BEHAVIORAL PHARMACOLOGY[1,2,3]

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Introduction

The intense interest in behavioral effects of drugs in recent years has led to an unusual number of symposia and reviews. Much of the most significant work through 1955 has been reviewed by Wikler under the title of *The Relation of Psychiatry to Pharmacology* (148), and selected topics are reviewed in *Psychopharmacology: Problems in Evaluation* (24). Many reports of conferences or symposia have appeared (5, 13, 14, 28, 30, 40, 49, 70, 71, 72, 85, 104).

The "Assessment of Tranquilizers" has been reviewed by Riley & Spinks (111), "Motivational Effects of Drugs" by Miller & Barry (88), and "Behavioral Pharmacology" by Sidman (119). In the *Annual Review of Medicine* some of the older work on the reticular formation of the brain stem has been surveyed under the title of "Psychopharmacology" (48), and in the *Annual Review of Psychology* series, "Psychopharmacology" has been reviewed by Ross & Cole (113). A relatively exhaustive account of the pharmacology of drugs distinguished for their behavioral effects is given, in German, in the volume by de Boor entitled *Pharmakopsychologie und Psychopathologie* (10). Therapeutic use of the newer drugs has been reviewed by Cole *et al.* (25), and the toxicology of tranquilizers is presented in a volume edited by Grebe (54). In addition, the Psychopharmacology Service Center periodically makes available to investigators exhaustive annotated compilations of the titles in specific areas of psychopharmacology.

Today, behavioral pharmacology is in the condition of physiology early in the nineteenth century when in 1837 Grainger remarked, "There is probably no branch of knowledge which, at the present day, offers so large a collection of insulated facts and which is yet so defective in general prin-

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

[2] Following is a list of some terms that may be unfamiliar to the reader, with reference to the page in which they are explained: Aversive stimulus, page 149; Avoidance behavior, page 150; Battery of tests, page 161; Continuous avoidance, page 163; Conditioned suppression, page 158; DRL schedule, page 168; Discrete avoidance, page 163; Escape behavior, page 150; Multiple schedule, page 153; Neutral stimulus, page 158; Schedule, page 152; SMA (spontaneous motor activity), page 148.

Abbreviations used in this chapter include: CPZ (chlorpromazine); UR (unconditioned response); CR (conditioned response).

[3] The preparation of the manuscript was supported, in part, by a grant from the U. S. Public Health Service (M 2094) and by the Eugene Higgins Trust.

ciple, as physiology" [quoted by Liddell (83)]. This makes the selection of area for coverage for a short review unusually arbitrary. This review will be limited to discussion of results of experiments relevant to the objective assessment of the effects of drugs on the behavior of more or less intact animals, and to only two classes of drugs: tranquilizers and amphetamines. In general, the starting point has been the review of Wikler (148).

Major Tranquilizers

Effects on unconditioned behavior.—Chlorpromazine (CPZ) and related drugs protect against the enhanced lethality of amphetamine to grouped mice. The toxicity of amphetamine to mice is greatly increased if the mice are aggregated following injection of the drug (see later under "Amphetamines and Related Compounds"). The LD_{50} of amphetamine was reduced from 111 mg./kg. when the mice were put singly in cages to 15 mg./kg. when the mice were put three to a cage following injection. Pretreatment with 5 mg./kg. of chlorpromazine increased the LD_{50} of amphetamine in single mice from 111 mg./kg. to 144 mg./kg., but increased the LD_{50} of grouped mice from 15 mg./kg. to 121 mg./kg. (80). Promazine and reserpine had similar protective actions, and so did phenobarbital, but only in doses causing ataxia. Interestingly, pentobarbital was without protective action. Essentially similar results have been obtained, apparently independently, by Burn & Hobbs (20) for reserpine and CPZ. These authors found that meprobamate and benactyzine were essentially devoid of protective actions against the toxicity of amphetamine in grouped mice.

This protective action of CPZ has been independently confirmed a number of times. For example, Nielsen & Neuhold (94) found that 1 mg./kg. of CPZ increased the LD_{50} of amphetamine from about 18 mg./kg. to about 110 mg./kg. (as estimated by the reviewers from the graphs presented by the authors). These authors also found chlorprothixene, a related compound, to have a protective action. Similar results have been reported for CPZ and thioridazine by Swinyard *et al.* (130), the latter drug being considerably less potent on a weight for weight basis. Comparisons have been made of CPZ and methoxypromazine by Gray *et al.* (53), and of CPZ and triflupromazine by Piala *et al.* (106); these three drugs are of approximately the same potency. The last authors introduced the additional feature of mechanical agitation of the grouped mice by putting them in a rotating cylinder, so that even when most members of the group had died, the survivors were subjected to continuing strong external stimulation.

What can be said about this protective action of CPZ and related compounds? Clearly, mice put together in groups after injection with large doses of amphetamine tend to induce in one another behavior which is prejudicial to their survival. Chlorpromazine appears to reduce the responsiveness of the individual mouse to the stimuli engendered by other mice. Rather than antagonizing "directly" the lethal actions of ampheta-

mine, CPZ protects the mice from the lethality-enhancing attributes of the environment. This ability of CPZ and related drugs to reduce the efficacy of stimuli in controlling and directing behavior seems to be an important property of this type of drug, as will become apparent in succeeding pages; it may well turn out to be the salient characteristic of major tranquilizers.

Chlorpromazine has been reported to have only slight protective action against the lethal actions of mescaline (109). Unfortunately, no information is given as to whether the mice were grouped or isolated following injection of mescaline. Thiopropazate, perphenazine, prochlorperazine, and promethazine were much more effective than CPZ, whereas promazine and reserpine were of comparable efficacy to CPZ in protecting against the lethal effects of mescaline.

The effects of tranquilizers on convulsive seizures induced by electricity, convulsant drugs, or sound have been the subjects of a number of investigations. Chen *et al.* (23) found that reserpine did not change the intensity of the electrical stimulation that had to be put through the brains of mice to produce in them maximal seizures, but reserpine did antagonize the ability of diphenylhydantoin to raise this threshold. Chlorpromazine has been reported to lower the intensity of alternating current necessary to induce minimal seizures in 50 per cent of mice; promazine, mepazine, and promethazine had similar actions, but trifluoperazine and prochlorperazine did not (132). Essentially no effect of CPZ on electrically induced complete extensor seizures was found by Kopf & Nielsen (74), although mepazine conferred some protection. Swinyard *et al.* (130) found CPZ and thioridazine to be ineffective against electroconvulsive seizures in mice.

No protective action of reserpine, even in doses of 100 mg./kg., against drug-induced convulsions was found by Tripod *et al.* (135); and Chen *et al.* (23) have found that reserpine reduces the dose of pentylenetetrazol and of caffeine, but not that of strychnine, necessary to cause convulsions. Swinyard *et al.* (130) found neither CPZ nor thioridazine to alter the amount of pentylenetetrazol necessary to cause convulsions.

On the other hand, Tripod *et al.* (135) found that 100 mg./kg. of reserpine could confer some protection against audiogenic convulsions in rats. Using very much smaller doses (0.2 to 1.0 mg./kg.), Bevan & Chinn (6) found that reserpine enhanced the convulsive responses of solitary rats to sound. Even apart from the difference in dosage, these two sets of experiments are hard to compare since few of the experimental circumstances are specified by Tripod *et al.* (135). In experiments on mice, Plotnikoff & Green (108) found that CPZ, mepazine, meprobamate, reserpine, and some other drugs conferred protection against audiogenic seizures, but Fink & Swinyard (47) report no protection against maximal audiogenic seizures with CPZ, promazine, or triflupromazine, except in neurotoxic doses. Neurotoxic doses were defined as doses that prevented mice from staying one minute on a slowly rotating rod, a feat that normal mice can accomplish with careless abandon. Fink & Swinyard found protection against audiogenic convulsions

only in proportion to protection against maximal electroconvulsive seizures. In subsequent experiments in the same laboratory, Swinyard *et al.* (130) have found CPZ and thioridazine to lead to some modification of audiogenic seizures in mice, but not to clear protection in the ordinary sense of the word. The difference in results between Plotnikoff & Green, on the one hand, and Fink & Swinyard, on the other, may be attributable to the circumstances of the tests; Plotnikoff & Green exposed their mice to sound in groups of five while Fink & Swinyard exposed them singly. In view of the results on toxicity of amphetamine, it may be that CPZ and other drugs minimize the tendency of interactions between the mice to enhance the convulsive properties of the sound stimulation without appreciably affecting the action of the sound per se. Plotnikoff & Green do not give any figures for solitary mice, but comment that grouping the mice led them to "seem to stimulate one another; and that thus the observed total response is a group phenomenon." Fink & Swinyard suggest also the possibility of a strain difference in the mice as a contributing factor in the difference in the results.

Another type of unconditioned behavior on which the effects of tranquilizers have been studied is the so-called spontaneous motor activity (SMA) of animals. Spontaneous motor activity refers to that activity the cause of which is unknown or unspecified. Three general techniques have been used for measurement of SMA: "jiggle-cage" devices; "rotating-drum" devices; and "photo-cell" devices. Jiggle cages consist of animal containers suspended in such a way that movements of the animal are transmitted to a displacement recording system. In rotating-drum devices the drum is mounted on a horizontal axle; the animal is free to run inside the drum; running causes the drum to rotate on the axle and these rotations are recorded. Photocell devices have light beams crossing a cage and impinging on a photo cell; animals are put in the cage and each break of the beam is counted. Jiggle cages presumably record all types of movements, whereas the latter two systems record mainly translational locomotion. In practice, the results obtained by the three methods tend to be rather similar. Most studies on SMA have been made in small animals—mice and rats—although use of a photocell device for monkeys has been reported (*29*).

Chlorpromazine has been reported to reduce SMA of small animals as measured by each of these three types of devices. Kopf & Nielsen (74) employed a jiggle cage using a phonograph pickup transducer; mepazine (74) and chlorprothixene (94) were studied in the same apparatus. The effects of CPZ and perphenazine were studied in a rotating drum by Irwin *et al.* (66). Mirsky *et al.* (91), Gray *et al.* (53), Swinyard *et al.* (130), and Tedeschi *et al.* (133) employed photo-cell devices to study chlorpromazine; meprobamate (91), methoxypromazine (53), thioridazine (130), and trifluoperazine (133) were also studied. In a carefully conducted study, Borsey *et al.* (11a) compared reserpine, deserpidine, CPZ, perphenazine, meprobamate, and trimethoxy-benzoyl-morpholine for their effects on SMA using a photocell device. The Rauwolfia alkaloids were most potent in depressing SMA,

meprobamate least potent, and the phenothiazine compounds intermediate in activity. The increase in SMA caused by amphetamine is antagonized by CPZ and some indolylethypyridine derivatives (91), by thioridazine (131), and by trifluopromazine (the latter as measured in a device counting the number of contacts made by a mouse between the floor of the cage and either the sides or some wires crossing the cage) (106).

Effects on conditioned behavior.—An effect of CPZ on conditioned behavior was described in the first acount of its pharmacology by Courvoisier *et al.* (27). Experiments were conducted on rats in a cage with a grid floor which could be electrified. The animal was put on the floor of the cage, and a tone was sounded for 10 seconds before the grid was electrified. The animal could then escape from contact with the electrified grid by jumping on an insulated pole that descended from the roof the cage. It was found that after a number of trials the rat climbed the pole during the 10 seconds of tone, thereby avoiding the shock. Following appropriate dose of CPZ, the rats failed to climb on the pole during the tone, but still did so when the grid was electrified. The climbing response to the shock was referred to as an unconditioned response (UR), and the climbing response to the tone as a conditioned response (CR); the effects of CPZ were described as abolition of CR while UR remained intact (27). This terminology has been adopted by a number of subsequent workers. It is misleading, unfortunately, since the climbing response to the shock is not an unconditioned response in the proper meaning of the term; that is, it is not a response which occurs on first presentation of the stimulus and in much the same general form in all members of the species. The misunderstanding probably arose because the shock, in contradistinction to the tone, does indeed elicit unconditioned responses; but it does not follow from this that all responses occasioned by the shock are unconditioned. On the contrary, the first time the rat is put in the cage and exposed to the shock, the response consists of "random escape movements" (26)—running around the cage, jumping in the air, sometimes biting the grid, or "freezing." Once the effective escape response is made, it rapidly becomes very consistent and prompt, but the process is clearly one of conditioning. Most rats then gradually develop the avoidance response to the tone. The distinction between response to shock and to tone is therefore not between UR and CR but rather between the tendency of the animal to make a specific discriminated conditioned response to each of two stimuli: one (the shock) which is from the first aversive but which comes to occasion a specific discriminated response (jumping on the pole) and the other (the tone) which is originally more or less neutral, but which comes to function as a conditioned aversive stimulus. An aversive stimulus is a stimulus which will sustain behavior that leads to its cessation or postponement.

This criticism of terminology does not, of course, reflect on the findings of Courvoisier *et al.* (27), which have, in fact, been repeatedly confirmed. Using a similar apparatus, Cook & Weidley (26) found that the dose of

CPZ necessary to cause 50 per cent loss of climbing response to tone (buzzer) was about 10.5 mg./kg. by mouth, but that 40 mg./kg. was required to cause appreciable loss of response to shock; barbital, in contrast, caused about a 40 per cent loss of response to shock at the dose that caused 50 per cent loss of response to tone. Differential loss was obtained with reserpine, but two doses of 25 mg./kg. each were apparently necessary. Methylparafynol and meprobamate produced an equal loss of response to both stimuli. Morphine gave essentially the same results as CPZ, and the effect of pentobarbital was intermediate. In a later contribution from the same laboratory, the ED_{50} for CPZ for loss of response to tone is given as 11.9 mg./kg. (133). Generally similar results have been obtained by other workers for CPZ (73, 106, 130) and for trifluoperazine (133), triflupromazine (106), thioridazine (130), and reserpine (73). Since the absolute values obtained must depend on the details of the apparatus and the exact experimental procedure (see later), no attempt will be made to combine the results from different laboratories.

It is clear that there is a differential sensitivity to suppression, by CPZ and relatives, of the response to the warning stimulus and to the shock; in other words, the avoidance behavior is more readily suppressed than the escape behavior. Avoidance behavior may be defined as behavior that occurs in the presence of originally neutral stimuli, correlated in the past with a succeeding aversive stimulus, such behavior having as its consequence the prevention or postponement of the aversive stimulus. Escape behavior is behavior that occurs in the presence of aversive stimulation and that leads to cessation of the stimulation. The distinction between avoidance and escape behavior as a basis for differential effects of drugs is implicit or explicit in the description of a number of experiments using more conventional psychological techniques, which, in contrast to the pole-climbing technique, do not involve repeated handling of the animal by the experimenter during the experimental session. Handling obviously introduces an uncontrollable and unspecifiable set of variables into the situation. One such technique is the "shuttle box," which is a cage divided into two equal compartments by a hurdle over which an animal can pass. Each compartment has a grid floor that can be electrified. The animal is put in one compartment; a visual or auditory stimulus (discriminative stimulus) is then presented, followed after a predetermined interval by electrification of the grid on the side of the animal. The animal can escape the shock by crossing the hurdle; alternatively it can avoid the shock by crossing the hurdle during the period of warning stimulus. After a predetermined intertrial interval the discriminative stimulus is again presented and the animal must recross the hurdle in the opposite direction to avoid or escape shock. This procedure can be continued indefinitely, the animal shuttling from compartment to compartment. In rats in this situation Nielsen & Neuhold (94) found that 4 mg./kg. of CPZ caused 50 per cent loss of avoidance with essentially no loss of escape, and Irwin *et al.* (66) found 50 per cent loss of avoidance at

1.4 mg./kg. and 50 per cent loss of escape only at 16.7 mg./kg. The comparable figures for perphenazine were 0.1 and 1.2 mg./kg., respectively. Methoxypromazine was found by Gray *et al.* (53) to be approximately equipotent with CPZ and to cause equivalent dissociation of avoidance and escape. Complete loss of both avoidance and escape responding occurred in a cat eight hours after administration of 0.07 mg./kg. of reserpine (67). Reserpine at a dose of 0.37 mg./kg. caused 50 per cent loss of avoidance responding in a monkey (123), and 1 mg./kg. of CPZ caused 100 per cent loss (124). Pentobarbital produced loss of avoidance behavior, possibly as a result of ataxia (124). Complex interactions between Rauwolfia alkaloids and CPZ and brain damage in monkeys in relation to avoidance responding have been reported (123). Brain-damaged monkeys are claimed to be less sensitive to reserpine and desmethoxyreserpine, but not less sensitive to rescinnamine and chlorpromazine. These surprising results have not been independently confirmed.

A still more refined situation for studying escape and avoidance behaviors has been applied by Verhave *et al.* (138) to drug studies. Rats received a shock through the grid floor of the cage unless they rotated a conveniently located wheel within seven seconds of onset of a buzzer. Once the shock had started, it could be terminated by rotation of wheel (escape). Their findings are in general agreement with those obtained with other procedures: 25 mg./kg. secobarbital caused about a 70 per cent loss of avoidance but about a 40 per cent loss of escape, while 4.0 mg./kg. CPZ caused about 80 per cent loss of avoidance and only about 5 per cent loss of escape.

The results just described with CPZ and reserpine and some of the other drugs are compatible with a differential effect of the drugs on avoidance behavior as opposed to escape behavior. They do not, however, serve to establish such a specific effect; other possibilities remain. Some information on this point has come from experiments on the pole-climbing situation. Workers using this technique have commonly observed that, on being put in the apparatus, well-trained rats promptly ascend the pole, even before the auditory stimulus is presented. This has been the subject of explicit study by Maffii (84) under the title of "Secondary Conditioned Response." He found that the ED_{50} of CPZ for preventing the climbing response before the auditory stimulus was 1.75 mg./kg.; the ED_{50} for preventing the climbing response during the auditory stimulus was 11.6 mg./kg.; and that the ED_{50} for preventing the climbing response when the shock was presented was 33 mg./kg. Thus there is a differential sensitivity to CPZ of the tendency to respond to the "environment of the box" and of the tendency to respond to the environment plus auditory stimulus, just as there is a differential sensitivity to CPZ of the tendency to respond to the tone and of the tendency to respond to the shock. This suggests that there may be a continuum of peremptoriness of stimuli in occasioning the response, that in this situation, shock $>$ auditory stimulus $>$ "box alone." If the effect

of CPZ were to attenuate the power of the stimuli to occasion the response, then it would be expected, as found, that the effects of CPZ would be seen first (in the sense of in lowest dosage) on the response to the stimulus of least efficacy. This concept has the advantage of much wider applicability than that which supposes the differential effects of CPZ to be based on a dichotomous distinction between avoidance and escape behavior; and, as will be indicated below, there are indications that this sort of an effect of CPZ occurs in situations where there are no aversive stimuli and, hence, no escape or avoidance behaviors in the present usages of the words. Maffii (84) studied a number of other drugs. Promazine, reserpine, and morphine gave differential effects similar to CPZ. However, meprobamate, hydroxyzine, azacyclonol, phenaglycodol, and phenobarbital abolished the response to the auditory stimulus only at doses very close to those abolishing responses to the shock, although the pre-buzzer responses were abolished at about one-third or less of this dose level. A different approach along the same lines has been reported by Gatti (50, 51). An analytical approach of this kind is obviously the right way to find out more about the drugs and the differences between them. It may be questioned, however, whether the pole-climbing situation is the best system for analysis of this type of phenomenon.

Other attempts have been made to account for the differential effects of CPZ or reserpine on different behaviors. Examples which will be discussed are that CPZ has differential effects depending on the type of motivation maintaining the behavior (e.g., aversive vs. positive reinforcement), on learning as opposed to performance, or on "emotional" behavior. A fundamental difficulty in establishing such distinctions as the basis of differential effects arises out of the finding that differential effects of CPZ can be seen on behaviors which have the same motivation, comprise the same response, and occur in the same animal during successive short periods of time; and which differ only as a result of certain procedural differences, that might, at first glance, appear to be trivial. These procedural differences relate to the programming of the temporal and sequential relations between stimuli presented to an animal, responses of the animal, and further stimuli consequent upon those responses. The first and last of this series of events are prescribed by a "schedule." These are not trivial matters; on the contrary, the importance attributed to schedules in determining behavior has been growing steadily since the days of Pavlov, and they are now beginning to overshadow the traditional variables—motivations, emotions, etc.—that, ever since the Greeks formulated them, have been supposed to be the essential and only determinants of behavior. The relevance of this for the present context is that it has been shown repeatedly, as will now be exemplified, that the behavioral effects of a drug are frequently critically dependent on schedule influences on behavior (see, for example, 32, 34, 38, 118). When attempts are made to compare the effects of drugs on, for example, behavior maintained by aversive stimuli as opposed to behavior maintained by food, it usually happens that, inadvertently or inevitably, the schedule is

different in the two situations. In such cases it is gratuitous to assume, in the absence of further information, that differential effects of the drug are based on motivational differences rather than on schedule differences. Similar remarks apply to most studies on learning and emotion. These basic considerations are still not usually appreciated. In the great majority of published studies such additional information is lacking. An extremely clear statement of some of the difficulties of establishing the specificity of a drug effect is given by Weiskrantz (141). Briefly, study at several values of the independent variables of the behavioral situation (so-called parametric studies) of more than one drug, each at a series of dose levels, is the minimum program before claims as to specificity of a drug effect can be seriously considered. It is recognized that this represents a prodigious amount of work; but when dealing with a subject matter as complex as behavior, surely inferences should be made with more than usual conservatism, rather than, as has so often been the case, just the opposite.

Dependence of drug effects on schedule considerations can be recognized in a great many descriptions of drug effects in the literature. It was first demonstrated explicitly, in pigeons, for pentobarbital (32). As regards CPZ, experiments on pigeons working in a positive reinforcement situation have led to the suggestion that one aspect of its effects is an attenuation of the power of stimuli, internal or external to the animal, to occasion the occurrence (or nonoccurrence) of the responses (8, 35, 36). This interpretation is, of course, similar to that advanced to account for the dissociation between escape and avoidance behavior by CPZ in the experiments described above, and indicates the generality of its applicability.

The effects of CPZ on performance of rats working under a multiple schedule of reinforcement have been reported by Weissman (146). (A multiple schedule is one in which two or more different schedules of reinforcement are imposed during each session, each correlated with a distinctive, different exteroceptive stimulus.) The effects were compared with those of morphine, amphetamine, pentobarbital, iproniazid, and nialamide. There were indications of differential effects both between the different components of the schedule and between the drugs.

Experiments have been made on the effects of CPZ, reserpine, meprobamate, and phenobarbital on rats in a Lashley jumping-stand apparatus (45, 82). In this procedure a rat is put on a small grid platform facing two windows but separated from them by a chasm across which the rat must jump. If the jump is towards the "correct" side, the window opens and the rat passes through to food; if toward the "wrong" side, the window does not yield, and after bumping its nose on the window the rat falls some distance into a net. In each trial one or the other of the windows is lighted. The gird of the platform is electrified some predetermined time (e.g., 30 seconds) after the rat is placed on it, so that it receives a shock if it has not already jumped. The situation is obviously complex, involving shock avoidance, food on a "correct" response, and punishment on a "wrong"

response; also "sidedness" and a visual discrimination. The clearest effect of CPZ, reserpine, and meprobamate was to increase the time before jumping so that the treated animal regularly received a shock before jumping; untreated animals did not. This effect is reminiscent of the effects in the pole-climbing situation. "Fixated" behavior (in the sense of producing an animal that jumps to the same side each time) can be developed in the Lashley apparatus by making neither side nor lighting of the window indicative of the "correct" side. Chlorpromazine and reserpine did not specifically annul this fixation at the doses used (82). It was also shown that CPZ, at the single dose studied, did not affect a brightness discrimination function (45). On the other hand, when fixated behavior was produced in a T-maze by making each arm equally likely to yield food or shock (under which schedule the rats went consistently to one side) the fixated behavior was modified by CPZ, since some six of 14 rats changed side with the dose selected (93). The complexities of these situations defy analytical comparisons at the present time.

A situation in which CPZ and pentobarbital had effects in opposite directions has been described by Blough (9). In these experiments, a pigeon obtained food by blocking both of two horizontal light beams crossing its cage at right angles at head height by keeping its head in the area of intersection of the beams. Each time food was obtained, the time that the beams had to be blocked for the next food presentation was increased by two seconds; concurrently and independently, the time necessary was reduced by two seconds every four minutes. This procedure led to stabilization of rates of reinforcement of about one per four minutes. The average required response time was used as the measure of the performance. From a control level of about five seconds this time increased to about 10 seconds following 10 mg./kg. of CPZ and decreased to less than two seconds following 10 mg./kg. of pentobarbital. Dose-effect curves were obtained permitting the specificity of the difference in the effects of two drugs on the particular behavioral performance to be established.

Effects on motivation.—Chlorpromazine caused a dose-dependent reduction in the food intake of rats during a one-hour period concluding 23 hours without food and a reduction in water intake under similar deprivation conditions (115). The dose levels used, however, are known to modify a variety of behaviors, and no evidence of the specificity of depression of consumatory behavior is given. Chlorpromazine has been reported to depress sexual behavior in male rats (149). Chronic dosage with 0.075 mg./kg. of reserpine depressed water intake by rats (140).

The ability of electric shocks delivered to certain parts of the brain (intracranial self-stimulation) to maintain behavior which has as its only programmed consequence the delivery of such shocks has been amply substantiated since its original description by Olds & Milner (100). The effects of CPZ and reserpine on this type of behavior have been described as differing, depending on the position of the electrode (98). Both drugs caused

marked depression of responding when the electrode was in the hypothalamus or amygdala, but only minor depression when the electrode was in the septal region. A later publication (99) described similar results for CPZ but not for reserpine. A still later publication by Olds & Travis (101) indicated that CPZ caused a large decrement in responding even when the electrode was in the septum. Olds (97) has also suggested a differential effect of a number of drugs on "positive" and "negative" reinforcing areas of the brain. The drugs fell into two groups:

> those effective against escape in doses that fail against self-stimulation—pentobarbital, morphine, and meprobamate—and those effective against self-stimulation in doses that fail against escape—chlorpromazine, and on the basis of earlier work, probably reserpine.

Olds concluded that "every chemical which inhibits approach mechanisms fails to inhibit escape mechanisms" and vice versa. Some of the difficulties in reaching conclusions of this kind have been mentioned already. In addition, the earlier work by the same author (98, 99) showing differential sensitivity for different "positive" areas of brain to CPZ would seem to make this suggestion untenable. The paper by Olds & Travis (101) also reported extensive experiments on brain mapping using CPZ, morphine, meprobamate, and pentobarbital. The reviewers have the impression that some of the other results described in this paragraph are rescinded by this extensive report, but they are not quite sure.

Other effects of CPZ on intracranial self-stimulation have been reported by Stein & Ray (126). In their experiments, rats were presented with two levers. Depression of one lever led to stimulation in either the posterior thalamus or the midbrain tegmentum; the shock intensity decreased progressively with each lever press, but could be reset to its original level by a single operation of the other lever. At a dose level of 1.5 mg./kg. of CPZ the animal pressed the reset lever after fewer consecutive presses of the primary reinforcing lever; it also pressed the primary reinforcing lever more frequently. This latter increase in rate was postulated to result from an effect of CPZ in shortening the aftereffects of the brain shock, but no direct evidence was presented. What was observed was increased rate of responding on both levers; there are many other situations, not involving brain shocks, in which CPZ also causes an increase in rate of responding.

A direct study of type of motivation as a possible basis of differential effects of reserpine has been made by Wenzel (147). Eight cats were trained to press one lever to obtain food in the presence of one stimulus and to press a second lever in the presence of a second stimulus to avoid or escape from electric shock. The cats were then given 35 μg./kg. of reserpine and tested repeatedly in the succeeding 124 hours. The median latencies of the responses to the stimulus for food were increased much less than those to the stimulus for shock. It was concluded that the type of reinforcement played a crucial role in determining the susceptibility of the responses to

the effects of reserpine. This conclusion is in contrast to the equivocal or even contrary findings on this point by other workers (see below); it therefore deserves careful evaluation. Wenzel's figures show that the prereserpine latencies for the avoidance response were, on the average, longer than the latencies for the food response (medians of four seconds and two seconds, respectively). If the latency, the only measure used in this study, is to be taken seriously as a quantitative measure, this difference cannot be dismissed. Immediately before reserpine, three out of the eight animals showed lower or equal median latencies to the preshock stimulus than to the prefood stimulus; after reserpine, in the 96 series of trials conducted, 22 still showed median latencies to the preshock stimulus equal or lower than those to the prefood stimulus. Considered this way, this is not very impressive evidence for specific reduction in shock motivated behavior. The statistical significance depends, presumably, on about one-half the cats that gave very high latencies for shock, in one or two series, at irregular intervals after the drug. The avoidance response showed greater resistance to extinction than did the food response, but this is not conclusive evidence for the greater "strength" of the avoidance response at the beginning of extinction, since in extinction of the food response the absence of reinforcement is apparent at every response, whereas in extinction of the avoidance response the lack of correlation between absence of shock and occurrence of responses is much less obvious. Another difficulty in interpreting the results arises from the earlier observations in the same laboratory (69) that reserpine caused a very similar dissociation in effects on latencies of response to an auditory and to a visual stimulus, both of which were occasioning an avoidance response; the latencies to the visual stimulus increased while the latencies to the auditory stimulus remain unchanged. The reserpine in these experiments was given into the cerebral ventricle in a dose of 200 μg., but, nevertheless, the experiments serve to show that the dissociation seen between avoidance and food response latencies can also be seen in a differential effect on the stimulus control of an auditory stimulus vs. a visual stimulus. The authors conclude that the differential susceptibility "is related to the difficulty in learning the two responses, for avoidance to tone was acquired in fewer trials. . . ." Thus the difference in the ability of different sensory modalities to pre-empt the behavior of the animal is as able as differences in motivation to lead to differential effects of reserpine. It is interesting that in these experiments, as in Wenzel's, the stimulus whose control was most markedly affected by reserpine was that to which the initial latency was the longer. It seems possible that all these differential effects of reserpine will turn out to be based on a continuum of strength of stimulus control of behavior as suggested earlier in this chapter for CPZ.

In contrast to the conclusions of Wenzel (147), Miller (86), Riopelle & Pfeiffer (112), and Weiskrantz & Wilson (142) found no evidence of greater sensitivity to reserpine of avoidance behavior than of positively reinforced behavior in monkeys, and Sidman (118) concludes that "the

nice classification that seemed to be developing for reserpine on the basis of positive- and negative-reinforcement contingencies did not hold." For CPZ, the converse hypothesis, that behavior maintained by positive reinforcement is more sensitive than that maintained by aversive stimulation, has been proposed by Olds (97), and Ferster & Skinner (46) show evidence pointing in the same direction. In Weissman's (146) multiple-schedule experiment, CPZ appeared to have rather more effect on shock-avoidance behavior than on food-maintained behavior.

In conclusion, it cannot be regarded as established that reserpine and CPZ have a greater effect on behavior related to aversive events than they do on behavior related to positive reinforcement. Researchers have been predisposed to look for differential effects of these drugs along these lines because of the general impression that they are useful clinically, especially in reducing the reactions to aversive stimuli and situations. It must be remembered, however, that few people consult physicians because their work has too much fascination for them, or because they enjoy their play too much; the people to whom the drugs are given most frequently are by no means a representative sample of the general population. The drugs might be just as effective in alleviating fascination and enjoyment. Indeed, one of the most dramatic therapeutic effects of the drugs is in quieting manic psychotics in most of whom there is no reason to infer aversive stimulation as the cause of hyperactivity.

Effects on acquisition and extinction.—Several attempts have been made to assess the effects of major tranquilizers on acquisition or extinction of behavior. Since these drugs cause such profound changes in performance, it becomes a matter of considerable difficulty to identify specific effects on changing performance. For example, although it has been shown that rats require significantly more trials to reach a criterion of 14 out of 15 avoidance responses in a shuttle box and also that these responses are extinguished more rapidly when under CPZ (1), these effects, as the authors point out, could be caused by "motor retardation," rather than effects on acquisition or extinction. They could also be caused by effects on stimulus control. Comparable difficulties apply to the interpretation of the semiobjective study of CPZ by Denenberg *et al.* (31), and no conclusions on the effects of reserpine in this regard can be drawn from the single, ineffective dose study of Wayner & Reimanis (140). Miller *et al.* (89) found that CPZ produced a dose-dependent decrease in the number of responses of rats during extinction in a shuttle box. Another study (90) reported more rapid extinction of a shuttle-box avoidance response in rats under CPZ than under saline and extinction persisted when the CPZ was discontinued. Although the CPZ clearly had an effect during extinction, this does not constitute proof that CPZ has an effect on the process of extinction. For example, prolongation of latencies under CPZ (an effect on performance) would lead from the beginning to more occasions in which the buzzer was terminated without a shock, which would surely speed the progress of

extinction. This may be what the authors have in mind when they suggest that their findings "were attributable to relearning of the avoidance situation by animals during administration of CPZ." A comparable explanation is suggested by Hunt (65) to account for his observation, under entirely different circumstances, of a failure of extinction under CPZ. Thiopropazate has been shown to depress both escape and avoidance behavior by rats during acquisition of the responses in a discrete, lever-pressing situation (128). Comparisons were made, at a single dose level, with benactyzine and pipradol.

Effects on conditioned suppression.—A great deal of interest has been directed toward the possibility that tranquilizers specifically modify "fear" or "anxiety," probably because of the general impression as to the clinical usefulness of the drugs. Experiments suggesting such an effect of reserpine have been described several times by Brady (15 to 18) using the procedure of Estes & Skinner (43). Rats or monkeys were trained to press a lever for positive reinforcement. While this lever-pressing behavior was continuing, a "neutral" stimulus (i.e., a stimulus which on initial presentation had little or no effect on behavior), such as a clicking noise, was presented for a period of time, ending coincidentally with delivery of an electrical shock to the animal; the shock was delivered irrespective of the behavior of the animal. If the durations of the "clicker-on" and the "clicker-off" periods are suitably chosen (127), the animal comes to respond at a very much lower rate during the clicker-on periods (conditioned suppression). After some days on a daily reserpine dose of 0.20 mg./kg. to rats or 0.75 mg./kg. to monkeys, the response rate during the clicker periods increased and the rate when the clicker was not on decreased so that the two rates became much more nearly alike. When the rate during the clicker period was reduced by making every response (later every second or third response) lead to a shock (i.e., a punishment situation), the rate did not increase under the influence of reserpine. This was interpreted as evidence of a relatively specific effect of reserpine on "anxiety" (15). There is no published independent confirmation of these findings. The possibility remains that the effects of reserpine could all be attributable to attenuation of the control of the behavior by the clicker. The rates during the clicker were much lower on the punishment procedure than on the conditioned suppression procedure indicating that the control of behavior by the clicker was more powerful in the former instance, and such differences in degree of stimulus control have been shown to be adequate to cause differences in susceptibility to disruption by drugs (33). On the other hand, evidence of specificity of the effects of reserpine is provided by comparison with amphetamine, which caused an increase in rate during the clicker-off periods with as great or greater than normal suppression during the clicker periods. Unfortunately, no information on dose-effect relationships is given for either drug. In rats in a comparable situation, except that the response was a lick of a water bottle by the rat, it has been shown that while small doses of ampheta-

mine did not attenuate the suppression, larger doses led to rapid responding through the stimulus period (134).

Description of this effect of reserpine on conditioned suppression in terms of anxiety conforms with contemporary psychological usage, but it is probable that it has led to interest in these findings in circles to which they would not otherwise have penetrated and has contributed to confusion among the psychologically unsophisticated. There appears to be no generally accepted definition of anxiety. Clinically, anxiety is usually characterized on the basis of the verbal behavior of patients; for example, Persky *et al.* (105) write that in their studies on anxiety "the criterion of anxiety was the patient's experience of a feeling of dread and foreboding—as if something dangerous were about to happen." To a large school of psychologists, anxiety is a drive—something that will sustain escape or avoidance behavior (87, 92). Again, other psychologists emphasize as a defining characteristic of an emotion such as anxiety that it affects a number of different behavioral activities simultaneously and nonspecifically (43). It is mainly in this last sense that the term is used by Brady, although in his experiments subjective assessment was also made of defecation, pilo-erection, and immobility. It does not seem to the reviewers that there is any question of "right" and "wrong" usage here, but merely one of convention. Of course, there has been a vast amount of illuminating work on the relations between the different "aspects" of anxiety, but it is still not possible to use the term interchangeably to mean any or all of these aspects. Attempts to do so lead to sterile arguments as to the applicability of findings in animals to man, and distract from the careful comparison of specific phenomena which is the only sound basis for such inferences.

Using a subjective assessment of a conditioned emotional response, Weiskrantz & Wilson (143) studied the effect of reserpine in monkeys; no validation of the scheme is given. On the basis of these observations, they suggest that reserpine interferes with the development of a learned emotional response. This suggestion has been challenged by Stein (125), who studied the development of conditioned suppression under reserpine. The animals were maintained under reserpine during the pairings of periods of clicking noise and shock. They were then taken off the reserpine and their performance during extinction (i.e., during continued presentations of the clicking noise but without shock accompanying its cessation) was compared with that of animals that had been similarly conditioned in the absence of reserpine. Although the dosage of reserpine used (0.5 mg./kg./day) was sufficient to reduce the rats to virtual inactivity by the end of the treatment period, they subsequently showed essentially as much suppression during the clicking periods in extinction as did the animals that had never received reserpine. Stein does not discuss the relation of his findings to those of Brady. Although there is no logical contradiction between them, the results of Stein should at least raise the possibility that reserpine does not affect fear as such, and that an alternative explanation for the results

of Brady should be sought. In addition to the ever present possibility of an effect on stimulus control, Heistad (61) has suggested an attenuation of conditioned suppression based on discriminable modification of the internal environment of the animal by the drugs; unfortunately, his experiments gave equivocal results.

The effect of reserpine on conditioned suppression in the guinea pig has been studied by Valenstein (136). Such suppression could be produced in the guinea pig as in the rat and monkey, although with the same schedule as had been used in rats, it was less complete. The effect of reserpine, however, was quite different in that it apparently never led to the type of effect reported in rats and monkeys. Reserpine caused either virtually complete abolition of responding only during the clicker periods, or, with larger doses, it abolished responding in the absence of the clicker periods while bursts of responding continued during the clicker periods. The difference between the results in rats and monkeys and in guinea pigs is attributed to a species difference, but it is clear that these fascinating but complex phenomena deserve further analysis. The tendency of the guinea pig to respond is reduced by doses of reserpine on the order of 100 times less than those required in the rat or monkey.

Effects observed by inspection.—The most immediately obvious way of studying the effect of a drug on the behavior of an animal is to give a dose of the drug and then to watch the animal. This has the advantage of simplicity so far as apparatus is concerned; but the apparatus is the only simple thing about this seductively simple-sounding common-sense approach. There are two major difficulties to such "straight forward" observational procedures: the difficulty of obtaining data in reproducible form—that is, reproducible by other people in other laboratories—and the difficulty of summarizing information on dose-effect relationships so that evidence of drug specificity can be substantiated. The former difficulty necessitates the development of relatively elaborate scoring systems, rigid definition of criteria of different types of behavior, use of blind techniques and statistical validation; these are by no means simple undertakings. It should be noted that many of the difficulties of these techniques are avoided when they are used, so to speak, intramurally, by one or a very few observers constantly involved, as, for example, in screening substances in an industrial laboratory. In these particular circumstances simple observational techniques have unquestionably proved their usefulness. The challenge is to convert these findings into permanent contributions in the scientific literature that can be independently verified in any place at any time. Schemes attempting to make this possible have been published for a number of species recently. Two of the most careful scoring schemes have been selected for discussion.

The first is for cats (96). This defines 20 behavioral activities of the species; these are grouped into four categories, each containing five components. The categories are entitled "hostility," "excitement," "contentment," and "sociability." The scheme was subjected to statistical analysis,

and an ingenious attempt was made to enhance the discriminatory power by giving greater weight to the components that occurred least frequently under control conditions. Some six drugs were studied, including CPZ and Rauwolfia. Chlorpromazine caused the least reduction in sociability of any of the drugs and the greatest reduction in hostility, and an increase in excitement. Rauwolfia, on the other hand, caused only a slight drop in contentment along with a drop in sociability, with no change in other categories.

Another scheme, applicable to cats, dogs, and monkeys, has been outlined (66). This also has some 20 items including "curiosity," "playfulness," and "aggressiveness." The complete scheme and its statistical validation have not yet been published. It is reported that the most consistent gross behavioral effect of CPZ was

> suppression of locomotor activity, and, where present, a reduction of fearfulness. A diminution of play and grooming activity and of fearfulness were among the earliest behavioral changes observed. Increased vocalization (meowing) in the cat also was observed with relatively small doses of drug. . . . Aggressive (biting, attacking) behavior of hostile animals usually was suppressed by small doses. . . . In less aggressive animals, however, aggressive behavior often was augmented by the drug(s).

A limitation of these observational schemes is illustrated by the fact that the reviewers are unable to decide to what extent this author agrees or disagrees with the previous author, who found CPZ to lead to "least reduction of Sociability, greatest reduction in Hostility, and an increase in Excitement." Again, neither author presents dose-effect relationships. Although the anthropomorphic terms in these schemes can be given careful definitions, it is somewhat to be feared that with the passage of time the careful definitions will be forgotten and the terms assumed to have their everyday or psychiatric meanings. It is perhaps worthy of note that the reviewers find little evidence in these descriptions of a specific action of CPZ on anxiety, although it is probable that the observers were alert to the possibility of such effects.

A much simpler observational scheme in mice and rats has been used to compare the potencies of reserpine with closely related substances and with whole root preparations of Rauwolfia (114). By this test, 11-desemethoxy-reserpine was equipotent with reserpine, but rescinnamine was much less potent, although in dogs rescinnamine was at least as potent as reserpine on blood pressure, on "sedation" (rated on a scale of one through four), and on miosis.

Observations in man.—Most of the observations on CPZ and related drugs on normal human subjects have involved psychological assessment by means of a "battery of tests"; that is to say, a series of tests intended to measure a variety of aspects of human performance, e.g., simple motor functions, complex motor functions, discriminatory behavior, learning, etc. The first such study was by Heimann & Witt (59), who obtained effects with 37.5 mg. of

CPZ, total dose, intramuscularly. Subsequent studies have usually used larger doses by mouth. Doses of 100 mg., 200 mg., and 400 mg. of CPZ by mouth were used by Kornetsky *et al.* (76), and the effects on performance on a battery of tests compared with those of secobarbital, meperidine, and *N, N*-diethyl-D-lysergamide (LSD). In later experiments using a modified battery of tests, Kornetsky & Humphries (75) showed significant differences from the placebo of 100 mg. and 200 mg. doses of CPZ. Two-hundred mg. of CPZ had a greater effect on motor co-ordination but a lesser effect on "intellectual functioning" than did 200 mg. secobarbital. Surprisingly, this dose of CPZ had a greater tendency to cause sleep in the subjects than did the same dose of secobarbital. This was also seen in a further study in which CPZ was found to have more effect than secobarbital in hastening onset of sleep when given at 7:00 p.m.; both drugs tended to cause "hangover" in the sense of impairment of performance on the test battery next morning between 9:00 and 10:00 a.m. (79). After single doses, 200 mg. CPZ causes more impairment than 200 mg. secobarbital in schizophrenics, but after 11 days of daily treatment with the same drug, 200 mg. CPZ no longer causes significant impairment, although 200 mg. secobarbital still does (78).

Miscellaneous.—Tolerance to CPZ has been studied in rats by Boyd (12). Chlorpromazine reduced spontaneous motor activity as measured in a revolving drum, but after daily dosing the effect was no longer seen, although it could be reinstated by an increment in dosage. Following abrupt withdrawal of CPZ after 40 weeks continuous treatment with doses that towards the end were as large as 200 mg./kg., a large increase in SMA resulted which was apparently sustained for weeks.

Ethiazine (N-2-dimethylaminoethyl phenothiazine; i.e., promazine with a two instead of a three carbon chain between nucleus and side chain nitrogen) has been studied for effects on a Pavlovian conditioned response (salivation) by Aganyants (2). It led to some increase in salivation by dogs to both "positive" and "negative" conditioned stimuli but to complete loss of a delayed reflex. There was loss of inhibition of respiration on presenting ammonia in inspired air, and an increase, instead of the usual conditioned decrease, in respiration during presentation of a stimulus succeeded on previous occasions by ammonia in inspired air. Although it is difficult to make a detailed comparison of these results with those obtained on CPZ previously described, the reviewers feel that they are generally concordant.

Raunescine and iso-raunescine have been reported to have effects qualitatively similar to reserpine on operant behavior in pigeons, although only, respectively, about 1/10 and 1/100 as active on a mg. per mg. basis (102).

Some benzoquinolizine derivatives have been reported by Pletscher *et al.* (107) to be two to five times less potent than reserpine on avoidance and escape behavior in a pole-climbing situation. It is interesting to note that iproniazid, dopamine, norepinephrine, epinephrine, serotonin, and morphine also abolished avoidance behavior before escape behavior; this leads to some

question as to the specificity of the effect. Another benzoquinolizine, tetrabenazine, has been shown by Heise & Boff (60) to produce loss of continuous avoidance in rats in a lever situation during the period between one-half and four hours following a 2 mg./kg. subcutaneous dose. This suppression of avoidance responding by tetrabenzine is antagonized by "monoamine-oxidase inhibitors" in a nicely dose-dependent manner, so that the situation has been proposed as a method of assay for this type of activity of "monoamine-oxidase inhibitors."

Morphine.—Morphine has been studied in a discrete avoidance situation. In discrete avoidance a warning stimulus is presented to the animal; if the animal does not make the required response within a specified period of time, an aversive stimulus supervenes. If the animal makes the required response soon enough, then the warning stimulus ceases and no aversive stimulation occurs. In either case, there is a period of dead time before the warning stimulus is next presented. The dependent variables are usually proportion of trials on which avoidance occurs and latency of the response. This type of situation is frequently referred to in the literature as "classical" or "Warner" avoidance. It is to be distinguished from the situation in which the animal receives shocks not preceded by a warning stimulus at regular intervals throughout the experiment unless responses occur; each response postpones the shock for a specified period. The dependent variables are usually rate of responding and number of shocks received. This situation will be referred to as continuous or "Sidman" avoidance.

The effects of morphine on discrete avoidance in rats with a lever press as the required response has been studied by Verhave *et al.* (139). The ED_{50} for loss of avoidance responding was of the order of 10 mg./kg., at which dose there was essentially no loss of escape responding.

Nalorphine (1 mg./kg.) has been shown by Weiss (144) to depress the rates of responding of rats working for food and to change the temporal distribution of the responding. Mixtures of morphine and nalorphine were also studied.

Morphine has been shown to cause a dose-dependent attenuation of conditioned suppression in rats (63). At a dose of 9 mg./kg. the rate increased approximately threefold during the preshock auditory stimulus while the rate in the absence of the auditory stimulus fell by about 25 per cent. The net effect was thus to make the rates more similar either in the presence of, or in the absence of, the auditory stimulus: i.e., to reduce the stimulus control of the auditory stimulus. As in the case of reserpine, whether there is an additional effect on the specific etiological factors of the suppression remains to be established.

These same authors studied the effect of motivation on the modification of behavior caused by morphine and pentobarbital in human subjects (62). Motivation was varied by varying the conditions under which morphine was given to addicts; standard incentive was to give a constant dose of morphine after experimental sessions, irrespective of performance; high incentive

involved making the dose of morphine dependent on the performance; for low incentive, the subjects received their morphine at least one week before the experiment and in constant dosage. The dependent variable was the average reaction time to visual stimuli. Fifteen milligrams of morphine or 250 mg. of pentobarbital were injected 50 minutes before the session. The effects of pentobarbital were changed from depressant (tending to lengthen reaction times) to stimulant (tending to shorten reaction times) when conditions were changed from low to high incentive, while the converse change took place in response to morphine. Although this type of pronounced dependence of drug effect on identifiable variables has now been shown a number of times in animal experiments, this study is of great importance as one of the very few in which a comparable analysis has been achieved in man.

Amphetamines and Compounds with Similar Behavioral Effects (81)

As mentioned in the opening section on the tranquilizers, the LD_{50} of amphetamines and related compounds is greatly dependent on environmental circumstances. This was first reported by Gunn & Gurd (56) and has subsequently been studied by Chance (21, 22) and by Höhn & Lasagna (64). The aggregation of several mice in a cage after administration of amphetamine reduced the LD_{50} to of the order of one-tenth of the dose necessary for mice in individual cages. Ambient temperature, size of cage, state of hydration, and ambient noise also had effects, although smaller (21, 22). Strain of mouse is also probably important. The administration of shocks to single rats enhanced the toxicity of amphetamine (145). In view of these gross effects of environmental influences on life and death after amphetamine, it is not surprising that environmental influences should greatly affect the more repeatable behavioral consequences of administration of amphetamine.

Amphetamine decreases the intake of food in a free feeding situation (120) and the intake of water in a free drinking situation (3). Different rates of eating were engendered in rats by permitting some animals access to food only during a two-hour period each 24 hours, while others had free access to food all through the 24 hours. The effects of amphetamine were not affected by differences in rate of eating, but they were shown to be dependent on dosage (120). The suppressant effects of amphetamine on rate of eating are exaggerated in rats taking in abnormally large quantities of food or water as a result of appropriate hypothalamic lesions (42). Ephedrine had similar effects and so did phenylpropanolamine, but epinephrine did not. The increased sensitivity of hypothalamic hyperphagic rats to the effects of amphetamine in reducing food intake has been confirmed by Reynolds (110).

The effects of amphetamine on hunger and thirst have been studied by Miller and his colleagues in rats (86). The dependence of hunger on number of hours of deprivation was studied using a variety of "measures of

hunger": volume of milk drunk, rate of bar pressing for food, the maximum concentration of quinine in milk that the rat would drink, and intensity of stomach contractions. Thirst was similarly "measured" in the hours following administration of 5 cc. 2 molar NaCl. The functional dependences found differed radically according to which method of measurement was used, and so did the effects of amphetamine. No method is given for combining these conflicting results to obtain a clear "measure" of the effect of amphetamine on hunger or thirst per se. On the contrary, the author writes, "We are forced to re-examine and perhaps abandon common-sense categories of generalization according to convenient words existing in the English language." But the author seems reluctant to abandon the terms hunger and thirst, even in face of the type of evidence just quoted. It should be emphasized that the "measures" are in conflict only in so far as they are regarded as measures of the hypothetical unitary variables hunger or thirst; otherwise they simply give valuable information on interesting situations. It may be questioned whether the continued use of terms such as hunger and thirst, fear and conflict can do anything other than hinder the search for scientifically defensible categories of generalization.

Amphetamine, but not metrazole, has been reported to antagonize some of the effects of thiopental on a "conditioned reflex" in rabbits; both drugs antagonized hexenal (95). Some iminazoledicarboxylic acid derivatives have been reported to have similar effects in rats (11).

Amphetamine has been shown to increase the output of avoidance behavior in a variety of situations. Methamphetamine led to an increase in the rate of responding of a rat pressing a lever to postpone a shock in a continuous avoidance situation (137). Amphetamine also increased the output of behavior of rats turning off a very loud noise by pressing a lever (57). In some of these experiments, the noise ceased while a lever was depressed but began again when the lever was released. Following 2 mg./kg. of amphetamine, both the rate of pressing the lever (defined as the number of times the lever was pressed divided by the time the noise was on) and the rate of releasing the lever (defined as the number of releases divided by the time the noise was not on) were increased. This is what would be expected if amphetamine nonspecifically increased the tendency to respond; it is against the suggestion that amphetamine specifically enhances the effects of aversive stimuli.

In spite of the fact that amphetamine decreases the intake of water in a free-drinking situation (3), it increased the rate of licking from a water bottle and also changed the temporal pattern of licking, when the lick was made the effective avoidance response in a continuous avoidance situation (134). In the rat, increased licking in this way seems to lead inevitably to increased water intake so this technique provides a means of accurately controlling the fluid intake of rats in amounts up to several times the normal intake.

The amphetamines will increase the rate of responding even when the reinforcement is food or water. This has been shown for food by Dews (37) in pigeons and by Teitelbaum & Derks (134) in rats, and for water in rats by Brady (15), Sidman (117), and Stone *et al.* (129). This is one of the clearest examples of the predominance of schedule contingencies over other controlling variables, such as motivation, in determining the modification of behavior by drugs.

Larger doses of the amphetamines frequently lead to reduction in output of behavior (37, 86). This is not surprising in itself, even though a profound reduction in behavior occurs with doses that are very much below lethal levels. What is surprising is that the dosage level at which behavioral output falls below control levels varies considerably according to the schedule of reinforcement even when all other features of the situation are kept constant (37). In addition, there are many behavioral situations in which the amphetamines cause virtually no, or only slight, stimulation. The identification of the features of a situation that determine whether optimum doses of an amphetamine will, or will not, cause a substantial increase in output of behavior is clearly a matter of great importance.

There is a tendency, as with other classes of drugs, to consider first the possibility that the effects of the drug are dependent on nature of motivation—that, for example, drugs may affect behavior maintained by positive reinforcement differently from behavior maintained by use of aversive stimuli such as electric shocks. As has been repeatedly emphasized such differences are hard to establish, especially when it has been shown that the drugs cause differential effects on performance depending on schedule of reinforcement under identical conditions of motivation. The reviewers have the impression that the stimulant effects of the amphetamines continue up to higher dose levels when performance is maintained by aversive stimuli than when it is maintained by positive reinforcement, but this has not been clearly established.

Some progress has been made in identifying other factors determining the effects of amphetamines. From the relative effects on performance on four different schedules of reinforcement of pigeons, it has been suggested that control rate of responding is an important factor, that sustained rates of responding are not susceptible to increase, but that very low rates or intermittent responding are readily increased (37). There is, of course, a limit to this relationship, in that if the tendency to respond is extremely low, then the output of behavior cannot be increased by the amphetamines. This has been shown by Verhave (137) in rats. He obtained very low rates of responding by programming no consequences to the lever presses of untrained rats. Six rats had daily one hour sessions of this kind for 12 days. There was a tendency for the number of responses made in the successive sessions to decrease. In the first session the mean was 15.7 responses per hour and all animals made at least one response during the hour. In the seventh session the mean was 0.8 responses per hour and three of the

six animals did not respond at all. This certainly represents a very low tendency to respond. Before the eighth session, the animals were given 2 mg./kg. of methamphetamine; the mean rate of responding remained 0.8 responses per hour and four of the six animals failed to respond. In other experiments in which the tendency to respond was somewhat higher, the effects of the methamphetamine were unpredictable, sometimes causing a substantial increase and sometimes not. When training in an avoidance situation had led to a substantial tendency to respond, the effects of the amphetamines became consistent in causing an increase in rate (134, 137). In pigeons, it has been shown likewise that methamphetamine does not cause an increase in rate of responding when the tendency to respond is extremely low because of prolonged extinction in the presence of a particular stimulus (33).

The effects of methamphetamine on behavior have been shown to be dependent not only on the nature of the schedule and the amount of training, but also on the parameter value of the schedule (38). Pigeons were studied under conditions of delayed reinforcement of the response, i.e., a period of time had to elapse between occurrence of the response and presentation of the reinforcing stimulus. When the delay time was 10 seconds, methamphetamine had little tendency to cause an increase in rate of responding, but it caused a large increase when the delay was 100 seconds. The effects of pentobarbital were also dependent on the delay value, but opposite to those of methamphetamine, since pentobarbital caused a large increase in rate of responding when the delay was 10 seconds but had essentially no effect, on the average, when the delay was 100 seconds.

All these findings are compatible with the view that an important determinant of the effects of the amphetamines is the control rate of responding per se, irrespective of species, or type of motivation, or response studied.

A more or less specific effect of amphetamine on the response of an animal to electric shock has been suggested by Teitelbaum & Derks (134). Superimposed on an intermittent schedule of positive reinforcement for food were two minutes during which a buzzer was sounded. If the rat pressed the lever during the last 30 seconds of this two-minute period, it received an electric shock and the buzzer ceased. Responding was greatly suppressed during the buzzer periods, and the animals only rarely received a shock. When they did, it had little effect on their subsequent behavior. Following 0.5 mg./kg. dose of amphetamine, the rate of responding increased when the buzzer was not sounding, but suppression during the buzzer period continued. When, however, the animal did receive a shock while under the influence of amphetamine, the behavior was disrupted for several minutes. This is interpreted by Teitelbaum & Derks as evidence for an increased effect of shock in the amphetamine-treated animal. As the authors point out, it is possible that amphetamine reduced the motivational potency of food reinforcement and that, despite the generally increased

rate of responding, the behavior was therefore more fragile and readily disrupted by a shock. The fact that the rate of responding for food was generally higher following amphetamine does not eliminate this possibility, since high rates have been seen at a time when food consumption was decreased (34, 86, 146). On the basis of inspection of their animals, Teitelbaum & Derks felt there was a strong resemblance between rates given a small dose of amphetamine and then subjected to electric shock and animals given much larger doses of amphetamine, as though the shock shifted the dose-effect curve of amphetamine. Indeed, electric shock has been shown to enhance the lethality of amphetamines in rats (145), but so have a variety of other environmental factors, in mice at any rate, including some that would not be expected to function as aversive stimuli. Finally, it has been reported that after reserpine relatively normal avoidance behavior by cats may be severely disrupted when the animal receives a shock (68). It must be concluded that a specific enhancement of the effects of aversive stimulation by amphetamine is an interesting possibility, but it has not been established.

The effect of amphetamine on the performance of rats working for water on a DRL schedule has been studied by Sidman (117). A DRL schedule specifies that a response will be reinforced only when it occurs after the elapse of a minimum interval of time since a previous response. The dependent variable was the distribution of interresponse times. The peak of the distribution was markedly shifted to the left by amphetamine, i.e., interresponse times tended to be greatly shortened. In a subsequent publication (119) the results with amphetamine are said to indicate that the effect is not a "simple excitatory one," although it is not clear what this implies. Alcohol, on the other hand, reduced the height of the peak of the interresponse time distribution without changing its position. It was concluded that alcohol had relatively little effect on timing behavior. Sufficient dosage of pentobarbital led to an almost complete flattening of the distribution of interresponse times except for a large proportion of very short ones. This is interpreted as abolition of all evidence of timing behavior (118). It does not seem to the reviewers that the description of these interesting findings in terms of timing behavior is helpful.

An effect of amphetamine on discriminative behavior has been suggested (33, 118). There is no doubt that under some circumstances, the quantitative differences in behavior in the presence of two stimuli were lessened by amphetamine, and so, in this sense, amphetamine modified discriminative behavior. It is not clear at present whether this is a useful component to include in a parsimonious account of the behavioral effects of the amphetamines. A related effect appears to have been noted following ephedrine in studies on conditioned salivation (55).

This is a convenient place to describe briefly some of the work done with methylphenidate and pipradrol. The behavioral effects of both these drugs seem similar to those of the amphetamines. Methylphenidate produced

an increase in SMA of normal monkeys in a photo-cell device but only over a narrow dosage range; 1 mg./kg. produced a slight increase but 2.5 mg./kg. produced a large decrease, particularly in "pacing" as opposed to "leaping" (29). Even 1 mg./kg. produced a large decrease in activity in already hyperactive monkeys, a finding further emphasizing the dependence of this type of effect on the on-going behavior. The effects of reserpine were partially antagonized by methylphenidate in this situation (29). Total activity in rats, assessed by inspection, has been fractionated using a previously worked out scoring system, and methylphenidate has been shown to have differential effects on different components (7). The observer pressed one of six different keys depending on the category of behavior currently indulged in by the animals, thus tabulating the frequency of occurrence of the various behaviors. Methylphenidate decreased unconditioned, but increased conditioned salivation in dogs (41). Finally, the drug has been reported to facilitate reconditioning in human subjects of a galvanic skin response to a one-second visual stimulus that was usually, but not invariably, followed after 0.5 seconds by two seconds of mild shock (116).

Pipradrol has been shown to increase SMA of mice as measured in a photo-cell device (19). It has also been reported to speed the development of lever-pressing avoidance behavior in rats, without affecting escape behavior under these circumstances (128); pipradrol was studied only at a single dose level, but was compared with other drugs in these experiments. A slight decrease in running times of rats in a maze following administration of pipradrol has been reported (121). In man, it has been shown that subjects can discriminate that they have received pipradrol in doses as low as 2 mg. and that, in one subject at least, the output of verbal behavior in words per minute increased after pipradrol (52). The "thematic content" of the speech was changed concurrently.

In spite of the fact that ingestion of 10 mg. or even 5 mg. of one of the amphetamines usually produces readily discriminable "subjective" changes in human subjects—frequently in the direction of "euphoria" (4)—it has not proved easy to demonstrate substantial objective behavioral effects in unfatigued normal subjects. For example, no effect was found in performance on a motor co-ordination type of task made more difficult by being performed with mirror vision (Pursuit Confusion Test) nor on the accuracy of the predictions of the subjects as to how well they were going to perform (58). Similarly, it was without detectable effect on simple or choice reaction times and on the progressive reduction in reaction time that occurred as an arbitrary pattern of sequence of responses was acquired (75). On the other hand, consistent effects could be obtained in some of these situations in subjects who had suffered a decrement in performance as a result of fatigue resulting from prolonged wakefulness (77), and amphetamines have been shown to be able to reverse a decrement in performance that had developed during a session (103).

Nevertheless, effects can be demonstrated in unfatigued subjects. The

distribution of interresponse times of subjects working on a DRL schedule was moved significantly toward shorter interresponse times by 5 mg. of dextro-amphetamine (39). This effect is qualitatively similar to that described in rats (117), though much smaller. That the effect was smaller is perhaps not surprising since the human subjects received about 0.06 mg./kg. by mouth, while the rats received 2 mg./kg. of dextro-amphetamine intraperitoneally. Again, 10 mg. of dextro-amphetamine given four hours before the test session have been reported to increase the total time that subjects were able to keep a stylus in contact with a metal disk rotating on a turntable (44). Finally, a finding of extremely great practical importance is that of Smith & Beecher (122) who have shown that amphetamine can improve the performance of trained athletes (swimmers) already working at peak performance. Although the effects were small on a percentage basis—comparable to those seen on DRL schedule performance —they were large compared to the margins decisive in competitive sports.

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