23. A. J. Eichler, S. M. Antelman, and C. A. Black, *Psychopharmacology* **68**, 287 (1980).
24. G. V. Rebec and D. S. Segal, *Pharmacol. Biochem. Behav.* **13**, 793 (1980).
25. B. Costall and R. J. Naylor, in *Cocaine and Other Stimulants*, E. H. Ellinwood and M. M. Kilbey, Eds. (Plenum, New York, 1977), pp. 47–76.
26. Naive rats (Holtzman, 300 to 400 g) were housed individually in standard wire mesh cages for at least 2 weeks before the beginning of the experiment in order to facilitate stereotypy (*29*). Stereotypy was rated in home cages by an observer (unaware of the rats' group membership) for 1-minute periods at 15, 30, 45, 60, 90, 120, 150, and 180 minutes after injections of *d*-amphetamine sulfate (Sigma) dissolved in physiological saline. In testing the correlation between dose and ratings (slope, .4988; standard error, .503), rats were injected with 3.0 (N = 7), 4.0 (N = 10), 5.0 (N = 8), or 6.0 (N = 8) mg of *d*-amphetamine per kilogram of body weight. The rating scale was: 0, inactive (no movement); 1, intermittent activity; 2, continuous activity; 3, intermittent stereotypy (stereotyped sniffing, rearing, or repetitive head movements); 4, continuous stereotypy over wide area; 5, continuous stereotypy in a restricted area; 6, pronounced, continuous stereotypy in a restricted area (for example, repeatedly falling over from rearing or vigorous sniffing through the same few holes in the cage). No stereotyped biting, licking, or gnawing was observed during any of these experiments.
27. S. H. Snyder, *Arch. Gen. Psychiatry* **27**, 169 (1972).
28. R. M. Post and H. Rose, *Nature (London)* **260**, 731 (1976).
29. J. Scheel-Krüger, C. Braestrup, M. Nielson, K. Golembiowska, E. Mogilnicka, in *Cocaine and Other Stimulants*, E. H. Ellinwood and M. M. Kilbey, Eds. (Plenum, New York, 1977), pp. 373–407.
30. Rats were rated for 1-minute periods starting 15, 30, 45, 60, and 75 minutes after cocaine hydrochloride injection on the following scale: 0, inactive; 1, intermittent activity; 2, continuous activity; 3, stereotypic rearing; 4, intermittent stereotypic sniffing, repetitive head movements, or both, with periods of nonstereotypic behavior longer than 2 seconds; 5, intermittent stereotypic sniffing, repetitive head movements, or both with periods of nonstereotypic behavior shorter than 2 seconds; 6, continuous stereotypic sniffing, repetitive head movements, or both; and 7, continuous and restricted stereotypic sniffing, repetitive head movements, or both. In testing the correlation between dose and ratings (slope, .0867; standard error, .606), rats were injected with 20 (N = 12), 30 (N = 16), or 40 (N = 12) mg of cocaine per kilogram of body weight.
31. E. H. Ellinwood, A. Sudilovsky, L. M. Nelson, *Am. J. Psychiat.* **130**, 1088 (1973).
32. We do not mean to imply, nor do we suspect, that all forms of coping behavior affect the stress-induced sensitization to stimulants. It is more likely that different coping responses vary in effectiveness.
33. B. Angrist and A. Sudilovsky, in *Handbook of Psychopharmacology*, L. L. Iversen, S. D. Iversen, S. H. Snyder, Eds. (Plenum, New York, 1978), vol. 5, part 2, p. 99.
34. C. Van Dyke and R. Byck, in *Cocaine and Other Stimulants*, E. H. Ellinwood and M. M. Kilbey, Eds. (Plenum, New York, 1977), pp. 1–30.
35. We thank R. C. Drugan and T. B. Moye for their valuable assistance. This work was supported by NSF grants BNS-78-00508 and RSDA MH-00314 to S.F.

15 March 1982; revised 3 August 1982

Prenatal Food Restriction and Subsequent Weight Gain in Male Rats

A report by Ravelli *et al.* (*1*) has stimulated interest in the relation between maternal undernutrition and subsequent obesity in human male offspring. Jones and Friedman (*2*) presented data demonstrating the existence of a similar effect in Charles River male rats. Male offspring of rats restricted to 50 percent of prepregnancy food intake during the first two trimesters of pregnancy had enhanced weight gains and heavier fat pads at 160 days of age than rats born to mothers given free access to food. Here we comment on our attempts to mimic "the Dutch famine effect." Experimentally naïve rats (from Charles River Laboratory) were allowed to mate in our laboratory at St. Lawrence University. The females were then randomly placed in one of three groups: control (N = 7; free access to food), yoked (N = 5; daily feeding restricted to 50 percent of control intake), and 50 percent restricted [N = 6; daily feeding restricted to 50 percent of prepregnancy (PP) intake]. They remained on these diets for the first two trimesters of pregnancy. During the last trimester, all rats were given free access to powdered Charles River Laboratory Chow.

Weight changes during the first two trimesters of pregnancy were control, +81.3 ± 1.8 g (mean ± standard error of the mean); yoked, −5.6 ± 3.6 g; and 50 percent of PP, −40.8 ± 4.3 g. Dams in the yoked and 50 percent PP groups that were given free access to food during the last trimester showed hyperphagia for 1 day [analysis of variance: day 1 refeeding, $F(2, 16) = 4.67$, $P < .05$] and incomplete recovery of body weight. Litter size and weight and gestation period were constant across groups. On day 3 after parturition, litters were culled to six rats (three males, three females). Pups were weaned at 21 days of age and given free access to Charles River rat pellets. They were housed in group cages and exposed to a cycle of 12 hours of light and 12 hours of darkness at 22°C. Food intake was measured over four consecutive 24-hour periods when the pups were 30, 60, and 90 days of age. There were no significant differences in food intake among pups from dams in any of the three groups [$F(2, 41) = 2.36$, not significant (N.S.)]. However, at 120 days of age the body weights of male offspring of dams in the yoked and 50 percent PP groups were lower than the body weights of offspring of control dams. At 160 days of age, epididymal but not retroperitoneal fat pads of offspring of the yoked and 50 percent PP groups weighed less than the corresponding pads of offspring of control dams (see Table 1, experiment 1).

In a second experiment (at the Rockefeller University), we restricted the food intake of one group of pregnant, experimentally naïve Charles River rats to 50 percent of control intake (yoked) for the first two trimesters of pregnancy. Weight changes during the first two trimesters for the control (N = 5) and yoked dams (N = 3) were +80.0 ± 3.5 g and +10.0 ± 3.5 g, respectively. Litter size, weight of the pups, and gestation period did not differ significantly between the two groups. Litters were culled, weaned, and monitored for food intake as in the first experiment. Food intakes did not differ between the two groups [$F(1, 15) = 0.28$, N.S.]. Body weights at 120 days, and epididymal and retroperitoneal fat

Table 1. Mean (± standard error) body weights and weights of epididymal fat pads (EP) and retroperitoneal fat pads (RP) of male pups born to mothers in control, yoked, or 50 percent prepregnancy (PP) groups during the first two trimesters of pregnancy.

Group	Experiment 1				Experiment 2			
	Body weight at 120 days* (g)	Weight at 160 days (g)			Body weight at 120 days (g)	Weight at 135 days (g)		
		Body	EP†	RP		Body	EP	RP
Control	632.9 ± 9.8 N = 20	683.2 ± 24.5 N = 9	13.04 ± 1.0 N = 9	17.91 ± 1.4 N = 9	554.9 ± 20.8 N = 8	570.1 ± 18.2 N = 7	6.42 ± 0.9 N = 7	10.28 ± 1.7 N = 7
Yoked	580.1 ± 10.8 N = 15	626.3 ± 12.3 N = 8	9.04 ± 0.6 N = 8	13.14 ± 1.8 N = 8	569.2 ± 10.0 N = 9	598.4 ± 9.2 N = 9	5.58 ± 0.4 N = 9	11.71 ± 1.0 N = 9
50 percent PP	598.7 ± 18.0 N = 14	605.7 ± 26.2 N = 6	11.30 ± 1.1 N = 6	16.07 ± 2.3 N = 6				

*Analysis of variance, $F(2, 46) = 4.84$, $P < .05$. †$F(2, 20) = 5.61$, $P < .05$.

pad weights at 125 days did not differ significantly between the two groups (see Table 1, experiment 2.)

Thus, in two separate experiments, a 50 percent restriction in the food intake of pregnant rats during the first two trimesters did not enhance food intake, overall growth, or the growth of adipose tissue of male offspring. These findings contrast with those reported by Jones and Friedman (*2*), but this may be partially due to the use of different dietary protocols. Our rat offspring were fed only laboratory Chow, while theirs were switched to a high fat diet at 110 days of age. The effects on weight gain and adipose tissue described by Jones and Friedman (*2*) are therefore of great interest but are not an inevitable consequence of prenatal undernutrition: the conditions necessary to achieve them remain to be explained. Housing conditions, other environmental factors, and stress should certainly be considered.

MELVIN P. ENNS
MARY W. WILSON
St. Lawrence University, Canton, New York 13617
JOEL A. GRINKER
IRVING M. FAUST
Rockefeller University, New York 10021

References and Notes

1. G. P. Ravelli, Z. A. Stein, M. W. Susser, *N. Engl. J. Med.* **295**, 249 (1976).
2. A. P. Jones and M. I. Friedman, *Science* **215**, 1518 (1982).
3. The work was supported in part by NIH grants AM27980 to J.A.G. and AM20508 to I.M.F.

27 April 1982; revised 4 October 1982

That Enns *et al.* (*1*) could not replicate our finding (*2*) that the Dutch famine effect (*3*) can be reproduced in rats does not surprise us. Enns *et al.* used a yoked group whose diet was restricted to 50 percent of that of pregnant control rats given free access to food. Since rats increase food intake by approximately 80 percent over the course of pregnancy, these animals received much more food than mothers that were restricted to 50 percent of their intake before pregnancy. Compared to the study of Ravelli *et al.* (*3*) and the Dutch famine in which caloric intakes declined at least 50 percent, this more severe undernutrition is the most relevant manipulation.

In experiment 1 of Enns *et al.*, which was germane both to our experiment and the Ravelli findings, the food intake of one group of rats was restricted to 50 percent of the prepregnancy (PP) intake. It is puzzling that, upon refeeding, these undernourished animals increased their food intakes for only 1 day. In studies conducted 2 years ago (*4*) we found that mothers whose food intake was restricted to a similar extent increased their food intake upon refeeding well into the first week after parturition. More important, we also found that if mothers were not allowed to overeat after food restriction (that is, pair-fed to controls), the male offspring did not become frankly obese. It is unclear to us why, in the experiment of Enns *et al.*, the 50 percent PP restricted mothers did not compensate for previous food restriction. Nevertheless, it appears that Enns *et al.* have confirmed our findings showing the importance of compensatory overeating after food restriction.

We have reported (*4*) that increases in fat pad weight in previously undernourished rats do not occur if the rats have been maintained on Purina Chow. Our data indicated, as Enns *et al.* now suggest, that this aspect of the condition appears to result from an interaction between prenatal undernutrition and subsequent exposure to a high-fat diet.

There are several ambiguities in the data of Enns *et al.* First, in experiment 1 the number of animals decreased almost by half in all groups between days 120 and 160; second, body weights significantly decreased in male offspring of previously deprived groups in experiment 1, whereas the body weights of these animals tended to increase relative to controls in experiment 2. The reasons for these inconsistencies are unclear. Third, the data should have been expressed in terms of the number of litters rather than number of offspring. Littermates share a common gene pool and thus tend to be more like one another than like rats from different litters. Thus the rats in the treatment groups of Enns *et al.* are "related" by more than treatment condition. For a discussion of this problem see Becker and Kowell (*5*) or Walsh (*6*).

Our results (*2*) demonstrating increased body weight, food intake, and adiposity following prenatal food restriction were not entirely unprecedented. We have recently become aware of two studies (*7, 8*) of rats that received low protein diets for ten generations and were subsequently fed a diet adequate in protein beginning on day 14 of gestation in the tenth generation. These rats, in contrast to those that received adequate nutrition beginning either at birth or weaning, showed significant increases in adult body weight above control levels despite the fact that there were no differences in birth weight.

The changes in food intake, body weight, and adipose tissue that we reported (*2*) were also observed in pilot studies [see reference 4 in (*2*)] and in several experiments performed subsequently (*4*). Differences in housing conditions or obvious environmental factors do not appear to account for the discrepancies between our results and those of Enns *et al.*, because we also housed offspring in groups after weaning and maintained them on the same cycle of light and darkness at 22°C. However, it is possible that perinatal stress accounts for the discrepancies, as Enns *et al.* suggest. It has recently been reported (*9*) that early stress factors interact with prenatal malnutrition to produce decreases in body weight that are delayed in onset; such decreases occur particularly in male rats. It seems more likely that perinatal stress would have blocked the increases in body weight in our male animals rather than produced them. Whether such factors affected the results of Enns *et al.* remains to be determined.

ALAN P. JONES
Department of Psychology, University of Massachusetts, Amherst 01003
MARK I. FRIEDMAN
Monell Chemical Senses Center, Philadelphia, Pennsylvania 19104

References and Notes

1. M. P. Enns, M. W. Wilson, J. A. Grinker, I. M. Faust, *Science* **219**, 1093 (1983).
2. A. P. Jones and M. I. Friedman. *ibid.* **215**, 1518 (1982).
3. G. P. Ravelli, Z. A. Stein, M. W. Susser, *N. Engl. J. Med.* **295**, 7 (1976).
4. A. P. Jones and M. I. Friedman, paper presented at the Eastern Psychological Association meeting in New York, April 1981.
5. G. Becker, and M. Kowall, *J. Comp. Physiol. Psychol.* **92**, 6 (1977).
6. J. E. Walsh, *Ann. Math. Stat.* **18**, 88 (1947).
7. R. J. C. Stewart, *Baroda J. Nutr.* **3**, 145 (1976).
8. _____, J. Shapart, R. Preece, J. C. Waterlow, *Br. J. Nutr.* **43**, 403 (1980).
9. F. Crutchfield and M. Dratman, *Biol. Neonat.* **38**, 203 (1980).

22 December 1982