22. J. Farges, B. Raoult, G. Torchet, *J. Chem. Phys.* **59**, 3454 (1973); J. Farges, *J. Cryst. Growth* **31**, 79 (1975).
23. H. Morimoto, *J. Phys. Soc. Jpn.* **13**, 1015 (1958); ——— and H. Sakata, *ibid.* **17**, 136 (1962); D. Watanabe and R. Miida, in (*18*); A. Yokozeki, *J. Chem. Phys.* **68**, 3766 (1978).
24. G. Apai, J. F. Hamilton, J. Stöhr, A. Thompson, *Phys. Rev. Lett.* **43**, 165 (1979).
25. B. Lang, R. W. Joyner, G. A. Somorjai, *Surf. Sci.* **30**, 454 (1972).
26. G. A. Somorjai, *Science* **201**, 489 (1978).
27. D. R. Kahn, E. C. Petersen, G. A. Somorjai, *J. Catal.* **34**, 294 (1974).
28. D. W. Blakely and G. A. Somorjai, *Surf. Sci.* **65**, 419 (1977).
29. R. Hoffmann, *J. Chem. Phys.* **39**, 137 (1963).
30. J. A. Pople, D. P. Santry, G. A. Segal, *ibid.* **43**, S129 (1965).
31. E. L. Muetterties, T. N. Rhodin, E. Band, C. F. Brucker, W. R. Pretzer, *Chem. Rev.* **79**, 91 (1979).
32. E. Clementi and D. L. Raimondi, *J. Chem. Phys.* **38**, 2686 (1963).
33. C. E. Moore, *Natl. Bur. Stand. (U.S.) Circ. 467* (1949).
34. R. C. Baetzold, *J. Chem. Phys.* **55**, 4363 (1971).
35. C. Bachmann, J. Demuynck, A. Veillard, *Gazz. Chim. Ital.* **108**, 389 (1978).
36. R. C. Baetzold, *J. Chem. Phys.* **68**, 555 (1978).
37. E. J. Robbins, R. E. Leckenby, P. Willis, *Adv. Phys.* **16**, 739 (1967).
38. G. Hortig and M. Mueller, *Z. Phys.* **221**, 119 (1969).
39. N. E. Christensen, *Phys. Status Solidi B* **54**, 551 (1972); A. Barrie and N. E. Christensen, *Phys. Rev. B* **14**, 2442 (1976).
40. G. A. Ozin and H. Huber, *Inorg. Chem.* **17**, 155 (1978).
41. F. W. Mueller and M. G. Priestley, *Phys. Rev.* **148**, 638 (1966); J. B. Ketterson, M. G. Priestley, J. J. Vuillemin, *Phys. Lett.* **20**, 452 (1966).
42. R. C. Baetzold, *J. Phys. Chem.* **82**, 738 (1978).
43. R. W. Gurney and N. F. Mott, *Proc. R. Soc. London Ser. A* **164**, 151 (1938).
44. R. C. Baetzold, *Photogr. Sci. Eng.* **19**, 11 (1975).
45. J. F. Hamilton and L. E. Brady, *ibid.* **8**, 189 (1964).

# Psychotropic Drugs as Behavioral Teratogens

Charles V. Vorhees, Robert L. Brunner, Richard E. Butcher

*Summary.* Three psychotropic drugs were administered to pregnant rats and were then evaluated for their behavioral and reproductive effects in the offspring. Control rats received either saline or vitamin A. Prochlorperazine had the most disruptive effects on reproduction and growth, but had the least effect on behavior. Propoxyphene had no apparent effects on reproduction or growth, but produced a variety of behavioral changes. Fenfluramine was intermediate in its effects on reproduction and growth and had behavioral effects that were revealed in tests of preweaning development. The data suggest that systematic tests of behavior add important information to evaluations of reproductive toxicity that cannot, at present, be obtained by other means.

Prenatal exposure to certain drugs, such as thalidomide, and environmental agents, such as methylmercury, can cause abnormal embryonic development that results in major physical malformations, that is, teratogenesis. Recently, it has been recognized that some agents may also induce abnormalities in the behavioral capacities of offspring (*1*). Examples of such abnormalities are the fetal alcohol, fetal hydantoin, and fetal trimethadione syndromes (*2*), as well as long-term effects of fetal methadone or heroin withdrawal and of some medications used during labor and delivery (*3*). The agents causing these syndromes may be classified as behavioral teratogens.

The consequences of prenatal exposure to behavioral teratogens were recognized initially only through the accompanying physical abnormalities, or, in the case of medications used during labor, by their documented use during delivery. It is questionable whether a pure behavioral teratogen, unaccompanied by overt congenital malformations, could be successfully uncovered in the human population. Behavioral deficits are usually recognized only at school age, at which time it is too late to establish a causal relationship with drug administrations that might have occurred before birth. One solution would be to develop animal models that could be used for screening for the effects of drugs and other chemicals on behavior, in a manner similar to the screening systems that have been developed for teratogenesis, mutagenesis, and carcinogenesis.

In the study described here we used pregnant rats and their offspring to screen for the effects of three psychotropic drugs that are known to produce little or no structural teratogenicity even when administered at very high doses. We found that one of these drugs may fulfill the criteria for being a pure behavioral teratogen in rats. The three psychotropic drugs were prochlorperazine, fenfluramine, and propoxyphene. Prochlorperazine has been compared to other phenothiazines of the piperazine type (*4*). Prochlorperazine was shown to have low teratogenic activity when cleft palate was used as the index of abnormality. Fenfluramine is widely prescribed as an appetite depressant, but has recently been incriminated as a potential neurotoxin (*5*). Fenfluramine and propoxyphene have been shown to be nonteratogenic in rodents, rabbits, and monkeys, although limited clinical data suggest a link between propoxyphene and cleft palate in humans (*6*).

Adult Sprague-Dawley rats (Laboratory Supply, Indianapolis) were used for breeding. Males weighed about 400 grams and females about 260 grams at conception. The date of conception was determined by expelled vaginal plugs, and was considered day 0 of gestation. All females were primiparous. Daily on days 7 to 20 of gestation females were given, by stomach tube, one of the following: prochlorperazine edisylate (Pz, 25 milligrams per kilogram of body weight), fenfluramine hydrochloride (Ffl, 20 mg/kg), propoxyphene hydrochloride (Pp, 75 mg/kg), vitamin A palmitate (40,000 international units per kilogram, or 12 mg/kg), or saline. All drugs were given in saline in a volume of 5 milliliters per kilogram of body weight except vitamin A, which was solubilized with 12 percent sorethytan oleate and given in a volume of 1 ml/kg. Vitamin A was included in this study as a "positive" control or reference treatment because of its well-known adverse effects on behav-

Drs. Vorhees and Brunner are assistant professors and Dr. Butcher is associate professor of Research Pediatrics in the Behavioral Sciences Unit, Division of Inborn Errors of Metabolism, Children's Hospital Research Foundation and the University of Cincinnati College of Medicine, Cincinnati, Ohio 45229.


0036-8075/79/0921-1220$01.25/0 

ioral development. Drug doses were based on experiments in which we demonstrated that these doses produced viable litters. All dams were given free access to food and water.

The dams were weighed daily during treatment and all were allowed to litter normally and nurture their offspring. Parturition was considered postnatal day 0. On day 1 all litters were examined externally for malformations. They were then sexed and weighed, and any dead fetuses were removed. Litters with less than six live progeny were discarded. Litters with more than 12 were reduced to 12, equal numbers of each sex being left when possible. For each drug to be tested we used 14 to 16 dams; for vitamin A, however, we used nine dams. Behavioral testing was conducted on eight offspring per litter (four males and four females). These rats were selected at random and marked for testing on day 1. Testing began on day 3 and extended to day 70, at which time the males were killed for neuroanatomic examination. The offspring were weaned on day 21. Only males were examined in some tests because of the lengthy procedures required.

We used behavioral tests that have been studied extensively [for details see (*7*)]. After completion of the behavioral testing all the males were killed and examined for histopathological or biochemical changes. One-fourth of these males were anesthetized and perfused by a cardiac catheter with formalin. Their brains were removed, blocked, and sectioned, and the sections were stained with hematoxylin and eosin so that we could count the cerebellar cortex granular cells and hippocampal pyramidal cells of Ammon's horn (*7*). The remaining males were killed and their brains weighed and frozen. Randomly selected brains from the first five litters in each treatment group were then analyzed for whole-brain DNA and protein (*8*). Body and other tissue weights and most behavioral data were analyzed by analyses of variance with an unweighted means solution for unequal numbers. Individual group comparisons were made by means of Newman-Keuls tests (*9*). Mortality and rotorod data were analyzed according to Fisher's test for uncorrelated proportions (*10*).

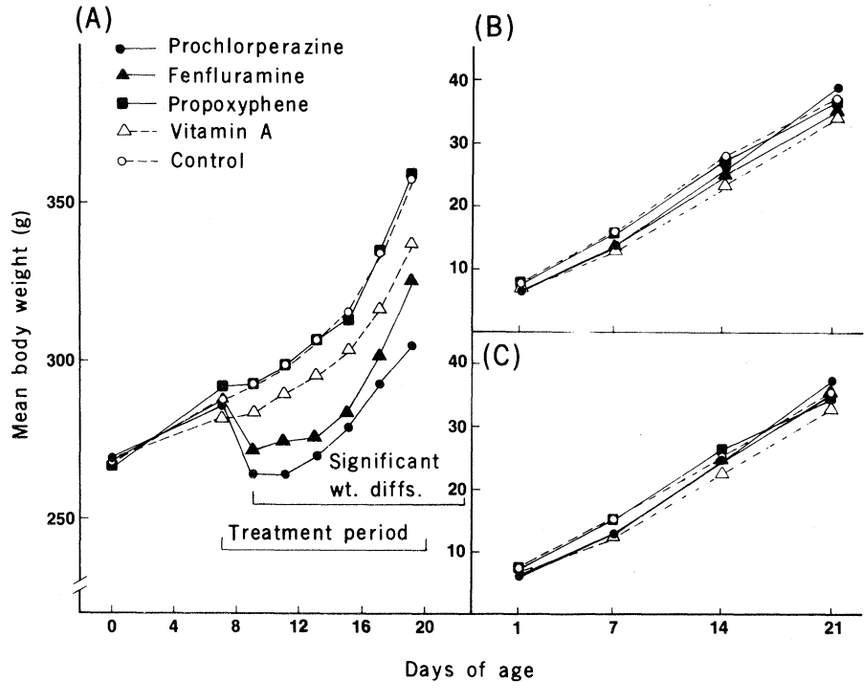


Fig. 1. Body weight. (A) Mean maternal body weight on days 0 to 20 of gestation of those dams producing viable litters. (B and C) Mean weights of (B) male and (C) female offspring prior to weaning of the dams shown in (A).

None of the drugs produced a significant reduction in delivery rate (Table 1). A few animals either died suddenly as a result of severe drug reactions prior to delivery, resorbed their litters, or had false positive pregnancies. A significant reduction in the number of viable litters ($P < .01$), that is, litters with less than six live offspring on day 1, was seen in the group that received Pz. Treatment with Pz also resulted in a significant lengthening of gestation by about $1^1/_2$ days ($P < .05$). Gestation length for the five Pz litters containing fewer than six live offspring was 24.4 ± 0.2 days, or almost $2^1/_2$ days longer than normal. The mean gestation length for the eight Pz litters with more than six live offspring was 23.0 ± 0.3 days, still a full day longer than normal. The number of offspring born to these last dams was lower than that of dams given other drugs, but the effect was not significant.

The group that received Pp had a higher ratio of male to female offspring, but the effect was not significant ($.05 > P < .10$). There was a significant increase in offspring mortality during the

Table 1. Reproductive performance and offspring mortality. A viable litter was defined as a litter with at least six live pups the day after birth. The mean number of pups born per litter was based on observations made 1 day after birth. Two Pz litters and one Ffl litter were resorbed. The second undelivered Ffl dam was not pregnant. Four pregnant Pp dams died during treatment.

| Treatment | Number of | | | Length of gestation (days) | Number of pups born per litter | Ratio of males to females | Total number of pups | | Offspring mortality at 1 to 21 days of age (%) |
|---|---|---|---|---|---|---|---|---|---|
| | Dams prepared | Litters delivered | Viable litters delivered | | | | Retained | Tested | |
| Prochlorperazine | 15 | 13 | 8 | 23.5 ± 0.3* | 9.3 ± 1.1 | 0.91 ± 0.15 | 72 | 48 | 14† |
| Fenfluramine | 16 | 14 | 14 | 21.1 ± 0.1 | 10.6 ± 0.8 | 1.31 ± 0.22 | 129 | 96 | 12† |
| Propoxyphene | 14 | 10 | 10 | 22.0 ± 0.0 | 11.9 ± 0.7 | 2.16 ± 0.71‡ | 113 | 62 | 3 |
| Vitamin A | 9 | 9 | 9 | 22.2 ± 0.2 | 10.7 ± 0.5 | 0.91 ± 0.21 | 96 | 72 | 7 |
| Saline | 15 | 15 | 14 | 22.1 ± 0.1 | 11.2 ± 0.7 | 1.08 ± 0.16 | 156 | 110 | 6 |

*Significantly lengthened gestation compared to saline controls for the 13 delivering litters ($P < .05$). The mean gestation length of the five nonviable litters was 24.4 ± 0.2 days and for the eight viable litters it was 23.0 ± 0.3 days. †Significantly different from saline controls, $P < .05$. ‡$P < .10$.

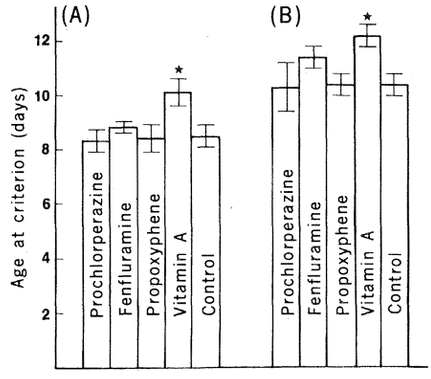


Fig. 2. (A) Cliff avoidance. Each pup was observed daily from day 6 until, when it was placed on an edge with forepaws and nose just over the edge, it showed retraction and backward or sideward movement within 60 seconds. (B) Surface righting. Each pup, observed daily from day 3, was given two trials per day, and was timed from being placed in a supine position until it had righted itself and all four feet were in contact with the surface. The rats were tested until they could right themselves in ≤ 2 seconds on both trials on a given day.

preweaning period in the groups that received Pz and Ffl (Table 1). Also, significant weight reductions were observed in these offspring during the preweaning period.

The effects of the treatments on dam weights are shown in Fig. 1A. Large weight reductions occurred shortly after institution of the Pz and Ffl treatments (all $P < .01$). Dams in the Pz group showed the largest weight reduction and the least rebound as tolerance to the drug developed. In contrast, dams given Ffl showed a marked rebound in weight on days 16 to 20 of gestation even though their initial weight reduction was similar to that of the Pz group. The group that received vitamin A also showed a significant weight reduction ($P < .01$), although the magnitude of this effect was much smaller than for either the Pz or Ffl groups. The dams given vitamin A exhibited no rebound in weight. Dams treated with Pp had weights similar to controls. Weights of offspring are shown in Fig. 1B. The Pz and Ffl litters showed significant weight reductions on days 1 and 7, but were similar to controls by day 14. Offspring in the vitamin A group showed reduced weights at all periods through day 21.

There was a significant delay ($P < .01$) in cliff avoidance development only in the group that received vitamin A (Fig. 2A). Similarly, the only significant delay ($P < .05$) in surface righting development occurred in the vitamin A group (Fig. 2B).

All groups except those that received Pz showed significant delays in one or more aspects of swimming development (Fig. 3). On day 6, the Ffl group showed delayed development of forward swimming movement ($P < .05$), a time when the control groups showed well-developed forward paddling. The vitamin A group showed almost no signs of forward

Table 2. Behavior of weaned rats in the open-field test on days 41, 42, and 43. The rats were observed for 3 minutes per day and scored for the number of sections they entered, the pattern of sections entered, latency to begin exploration, the number of rearing instances, and the number of fecal pellets deposited. The open field was circular and 91.4 cm in diameter and twice the scale of the open field used for the unweaned rats. The rats used had not been tested in the open field before they were weaned. Values are means ± standard error.

| Treatment | N | Ambulation | | Rearing (male and female combined) | Start latency (male and female combined) | Defecation | |
|---|---|---|---|---|---|---|---|
| | | Males | Females | | | Males | Females |
| Prochlorperazine | 13 | 40.4 ± 5.4 | 59.5 ± 4.3 | 9.0 ± 1.6* | 1.7 ± 0.5 | 1.1 ± 0.5 | 1.2 ± 0.7 |
| Fenfluramine | 19 | 68.1 ± 6.3* | 71.7 ± 3.5* | 15.6 ± 1.8* | 1.8 ± 0.3 | 1.9 ± 0.6† | 1.3 ± 0.6‡ |
| Propoxyphene | 17 | 57.7 ± 4.3* | 62.1 ± 4.7* | 15.9 ± 2.0* | 1.6 ± 0.3 | 1.3 ± 0.5 | 1.3 ± 0.6 |
| Vitamin A | 15 | 60.6 ± 4.8* | 60.3 ± 4.1 | 15.4 ± 1.8* | 2.0 ± 0.4 | 1.8 ± 0.5 | 1.7 ± 0.7‡ |
| Saline | 24 | 47.7 ± 3.8 | 56.3 ± 3.6 | 12.4 ± 1.6 | 2.8 ± 1.5 | 1.0 ± 0.3 | 0.7 ± 0.2 |

*$P < .05$. †$P < .05$ on day 3 of testing only (Ffl = 2.9 ± 0.7; saline = 1.3 ± 0.4). ‡$P < .05$ on day 1 of testing only (Ffl = 2.2 ± 0.8; vitamin A = 1.9 ± 0.8; saline = 0.6 ± 0.2).

Table 3. Behavior of weaned rats in tests of spontaneous choice alternation, the Biel water maze, active avoidance acquisition, and passive avoidance retention. For the test of alternation frequency the rats were placed in a T maze and allowed to make a spontaneous left or right choice. Trials were given in pairs and choices were unreinforced. Alternation frequency was calculated as the percentage of trials in each pair on which the second trial was to the opposite side as the preceding trial. Each male was given four trials in the T maze on day 45 (stem 45.7 cm, arms 50.8 cm each). In the Biel water maze the rats were given 11 trials, five on the first day in a 50-cm straight channel as a test of swimming speed, and two trials per day on days 2, 3, and 4 in the complete maze to find their way to the exit ramp. All males were tested on days 50 to 53 (*17*). Shock avoidance was assessed in a single 40-trial session in selected males on day 65. On each trial a warning noise came on for 9 seconds during which a one-half turn of the wheel terminated the trial and an avoidance was scored; if no turn was made by the end of the 9-second warning interval, a 0.75-mA shock was delivered until a wheel-turn response was made. There was a variable interval between trials that averaged 45 seconds (*18*). For passive avoidance testing the rats were placed in the lighted side of a two-chamber apparatus. On the first day the time required for the rat to enter the dark chamber was recorded. Once in the dark chamber the rat was given a 1.0-mA, 1-second inescapable shock. On the next 2 days (retention) the rat was again placed in the lighted side and timed for dark-side reentry up to a limit of 3 minutes. Rats were tested at 55 to 57 days of age.

| Treatment | Spontaneous choice alternation frequency (%) | Biel water maze | | N* | Active avoidance response | Passive avoidance retention | | N† |
|---|---|---|---|---|---|---|---|---|
| | | Straight channel time (minutes) | Total cul-de-sac errors | | | Day 1 | Day 2 | |
| Prochlorperazine | 71 | 0.19 ± 0.02 | 120.8 ± 12.8 | 22 | 31.5 ± 1.3 | 100.3 ± 23.7 | 65.4 ± 25.2 | 13,10 |
| Fenfluramine | 69 | 0.18 ± 0.10 | 125.7 ± 11.0 | 37 | 30.0 ± 1.8 | 115.8 ± 17.2 | 70.7 ± 18.2 | 16,19 |
| Propoxyphene | 71 | 0.15 ± 0.01 | 95.1 ± 9.0 | 32 | 32.9 ± 0.8‡ | 80.4 ± 18.9 | 68.3 ± 18.0 | 18,17 |
| Vitamin A | 79 | 0.22 ± 0.02‡ | 129.0 ± 11.2 | 30 | 33.4 ± 1.0‡ | 101.6 ± 21.4 | 96.2 ± 21.9 | 17,14 |
| Saline | 69 | 0.16 ± 0.02 | 112.6 ± 10.5 | 42 | 29.4 ± 1.1 | 109.3 ± 17.8 | 84.4 ± 15.7 | 24,20 |

*Number of subjects tested in spontaneous choice alternation and Biel water maze. †Number of subjects tested in active and passive avoidance, respectively. ‡$P < .05$.

paddling on day 6 ($P < .05$), and there was evidence of more severe impairment on day 8. Swimming angle development was delayed to a similar degree in both the Ffl and Pp groups ($P < .05$); these animals swam with their heads completely submerged on day 8, whereas controls had advanced to the point at which their noses and much of their heads were above the water. Offspring in the vitamin A group were even more delayed on this measure, since they swam with heads and noses submerged on day 8 ($P < .01$), and the tops of their heads were not held above the water even by day 10 ($P < .01$).

Negative geotaxis reflects both motor development and activity (Fig. 4). The vitamin A group showed the largest and most persistent departure from controls, exhibiting lethargic turning times ranging from 20 to 44 percent slower than controls on days 6 to 10 ($P < .01$). However, the departures were delays rather than inabilities, for these animals achieved levels of performance similar to controls by day 12. The Ffl group showed a more transient lag on 1 day (21 percent) (day 8, $P < .01$). In contrast, the Pz and Pp groups showed an initial 22 percent enhancement of turning performance on day 6 compared to controls ($P < .01$).

All groups except those that received Pz showed significant alterations in pivoting time, though only the vitamin A group actually completed a lower number of 90° turns (Fig. 5). On both measures the vitamin A group showed impaired performance that extended across all 3 days of testing ($P < .05$). The Pp group showed a higher peak in pivoting activity on day 9 than controls ($P < .05$), and a similar though not significant trend on day 11. The Ffl group showed the most unusual pattern, exhibiting diminished pivoting on day 7 and increased pivoting on days 9 and 11 ($P < .05$). The persistence of high levels of pivoting after day 9 is usually regarded as a reflection of delayed forward locomotor development, since in normal animals pivoting diminishes beyond this age. However, the heightened pivoting activity on day 9 in the Pp and Ffl groups suggests that hyperactivity may also be a factor. The pattern in the vitamin A group is quite different and seems to reflect a general delay in the onset of pivoting behavior.

Neither Pz nor Pp had any significant effect on auditory startle development, that is, the day on which all pups startled in response to a 0.3-second signal from an automobile horn. The group means (± standard error) were: Pz = 13.6 ± 0.7, Pp = 12.9 ± 0.4, and controls = 13.9 ± 0.5. No data were available for Ffl and vitamin A groups because of a mechanical failure in the apparatus.

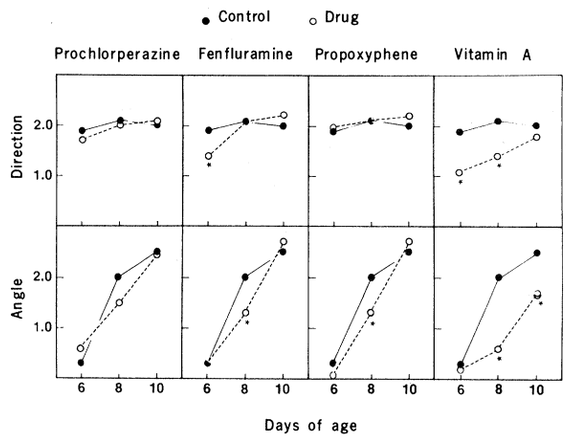


Fig. 3. Swimming development. On days 6, 8, and 10 each pup was placed in a tank of water (26.7°C) for a period of 5 to 15 seconds and rated for three aspects of swimming: direction, angle in the water (or head position), and use of limbs. Scoring for direction was: 0, sank; 1, floated; 2, swam in circle or arc; 3, swam in a straight or nearly straight line. Scoring for angle was: 0, submerged; 1, nose at surface; 2, nose and top of head at or above surface, but ears still below surface; 3, same as 2 except with waterline at mid-ear level; and 4, same as 3 except with waterline at bottom of ears. Scoring for limb usage was: 0, no paddling; 1, paddling with all four limbs; 2, paddling with hind limbs only, forelimbs held stationary (*7*).

In preweaning open-field testing, females were consistently more active than males ($P < .01$). Since there were no interactions between sex and other variables, this dimension was combined in Fig. 6. The Pp animals ambulated more ($P < .05$), reared more ($P < .05$), and had shorter starting latencies than controls ($P < .05$). The Pz animals showed a trend toward increased ambulation ($P < .10$) but no other effects. The Ffl animals showed no changes in ambulation or rearing but had significantly longer starting latencies than controls ($P < .05$). The vitamin A group showed only one effect, this being increased rearing activity ($P < .05$).

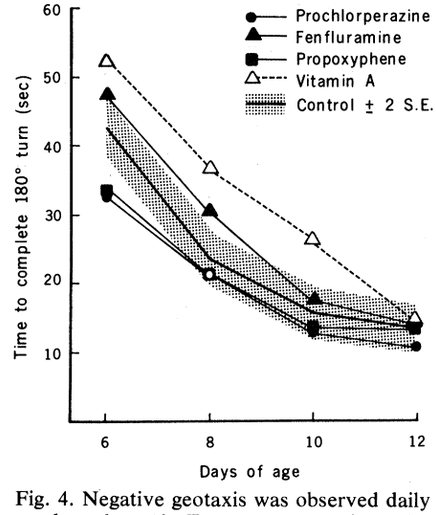


Fig. 4. Negative geotaxis was observed daily on days 6 to 12. Test pups were timed for completing a 180° turn when placed in a head-down position on a 25° inclined plywood surface. Pups were given one trial per day and allowed a maximum time of 60 seconds per trial.

In postweaning open-field testing (Table 2), the Pz animals showed no overall change in ambulation, despite the fact that Pz males and females showed a greater disparity in activity than the controls or any other drug group. This effect was manifested in a significant treatment by sex interaction ($P < .05$). The Ffl ($P < .01$) and the Pp ($P < .05$) groups both ambulated more than controls, regardless of sex, whereas in the vitamin A group only the males showed increased ambulation ($P < .05$). Regarding rearing frequency, the Pz group reared less, and all other groups reared more, than the saline controls irrespective of sex ($P < .01$ and $P < .05$, respectively). There were no significant effects for starting latencies. Animals in the Ffl and vitamin A groups defecated more often than controls (both $P < .05$).

Table 3 shows that there were no significant effects on spontaneous alternation rate, though the vitamin A group showed a trend toward increased alternation. In the Biel water maze the group given vitamin A took longer to complete the straight channel swimming than controls ($P < .01$), reflecting a performance deficit, but there were no significant differences in problem-solving in any of the groups as measured by maze errors. In active avoidance testing both the Pp and vitamin A groups showed comparable and significant increases in avoidance acquisition (both $P < .05$). This reflects about a 10 percent facilitation of normal avoidance acquisition rates. There were no significant differences in passive

avoidance training or retention latencies in any group.

The performance of each drug-treated group on the rotorod is shown in Table 4 as a percentage of the controls' performance. Overall, the Pz, Pp, and vitamin A groups showed significantly poorer rotorod performance than controls (all $P < .01$). In all cases this effect was more pronounced in the males than in the females ($P < .01$). Of all groups only the Pp group showed a deterioration in performance on this task from the first to the second day of testing.

Biochemical and histologic measurements are shown in Table 5. There were no significant differences in body weight at the end of the experiment when the rats were 70 days of age. There was, however, a significant reduction of 5 percent in total brain weight of the Ffl group ($P < .05$). There were no significant effects in any of the groups on the amount of DNA per gram of tissue, on total DNA, or on the amount of DNA per gram of protein. Neuronal cell counts in the cerebellum were unchanged, but there was a significant 25 percent increase in the neuronal density in the hippocampus in the Pp and vitamin A groups ($P < .05$). The significance of these hippocampal effects is not clear.

Previous research in behavioral teratology suggests the following working principles: (i) Agents that are teratogens of the central nervous system are also behavioral teratogens even when given at doses below which major malformations are induced in any members of the litter (*11-13*). (ii) The pattern of behavioral effects is dependent on the stage of development at which the agent is administered (*14. 15*). (iii) The period of fetal susceptibility to effects producing behavioral abnormalities is broader than that for producing malformations of the central nervous system (*14*), even though the period of maxiumum susceptibility is

Table 4. Rotorod performance as a percentage of the time spent on the rod by the saline controls. There were 28 males and 29 females in the control group. The rod was 11.4 cm in diameter with its surface roughened by a mixture of paint and sand. All rats were given two trials per day on two consecutive days between days 60 and 65. On each trial the rat was placed on the rod and gradually accelerated until it reached 30 revolutions per minute at which point the trial was timed until the rat fell (up to a limit of 3 minutes).

| Treatment | Males | | | Females | | | Overall |
|---|---|---|---|---|---|---|---|
| | *N* | Day 1 | Day 2 | *N* | Day 1 | Day 2 | |
| Prochlorperazine | 23 | 59.0 | 57.0 | 26 | 80.5 | 138.2 | 83.7* |
| Fenfluramine | 38 | 87.0 | 108.4 | 33 | 104.5 | 148.0 | 112.0 |
| Propoxyphene | 31 | 64.4 | 42.6 | 26 | 91.6 | 88.8 | 71.8* |
| Vitamin A | 31 | 65.4 | 79.3 | 32 | 88.1 | 96.4 | 82.3* |

*$P < .01$.

Table 5. Brain weight, DNA, neurohistology, and body weight at 70 days of age in selected offspring from each litter. Weight determinations were made on at least two males from each litter. The DNA and protein were determined on one male from the first five litters in each treatment group. Neuron cell counts per unit area at a magnification of ×500 in hematoxylin and eosin-stained sections were made on one male from each litter; however, the final number of litters represented is lower than the number taken in some groups because of the elimination of subjects in which the tissue was not adequately fixed. The results are expressed as means ± standard error.

| Treatment | Weight | | | DNA | | Cell counts | | |
|---|---|---|---|---|---|---|---|---|
| | Body (g) | Brain (mg) | *N* | DNA (μg/mg protein) | *N* | Cerebellum | Hippocampus | *N* |
| Prochlorperazine | 275 ± 9 | 1773 ± 20 | 16 | 16.7 ± 1.2 | 5 | 320 ± 17 | 18 ± 1 | 7 |
| Fenfluramine | 266 ± 8 | 1706 ± 20* | 30 | 15.8 ± 0.2 | 5 | 290 ± 9 | 15 ± 1 | 10 |
| Propoxyphene | 271 ± 6 | 1830 ± 17 | 26 | 16.4 ± 0.9 | 5 | 339 ± 14 | 20 ± 1* | 9 |
| Vitamin A | 256 ± 9 | 1803 ± 27 | 23 | 16.1 ± 0.9 | 5 | 330 ± 8 | 20 ± 1* | 6 |
| Saline | 267 ± 6 | 1790 ± 19 | 32 | 16.0 ± 0.8 | 5 | 301 ± 12 | 16 ± 1 | 12 |

*$P < .05$.

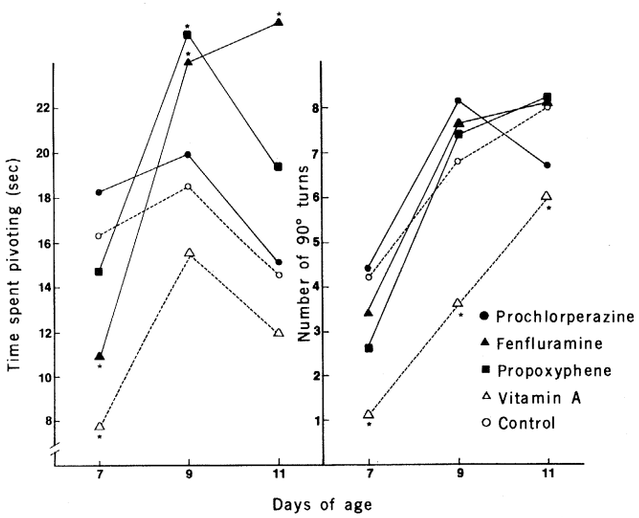


Fig. 5 (left). Locomotor development. Pivoting was observed on days 7, 9, and 11. Test pups were observed for 60 seconds and the number of seconds of pivoting and 90° turns was recorded.

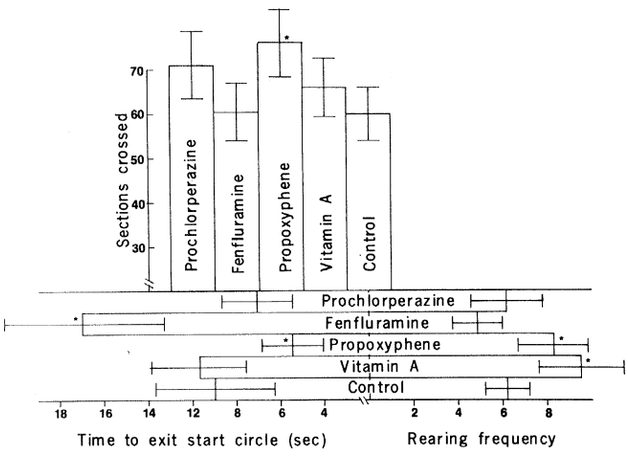


Fig. 6 (right). Tests of rats in open field prior to weaning. Half of the males and half of the females from each litter were observed for 3 minutes per day in a circular open field (45.7 cm in diameter) in which the floor was marked off in 20 sectors. Rats were scored for sector crossings, number of rearings, and latency to exit the central start circle on days 15 to 17 (*7*).

similar to that for morphological susceptibility of the central nervous system (*15*). (iv) Agents which are teratogenic to non-central nervous system structures are not behavioral teratogens (*16*). (v) Genotype interacts with the agent in determining the behavioral effects [see (*12*, *13*)]. (vi) The extent of the behavioral effect is dependent on the dose of the agent (*11*). The results of our experiments allow us to add two more working principles. (vii) Some agents that are behavioral teratogens are apparently not structurally teratogenic. (viii) Some behavioral teratogens may be called "pure," in that they can produce behavioral abnormalities without accompanying alterations in growth or other physical measures of postnatal vitality.

The data suggest that among the drugs tested herein, propoxyphene appears to meet the criteria for being a pure behavioral teratogen. This conclusion is at best preliminary and should not be extrapolated to humans. Prochlorperazine and fenfluramine were also found to be behavioral teratogens, but they had reproductive and growth effects that foreshadowed the untoward behavioral outcomes. It was not anticipated, however, that the drug with the most severe reproductive effects, prochlorperazine, would show the fewest behavioral effects in the survivors. This observation adds credence to the tenet that behavior represents a different sphere of effects not readily predicted from traditional toxicological end points, at least with current methods.

### References and Notes


1. D. E. Hutchings, in *Studies on the Development of Behavior and the Nervous System*, vol. 4, *Early Influences*, G. Gottlieb, Ed. (Academic Press, New York, 1978), p. 7.
2. K. L. Jones and D. W. Smith, *Lancet* **1973-II**, 999 (1973); S. K. Clarren, E. C. Alvord, S. M. Sumi, A. P. Streissguth, *J. Pediatr.* **92**, 64 (1978); S. K. Clarren and D. W. Smith, *N. Engl. J. Med.* **298**, 1063 (1978); A. P. Streissguth, C. S. Herman, D. W. Smith, *J. Pediatr.* **92**, 363 (1978); J. W. Hanson, A. P. Streissguth, D. W. Smith, *ibid.*, p. 457; J. W. Hanson and D. W. Smith, *ibid.* **87**, 285 (1975); G. L. Feldman, D. D. Weaver, E. W. Lovrien, *Am. J. Dis. Child.* **131**, 1389 (1977).
3. S. R. Kandall, in *Drug Abuse in Pregnancy and Neonatal Effects*, J. L. Rementaria, Ed. (Mosby, St. Louis, 1977), p. 116; Y. Brackbill, *Dev. Psychobiol.* **10**, 529 (1977).
4. K. T. Szabo and R. L. Brent, *Lancet* **1974-I**, 565 (1974).
5. J. A. Harvey and S. E. McMaster, *Commun. Psychopharmacol.* **1**, 3 (1977).
6. D. L. Gilbert, B. V. Franko, J. W. Ward, G. Woodward, K. D. Courtney, *Toxicol. Appl. Pharmacol.* **19**, 705 (1971); J. L. Emmerson, N. V. Owen, G. R. Koenig, J. K. Markham, R. C. Anderson *ibid.*, p. 471; J. G. Wilson, in *Handbook of Teratology*, J. G. Wilson and F. C. Fraser, Eds. (Plenum, New York, 1977), vol. 1, p. 309.
7. C. V. Vorhees, R. E. Butcher, R. L. Brunner, T. J. Sobotka, *Toxicol. Appl. Pharmacol.*, in press; C. V. Vorhees, R. L. Brunner, C. R. McDaniel, R. E. Butcher, *Teratology* **17**, 271 (1978); R. L. Brunner, M. S. McLean, C. V. Vorhees, R. E. Butcher, *ibid.* **18**, 379 (1978); R. L. Brunner, C. V. Vorhees, L. Kinney, R. E. Butcher, *Neurobehav. Toxicol.* **1**, 79 (1979).
8. S. Zamenhof, H. Bursztyn, K. Rich, P. J. Zamenhof, *J. Neurochem.* **11**, 505 (1964); O. H. Lowry, N. J. Rosenbrough, A. L. Farr, R. J. Randall, *J. Biol. Chem.* **193**, 265 (1951).
9. R. E. Kirk, *Experimental Design: Procedures for the Behavioral Sciences* (Brooks/Cole, Belmont, Calif., 1968); C. Y. Kramer, *Biometrics* **12**, 307 (1956).
10. J. P. Guilford, *Fundamental Statistics in Psychology and Education* (McGraw-Hill, New York, 1965).
11. R. E. Butcher, C. V. Vorhees, C. A. Kimmel, *Nature (London) New Biol.* **236**, 211 (1972); R. E. Butcher, W. J. Scott, K. Kazmaier, E. J. Ritter, *Teratology* **7**, 161 (1973); R. E. Butcher, K. Hawver, K. Kazmaier, W. Scott, in *Basic and Therapeutic Aspects of Perinatal Pharmacology*, P. L. Morselli, S. Garattini, F. Sereni, Eds. (Raven, New York, 1975), p. 171; C. A. Kimmel, R. E. Butcher, C. V. Vorhees, H. J. Schumacher, *Teratology* **10**, 293 (1974); J. M. Spyker, S. B. Sparber, A. M. Goldberg, *Science* **177**, 621 (1972).
12. R. E. Butcher, R. L. Brunner, T. Roth, C. A. Kimmel, *Life Sci.* **11**, 141 (1972).
13. C. V. Vorhees, *Teratology* **10**, 269 (1974).
14. P. M. Rodier, *ibid.* **16**, 235 (1977); D. E. Hutchings, J. Gibbon, M. A. Kaufman, *Dev. Psychobiol.* **6**, 445 (1973); D. E. Hutchings and J. Gaston, *ibid.* **7**, 225 (1974).
15. P. M. Rodier, S. S. Reynolds, W. N. Roberts, *Teratology* **19**, 327 (1979); C. V. Vorhees *et al.*, *ibid.* **17**, 271 (1978).
16. R. E. Butcher, K. Hawver, T. Burhacher, W. Scott, in *Aberrant Development in Infancy*, N. Ellis, Ed. (Erlbaum, Potomac, Md., 1975), p. 147.
17. R. E. Butcher, C. V. Vorhees, C. W. Kindt, K. J. Kazmaier-Novak, H. K. Berry, *Pharmacol. Biochem. Behav.* **7**, 129 (1977); W. C. Biel, *J. Genet. Psychol.* **56**, 439 (1940).
18. L. Kinney and C. V. Vorhees, *Pharmacol. Biochem. Behav.* **10**, 437 (1979).


19. Preliminary reports of these data were presented at the Teratology Society meetings, Mackinac Island, Mich., June 1978, the Society for Research in Child Development, San Francisco, Calif., March 1979, and the Environmental Protection Agency Workshop on Methods in Behavioral Toxicology proceedings, San Antonio, Tex., April 1979. This work was supported by FDA project 223-76-3026 and NIH grant HD-05221. We acknowledge S. Krop of the FDA, H. K. Berry, director of the Division of Inborn Errors of Metabolism, and L. Jonas, statistical assistant, for their invaluable contributions to this project. We also thank Smith Kline & French, A. H. Robins, and Eli Lilly & Co. for their donations of prochlorperazine, fenfluramine, and propoxyphene.


# Geographic Constraints on Women's Careers in Academia


Gerald Marwell, Rachel Rosenfeld, Seymour Spilerman


Recent federal legislation (*1*) requires institutions of higher education to correct their discriminatory practices against women. Court decisions have made it clear that "statistics can be used as *prima facie* evidence of discrimination" (*2*). The statistics to show that women have fared less well than men in academia are available in quantity. Women have been at lower academic ranks and in less prestigious positions, have taken longer to advance, and have received lower pay than men (*3*-*9*). As many writers on this subject realize, factors other than the policies and decisions of educational institutions contribute to these differences. Attention has tended to focus on personal attributes such as age and publication record. Still, some commentators [see, for example, (*10*) and (*11*)] imply that discrimination accounts for all status differences between male and female academics, and others attribute all the residual differences between males and females, after personal attributes are taken into consideration, to the same source (*9*).

In contrast, we shall argue that a considerable part of the disparity between men and women in academic status and earnings derives from neither of those sources but from the disadvantages that marriage imposes on the women. In a two-career family many crucial decisions (for example, whether or not to have children and where to reside) can have an adverse effect on one or both careers. In this situation, two-career couples will be at a handicap, in comparison with one-career couples, with respect to maximizing job prospects. We will argue that, in the aggregate, in academia women's careers suffer more as a result than men's.

The factors of particular interest in


Dr. Marwell and Dr. Spilerman are professors of sociology, the former at the University of Wisconsin, Madison 53706, the latter at Columbia University, New York 10027. Ms. Rosenfeld is a senior study director at the National Opinion Research Center, University of Chicago, Chicago, Illinois 60637, and assistant professor of sociology (on leave), McGill University, Montreal, Canada H3C 3G1.




0036-8075/79/0921-1225$01.50/0