by such stimulus-control relationships represents an important if somewhat complex problem area. Dews (86) has shown that the effects of pentobarbital and methamphetamine on visual discriminations established in pigeons depends upon the complexity of the stimulus array used. In one procedure, a yellow stimulus on the response key was the occasion for reinforcement, and a white stimulus was the occasion for nonreinforcement; when red or blue lights were used, the condition of a 'house light', illuminating the experimental chamber, determined whether reinforcement or extinction was in effect. The latter condition is referred to as a 'conditional' discrimination since the schedule in effect when the red light is on is conditional on the state of the house light. Both pentobarbital and methamphetamine weakened the difference in responding more on the conditional discrimination than on the simple discrimination, although control performances were only slightly different. A similar result in an avoidance situation was shown by Doty & Doty (51). The manner in which the animal acquires the stimulus discrimination has also been shown by Terrace (49) to be relevant in determining drug effects. Pigeons exposed to errorless

learning, "obtained if training starts with an easy-to-learn discrimination of color and shifts progressively to the more difficult" discrimination between horizontal and vertical lines, were not affected by CPZ (1 to 17 mg) or imipramine (1 to 17 mg). Pigeons trained to perfect discrimination performance but having made errors in the course of learning, however, showed decrements in performance (reappearance of errors) under the influence of the drugs. This interaction with training method is quite important, both for elucidating the behavioral processes involved in discrimination learning and in analyzing the effects of drugs on such performances.

Another important aspect of the stimulus control of behavior with relevance for psychopharmacology is reflected in studies on aversive control involving variations in shock intensity. Appel (183), for example, demonstrated that the degree of suppression of responding by a stimulus paired with shock was reduced by reserpine (0.2 mg per kg, daily) when the shock level was 0.8 mA, but not in all subjects with a 1.0 mA shock. And, of course, the previously mentioned study by Domino, Karoly & Walker (11), demonstrating the interacting effects of shock level and drugs on escape behavior, is relevant to this point.

Drugs as Stimulus Events

Although the psychopharmacological activity of drugs is generally accounted for in terms of complex alterations and interactions involving physiological and biochemical mediators of behavior, some drug effects might be more simply explained. Drugs may act as, or at least produce physiological states which act as, stimuli in the control of behavior, by virtue of their association with reinforcing environmental events. Indeed, the analysis of such differential associative relations involving drug and nondrug states would seem to have important implications for both the design of psychopharmacological experiments and the clinical application of pharmacologic agents.

Several investigators have made explicit attempts to establish drug state as a stimulus for a response. Stewart (184) trained rats to escape electric shock by running into one compartment of a two-choice shuttle box if CPZ (3 to 20 mg per kg) had been administered and into a second compartment if saline was given. Imipramine (20 mg per kg) was used in the same way. Transfer trials were also run in which a new drug was injected and the direction in which the animal ran, noted. Acepromazine, perphenazine, and prothipendyl, at appropriate doses, produced the same response previously conditioned to CPZ; but prochlorperazine and imipramine did not. Neither CPZ nor acepromazine elicited the response conditioned to imipramine. Stewart has interpreted these results as indicating a similarity in the physiological states produced by these different drugs. Cook et al. (185) have also established avoidance conditioning in dogs, using the infusion of *l*-epinephrine, *l*-norepinephrine, or acetylcholine as a warning stimulus. Polygraph monitoring of respiration, EKG, and jejunal activity in relationship to drug adminis-

tration and avoidance responding supported the conclusion "that physiological changes consistently preceded the occurrence of the avoidance response."

Schuster & Brady (186) succeeded in establishing stimulus control of a lever-pressing response for food in monkeys by intravenous infusion of epinephrine. These investigators also observed that the infusion of saline, alone, during control trials could produce the lever-pressing response; and further analysis of the problem revealed that under explicit conditions, infusion per se could acquire the properties of a discriminative stimulus for such operant behavior. Overton (187) has also demonstrated that rats could be trained to discriminate the appropriate turn in a T-maze to escape shock based upon the administration of pentobarbital (10 to 25 mg per kg). Speed of acquisition of the appropriate response was found to vary with dosage, leading the author to conclude that "complete state dependence is only the extreme form of a phenomenon of graded intensity." Overton has also shown that pentobarbital (20 mg per kg) can be superior to a combination of external stimuli (light, tone, and shock intensity) for establishing such a discrimination, indicating that compounds like pentobarbital apparently produce extensive and discriminable sensory alterations.

One of the more important implications of the finding that drug administration can come to acquire explicit stimulus control of behavior would seem to be that responses acquired under the influence of a pharmacologic agent may be less adequately performed in the absence of such drug treatment. Similarly, if a change in drug condition is viewed as a change in stimulus events, then the findings of many psychopharmacological investigations, in which subjects are trained without drugs and the performance later evaluated following drug administration, may require interpretation in terms of changes in stimulus properties produced by drugs rather than alterations in dynamic biochemical or physiological events. Attempts to investigate such relationships experimentally, however, have failed to produce consistent results. Grossman & Miller (18) trained rats in the telescope alley either under drug conditions (15 mg per kg of 10 per cent alcohol or 2 mg per kg CPZ), or with saline, subsequently testing the subjects either under the drug or under saline. These investigators found the drugs to have effects in the test trials, but no training effects could be demonstrated. Barry, Miller & Tidd (188) found only slight effects in a similar study with amobarbital (20 mg per kg). More recently, however, Otis (189) trained rats on a pole-climb avoidance response with half the subjects receiving CPZ (1.25 mg per kg) and half administered saline. Retraining with and without shock was given under the same or different injection conditions. Small, but statistically reliable differences were found, with more responses emitted by rats tested under conditions (drug or saline) identical to those under which they were trained. Belleville (190) has recently reported similar results in a study of the effects of *dl*-amphetamine (2 mg per kg), morphine sulfate (3 mg per kg), and saline upon a food-reinforced lever response. One week after training, the response was extinguished under the same or a different drug condition, and a

second extinction session was conducted one week later. Belleville found that "animals which acquired the lever-pressing response under either amphetamine or morphine and extinguished under the same drug, made significantly more responses during extinction than animals trained under the drug and extinguished under the placebo condition." The results of the second extinction test also confirmed the stimulus effects of drug administrations. As is usually the case in such instances of conflicting results, there were many procedural differences between the several experiments addressed to this problem of drugs and the stimulus control of behavior, and a more thorough analysis will be required before an adequate explanation of these inconsistencies can be provided.

The extensive literature in the closely related area of drug-associated states under curare and similar drugs has been summarized historically by Solomon & Turner (191). Experiments by those authors, as well as other studies (192), have shown that the Pavlovian conditioning of cardiac responses to electric shock transfers when conditioning is performed under *d*-tubocurarine or gallamine and later is tested without drug. Other recent studies on the dissociation of conditioning under curare have confirmed the finding that conditioning under *d*-tubocurarine transfers to the undrugged state (193, 194). When, however, conditioning was carried out under erythroidine which differs considerably from raw curare, dissociation of the drugged and undrugged state was reported (194).

Some recent experimental attention has also been directed to an elucidation of the placebo effect which would seem to be properly considered in relationship to drug-dissociation phenomena and the stimulus control of behavior. The clinical relevance of inactive compounds producing effects simulating presumably active drugs has long been recognized and carefully controlled. Only recently, however, have approaches to this problem emerged in the animal laboratory. Herrnstein (195), for example, reported a study in which rats, bar pressing for food, were subjected to intraperitoneal injections of scopolamine (1 mg per kg) and saline. The depressing effect of scopolamine upon the response rate was found to carry over to the saline injections as a function of the temporal relationship between the scopolamine and saline administrations. Saline depressed responding more after two consecutive scopolamine injections than it did after just one. Herrnstein has interpreted this effect as a direct analogue of the placebo problem (196). Rushton, Steinberg & Tinson (197) have shown that the exploratory behavior of rats in a Y maze can be affected differentially as a function of whether or not the animal has previously been treated with a drug in that environment. These investigators measured the number of alley entries in 3 min by rats under saline or under a mixture of amphetamine (0.75 mg per kg) and amylobarbitone (15 mg per kg). A second trial was given three days later with half the rats under the original treatment and half under a different one. The drug mixture increased activity whether given on the first trial or on both trials. If, however, one saline trial had preceded the drug trial, no significant increase in activity occurred. Although any account of this finding must necessarily

be complex, the results point to possible drug-behavior interactions which might be important in repeated use of animals in a given environmental situation. A similar conclusion has been reached by Adler (198), who demonstrated that the depressant effect of tetrabenazine (1.5 to 3 mg per kg) on a motor-activity test was greater on the second than on the first administration, when 1 wk intervened between the drug trials. When the second drug test followed the first by 4 wk, however, no such effect was apparent. References to studies cited by Adler indicate that other behavioral effects and brain amine levels altered by tetrabenazine show recovery within 24 hr, suggesting an interpretation of these findings in terms of a drug-behavior interaction, possibly similar to Herrnstein's placebo effect.

METHODOLOGICAL CONTRIBUTIONS

A number of methodological advances have been reported in the recent psychopharmacological literature which would seem to require at least brief reference in a review of even this limited scope. Several techniques have been developed which permit drug administration to animal subjects during an actual experimental performance without disruption of that performance by the injection procedure itself. Reports of such techniques have covered intravenous infusions in mobile rats (199–201) and the study of morphine self-administration (202); intravenous infusions and withdrawals in monkeys, morphine self-administration in monkeys, and the effects of morphine on food- and water-reinforced behavior (203); intraventricular drug administration in mobile dogs (204). and the local application of drugs to selected parts of the brain (205–208). To provide an appropriate finale for such a review of behavioral pharmacology, Levison et al. (209) have reported on the development of a behavioral method for training baboons and chimpanzees to accept hypodermic injections and cooperate in the administration of drugs.

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