Pharmacological differentiation of species-typical and instrumental responding in mice with septal lesions/

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PHARMACOLOGICAL DIFFERENTIATION
OF SPECIES-TYPICAL AND INSTRUMENTAL RESPONDING
IN MICE WITH SEPTAL LESIONS

A Thesis Presented
By
ANNE ELIZABETH POWELL

Submitted to the Graduate School of the University of Massachusetts in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

February 1982

Department of Psychology
PHARMACOLOGICAL DIFFERENTIATION
OF SPECIES-TYPICAL AND INSTRUMENTAL RESPONDING
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ABSTRACT
Pharmacological Differentiation
of Species-Typical and Instrumental Responding
in Mice with Septal Lesions
February 1982
Anne Elizabeth Powell, B.A., Smith College
M.S., University of Massachusetts
Directed by: Professor Neil R. Carlson

The effect of the dopaminergic drugs amphetamine and pimozide on reinforced and nonreinforced species-typical responding was observed in normal mice and mice with lesions of the septal area. In Experiment 1 amphetamine increased wheel running in the reinforced groups with septal lesioned subjects showing greater enhancement than normal animals. Amphetamine depressed wheel running in nonreinforced septal animals and had no effect on nonreinforced normals. Pimozide decreased wheel running in all groups. In Experiment 2, amphetamine increased string pulling in reinforced normal and septal lesioned mice, but this increase was not dose dependent. Nonreinforced septal and normal animals exhibited amphetamine induced decreases in response rate. Again pimozide decreased string pulling in all groups. Throughout both experiments, normal animals responded significantly more than those with septal lesions and reinforced
animals responded significantly more than nonreinforced mice. Experiment 3 evaluated the effect of amphetamine and pimozide on cage playing. Although the drug effects were unclear, normal animals exhibited significantly more cage playing than those with septal lesions. In addition, deprived animals responded significantly more than nondeprived animals. From these experiments it is clear that mice with septal lesions exhibit depressed species-typical responding. Facilitation of instrumental responding in lesioned mice was not observed. The anticipated pharmacological differentiation of species-typical and instrumental responding was only partially evident in Experiments 1 and 2 with amphetamine. Pimozide most likely has non-specific motor effects, resulting in suppression in all groups.
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Lesions of the septal region in rodents produce a syndrome characterized by transient rage (primarily in rats), hyper-reactivity to stimuli such as shock or bright lights, impaired performance in conditioned emotional tasks and passive avoidance paradigms, deficits in tasks requiring withholding of previously reinforced responses, enhanced two-way active avoidance performance, hyperdipsia, and increased responsiveness to palatability of substances such as saccharin and quinine (see Fried, 1972 and Grossman, 1978 for reviews). In addition, a prominent feature of the syndrome is increased responding on operant tasks.

Over-responding on instrumental tasks. Enhanced responding on instrumental tasks has been observed in animals with septal lesions tested on continuous and intermittent reinforcement schedules, as well as discrete trial runway tasks. Lorens and Kondo (1969) reported that rats with septal lesions responded at a significantly higher rate than controls when placed on a continuous reinforcement (CRF) schedule for 30 days. Hothersall, Johnson and Collen (1970) found that rats with septal lesions acquired the bar pressing response sooner than normals, and obtained 150 reinforcers on CRF in a quarter of the time taken by control animals to reach the same
criterion. In another study, the response rate of septal rats on CRF was significantly higher than that of normal animals for all 16 minute sessions, but rates for both normal and septal groups converged toward the end of a 60 minute session (Harvey & Hunt, 1965).

In addition, response rate increased for normal animals when deprivation was extended from 23 to 48 hours, whereas rats with septal lesions did not show this effect, presumably because they were already pressing at maximal rates. Mothersall et al. (1970) reported similar enhanced responding by septal rats placed on fixed ratio (FR) schedules. In this experiment, after obtaining a fixed number of reinforcers on a given ratio each animal was placed on the next higher ratio in a pre-determined series. Progress through the series was terminated when an animal exhibited ratio strain, at which point the average FR attained by animals with septal lesions was 627, whereas normals achieved a mean FR value of 123. Ellen, Gillenwater and Richardson (1977) found increases in FR responding after septal lesions as did Carey (1969), but only when the anterior septum was damaged.

Similar enhanced instrumental responding has been observed in animals with septal lesions placed on fixed and variable interval schedules. Lorens and Kondo (1969) reported significantly higher response rates for rats with septal lesions as opposed to sham lesions on fixed interval (FI) schedules. In another study, animals with septal lesions trained on a FI-60 second schedule produced significantly more responses than controls in the last 15 seconds of the
interval on days 7 and 14 post-surgery (Ross & Grossman, 1975).
Increases in responding by animals with septal lesions in the terminal
portion of the interval have been found by others (Beatty &
Schwartzbaum, 1968; Ellen & Powell, 1962a, 1962b). Other inves-
tigators reported increased responding by rats with septal lesions
in the early segment of the FI interval (Schwartzbaum & Gay, 1966).
Harvey and Hunt (1965) credited septal animals with an 83% increase
in response rate on FI schedules. Increases in responding on
variable interval (VI) schedules have also been noted (Sodetz &
Koppell, 1972). Lockhart and Moore (1975) found acquisition on a
VI schedule to be more rapid in rabbits with septal lesions, although
asymptotic performance was not significantly different when septal
lesioned animals were compared to controls.

Increased running speed in a runway apparatus has been reported
by Isaacson and Douglas (1966). Facilitated acquisition of runway
responding for sucrose pellets has also been observed in animals

Increased responding during extinction. Animals with septal lesions
even overrespond during extinction, when reinforcement is not con-
tingent upon responding (Grossman, 1976; Pubols, 1966; Schwartzbaum,
Kellicut, Spieth & Thompson, 1964). Fallon and Donovick (1970) re-
ported that the septal-normal differences in extinction are observed
only if animals are maintained on the same deprivation schedule as
occurred during the reinforcement phase. Ellen et al. (1977) re-
ported that septal animals responded more than normals during ex-
tinction following training on DRL, FR, FI and VI schedules.

Explanation for over-responding. A variety of explanations have been put forth to explain this over-responding. One of the earliest ideas held that septal lesions attenuate normal inhibitory processes, resulting in facilitated responding on certain tasks (McCleary, 1966). Such disinhibition of responding may result in an increase in perseveratory or anticipatory responses. Schwartzbaum et al. (1964) support the notion of perseveratory responding because septal animals produce approximately nine times as many perseveratory errors as controls in a lever alternation task, and make significantly more responses than controls during extinction. Grossman (1978) contends that the over-responding is anticipatory in nature, as septal animals over-respond in the terminal portion of the fixed interval and shuttle early between two correct levers rather than remain at the previously correct lever.

A more recent hypothesis states that septal lesions somehow increase reinforcement salience or value and hence lead to over-responding (Carlson, Carter & Vallante, 1972; Carlson, El-Wakil, Standish & Ormond, 1976; Carlson & Norman, 1971; Carlson & Vallante, 1972; Fallon & Donovick, 1970; Lorens & Kondo, 1969; Neill et al., 1974). This view is clearly supported in an experiment showing increased responding for lateral hypothalamic stimulation following lesions of the septal area (Keesey & Powley, 1968). Carlson et al. (1976) also showed that increasing the appetitive value of food
reinforcement impaired DRL performance in the septal animal by increasing response rate. When sucrose pellets were utilized as reinforcers, response rate was highest. However, septal mice receiving cellulose pellets as reinforcers responded at rates similar to those observed in normal mice receiving standard pellets. In addition, lesioned animals trained on CRF with sucrose pellets emitted more responses during extinction than septal mice reinforced on CRF with standard or cellulose pellets.

Another explanation concerns the possibility that septal lesioned animals over-respond on instrumental tasks because interim behaviors are unavailable to them. Several investigators have observed that interim or mediating behaviors help an animal distribute responses appropriately on temporally defined schedules (Laties, Weiss, Clark & Reynolds, 1965; Laties, Weiss & Weiss, 1969). These mediating behaviors are usually chains of species-typical responses such as tail-nibbling, gnawing, licking, and so forth. Animals with septal lesions placed in a "mediation chamber" (equipped with a block of wood and cardboard strips to encourage interim behaviors) increased efficiency on a DRL task to that of normal animals responding in the usual DRL chamber (Slonaker & Hothersall, 1972).

Deficits in species-typical responding. In light of the last hypothesis, it is interesting to note that animals with septal lesions are deficient in a number of behaviors that might be classified as species-typical. Among the behaviors that are adversely affected are maternal behavior, social and aggressive behavior, exploratory be-
behavior, mating, grooming and wheel running.

Maternal behavior. Deficits in maternal behavior in animals with septal lesions have been reported by a number of authors. Mice with septal lesions were inferior to normals on a number of measures of maternal behavior, as noted by Carlson and Thomas (1968). Septal mice made many unnecessary responses during the course of pup retrieval, had significantly longer retrieval latencies, and constructed much poorer nests than normal animals. These animals exhibited all the components of a particular maternal act, such as pup retrieval, but in a disordered sequence. Similar deficits were observed in mice with septal lesions by Slotnick and Nigrosh (1975), although there was some improvement over the observation period. In addition, Fleischer and Slotnick (1978) observed that septal rats tended to deliver pups outside the nest and even carried pups between and during subsequent births, had fewer live pups, constructed inadequate nests, required more time to complete pup retrieval, and did not assume nursing positions in the nest. These authors stated that septal animals appear to have difficulty distributing their activities in an orderly manner and tend to become fixated on a particular class of behaviors, such as pup carrying, to the exclusion of all others. Deficient nest-building, cannibalism, and absence of nursing behaviors were also found in female rabbits with septal lesions (Cruz & Beyer, 1972).

One study reported increases in nesting behavior in rats with septal lesions (Hermann & Luber, 1976). However, these authors
pointed out that these increases could be attributed to frequent rebuilding efforts, as 30 animals were housed together in a semi-naturalistic environment for the observations. Under these conditions, rats with septal lesions tended to build nests in the most densely populated area of the cage, resulting in frequent disruption and subsequent rebuilding of nests. In this case, increases in nesting activity did not necessarily result in the construction of qualitatively better nests.

**Aggressive/social behavior.** Animals with septal lesions also exhibit altered aggressive and social behaviors. Bunnell and Smith (1966) noted that although frequency of interactions increased in cotton rats with septal lesions, these animals typically terminated the attack sequence quickly and switched to another activity. These animals never bit their opponents and if attacked would exhibit intense and poorly coordinated flight reactions. Studying the hooded rat, Bunnell, Bemporad and Flesher (1966) found that septal animals won more encounters and increased rank in the social hierarchy compared to preoperative levels. The authors concluded that this was due to extreme reactivity resulting in exaggerated defensiveness and aggressiveness in septal animals. Poplawsky and Johnson (1973), also studying hooded rats, discovered that medial septal lesions increased submissive behavior and duration of contact between animals, whereas lateral septal lesions increased aggressive behaviors and emotionality. A significant increase in social cohesiveness was noted in rats with septal lesions by Jonason and Enloe (1971).
These authors noted that septal animals spend a large proportion of time huddling together to the exclusion of exploratory activities. Slotnick and McMullen (1972) observed that albino mice with septal lesions typically lost fights with sham operated partners, would flee when approached, and would jump into the air periodically during aggressive encounters. Even septal mice with preoperative fighting successes failed to initiate and win fights. In conclusion, the nature of the agonistic behavior occurring after septal lesions depends upon species studied (Lau & Miczek, 1977) and the exact location of the lesion (Poplawsky & Johnson, 1973).

Exploratory behavior. Exploratory behaviors such as locomotion, rearing and sniffing are also altered in animals with septal lesions. Gotsick (1969) reported that septal rats exhibited low activity on control days in an open field test, but increased activity upon exposure to novel stimulus situations such as auditory stimulation and water or food deprivation. Corman, Meyer and Meyer (1967) found transient decreases in activity after surgery along with longer latencies to initiate activity in the open field. Septal animals with high emotionality ratings were found to perform significantly less efficiently in a maze when compared to normal animals (Nielsen, McIver & Boswell, 1965). In a comprehensive study of rearing behavior in an open field apparatus, Kemble and Nagel (1975b) observed significant decreases in septal rearing which persisted 76 days after surgery. Similar deficits were found in septal rats for sniffing responses to urine from male rats smeared on the apparatus
walls. Septal animals exhibited fewer sniffing bouts of shorter duration than operated controls (Kemble & Nagel, 1975a). Gray (1971) also observed disturbances in vibrissal movements closely correlated with altered hippocampal theta rhythm following septal lesions. In these cases, the septal rat exhibited vibrissal movement that was restricted to one side of the face, out of phase, or tended to follow a nearby object.

**Mating behavior.** Thomas (1968) reported altered mating behavior in septal animals such that increases in courtship but not copulation frequency were observed. Male septals would court and nose the female aggressively but would not mount. Lubar, Hermann, Moore and Shouse (1973) also noted that septal males exhibited fewer homosexual mounts compared to the preoperative phase. McGinnis and Gorski (1979) reported no effect of septal lesions on male sexual behavior but a facilitation of lordosis in female rats following estrogen treatment.

**Grooming.** Hermann and Lubar (1976) also observed changes in grooming patterns after septal lesions. Rats with lesions did not groom in the usual caudal to rostral direction, covering the entire body surface. Instead, these animals performed "focussed grooming" of a single body area to the exclusion of other areas.

**Wheel running.** Wheel running is also depressed in septal animals under nondeprived home cage conditions (Clody & Carlton, 1969) and in activity cages (Douglas & Raphelson, 1966; Nielson et al., 1965). However, Capobianco and Hamilton (1976) found increases in
running wheel responding when animals were given lesions of the fornix (destroying interconnections between the septum and dorsal structures) and the diagonal band (destroying interconnections between the septum and ventral structures). These authors and Strong (1957) suggested that running in wheels serves a metabolic regulatory function which interacts with the level of food deprivation.

Wheel running has typically been regarded as a measure of general activity level in an animal. However, it will be regarded as more than an activity measure in this experiment for the following reasons. To begin with, different species and different activity assessing devices yield inconsistent results with regard to activity level (Bolles, 1975). For example, Eayrs (1954) reported a .18 correlation between running scores in activity wheels and activity scores in stabilimeter cages. In addition, most of the data that led to the general activity theory was collected from deprived rats in activity wheels; these effects seem to be specific to rats, increased hunger conditions, and activity wheels. Wheel running has been related to a number of conditions such as deprivation level, body weight, blood glucose level, stomach contractions, and so forth (Bolles, 1975). Sheffield and Campbell (1954) conceptualized wheel running as a conditioned response to environmental stimuli associated with food delivery. In summary, the mechanism behind wheel running is not at all clear. Although running wheels do not exist in an animal's typical natural environment, the running wheel behavior seems to share some properties with species-typical behaviors such as grooming.
and nest-building, and will be considered here as belonging to this class.

**Preliminary studies and proposal.** The goal of the present study is to evaluate the possibility that the increases in instrumental responding and decreases in species-typical behaviors seen after lesions of the septal region might be mediated via distinct pharmacological and anatomical systems. A study by Standish and Feldman (1979) showed that conditioned responding on a VI schedule and unconditioned reactivity to tactile stimuli were differentially affected by the benzodiazepine chlordiazepoxide in mice with septal lesions. These authors suggested that separate neurochemical/anatomical pathways might be involved, and went on to postulate a serotonergic mediation of the unconditioned behavior. However, these investigators noted that benzodiazepines affect a number of transmitter systems (adrenergic, dopaminergic, cholinergic, serotonergic, glycinergic, gaba-ergic). The present study was designed to determine whether dopaminergic drugs would differentially affect conditioned (reinforced) and unconditioned (nonreinforced species-typical) behaviors in mice with septal lesions.

A number of studies have established that dopamine plays a critical role in reward processes (Fibiger, 1978; Liebman and Butcher, 1973; Lippa, Antelman, Fisher and Canfield, 1973; Wise, 1978a). Tilson and Sparber (1973) noted that at low to moderate doses, amphetamine (a dopamine and norepinephrine agonist) increased overall response rate on FI schedules. Harris, Snell and Loh (1978)
found amphetamine-induced increases in response rate in the early portion of the FI interval. Other investigators have reported similar amphetamine-induced increases in response rate on a variety of instrumental tasks (Branch and Gollub, 1974; Davis, Kensler and Dews, 1973; Graeff and DeOliveira, 1975). Conversely, a number of studies have shown that pimozide, a dopamine antagonist, attenuates the reinforcing value of food (Wise, Spindler, DeWit and Gerber, 1978) and electrical stimulation of the brain (Fouriezos, Hanssen and Wise, 1978; White and Major, 1978; Wise, 1978b).

If two distinct systems are involved in conditioned and unconditioned behavior, drugs altering dopamine neurotransmission should affect reinforced responding in a dose-dependent manner and have less of an effect on nonreinforced species-typical responding. For example, pimozide would be expected to reduce reinforced responding but have relatively less effect on nonreinforced responding. In fact, preliminary studies in this laboratory have shown that pimozide may attenuate the reinforcing value of food, thereby allowing animals with septal lesions to achieve low rates of responding on a DRL task. Typically animals with septal lesions overrespond on DRL schedules, even though such responding delays reinforcement (Ellen, Wilson and Powell, 1964).

The role of dopamine in the septal syndrome has not been carefully studied. Cholinergic agents have received by far the most attention (Grossman, 1978). Grossman recommends the investigation of catecholamines in view of the existence of noradrenergic and
dopaminergic pathways to the septum. Substantial dopaminergic input to the septal area from the ventral tegmental area has been noted (Moore, 1978; Robinson, Malthe-Sørensen, Wood, and Kommissions, 1979).

In light of this evidence, the choice of dopaminergic drugs seems to be a reasonable one. Normal and septal animals would be expected to respond similarly to these drugs, with septal lesioned animals exhibiting higher response rates on instrumental tasks and depressed species-typical responding.

Pilot studies were conducted to determine if this hypothesis was worth pursuing. Mice were given septal lesions or no treatment and placed in running wheels under reinforced and nonreinforced conditions until responding was stable for several days. Injections of amphetamine, a dopamine agonist, and pimozide, a dopamine antagonist, were then alternated with saline injections to determine whether these drugs would differentially affect reinforced and species-typical behavior in septal and normal animals.

The pre-drug response rate of normal animals exceeded that of animals with septal lesions in both the reinforced and nonreinforced condition. However, when reinforced animals were compared to non-reinforced animals, the effect of reinforcement was estimated to be considerably larger for mice with septal lesions. This difference was about five times that observed for normal mice. These results were as predicted, with mice with septal lesions exhibiting increased responsivity to reinforcement and depressed nonreinforced responding.
As expected, amphetamine increased responding in the wheel for reinforced animals. In the nonreinforced groups, however, amphetamine increased responding in normal mice. Mice with septal lesions showed drug-induced decreases in wheel running. Pimozide decreased responding in the wheel in a dose dependent manner for all groups. The decreases in the reinforced condition were as predicted. However, the decreases in the nonreinforced condition were unexpected and problematic, suggesting a possible nonspecific depressant effect of pimozide.

In summary, facilitation of operant responding and depression of nonreinforced responding were observed in these pilot studies. In addition, dopaminergic agents affected reinforced groups as anticipated, but produced unexpected results for the nonreinforced groups. These results indicated that further studies utilizing a larger subject pool and different tasks were warranted. To this end, the following experiments were conducted.
Experiment 1: Wheel Running

In this experiment the basic design described for the pilot studies was used to investigate the effects of amphetamine and pimozide on reinforced and nonreinforced wheel running in septal and normal mice.

Method.

Subjects. Twenty-four male B6D2F1 hybrid mice from Jackson Laboratory, Bar Harbor, Maine were the subjects in this experiment. These animals were approximately 10 weeks old at the start of testing. The 24 mice were assigned to the following groups prior to training: Reinforced Septal (N = 6), Reinforced Normal (N = 6), Nonreinforced Septal (N = 6) and Nonreinforced Normal (N = 6). Animals in the reinforced groups were placed on deprivation approximately four days prior to training. Nonreinforced animals had free access to food throughout the experiment. Because of the possibility that deprivation level may have affected results, four normal and four septal lesioned mice were assigned to a deprived nonreinforced condition for comparison purposes.

Apparatus. The apparatus consisted of a 21.5 cm by 23.3 cm by 20.3 cm deep Plexiglas chamber with a Plexiglas lid and grid floor. Each chamber contained a 17 cm diameter steel wire running wheel which
was connected to a magnetic switch to record wheel revolutions. Four chambers were maintained in a dark room during the experimental session, two of which were equipped with food dispensers that delivered 45 mg Noyes pellets.

**Surgery.** Septal lesions were performed by anesthetizing mice with sodium pentobarbital (75 mg/kg body weight). Animals were then placed in a Kopf No. 900 stereotaxic apparatus, using a Slotnick head-holder to keep the animal's head in place during surgery (Slotnick, 1972). Lesions were made by passing current from a Grass Instrument radiofrequency lesion maker through stainless steel insect pins insulated with enamel except at the tip. Lesions were placed (relative to bregma) at .7 mm anterior, 3.5 ventral and ± .4 mm lateral. Animals were allowed to recover for approximately one week prior to testing.

**Procedure.** One week after surgery, all subjects were placed in the running wheels for 15 minutes a day until responding was fairly stable for four consecutive days. Animals in the reinforced groups were gradually shifted from CRF to an FR-40 schedule. After training to stability, saline injections were given for two days to habituate the animals to the intraperitoneal injections. Amphetamine was then administered at the following doses: 0.25, 0.5, 1.0, 1.5, and 2.0 mg/kg body weight. Only one dose was given per day, and saline injections alternated with drug injections. Each dose was repeated four times. Following the amphetamine sequence, pimozide injections began at the following doses: 0.5, 1.0, and 2.0 mg/kg body weight.
Again, each dose was repeated four times with saline injections on alternate days. All injections were given intraperitoneally 30 minutes prior to testing.

**Drugs.** D-amphetamine sulfate, purchased from Sigma Chemical Company, was dissolved in distilled water to make a 2.5 mg/ml stock solution which was kept frozen. Fresh doses were made from the stock solution on each drug day. Amphetamine is a dopamine and norepinephrine agonist that facilitates catecholamine release and blocks re-uptake of these amines into the presynaptic terminal (Ahlenius, 1979; Groves & Rebec, 1976). Although amphetamine affects noradrenergic as well as dopaminergic synapses, the primary influence of d-amphetamine seems to be on the latter (Bunney, Walters, Kuhar, Roth & Aghajanian, 1975; Cooper, Bloom & Roth, 1978; Groves & Rebec, 1976). Specific dopamine agonists lacking complicating side effects are not readily available. Apomorphine induces nausea and most likely interacts with presynaptic receptors (Skirboll, Grace & Bunney, 1979). L-DOPA is not particularly soluble in water so that large doses of dilute drug and sometimes multiple injections are required, which are not practical for use in mice (Gronan, 1975). Pergolide mesylate, another dopamine agonist, yields unreliable results in paradigms such as DRL (personal observations).

Pimozide, supplied by Janssen Pharmaceuticals, was dissolved in a tartaric acid vehicle and distilled water. A 1.0 mg/ml stock solution was utilized to make all doses. Pimozide was selected for its well documented specificity and potency in blocking dopamine
receptors (Janssen, Niemegeers, Schellenkens, Dresse, Lenaerts, Pinchard, Schaper, Van Nueten & Verbruggen, 1968). In addition to the effectiveness of pimozide as a dopamine antagonist, the drug has a gradual and smooth onset and is relatively non-toxic compared to haloperidol and chlorpromazine, other dopamine receptor blockers.

Histology. Mice with lesions were sacrificed and perfused through the heart with 10 ml of a .9% saline solution followed by 10 ml of 10% formalin in .9% saline. The brain was removed from the skull and placed in formalin for at least 24 hours. After another 24 hours in a 30% sucrose solution, frozen sections were taken at 40 μm. Typically 24 slices (collecting alternate slices) were sufficient to cover the extent of the lesion. These slices were mounted on slides, dried and stained with cresylecht violet. Lesions were evaluated by determining degree of destruction to target structures; including the lateral septal nucleus, medial septal nucleus, vertical limb of the diagonal band, precommissural fornix and columns of the fornix. A rating of at least 75% bilateral destruction of the medial and lateral septal nuclei was required for inclusion in the study. In addition, destruction to extraseptal structures such as the caudate-putamen, stria medullaris, and dorsal thalamus was noted.

Data analysis. Mean revolutions were computed for the last four days of baseline wheel running, at which point responding had stabilized. The data were analyzed with a two way analysis of variance, the main factors being Lesion (Septal vs. Normal) and Condition (Reinforced vs. Nonreinforced). The baseline data from the control
group of deprived nonreinforced animals were compared to data from nondeprived nonreinforced animals with a two-way analysis of variance, the main factors being Lesion and Deprivation state. Mean revolutions were computed for all doses of amphetamine and pimozide and all days on which saline was administered. For each drug, data were analyzed with a three way analysis of variance, the main factors being Lesion, Condition and Dose (Myers, 1979). In addition, the scores obtained during the drug phase were expressed in terms of per cent saline responding and reanalyzed with a three way analysis of variance, the main factors being Lesion, Condition, and Dose.

Results.

**Pre-drug phase.** Figure 1 shows that the pre-drug response rate of normal animals exceeded that of animals with septal lesions in both the reinforced and nonreinforced conditions. In addition, reinforced animals consistently responded more than nonreinforced animals. Both the Lesion and Condition effects were significant (p < .001). The Lesion by Condition interaction was not significant however, suggesting that normal and septal animals were similarly affected by reinforcement. This can be confirmed by comparing the difference between nonreinforced and reinforced rates of responding for normal mice to the difference between nonreinforced and reinforced rates of responding for septal mice in Figure 1. The results of the analysis of variance on baseline wheel running can be found in Table 1.

To determine if deprivation level was a confounding factor in this experiment, a group of deprived nonreinforced mice were trained
Figure 1. Baseline wheel running for 10 days prior to drug administration (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
TABLE 1

ANALYSIS OF VARIANCE FOR BASELINE WHEEL RUNNING

<table>
<thead>
<tr>
<th>Source</th>
<th>MS</th>
<th>df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>335357.08</td>
<td>1</td>
<td>45.91</td>
<td>.001</td>
</tr>
<tr>
<td>Condition</td>
<td>159985.07</td>
<td>1</td>
<td>21.90</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Cond</td>
<td>931.15</td>
<td>1</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
<td>7304.22</td>
<td>20</td>
<td></td>
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</tr>
</tbody>
</table>

in the wheels for comparison to the nondeprived nonreinforced animals. An analysis of variance on the last four days of baseline wheel running in these two groups revealed a significant Lesion effect, as expected (p < .001). Unfortunately, the effect of deprivation state was also significant (p < .05). Deprived animals ran more in wheels than nondeprived animals. The Lesion by Deprivation State interaction was not significant. The statistical results can be found in Table 2. These findings suggest that deprivation level is an important variable that should be controlled or systematically manipulated in future studies.

Wheel running after amphetamine. The Lesion and Condition effects observed in the baseline phase continued to be evident in the second phase of the experiment during which amphetamine was administered. Normal mice responded significantly more than animals with septal lesions (p < .001) and reinforced animals responded significantly
TABLE 2

ANALYSIS OF VARIANCE FOR BASELINE WHEEL RUNNING
NONREINFORCED DEPRIVED VS. NONDEPRIVED

<table>
<thead>
<tr>
<th>Source</th>
<th>MS</th>
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<th>p</th>
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</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>550193.07</td>
<td>1</td>
<td>69.98</td>
<td>.001</td>
</tr>
<tr>
<td>Deprivation State</td>
<td>43767.92</td>
<td>1</td>
<td>5.57</td>
<td>.05</td>
</tr>
<tr>
<td>Les x Dep</td>
<td>32583.65</td>
<td>1</td>
<td>4.14</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
<td>7862.40</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

more than nonreinforced animals (p < .001). The results of the analysis of variance performed on this data can be found in Table 3.

TABLE 3

ANALYSIS OF VARIANCE FOR WHEEL RUNNING AFTER AMPHETAMINE:
ORIGINAL SCORES

<table>
<thead>
<tr>
<th>Source</th>
<th>MS</th>
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</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>1498200.67</td>
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<td>28.57</td>
<td>.001</td>
</tr>
<tr>
<td>Condition</td>
<td>985221.78</td>
<td>1</td>
<td>18.79</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Cond</td>
<td>90130.42</td>
<td>1</td>
<td>1.72</td>
<td>NS</td>
</tr>
<tr>
<td>Error₁</td>
<td>52438.36</td>
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<tr>
<td>Dose</td>
<td>5634.57</td>
<td>5</td>
<td>5.26</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>1745.62</td>
<td>5</td>
<td>1.63</td>
<td>NS</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>7113.56</td>
<td>5</td>
<td>6.64</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
<td>283.07</td>
<td>5</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Error₂</td>
<td>1071.10</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Means calculated from the original data can be found in Table 15 in the Appendix.

In order to evaluate the effect of amphetamine dose on wheel running, data were expressed in terms of per cent saline responding. This transformation was undertaken because of the considerable difference in saline responding between the groups. In order to compare the effect of amphetamine on these four groups of animals, it is essential that the groups have the same point of comparison (saline control). Figure 2 shows a clear increase in responding produced by amphetamine in reinforced septal mice. Reinforced normal animals responded slightly more with increasing amphetamine dose. Nonreinforced normal mice exhibited rates that fluctuated around saline levels. Nonreinforced septal animals exhibited dose dependent decreases in response rate. The Condition effect was significant \((p < .01)\) as was the Lesion by Condition interaction \((p < .05)\). In addition, although the overall Dose effect was not significant, the Dose by Condition interaction was significant \((p < .01)\). This interaction is due to reinforced animals exhibiting dose dependent increases in response rate with nonreinforced animals showing suppressed rates or no change from saline levels. These results are summarized in Table 4.

**Wheel running after Pimozide.** During the third phase of the experiment in which pimozide was administered, reinforced animals continued to respond significantly more than nonreinforced animals \((p < .01)\). However, the Lesion effect was not significant. These results are summarized in Table 5. Means calculated from the original
Figure 2. Per cent saline wheel running as a function of amphetamine dose. (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
### TABLE 4

**ANALYSIS OF VARIANCE FOR WHEEL RUNNING AFTER AMPHETAMINE:**

**PER CENT SALINE RESPONDING**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Lesion</td>
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<td>Condition</td>
<td>47037.58</td>
<td>1</td>
<td>10.51</td>
<td>.01</td>
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<tr>
<td>Les x Cond</td>
<td>27612.35</td>
<td>1</td>
<td>6.17</td>
<td>.05</td>
</tr>
<tr>
<td>Error&lt;sub&gt;1&lt;/sub&gt;</td>
<td>4477.49</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>696.01</td>
<td>4</td>
<td>1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>214.12</td>
<td>4</td>
<td>0.34</td>
<td>NS</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>2723.74</td>
<td>4</td>
<td>4.32</td>
<td>.01</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
<td>1514.27</td>
<td>4</td>
<td>2.40</td>
<td>NS</td>
</tr>
<tr>
<td>Error&lt;sub&gt;2&lt;/sub&gt;</td>
<td>629.98</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 5

**ANALYSIS OF VARIANCE FOR WHEEL RUNNING AFTER PIMOZIDE:**

**ORIGINAL SCORES**

<table>
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<tr>
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<th>df</th>
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<th>p</th>
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</thead>
<tbody>
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<td>2.94</td>
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</tr>
<tr>
<td>Condition</td>
<td>508804.88</td>
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<td>.01</td>
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<tr>
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<td>54555.77</td>
<td>1</td>
<td>1.42</td>
<td>NS</td>
</tr>
<tr>
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<td>38344.64</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>76610.47</td>
<td>3</td>
<td>54.47</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>12565.13</td>
<td>3</td>
<td>8.93</td>
<td>.001</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>8473.63</td>
<td>3</td>
<td>6.02</td>
<td>.01</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
<td>132.15</td>
<td>3</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Error&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1406.55</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
data can be found in Table 16 in the Appendix.

Data were reanalyzed in terms of per cent saline responding in order to determine the effect of pimozide dose on wheel running. Figure 3 shows dose dependent decreases in all groups. The Dose effect was the only significant finding (p < .001). These values can be found in Table 6.

---

**TABLE 6**

ANALYSIS OF VARIANCE FOR WHEEL RUNNING AFTER PIMOZIDE:

PER CENT SALINE RESPONDING

<table>
<thead>
<tr>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>1081.08</td>
<td>1</td>
<td>2.73</td>
<td>NS</td>
</tr>
<tr>
<td>Condition</td>
<td>208.17</td>
<td>1</td>
<td>0.53</td>
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<td>Les x Cond</td>
<td>8.16</td>
<td>1</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Error₁</td>
<td>396.32</td>
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<td></td>
</tr>
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<td>Dose</td>
<td>14644.48</td>
<td>2</td>
<td>58.04</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>23.70</td>
<td>2</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>47.80</td>
<td>2</td>
<td>0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
<td>127.31</td>
<td>2</td>
<td>0.49</td>
<td>NS</td>
</tr>
<tr>
<td>Error₂</td>
<td>261.30</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion. As predicted, nonreinforced normal animals responded more than nonreinforced mice with septal lesions in the pre-drug phase. This suggests that septal lesions impair expression of unconditioned (species-typical) responses. However, septal and normal animals were affected to a similar degree by reinforcement. The expected facilitation of reinforced responding in animals with septal
Figure 3. Per cent saline wheel running as a function of pimozide dose (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
lesions was not observed. This could be understood with reference to the literature on constraints on learning. A response (such as wheel running) that does not readily occur under nonreinforced conditions in lesioned animals might not be easily reinforced. Shettleworth (1972) noted that an organism's species-typical behavioral organization is likely to influence conditioned responding. For example, responses that occur with high probability in hungry hamsters are easily conditioned (Shettleworth, 1975). Perhaps wheel running is not easily reinforced in septal lesioned animals because it is not a part of their species-typical behavioral repertoire. It is essential to know why the response does not occur under nonreinforced conditions. Is the animal simply unable to perform the motor components of the response? Are there other behaviors occurring that are incompatible with the expression of this response? More will be said on this issue later.

Because normal mice received more reinforcers than mice with septal lesions during the pre-drug phase, it could be argued that the differences in reinforced responding are due to differences in reinforcement density. However, when both groups of animals are compared after receiving approximately the same number of reinforcers (average of 139 for normals after 11 days, average of 141 for septal animals after 16 days) the same differences in rate are observed. Hence, numbers of reinforcers earned during training is not a critical factor.

The effects of amphetamine are in the anticipated direction, with
reinforced animals showing drug-induced increases in response rate. The more pronounced increase for reinforced animals with septal lesions as compared to normal mice is consistent with the literature on facilitation of reinforced responding in septal animals. The effect of amphetamine on reinforcement may be accentuated in animals with septal lesions for the same reason that electrical stimulation of the brain is more reinforcing for animals with septal lesions (Keesey and Powley, 1968). These effects on reinforced responding do not appear to be due to a simple increase in activity level as amphetamine did not increase responding in nonreinforced normal mice and actually decreased responding in nonreinforced mice with septal lesions. The drug-induced decrease in wheel running exhibited by the nonreinforced mice with lesions is similar to the results obtained in the pilot study. One explanation for this result could be that wheel running is occurring at such a low rate in this group that any manipulation is likely to produce a disruptive effect on behavior.

The dose dependent decreases in wheel running occurring after pimozide in all groups were not anticipated, but are similar to the results obtained from the pilot study. The decreases were predicted for reinforced animals but not for nonreinforced subjects. The dose dependent suppression of reinforced wheel running by pimozide can be interpreted in several ways. Pimozide could be interfering with reinforcement mechanisms as predicted, and/or the drug could simply be decreasing rate by suppressing motor responses in general. The dose dependent decreases observed in the nonreinforced groups lend support
to the notion of motor suppression. Rolls, Rolls, Kelly, Shaw, Wood, and Dale (1973) attribute the suppressant effects of pimozide on operant responding to its disruption of complex motor sequences involved in producing the operant or consuming the reinforcer. Fibiger, Carter and Phillips (1976) suggest that pimozide does not decrease response rate by decreasing hunger or reinforcement value, but rather by producing motor deficits, particularly in the initiation of voluntary behavior. Although a number of authors such as Wise (1978b) do not favor the motor hypothesis and instead attribute the effects of pimozide to a reinforcement deficit, the results of this experiment indicate that most likely motor and reinforcement effects are present. Unfortunately, when a drug decreases response rate it is difficult to determine whether the effects are on motor components of the response or reinforcement mechanisms or both. A rate-independent measure is often required. A DRL schedule, in which low rates of responding are reinforced might be useful in this regard.

Experiment 2: String Pulling

In this experiment the effects of pimozide and amphetamine on reinforced and nonreinforced string pulling in normal and septal animals were investigated. String pulling was selected as a task that is closely related to nest-building. In fact, animals typically fashion a crude nest out of the string pulled in similar experiments.

Method.

Subjects. The subjects used in this study were 24 male B6D2F1
hybrid mice. Six animals were assigned to each of the following groups: Reinforced Septal, Reinforced Normal, Nonreinforced Septal and Nonreinforced Normal. Animals were approximately ten weeks old at the start of training. Mice in the reinforced conditions were placed on a deprivation schedule four days prior to running. Non-reinforced subjects were maintained on an ad libitum feeding schedule.

**Apparatus.** Animals were run in four operant chambers enclosed in sound-proof boxes. Each chamber measured 15 cm by 15 cm by 24 cm deep with Plexiglas walls and ceiling and a grid floor. All boxes were quipped with food dispensers that delivered 20 mg Noyes pellets into a cylindrical Plexiglas poke hole. Cones of string were mounted above the boxes on a shelf. The string from these cones was threaded through a screw eye in the ceiling and down around a pulley (diameter 9 cm). After winding twice around the pulley to prevent slippage, the string was threaded through a copper tube that protruded through the outer box. The free end of the string passed through a hole drilled in the Plexiglas ceiling of the operant chamber and was positioned approximately 4 cm above the chamber floor prior to each run. Each revolution of the pulley made a switch closure on a magnetic switch. Reinforcements were controlled and data recorded by a MODCOMP II computer.

**Surgery.** Animals were surgically prepared as described in Experiment 1.

**Procedure.** The procedure followed was identical to that described in Experiment I with the exception that animals in the rein-
forced condition were maintained on an FR 35 schedule and all sessions were 30 minutes long.

**Drugs.** The drugs amphetamine and pimozide were used as described in Experiment 1.

**Histology.** Tissue was histologically treated as described in Experiment 1.

**Data analysis.** The data were analyzed as in Experiment 1. The dependent variable was revolutions of the pulley. Amount of string pulled correlated highly with pulley revolutions, as determined by periodically measuring string length by hand and comparing to number of pulley revolutions.

**Results.**

**Pre-drug phase.** Figure 4 shows pre-drug levels of string pulling in all groups. As in Experiment 1, reinforced animals responded more than nonreinforced animals. In addition, normal animals responded more than animals with septal lesions within each condition. Both the Condition and Lesion effects were significant (p < .001). However, a comparison of nonreinforced and reinforced groups in Figure 4 shows that normal and septal mice were similarly affected by reinforcement. These results can be found in Table 7.

**String pulling after amphetamine.** During amphetamine administration, normal animals continued to respond significantly more than animals with septal lesions (p < .001). Reinforced animals also responded significantly more than nonreinforced animals (p < .001). These results are recorded in Table 8. Means calculated from this
Figure 4. Baseline string pulling for 10 days prior to drug administration (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
TABLE 7

ANALYSIS OF VARIANCE FOR BASELINE STRING PULLING

<table>
<thead>
<tr>
<th>Source</th>
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<tbody>
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<td>27.51</td>
<td>.001</td>
</tr>
<tr>
<td>Condition</td>
<td>173570.05</td>
<td>1</td>
<td>45.48</td>
<td>.001</td>
</tr>
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<td>Les x Cond</td>
<td>6533.99</td>
<td>1</td>
<td>1.71</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
<td>3816.37</td>
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</tr>
</tbody>
</table>

TABLE 8

ANALYSIS OF VARIANCE FOR STRING PULLING AFTER AMPHETAMINE:

ORIGINAL SCORES

<table>
<thead>
<tr>
<th>Source</th>
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<th>p</th>
</tr>
</thead>
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<td>19.05</td>
<td>.001</td>
</tr>
<tr>
<td>Condition</td>
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<td>1</td>
<td>24.75</td>
<td>.001</td>
</tr>
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<td>Les x Cond</td>
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<td>Error\textsubscript{1}</td>
<td>25420.25</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
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<td>1.36</td>
<td>NS</td>
</tr>
<tr>
<td>Les x Dose</td>
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<td>0.68</td>
<td>NS</td>
</tr>
<tr>
<td>Cond x Dose</td>
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<td>1.26</td>
<td>NS</td>
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</table>

data can be found in Table 17 in the Appendix.

To evaluate the effect of amphetamine on string pulling, absolute rate of string pulling was expressed in terms of per cent saline
responding. Again, this adjustment was made to correct for initial differences between groups in responding after saline. Figure 5 shows that amphetamine increased responding in reinforced septal animals above saline levels, but these effects were not dose dependent or significant, \( t(34) = 1.10 \). Reinforced normal animals exhibited smaller increases in response rate after amphetamine. These effects were also not dose dependent or significant, \( t(34) = .58 \). Both nonreinforced normal and septal groups show dose dependent decreases in response rate except for the highest dose (2.0 mg/kg). At this dose, response rate increased somewhat for normal animals and increased to 167 per cent of saline responding for animals with septal lesions. This 167 per cent increase is due to a single animal averaging 1.2 pulley revolutions after saline and 4 revolutions after 2.0 mg/kg amphetamine, representing 330 per cent of saline responding. When this value is averaged with the other data, the result is the apparent marked increase at the 2.0 mg/kg dose. All main effects and interactions were not significant with the exception of the Condition by Dose interaction. This interaction was significant \( (p < .05) \), suggesting that the effect of amphetamine is dependent upon reinforcement status. The statistical values can be found in Table 9.

String pulling after pimozide. As in all other phases of this experiment, during administration of pimozide normal animals responded significantly more than animals with septal lesions \( (p < .05) \) and reinforced animals responded significantly more than nonreinforced animals \( (p < .05) \). The results of this analysis can be found
Figure 5. Per cent saline string pulling as a function of amphetamine dose. (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
TABLE 9

ANALYSIS OF VARIANCE FOR STRING PULLING AFTER AMPHETAMINE:
PER CENT SALINE RESPONDING

<table>
<thead>
<tr>
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<th>p</th>
</tr>
</thead>
<tbody>
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<td>0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
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<td>2.26</td>
<td>NS</td>
</tr>
<tr>
<td>Les x Dose</td>
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<td>4</td>
<td>0.40</td>
<td>NS</td>
</tr>
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<td>Cond x Dose</td>
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<td>2.84</td>
<td>.05</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
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<td>4</td>
<td>1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
<td>1125.92</td>
<td>80</td>
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</tr>
</tbody>
</table>

in Table 10. Means can be found in Table 18 in the Appendix.

Dose effects and interactions were evaluated with string pulling expressed in terms of per cent saline responding. Pimozide decreased string pulling in all groups, as indicated in Figure 6. These decreases were dose dependent and significant (p < .001). Pimozide did not decrease responding in the nonreinforced groups to the same degree that reinforced animals were affected. This is particularly true of animals with septal lesions. The Condition effect was significant (p < .05). The Lesion effect and all interactions were not significant. This data appears in Table 11.

Discussion. Nonreinforced normal animals pulled consistently more string than nonreinforced animals with septal lesions, as expected.
Figure 6. Per cent saline string pulling as a function of pimozide dose (rs = reinforced septal, rn = reinforced normal, ns = nonreinforced septal, nn = nonreinforced normal).
### Table 10

**Analysis of Variance for String Pulling After Pimozide:**

**Original Scores**

<table>
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<tr>
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<th>P</th>
</tr>
</thead>
<tbody>
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<td>Les x Cond</td>
<td>175.89</td>
<td>1</td>
<td>0.02</td>
<td>NS</td>
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<tr>
<td>Error&lt;sub&gt;1&lt;/sub&gt;</td>
<td>8232.12</td>
<td>20</td>
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</tr>
<tr>
<td>Dose</td>
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<tr>
<td>Les x Dose</td>
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<td>3</td>
<td>5.70</td>
<td>.01</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>5011.14</td>
<td>3</td>
<td>6.25</td>
<td>.001</td>
</tr>
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<td>Les x Cond x Dose</td>
<td>97.23</td>
<td>3</td>
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<tr>
<td>Error&lt;sub&gt;2&lt;/sub&gt;</td>
<td>801.42</td>
<td>60</td>
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</table>

### Table 11

**Analysis of Variance for String Pulling After Pimozide:**

**Per Cent Saline Responding**

<table>
<thead>
<tr>
<th>Source</th>
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<td>Lesion</td>
<td>4.29</td>
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<td>0.00</td>
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<tr>
<td>Condition</td>
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<td>.05</td>
</tr>
<tr>
<td>Les x Cond</td>
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<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Error&lt;sub&gt;1&lt;/sub&gt;</td>
<td>4718.76</td>
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<td></td>
</tr>
<tr>
<td>Dose</td>
<td>18476.00</td>
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<td>15.22</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>2459.56</td>
<td>2</td>
<td>2.03</td>
<td>NS</td>
</tr>
<tr>
<td>Cond x Dose</td>
<td>1585.88</td>
<td>2</td>
<td>1.31</td>
<td>NS</td>
</tr>
<tr>
<td>Les x Cond x Dose</td>
<td>1455.04</td>
<td>2</td>
<td>1.20</td>
<td>NS</td>
</tr>
<tr>
<td>Error&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1213.69</td>
<td>40</td>
<td></td>
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</tbody>
</table>
This can be viewed as further evidence of species-typical behavior deficits in animals with septal lesions.

As predicted, reinforced animals pulled more string than non-reinforced animals during baseline and drug phases of this experiment. The difference between reinforced rates and nonreinforced rates was approximately equal for normal animals and those with septal lesions. As in Experiment 1, the anticipated facilitation of reinforced responding in animals with septal lesions was not observed. This was perhaps due to the difficulties encountered in conditioning a response which is not readily emitted by the animal, as the data from the Nonreinforced Septal group suggest.

The effects of amphetamine on string pulling were unexpected. Amphetamine increased responding in reinforced groups, but this effect was not dose dependent. Had this effect occurred for all groups, one could argue that the doses chosen were not sensitive enough to detect a dose dependent effect (perhaps the asymptotic portion of the dose response curve was sampled). However, Experiment 1 showed dose dependent effects after administration of the same doses of amphetamine used in this experiment. In addition, according to the literature on amphetamine, the doses selected represent a reasonable range of possible doses and have been utilized in similar studies.

Some of these effects could be explained with reference to data from individual animals. The effect of amphetamine is partially dependent upon the animal's baseline rate of responding. Rate dependency effects of amphetamine have been reported in the literature.
Heffner, Drawbaugh and Zigmond (1974) found that animals with low baseline response rates on a VI-90 second schedule generally increased responding after amphetamine, whereas high baseline rates produced by an FR-20 task were largely suppressed by amphetamine. For example, for half of the reinforced (N = 6) animals in this experiment, the 2.0 mg/kg dose of amphetamine clearly decreased response rate, whereas in the other six reinforced animals, responding was substantially increased. Increases were generally found in animals with low saline rates and decreases were noted in animals with high saline rates, as predicted by the rate dependency hypothesis.

In addition, a number of studies have shown that amphetamine does not reliably facilitate instrumental responding. Carlson, Doyle and Bidder (1965) reported that amphetamine significantly decreased responding in a runway task. Novick and Pihl (1969) reported that amphetamine disrupted active avoidance acquisition in normal but not septal animals, and increased the number of trials required for normal animals to learn a passive avoidance task (septals did not learn the task at all). Owen (1960) has also noted that amphetamine leads to a lowering of the threshold for fixed ratio strain.

The decreases in response rate seen in nonreinforced animals after amphetamine administration were not predicted, but are consistent with the results from Experiment 1 and the pilot study. Because mice with septal lesions responded at such low rates in the nonreinforced condition, it is likely that any manipulation would have been disruptive. According to the literature, amphetamine generally
increases locomotor activity (Segal, 1975; Taylor and Snyder, 1970). However, string pulling (and wheel running) are considered here to be species-typical behaviors. File and Wardill (1975) found a reduction in exploratory behavior in mice after high doses of amphetamine. Miczek (1974) also reported a disruption of intraspecies aggression in rats following moderate doses of amphetamine (0.5, 1.0 mg/kg). Hence, amphetamine may increase general activity level and at the same time disrupt species-typical behavior, such as string pulling.

As in Experiment 1, pimozide significantly decreased string pulling in all groups in a dose dependent manner. This finding further supports the hypothesis that pimozide suppresses motor components of responding. However, response rates of nonreinforced animals do not seem to be suppressed to the same degree as response rates of reinforced animals, particularly at the 0.5 mg/kg dose of pimozide. This is consistent with the prediction that pimozide, due to attenuation of reinforcement mechanisms, would suppress reinforced responding more than nonreinforced responding. The fact that some suppression is seen in the nonreinforced groups suggests that motor effects are involved and could conceivably be measured.

Experiment 3: Cage Playing

Prior observations of mice with septal lesions in our laboratory revealed striking deficits in one aspect of species-typical behavior that has not been reported in the literature. Our mice are housed in
plastic cages with covers consisting of metal bars that are approximately 1 cm apart. Normal mice frequently hang upside down on the bars and climb across the cage covers, a behavior we labelled "cage playing". In repeated observations, cage playing was never reported for mice with septal lesions. The goal of this experiment was to determine how frequently this behavior is exhibited by animals with septal lesions and how it might be affected by dopaminergic drugs.

Method.

Subjects. The subjects were the 24 mice utilized in Experiment 1.

Apparatus and procedure. Subjects were observed in their home cages approximately 30 minutes after completing the sessions in the wheels (animals on deprivation did not receive their daily allotment of food until after these observations were completed). Recording was accomplished in the following manner. Every 15 seconds for 10 minutes each animal was momentarily observed to see if cage playing was absent or present. If the animal was clinging to the bars with all feet off the cage floor, a positive score was made on the data sheet for that animal. A maximum of 40 cage playing counts per session were possible; the percentage of this total actually occurring was computed for each animal. Effects of the particular doses of amphetamine and pimozide were also evaluated.

Surgery, drugs, histology. As described in Experiment 1.

Data analysis. A three-way analysis of variance was performed on the data, the dependent variable being the percentage of time an animal spent cage playing. The main factors were Lesion, Deprivation
State and Dose. Analyses were not undertaken for data expressed in terms of per cent saline responding, as many animals exhibited no cage playing at saline levels.

Results. As indicated in Figures 7 and 8, normal animals generally responded more than animals with septal lesions. Furthermore, deprived normal mice exhibited more cage playing than normal animals maintained on an ad libitum food regimen. Although septal mice exhibited infrequent bouts of cage playing, they generally responded more when deprived of food as opposed to being fed ad libitum.

Amphetamine did not significantly alter cage playing. However, as Table 12 indicates, the Lesion and Deprivation effects were significant (both \( p < .01 \)), with normal mice responding more than septal mice and deprived animals more than nondeprived subjects.

### TABLE 12

ANALYSIS OF VARIANCE FOR CAGE PLAYING AFTER AMPHETAMINE

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Lesion</td>
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<td>12.54</td>
<td>.01</td>
</tr>
<tr>
<td>Deprivation State</td>
<td>18884.00</td>
<td>1</td>
<td>11.07</td>
<td>.01</td>
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<tr>
<td>Les ( \times ) Dep</td>
<td>13982.08</td>
<td>1</td>
<td>8.20</td>
<td>.01</td>
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<td>Error(_1)</td>
<td>1706.15</td>
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<tr>
<td>Dose</td>
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<td>5</td>
<td>0.66</td>
<td>NS</td>
</tr>
<tr>
<td>Les ( \times ) Dose</td>
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<td>5</td>
<td>1.36</td>
<td>NS</td>
</tr>
<tr>
<td>Dep ( \times ) Dose</td>
<td>37.88</td>
<td>5</td>
<td>1.42</td>
<td>NS</td>
</tr>
<tr>
<td>Les ( \times ) Dep ( \times ) Dose</td>
<td>12.84</td>
<td>5</td>
<td>0.48</td>
<td>NS</td>
</tr>
<tr>
<td>Error(_2)</td>
<td>20.69</td>
<td>100</td>
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</tbody>
</table>
Figure 7. Per cent time cage playing as a function of amphetamine dose (ds = deprived septal, dn = deprived normal, as = ad libitum septal, an = ad libitum normal).
Figure 8. Per cent time cage playing as a function of pimozide dose (ds = deprived septal, dn = deprived normal, as = ad libitum septal, an = ad libitum normal).
Pimozide decreased cage playing in a dose dependent manner in the deprived normal group. In the other groups, the amount of cage playing that occurred on days when saline was administered was already so low that decreases after pimozide were difficult to detect. These dose effects were significant (p < .001). The Lesion effect and effect of deprivation condition were also significant (p < .001 and p < .01 respectively), as was the Lesion by Deprivation State interaction (p < .01). All other interactions were significant, suggesting that the dose effect depended on both the lesion status and the level of deprivation. The results of this analysis appear in Table 13.

<table>
<thead>
<tr>
<th>Source</th>
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</tr>
<tr>
<td>Deprivation State</td>
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<td>11.22</td>
<td>.01</td>
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<tr>
<td>Les x Dep</td>
<td>2963.46</td>
<td>1</td>
<td>10.24</td>
<td>.01</td>
</tr>
<tr>
<td>Error₁</td>
<td>289.42</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>576.42</td>
<td>3</td>
<td>11.19</td>
<td>.001</td>
</tr>
<tr>
<td>Les x Dose</td>
<td>529.52</td>
<td>3</td>
<td>10.28</td>
<td>.001</td>
</tr>
<tr>
<td>Dep x Dose</td>
<td>232.60</td>
<td>3</td>
<td>4.52</td>
<td>.01</td>
</tr>
<tr>
<td>Les x Dep x Dose</td>
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<tr>
<td>Error₂</td>
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<td>60</td>
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<td></td>
</tr>
</tbody>
</table>
Discussion. The results of Experiment 3 show that deprived animals clearly respond differently from animals maintained under nondeprived conditions. In addition, lesioning the septal area depresses, even abolishes, cage playing behavior. Normal mice always played more than septal animals, and deprived mice in general played more than nondeprived animals. Because septal mice exhibited this behavior so rarely, comparisons on the basis of deprivation level are not very meaningful. However, there is a substantial difference when deprived normal mice are compared to normal animals given unlimited access to food.

It should be pointed out that nondeprived animals differed from deprived subjects in a number of respects. The nondeprived animals had access to food at all times except for the 15 minutes spent in the wheel chamber. Furthermore, the food provided continuously consisted of rat pellets that rested on the cage bars making up the cage lid. It is possible that this arrangement may have restricted cage playing somewhat, although it is equally likely that mice might have exhibited more cage playing in order to gain access to the pellets. At the time of observation, all animals had typically just completed their sessions in the wheel where deprived subjects obtained a number of reinforcers (usually around 10 pellets).

The increase in cage playing in deprived animals observed here is comparable to the increases in locomotor and environment-oriented behaviors (i.e., picking up sawdust, open rearing and digging) observed in food deprived hamsters by Shettleworth (1975). Interestingly enough, these behaviors were more readily reinforced than behaviors
such as grooming that were not elevated in the hungry hamster. Sheffield and Campbell (1954) also reported that hungry animals are maximally active prior to feeding (if this event is regularly preceded by environmental cues). Although the animals in this experiment were given their daily allotment of food at varying times following the cage playing observation, being placed back in the home cage after running in the wheel might have provided a cue for upcoming feeding and hence may have stimulated cage playing activity.

The failure of amphetamine to increase cage playing lends support to the contention that amphetamine does not increase response rate (as in Experiment 1) by increasing activity level or reactivity. The depressant effects of pimozide on deprived normal animals further corroborates the notion that this drug suppresses motor components of the response.

General Histological Results

The mice with septal lesions utilized in all three experiments possessed adequate bilateral destruction of the septal region as illustrated in Table 14. Damage to extraseptal structures was noted, particularly the corpus callosum and anterior commissure, but was not related to any behavioral measure. No animal was excluded for having too large a lesion, as defined by damage to extraseptal structures.
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
<td>L R</td>
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<tr>
<td>EXP. 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Reinforced</td>
<td>100 96</td>
<td>100 100</td>
<td>46 46</td>
<td>100 96</td>
<td>100 100</td>
</tr>
<tr>
<td>Nonreinf.</td>
<td>88 88</td>
<td>96 100</td>
<td>58 67</td>
<td>79 67</td>
<td>96 88</td>
</tr>
<tr>
<td>EXP. 2</td>
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<td></td>
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</tr>
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<td>92 92</td>
<td>92 92</td>
<td>33 38</td>
<td>83 83</td>
<td>96 96</td>
</tr>
<tr>
<td>Nonreinf.</td>
<td>96 96</td>
<td>100 100</td>
<td>46 54</td>
<td>83 83</td>
<td>100 96</td>
</tr>
<tr>
<td>AVE.</td>
<td>94 93</td>
<td>97 98</td>
<td>46 52</td>
<td>86 82</td>
<td>98 95</td>
</tr>
</tbody>
</table>
The results of these experiments consistently showed deficits in nonreinforced "species-typical" responding in animals with septal lesions. Septal animals ran less in wheels, pulled less string and exhibited less cage playing than normal animals.

Reinforced responding in the wheel running and string pulling tasks did not show the expected septal facilitation. Normal animals and those with septal lesions were similarly influenced by reinforcement. The failure to obtain this over-responding on instrumental tasks in animals with septal lesions and the observation that mice with lesions consistently responded less (in terms of absolute response levels) than normal animals require explanation. Observation of the patterns of responding in septal and normal mice revealed some notable differences. Septal animals engaged in a number of behaviors that were incompatible with expression of the operant. In the wheel running task, mice with lesions did not run continuously throughout the session as normal mice did, but instead ran in brief bursts and frequently ran through the wheel in a haphazard fashion that did not cause the wheel to turn. They also sat under the wheels and frequently checked the food bin for pellets. Because of the location of the food bin, animals had to step off the wheel to explore its contents resulting in disruption of wheel running. In
the string pulling tasks, animals with lesions pulled string in short bursts, gnawed on what was pulled into the chamber, and allocated a large portion of time to exploration of the poke hole into which food pellets were delivered. This involved frequent nose pokes into a Plexiglas tube, a behavior that was incompatible with string pulling. On the other hand, normal mice pulled almost continuously until the ratio was completed and usually examined the poke hole only when a reinforcer had actually been delivered. These differences could easily account for the slightly suppressed responding exhibited by animals with septal lesions in the reinforced condition.

In both the wheel running and string pulling tasks, the animal was required to emit a continuous response. Most studies showing septal facilitation have utilized discrete responses such as bar pressing or nose poking. Shettleworth (1975) has reported that not all behaviors respond equally well to reinforcement contingencies. For example, Annable and Wearden (1979) found that not all aspects of grooming (paw washing, face washing, body washing) increased in frequency when reinforced. Perhaps whereas tonic and discrete responses are readily reinforced in normal animals, discrete responses only are easily reinforced in mice with septal lesions. Attempts to reinforce animals for nondiscrete responses such as holding the head in a poke hole for a period of time have shown that mice with septal lesions have difficulty sustaining this response (Rice, 1978). Wheel running and string pulling are similar to sustained head poking in that they are continuous responses.
The use of dopaminergic agents to differentially affect species typical and reinforced responding has not produced clear results. Pimozide apparently had substantial nonspecific depressant effects in all three experiments. Because amphetamine affects noradrenergic as well as dopaminergic systems and has rate dependency effects, its effects on response rate are difficult to interpret.

Future studies should be directed toward defining the anatomical basis of these differences in nonreinforced and reinforced responding in animals with septal lesions. It must be stressed that destroying the septum affects a number of septal efferents and afferents as well as fibers coursing through the region. The role of specific septal nuclei, target structures and fiber bundles related to the septum in species-typical and instrumental responding should be examined before one can hope to unravel the pharmacology of this system.
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rat as indicated by water consumption and operant responding for
water reward. Journal of Comparative and Physiological Psychology,
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ant behavior in rats: Relationship between drug effect and con-
trol response rate. Journal of Comparative and Physiological

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septal and frontal ablations on the species-typical behavior of
the rat. In P. DeFrance (Ed.) The Septal Nuclei. New York:

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following septal lesions in the rat. Journal of Comparative and

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### TABLE 15

**WHEEL RUNNING AFTER AMPHETAMINE: MEANS**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Reinforced Septal</th>
<th>Reinforced Normal</th>
<th>Nonreinforced Septal</th>
<th>Nonreinforced Normal</th>
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<tr>
<td>sal</td>
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<td>.25</td>
<td>259.75</td>
<td>417.82</td>
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<td>313.40</td>
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<td>.50</td>
<td>253.41</td>
<td>397.42</td>
<td>61.49</td>
<td>308.77</td>
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<td>1.00</td>
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<td>306.77</td>
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<td>48.77</td>
<td>324.13</td>
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</table>
TABLE 16

WHEEL RUNNING AFTER PIMOZIDE: MEANS

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Reinforced Septal</th>
<th>Reinforced Normal</th>
<th>Nonreinforced Septal</th>
<th>Nonreinforced Normal</th>
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<td>185.52</td>
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<td>Dose (mg/kg)</td>
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<td>Nonreinforced Septal</td>
<td>Nonreinforced Normal</td>
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TABLE 18

STRING PULLING AFTER PIMOZIDE: MEANS

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<th>Dose (mg/kg)</th>
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<th>Reinforced Normal</th>
<th>Nonreinforced Septal</th>
<th>Nonreinforced Normal</th>
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<td>127.74</td>
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