ORIGINAL ARTICLES

Influence of Prepartum Chronic Ultramild Stress on Maternal Pup Care Behavior in Mice

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Background: *Stress administered to pregnant rodents has been shown to lead to biological and behavioral alterations in both mother and pups. Most of these stress procedures use noxious stressors. Chronicity is obtained by simple repetition of one or two stressors and may be more representative of moderate daily stress experienced during normal life than stress during severe life events. The effects of this procedure were assessed by observing maternal pup-care behavior and testing maternal aggression.*

Methods: *The subjects included eight controls and eight stressed B6D2F1 females. Chronic ultramild stress was applied from mating to postpartum day (PD) 0. Pup-care behavior was observed on PD 1. Maternal aggression against a male intruder was tested on PD 8, which corresponds to the peak in the display of this behavior.*

Results: *Prenatal stress did not affect basic pup-care behavior, but dramatically impaired defense behavior designed to protect the pups from an external attacker.*

Conclusions: *The results suggest that gestating females subjected to chronic ultramild stress suffer from a long-lasting decline in recognition of external distress cues either from a resident intruder and/or their own litter. It is assumed these effects are due to the chronicity of the stress rather than its severity.* Biol Psychiatry 2000;47: 858–863 © *2000 Society of Biological Psychiatry*

Key Words: Stress, mouse, pup-care behavior, maternal aggression, animal models of stress-related disorders

Introduction

The different types of stress procedures applied to pregnant rodents are well documented and have been shown to produce numerous behavioral and biological dysfunctions, both in the mother (Becker and Kowall 1977; Power and Moore 1986) and in the pups (Barlow et al 1978; Henry et al 1994; Maccari et al 1995; Peters 1988; Politch and Herrenkhol 1984). Some of these stress procedures are, to use the terms chosen by the authors, *mild* or *low*. They include chronic daily cutaneous injections (Grimm and Frieder 1987) and "low immobilization" in a plastic cylinder (Rojo et al 1985). The category could also include the simple placement of the animal in a new environment (Maestripieri et al 1991). Other repeatedly used stressors are more intense and include sleep deprivation (Suchecki and Palermo Neto 1991), hyperthermia (Shiota and Kayamura 1989), and immersion in cold water (Guo et al 1993), or even overtly noxious stressors such as the application of an electric current (Becker and Kowall 1977). In addition to these physical types of stress procedures, other protocols can be used to modify the social environment—e.g., certain overcrowding protocols (Harvey and Chevins 1985). However, most of the stress models are composite procedures combining two or (very occasionally) more stressors (Fride and Weinstock 1988; Harvey and Chevins 1985; Peters 1986). Of these different models, the model proposed by Ward (Ward 1972; Ward and Weisz 1984) involving physical constraint in a plastic cylinder under strong light remains the most commonly used (Maccari et al 1995; Vallée et al 1996, 1997). Other compound protocols use various stressors applied in sequence and repeated on a daily basis (De Fries et al 1967). These stress protocols have been applied over the entire gestation period (Rojo et al 1985) or over the first (Suchecki and Palermo Neto 1991) or second halves (Szuran et al 1994).

The important observations to be drawn from this brief review are the general use of a noxious stressor and chronicity obtained by simple repetition of one or two stressors. Protocols for "chronic mild (unpredictable) stress" (CMS) as initiated by Katz et al (1981) and later adapted by Willner (Willner 1997; Willner et al 1987) do not yet appear to have been applied to gestating females.

These studies have shown that rats exposed to a CMS regimen, comprising "mild" and "unpredictable" stressors administered over a few weeks, exhibited marked behavioral disturbances. These disturbances persisted longer after cessation of the stress procedure than after an acute or repeated physical stress (Willner 1997). The major interest of the model was the demonstration that the

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Table 1. Stress Regimen

	Morning (1 hour)	Afternoon (2 hours)	Night (6:00 PM to 9:00 AM)
Monday	Confinement	Cage tilt (30°)	Difficult access to food
Tuesday	Cage tilt	Paired housing	Overnight illumination
Wednesday	Cage tilt	Confinement	Soiled cage
Thursday	Confinement	Paired housing	Cage tilt
Friday	Confinement	Cage tilt	Reversed light/dark cycle
Weekend	Reversed light/dark cycle	Reversed light/dark cycle	Reversed light/dark cycle

uncertainty generated by continuous exposure to novel nontraumatic events may incur severe consequences (Cabib 1997).

None of the different versions of the CMS protocol can be applied to gestating females. The CMS models include long periods of exposure to stroboscopic light, whereas 17- to 20-hour periods of food and water deprivation may be harmful to pregnant animals. Nevertheless, when properly adapted to the situation, this type of stress regimen (mild and chronic, and allegedly unpredictable because of the variety of the stressors) could be of interest for the study of biological and behavioral disorders triggered by environmental factors during gestation, as they could provide an animal model of the "etiological role of life events" (Willner 1990). During the gestational state they may be of etiologic significance in human pre- and postpartum disorders (O'Hara 1986; O'Hara et al 1991).

Our study was designed to investigate the effects on maternal behavior of a modified CMS procedure, eliminating any noxious stressors or food and water deprivation (i.e., a CUMS procedure applied to female mice during pregnancy).

The term *maternal behavior* in rodents covers a wide range of behavior patterns that can be divided into prenatal care (e.g., nest building before parturition) and neonatal or postnatal care, such as lactation, pup transportation to the nest, pup licking, and aggression against intruders (see Cohen-Salmon 1988 for review). In our study, maternal behavior was operationalized by observing and quantifying the following variables: 1) nest building, 2) pup weight, 3) retrieval of pups removed from the nest by the experimenter, and 4) maternal aggression against a male intruder during the lactating period.

Methods and Materials

Animals and Mating Procedure

Sixteen virgin female B6D2F1 mice were provided by Iffa-Credo (Lyon, France). Aged 8 weeks on arrival in the laboratory, they were housed in groups of four per cage in our animal research facility and kept on a 12-hour light/dark cycle, at 22 ± 2° C, with food and water ad libitum. All females were mated at 16 weeks with a male of the same genotype. The females were placed in a cage with two females per one male for 4 days. At the end of this 4-day period, the females were divided into two groups of eight. The first group (control) was left undisturbed during the entire gestation period. The females were housed in conditions as previously described for the first 2 weeks after the mating period and were then housed individually in cages measuring 38 × 22 × 15 cm and containing sawdust (1 L) and cotton-wool (1 g). Food and water were provided ad libitum. The second group (stressed) was subjected to a CUMS procedure from the end of the mating period to postpartum day (PD) 0. After a few days it transpired that one control female was not gestating and as a result only seven subjects were included in the control group, as opposed to eight in the stressed group. The eight females in the stressed group were housed individually in a stress room maintained at 22 ± 2° C, with food and water ad libitum. Two weeks after the mating period (i.e., 4 to 7 days before parturition), all females were placed in individual cages measuring 38 × 22 × 15 cm, with sawdust and cotton-wool as mentioned above. Food and water were available ad libitum.

Chronic Ultramild Stress Procedure

In this CUMS procedure, no food or water deprivation was applied to the subjects because of the consequences for the neurobehavioral development of the pups (Ward and Wainwright 1988). Similarly, any clearly noxious stimuli, such as long sequences of stroboscopic light or throbbing noise (as used by Willner et al 1987 and Gorka et al 1996), were eliminated. In addition, 2-hour stress-free periods were scheduled between each diurnal stressor.

The stress regimen consisted of six ultramild stressors delivered over a period of 1 or 2 hours (Table 1): periods of cage tilt (30°), confinement in a small cage (11 × 8 × 8 cm), and paired housing (one period in each cage during the first 2 weeks, and in a new cage during the third week); one overnight period of difficult access to food; one overnight period of permanent light; and one overnight period in a soiled cage (50 mL water in 1 L of sawdust bedding). Unlike previous CMS protocols, the stress periods were always separated by stress-free intervals of at least 2 hours, to avoid any habituation process. The animals were also placed on a reversed light/dark cycle from Friday evening to Monday morning. This procedure was scheduled over a 1-week period and repeated throughout the period from the time of separation from the male until parturition (approximately 3 weeks).

Pup-Retrieval Test

This procedure, during which the female's behavior towards her pups after they have been removed from the nest by the experimenter can be observed, has often been cited as an accurate marker of maternal care (Carlier et al 1982; Cohen-Salmon 1988; Cohen-Salmon et al 1985). Some of the variables measured during the procedure show a strong correlation with pup survival (Cohen-Salmon et al 1985).

According to a previously described procedure (Carlier et al 1982; Cohen-Salmon et al 1985), observations were made 24 ± 10 hours after parturition. While the female was isolated in a separate cage outside the parturition cage, the pups were removed and placed together 20 cm from the nest. Observations commenced once the female had been returned to the nest by the experimenter. Over the 900-sec period after the female's return to the nest, the following three observations were measured: 1) the time elapsed between the first contact and the picking up of the first pup in the mouth ("first retrieval"; a maximum score of 900 sec was recorded when none of the pups was retrieved); 2) the number of times the female moved away from one of her pups, positioned outside the nest, without transporting it ("moves away"); and 3) the percentage of females remaining in the nest with all their pups for 2 consecutive minutes during the 15-min observation period ("nest with all pups").

At the end of the test, the pup body and nest weights were noted. The pups were weighed 2 and 8 days after parturition.

Maternal Aggression Test

Maternal aggression against intruders was one of the first recognized components of "maternal behavior" (Causey and Waters 1936). Such behavior may be a factor in enhancing survival of the pups by protecting them against potentially infanticidal conspecifics (Maestripieri and Alleva 1990). According to Ostermeyer (1983), a display of intensely aggressive behavior towards conspecifics is one of the main characteristics distinguishing "maternal" from "non-maternal" female rodents. Genotype, anxiety, and a number of environmental variables (e.g., the test environment, the physical and physiologic characteristics of the opponent) play major roles in modulating inter-individual variation in maternal aggressive behavior (see Maestripieri and D'Amato 1991 for review). Aggression is low immediately after parturition and increases throughout the period of lactation. The experiential and endocrine changes that occur during reproductive states appear to be a factor in this increased aggression (Ghiraldi et al 1993).

All females in both groups were tested for maternal aggression on PD 8, which, according to Ostermeyer (1983), is the first day after the peak display of maternal aggression. The maternal aggression test was based on the procedure of Maestripieri et al (1991). Sexually naive adult BALB/c male mice were used as intruders. The BALB/c male was placed in the home cage of the female in the presence of her litter for 10 min. Each test session was recorded on videotape and subsequently analyzed for behavioral scoring. Each intruder was used only once.

The following behavioral features were recorded for both the intruder and the female: 1) number of lunges (lunges were defined as rapid thrusts toward the intruder, falling short of physical contact), 2) number of attacks (attacks were defined as bouts of fighting, characterized by biting or intense body contact), 3) time spent in the nest, 4) number of tail-rattling episodes, 5) number of pup retrievals (by the female), and 6) pup survival at the end of the test.

All behavioral observations were performed blind with respect to the stress condition.

Ethical Considerations

All procedures described in this study complied with the ethical guidelines laid down by the French Ministry of Agriculture. Taking into account the needs of our study, care was taken to minimize the suffering caused to the animals (both adults and pups). As the presence of the whole litter is required to test maternal aggression (Elwood 1991), the use of a single stimulus pup was not feasible. Maternal aggression behavior was considered to be the result of an interaction between the female, her litter, and the intruder. Any intervention by the experimenter when an animal is clearly attacked would disrupt the entire behavioral pattern. Following Elwood's (1991) recommendations, all subjects were humanely killed immediately after the maternal aggression test.

Statistical Analyses

SAS software (SAS Institute Inc. 1990) was used for all statistical analyses. Data on litter size and nest weight were compared by one-way analysis of variance (ANOVA). Data on pup body weight was compared by ANOVA with nested structure (stress and mother [stress]) to eliminate the effect of the litter size. All duration data were analyzed by *t* tests. Data on the proportion of subjects presenting behavioral reactions were compared using Fisher's Exact Test (two-tailed). Values of $p < .05$ were considered significant.

Results

The data on pup body weight and variables measuring maternal behavior in the pup-retrieval test are summarized in Table 2. Pup body weight on PD 1 was lower if the mother was stressed during pregnancy. This effect was independent of litter size and disappeared on PD 2.

No statistically significant difference between stressed and control groups was found for the nest weight on PD 1, or for any of the variables in the pup-retrieval test despite a tendency to increase the first retrieval latency.

The maternal aggression test results are summarized in Tables 3 and 4. With the exception of the time spent in the nest by the female or the intruder, the observations were analyzed in terms of the presence or absence of a behavioral event. This statistical choice was dictated by the structure of the data, and in particular by the large number of nil results showing the absence of any behavioral reaction (see Table 3). Consequently, statistics calculated

Table 2. Mean Values ± SE of Litter Size, Pup Body Weight, and Variables Measuring Maternal Behavior in the Pup-Retrieval Test for Stressed and Control Groups

	Females	
	Stressed	Controls
Pup body weight (g)		
PD 1	1.49 ± 0.014[a]	1.57 ± 0.019
PD 2	1.80 ± 0.018	1.83 ± 0.023
PD 8	4.39 ± 0.044	4.40 ± 0.057
Nest weight (g)		
PD 1	13.52 ± 0.98	11.35 ± 0.98
Pup-retrieval test		
First retrieval latency (sec)	10.82 ± 2.92	5.80 ± 1.01
Number of moves away	3.00 ± 1.1	1.7 ± 0.71
Nest with all pups (%)	100%	100%

PD, postpartum day.
[a] $p < .001$.

to reflect comparative proportions were chosen. To determine the thresholds of significance the two-tailed Fisher's Exact Test was used. The following observations can be made:

1. Stressed females, with only one exception, did not adopt a lunging posture ($\chi^2 = 5.4$, $p = .04$) and did not attack the male ($t = 3.87$; $p = .004$).
2. With only one exception, the males only attacked the pups if the female was suffering from stress. In other words, the males attacked the pups of stressed females more often ($\chi^2 = 11.43$, $p = .0001$), as the stressed females let the males into the nest more often.
3. With only one exception, the males did not display any tail rattling ($\chi^2 = 30.84$, $p = .007$) unless confronted by an attacking female.
4. With only one exception, stressed females displayed no tail rattling.

Table 3. Occurrence of Different Behavioral Events Displayed by Each Female and Male Intruder during the Maternal Aggression Test

	Behavior				
	Female			Intruders	
	Lunges	Attacks on males	Retrieving	Attacks on pups	Rattling
Stressed					
1			1	11	
2			7	29	
3			10	20	
4				9	
5			6	32	
6			12	17	
7	4	4		8	3
8			8	39	
Controls					
1	2				
2		28			1
3	1		1	2	
4	10	25			8
5		13			14
6	2	14			13
7	10	15			24

It can be noted that only one of the eight stressed females adopted any lunging or attacking postures, and that this was only when the male intruder displayed tail rattling to a stressed female. It was noted throughout the test that the mothers retrieved the pups scattered outside the nest by the intruder. This retrieving behavior occurred more often with stressed females ($p = .04$), which reflects both the higher incidence of pups being scattered by the male in the course of the test and the almost systematic retrieval of the pups to the nest by the mother during the test ($\chi^2 = 5.4$, $p = .04$), even when the male intruder was actually inside the nest.

Discussion

The first observation to note is that nest building, considered a prenatal maternal activity (Cohen-Salmon 1988), was not affected by the CUMS procedure. However, chronic exposure to the CUMS regimen during pregnancy had clear-cut effects on postnatal maternal behavior. Care giving, as operationalized by the variables recorded in the pup-retrieval test, did not seem to be statistically significant in relation to the effect of previous exposure to the CUMS procedure, despite the fact some maternal care patterns tended to be reduced. The situation was quite different in the maternal aggression test, in which the stress procedure dramatically impaired the mother's ability to protect offspring against an infanticidal conspecific, as shown by all the records of the variables measured in the test. To sum up, CUMS during gestation disrupted the mothers' ability to protect the pups (8 days after the end of the period of stress). Stressed females did not display any hostile behavior towards the intruder: they did not attack it, they let it inside the nest, and let it attack the pups. Maestripieri et al (1991), using two stressors differing in severity applied from day 4 to day 14 of gestation, evidenced a general tendency for stressed females to increase some maternal care patterns and decrease maternal aggression. These effects were clear-cut after the physical restraint stress, but significant in females subjected to a novel environment. The more pronounced effects of our stress procedure on maternal aggression suggest that the chronicity of stress or the failure to habituate to adverse events are more important than the physical severity of stressors.

Results obtained under conditions when the female was

Table 4. Proportion of Subjects Displaying Different Behavioral Events and Mean Values ± SE of Time Spent in the Nest by Females and Male Intruders during the Maternal Aggression Test

	Females	
	Stressed	Controls
Females		
Lunges	1/8[a]	5/7
Attacks on male	1/8[a]	5/7
Retrieving	6/8[a]	1/7
Time on nest (sec)	210 ± 29.0	159 ± 52.2
Intruders		
Attacks on pup	8/8[b]	1/7
Time on nest (sec)	188.5 ± 40.64[b]	24.57 ± 11.64
Tail-rattling behavior	1/8[a]	5/7
Pup survival (%)	60.67%[c]	100%

[a] $p = .04$, Fisher's Exact Test.
[b] $p = .001$, Fisher's Exact Test.
[c] $p = .0001$, Fisher's Exact Test.

subjected to intense repeated stress have shown that anxiety may underlie the difference between stressed and nonstressed mothers. Indeed, Maestripieri et al (1991) maintain that maternal aggression and its varying intensity may be due to the differences in the extent to which individuals perceive an aversive situation as being anxiogenic and try to cope with it. Pregnant mice subjected to a repeated aversive stressful experience (restraint stress) exhibited lower postpartum aggression, whereas repeated aversive single stress was found to enhance anxiety (Maestripieri et al 1991).

In the presence of an aggressive male intruder, the CUMS-treated mother did not appear to behave in a disorganized fashion, but rather in a way that was inappropriate to the situation. In fact, neither agitation nor freezing was observed when the male was treating the pups violently. On the contrary, the stressed female systematically brought the scattered pups back to the nest, following a perfectly "normal" sequence for pup retrieval, regardless of the fact that the pups, when returned to the nest, were nearly always confronted with the aggressor as a result of the mother's behavior. Rather than being an anxious type of reaction, the behavior appeared to be more of a perseverance of a normal behavior pattern with normal motor responses, but was inappropriate to the new situation created by the intrusion of the male into the mother–litter dyad. Moreover, in the study of Maestripieri et al (1991) anxiety scores were subjected to correlation analysis with maternal aggression, but not with maternal care patterns. It is indeed possible that anxiety may be the underlying cause of increasing maternal care in stressed females.

In this situation of attack, the stressed females reacted as if there were only one possible response. All the stressed females systematically retrieved any scattered pups, bringing them back to the nest occupied by the male intruder, and displayed a totally passive attitude to the intruder. Given the lack of any clear-cut effect of CUMS on variables reflecting basic maternal behavior (nest building and retrieval), it appears that the CUMS procedure only has an effect on maternal behavior patterns if a party outside the mother–litter unit is involved. This finding reveals an interesting anomaly and can give rise to a number of hypotheses offering explanations as to why the female does not respond in an appropriate manner. One possible argument concerns the mother–infant dyad and the system of communication. On a sensory level, it is well known that rodent pups placed in distressful situations (subjected to cold, physical attacks, pain, isolation outside the nest, hunger, handling, strange smells, etc.) will emit ultrasonic distress vocalizations (Cohen-Salmon 1988; Cohen-Salmon et al 1985; Ehret 1975; Noirot 1972). It may be that physiologic damage to the sensory systems of the pups or the mother could impair the ongoing efficiency of such a system. On a more cognitive level, possibilities may include stress-induced changes in problem-solving coping strategies. The analysis of all the variables shows that a female subjected to a CUMS procedure will display withdrawal behavior in her environment. This is most apparent when an element not party to the mother–litter unit is introduced. Such failure to respond to the environment in the face of a foreign intruder may be the expression of a more general indifference felt by stressed females to any modifications in their environment, and may be considered a relevant behavioral marker for changes induced by chronic exposure to mild stress during pregnancy.

It can be concluded that negative outcomes are less related to the severity than to the chronicity of the stress. The severe consequences of prenatal exposure to CUMS may be more representative of a moderate daily stress experienced during normal life than of a stress induced by severe life events. This raises the question of whether the gestational state is one of particular vulnerability to chronicity of stress.

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References

Barlow SM, Knight AF, Sullivan M (1978): Delay in postnatal growth and development of offspring produced by maternal restraint stress during pregnancy in the rat. *Teratology* 18: 211–218.

Becker G, Kowall M (1977): Crucial role of the postnatal maternal environment in the expression of prenatal stress effects in the male rats. *J Comp Physiol Psychol* 91:1432–1446.

Cabib S (1997): What is mild in mild stress? *Psychopharmacology* 134:344–346.

Carlier M, Roubertoux P, Cohen-Salmon C (1982): Differences in patterns of pup care in *Mus musculus domesticus*. I Comparisons between eleven strains. *Behavioral Neural Biol* 35:205–210.

Causey D, Waters RH (1936): Parental care in mammals with special reference to the carrying of young by the albino rat. *J Comp Psychol* 22:241–254.

Cohen-Salmon C (1988). What role does sensory perception play in the onset and maintenance of pup care behavior in laboratory rodents? *Eur Bull Cogn Psychol* 8:53–94.

Cohen-Salmon C, Carlier M, Roubertoux P, Jouhaneau J, Smal C, Paillette M (1985): Differences of patterns of pup care in mice. V Pup ultrasonic emissions and pup care behavior. *Physiol Behav* 35:167–174.

De Fries JC, Weir MW, Hegman JP (1967): Differential effects of prenatal maternal stress on offspring behavior in mice as function of genotype and stress. *J Comp Physiol Psychol* 63:332–334.

Ehret G (1975): Schallsignale der Hausmaus (*Mus musculus*). *Behaviour* 52:38–55.

Elwood RW (1991): Ethical implications of studies on infanticide and maternal aggression in rodents. *Anim Behav* 42:841–849.

Fride E, Weinstock M (1988): Prenatal stress increases anxiety and alters cerebral lateralization of dopamine activity. *Life Sci* 42:1059–1065.

Ghiraldi LL, Plonsky M, Svare B (1993): Post-partum aggression in mice: The role of ovarian hormones. *Horm Behav* 27:251–268.

Gorka Z, Moryl E, Papp M (1996): The effect of chronic mild stress on circadian rhythms in the locomotor activity of rats. *Pharmacol Biochem Behav* 54:229–234.

Grimm VE, Frieder B (1987): The effects of mild maternal stress during pregnancy on the behavior of rat pups. *Int J Neurosci* 35:65–72.

Guo A, Nappi RE, Griscuolo M, Ficarra G, Amram A, Trentini GP, et al (1993): Effect of chronic intermittent stress on rat pregnancy and postnatal development. *Eur J Obstet Gynecol* 51:41–45.

Harvey P, Chevins PF (1985): Crowding pregnant mice affects attack and threat behavior of male offspring. *Horm Behav* 19:86–97.

Henry C, Kabbaj M, Simon H, Le Moal M, Maccari S (1994): Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young adult rats. *J Neuroendocrinol* 6:341–345.

Katz RJ, Roth KA, Carroll BJ (1981): Acute and chronic stress effects on open-field activity in the rat: Implication for a model of depression. *Neurosci Biobehav Rev* 5:247–251.

Maccari S, Piazza V, Kabbaj M, Barbazanges A, Simon H, Le Moal M (1995): Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *J Neurosci* 15:110–116.

Maestripieri D, Alleva E (1990): Maternal aggression and litter size in the female house mouse. *Ethology* 84:27–34.

Maestripieri D, Badiani A, Puglisi-Allegra S (1991): Prepartal chronic stress increases anxiety and decreases aggression in lactating female mice. *Behav Neurosci* 105:663–668.

Maestripieri D, D'Amato FR (1991): Anxiety and maternal aggression in house mice (Mus musculus): A look at interindividual variability. *J Comp Psychol* 105:295–301.

Noirot E (1972): Ultrasounds and maternal behavior in small rodents. *Dev Psychobiol* 5:371–385.

O'Hara MW (1986): Social support, life events and depression during pregnancy and the puerperium. *Arch Gen Psychiatry* 43:569–573.

O'Hara MW, Schlechte JA, Lewis DA, Wright EJ (1991): Perspective study of postpartum blues. Biological and psychosocial factors. *Arch Gen Psychiatry* 48:801–806.

Ostermeyer M (1983): Maternal aggression. In: Elwood R, editor. *Parental Behavior of Rodents.* New York: Wiley, 151–179.

Peters DAV (1986): Prenatal stress increases the behavioral response to serotonin agonists and alters open field behavior in the rat. *Pharmacol Biochem Behav* 25:873–877.

Peters DAV (1988): Both prenatal and postnatal factors contribute to the effects of maternal stress on offspring behavior and central 5-hydroxytryptamine receptors in the rat. *Pharmacol Biochem Behav* 30:669–673.

Politch JA, Herrenkhol LR (1984): Effects of prenatal stress on reproduction in male and female mice. *Physiol Behav* 32:95–99.

Power KL, Moore CL (1986): Prenatal stress eliminates differential maternal attention to male offspring in Norway rats. *Physiol Behav* 38:667–671.

Rojo M, Marin B, Menendez-Paterson A (1985): Effects of low stress during pregnancy on certain parameters of the offspring. *Physiol Behav* 34:895–899.

SAS Institute Inc. (1990): *SAS/STAT User's Guide*, version 6, 4th ed, Vol 2. Cary, NC: SAS Institute.

Shiota K, Kayamura T (1989): Effects of prenatal heat stress on postnatal growth, behavior and learning capacity in mice. *Biol Neonate* 56:6–14.

Suchecki D, Palermo Neto J (1991): Prenatal stress and emotional response of adult offspring. *Physiol Behav* 49:423–426.

Szuran T, Zimmerman E, Welzl H (1994): Water maze performance and hippocampal weight of prenatally stressed rats. *Behav Brain Res* 65:153–155.

Vallée M, Mayo W, Dellu F, Le Moal M, Simon H, Maccari S (1997): Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: Correlation with stress-induced corticosterone secretion. *J Neurosci* 17: 2626–2636.

Vallée M, Mayo W, Maccari S, Le Moal M, Simon H (1996): Long-term effects of prenatal stress and handling on metabolic parameters: Relationship to corticosterone secretion response. *Brain Res* 712:287–292.

Ward IL (1972): Prenatal stress feminizes and demasculinizes the behavior of males. *Science* 175:82–84.

Ward IL, Wainwright PE (1988): Reductions in maternal food and water intake account for prenatal stress effects on neurobehavioral development of B6D2F2 mice. *Physiol Behav* 44:781–786.

Ward IL, Weisz J (1984): Differential effects of maternal stress on circulating levels of corticosterone, progesterone, and testosterone in male and female rat fetuses and their mothers. *Endocrinology* 114:1635–1644.

Willner P (1990): Animal models as simulations of depression. *Trends Pharmacol Sci* 12:131–136.

Willner P (1997): Validity, reliability and utility of the chronic mild stress model of depression. *Psychopharmacology* 134:319–330.

Willner P, Towell A, Sampson S, Sokholeous S (1987): Reduction of sucrose preference by chronic unpredictable mild stress and its restoration by a tricyclic antidepressant. *Psychopharmacology* 93:358–364.