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Learning Experiments with Chlorpromazine-Treated Animals

A Review

by

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CONTENTS

With the relatively recent addition of the tranquilizing drugs to widespread psychiatric and general medical use, the field of psychopharmacology has shown a tremendous increase in the amount of research. As a part of this growth, there has been a considerable increase in the performance of learning experiments on animals under the influence of tranquilizing drugs. Although it must be admitted that the primary emphasis has been on the use of learning paradigms to evaluate the effects of psychoactive drugs, there has been a concurrent gain in understanding of learning processes.

The recent literature on experiments dealing with learning and tranquilizing drugs will be reviewed and discussed, giving particular emphasis to their contributions to the field of learning. The review will cover the four-year period from 1960 through 1963, and into 1964. An attempt will be made to review all relevant journal articles in the English language, along with abstracts of articles in other languages, when available.

Choice of Drug

Since it would be impossible to review all the relevant articles in which tranquilizing drugs have been administered to animals in learning experiments, it was decided to concentrate on one particular drug--chlorpromazine (CPZ). This drug was chosen for several reasons, of which the following are the most important:

1. It is currently one of the most widely used of all tranquilizers, perhaps second only to meprobamate.
2. It is the most widely studied of all tranquilizers. This offers two distinct advantages:
    a. At least a start has been made toward the understanding of the mechanisms of action of this compound.
    b. Experimentation involving learning experiments has progressed beyond the initial naive stage of determining

whether or not the compound has any activity under certain standardized criterion experiments such as conditioned avoidance.

3. It is reasonably representative of a larger class of compounds, the phenothiazines, none of which has been studied as thoroughly.
4. It is often used as a standard against which other drugs are tested.

The phenothiazines, as major tranquilizers, have the following clinical profile in man (7):

1. produce emotional calmness with relatively little sedation
2. used frequently or primarily in psychotic patients
3. produce a reversible extrapyramidal syndrome
4. produce little, if any, habituation
5. produce a relatively high incidence of side effects, including some possibly dangerous ones.

According to Killam (165), the major pharmacological effects of chlorpromazine "... appear to be depression without hypnosis or anesthesia, good antiemetic action, and mild adrenergic blockade.... Physiological effects in man include a fall in blood pressure... orthostatic hypotension ... cutaneous pallor...." "The compound depresses the response of skeletal muscle to direct and indirect muscle stimulation." Chlorpromazine affects the thermo-regulatory mechanism centrally. The phenothiazines have greater autonomic effects than tranquilizers such as the diol-carbamates. They tend to depress the hypothalamus as opposed to the cortex, and stimulate the rhinencephalic system. There appears to be conflicting evidence as to whether or not CPZ acts on the reticular activating system.

General Behavioral Orientation

In a general review of this type, it is necessary to maintain an eclectic approach, since the experimenters reviewed hold a wide variety of theoretical approaches. On the one hand, it is important to keep in mind the work of Skinner, since his experimental methods have been extensively used in the evaluation of behavioral drugs. On the other hand, since one of the prime therapeutic targets of the tranquilizers is the highly subjective state of felt anxiety, one of the very possible uses of tranquilizers in learning experiments might be to investigate the effect of hypothesized internal states, such as motivation or emotion, on learning. Thus, certain aspects of an approach such as Mowrer's, which permits internal variables such as fear and hope, might be relevant to some experiments.

Rather than accept the restrictions of a particular theory, it seems more adventitious simply to keep in mind certain distinctions and/or open and unsolved issues within the field of learning which might be particularly amenable to investigation with the use of tranquilizing drugs. The first of these is the difference between classical and instrumental conditioning. Leaving the theoretical differences aside for the moment, most learning theorists at least agree that these two types of conditioning apply to different classes of muscular responses--classical conditioning being mediated by autonomic responses and instrumental conditioning by voluntary muscle responses (86). This correlates with the respective sites of action of the major and minor tranquilizers.

As a corollary, certain of the two-factor theories of learning, such as Mowrer's, use the concept of fear as a classically conditioned drive which can be used to motivate instrumental avoidance conditioning. Tranquilizing drugs might be useful in investigating the nature of fear

as a motivator, as well as the distinction between anxiety and the more directly aversive stimuli.

On a more general level, the whole question of motivation has been a particularly active topic in learning theory. Certain aspects, especially the nature of acquired drives, should be susceptible to experimentation with tranquilizing drugs. As Kimble (86, p. 435) states, "They should ... be regarded as motives if they show the same properties as other motives; ..." Since some variables often regarded as motives show marked changes due to the effects of tranquilizers, experiments involving these drugs add to the network of constructs defining the nature of a motive.

A related problem is the distinction between learning and performance. To quote again from Kimble (86, p. 5), "... learning is an intervening variable, an unobservable. As such we recognize it and gauge its strength through its symptoms in performance. But ... performance may be a good indicator of learning or a poor one, depending upon other factors. Thus, to arrive at a detailed and quantitative knowledge of learning it is necessary to study its progress under conditions where these other factors are optimal, or where their effect is exactly known." Here, as in the above instances, the importance of the use of tranquilizing drugs in the investigation of behavior lies in the ability they have for controlling or varying internal states of the organism including both neurological and physiological variables. Certainly these drugs are not the only ones which behavioral experimenters have found useful. Among others might be mentioned curare, and the various stimulants and sedatives.

One additional topic, of more restricted relevance to learning theory, must be mentioned because of its analogy to the therapeutic use of tranquilizing drugs. It would seem worthwhile to investigate in detail how tranquilizing drugs affect experimentally induced neuroses.

Literature Before 1960

Before proceeding to the review of the literature, a brief summary of experiments performed before 1960 will prove useful. One of the most significant developments during this period was the evolving of techniques for screening and evaluating psychotropic drugs. Methods developed by the psychology of learning played a prominent role. Initially, the primary emphasis was on the use of maze learning and conditioned avoidance responses, but the experimental models introduced by Skinner achieved increasing importance. Brady (164) summarizes this development as follows:

> This enthusiastic acceptance of the free operant in comparative psychopharmacology is not difficult to understand when one considers the pressing need for sensitive and reliable preclinical assay techniques and the woefully inadequate techniques described in the extensive literature. Indeed, with operant conditioning methods many of the critical shortcomings which limit the usefulness of the maze technique and "conditioned neurosis" situations in this area appear less restrictive. First, a relatively broad spectrum of behavioral response patterns can be quantitively and operationally identified and defined. Simple and complex discriminative capacities are assessable within the limits of an experimental situation which also provides a reliable estimate of general activity level, motor functioning, and sensory decrements. Second, specific aspects of an organism's behavioral repertoire can be selectively evaluated and dependably separated within a response pattern. Emotional or affective reactions can be independently assessed without complicated and equivocal interpretive problems involving nonspecific behavioral and motor disturbances, debilitation, and the like. And finally, it is now quite clear that such operant conditioning techniques are sensitive to a wide variety of experimental operations, including central nervous system damage, electrical stimulation, and pharmacologic agents. Specific aspects of a behavioral repertoire can be altered differentially with experimental controls inherently present within the remainder of the response pattern.

A number of reviews during this period were devoted primarily to problems of methodology. Three of these are Psychopharmacology: Problems in Evaluation (169), from which the above quote was taken, "Techniques for the study of the behavioral effects of drugs" in the Annals of the New York Academy of Sciences (170), and Drugs and Behavior (171). Besides several

articles presenting variations of Skinner's techniques and three articles by Hunt discussing conditioned emotional responses, other approaches which might be relevant to the field of learning were: a method for evaluating social behavior in cats; a number of ways of measuring strength of motivation, discussed by Neal Miller, among which was his classical method for measuring approach and avoidance gradients; the use of discrimination experiments to test drug effects; experimentally induced neuroses; self-stimulation by implanted electrodes; and the use of imprinting behavior to test drug effects. No attempt will be made to review the literature prior to 1960, but some of the results included in the above mentioned reviews will prove illustrative of the work that was being done.

Hunt (65, 66) suggested the conditioned emotional response (CER) as a useful method in screening and evaluating ataraxic drugs.

> A neutral signal is presented for several minutes, and then terminated approximately contiguously with one or two painful electric shocks to the feet. After such pairings, the signal acquires the power to evoke an emotional disturbance sufficiently strong to reduce or stop completely the emission of lever pressing for water reward, even though the painful shocks were paired only with the termination of the signal and every effort was made to avoid 'punishing' lever responses .... The superimposition of conditioned fear on some regularly recurring behavior such as lever pressing permits a distinction between loss of conditioned fear behavior following treatments as a direct and specific effect of the treatment, and the disappearance of the behavior as a function of any general deterioration, debility, or inactivity produced by the procedure.

Hunt also suggests using a conditioned avoidance response, as well as various neurological and environmental manipulations which predispose to increased emotionality in the experimental animals.

Hunt presents a typical complication in experiments using chlorpromazine.

> In the more complicated instrumental avoidance situation, the warning bells or buzzers acquire their power through conditioning similar to that in the CER. In addition, however,

> the animal must learn to do something (usually arbitrary) to avert the shocks and terminate the complex of stimulation which warns him that the shock is coming. This something becomes the indicator behavior. Heavy doses of a drug such as chlorpromazine, which makes the animal ataxic, can interfere with the acquisition of the indicator independently of any effects it might have on the underlying Type S conditioning of fear along CER lines.

This double effect complicates the interpretation of the experiment. One of the results of this type of experimentation was to show that "CPZ, in heavy doses, interferes markedly with both the expression and extinction of the CER, but only slightly with acquistion ... [while it] ... in moderate doses, facilitates extinction of avoidance and conditioned fear in the cat."

Norton and de Beer (112), in their experiments of the social behavior of cats, showed that CPZ reduced hostility without affecting sociability, and actually caused an increase in excitement.[1]

Dews (30) described the use of pigeons trained to respond to a multiple schedule reinforcement pattern. Performance under fixed-interval reinforcement proved to be more sensitive to drugs than did performance under fixed-ratio reinforcement. Moderately heavy doses increased the total number of pecks on the fixed-interval schedule, decreased the amount of time spent in pausing between responses, and increased the number of responses before the first pause. Considerably heavier doses of CPZ produced the opposite effects.

Berryman, Wagman, and Keller (10) conditioned rats to a schedule whereby they were reinforced if they pressed one lever a set number of times or more, and then pressed a second lever. This produced a stable performance in which the modal number of responses was the minimum required for reinforcement, and the distribution of the number of responses was approximately normal. Very light doses of CPZ reduced the rat's abil-

ity to discriminate on the basis of response-produced cues as shown by greater variablility in the numbers of responses to the first bar.

In experimenting with induced "neurotic" behavior in animals, Masserman (98) found that drugs could reduce conflict behavior by disorganizing the more complex and/or the more recently acquired habits. Although CPZ produced this effect, it was less marked and resulted in more side effects than did drugs such as alcohol, morphine, or barbiturates. Mephenesin produced almost no significant therapeutic effects.

Olds and Travis (167) used an experimental procedure in which electrodes are implanted in the brains of rats. Mild electric currents function as either positive or negative reinforcers depending on the location. High rates of responding can be maintained under the positive stimuli, and the animal will persist in this type of behavior to exhaustion. They call this a "positive feedback process" and liken it to psychotic excitation. CPZ reduces the rate of responding both in situations which lead to positive stimulation and which avoid negative stimulation.

In this highly condensed survey of the literature before 1960, prime attention was given to developments in the methodology of applying learning paradigms to the study of psychoactive drugs, because it was felt that this was the most significant work of this period, and because this should provide a foundation on which to proceed. It is evident that a large number of techniques had been developed and that it was possible to begin a thorough evaluation of the effects of the tranquilizing drugs on various aspects of learning. It is also clear that tools are available for the application of tranquilizing drugs to exploring theoretical questions in the field of learning.

Qualifications

Certainly limitations are inherent in a review of this type concentrating in detail on a very narrowly restricted body of knowledge. Questions raised here might well be answered if an equally detailed study of the relevant pharmacological and physiological research were made. Such a detailed study was impossible within the scope of this paper. Although an attempt has been made to remain cognizant of the basic physiological and pharmacological facts related to a study of CPZ and not to do gross violation to any of them, no consistent attempt has been made to integrate the results obtained from the experiments reviewed here with the broader literature on CPZ. A complete appraisal of the drug's effects on learning would certainly demand that additional step.

It also must be remembered that CPZ is only one of many tranquilizing drugs, and tranquilizers as a class are only one of many types of psychoactive drugs. No attempt has been made to integrate learning experiments across drugs. This imposes two rather serious limitations on the material included. First, the problem of scaling qualitatively different aspects of behavior is almost insurmountable without cross-drug comparisons. Thus, to say that CPZ is able to reduce activity more than can be explained on the basis of its effects on the voluntary motor system is meaningless unless the activity levels under CPZ are compared with those under a dose of another drug, for instance, a barbiturate, which has the same degree of effect on the voluntary motor system. Secondly, the literature abounds with studies treating comparisons across drugs or the interactions of two drugs. Especially significant examples of this type of study are comparisons of the effects of tranquilizers and energizers or studies involving the ability of an energizer to antagonize a tranquilizer. Of particular relevance are the studies designed to provide profiles of

behavioral action which will differentiate among the various classes of tranquilizers. All of this material is treated only occasionally and tangentially in this review, but should, if covered, both extend and qualify the material presented here.

Finally, a vast body of literature has accumulated regarding the effects of CPZ on man. The bulk of it is clinical material. What learning experiments occur often involve complex social or verbal situations. All of it is extremely difficult to integrate with the rather narrow body of material included in this paper.

Review of the Literature

This review covers the years 1960 through the first half of 1964. The review is necessarily more complete for the first part of this period, due primarily to the use of Psychopharmacology Handbook, Volume II, (168) for the year 1960. The following sources were used to locate relevant articles:

1. Psychopharmacology Handbook, Volume II, 1960; all abstracts listed under the chlorpromazine drugs, under the sub-heading of "Behavior."
2. Psychological Abstracts, Vols. 34-37 and 38, Nos. 1-3; January, 1960 through June, 1964; all abstracts under the sections sub-titled "Learning" and "Physiological Psychology," as well as all abstracts cross-referenced under chlorpromazine.
3. Psychopharmacology Abstracts, Vols. 1 and 2, 1961-62; all abstracts cross-referenced under chlorpromazine.
4. In addition, the following periodicals, chosen because they had yielded the greater number of articles via the above

procedures, were surveyed for the period January-October, 1964:

a. Biochemical Pharmacology
b. Diseases of the Nervous System
c. Journal of Comparative and Physiological Psychology
d. Journal of Experimental Analysis of Behavior
e. Journal of Experimental Psychology
f. Journal of Genetic Psychology
g. Nature
h. Psychological Reports
i. Psychopharmacologia
j. Quarterly Journal of Experimental Psychology
k. Science

The following criteria were used in accepting or rejecting an article for this review:

1. Only articles dealing with infra-human behavior were included.
2. Articles concerned only with physiological or strictly pharmacological parameters were not included.
3. Articles concerned only with the relative effectiveness of the various phenothiazines, and not otherwise significant, were not included, even though they included reference to behavioral variables.
4. Articles dealing with the interaction in behavioral parameters of phenothiazine drugs with other psychopharmacological agents were not included (with some exceptions) because it was felt that they introduced complexities beyond the limits of the current review.

5. Only the abstracts were reviewed for articles written in foreign languages or from periodicals not included in the libraries of the University of Minnesota.
6. A number of the articles included are concerned with the effects of more than one drug and some include materials on CPZ only incidentally, as for instance, a control. Only the portions of these articles directly related to the effects of CPZ are included in this review.

Approximately 165 articles were selected as relevant for this review.

The review which follows is organized according to type of experiment. Certain rather standardized types appear repeatedly in the literature. These are grouped and discussed together with the results of each type of experiment summarized to the extent that the data permit. To conclude, some attempt will be made to integrate the results from the different experimental methods. Following is a list of the experimental types to be discussed in order:

1. Measurements of activity level and drive levels
2. Classical conditioning
3. Conditioned emotional responses
4. Conditioned avoidance behavior
5. Operant behavior
6. Direct brain stimulation
7. Approach-avoidance behavior
8. Maze running
9. Lashley jumping stand
10. Miscellaneous experiments

Measurements of Activity Level and Drive Levels under CPZ. Though these are not strictly learning experiments, they are reviewed, because

they provide a baseline against which learning experiments must be measured, that is, it must first be shown that the results cannot be explained on the basis of e.g., the simple sedative effects of the drug. These experiments may be subdivided in three groups--those dealing with activity level, with aggressive tendencies, and with drive strength.

Experiments designed to measure activity level commonly employ some measure of spontaneous activity such as photocells, activity wheels, "jiggle cages," amounts of exploratory activity, etc. Animals are given doses of the drug and compared with their own base behavior or with saline controls. More sophisticated attempts involve defining simple dose-response curves or locating the ED_{50} (the dose required to produce an effect in 50% of the subjects) of some behavior change. Table I, part A summarizes the results of a number of these experiments.

One interesting variant is an experiment performed by Key (82, 83) in which he measured the effects of CPZ on the sleeping threshold of arousal and habituation of arousal on repeated presentation of the same arousal stimulus. His results, a dose-related increase of the threshold and a facilitation of the habituation, are consistent with the results on the more usual type of experiment, but might also have some interesting implications regarding the effect of CPZ on perceptive processes. Key, however, explains his results on the habituation as a facilitation by CPZ of "negative learning."

The following summarizes the experimental results concerning the effects of CPZ on activity:

1. There is reduction of spontaneous activity over a wide range of doses (almost the entire range of experimental use of the drug).

2. The doses required for reduction of spontaneous activity, when compared with hypnotic doses, are much smaller than for sedatives such as the barbiturates.
3. There is no activation phase in sub-hypnotic doses, as found in barbiturates and some anesthetics.[2]
4. Reduction in amount of activity is more marked than the reduction in the ability to perform the activity (21). This will be more evident from experiments listed below under other classifications.

Many of the experiments dealing with the effects of CPZ on aggressive behavior are similar in design to those designed to measure its influence on activity level, with the exception that the subjects are either selected or treated in a manner designed to maximize the occurrence of aggressive behavior. The subjects may be Siamese fighting fish (110, 113), or special "biter" strains of mice (63), or the subjects may be isolated for a period of time prior to the experiment (27, 74, 96). Some experimenters (56, 74, 96) state that aggression was reduced more markedly than activity, but because of the problems of creating equivalent scales, these must be regarded as, at best, subjective impressions. Table 1, part B, includes the results of a number of typical experiments illustrating the effects of CPZ on aggressive behavior. The varying results may be attributed primarily to the variety of animals used as subjects and to the divergent criteria used to determine reduction of aggressive activity. These results may be summarized as follows:

1. Almost the full range of experimental doses have been reported as reducing aggression. (The experiment of Knight, Holtz, and Sprogi (89) is an unexplained exception.)

2. Aggression may be blocked or reduced by dose levels which do not disrupt the neuromuscular components of aggressive behavior. That is, the blockage is not due to hypnosis, incoordination, etc.
3. Some experimenters note the impression that aggressive activity is reduced more than general activity levels.

Regarding experiments dealing with drive strength, only those measuring directly the consummatory behavior will be included here. The problem of drive level or motivation enters into many of the experimental designs discussed under subsequent headings. Table 1, part C reports some relevant experiments. In general, CPZ reduces food intake (130, 134, 142), water intake (133, 142), and sexual activity (47). (The experiment of Reynolds and Carlisle (129) is an interesting exception.) The results are difficult to explain simply on the basis of reduced activity.

Effects of CPZ on Classical Conditioning Parameters. Only the simpler classical conditioning paradigms will be included here. Classical conditioning phenomena also play a prominent part in experiments involving CER and CAR, which are discussed separately below. Aganyants (1), working with two dogs, classically conditioned the salivary response to a variety of stimuli. Conditioned responses (CRs) were reduced by .5 mg/kg CPZ and abolished by 1-1.5 mg/kg. Differentiation of responses was not disinhibited by the drug. In working with a delayed CR (trace), .5 mg/kg CPZ caused a shortening of the delay, while 1-1.5 mg/kg abolished the response. In all cases, responses returned to predrug levels after the effects of the drug wore off. The defensive respiratory reflex to ammonia was also used as an unconditioned stimulus (US). This was abolished only at doses which caused incoordination and unresponsiveness

(5 mg/kg CPZ).

Khruleva (85) also used the salivary response in dogs as the CR. With very small doses of CPZ (.005-.1 mg/kg), the CR to all stimuli used was increased. Larger doses, though still of a moderate level (.1-2 mg/kg), caused a sharp drop in the CR followed at three or more days by a slight rise above predrug levels. Again, there were no marked effects on differentiation.

The numerous experiments noted below which use a classically conditioned response as an aversive stimulus to motivate avoidance behavior are consistent with the above experiments in noting that adequate doses of CPZ can reduce or eliminate the effectiveness of the CR. In addition, they note a consistent effect of an increased latency of the avoidance behavior, but it is difficult to demonstrate that this is due to an alteration in the CR.[3]

Irwin and Armstrong (70) report an interesting complication which may affect animal experiments using drugs. The drug itself functions as the US (probably the altered internal physiological state), the behavioral response to the drug as the unconditioned response (UR) (e.g., changes in activity levels, incoordination, etc.), and the experimental test situation as the CS. Animals which have previously been evaluated in a test apparatus (here an activity wheel) under the effects of CPZ are later evaluated following injections of saline. Activity levels are reduced below predrug levels, below saline controls, and below later activity levels for the same animals. The effects last up to two weeks before extinguishing, which is longer than drug effects can be reasonably expected to have any effect (similar drug levels in the above experiments showed no effects after less than a week). The effects are extremely variable and difficult to reproduce.

Effects of CPZ on the Conditioned Emotional Response. Mice and rats, when repeatedly presented with a painful and unavoidable electric shock, develop signs of what has been called emotionality when the experimental situation is similar to that in which the shock occurred. This situation develops quickly, often in as few as two or three trials, when difficult discriminations are not required. The "emotional" state has been defined behaviorally by cringing, random aggressive acts, and most frequently, defecation.

A CER was established in rats by Navarro (108) by presenting two three-minute acoustic stimuli daily for four days. Shock was presented on the initiation and termination of the stimulus. Tense and aggressive behavior and emotional defecation were present in all animals by the fourth day. CPZ was administered in doses from .1-10.0 mg/kg, and the rats were presented with the stimuli one hour after injection. Doses of 5 mg/kg and higher blocked the emotional defecation, and 10 mg/kg abolished the aggressiveness.

Deneberg, Rose, and Ellsworth (29), using mice as subjects, paired a 3-second tone with a shock developing a CER to the tone. The CER was recognized behaviorally by running and jumping. CPZ given during the acquisition of the response reduced the number of trials to extinction. CPZ given during extinction did not have a significant effect. This latter result is somewhat open to question because lower doses were used during extinction trials. When equal dose levels are compared, CPZ has at least as much effect during extinction as during acquisition.

Taeschler (149) found that a CER did develop in a group of rats that could avoid a shock by climbing a pole. The amount of defecation associated with the CER was reduced by 50% with 1.7 mg/kg CPZ, but this dose is above the dose which inhibits the CAR (1.2 mg/kg). Boissier (15) obtained

essentially similar results.

In order to demonstrate that the effects of CPZ on the CER were not due to the sedative or hypnotic properties of the drug, Barry (4) trained rats to press a lever for food on a variable interval (VI) schedule. A CER was established by pairing a shock with a tone. The intensity of the tone varied with the intensity of the shock. Presentation of the tone without the shock, while the rat was operating the lever, depressed the rate of lever-pressing markedly. Two mg/kg CPZ decreased the rate of lever-pressing without the tone, but increased the rate of lever-pressing during the tone. Dinsmoor and Lyon (31) found a relative increase in responding during the tone, but this was due primarily to a decrease in response rates under positive reinforcement, rather than an increase in responding while the CER was in effect.

Kinnard, Aceto, and Buckley (87) performed essentially the same experiment, but continued the tone-shock pairings until operant responding was completely suppressed when the tone was presented. Response rate during the presenting of the tone showed no increase with doses of CPZ up to 2.0 mg/kg, nor did two other tranquilizers have any effect. Apparently, the over-training created a response similar to the experimental neuroses noted below, which are relatively refractory to tranquilizers.

Heistad (59) hypothesized that the effect of CPZ on the CER was due to an alteration of the internal autonomic environment which formed a part of the total stimulus complex functioning as the CS. Thus, two physiologically antagonistic agents might each reduce the effectiveness of the CER along dimensions of a stimulus generalization gradient, while acting in conjunction they might have less effect. To test this, rats were trained to run from one end of a cage to another for a water reward. A CER was conditioned to a flashing light as the external stimulus.

Presentation of the flashing light markedly reduced the running rates for the reward. CPZ, 5 mg/kg, and electroconvulsive shock (ECS) partially blocked this effect with the ECS being by far the most effective. ECS was less effective when followed by CPZ. These results are consistent with the hypothesis but do not rule out other possibilities.

Very similar to the CER is induced neurotic behavior in animals. Pechtel (117) conditioned kittens to press one of two levers depending on a signal in order to obtain food. Irregular periods of shock were then presented with food-taking for a period of 3 to 15 weeks to induce an experimental neurosis. Neurosis was indicated behaviorally by "tics, tremors, disruptions of learned behavior, and generalized phobias." Heavy doses of CPZ had only a minimal and transient effect on the "neurotic" behavior. Differences between induced neuroses and CER and the differential effects of CPZ appear to depend in part on the extensity of the conditions invoked in establishing the response and the resultant stability of the behavior. (Note also experiments reviewed below involving the Lashley Jumping Stand.)

Effects of CPZ on Conditioned Avoidance Responses. The experimental model is carried one step further by using the CAR. A painful stimulus, usually an electric shock, is paired with some signal or stimulus complex by what are essentially classical conditioning methods. Sometimes the experimental situation itself functions as the CS. Some escape behavior is then provided for the animal. Common escape behaviors are leaping from the experimental field, running to another part of the apparatus, climbing a pole, pressing a bar, etc. One of the purposes of this type of experiment is to guarantee that the failure to perform the learned behavior is not due to the inability, physically, of the drugged animal to do so. Two types of responses are usually distinguished--avoidance and

escape responses. Avoidance responses occur to the CS. Escape responses are responses delayed until the presentation of the UCS. The four levels of response typically noted in experiments of this kind are:

1. no difference from controls
2. increased latency of avoidance response
3. no avoidance response, but escape response still present (or reduction in probability of avoidance response)
4. no avoidance or escape response (or reduction in probability of escape response)

When the experimental method includes alternate responses to differential stimuli, an additional class of response behaviors is added in which an escape or avoidance response is made, but it is the wrong response to the given stimulus. For a summary of selected CAR experiments see Table II.

The simplest type of CAR experiment involves placing an animal in an experimental apparatus, shocking the animal, and providing some response within the animal's repertory which will lead to relief from the shock. The shock occurs at some set time after the animal is placed in the apparatus, and the animal learns to perform the escape behavior before the occurrence of the shock with a high degree of consistency. McMurray and Jaques (94) trained rats to jump to a white compartment when placed in a black compartment in order to avoid shock. The compartment itself functions as the CS. One mg/kg significantly reduced the frequencies of the CAR although most rats still performed the escape response.

Stone (146) pretrained rats to a stable CAR consisting of turning a wheel on an auditory signal presented seven seconds before an electric shock. The wheel opened an escape route. After 2 and 4 mg/kg CPZ the CAR was reduced by 40% and 100%, respectively. The number of escape responses was not altered. High (61), Pellmont (118), Ekstrom and Sandberg

(34), and Heise and McConnell(58) all obtained essentially similar results with a variety of CARs. High found the ED_{50} for CAR inhibition to be 4.5 mg/kg CPZ, while Ekstrom and Sandberg found the ED_{50} for a reduction in the CAR to be 4.85 mg/kg CPZ. Pellmont found a dose-related increase in latency and a decrease in frequency of a CAR to absence at 4.0 mg/kg CPZ and a decrease in escape response above 4.0 mg/kg to absence at 16.0 mg/kg.

Although a drug response-time relationship is more strictly of purely pharmacological interest and in general bears on the present topic only as an important experimental control, still since the CAR involves a hierarchy of possible effects, it is of interest to observe the progressive effects in time on this response hierarchy as the drug is being induced. Admittedly, if the drug has multiple sites of action, a time-response curve may reflect the different speeds with which the respective mechanisms occur, but it is interesting to note that in at least one series of experiments the time-response curve parallels the dose-response curve. Gatti and Frank (43) report that after injection of 2 mg/kg s.c. of CPZ the following effects were noted on a pole-climbing CAR: (1) increasing response latency up to one-half hour, (2) decreasing frequency of CAR after one-half hour to total absence at two hours, escape response is still present but reaction time is slowed, (3) decreasing frequency of escape response up to total absence at four hours. In comparison with other drugs given in doses producing an equivalent effect on the CAR and escape response, comparatively little effect was noted on muscle coordination or the ability to perform the response. An incidental observation that some rats, after failing to respond to both the CR and the following UCR, respond to a repetition of the CR gives some additional support to the frequently stated contention that the failure to respond to initial

CR is not due to the inability to do so.

Marczynski and Vetulani (97) found that in an experimental situation demanding a pole-climbing response to an auditory stimulus the animals regularly performed an avoidance response when put in the apparatus prior to the presentation of the auditory stimulus. The stimulus complex of the apparatus is referred to, perhaps not too accurately, as the secondary conditioned response. With increasing doses of the drug, the response to the apparatus first drops out, then the CAR, and finally the escape response. Though a secondary conditioned response could be expected to act in this manner, it is difficult to see how a response to the stimuli arising from the apparatus can be considered as a secondary conditioned response in the classical sense, since in other experiments a CAR develops to these stimuli without the mediation of the signal stimulus. The results could be alternately explained by the relative intensity of the two sets of stimuli and by the directness of association with the US.

Wolf, Swinyard, and Clark (161) used as experimental animals a subspecies of mice, Peromyscus maniculatus gracilus, whose escape response in its natural habitat is to climb and hide among the branches of bushes. This was hypothesized to be a "phenotypically predisposed" conditioned response. One experimental group was trained to avoid shock by performing, on signal, a pole-climbing CAR, which was designated as the "arboreal" CAR and, as a response similar to the animal's escape response in its natural habitat, was assumed to be a "prepotent" response in the animal's response repertoire. The second experimental group was trained to run to a pan located on the cage floor as a CAR. This was designated as a "terrestrial" CAR. Equal doses of CPZ had a greater effect on the "unnatural" terrestrial CAR than on the prepotent

arboreal CAR. Although it may be necessary to assume some concept of prepotent responses to explain the fact that the first group learned the CAR at a significantly faster rate (assuming other species of mice do not), such a concept is not needed to explain the differential responses of the experimental groups under CPZ. Although both groups underwent the same number training trials, the first group learned the CAR faster. Thus, though both groups achieved the same final criterion, the "aboreal" group performed a significantly greater number of successful escapes in its training trials. This is supported as an alternate explanation of the differential drug effects by the fact that under extinction trials without the drug, the "terrestrial" response dropped out sooner than the "arboreal" response.

The use of the CAR to test drug differential effects is based on the assumption that a CER is formed to the CS, and that this functions as an aversive drive stimulus to motivate the CAR. It is then hypothesized that if CPZ is a tranquilizing drug, it should reduce the driving power of a CER, which is conceived as a sort of animal analogue of anxiety, while leaving functional behavior intact as shown by the escape response. In order for this argument to stand, it is necessary to demonstrate that a CER is formed and that it is reduced by CPZ. It is also necessary to rule out a number of other possibilities. Perhaps the drug also acts on the central association centers, so that the aversive drive is still acting, but appropriate behavior patterns are no longer intact. Or perhaps, on the other hand, there is a drug action on sensory input causing the less intense CS to lose effectiveness before the US, which is usually an electric shock. The effects of CPZ on activity levels have already been discussed. Two different lines of experimentation attempt to answer separate aspects of the problem. The first of these to be

discussed will be the attempts to separate out the CER components of the CAR. The second approach to be discussed later adds a discrimination to the experimental model.

Taeschler (149) conditioned rats to perform a pole-climbing CAR on an auditory signal to avoid shock. Amount of defecation was used as a measure of the CER component of the CAR. ED_{50} to inhibit the CAR was 1.2 mg/kg CPZ; ED_{50} to reduce the CER by 50% was 1.7 mg/kg. These are equivocal results at best since CPZ also reduces gastrointestinal transit time.

Fuller (41), in an experiment complicated by including both developmental and environmental factors along with drug effects, tested, among other things, the effect of CPZ on the acquisition and extinction in dogs of a learned avoidance of electrified objects and also on the learned avoidance of contact with the experimenter (punished by slapping). A crossover design was used. The results were not clearcut, but CPZ had slight, if any, effects on acquisition of the avoidance behavior but produced a significant increase in the speed of extinction. The experimenter does not deal with simple avoidance behavior since the objects, contact with which occasioned punishment, were desired objects (play-ball, experimenter).

Gonzales and Shepp (49) designed a variation of the CAR experiment to try to show whether or not CPZ had any effect on fear as a motivating response. Fear was defined operationally as the motivating force of a CER in a CAR experimental situation. In order to assure that the signal stimulus (CS) was effective due to its association with the electric shock rather than due to its pairing with the escape behavior, the learning of the CER was separated from the learning of the CAR. In the first part of the experiment, half the animals received paired trials

of signal stimulus and shock, the remaining half received signal stimulus only. No escape was possible. Half of each group received 4 mg/kg CPZ. All animals were then tested under the same drug conditions for their ability to learn a barrier-jumping CAR on presentation of the signal stimulus alone. No shock was presented during the learning of the CAR. Response latency was used as a measure of learning. During 40 trials there was no change in the latencies of the two groups who had received the signal stimulus only nor was there any change in the drugged animals who had received stimulus-shock pairing. There were no marked differences between these groups either at the start or finish of the 40 trial test period. On the other hand, the group that had received stimulus-shock pairing, but no drug, showed a marked decrease in response latencies across the test period. Thus, when a stimulus is paired with an electric shock, the animal then will react to it in a CAR situation as if it were an aversive stimulus. CPZ eliminates this effect.

Gonzales and Shepp then go on to try to determine whether the primary effect of CPZ was on the acquiring of the CER or on its aversive properties in CAR situation. The same experiment was performed using two groups and a crossover design. One group received CPZ during the CER conditioning but not during the CAR conditioning. For the other group the conditions were reversed. The group receiving no drug during the CER conditioning but receiving drug during the CAR conditioning showed no change in CAR latencies. The group receiving the drug during CER conditioning gave a bimodal distribution of responses when tested for CAR learning. Five of the rats did not learn the CAR and did not differ from the group above. Three rats showed a marked and immediate decrease in response latency. Gonzales and Shepp conclude that CPZ reduces the

aversive properties of a learned CER and probably also has some effect on acquiring the CER.

Davis, Capehart, and Llewellin (28) carried the design one step further. There were three phases to the experiment. In phase one, rats are placed in a shuttlebox and shocked until they jump a barrier to an adjacent compartment. Thirty trials are presented and all rats achieved 100% proficiency on the last 10 trials. In phase two, the rats are blocked into one corner of the shuttlebox and shocked without the possibility of escape. A buzzer is paired with the shock. Phase three is the same as phase one, but with the buzzer instead of the shock. Rats are given 1.25 mg/kg CPZ during one of the three phases and compared with controls for the number of CARs performed during phase three. Rats drugged during phase one performed 78% as many CARs as their control group. This difference was not statistically significant. Rats drugged during phase two performed at 59% of controls which is significant at the .01 level. Rats drugged during phase three performed at only 12% of the control level which is significant at the .001 level. Extinction of the CAR occurred most readily in this third group. On shock-escape trials, there was no difference in latencies between drugged and nondrugged animals, strengthening the belief that the results are not due to differences in activity level or muscle coordination. These results reinforce the hypothesis that the primary effects of CPZ in CAR experiments is to reduce the aversive properties of the CS.

One possible criticism of CAR experiments (though in part ruled out by those experiments just reviewed) is that CPZ may not reduce the CER occasioned by the signal stimulus, but might reduce the animal's ability to perceive the stimulus itself. Discrimination CAR experiments in part answer this objection. Hughes and Kopman (64) trained rats to jump to

the lighter of two compartments on the presentation of a light CS. Failure to jump, or jumping to the wrong compartment, caused them to be shocked. One and 2 mg/kg CPZ reduced the number of CARs but not the number of correct discriminations. Five mg/kg reduced escaped responses markedly. Thus, a drugged rat was less likely to respond to the CS, but if he responded to the CS or to the US, he responded correctly. Niemegeers (109) performed essentially the same experiment using green and yellow compartments and got the same results. This indicates that rats under moderate doses of CPZ are able to perceive and discriminate stimuli adequately but respond to some in a different manner from undrugged rats.

Key (81), in order to test hypotheses resulting from previous experiments which showed that CPZ reduced responsiveness to sensory stimulation (see Key, 82), trained cats to jump a barrier on the presentation of a particular tone in order to avoid shock. He then tested: (1) rate of extinction, (2) number of responses generalized to other frequencies and their rates of extinction, and (3) rates of extinction to two tones differentially reinforced. All response rates decreased and all extinction rates increased, but discriminations were not disrupted.

The clearest retort to critics who contend that the results of CAR experiments may be accounted for on the basis of an altered sensory threshold is an experiment by Posluns (121) in which he varied a number of parameters in the CAR experiment. No relation was found between intensity of CS and percent of CAR with other conditions held constant.

There is one problem inherent in the design of CAR experiments which does not invalidate their use in discriminating between so-called tranquilizing drugs and sedative or hypnotic drugs, but which does make it difficult, from a psychological point of view, to disentangle the dimensions along which this discrimination occurs. The experimental model

uniformly consists of the presentation of an established CS for a specified period of time. If the subject does not perform the CAR within this time limit, the US is presented, again, for a specified period of time. If the animal does not respond during this second period, the trial is terminated. Although the results are usually reported in terms of decreased percentage of CARs, with no decrease in escape responses, it must be pointed out that increased response latencies will produce the effect of a decrease in percentage of CARs. Dose-response curves indicate that there is, in effect, an increase in response latency with increasing doses of CPZ until the appropriate response is no longer performed before the presentation of the US.

It is important to remember that there are definite differences between the effects of sedative drugs and of tranquilizing drugs of the nature of CPZ on CARs, and that this consists of a relatively greater effect on the CAR than on the escape response, whether this effect can be described in terms of latency or decrease in percent of CARs. The standard explanation is that this differential effect is due to a reduction in the aversive driving force of the CS. In the succeeding paragraphs two alternate explanations will be considered.

In an experiment designed to test the effects of a variety of drugs on a CAR, Ekstrom and Sandburg (34) pretrained mice until they performed a prescribed CAR within three seconds of the onset of the CS. Unfortunately the details of this experiment are not available in English, but it is clear from the abstract that this required a considerable number of trials. Two explanations of the effects of CPZ on CARs are possible, other than that based on a reduction of the aversive effects of the CER. It takes a longer time to condition a response to occur within a specified time limit if the response is motivated by a CER, than if it is motivated directly by

a painful stimulus. The two primary effects of moderate doses of CPZ on CAR performances--increased latency and decreased frequency of the avoidance response, without equivalent changes in the escape response--are the same as conditions existing without drugs at an earlier stage in learning. Thus, it is possible to explain some of the results of these experiments on the basis of partial disruptions of learned associations. Experiments involving discriminations indicate that, if this is a possible factor, it is a rather complex one. However, it may be recalled that this explanation also serves to explain the results of Wolf, Swinyard and Clark (161) who used "arboreal" and "terrestial" responses. It will be seen that it also explains the experiments of Bindra and Mendelson (13) using operant conditioning and various training levels.

Doty and Doty (33) performed an experiment testing the effects of 1.25 mg/kg CPZ versus saline controls on the acquisition and extinction of a simple CAR and a CAR requiring a discrimination. Both groups received the same number of training trials. CPZ had a greater effect on the more difficult problem, both during acquisition and extinction. These results are also explainable in terms of response-learning curves.

Another explanation offered for the effects of CPZ on a CAR derives from a series of experiments by Posluns (121). In the experiment referred to above he varied a number of parameters of the CAR experiment to determine what effects this would have on the percentage of CARs performed under drug conditions. Increasing the intensity of either the CS or the US had no effect. Increasing the length of time between the onset of the CS and the onset of the US markedly increased the percentage of CARs performed. This gives added verification to the contention that the decrease in percentage of CARs performed is a function of increased response latencies. (It does not, however, rule out the explanation offered above in

terms of response-learning curves.)

Posluns goes on to analyze the nature of this increased response latency. The CAR is broken down into its various components and these are individually timed. Motor acts, such as running to a different part of the apparatus, are not slowed. Nor are additional irrelevant motor acts added to the sequence as might occur with amphetamine. Vacillation at choice points, Posluns calls it "locomotor initiation latency," accounts for almost the entire increase in response latency. In fact, running time is correlated -.69 with number of shocks received (failed CARs), while locomotor initiation latency is correlated +.94. These results are qualitatively supported by observations made with operant learning experiments (11, 147). Murray (107), using the time spent in traversing a single alley runway as a means of distinguishing between drugs, found that CPZ decreased the speed of traversing the alley, and that this was not due to motor side effects. Details were not available.

Before summarizing the CAR experiments, two experiments will be discussed which are atypical because of the nature of the avoidance response conditioned. Bindra and Anchel (12) conditioned an immobility response by shocking rats whenever they moved in the experimental apparatus. Doses of CPZ ranging from 2 to 12 mg/kg were administered. Only the lowest doses affected the CAR (increased mobility) and these effects were minimal. These results provide one of the most potent criticisms of the hypothesis that the reduction in the CAR is due to a reduction of the aversive properties of the CER. However, since the tendency of CPZ to reduce activity complicates this experiment by acting in conjunction with the CAR to reduce movement, the results are not conclusive. The results are difficult to explain in terms of response-learning curves, but quite compatible with explanations such as "increased motor latency."

Clark, Jackson, and Brady (25) trained a monkey to hold a slightly weighted lever in a constant position by shocking the subject whenever the lever fell below a specified position or was raised too high. The fully conditioned monkey held the lever almost steady during a one-hour test session and received no shocks. Different drugs had a variety of effects on this response. CPZ had the most marked effect on the response of any drug tried with a dose of of only .5 mg/kg so disruptive to the response that the test session had to be discontinued because of the large number of shocks the animal was receiving.

In summary, CPZ reduces the percentage of CARs performed in a dose--dependent fashion and at dose levels which do not markedly affect escape responding. Effective dose levels apparently do not affect perceptive or discriminative abilities nor motor capacities--at least not to the degree necessary to explain the results obtained. Decreases in CARs are closely related to increases in response latency. CPZ affects CARs maximally when administered when a learned CAR is elicited, rather than during the learning of either the CER or the escape response. Results are most frequently explained in terms of a decrease in the aversive properties of the CER, but alternate explanations have been offered involving learning decrements and motor initiation latencies.

Effects of CPZ on Behavior Acquired under Operant Learning Schedules. Of all the classes of experiments dealt with in this review, the operant learning schedules are the most difficult to grasp as a totality or to relate to the rest of the literature. Too often the drug effects do not seem to generalize beyond a trivial relationship to the particular learning schedule on which they are measured, and one is left with an extremely molecular view of behavior. However, occasional results create a feeling of uneasiness toward the easy, molar solutions provided by the foregoing

methods and one or two rare experiments appear rather striking. For a summary of operant learning experiments involving CPZ see Table III.

The typical approach of this type of experiment is to establish a reinforcement schedule in an animal so that stable behavior is maintained, then administer the drug and compare the performance under the drug against the baseline or control behavior. Although response rate is the standard criterion of performance used, a number of other measures have been shown to be of value in describing behavior under drugs. At the extreme are qualitative comments on the response curves themselves, including their texture, which become too esoteric for anyone but an ardent Skinnerian. Often only one or two animals are used in the experiment.

The simplest experiments are those using one schedule of positive reinforcement. Numerous experimenters working with continuous reinforcement (CRF) (11, 13, 14, 99, 139, 147, 151, 152),fixed ratio reinforcement (FR) (80, 110) and variable interval reinforcement (VI) (18, 44, 148) have come up with uniform results. There is a dose-dependent decrease in response rates which is very marked at high doses. Although the effects of equivalent doses vary from experimenter to experimenter, the accumulated evidence indicates that this relationship holds over the full dose range usually used in CPZ experiments (.5 to 10.0+ mg/kg). Boren (18), working with fixed interval (FI) reinforcement, found similar results with no loss of temporal discrimination, but experiments using complex schedules suggest that FI schedules are more sensitive to the effects of CPZ than are other schedules.

Bindra (11) attempted to break down the response patterns into smaller units in order to determine more accurately the nature of the slowing of response. He found that while stimulants slowed a response rate by producing an increase in irrelevant behavior, depressants cause a decrease in

speed of relevant behavior. Though it is not possible to trace how he derives his conclusions from the data he presents, he concludes that CPZ slows response rates by decreasing muscular speed or coordination and by an increase in behavioral inertia, that is, in the inability or unwillingness to initiate or change behavior as seen by hesitancies or pauses in the normal flow of behavior. Stone et al. (147) might well be referring to the same thing when they note errors and interruptions in response performance. Any effects of the nature of sedation or decreased muscular coordination must undoubtedly have a marked effect on the high rates of behavior maintained under operant learning conditions. The question remains as to whether this is the full nature of their effects since the assumption is that clinical effects on human behavior cannot be fully understood in terms of sedative effects. This topic will be discussed in more detail later.

Bindra and Mendelson (13, 14) attempted to determine the relationship of level of training to drug effects. Unfortunately, under training for CRF schedules, during the early stages of training response rate increases with increase in training. The results obtained, which show the greatest absolute drug effect (decrease in response rates) at the highest level of training are confounded by the higher response rates noted with greater training.

Mendelson and Bindra (99) studied the effects of CPZ under different levels of drive on a CRF schedule. Drive was varied by altering thirst deprivation. No relationship was found between level of deprivation and absolute or relative depression in response rates.

Included under CAR experiments was an experiment by Heise and McConnell (58, see table II) in which the CAR was to press a lever when a signal was presented. A frequent variation of this experiment is one in which a

regular pattern of responding under an operant avoidant schedule is developed. Shocks occur at regular intervals (SS intervals) unless the animal presses the lever. Each lever press guarantees a specific succeeding shock--free interval (RS interval). The typical response to such a schedule is for the animal to respond at a rate just adequate to prevent shocking.

Stone (146), using a five-second SS interval and a 20-second RS interval, found a dose-dependent decrease in response rate over a range of .75 to 3 mg/kg CPZ. Geller (44) found that a variety of phenothiazines suppressed this type of operant avoidance behavior. Bernstein and Cancro (8) found that by varying the SS and RS intervals, they could differentiate between drugs. The responses to CPZ were similar under all the schedules tried and consisted of a dose-dependent decrease in overall response rate and a decrease in effective avoidance responses. Boren (18), on the other hand, found a decrease in avoidance responses, but not a decrease in overall response rates due to bursts of responses following any shock administered. This latter result is similar to results obtained in CAR experiments.

The Sidman avoidance schedule is the operant schedule most comparable to CAR experiments. The subject is presented with two levers, the first of which postpones shock for 40 seconds. If 40 seconds elapse without this lever being pressed, the rat is shocked for 5 seconds. The subject may obtain immediate relief from the shock by pressing the second lever. Thus, both an avoidance and an escape response are provided for, yet the subject is maintained on a continuous and regular response schedule. Hanson (54) and Heise (56), using the Sidman avoidance schedule, found a dose-dependent decrease in avoidance responding, with decreased escape responding at highest doses. Heise and Boff (57) found that it required 3.4 times the minimum effective dose (MED) for increased shock rates to

depress the escape response (dose given sub-cutaneously, less effective by other routes). The MED for increased shock rates of .21 mg/kg when compared (by Heise and Boff) with other results noted in the literature indicated that the Sidman avoidance schedule was more sensitive to drugs than the CAR or than measures of activity level.

Complex schedules involving both positive and negative reinforcement have been used in the attempt to determine which is most subject to drug effects. Weissman (159) conditioned rats to respond to a cycle of behavior consisting of no reward, shock avoidance, and continuous reinforcement. Avoidance responding was depressed at lower drug levels than was CRF responding. Waller and Waller (158) used essentially the same schedule in dogs, except that VI reinforcement was used instead of CRF. They found dose-dependent decreases in response rates for both positively and negatively reinforced schedule components which were essentially the same, except that there was a slight tendency towards increased rates of responding under positive reinforcement at low dosages. The difference between these results and those of Weissman could be due to the difference in density of reinforcement.

Cook and Kelleher (26) superimposed an avoidance schedule concurrently on a FR 150 schedule in a monkey. The FR 150 produced a scalloped response curve; thus, following each positive reinforcement the responding was maintained at a low rate by the avoidance schedule. The positively reinforced behavior was suppressed at lower doses than the negatively reinforced. Geller, Kulark, and Seifter (45) conditioned rats to respond to a VI 2' schedule, then interspersed periods of CRF with superimposed shock at every response. A signal indicated the change. Shock levels were adjusted prior to drug administration to levels permitting a moderate response. One mg/kg CPZ suppressed behavior under the schedule with CRF plus superimposed shock.

The experimenters interpret this as a decreased willingness to take shock in order to be rewarded, although it could also be a decrease in CRF behavior. However, the behavior under the VI 2' schedule was not markedly altered.

Ray and Marrazzi (126) conditioned rats to respond to one lever for milk reinforcement and to a second lever to avoid shock. Auditory signals served as discriminatory stimuli. CPZ, .75 to 3 mg/kg, increased the response latency to the avoidance signal, but did not affect the positively reinforced responding.

Cook and Kelleher (26) and Fry, Kelleher, and Cook (40) worked with a schedule involving FI 10' and FR 30 components in alternation, with a 2 1/2' time out following each reinforcement. Discriminitive stimuli occur with each component of the schedule. In monkeys, low doses of CPZ (.3 - 1.2 mg/kg) completely suppressed the FI performance without markedly altering the FR responses. In pigeons, on the other hand, much larger doses (5-10 mg/kg) had inconsistent effects on the response rates of the FI component, functioning rather to eliminate the curvature normally found in such response curves, making them more like the FR curves in shape.

Waller (156), using either a FI or VI schedule in combination with a FR segment and a nonreinforced period, obtained results that are difficult to integrate with the rest of the literature. Two dogs were used as subjects. From 1 to 8 mg/kg there was an increase in response rates for both the interval and the ratio components, with the increase being greater for the interval component. There was a marked drop in response rates between 8 and 16 mg/kg, but moderate response levels were maintained even up to 24 mg/kg. The FI component maintained better than 75% of base rates at

maximum dosage. Above 4 mg/kg there was an increased responding during the nonreinforced periods. Feeling that the high response rates at high doses under FI schedule may have been due to a confusion of response patterns to the respective stimuli, causing some FR type responding (which had a considerably higher base rate) during an FI period, Waller extinguished the FR component and repeated the experiments. Under the new conditions there was a much lower response rate at high dose levels. The responding during the nonreinforced periods supports the hypothesis that there was a confusion of response modes.

Cook and Kelleher (26), working with pigeons, found drug effects which could also be explained in terms of a confusion of response modes. Pigeons were trained to respond differentially to two keys. At the start of the cycle, both keys were white. If the pigeon pecks 20 times on the stimulus-producing key, both keys become either green, indicating a 30-second reinforcement period, or they both become red, indicating a 30-second nonreinforcement period. During the time when both keys are green the pigeon is rewarded for pecking at the food-producing key on a VR 100 schedule. This produces high rates of response to the food--producing key during the green light with bursts of responses to the stimulus-producing key when both keys are white. Doses of CPZ ranging from 5-30 mg/kg cause depression of responding to the food-producing key, but marked increase in responding to the stimulus-producing key. There must be some sort of dissociation between differential stimuli and differential response.

Terrace (150) provides evidence that the foregoing results are not due to a drug-induced impairment in sense input or discriminative

ability per se. Four pigeons were trained to discriminate between a vertical and a horizontal white line projected on a key. Two pigeons were trained in the standard manner consisting of a random presentation of the alternate stimuli with the horizontal line consistently reinforced and the vertical consistently nonreinforced. The remaining two pigeons were trained to make the same discrimination by a method which allowed them to learn the discrimination without ever having made an error. Both groups were given an equal number of training sessions, and the pigeons trained by the standard method attained a level of performance at which they averaged less than one error per training session. Both groups then were given a series of doses of CPZ ranging from 1-17 mg/kg. The drug did not alter the frequency of response to the reinforced stimulus, although the response latency was increased in a dose-dependent fashion. The pigeons trained in the standard manner made an increasing number of responses to the nonreinforced stimulus as dose increased, making more than 2000 "wrong" responses per session at the highest dosage. The pigeons trained without error made no wrong response at any dose.

Thompson (151, 152) used the increased rate of responding which occurs at the start of extinction following a CRF schedule as an operational indication of emotionality or aggressiveness. Low doses of CPZ, .6-1.5 mg/kg, cause a decrease in response rates, but an increase in rate following the onset of extinction, showing that low doses of CPZ do not reduce this type of emotionality. However, increasing doses reduce this relative increase in a dose-dependent fa-

shion, until at 3 mg/kg there is a decrease in response rate following the onset of extinction.

In summary, operant learning experiments appear to raise more questions than they answer. However, certain general statements may be made. The general overall depression of response rates noted are consistent with the experiments investigating spontaneous activity levels. The high rates of behavior maintained under most operant learning schedules would likely be especially sensitive to depressant effects. The scanty indications that the decrease in response rates involves some kind of behavioral inertia are in agreement with stronger impressions gained from the observation of spontaneous activity. It is hardly conceivable that the decrease in response rates can be due solely to decreased motor control. Although a careful evaluation by Thompson (152) showed mild motor incoordination and ataxia from as little as 3 mg/kg, this was still significantly less incoordination than was produced by a dose of phenobarbital giving an equivalent depression in the response rate.

The comparable effects on positive and negative reinforcement schedules demands caution in interpreting the CAR experiments, but the operant learning experiments are themselves subject to question. As Waller and Waller (158) aptly point out, it is impossible to equate reinforcement and avoidance schedules. Both the nature and density of the reinforcing agent is different. Even the conditioned responses vary. Since response rates have been shown to fluctuate with these variables, it is difficult to make comparisons across grossly different schedules. Perhaps more crucial is a comparison between the types of avoidance behavior. A detailed analysis would be a project in itself, but an es-

tablished operant avoidance response may easily have more in common with positively reinforced operant behavior than it does with the CAR which implies an accompanying CER. If this is so, then it is not so surprising that operant avoidant behavior is affected by drugs in a manner similar to positively reinforced operant behavior.

The disruption in schedule occurring especially when FI or stimulus decrement segments are included indicates that CPZ not only depresses a single response mode, but that it also disrupts learned associations. CAR experiments suggested that this is not a disruption of sensory discrimination under drug, and this hypothesis is supported by the striking results of Terrace (150).

Direct Brain Stimulation and CPZ. Experiments involving direct stimulation of the brain are very similar to those involving operant behavior, fundamentally differing only in the nature of the reinforcing agent, which in these experiments consists of an electric current applied directly to pleasure or pain centers of the brain by implanted electrodes. Ideally, these experiments might be expected to add to the knowledge of the central action of CPZ. In practice, little is added that was not discerned through other modes of experimentation, although differential placement of electrodes does permit some rudimentary discrimination between drugs.

Areas for implantation include the caudate nucleus, a variety of hypothalamic regions, the septal area, and the tegmentum and reticular formation of the midbrain. Little relationship was found between area of implantation and the effects of CPZ (assuming the implanted area was capable of maintaining a behavior schedule), although Olds and Travis (114) found CPZ to have less effect on behavior maintained with teg-

mental stimulation than with other areas.

Two basic experimental models are used in brain stimulation experiments. The first (62, 95, 114) involves a simple electric stimulus to the brain contingent upon some behavior (usually pressing a bar). The animal responds as to a positive reinforcement, and extremely high rates of behavior may be maintained indefinitely, although by lowering the intensity of the stimulus, lower rates of behavior more sensitive to drug modification may be maintained. Any operant schedule may be used, although in the experiments reviewed CRF schedules were most common. By placing the electrodes in selected areas, a typical operant avoidance schedule may be maintained.

The second type of experiment (143, 144, 154) permits the animal to determine his own reinforcement threshold. Each response of the animal is reinforced with a slightly less intense current. When the strength of current is reduced to the point where it is no longer reinforcing, the animal is able to reset the current to its maximum level. Very reliable thresholds may be determined in this manner. Positively or negatively reinforcing stimulation may be used.

The results are uniform regardless of area stimulated, type of experiment, or whether positively or negatively reinforcing areas are used. Rates of responding are decreased or blocked entirely, and thresholds are raised. These effects occur reliably with as little as 1.5 mg/kg.

Weitzman and Ross (16) implanted the electrodes outside the central nervous system in the Gasserian ganglion. Electric stimulation here elicits a typical pain response, and a typical avoidance schedule is maintained. Results are somewhat different than with subcortical

stimulation. Instead of a regular increase in threshold a very erratic response curve is produced, which, though generally elevated in threshold, shows extreme fluctuation. The authors describe this as behavior typically elicited from an animal after 17 hours of sleep deprivation. It seems likely that this type of response is more similar to an escape response than to a CAR, although these effects are produced with extremely low doses (.3 mg/kg in monkeys).

CPZ and Approach-Avoidance Behavior. Experiments already included under operant behavior combined positive and negative reinforcement in the same schedule. From these experiments it was concluded that CPZ reduces levels of operant responding under both conditions, and that it is very difficult to estimate comparative effects. Geller, Kulak, and Seifter (45), in an experiment already discussed, but which could just as easily be included in this section, superimposed aversive shock on a positively reinforced schedule. CPZ reduced all responding, but it was the experimenter's conclusion that approach behavior was reduced more than was avoidance.

Miller (102) reports an experiment in which a shock is introduced unpredictably into a CRF schedule with increasing intensity until responding stops. On the following day, four testings are made under drug and control saline conditions. Significantly more animals resume responding when given CPZ than under saline control. On the succeeding day the animals are again tested four times under no-drug conditions. The improved behavior is maintained, with the differences approaching significance, lending support to the clinical hope that gains made under drug conditions will be maintained after withdrawal.

Grossman (52) and Barry, Wagner, and Miller (5) first conditioned animals to a positively reinforced schedule, then made a shock also contingent on the lever-press response (with a VI schedule). During the period when a response might possibly bring a shock as well as positive reinforcement, a buzzer was continuously sounded. The intensity of the shock was varied in succeeding periods, and the intensity of the buzzer was varied in conjunction with the intensity of the shock. In this way, an approach response could be paired with an avoidance response of varying intensity. Results of the two experiments differed slightly, but in general agreed. CPZ, 2 mg/kg, improved behavior while the buzzer was sounded, and either depressed or did not affect pure approach behavior. CPZ, 4 mg/kg, produced response curves parallel to those for 2 mg/kg, but with lower levels of responding under all experimental conditions.

Ray (125) worked with discrete lever press responses. Rats were conditioned so that when a green flashing light was on, the animals responded 95+% of the time (for positive reinforcement); however, when a buzzer preceded the green light, a shock accompanied the lever-press. The buzzer preceded the light by 10 seconds, and continued for 20 seconds after the light came on. A lever-press terminated the light when only the approach conditions were in force, but when the buzzer was on, a response did not terminate either the light or the buzzer, and up to four positively reinforced-shocked lever presses were possible each time the buzzer came on. CPZ, up to 2.5 mg/kg, had no effect on either the approach or the approach-avoidant behavior. Above 2.5 mg/kg, approach responding was decreased.

Barry and Miller (3) and Grossman and Miller (168a) used a telescope-alley to test drug effects on approach-avoidance conflicts under a variety

of avoidance strengths. An animal is conditioned to run an alley for positive reinforcement. Then shock is paired with reinforcement in intensities which vary systematically with the length of the alley. Barry and Miller found running speeds reduced under all conditions with CPZ, 2 mg/kg, but reduced less in approach-avoidance situations than in pure approach situations. This was considered consistent with the hypothesis that CPZ affects both approach and avoidance gradients. Grossman and Miller, on the other hand, found that CPZ increased running rates over control values where both pain and fear provided the avoidance motivation, but reduced running rates when only fear was involved. This is close to being diametrically opposed to results obtained in CAR experiments. As Barry and Miller conclude, "Apparently, the effects of chlorpromazine on conflict behavior interact with the details of the testing situation in ways which we do not yet understand."

Effects of CPZ on Performance in a T-Maze. Seven experiments fall under this classification. Unfortunately, for four of them only abstracts were available. Muller and Gebhard (106), Meuwly (100), and Domer and Scheuler (32) trained rats to run a complex maze to a set criterion. CPZ, in doses up to 6 mg/kg, slowed running a little, but did not increase errors. Higher doses blocked performance altogether. It is interesting to note that after the higher doses there was a tendency for the animals to pause for long periods in the maze, although accuracy of performance was not significantly disrupted. This is remindful of observations made with other experimental models on initiation of activity under CPZ. Shaklee (136) found that CPZ, 2.5 mg/kg, did not affect the learning and relearning of a habit reversal in a single-unit T-maze. Zahner, Battig, and Grandjean (162) ran rats in a single-unit T-maze, every other trial being a forced choice with the opposite choice blocked. CPZ increased the

frequency with which the opposite alternative was chosen on trials following a forced choice. Brown (22) attempted to verify some hypothesis (unstated in the abstract) regarding the effects of CPZ on the spatial gradient of cul entries of a linear maze with a feared goal. None of the results supported the hypothesis.

Mitchell and King (104) obtained interesting results in working with a water maze. A single-unit T-maze was used. Work by other researchers had indicated that regular submersion prior to each trial produced an increase in stereotyped solutions. It was hypothesized that CPZ might reduce the frequency of stereotyped solutions. However, 2.5 mg/kg CPZ so disrupted behavior as to markedly reduce solutions of any kind, both for learning under CPZ and for performance under CPZ after learning under normal conditions. It is difficult to explain the results on the basis of either sedative effects or decreased motivation, since the rats showed a marked increase in activity levels (of a disorganized and unadaptive nature).

CPZ and Behavior in the Lashley Jumping Stand. Four experiments using the Lashley jumping stand were reviewed. Feldman and Lewis (38) review experiments demonstrating that CPZ in doses up to 5 mg/kg (the highest dose compatible with performance in the experimental situation) neither prevented nor corrected fixations developed through the method introduced by Maier. Latencies were increased, but discrimination was not impaired. Feldman, Ellen, Liberson, and Robins (37), using the same experimental situation, showed that brightness discrimination thresholds were not altered by 2 mg/kg CPZ. Again the drug had no affect on fixations. CPZ increased jumping latencies, and this was interpreted as a decrease in motivation.

Liberson (92), again working with fixated behavior induced by presenting an insoluble forced choice in the Lashley apparatus, increased

latencies and delayed the discrimination which is indicated by differing latencies between the rewarding and punishing choices. He found that no drug cured an established fixated compulsive behavior; but when given when the fixation was developing, certain drugs decreased the proportion of animals remaining permanently fixated. Of those animals that did break their fixation, the animals that received CPZ (as compared to meprobamate and chlordiazepoxide) took longer to differentiate between the punishing and rewarding responses, as indicated by differing latencies (while still maintaining fixated behavior). They also maintained their fixation longer after first discriminating, until the first occurrence of an adaptive response. However, once they had performed the adaptive response, they were quicker to reach the set criterion of learning established by the experimenters. That is, the rats receiving CPZ, once having differentiated, took longer to initially break the fixation, but no longer to learn the new habit (from the time of first differentiating). This is suggested as an example of "latent learning." The experimenters explain the differences by hypothesizing that chlordiazepoxide is more apt to increase variability, while CPZ is more likely to reduce anxiety.

Gonzalez and Ross (48), using the Lashley apparatus, trained rats to jump for rewards dependent on spatial or visual discriminations (two experiments). After the behavior reached the criterion of learning, a habit reversal was initiated by reversing the reward-response relationship. The new habit was learned to criterion, and the number of errors recorded. This was repeated for a total of 10 reversals, by which time the error scores had begun to approach an asymptote. Rats given CPZ had fewer errors, and reached a lower error-per-reversal asymptote. Significantly more control rats fixated early in the experiment. The experimenters interpreted

these results as indicating that CPZ was capable of maintaining more flexible and adaptive behavior in a frustrating situation.

Miscellaneous Experiments Involving Complex Learning. Many of the results reported under other classifications in this paper could be explained, at least in part, on alterations of sensory and/or sensory-discriminative thresholds. These were discussed in context, as were relevant experiments which lent grave doubts to this hypothesis. Thus, both Aganyants (1) and Khruleva (85) reported that doses of CPZ which partially disrupted an established CR did not affect differential responding along natural or established gradients. Key (81) performed essentially the same experiment using the CAR paradigm and obtained similar results. Hughes and Kopman (64) and Niemgeer (109) performed experiments in which the correct CAR was contingent upon discriminating along a stimulus parameter separate from that on which the CER was based. Doses of CPZ which disrupted responding to the CER left the response discrimination intact. Terrace (150) reported a striking interaction between learning history and the effects of CPZ on discrimination. Feldman, Ellen, Liberson, and Robins (37), using the Lashley jumping stand, made a careful determination of brightness discrimination thresholds, and found the CPZ had no effect on them in moderate doses.

Berryman, Jarvik, and Nevin (9) trained pigeons to peck at the one of two outer discs which matched a central disc. Although CPZ appeared to reduce accuracy, the differences were not significant with doses as high as 20 mg/kg. Jarvik and Chorover (75), working with monkeys, conditioned them to respond alternately to two discs at 5-second intervals. The correct response involved both the alternation and at least a 5-second delay. CPZ, .5 mg/kg, drastically reduced rates of responding without affecting accuracy.

Two experimenters found a reduction in accuracy with CPZ. Unfortunately, only the abstracts were available. The relevant parts of the abstracts will be quoted in full. In an experiment by Rahmann (123):

> The influence of chlorpromazine (0.5, 1 and 2 mg/kg s.c.) on discrimination learning, retention and transposition ability was tested after methods developed by Rensch and Rahmann (1960) in golden hamsters. Three groups of hamsters were trained to discriminate 2 simple visual patterns while given injections. Controls received an equivalent injection of saline. During conditioning the 3 chlorpromazine groups showed significantly impaired function in relation to controls. Retention was tested 14 days after the criterion had been learned and then at 10-day intervals. The memory of all chlorpromazine-treated animals was very poor in comparison to controls. In relation to transposition ability (ability to recognize the visually learned pattern in a changed form), hamsters which received chlorpromazine during conditioning and retraining, but not before the transposition test, showed a much more impaired performance than controls. Chlorpromazine acts as a CNS sedative, reducing the intensity of association formed during conditioning so the impaired memory and transposition ability results.

Schieckel (132) performed an experiment in which:

> Monkeys trained on an automatically controlled, delayed matching schedule were tested under several doses of chlorpromazine (Thorazine), 0.31 to 1.0 mg/kg.... The delay intervals which could be presented to the subjects extended from 1 to 105 seconds, but the particular delays presented in any session were a function of the subject's responses, and were programmed on a self-adjusting schedule. By this procedure correct matching responses increased the delay on successive trials, and incorrect responses decreased the delay; thus allowing the subject to determine its own limit of delay under drugged and nondrugged conditions. Large doses of chlorpromazine ... produced significant decrease in the limit for all subjects. Smaller doses of chlorpromazine produced a slight increase in the limit in one subject....

Pautler and Clark (116) analyzed the learning curves of monkeys on a flicker discrimination, and hypothesized that two modes of learning were involved; at low frequencies the learning was hypothesized to be mediated by the striate cortex, at high frequencies by the reticular formation. It was also hypothesized that CPZ would differentially block

the learning via the reticular formation. A two factor design involved comparing saline controls with animals receiving 1.9 mg/kg CPZ, and comparing animals with the striate cortex ablated with intact animals. There were no differences between pre-operative and post-operative animals in the saline controls. CPZ caused a significant increase in errors both pre- and post-operatively at the higher frequency, and only post-operatively at the lower frequency, as would be predicted from the hypotheses.

It is clear that it is not possible to simply state that CPZ does or does not affect discrimination without taking into account the difficulty of the discrimination, the learning history through which it was acquired, and the central processes through which it is mediated.

Summary

In attempting to integrate the results obtained in the experiments reviewed above, it becomes apparent that no one posited mechanism of action can account for all the phenomena. It is less apparent, but equally valid, that no set of interacting mechanisms will provide any explanation above the level of post hoc rationalization, simply because too often the needed details of experimental procedure are missing, or the necessary controls were not maintained. Finally, any attempt to provide exact explanations of specific results will be overwhelmed by a mass of unknowns regarding animal specificity, dose level effects, and comparability of different response modes. Explanations on the molar level, at best, are in danger of rash oversimplification, and molecular analyses provide sets of unrelated and unintegrated data.

In spite of these limitations, certain generalizations may be extended.

It is clear that CPZ suppresses activity levels. This effect appears two-fold. At high doses (toxic, but not lethal), there is a definite

sedative effect. This is manifest by limpness, ataxia, and decreased responsiveness. This effect does not differ greatly from sedation produced by such drugs as the barbiturates, with the notable exception that there is no marked increase in excitability at sub-sedative doses.

At lower doses, delimited as sub-sedative because the animals are able to perform adequately under forced-activity conditions, CPZ still suppresses activity levels. Although careful testing such as that by Thompson (152) may indicate some motor impairment, this does not seem, of itself, to be sufficient to account for the decreased activity levels. This type of effect is perhaps best typified by the experiments involving spontaneous activity and exploratory behavior, but detailed analyses of behavior in both CAR and operant experiments have indicated that in these situations, also, at least part of the drug effect can best be described as a decrease in the initiation of behavior.

As Skinner has succinctly put it, there is no spontaneous behavior, but only unexplained behavior. There is no clear reason for separating decreased behavioral levels in an unstructured situation from the same phenomenon occurring in a multitude of other experimental contexts. Thus, under the influence of CPZ animals eat less, drink less, perform fewer copulations, show less overt aggressive behavior, are less apt to show behavior elicited by a CER, and perform at lower rates in operant situations, whether the behavior is maintained by positive or adversive stimuli, and whether the reinforcement is administered peripherally or directly to hypothesized pleasure and pain centers in the brain. The only major exception appears to be intense aversive stimuli, such as electric shock, which are only affected at relatively high doses.

Thus, it is clear that one of the most all-pervasive effects of CPZ is to block, at some point, whatever it is that maintains behavior. Behavior that would normally occur fails to occur as quickly or as frequently when CPZ is administered, even though the animal, if forced, is capable of performing the action. Since this effect is noted in spite of adequate motor performance, and when the reinforcement is administered directly to the brain, it is almost certainly an effect on the central processes maintaining behavior and might be considered an argument for a generalized drive concept.

Whether or not CPZ has a greater effect on behavior maintained under aversive drive conditions than on positively reinforced behavior is a moot point. Certainly a larger number of experiments have been performed utilizing aversive stimuli, since this seems intuitively more relevant to the clinical effects of the drug. However, it is exceedingly difficult to equate, quantitatively, positive and negative reinforcements. Perhaps the only feasible means at present is via comparisons across drugs, which are beyond the scope of this paper.

One of the strongest arguments for maintaining that CPZ has a specific effect on phenomena classified in humans as anxiety are experiments showing effects on the autonomic system. If anxiety is defined as an emotion consisting of certain specifiably physiological changes, it is possible to distinguish conceptually between the emotion as an aversive stimulus and the aversive drive force of that stimulus. It may be reasonably concluded from the arguments already presented that CPZ reduces the aversive drive force. Does it also directly affect the physiological phenomena involved in the emotion of anxiety?

Undoubtedly, any attempt to provide a definitive answer to this question would involve reviewing a number of experiments of a strictly neurological or physiological nature which have not been included in the present review. The comments presented below are based primarily on the articles in this review. A number of experiments were presented which purported to show that CPZ reduced anxiety as exemplified by a CER. Typically, one of two types of observable criteria were used to identify and quantitate the CER: the first type involved some type of motor behavior such as running, jumping, squealing, crouching, etc.; the second type used frequency of defecation. Neither of these provides an unequivocal criterion. The use of elicited motor behavior may be criticized because it is possible that what is reduced is not the emotion, but its effectiveness as an aversive drive stimulus. Defecation may be criticized as a criterion because CPZ increases bowel transit time (which, however, may also be an autonomic effect).

A third possibility presents itself when the emotion is considered not as an aversive drive stimulus but as a learned response in itself. It has been the operating hypothesis of this paper that an emotion is a result of classical conditioning. The experiments reviewed involving classical conditioning and CERs indicate that CPZ reduces both the learning and the expression of a classically conditioned response. However, carefully controlled designs using the CAR paradigm indicate that this effect is not as strong as the effect on the emotion as an aversive stimulus. Thus, CPZ appears to reduce the effectiveness of both positive and negative drive conditions. It also acts on the learning of the emotion. Whether it effects the autonomic and physiological concomitants of the emotion itself is a problem for physiologists.

The state of affairs is even less clear when the effects of CPZ on sensory and discriminatory processes are considered. Little can be done beyond defining the limits of probable conclusions. The following seem indicated:

1. Doses on the order of sedative doses certainly reduce sensory responsiveness.
2. What effects CPZ does have on sensation and perception are not of a magnitude which would explain the bulk of the results reviewed here.
3. Experiments have been reviewed which show that CPZ both does and does not affect sensory and discriminative thresholds.
4. It is possible that CPZ has more effect on discriminations mediated by lower centers than by cortical processes.
5. The effect of CPZ on a learned discrimination may be dependent on the way in which that discrimination was learned.

By far the most inadequate area, and yet possibly the most exciting, is concerned with the effects of CPZ on the central learning centers specifically. The animal evidence here is extremely tenuous. It was suggested that some of the results observed in CAR experiments might be understood on the basis of alterations in the learning parameters. Certainly, the experiment by Terrace (150) showing radically different effects of CPZ on identical discriminations depending only on the learning history demands extensive follow-up. This whole area deserves thorough investigation.

Footnotes

[1] The increase in excitability noted conflicts with results obtained by almost all other experimenters.

[2] Irwin (69) notes some exceptions to this generalization. "...With still more active compounds, as with trifluoperazine or fluphenazine, little or no sedation occurs and one may even observe slightly increased activity and/or insomnia." "In studies with the cat or dog, it is not uncommon to observe certain individuals prone to respond to moderate doses of phenothiazines with amphetamine-like stimulation."

[3] The term conditioned response (CR) is used in this paper to refer to a strictly classical conditioning paradigm. The literature reviewed used the terms classical conditioning and CR at times in a very loose sense. In this paper a distinction is kept between the classically conditioned response which functions as an aversive stimulus and the operant response, learned or elicited, which removes the animal from the condition of the aversive stimulus. In some cases, as in the leaping behavior of a rat in response to an electric shock, the distinction is difficult to maintain, but if the behavior is what can be normally considered "voluntary motor behavior," it will be classed as operant.

Table 1: A Summary of Studies Dealing with the Effects of Chlorpromazine on Selected Dimensions of Behavior

Researcher	Refer. No.	N	Dose mg/kg	Summary of Results
A. Effects on Activity Levels				
Boisier, Simon	17	a	.25-1.5	Mice--Dose-related reduction in an objective measure of exploratory activity--up to 50% reduction at 1.5 mg/kg.
Borsy	19	25/dose	.5-4	Mice--Dose-dependent decrease in orientational hypermotility to a decrease of 78% at 4 mg/kg.
Brown	21	10/dose	.36-365	Mice--Dose related decrease in spontaneous activity at all levels.
Chen, Weston	23	a	5	Monkeys--Docility, unresponsiveness.
Chorover	24	30	5	Rats--Reduced spontaneous activity.
Fuller	41	8/group	20	Dogs--Reduced locomotion.
Gantt	42	a	a	Dogs--Inhibited both the cardiac and motor components of the orienting response.
Heise	56	4	2	Monkeys--Reduced rates of activity levels.
Janssen	73	20/dose	2.5-10	Rats--Inhibited spontaneous locomotion as measured in an open field test.
Kneip	88	15/group	2.5	Mice--ED_{50} to prevent spontaneous net-climbing activity.
Nieschulz	100	25+/dose	2-8	Mice--31 to 63% reduction in activity.
Pellmont	118	a		Rats--Reduced motor activity in activity wheel and "jiggle cages".
Randall	124	3-7	.6	Monkeys--Ratings for activity reduced by 50%.

a Information not reported in source used.

Table 1 (cont.): A Summary of Studies Dealing with the Effects of Chlorpromazine on Selected Dimensions of Behavior

Researcher	Refer. No.	N	Dose mg/kg	Summary of Results
Read	128	5	1	Mice--Reduction of spontaneous activity.
Sparviere	141	12	2-5	Mice--Marked decrease in activity in jiggle cage.
Stone	148	a	9.8	Squirrel monkeys--ED_{50} for reduction of spontaneous activity.
		a	4.7	Rhesus monkeys--ED_{50} for reduction of spontaneous activity.
Taeschler	149	≥36	1.9	Mice--ED_{50} for reduction of activity as measured by a photocell.
B. Effect on Aggressive Behavior				
Cook, Weidley	27	a	11.3	Mice--ED_{50} to prevent fighting behavior after 25 days isolation.
Heise	56	4	2	Monkeys--Ratings for aggression reduced more than for activity.
Hotovy, Kapff-Walter	63	10/dose	2-5	Mice--Markedly reduced attacks by biter-mice.
Janssen	74	10/dose	1.0	Mice--ED_{50} to prevent fighting behavior in at least one of several trials.
Knight, Holtz, Sprogis	89	64	2.4[b]	Mice--Time spent in fighting markedly increased.
Mantegazzini	96	a	4.0	Mice--ED_{50} to abolish aggressive behavior in 3/3 trials (after isolation; did not markedly alter activity level).
Navarro	108	a	10	Rats--Aggressive component of CER blocked.

b Dose of actophenazine

Table 1 (cont.): A Summary of Studies Dealing with the Effects of Chlorpromazine on Selected Dimensions of Behavior

Researcher	Refer. No.	N	Dose mg/kg	Summary of Results
Nieschulz	110	10	a	Siamese fighting fish--Suppressed fighting behavior.
Oelkers	113	a	a	Siamese fighting fish--Suppressed fighting behavior.
Randall	124	3-7	.6	Monkeys--Ratings for aggression reduced 50%.
Scriabine, Blake	135	a	4-8	Mice--Maximum sub-toxic doses were 13.1 times more effective than equivalent doses of chlordiasepoxide and 8.1 times more effective than meprobamate in reducing time spent in fighting.
C. Effects on Selected Drive States				
Gillett	47	12	2.5	Rats--Significantly reduce number of copulations.
Janssen	73	20/dose	5-10	Rats--Reduced emotionality in open field test (rearing and defecating).
Leary, Slye	91	2	1	Monkeys--Reduced dominance in food-getting activities.
Reynolds, Carlisle	129	10	.7-3.4	Rats--Food intake increased at all levels.
Ross, Rhoades	130	6/dose	2.5, 25	Rats--Food, but not water, intake depressed.
Schmidt	133	a	a	Rats--Water intake depressed as a linear function of dose.
Schmidt	134	a	up to 2.5	Rats--Food intake depressed as a linear function of dose.
Spengler	142	4/group	.5-10	Rats--Reduced food and water intake.
			4-5	Rats--Reduced food and water intake 50%.

Table II. Selected Experiments Illustrating the Effects of CPZ on CARs

Researcher	Refer. No.	N	Dose mg/kg	Type of Avoidance Behavior	Summary of Results
Aston, Sekino, Greifenstein	2	6/dose	1.4-2.4	Pole climbing on signal	Rats--Reduction in CAR due more to a specific indifference to the test situation than to general neuro-muscular effects.
Bindra, Anchel	12	13	2-12	Immobility	Rats--Maximum reduction of CAR at lowest dose. Response less disrupted at higher doses.
Cook, Kelleher	26	a	9.9	Pole climbing on signal	Rats--ED_{50} for eliminating CAR.
Davis, Capehart, Llewellin	28	30	1.25	Jumping barrier to adjacent cage on signal	Rats--Maximum effect when drug given during performance of CAR as opposed to during learning. Occurrence of CAR reduced in frequency, extinction facilitated, no change in latency of escape response.
Ekstrom, Sandberg	34	10	4.85	Undefined response on signal	Mice--ED_{50} for reduction in frequency of CAR.
Fuller	41	8/group	20	Avoiding elect. object	Dogs--Did not affect acquiring of avoidance behavior, but facilitated extinction.
Gonzales, Shepp	49	32 16	4 4	Jumping barrier to adjacent cage on signal	Rats--Prevented learning of CAR based on CER. Rats--Bimodal results when CPZ given during acquiring of CER.
Gowdey	50	88	5	Leave cage thru opening	Rats--ED_{50} for blocking CAR without blocking escape response.
Gray	51		40	Move to adjacent cage on signal	Mice--Dose which maximally blocks CAR without affecting escape behavior.

a Information not available in sources used.

Table II (con't.): Selected Experiments Illustrating the Effects of CPZ on CARs

Researcher	Refer. No.	N	Dose mg/kg	Type of Avoidance Behavior	Summary of Results
Heise	56	a	1.4	Pressing lever on signal	Rats--Decreased CAR 25%
Heise, McConnell	58			Pressing lever on signal	Rats--CAR decreased from 90% to 10%
High	61		4.5	Pole climbing on signal	Rats--ED_{50} for CAR inhibition
Ishikawa	71	1-2/dose	1-?	Pole climbing on signal	Rats--Dose-dependent increase in response latency to omission of CAR at maximum dose
Ito	72	6/dose	.3-1	Turning a wheel to open door on signal	Rats--Dose-dependent increase in latency of CAR
Keleman, Bovet	78	6	1	Jumping from heated plate	Rats--Decreased CAR more than sensing of painful heat stimulus
Lynch	93	5/dose	4	Pole climbing on signal	Rats--Minimal effective dose for increasing response latency
McMarray, Jaques	94	12	1	Jumping bar to adjacent cage	Rats--Significant reduction of CAR without affecting escape response
Marczynski, Vetulani	97	15	4	Pole climbing on signal	Rats--84% reduction in CAR with all but 30% still completing escape response
Nieschulz	110	8/group	5	Running down a runway	Rats--Increased latency, decreased proportion of CAR

Table II (con't.): Selected Experiments Illustrating the Effects of CPZ on CARs

Researchers	Refer. No.	N	Dose mg/kg	Type of Avoidance Behavior	Summary of Results
Nike	111	8/group	5	Running down a runway	Rats--Latencies were increased when CPZ given during training, but no difference from controls after drug effects had worn off
Pellmont	118		.25-4	Pole climbing on signal	Rats--Dose-dependent increase in latency, decrease in occurrence of CAR to absence at 4 mg/kg
			4-16	Pole climbing on signal	Rats--Dose-dependent increase in escape response to absence at 16 mg/kg
Stone	148	7	2	Turning a wheel to open a door	Rats--40% loss in CAR, no loss in escape response
		3	4		Rats--100% loss in CAR, no loss in escape response
Taeschler	149	204 tests	1.2	Pole climbing on signal	Rats--ED_{50}% to inhibit CAR
Vinnik	155	2	.05	Keeping shocked leg stationary and lifting another leg (on signal)	Dogs--Shock leg disinhibited, latency of avoidance response increased, CAR reduced or eliminated, escape response reduced
Wolf, Swinyard Clark	161	44	2-4	Pole climbing or moving to safe location on signal	Mice--CAR significantly depressed at both doses

Table III: Selected Experiments Illustrating the Effects of Chlorpromazine on Operant Behavior (Simple Schedules)

Researchers	Refer. No.	N	Dose mg/kg	Reinforcement Schedule	Summary of Results
Bindra	11	5	1-4	CRF	Rats--Dose-dependent decrease in response rate
Bindra, Mendelson	13	70	1.5-2.5	CRF	Rats--Dose-dependent decrease in response rate, greatest absolute depression at highest levels of training
Bindra, Mendelson	14	24	2	CRF	Rats--Decrease in response rate
Mendelson, Bindra	99	28	1.5	CRF	Rats--Decrease in response rate, independent of drive level
Sines, Keefe	139	10	5	CRF	Rats--Decrease in response rate
Stone	147	8	1.5	CRF	Rats--Decrease in response rates due to interruptions
Thompson	151	72	1.5	CRF & Ext.	Rats--Reinforced and extinction rates decreased, but extinction inflection ratio greater
Thompson	152	9	.9-3.0	CRF & Ext	Rats--Dose-dependent decrease in response rates, extinction in inflection ratio increased at lower doses, markedly depressed at higher doses
Boren	18		2	FI 2'	Rats--Markedly depressed response rates, no loss of temporal discrimination
		4	1-2	VI 30"	Rats--Markedly depressed response rates
Geller	44	2	6.5	VI 2'	Rats--Response rates depressed

Table III: Selected Experiments Illustrating the Effects of Chlorpromazine on Operant Behavior (Simple Schedules) (cont.)

Researchers	Refer. No.	N	Dose mg/kg	Reinforcement Schedule	Summary of Results
Stone	148	3-4/dose	.5-4	VI 1'	Rats--Dose-dependent decrease in response rates.
Kelleher	80	3-6	1.5-10	FR 50	Rats--Dose-dependent decrease in response rates.
Nieschulz	110	10	3	FR 10	Rats--Decreased response rates.

Table III (cont.): Selected Experiments Illustrating the Effects of Chlorpromazine on Operant Behavior (Avoidance and Complex Schedules)

Researcher	Refer. No.	N	Dose mg/kg	Reinforcement Schedule	Summary of Results
Bernstein Cancro	8	4 4 4	1-4 1-4 104	avoid SS_5"RS_{10}" avoid SS_{10}"RS_{20}" avoid SS_{20}"RS_{40}"	Rats--Dose-dependent decreases in total responses and effective avoidance responses to almost complete absence at highest doses.
Boren	18	6	2	avoid SS_{16}"RS_{20}"	Rats--Decrease in avoidance behavior, but not escape behavior; maintenance of overall response rates.
Geller	44	1	a	avoid SS_5"RS_{15}"	Rats--Depressed response rates.
Stone	146 148	12 2-4/dose	.75-3 1-4	avoid SS_5"RS_{20}" avoid SS_5"RS_{20}"	Rats--Dose-dependent decrease in response rates. Rats--Dose-dependent decrease in response rates.
Hanson	54	e	1.25-5	Sidman avoidance schedule	Rats and monkeys--Loss of CAR at moderate doses, decreased escape responses at highest doses, erratic bursts of responses at high doses and depressed behavior.
Heise	56	e	.20	Sidman avoidance schedule	Rats--Minimum effective dose, dose-dependent decrease in responding and increase in shocks received.
Heise Boff	57	4	.21[d] .36 .72	Sidman avoidance schedule	Rats--MED for increasing shock rate. Rats--MED for decreasing avoidance rate. Rats--MED for escape failure.
Kelleher	80	3-6	2.5-10	DRL_{18}"LH_3"	Rats--Slight decrease in response rates, significant at highest doses only; altered distribution of interresponse time intervals.

Table III (cont.): Selected Experiments Illustrating the Effects of Chlorpromazine on Operant Behavior (Avoidance and Complex Schedules)

Researcher	Refer. No.	N	Dose mg/kg	Reinforcement Schedule	Summary of Results
Cook Kelleher	26	b	.5-2	Concurrent FR_{150}" avoid RS_{20}"	Monkey--Reinforced responding suppressed at 1.0 mg/kg; avoidance responding suppressed at 2.0 mg/kg.
Ferster, Appel Hiss	39	1	0-10	FR_{100} ($7.5^{+}2$) to 10'	Pigeon--Increased rates of responding; at low doses decreased time/reinforcement; at high doses, also increased variability of inter-response time interval.
Fry, Kelleher Cook	40	b	5-10	FI_{10}' FR_{30}, with 2.5' to follow each reinf.	Pigeons--Inconsistent effects on response rates, but a dose-dependent tendency to eliminate the curvature in the FI component.
Geller, Kulak Seifter	45	9	.25-3	VI_2' with 3' of CRF & shock every 15'	Rats--Dose-dependent decrease in willingness to take shock with reinforcement.
Heise	56	3	e	Sidman avoid. FR_{10} S^{Δ}	Rats--Dose-dependent decrease in responding, with avoidance slightly more affected than FR_{10}, disruption of S^{Δ} component.
Sidley, Schoenfeld	138	2	1-4	$t_A{}^{D}$=0.5, $t_A{}^{\Delta}$=59.5 to 10"	Rats--Dose-dependent decrease in response rates and increase in shock frequency.
Waller	156	1	0-24	FI_3'FR_{50} $S^{\Delta}25$	Dogs--1-8 mg/kg, increased response rates, greater in FI; 4-8 mg/kg, increased response rates in S^{Δ}, 8^{+} mg/kg decrease in response rates for FI and FR, but increase in S^{Δ}.
		1	0-24	VI_3'FR_{50} $S^{\Delta}25$	
		1	0-24	FI_3'FR_{50} ext $S^{\Delta}25$	Dogs--Greater decrease in FI on higher doses than in above experiment.

Table III (cont.): Selected Experiments Illustrating the Effects of Chlorpromazine on Operant Behavior (Avoidance and Complex Schedules)

Researcher	Refer. No.	N	Dose mg/kg	Reinforcement Schedule	Summary of Results
Waller Waller	157, 158	2	c	VI_1' $S^{\Delta}25'$ avoid $RS_{20}"SS_{20}"S^{\Delta}25'$	Dogs--Dose-dependent decrease in response rate for both positive and negative reinforcement at all drug levels.
Weissman	159	4	1-5	CRF avoid $RS_{10}"SS_{10}"$	Rats--Avoidance performance affected by lower drug levels than CRF with food.

[a] A variety of doses of several phenothiazines produced these results.

[b] Experimenters report these results as typical of those obtained from several experimental animals.

[c] Dose is not reported in mg/kg.

[d] Subcutaneous doses. Higher doses needed by other routes.

[e] Information not available in sources used.

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