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# Sensorimotor Deficits Produced by Phenytoin and Chlorpromazine in Unanesthetized Cats

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CARP, J S AND R. J ANDERSON *Sensorimotor deficits produced by phenytoin and chlorpromazine in unanesthetized cats* PHARMAC. BIOCHEM BEHAV 10(4) 513–520, 1979 —Unanesthetized adult cats were evaluated for suprasegmental reflex activity and motor skills before and after administration of chlorpromazine (0 0625–0 5 mg/kg) alone and in combination with phenytoin (20 mg/kg). The greatest deficits were seen in the tests of balance and coordination in which half the animals failed to match their control responses after administration of chlorpromazine and phenytoin The impairment was most noticeable with the most stringent test (walking a 4 cm wide beam), and the effects of the two drugs were additive Although there was no effect of either drug on muscle strength, the two drugs in combination depressed the animals' motivational state, making them less willing to work against imposed loads Neither drug, alone or in combination, altered responses to the flexor reflex, blind placing, the hopping response or visually aided placing It is concluded that the effects of chlorpromazine and phenytoin on motor control are selective for the CNS loci which control balance and coordination Although the two drugs produce additive responses, the deficits occur only at doses which are well above those needed for clinical efficacy and thus may not pose a problem in their long term clinical use

Sensorimotor deficits Phenytoin Chlorpromazine

THE neurologic side effects of both phenytoin (PHT) and chlorpromazine (CPZ) are well known and have been extensively documented in the clinical literature. Phenytoin, an anticonvulsant, can produce nystagmus, tremor, ataxia, and dizziness [10, 17, 18] Chlorpromazine, a major tranquilizer, decreases motor activity and in toxic doses produces an extrapyramidal syndrome including tremors, rigidity and tardive dyskinesia [9,11]. Since chlorpromazine lowers seizure threshold, it is contraindicated in epileptics, the largest group of patients taking phenytoin. Consequently, the two drugs have rarely been used together. Recently, however, phenytoin and chlorpromazine have been cited for their efficacy as a combination drug therapy The two drugs have been shown to reduce hostile and aggressive behavior in chronic schizophrenic patients [20,22], and we have shown that the drug combination selectively reduces spasticity resulting from upper motor neuron lesions [2,7].

Since both of these new indications would require long term drug therapy, it is important to establish what side effects CPZ and PHT have when given in combination. It has been suggested [13,16] that CPZ alters the blood concentration of PHT, but the possible functional defects produced by the combination on motor behavior have not been investigated. In view of their newly discovered efficacy as a drug combination in two chronic diseases and of their well-known individual side effects, the present study was undertaken to determine the extent of sensorimotor dysfunction induced in freely moving animals by the combined drugs.

## METHOD

Nine conditioned cats of either sex (mean weight ± SEM =2.7 ± 0.2 kg) were trained to perform a battery of behavioral and motor function tests described below

The first few training sessions were used merely to acclimate the animal to the laboratory surroundings and to being handled Following this, a schedule of three training sessions per week was established in which the cat was evaluated according to each test parameter The tests were always made in the same sequence at approximately the same time of day These data, although not used for statistical purposes, were used in determining when the cat's responses to all tests had stabilized. The experimental schedule was begun when these responses varied less than 10% from day to day.

The responses of each cat on the day prior to drug administration served as control measurements. CPZ was administered IV in a dose of 0 0625, 0.125, 0 25 or 0.5 mg/kg, and the cat's performance on all of the tests was evaluated 15 minutes after administration of the drug. A dose of 20 mg/kg PHT which is the lowest dose to have significant effects using the test parameters [4] was then given IV over 10 minutes, and the animals were again tested one hour after infusion was begun This schedule insured adequate equilibration of the drugs at the time the animals were tested At least five days were allowed between drug trials to allow complete elimination of the drugs administered The doses of CPZ were randomly assigned at each trial, so that within five

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weeks each cat received all 4 doses of CPZ as well as solvent injections of both drugs In addition, the combination of 0.25 mg/kg CPZ and 20 mg/kg PHT was given to 8 of the 9 cats in the reverse sequence That is, each cat was tested 1 hr after initially receiving PHT and then tested again 15 minutes after CPZ.

*Test of Balance and Coordination*

*1 Balance Beam* A 4 cm × 9 cm × 1 5 m wooden beam was used to evaluate the balance and walking ability of each animal Cats who were able to remain poised for 10 sec on both the wide and narrow edges of the beam were judged to have normal balance Locomotor ability was assessed by measuring the accuracy with which the cat traversed the wide and narrow edges of the beam set at a 10° incline Those failing to walk the entire length were judged to have lost normal walking ability

*2 Righting Reflex* The righting reflex was elicited by holding the cat in a supine position 1 meter above the floor In order to demonstrate a normal response, the cat, upon release, had to rotate in mid-air and land on all four limbs simultaneously Both the rotation and landing accuracy are components of the righting reflex and were measured in this test

*Muscle Strength Tests*

*1 Passive* The ability to resist imposed loads was evaluated by harnessing the cat and placing it on a table which was carpeted for traction A nylon line, which was affixed to the harness, ran over a pulley directly behind the cat for adding cumulative 100 gram weights Gravitational loads were thus converted to a horizontal force pulling the cat backwards Under maximal load, each animal resisted this force by assuming a characteristic posture, varying from a partially erect stance with the two forelimbs extended to a crouched position with all four limbs flexed beneath its body Because of this variation, passive muscle strength was assessed as the maximal load a cat could resist for five sec without retrograde movement, regardless of posture

*2 Active* The active strength test measured the cat's ability to pull an imposed load The procedure was similar to that of the passive test, except that the cat had to walk 15 cm to reach a food reward and remain there at least 5 sec in order to meet the test criteria. Although the cats were maintained ad lib on standard laboratory cat chow, the commercial meat/fish supplement which was used for these rewards was sufficient to maintain the behavior Small quantities of food were used for each trial to avoid satiation. The largest load at which the cat could successfully complete this test was reported as a fraction of the animal's body weight

*Reflex Tests*

*1 Blind Placing Response* To evaluate blind placing in the animals, three limbs were immobilized and the cat's vision was obscured The free limb was then brought into contact with the edge of a table three times The number of proper limb placements onto the table was recorded The test was repeated for each of the other limbs For statistical purposes, one or more failures to place a limb constituted a loss of the blind placing response in that animal

*2 Visually Aided Placing* Two other placing responses were measured In one case, three limbs were immobilized and the cat was moved slowly towards a narrow discrete surface which was in full view of the animal The expected response is extension of the free limb to meet the surface The test was repeated three times for each of the forelimbs and the number of correct placements recorded. In the other test, three limbs were immobilized and the cat was moved quickly towards the surface and proper placement of the forelimbs was evaluated in a similar manner. Any failure to place a limb properly constituted a loss of the slow or fast placings respectively

*3 Hopping Reflex* In the hopping reflex test, three limbs were immobilized, and with the body supported and the footpad of the free limb in contact with a hard surface, the body of the cat was shifted to one side. The normal response of the cat is shifting the position of the free limb (i e , hopping) towards the new center of gravity. Each of the four limbs was tested in two directions (movement to the left and right). The number of successful limb movements in three trials were recorded. Any failure to shift a limb in the proper direction represented a loss of the hopping reflex in that animal

*4 Flexor Reflex* The flexor reflex was elicited by squeezing the footpad of the cat between two pressure arms until reaching the threshold for eliciting withdrawal of the limb Thresholds were quantified by measuring the degree of deformation required to evoke withdrawal This was measured as the distance in millimeters between the two pressure arms To avoid tissue damage, measurements were stopped at a distance of 5 mm between the pressure arms even if limb withdrawal had not occurred. Animals exhibiting such an absence of withdrawal in one or more limbs were reported as failing to show normal flexor reflex activity Data were analyzed for changes in withdrawal threshold as well as complete loss of flexor reflex

*Drugs*

CPZ (Thorazine®, Smith, Kline and French, Philadelphia, Pa.) in the commercial preparation was diluted in 0.9% sterile saline to a concentration of 0.5 mg/ml Solvent injections were based on the 0.5 mg/kg dose using a stock solution containing 2% benzyl alcohol, and 2 mg ascorbic acid, 1 mg sodium bisulfite, 1 mg sodium sulfite, and 1 mg sodium chloride per ml PHT (Dilantin®, Parke Davis, Detroit, Mich ) was prepared from the sodium salt in 0 9% sterile saline adjusted to a pH of 11 with sodium hydroxide

*Statistical Analysis*

Muscle strength tests were evaluated by one-way analysis of variance of control responses, the responses to CPZ alone, and the two drugs in combination Comparison of the two drug-treated groups to the control group were made using Dunnet's multiple range test. All other tests were evaluated by nonparametric statistics using the Chi-square test For all tests, differences were judged to be statistically significant at $p<0$ 05

## RESULTS

A median of nine conditioning test sessions was required for the cats to display stable responses. The simple reflex tests required no training and remained stable from the first sessions The tests of balance and locomotor ability were rather stringent and required about 3 training sessions before the cats consistently met the test criteria for successful per-

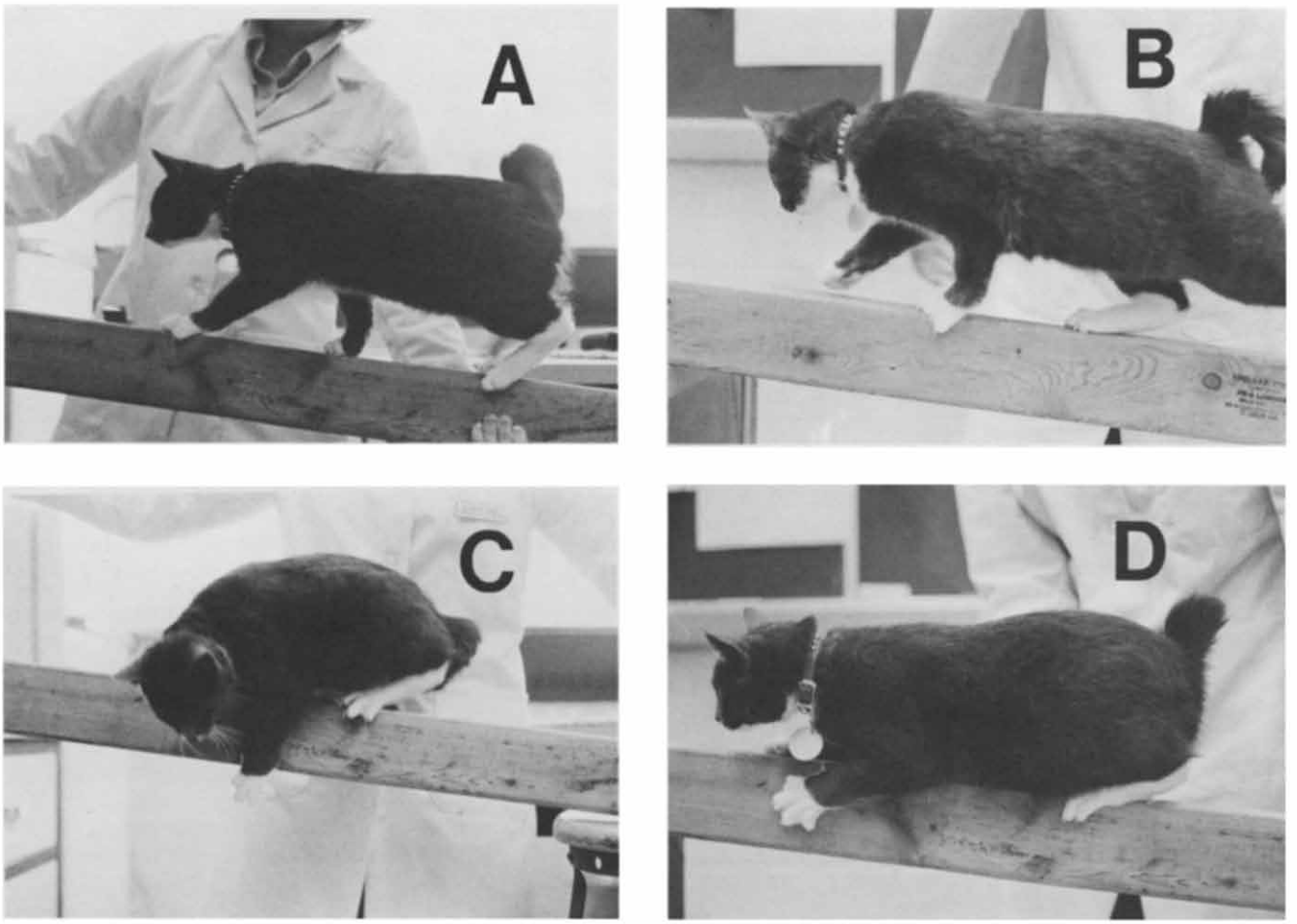


FIG 1 Ability of one cat to balance on a narrow beam after chlorpromazine (CPZ) and phenytoin (PHT) (A) Control (B) After 0 5 mg/kg CPZ (C) After 20 mg/kg PHT (D) After 0 5 mg/kg CPZ and 20 mg/kg PHT

formance. The tests of muscle strength took the longest to plateau, as the animals were shaped to perform at their maximum ability Once the cats were entered into the experimental cycle, two practice sessions on alternate days between the experimental sessions were sufficient to maintain stable responses to all test parameters

Immediately after the drug injections, during which the animals were restrained, the cats frequently appeared disoriented and had some difficulty walking Since the cats always recovered within 5 minutes, these effects were attributed to the stress of restraint during drug injection and postural hypotension upon suddenly rising after drug administration. These effects were transient and were never a complicating factor at the time the test parameters were evaluated

*Balance and Coordination*

All cats were capable of performing these tests correctly on days prior to drug administration and after solvent administration CPZ alone had no significant effect on the cat's ability to balance on the beam None of the cats was affected by any dose on the wide beam, and only 2 out of 9 were unable to balance on the narrow beam after doses of 0.25 and 0.5 mg/kg CPZ. PHT alone did not impair the cats' ability to balance on the wide edge of the beam, but PHT did cause 5 of 8 cats to fail to balance on the narrow edge ($p<0$ 05) The combination had no significant effect on the cats' ability to balance on the wide beam, where only 1 cat of each group failed after 0 125 and 0 25 mg/kg CPZ followed by 20 mg/kg PHT However, the combined drugs did cause significant impairment of balancing on the narrow edge of the beam. Five out of 9 cats each failed after doses of 0 125, 0.25 and 0 5 mg/kg CPZ followed by 20 mg/kg PHT, respectively The effects of CPZ and PHT on narrow beam balancing in one cat are shown in Fig 1

Figure 2 illustrates the effects of the drug treatments on locomotive ability on the wide edge of the beam Only 2 out of 9 cats could not perform this test correctly after 0 25 mg/kg CPZ Likewise, a dose of 20 mg/kg PHT alone only affected walking ability in 1 out of 8 animals. However, significant losses in walking ability were observed after 0.125, 0.25, and 0.5 mg/kg CPZ each followed by 20 mg/kg PHT Figure 3 shows the results of the drug treatments on the cats' ability to walk on the narrow edge of the beam. Although CPZ alone had no significant effect on this test, a significant

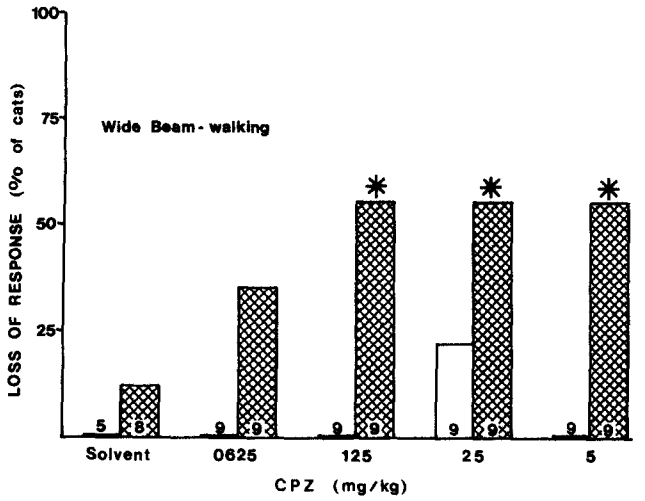


FIG 2 Effect of chlorpromazine (CPZ) alone and CPZ followed by 20 mg/kg phenytoin (PHT) on walking ability on the wide beam The percentage of cats losing the walking response after CPZ alone (bars on left) and CPZ followed by 20 mg/kg PHT (cross-hatched bars) is shown on the ordinate The solvent bars show the response to CPZ solvent on the left and the response to 20 mg/kg PHT alone on the right The number at the base of each bar is the number of cats tested in that group An asterisk indicates that the response is significantly different from control ($p<0$ 05).

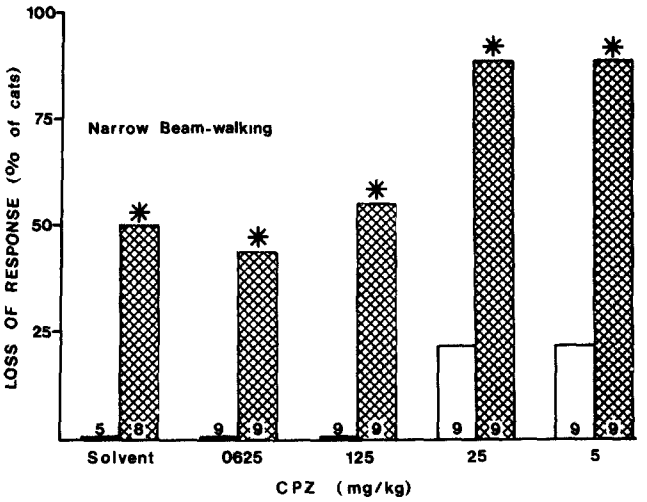


FIG 3 Effect of chlorpromazine (CPZ) alone and CPZ followed by 20 mg/kg phenytoin (PHT) on walking ability on the narrow beam The percentage of cats losing the walking response after CPZ alone (bars on left) is shown on the ordinate The solvent bars show the response to CPZ solvent on the left and the response to 20 mg/kg PHT alone on the right The number at the base of each bar is the number of cats tested in that group An asterisk indicates that the response is significantly different from control ($p<0$ 05)

loss of performance was observed after 20 mg/kg PHT alone Significant losses of walking ability were also observed following the administration of all doses of CPZ followed by 20 mg/kg PHT

The righting reflex was not significantly affected by either CPZ or PHT alone As shown in Fig 4, only 1 of 9 cats after

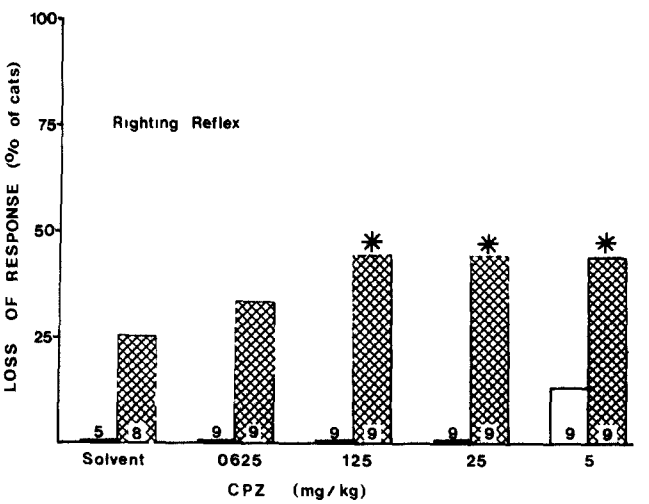


FIG 4 Effect of chlorpromazine (CPZ) alone and CPZ followed by 20 mg/kg phenytoin (PHT) on the righting reflex The percentage of cats losing this response after CPZ alone (bars on left) and CPZ followed by 20 mg/kg PHT (cross-hatched bars) is shown on the ordinate The solvent bars show the response to CPZ solvent on the left and the response to 20 mg/kg PHT alone on the right The number at the base of each bar is the number of cats tested in that group An asterisk indicates that the response is significantly different from control ($p<0$ 05)

0.5 mg/kg CPZ and 2 of 8 cats after 20 mg/kg PHT administered alone were unable to perform this test correctly. The combination of 0.125, 0 25, or 0.5 mg/kg CPZ followed by 20 mg/kg PHT caused a significant decrease in the cats' ability to perform the righting reflex

*Muscle Strength*

Each cat's ability to perform these tests improved with training, but the response usually stabilized within 5 to 10 training sessions After the cats' performance reached a steady state in both the active and passive tests, the experimental schedule was begun. The control responses taken during the experiment were variable but showed no consistent trends. The mean ± SE of all the active strength test responses taken on the days before drug treatment was 0 56 ± 0.03 (in kg load per kg of body weight) Similarly, the control passive strength responses averaged 0.75 ± 0 03 Occasionally a cat refused to perform the strength tests on the day before drug treatment When this occurred neither the control response nor the post drug response was included in the final data analysis.

Neither CPZ nor PHT alone or in combination had a significant effect on the cats' ability to perform the passive strength test This is indicated in Table 1

While neither drug alone affected the cat's responses in the active strength test, the combination of 0.125, 0.25 or 0 5 mg/kg CPZ followed by 20 mg/kg PHT did cause a significant decrease in the cat's ability to pull a load This is illustrated in Fig 5

*Reflex Texts*

Table 2 shows the drug effects on the reflex tests The hopping reflex and the visually assisted placing tests were

TABLE 1

EFFECT OF CHLORPROMAZINE ALONE AND CHLORPROMAZINE FOLLOWED BY 20 MG/KG PHENYTOIN ON THE PASSIVE STRENGTH TEST

| | Load Resisted (in kg) per kg of Body Weight CPZ (mg/kg) | | | | |
|---|---|---|---|---|---|
| | CPZ Solvent | 0 0625 | 0 125 | 0 25 | 0 5 |
| Control | 0 66 ± 0 08 | 0.69 ± 0 07 | 0 81 ± 0 12 | 0 76 ± 0 10 | 0 73 ± 0 06 |
| CPZ alone | 0 78 ± 0 11 | 0 61 ± 0.05 | 0 85 ± 0 14 | 0 72 ± 0 11 | 0 67 ± 0 09 |
| CPZ+PHT | — | 0 55 ± 0 02 | 0 58 ± 0 08 | 0 59 ± 0 09 | 0 52 ± 0 08 |
| n | 4 | 9 | 8 | 9 | 9 |

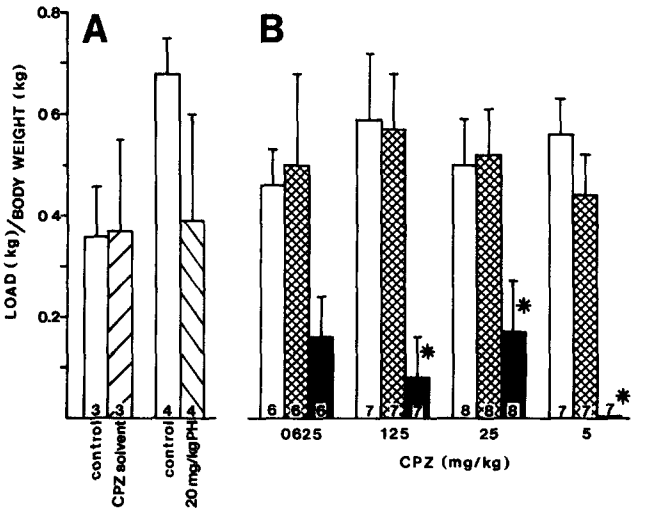


FIG 5 Effect of chlorpromazine (CPZ) alone and CPZ followed by 20 mg/kg phenytoin (PHT) on the active strength test All responses are shown on the ordinate as the mean of the loads in kg pulled by the cats per kg of body weight ± SE (A) The responses on control days (clear bars) and after either a dose of CPZ solvent or 20 mg/kg PHT (lined bars). (B) The response on control days (clear bars), after the dose of CPZ indicated on the abscissa (cross-hatched bars), and after the same dose of CPZ followed by 20 mg/kg PHT (solid bars) All control measurements were made on the day prior to drug treatment The numbers at the base of each bar indicate the number of animals tested in each group An asterisk indicates that the response after treatment is significantly different from control response ($p<0$ 05)

not significantly affected by either CPZ or PHT alone or in combination. Some cats were found to lose the blind placing response after either CPZ or PHT but a significant loss of blind placing occurred only after a dose of 0.125 mg/kg CPZ followed by 20 mg/kg PHT It should be born in mind that 1 out of 6 PHT solvent control animals also lost this response

Using a minimum distance of 5 mm between the pressure arms as the cut off point, the flexor reflex was not affected by the drugs alone or in combination. One cat each failed to meet this criterion after CPZ solvent and 0.125 and 0 25 mg/kg CPZ, and no flexor responses were affected by 20 mg/kg PHT alone Only 1 animal each failed to respond correctly after doses of 0.125 and 0.25 mg/kg CPZ followed by 20 mg/kg PHT. In addition, there was no correlation between the tissue displacement required for limb withdrawal and the dose of drug administered ($p>0.10$)

TABLE 2

EFFECT OF CHLORPROMAZINE ALONE AND CHLORPROMAZINE FOLLOWED BY 20 MG/KG PHENYTOIN ON REFLEX TESTS

| | % of Animals Showing Loss of Response CPZ (mg/kg) | | | |
|---|---|---|---|---|
| Test | 0 0625 | 0 125 | 0 25 | 0 5 |
| Blind Placing | | | | |
| CPZ alone | 33 | 11 | 22 | 33 |
| CPZ+PHT | 33 | 44* | 22 | 22 |
| Hopping | | | | |
| CPZ alone | 0 | 0 | 11 | 0† |
| CPZ+PHT | 11 | 22 | 0 | 13† |
| Visually Aided Placing-Fast | | | | |
| CPZ alone | 0 | 0 | 0 | 11 |
| CPZ+PHT | 0 | 0 | 0 | 11 |
| Visually Aided Placing-Slow | | | | |
| CPZ alone | 0 | 0 | 0 | 22 |
| CPZ+PHT | 11 | 11 | 0 | 22 |
| n | 9 | 9 | 9 | 9 |

*$p<0$ 05
†n=8

Several uncontrolled variables complicated these measurements of the flexor reflex. First, daily variation was observed in the excitability of each animal. The reflex was augmented on days when the animal appeared to be agitated and was depressed on days when the muscle tone was unusually high Second, many of the animals became apprehensive after the first few trials This test constituted an aversive stimulus in spite of the fact that the pressure applied to the footpad was never allowed to reach the point where tissue damage would occur. If an animal failed to exhibit limb withdrawal on the control day, its responses before and after drug treatment were not included in the data analysis.

*Sequencing and Drug Combination Effects*

Table 3 compares the effects of 0 25 mg/kg CPZ and 20 mg/kg PHT administered alone and in the two possible sequences of the combination Chi square analysis of the effects of the two sequences of drug administration shows no significant difference ($p>0$ 05) between the two combination

TABLE 3

COMPARISON OF THE EFFECTS OF 0 25 MG/KG CHLORPROMAZINE AND 20 MG/KG PHENYTOIN ALONE AND IN COMBINATION ON REFLEX TESTS AND TESTS OF BALANCE AND COORDINATION

| | % of Animals Showing Loss of Response | | | | |
|---|---|---|---|---|---|
| | 0 25 mg/kg CPZ | 20 mg/kg PHT | Arith sum of CPZ alone and PHT alone | 0 25 mg/kg CPZ + 20 mg/kg PHT | 20 mg/kg PHT + 0 25 mg/kg CPZ |
| Narrow Beam- | | | | | |
| Balance | 22 | 63 | 85 | 56 | 75 |
| Walk | 22 | 50 | 72 | 89 | 50 |
| Wide Beam- | | | | | |
| Balance | 0 | 0 | 0 | 11 | 13 |
| Walk | 22 | 13 | 35 | 56 | 25 |
| Righting | 0 | 25 | 25 | 44 | 25 |
| Flexor | 11 | 0* | 11 | 11 | 17* |
| Blind Placing | 22 | 25 | 47 | 22 | 25 |
| Hopping | 11 | 0 | 11 | 0 | 25 |
| Visually aided placing-fast | 0 | 0 | 0 | 0 | 0 |
| Visually aided placing-slow | 0 | 13 | 13 | 0 | 0 |
| n | 9 | 8 | | 9 | 8 |

*n=6

treatments in each of these tests For the balance beam tests and the righting reflex, each of which were impaired by PHT and/or CPZ, the responses observed from administration of the combined drugs were not significantly different ($p>0.05$) from the arithmetic sum of the effects of the two drugs administered separately, using Chi square analysis Given the variation in numbers shown in Table 3, the lack of statistical significance may be the result of our small sample size

The sequence of drug administration did not affect the animal responses in either the passive or active muscle strength test. A comparison of the mean responses on the day prior to drug administration using Student's $t$ test shows there is no difference in the cats' ability to pull a load ($p>0.20$). A similar comparison of the two drug treated groups shows that their responses are not significantly different ($p>0.10$).

*Incidental Observations*

A number of observations were made during the course of this study in addition to measuring the drug effects on the test parameters Table 4 compares the responses of the animals after CPZ followed by 20 mg/kg PHT. Some of the cats showed a widened gait which was most noticeable in the hindlimbs after CPZ alone All combinations of CPZ and 20 mg/kg PHT caused the ataxic gait Secondly, a low frequency head tremor, which was labelled "head bobbing," was observed in some animals after combination treatment, but not after CPZ alone This was readily observable in the resting animal, but virtually disappeared during walking Third, relaxation of the nictitating membrane was observed after all doses of CPZ alone and CPZ followed by 20 mg/kg PHT Finally, nystagmus was not observed after any of these drug treatments Analysis for the sequence of drug administration showed that none of these responses after 0.25 mg/kg CPZ followed by 20 mg/kg PHT were significantly different from those observed after 20 mg/kg PHT followed by 0.25 mg/kg CPZ ($p>0.4$)

## DISCUSSION

The results show that chlorpromazine and phenytoin have their greatest effect on balance and coordination and produce little or no impairment of simple reflexes such as the flexor reflex. Although the drug-treated animals showed only a widened gait on a flat surface, coordination was increasingly impaired as the requirements for walking became more stringent Likewise, the drug treated animals had greater difficulty balancing as the surface was narrowed. Locomotion, balance and the righting reflex were affected more by the combination of PHT + CPZ than by comparable doses of either drug alone Although impairment by the single drug often did not reach statistical significance, the solvent control animals always met the test criteria without failure. The small sampling size probably contributed to the inability to reach statistical significance, but the single drug response did represent a near-threshold impairment which was enhanced by the addition of the second drug.

The observation that CPZ and PHT have their most marked effect on balance and coordination is not surprising Both drugs have selective effects on the extrapyramidal pathways of the motor control system which could contribute to this impairment PHT, first of all, selectively accumu-

TABLE 4

SIDE EFFECTS OF CHLORPROMAZINE ALONE AND CHLORPROMAZINE FOLLOWED BY 20 MG/KG PHENYTOIN

| Observation | | % of Cats Showing Response After Drug Treatment Dose CPZ (mg/kg) 0 0625 | 0 125 | 0 25 | 0.5 |
|---|---|---|---|---|---|
| Ataxia | CPZ alone | 0 | 0 | 22 | 56 |
| | CPZ + PHT | 67 | 33 | 78 | 89 |
| Relaxation of Nictitating Membrane | CPZ alone | 44 | 44 | 78 | 89 |
| | CPZ + PHT | 11 | 44 | 56 | 89 |
| Head Bobbing | CPZ alone | 0 | 0 | 0 | 0 |
| | CPZ + PHT | 89 | 67 | 56 | 100 |
| Nystagmus | CPZ alone | 0 | 0 | 0 | 0 |
| | CPZ + PHT | 0 | 0 | 0 | 0 |
| n | | 9 | 9 | 9 | 9 |

lates in the cerebellum [23] and after chronic therapy results in the loss of Purkinje cells [14,21] Even acutely PHT disrupts a large input to the cerebellum from muscle spindles [1] and this alone can account for the impairment of fine movement patterns requiring sensory feedback. Similarly, CPZ by blocking dopamine receptors [6,11] seems to cause significant disruption in the basal ganglia which can account for its effects on extrapyramidal function [3]. Although acute dosing would not be expected to induce a full Parkinson-like syndrome, the pronounced effects of CPZ on descending extrapyramidal tracts which influence gamma motor neurons [12] has a marked effect on motor control. Since the central effects of CPZ and PHT in disrupting motor output are largely via separate ascending and descending parts of the motor control system, it is not surprising that their effects add when they are given together.

Closely related to the drug effects on balance and coordination are our incidental observations of ataxia, head tremor and relaxation of the nictitating membrane in the drug treated animals. Ataxia can be an indication of cerebellar or basal ganglia dysfunction and was most noticeable after the combination of CPZ and PHT. We have previously noted that PHT produces a characteristic "head bobbing" response in a dose related fashion and have attributed this to disruption of inputs to the cerebellum from neck proprioceptors by PHT [4]. "Head bobbing" was never seen after CPZ alone. In cats receiving the drug combination, the incidence of this effect was independent of the dose of CPZ administered. These observations provide further support for PHT being solely responsible for "head bobbing " Interestingly, relaxation of the nictitating membrane was seen only with CPZ. This probably was due to the drug's peripheral adrenergic blocking properties, an action not shared by PHT Although these incidental observations were not rigorously defined to meet specified criteria, as were our other observations, they are all consistent with our hypothesis of separate sites of action for PHT and CPZ.

Only one test showed a greater than additive response with the drug combination The active weight pull test was not affected by either drug alone, but in combination there was a marked reduction in the load the cat was willing to pull. This effect cannot be attributed to an absolute loss in muscle strength since the passive weight pull test in the same animals was unaffected. In addition to monitoring strength, however, the active test contained a motivational component and was reinforced by food reward. Since CPZ alone produced no change in performance, it is unlikely that the well-known tranquilizing property of the drug is a complicating factor Nevertheless, we cannot rule out that this effect was subliminally present and that by adding PHT it was potentiated. Although PHT is distinctive for its lack of sedative effects, it has been known to suppress fighting behavior [5] and locomotor behavior [19] in experimental animals. It is possible, therefore, that these subtle effects of PHT on motivation are enhanced by and contribute to the psychoactive effects of CPZ. The data suggest that CPZ and PHT are interacting at a common site in the brain, perhaps in the limbic system, to alter the motivation or willful behavior required in the active weight pull test. It is not clear from our experiments what type of interaction is involved and warrants further investigation

Since the sequence in which CPZ and PHT were administered made no difference in their ultimate effect on any of these tests, it is clear that neither drug is acting merely as a cofactor for the other. Each drug is, in fact, effective by itself in altering balance and coordination It is not surprising that the two drugs have additive effects on these motor functions With respect to the active strength test, the reduction in performance by the combined drugs was also seen regardless of which drug was given first. Although it is not clear what mechanism is involved in this combined drug response, the sequence of drug administration is not an important determinant of it.

In spite of the fact that our requirements for normal reflex performance were quite rigorous, it was not surprising that the more basic reflex pathways we tested were unaffected by either drug, alone or in combination Being comprised almost exclusively of spinal or subcortical reflex loops, they represent pathways which are essential for the animal's survival and would be expected to be the most resistant CPZ

and PHT seem only to interfere with the more highly developed components of nervous system which control motor function.

Although the combined drugs were shown to produce a marked impairment of motor control, it should be mentioned that the doses used exceeded those necessary for their combined therapeutic effects. A standard PHT dose of 20 mg/kg was chosen in these experiments because it produces a near toxic blood concentration in both man [16] and cat [15], and we had previously shown [4] that this was the lowest dose with which functional deficits could be seen. This dose of PHT produced some impairment of balance and coordination but had no effect on the reflex responses. Doses larger than 20 mg/kg produce cardiovascular toxicity in the cat and were thus avoided. However, this is over twice the dose needed when combined with CPZ for the treatment of schizophrenics [22] or patients with spasticity [7]. Likewise, CPZ doses greater than 0.125 mg/kg, even when combined with PHT, were needed to produce significant impairment in our tests. After allowing for the significantly different blood concentrations of CPZ following oral vs intravenous administration [8], the impairment by CPZ was also seen at doses which would be expected to have some tranquilizing effects clinically.

In conclusion, CPZ and PHT appear to produce an additive impairment of balance and coordination. There was an apparently greater than additive deficit in the willingness of the animals to pull against imposed loads, although muscle strength was unimpaired, and simple reflexes remained intact. Since the deficits in motor function required doses which exceeded those needed for their therapeutic efficacy, it is possible that the side effects of CPZ + PHT therapy can be avoided with a careful dosing schedule and adequate monitoring of plasma drug concentrations.

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