EFFECTS OF DRUGS ON BEHAVIOR[1,2]

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Meprobamate (MPB) and chlordiazepoxide (CDP) are prescribed for mild behavioral disorders. Laties & Weiss (51) have thoroughly reviewed the clinical studies of MPB. However, there has been no critical review of the experimental literature relevant to either MPB or CDP. The present review will analyze this experimental literature. The behavioral pharmacology of chlorpromazine (CPZ) and other potent tranquilizers, as well as related compounds and amphetamines, has recently been reviewed by Dews & Morse (19). Important classes of psychopharmacological agents which are not emphasized in the present review include the potent tranquilizers, amphetamine-like agents and antidepressants (monoamine oxidase inhibitors and imipramine-like agents); however, there are numerous publications available which discuss these drugs (13, 60, 66, 71, 73, 79, 80, 81, 85, 91, 93, 96).

As indicated by Dews & Morse (19), CPZ, related phenothiazines, and reserpine were consistently effective in blocking conditioned avoidance responses. Cook & Kelleher (15) indicated that the potency of phenothiazines in blocking these responses was correlated with their clinical potency. MPB and CDP have only weak effects on conditioned avoidance behavior. Nevertheless, because of assumed "face validity," many procedures involving aversive stimuli have been used to evaluate these two agents. In addition, this difference between the behavioral properties of the phenothiazines and

[1] The survey of the literature for this review was concluded in July, 1962.

[2] The following abbreviations will be used: CAR (conditioned avoidance response); CFF (critical frequency of flicker); CR (conditioned response); CRF (continuous reinforcement schedule); CS (conditioned stimulus); DRL (a schedule in which responses must be spaced in time); FR (fixed-ratio schedule); GSR (galvanic skin resistance); R-S (response-shock interval); SMA (spontaneous motor activity); S-S (shock-shock interval); UR (unconditioned response); US (unconditioned stimulus); VI (variable-interval schedule); i.p. (intraperitoneal); p.o. (oral); s.c. (subcutaneous); CPZ (chlorpromazine, Thorazine®); MPB (meprobamate, Miltown®); CDP (chlordiazepoxide, Librium®). The generic name of chlordiazepoxide was previously methaminodiazepoxide.

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MPB or CDP has led to investigations of types of behavior not controlled by aversive stimuli.

In establishing profiles of behavioral pharmacological action, authors have placed one type of behavior in relationship to another in order to estimate ratios purporting to show specificity of action. The use of these ratios involves the assumption that pharmacological alterations of certain types of behavior are more desirable or more relevant than alterations of others. Although it is important to evaluate the "cost to the animal" in altering a specific behavior, such a procedure often encourages arbitrary classification of some behavioral effects as "specific," while referring to others as "neurotoxic." Such arbitrary classifications of responses often lead to contradictory interpretations of similar findings from different laboratories.

Our survey of the literature indicated that the effects of MPB and CDP can be classified according to the following empirical categories: (*a*) taming of monkeys; (*b*) spontaneous motor activity; (*c*) experimentally induced aggressive behavior; (*d*) conditioned avoidance (discriminated or non-discriminated); (*e*) conditioned suppression (unavoidable shock or punished behavior); (*f*) schedules of positive reinforcement.

Taming of Monkeys

Several reports with MPB and CDP have emphasized that these drugs can tame monkeys. Taming of monkeys is usually assumed to have relevance to hostility and aggression in humans. Hendley *et al.* (32) found that MPB (250–400 mg/kg, p.o.) had a "remarkable tranquilizing effect in man and in the monkey." Aggressive Rhesus monkeys were "tamed" to the point where they showed no hostility to the experimenters and very little "fear," while retaining alertness to sensory stimuli, good appetite, and full awareness of the environment; some ataxia and muscle weakness were also present. After CPZ and reserpine the monkeys appeared to be more insulated from their environment and were not as reliably tamed.

Berger and his colleagues (5 to 7) noted that after MPB (200 mg/kg, p.o.) animals did not object to petting and did not show signs of fear. Thirty minutes later, however, "the animals rested peacefully on their sides and were unable to walk" (5). Gross & Weiskrantz (29) found that at paralyzing doses of MPB (400 mg/kg, i.m.), "the monkeys appeared to be even more frightened of humans than normally, presumably because of their inability to move away." At lower doses (150 mg/kg, i.m., and higher) these investigators observed no taming effects.

It has also been reported that CDP causes taming in monkeys (3, 31, 69, 70). Randall *et al.* (69, 70), and Heise & Boff (31) have attemped to work out an observational behavioral check list for monkeys. The list included items that supposedly differentiate between activity and aggression. Randall (67) presented figures showing that CPZ (s.c.) produced taming at lower doses than CDP (p.o.). However, Randall and colleagues compared these drugs on the basis of the ratio of the effective dose decreasing aggression to the effec-

tive dose decreasing activity. Aggression was defined as forward lunges at experimenter, baring teeth, and attacking experimenter's glove; activity was defined as general activity level, or response to visual or auditory stimulation, or ataxia (69, 70). These investigators used a complex procedure for quantifying their data. The minimum dose that decreased either the activity or aggression score of a monkey to about 25 per cent of its corresponding control score was determined. The median of these scores was called the depressant minimum effective dose (MED). Each monkey then was given a suprathreshold dose ("usually twice the MED"). At this dose the aggression and activity scores (as percentages of control scores for each monkey) were computed as a ratio of aggression to activity. The medians of the ratios of these empirically determined observations were the aggression-activity ratios of the drug (69, 70). Results indicated that animals were "tame" but not sluggish or ataxic if the ratio was less than 0.5; ratios of about 1.0 indicated that the drug action on "aggression" was not specific, "aggression" and "activity" were affected to about the same proportional extent (70). CDP and diazepam both had ratios of 0.3; pentobarbital had a ratio of 0.9; MPB and CPZ had ratios of more than 1.0 (70). Elsewhere, this group (67) noted that phenobarbital, as well as MPB and CPZ, reduced aggression only at doses that depressed activity or produced ataxia. However, Heise & Boff (31) reported that phenobarbital had the same ratio (.4) as CDP. This discrepancy is difficult to reconcile because a great deal of emphasis has been placed on the "powerful and unique taming effects in monkeys" of CDP. Indeed, "it was this taming effect in monkeys, initially observed in the laboratory, that led to widespread use in human subjects for the anti-anxiety effects" (68). This technique of relating one behavioral effect to another for determining specificity involves the assumption that some experimental behavioral measures are known to be more relevant to therapeutic effects, or to undesirable effects, than others.

Effects on Spontaneous Motor Activity (SMA)

Many investigators have attempted to quantify levels of activity in animals by objective techniques. The three general techniques for measuring SMA (jiggle cage, rotating drum, and photo-cell devices) have been discussed by Dews & Morse (19), who noted that results obtained with these three techniques tend to be similar with phenothiazines. Effects of MPB and CDP were less consistent, apparently because they are more dependent on the experimental variables of the procedure.

Experiments with mice in photocell chambers have shown that MPB decreases SMA at doses of 92 mg/kg, i.p. and higher (9, 47, 90). Experiments with rats in jiggle-cages indicated that MPB (240 mg/kg, s.c.; or more than 640 mg/kg, p.o.), CDP (125 mg/kg, s.c.; or 60 mg/kg, p.o.), and phenobarbital (137 mg/kg, p.o.) all decreased SMA (67 to 70, 74, 95). One study with mice in a photocell chamber indicated that MPB increased SMA at 100 and 160 mg/kg, p.o.; phenobarbital also increased SMA, but

CDP did not affect SMA at doses up to 12 mg/kg, p.o. (28). Bastian (4) using mice in a tilt cage also showed that MPB (200 mg/kg, p.o.), CDP (50 mg/kg, p.o.), phenaglycodol (100 mg/kg, p.o.), and phenobarbital (60 mg/kg, p.o.) all significantly increased SMA.

One general principle in behavioral pharmacology is that drug effects can be markedly altered by environmental changes. For example, in Bastian's study (4), which showed increased SMA after MPB, CDP, and phenobarbital, the mice were kept in beakers from the time of drug administration until transfer to the SMA cage. Bastian noted that "Apparently the changed environment awakens the animals and high counts are recorded at any time within the period of drug action with most anti-Metrazol drugs" (4). Schallek *et al.* (74) showed decreases of SMA after MPB, CDP, and phenobarbital; however, drugs were administered at 5 P.M. and activity was recorded for the next six hours. The drug effects were, therefore, measured during a long session of high nocturnal activity in rats, and decreases in SMA were more likely to occur. All too often, SMA is discussed as though it were a unitary aspect of behavior. It is obviously necessary to consider the variables which affect SMA. It is likely that qualitative differences (increased or decreased SMA) observed were due to either these defined environmental variables or other procedural differences such as doses tested, differences between mice and rats, different pretreatment times, or the time course of drug effects.

The role of SMA in behavioral pharmacology is interpreted differently by different investigators. Gray *et al.* (28) state that reduction of SMA "can be predictive of an action on 'affect' in man. . . . It appears that the predictive value of reduction in motor activity can be generalized as follows: low potency agents with moderate dose-action curves are probably most useful in the minor ailments; high potency agents with moderate dose-action curves are probably most useful in the psychotic states." Others interpret decreased SMA as undesirable and use SMA in a ratio to indicate the specific effects of drugs on other types of behavior (see below). Gray *et al.* (28) use other drug effects, such as ataxia, to show the specificity of drugs on SMA.

Experimentally-Induced Aggressive Behavior

Investigators have attempted experimentally to induce behavior that is interpreted as aggression by using techniques such as septal lesions, isolation, or foot shock. These techniques have "face validity" because they produce behavior that has a superficial resemblance to hostile or aggressive behaviors in man. It is assumed that drugs which eliminate such behaviors would have desirable clinical effects.

Septal lesions.—Brady & Nauta (11) found that rats with lesions in the septal forebrain became vicious within 24 to 48 hours; this viciousness persisted for 12 to 14 days. Hunt (38) reported that MPB (240 mg/kg, i.m. or p.o.) "dramatically offset septal irritability" and that mephenesin had practically identical effects of shorter duration; following CPZ (3.75 mg/kg,

s.c.), the animals were sedated, but still vicious when aroused. Randall and colleagues reported that i.p. doses of MPB (95 mg/kg), CDP (11 mg/kg), diazepam (16 mg/kg), reserpine (4.5 mg/kg), CPZ (5.8 mg/kg), and pentobarbital (17 mg/kg) reduced the viciousness of rats with septal lesions, whereas scopolamine (10 mg/kg) did not (69, 70, 76).

Isolation-induced aggression.—Yen *et al.* (94) found that attack behavior developed when mice were isolated in individual cages for two to three weeks. Drugs were chronically administered orally for one to two weeks prior to testing for decreases in this "aggressive" behavior. Reserpine (3 mg/kg/day), serotonin (50 mg/kg/day, i.p.), CPZ (10 mg/kg/day), and benactyzine (75 mg/kg/day) significantly decreased fighting. At the "maximum subneurological" dose level, MPB was less effective than any of these compounds, and phenobarbital (50 mg/kg/day) did not decrease fighting.

In similar investigations duration of isolation varied from one day (41) to 25 days or longer (17, 28). Cook & Weidley (17) found that CPZ (11 mg/kg, p.o.), phenobarbital (90 mg/kg, p.o.), and MPB (200 mg/kg, p.o.) decreased fighting. Janssen *et al.* (41) found that CPZ (3.1 μ mols/kg, s.c.), phenobarbital (210 μ mols/kg, s.c.), MPB (640 μ mols/kg, s.c.), and scopolamine (0.18 μ mols/kg, s.c.) decreased fighting. Gray *et al.* (28) found that fighting was significantly decreased by CPZ (12.5 mg/kg, p.o.), slightly decreased by phenobarbital (100 mg/kg, p.o.) or MPB (202 mg/kg, p.o.), but unaffected by CDP (31 mg/kg, p.o.).

Foot-shock-induced fighting.—O'Kelly & Steckle (61) discovered that electric foot-shock would induce fighting in pairs of rats. Many drugs have been shown to reduce this fighting. Tedeschi *et al.*
sodes in mice were decreased by CPZ (6.8 mg/kg, p.o.), reserpine (4.4 mg/kg, p.o.), phenobarbital (37 mg/kg, p.o.), and MPB (84 mg/kg, p.o.); whereas mephenesin (250 mg/kg, p.o.) was only slightly effective. Gray *et al.* (28) found that fighting was diminished by CPZ (8 mg/kg, p.o.), phenobarbital (43 mg/kg), and MPB (135 mg/kg, p.o.). Randall (68) found that this type of fighting was diminished by CPZ (20 mg/kg, p.o.), phenobarbital (80 mg/kg, p.o.), MPB (300 mg/kg, p.o.), and CDP (40 mg/kg, p.o.).

It is improbable that aggressive behavior generated by the three techniques just described would involve the same mechanisms. However, in these experiments with different types of induced aggression there is general consistency in the rank order of potency of drugs; CPZ is most potent, phenobarbital is intermediate, and MPB is least potent. In view of these consistencies in relative potency it is interesting to observe how workers interpret their results. Most investigators distinguish between drugs by using ratios of doses which diminish aggression to doses which produce other behavioral effects (decreased SMA, ataxia, loss of righting reflex, muscle relaxation, analgesia, anticonvulsant effects, disruption of rotating rod performance, and mydriasis). Randall (70) states that CDP and phenobarbital both abolished foot-shock-induced fighting episodes at doses below the doses that produced muscle relaxation, while MPB and CPZ abolished fighting at the

muscle relaxant dose. Tedeschi *et al.* (82) compared the effects of CPZ, phenobarbital, and MPB by relating effects on foot-shock-induced fighting behavior to SMA or anticonvulsant effects. These comparisons indicated that MPB selectively blocked this fighting while CPZ had no selectivity. Although phenobarbital was more effective than MPB in decreasing fighting, phenobarbital was classified as being poorly selective because it had anticonvulsant properties at doses below those which decreased fighting episodes. However, if the effects of phenobarbital were compared to its effects in decreasing SMA, phenobarbital would be highly selective (according to the authors' criteria for the selectivity of MPB) because phenobarbital depressed SMA only at high prostrating doses. Gray *et al.* (28) compared doses that decreased foot-shock-induced fighting with doses that produced ataxia in 50 per cent of the mice. Their data indicated that MPB and phenobarbital had no selectivity (on the basis of this comparison) whereas CPZ had highly selective effects on fighting. Although it is useful to consider the relative specificity of action of a drug, there is no established rationale for selecting muscle relaxation, decreases in SMA, anticonvulsant activity, or ataxia as the criterion for judging specificity. With one exception (94), the above studies were consistent in establishing the rank order of potency of CPZ, phenobarbital, and MPB on foot-shock-induced fighting or isolation-induced fighting behavior in mice. The arbitrary selection of different CNS actions as reference effects thus enables one to classify either CPZ, phenobarbital, or MPB as having selective effects on foot-shock-induced fighting, with the two remaining drugs having nonselective effects.

Conditioned Avoidance Responses

The effects of MPB and CDP on conditioned avoidance responses have been studied with several techniques. These include discriminated (discrete) avoidance (89), non-discriminated (continuous) avoidance (77), and combination of avoidance behavior and food reinforced behavior (43).

Discriminated avoidance.—Many drugs have decreased discriminated avoidance responses (19). The basic technique involves presentation of a stimulus (CS) for a period of time before the delivery of a shock (US). A specified response during the CS terminates the CS and avoids the shock. If the conditioned avoidance response (CAR) does not occur, the US is presented and an escape response will terminate the US. In some situations, CPZ, reserpine, and other potent tranquilizers have been shown to block CAR at doses having little effect on the escape response (16). Many studies have shown that MPB has only slight effects on CAR or blocks CAR only at relatively high dose levels (in rats: 16, 23, 24, 54, 55, 59, 64, 69, 88; in dogs: 18; and in monkeys: 64).

Little work has been carried out with CDP on discriminated avoidance. The results of Randall *et al.* (70) suggest that in rats CDP is weaker than CPZ. It is difficult to estimate the degree of avoidance block or whether CDP blocked the CAR at lower doses than escape, because these investi-

gators found that the dose response curves had low slopes. Also they compared CDP to other drugs only at doses that produced a 25 per cent decrease in CAR. They noted that CDP, diazepam, MPB, and pentobarbital were active only in doses approaching the dose that produced response failure and ataxia.

Maffi (55) reported the effects of several drugs on the so-called secondary CAR described by Cook & Weidley (16). This response is frequently observed in discriminated avoidance procedures. When the rat is placed in the experimental chamber it occasionally responds before the CS is presented. Maffii found that MPB and phenobarbital blocked this secondary CAR, although responses to the CS were not affected. This same effect can be achieved with low doses of CPZ and other drugs that block CAR. Maffii classified MPB and phenobarbital as "secondary deconditioning agents," as distinguished from CPZ ("primary deconditioning agent").

Another variation of the discriminated avoidance procedure was described by Randall and his associates (68, 70) as "trace conditioning" in rats. In this procedure the CS terminated several seconds before the US. Responses occurring during this interval were referred to as "gap responses." Results showed that CDP, diazepam, and to a lesser extent MPB, increased the latency of the avoidance response and therefore increased the number of "gap" responses. CPZ, on the other hand, blocked both types of avoidance response completely. The most parsimonious interpretation of these results is that they are consistent with those of Maffii in showing that drugs such as MPB increase the latency of conditioned avoidance responses, while CPZ causes more complete block of all avoidance behavior.

Nondiscriminated Avoidance.—The nondiscriminated avoidance schedule was first described by Sidman (77). Shocks of brief duration are delivered at regular shock-shock intervals (S–S) unless the animal responds; each response postpones the shock for a specified response-shock interval (R–S). The delivery of shock is the only exteroceptive stimulus change in this procedure. Boren (8) included an escape component in the nondiscriminated avoidance procedure. In his avoidance-escape procedure the experimental chamber contained two levers. Responses on the first lever (avoidance) postponed shocks; however, when a shock was delivered it stayed on until the animal responded on the second lever (escape). The potent tranquilizers (phenothiazines, reserpine) decreased average response rates while producing corresponding increases in the number of shocks delivered (30, 75). Schallek (75) indicated that the nondiscriminated avoidance-escape procedure was more sensitive to these drugs than the discriminated avoidance procedures; however, the nondiscriminated avoidance-escape procedure "did not differentiate between a generalized, nonselective depression of behavior and a selective, or tranquilizing effect."

Randall (67) showed that in monkeys, avoidance (nondiscriminated) was reduced by 0.24 mg/kg, s.c., of CPZ, and "somewhat reduced by relatively high doses" of CDP (20 mg/kg, p.o.), while MPB was ineffective even at

hypnotic doses (200 mg/kg, p.o.). CDP produced these effects at doses above those (10 mg/kg) producing ataxia. In another article Randall *et al.* (69) noted that in rats CDP increased the number of shocks at 6 mg/kg, p.o., whereas response rates were decreased 75 per cent at 49 mg/kg, p.o. In these studies MPB simultaneously increased shocks and decreased response rates at doses ranging from 27 to 150 mg/kg, p.o. Randall *et al.* (69) indicated that in monkeys on a nondiscriminated avoidance procedure CDP "affected only the regularity of responding, as indicated by the significant increase in shock rate beginning between 5 and 40 mg/kg, p.o., and higher doses of methaminodiazepoxide[2] (up to 80 mg/kg) failed either further to increase shock rate or to depress overall rate of avoidance responding." MPB failed to affect avoidance behavior in monkeys at doses up to 200 mg/kg, p.o. In another report on nondiscriminated avoidance-escape in rats, Randall *et al.* (70) showed that CDP (4.2 mg/kg, i.p.), diazepam (10 mg/kg, i.p.), and CPZ (0.21 mg/kg, s.c.) had more "specificity" than MPB (103 mg/kg, i.p.), or pentobarbital (12 mg/kg, i.p.) with respect to effects on avoidance as opposed to effects on escape behavior. In addition, increases of avoidance response rates (responses per minute over the entire session) were produced by CPZ, pentobarbital, and diazepam; whereas, CDP and MPB did not increase rates. Although Randall *et al.* (70) did not explain the phenomenon of increased avoidance rates in the presence of increased shocks, it was apparently due to periods of rapid responding alternating with periods of slow responding. A similar phenomenon was shown by Gray *et al.* (28) in a limited study of nondiscriminated avoidance in rats.

Cook & Kelleher (15) used another type of procedure involving nondiscriminated avoidance. This procedure (43) was a concurrent avoidance fixed-ratio schedule with squirrel monkeys. Throughout each session a nondisriminated avoidance schedule was in effect; the S–S and R–S intervals were both 30 seconds. In addition, every 100th response was reinforced with food (fixed-ratio). The monkeys performed with a consistent response pattern; low response rates characteristic of avoidance alternated with high response rates characteristic of fixed-ratio schedules. CPZ (1 to 2 mg/kg, p.o.) characteristically decreased average response rates and increased shocks. Although MPB and phenobarbital decreased average response rates, the number of shocks delivered did not increase until relatively high doses were administered. CDP (20 and 40 mg/kg, p.o.) increased the number of shocks delivered; however, the average response rate was not decreased, even though the monkeys were ataxic.

The effects of CDP on nondiscriminated avoidance were unlike the effects of the potent tranquilizers. Prior to the studies with CDP, it was usually found that avoidance response rates were either decreased, with a corresponding increase in the number of shocks delivered (CPZ, reserpine), or that avoidance rates were increased (amphetamine). The studies with CDP and diazepam show that this type of pharmacological agent can either increase the number of shocks delivered without decreasing average response rates or,

in some instances, can actually increase both the number of shocks delivered and the average response rates. MPB has not been reported to have this effect, and it has relatively weak effects on nondiscriminated avoidance behavior. Although this indication of a qualitative difference between CDP and MPB has been observed, it has not been fully emphasized nor investigated. It is the reviewers' opinion that this phenomenon may represent a unique aspect of the pharmacology of CDP and diazepam.

Conditioned Suppression

The use of aversive stimuli in developing and maintaining behavior has been discussed in the portion of this review on conditioned avoidance bevior. Another use of aversive stimuli is to suppress ongoing behavior. In this case, drugs are usually tested for effects in restoring the behavior. Two general techniques for producing suppression are: (*a*) to present a stimulus that precedes an unavoidable aversive stimulus, and (*b*) to punish responses by having them produce an aversive stimulus.

Unavoidable shock.—The most frequently used procedure for suppressing behavior with an unavoidable shock is the technique described by Estes & Skinner (21). These investigators found that a stimulus which briefly preceded an unavoidable shock suppressed the conditioned lever-pressing of rats for food. Of the drugs that were effective in blocking conditioned avoidance responses, morphine and reserpine have been reported to attenuate the conditioned suppression of lever pressing on a variable-interval schedule of positive reinforcement (10, 34). Others found that CPZ did not attenuate this type of conditioned suppression (23, 37). To date, CDP has not been reported on this procedure; however, it has been found that MPB is ineffective (23, 38).

Response-contingent shock.—This procedure makes the aversive stimulus contingent upon the occurrence of a specific response; that is, ongoing behavior is suppressed by punishing it. In some studies, investigators punished responses that required little or no training. Sacra *et al.* (72) selected adult cats that readily attacked mice. Then each cat received an electric shock whenever it touched the mouse. After an average of three shocks, the cats' attack behavior was suppressed for several weeks even without further shocks. After certain drugs were administered to these cats, they attacked the mice despite repeated electric shocks. The i.p. ED 50's reported for drugs that attenuated this suppression were: benactyzine (3.3 mg/kg), CPZ (4.7 mg/kg), MPB (19 mg/kg), and β-dimethylaminoethyl *p*-chloro-α-methyl benzhydryl ether hydrochloride (5 mg/kg). Although we have classified this "cat and mouse" procedure as conditioned suppression of attack behavior, it could also be classified as shock-induced "taming" according to the criteria utilized in some studies discussed earlier in this review. Sacra *et al.* (72) refer to it as a "conflict" procedure. It is especially interesting that the same drugs that decreased shock-induced fighting or isolation-induced fighting in pairs of mice increased the frequency of attack behavior in cats. These find-

ings are not necessarily inconsistent; rather they emphasize the importance of the experimental contingencies in influencing the quality of the drug effect. Investigators should be more concerned with the relevant variables in a given experimental procedure than with catchy descriptive terms such as "hostility," "rage," or "conflict."

Naess & Rasmussen (58) suppressed the drinking behavior of water-deprived rats by punishing each drinking response with electric shock. They found that rats drank despite repeated shocks after amobarbital (5 mg/kg, s.c.), and even more after MPB (40 mg/kg, i.p.). Neither CPZ (3 mg/kg, s.c.) nor benactyzine (4 to 5 mg/kg, s.c.) increased the drinking behavior. CPZ decreased all behavior at the dose tested.

The studies of Sacra *et al.* (72), and Naess & Rasmussen (58), both using the suppression of responses that required little or no training, were consistent in showing that MPB attenuated the suppression; however, they did not report consistent results with benactyzine and CPZ.

Other investigators studied suppression by punishing conditioned responses. Jacobsen (40) studied the effects of CPZ, reserpine, alcohol, MPB, and benactyzine on suppressed feeding behavior in cats. Cats were trained to press a switch and then open the lid of a box in which food was presented. After three to four months of training on this procedure, the cats received an airblast and a hissing noise about every tenth time they lifted the lid of the box. Whereas Jacobsen observed a number of behavioral changes, the actual punished response was lifting the lid of the food box. Both reserpine (0.02–0.1 mg/kg, s.c.) and CPZ ("0.5 to 0.1 mg/kg," s.c.) markedly decreased all behavior. Jacobsen states that the stupor induced by these drugs may have masked specific effects. Alcohol in ataxic doses (unspecified) increased the number of lid-lifting responses; sub-ataxic doses were ineffective. MPB ("ca 50 mg/kg," s.c.) and benactyzine (0.2 mg/kg, s.c.) increased the number of lid-lifting responses. Jacobsen concluded that both MPB and benactyzine had a considerable "normalizing" effect.

Geller & Seifter (25, 26, 27) used a punishment procedure imposed on a baseline of conditioned operant responding. Rats were reinforced with food for pressing a lever. These reinforcements occurred at irregular time intervals averaging every two minutes (VI_2). Every 15 minutes of the experiment a tone was presented for two minutes. In the presence of the tone every lever press was reinforced; this is a continuous reinforcement schedule (CRF). After training on this multiple (VI_2) (CRF) schedule, each response in the presence of the tone was both reinforced with food and punished by an electric shock. The rate of responding in the presence of tone was inversely related to the intensity of the electric shock. High shock intensities (0.6 to 0.75 ma.) almost completely suppressed responding in the presence of the tone; low shock intensities (0.35 to 0.5 ma.) had less suppressant effect. Preliminary studies with intermediate shock levels showed that promazine and d-amphetamine decreased the number of shocks while MPB, pentobarbital and phenobarbital increased the number of shocks. Geller & Seifter used a

high shock level to test drugs that increased the number of shocks, and a low shock level to test drugs that decreased the number of shocks. Promazine (5.0 to 15 mg/kg, i.p.), and d-amphetamine (0.5 to 2.0 mg/kg, i.p.) decreased the number of shocks when tested against a low shock level. MPB (120 to 135 mg/kg, i.p.), pentobarbital (5 to 15 mg/kg, i.p.), and phenobarbital (5 to 15 mg/kg, i.p.) all increased the number of shocks when tested against the high shock level. In another study (26) using the high shock level, these authors studied the effect of monourethanes, diurethanes, and barbiturates on this punishment procedure. This study (26) analyzed the degree of attenuation of conditioned suppression at the highest dose of the respective drug that did not decrease response rates on the VI schedule. They concluded that the drugs ranked in the following order with respect to maximum effect in attenuating the suppression: MPB (120 mg/kg, i.p.), pentobarbital (8.5 mg/kg, i.p.), phenobarbital (33 mg/kg, i.p.) hedonal (75 mg/kg, i.p.), emylcamate (30 mg/kg, i.p.), and urethane (167 mg/kg, i.p.). In their most recent publication Geller & Seifter (27) reported that CDP, in a manner similar to MPB, phenobarbital, and pentobarbital, attenuated the conditioned suppression ("punishment discrimination") of responding. CDP (7.5 to 30 mg/kg, i.p.) caused rats trained at a high-shock level to respond during the tone periods and to receive more shocks as well as more food. CPZ (0.25 to 3.0 mg/kg, i.p.) caused rats trained at a low shock level to produce fewer shocks during the tone periods, in a manner similar to promazine and trifluoperazine. These authors assumed that decreased rates of VI responding were an indication of nonspecific debilitating effects.

This assumption that decreased rates of VI responding represented debilitating effects or "side effects" seems unwarranted. This again assumes that one behavioral effect is desirable while another is undesirable. It has been shown (14, 15) that so-called side effects such as observable signs of sedation and ataxia can occur without decreased response rates on schedules of positive reinforcement. It is necessary to be more cautious in assuming that any particular behavioral effect is highly correlated with side effects or undesirable effects.

Conditioned suppression can obviously be produced in a number of ways. According to the methods employed, different drug effects were obtained. Although MPB did not attenuate conditioned suppression established by unavoidable shock, it consistently attenuated conditioned suppression produced by response-contingent shocks (punished behavior). With the exception of Sacra's study (72), CPZ was ineffective in the various types of conditioned suppression experiments. On the other hand, CPZ was effective in decreasing conditioned avoidance behavior, while MPB was relatively ineffective. These results with punished behavior show that in certain types of behavior controlled by aversive stimuli, MPB and CDP may have more pronounced effects than CPZ. These effects of both MPB and CDP indicate the danger of assuming that drug effects on one type of aversively maintained behavior can be readily generalized to other types of aversively maintained behavior.

It is necessary to specify carefully the experimental contingencies when analyzing the interaction of drugs and behavior.

Schedules of Positive Reinforcement

A positive reinforcer is an event that increases the probability of occurrence of responses that precede it. Examples of positive reinforcers that are frequently used to develop and maintain behavior are food, water, and intracranial electrical stimulation. The schedule of reinforcement is such a powerful determinant of behavior that many diverse types of behavior can be generated and maintained by positive reinforcement. These scheduling techniques are especially relevant in studying the effects of drugs on behavior because different types or patterns of behavior are differentially sensitive to various drugs. Indeed, the same drug can increase responding on one schedule while decreasing responding on another schedule. As others have noted (19), slight changes in schedules are not trivial; different schedules are strong determinants of the effects of drugs.

MPB and CDP have been shown to have marked effects on performance in several schedules of positive reinforcement (14, 15). In one schedule (44), rats were reinforced by food for each response that occurred between 18 and 21 seconds after the preceding response (DRL). Other responses were not reinforced; they only started the timing cycle again. This schedule generated low stable response rates. MPB (25 to 100 mg/kg, p.o.) and d-amphetamine (0.75 to 3.0 mg/kg, p.o.) increased rates of responding; although phenobarbital (20 to 40 mg/kg, p.o.) did not significantly increase average response rates, short periods of rapid responding alternated with periods of pausing throughout each session. CPZ (10 mg/kg, p.o.), and prochlorperazine (5 mg/kg, p.o.) significantly decreased average response rates. Mephenesin (50 to 400 mg/kg, p.o.) did not affect DRL performance, suggesting that muscle relaxation did not account for the effects of MPB. MPB and d-amphetamine were differentiated from each other on a 50-response fixed-ratio schedule (FR 50), which generates high response rates. At doses comparable to those that increased response rates in the DRL schedule, MPB did not affect performance on FR 50, whereas d-amphetamine significantly decreased responding. Phenobarbital produced small but consistent increases in the already high FR 50 response rates; CPZ, prochlorperazine, and d-amphetamine decreased these response rates. The decreases produced by d-amphetamine in the FR study do not appear related to anorexic effects because comparable doses increased responding in the DRL studies. It was also shown in rats that MPB and d-amphetamine, at the same range of doses described above, increased response rates in both a 5-minute fixed-interval schedule (FI_5) and a $VI_{1.5}$ schedule (44). Hunt (38) noted that MPB occasionally increased response rates on a VI schedule, and Geller & Seifter (25, 26, 27) present several instances in which MPB and CDP increased response rates on a VI schedule. These results militate against super-

ficial classification of drugs as CNS depressants or stimulants. The effects of MPB and d-amphetamine on schedules of positive reinforcement cannot be considered as evidence of either CNS stimulation or depression, but should be specified as effects on certain types of behavior.

Cook & Kelleher (15), using monkeys on a multiple FI_{10} FR 30 schedule, reported that MPB (50 and 100 mg/kg, p.o.), CDP (2.5 to 20 mg/kg, p.o.), and d-amphetamine (0.12 to 1 mg/kg, p.o.) significantly increased rates of responding on the FI_{10} component of the schedule. These increases lasted for 48 hours after 20 mg/kg, p.o., of CDP. CPZ (0.3 to 1.2 mg/kg, p.o.) decreased FI_{10} responding, and mephenesin (100 mg/kg, p.o.) decreased all responding. Cook & Kelleher (14, 15) found that the gross overt effects of these drugs did not correlate with or indicate the manner in which they affected specific types of conditioned behavior. Although d-amphetamine, CDP, and MPB had similar effects on the FI schedules, d-amphetamine produced overt signs of stimulation; whereas, MPB and CDP produced overt signs of depression or ataxia.

Olds (62), and Olds & Travis (63) used intracranial stimulation of various areas of rat brains as positive reinforcers for lever pressing. With electrodes in the tegmental area, MPB (80 mg/kg, i.p.) and d-amphetamine (3 mg/kg, i.p.) increased rates of responding on a CRF schedule. CPZ (2 mg/kg, i.p.) decreased response rates in the same rats. Olds (62) also studied rates of responding as a function of changes in current intensity. In the tegmental area, he found that increasing the current intensity had variable effects on the rate of responding. When the experiment was repeated after the administration of MPB or d-amphetamine, the rate of responding was shown to be directly related to current intensity. These results, as well as those reported above (14, 15, 44) show that both MPB and d-amphetamine increase the response rates on some schedules of positive reinforcement. Although similarities between MPB and d-amphetamine have been shown, there is insufficient data to assume that these drugs have similar mechanisms of action.

To summarize the experimental data presented so far in this review, many studies of MPB and CDP have emphasized "taming," anti-aggressive effects, SMA, and conditioned avoidance. These are procedures which were also used in describing the behavioral pharmacological properties of CPZ, reserpine, and other potent tranquilizers. Relatively few investigators have studied the effects of MPB and CDP on punished behavior or schedules of positive reinforcement. This is unfortunate because these latter procedures were fairly consistent in showing effects of MPB and CDP. These procedures showed qualitative differences between effects of MPB and CDP and the potent tranquilizers without resorting to arbitrary ratios of behavioral effects. Apparently, the procedures utilized in the analysis of CPZ influenced many studies with MPB and CDP. It is probable that those procedures which show unique actions of MPB and CDP will receive more attention in the future.

Miscellaneous

Phillips *et al.* (65) showed that tolerance to MPB developed in rats following the daily administration of MPB (270 mg/kg, route unspecified) for 35 days. In addition to several types of metabolic studies, they studied effects on SMA. In the chronically pretreated rats, MPB (100 mg/kg, i.p.) produced a significantly smaller decrease in activity than it did in nontolerant unpretreated rats. Their findings indicated that an increased rate of metabolic inactivitation played an important role in the development of MPB tolerance. Swinyard *et al.* (78) used low-frequency electroshock seizure thresholds to study tolerance development in mice. The "administration of 300 mg/kg, p.o., of MPB to nontolerant mice increased the threshold more than tenfold, whereas after treatment for 6 days with 1200 mg/kg/day and then for 10 days with 1800 mg/kg/day, this same dose of MPB increased the threshold only 2.5 fold." Following chronic administration of MPB (656 to 814 mg/kg, final doses) to dogs, abrupt withdrawal produced convulsions, and three out of four dogs died (20). Hess (33) reported that MPB, but not CPZ, interfered with the development of imprinting in chicks. He gratuitously attributed the results to muscle relaxant effects. Mallov & Witt (56) found that production of increased plasma free-fatty-acid concentrations induced in rats by irregular unavoidable electric shocks did not occur following administration of MPB (200 mg/kg, p.o.) or CPZ (8 mg/kg, s.c.). Randall *et al.* (70) report that CDP produces reliable weight gains in rats as a result of increased food consumption. Feldman (22) studied the effects of CDP (15 mg/kg, i.p.) on the performance of rats on a Lashley jumping stand. The results showed that CDP decreased response latencies even more then d-amphetamine did, while MPB (80 mg/kg, i.p.), CPZ, and reserpine increased latencies. Also, CDP was the only drug tested that prevented "fixated" behavior when the discrimination was made insoluble. Dews & Morse (19) have previously described the complexities of this procedure.

Studies with Human Subjects

Many studies with human subjects have used batteries of tests in an attempt to establish behavioral pharmacological profiles. These batteries characteristically include measures of psychomotor tasks, perception, and simple learning. An example of a psychomotor task that has been frequently used is simulated driving of an automobile. Marquis *et al.* (57) reported that MPB (800 mg) had no effect on this performance. Kelly *et al.* (45, 46) found that two daily doses of 800 mg of MPB administered for 21 to 28 days did not disrupt the driving test. On the other hand, Loomis & West (53) reported that a single dose of 400 mg of MPB decreased performance of a similar driving task, and a second 400 mg dose ($3\frac{1}{2}$ hours later) significantly impaired this function. More recently, Uhr *et al.* (87) found that chronic doses of MPB of 1600 mg/day for 21 days disrupted the driving task in patients

diagnosed as anxiety neurotics. And Uhr & Miller (83, 84) found that 800 mg of MPB, or of emylcamate slowed reaction times in this performance.

An example of a "perceptual" test that has been employed to study the effects of MPB is the critical frequency of flicker (CFF). In this test the experimenter varies the frequency at which a light source flickers. The subject is instructed to indicate when the lights appear to be fused (no longer appear to be flickering). Aiba (1) found that amobarbital lowered CFF under certain conditions, and 300 mg. of MPB produced similar effects, but these were not statistically significant. Similarly, Jonssen & Andersen (42) found that 1200 or 1800 mg of either MPB or emylcamate did not affect CFF. However, Holland (35) found that 400 mg of MPB, as well as amobarbital, lowered the frequency at which the light appeared to be fused. Idestrom (39) found that 1600 mg of MPB lowered CFF, but this effect was apparently nonspecific in this test battery, since standing steadiness, reaction time, and working time in a coordination test were all impaired.

Other testing batteries include simple learning tasks. Kornetsky (49) required subjects to learn to press different buttons corresponding to the appearance of different lights. Doses of 800 or 1600 mg of MPB impaired learning of this task and 1600 mg impaired reaction time. Burnstein & Dorfman (12) studied the learning of lists of paired words. When presented with a stimulus word, the subject was required to respond with the word with which it was previously paired. Doses of 1200 mg of MPB facilitated the rate of learning of the list. Klerman *et al.* (48) reported that 800 mg of MPB slightly increased the speed with which subjects could do serial addition of numbers. This dose did not impair tapping or steadiness, but did improve visual motor coordination.

The gross inconsistent effects of MPB on simulated driving, CFF, and simple learning tasks may be due to the limited number of doses tested. Although these procedures, and the use of profiles, seem reasonable for testing the effects of drugs, the inconsistent results obtained suggest that efforts should be directed toward other approaches. For example, Holliday & Dille (36) found that MPB (800 mg, p.o.) prevented the disruptive effects of randomly presented shocks to subjects performing perceptual-motor tasks under induced stress conditions. CPZ (50 mg), and pentobarbital (100 mg) did not produce protective effects under these experimental conditions. It would be interesting to determine the effects of MPB and CDP on punished behavior or behavior maintained by schedules of positive reinforcement in humans.

Several investigators have studied Pavlovian conditioning in humans. The most frequently used response for studying human conditioning has been the galvanic skin response (GSR). It is important that most investigators report that MPB increases the basic skin resistance (2, 52, 84). Probably related to this is Laties' (50) report that 1600 mg of MPB reduced palmar sweating; however, Marquis *et al.* (57) reported that palmar perspiration was

increased with MPB. Despite the effects of MPB on basic skin resistance, experiments have consistently showed that MPB has little effect on this Pavlovian conditioned GSR, even at relatively high doses (2, 86). On the other hand CPZ (100 or 200 mg, p.o.) produced a reduction of conditioned GSR (for example; 2). Similarly, Winsor (92), using Pavlovian conditioning of vasoconstriction of the finger with electric shock as the unconditioned stimulus, showed that this conditioned response was not affected by pentobarbital (50 mg) or MPB (800 mg); CPZ (50 mg) did block this conditioned vasoconstriction. The effects of MPB and CPZ on conditioned avoidance responses are consistent in both animal and human studies. CPZ effectively blocks this type of response but MPB does not. It would seem advisable to extend studies with human subjects to other types of conditioning, including avoidance and other schedules of reinforcement.

Uhr *et al.* (86) established a conditioned GSR using an "affectively positive stimulus" as the US. These positive stimuli were "sexually exciting pin-up pictures." In order to test some complex hypotheses about drive level, a female experimenter tested some of the male subjects. MPB (1200 mg) was administered to the subjects prior to extinction of the conditioned GSR. MPB enhanced the resistance to extinction with those subjects tested by the female experimenter. At the present time we find it difficult to relate these findings to the more prosaic animal experiments.

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CONTENTS