the milk output to the senior litter does not peak until after another week (*6*). During this week dams, without increasing their food intake or catabolizing their tissue, can nurture the litter in utero and nurse the senior litter normally. Dams may be using their food with increased efficiency. In fact, the elevated progesterone in mother rats (*8*) increases the efficiency of diet utilization (*9*).

While mother rats can compensate for the separate strains either of food restriction (*4*) or of concurrent pregnancy and lactation, it seemed unlikely that they could deal adequately with both simultaneously. It seemed more likely that either the senior litters would suffer from a decreased milk supply, or that the junior litters would be resorbed in utero, or both. In the next experiment, we determined the effect of food restriction on pregnant, lactating mothers and on their litters.

Sixteen mother rats were impregnated during their postpartum estrus. Eight dams were given free access to Purina Lab Chow (*10*) while the other eight were restricted to 25 g of the diet each day, an amount slightly more than virgin females normally eat. After 15 days postpartum, the restricted group was allowed to eat freely. Senior litters of eight pups were switched each day between a restricted and an unrestricted dam to ensure the equality of pup stimuli for these two groups of mothers. These litters were weaned at 25 days of age. Junior litters were not switched.

Diet restriction in pregnant, lactating dams proved to be a great strain. Although food-restricted dams lost a mean of 41.25 g during the first 15 days postpartum, compared to a gain of 44.29 g by unrestricted dams (t = 12.46; $P < .005$), the senior litters consistently gained less weight with the restricted dams ($\bar{X}$ gain per day per pup = 0.48 g) than pups with dams unrestricted in diet [$\bar{X}$ gain per day per pup = 1.61 g, $F(1, 14) = 16.64$; $P < .01$]. Moreover, 50 percent of the junior litters were resorbed before parturition, while all of the control dams gave birth. The 50 percent of food-restricted dams that did give birth had pups that weighed as much as those of unrestricted dams (t = 0.68, $P > .05$), and the number of live pups born to restricted dams ($\bar{X}$ = 10.5) was no different from the number born to unrestricted dams ($\bar{X}$ = 12.5; U = 11, $P > .05$).

For those mothers that succeeded in delivering normal offspring, the length of time between impregnation and parturition was prolonged ($\bar{X}$ = 37.0 ± 0.4 days) relative to pregnancies of nonlactating dams ($\bar{X}$ = 22.75 ± 0.16 days)

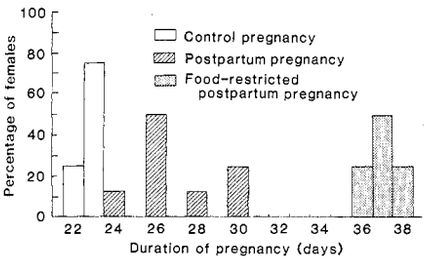

Fig. 2. The percentage of mothers giving birth at different times after conception.

or pregnant, lactating dams unrestricted in food ($\bar{X}$ = 27.0 ± 0.76 days; $U < 0$; $P < .01$) (Fig. 2).

Milk production, as we have noted, peaks on day 15 postpartum (*7*), and it was by just that period that the postpartum pregnancy was extended under conditions of food restriction, although in our experiment this period also coincided with the period of food deprivation.

It appears that rat dams may be using one of two mechanisms in this situation (i) The rate of growth of the litter in utero may be reduced, thus presumably necessitating less investment of limited resources in these offspring. (ii) Alternatively, implantation may be delayed in the food-restricted dams until after either the period of food deprivation ends or the period of peak milk production has passed. In either case, maximal competition for extremely limited energy resources between the dam and her two litters would be avoided.

The Norway rat, therefore, can use various mechanisms to ensure the success of reproduction: (i) an increase in food intake in response to increased suckling, (ii) the catabolism of maternal body tissue to increase available resources for milk production, (iii) possible increased efficiency in the use of food, and (iv) the facultative prolongation of postpartum pregnancies.

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3. Females were housed in Wahman rabbit cages (61 by 61 by 46 cm) with grid floors (0.6 cm). Each cage contained a wooden nest box (30 by 30 by 15 cm) with two 5-cm square entrances, and dams were given paper strips for nest material. All dams built their nests and gave birth in these nest boxes. Water and Purina Lab Chow were provided freely, the food being placed in jars that could not be overbalanced. Lights came on at 9 a.m. for 12 hours, and room temperature was kept at 20° ± 1°C. Eight pups were selected from each litter at birth.
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11 November 1979; revised 11 August 1980

A Metric for Thought: A Comparison of P300 Latency and Reaction Time

Abstract. *We confirm that the latency of the P300 component of the human event-related potential is determined by processes involved in stimulus evaluation and categorization and is relatively independent of response selection and execution. Stimulus discriminability and stimulus-response compatibility were manipulated independently in an "additive-factors" design. Choice reaction time and P300 latency were obtained simultaneously for each trial. Although reaction time was affected by both discriminability and stimulus-response compatibility, P300 latency was affected only by stimulus discriminability.*

In his autobiography, Charles Darwin described his fall from the parapet of an old fortification: ". . . the height was only seven or eight feet. Nevertheless the number of thoughts which passed through my mind during this very short, but sudden and wholly unexpected fall, was astonishing, and seem hardly compatible with *what physiologists have, I believe, proved about each thought requiring quite an appreciable amount of time* . . ." [italics added] (*1*). Darwin was presumably referring to the work of his "friend and contemporary" (*2*), the Dutch physiologist F. C. Donders who, in 1868, described a technique he used to demonstrate that mental acts have measurable durations. Donders' method was based "on the idea that the time between stimulus and response is occupied by a

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train of successive processes: each component process begins only when the preceding one has ended'' (*2*). Donders devised a subtractive technique in which ''new components of mental action'' were interposed in a simple response task. The duration of the added mental component could be determined by subtracting the time required to make a simple response from the time required to make the same response with the additional mental act. From this beginning has developed the study of mental chronometry which seeks to enumerate component mental processes and their characteristics, and to develop models that specify the manner in which these components combine.

Traditional chronometric techniques base inferences about component mental processes on experimental decomposition of the composite reaction time (RT). The analytic power of chronometric techniques would be enhanced if the duration of a subset of the component processes could be recorded concurrently with the composite measure RT. Kutas *et al.* (*3*) suggested that the latency of P300, an event-related brain potential (ERP) recorded in humans, can serve as such a measure.

There is much evidence that P300 is a manifestation of brain activity invoked during the processing of task-relevant, surprising events (*4*). The latency of P300 is often positively correlated with RT. However, the correlation between P300 latency and RT can be altered or eliminated by introducing or emphasizing particular factors (*3, 5*). This pattern of correlation suggests that P300 latency is affected by only some of the component processes that contribute to RT. Our hypothesis is that processes concerned with the categorization of stimuli affect P300 latency and RT. Processes of response selection and execution have no effect upon P300 latency. We report here a direct test, and confirmation, of this hypothesis.

We manipulated, in a choice RT experiment, two variables whose effects on RT have been shown to be additive. Thus, we could be reasonably certain that each of the variables was affecting a different processing stage (*6*). The duration of one stage, which we label stimulus evaluation, was altered by varying the ease with which a target stimulus could be identified (that is, stimulus ''discriminability''). Response selection was varied by changing the compatibility between the target stimulus and the response required of the subject. Because stimulus evaluation is necessary for the categorization of the target, P300 latency should reflect the changes in stimulus discriminability. Changes in stimulus-response compatibility should not affect P300 latency, because the response is selected after identification of the target (*7*). The subject was required to identify which of two target words (RIGHT or LEFT) was embedded in a matrix of characters exposed briefly on a cathode-ray tube. Four such matrices (*8*) are illustrated in Fig. 1A. In ''noise'' (or low discriminability) trials, the background positions of the matrix were filled with randomly chosen alphabetic characters. In the ''no noise'' (or high discriminability) trials, these positions were filled with the # symbol.

Subjects indicated the identity of the target word by pressing one of the two response buttons on which the thumb of each hand rested. A cue word, presented in the center of the screen, preceded the exposure of each matrix. The cue SAME indicated that the right button (right thumb) was the appropriate response for the target RIGHT, while the left button was correct for LEFT. The cue OPPOSITE indicated a crossed mapping: the

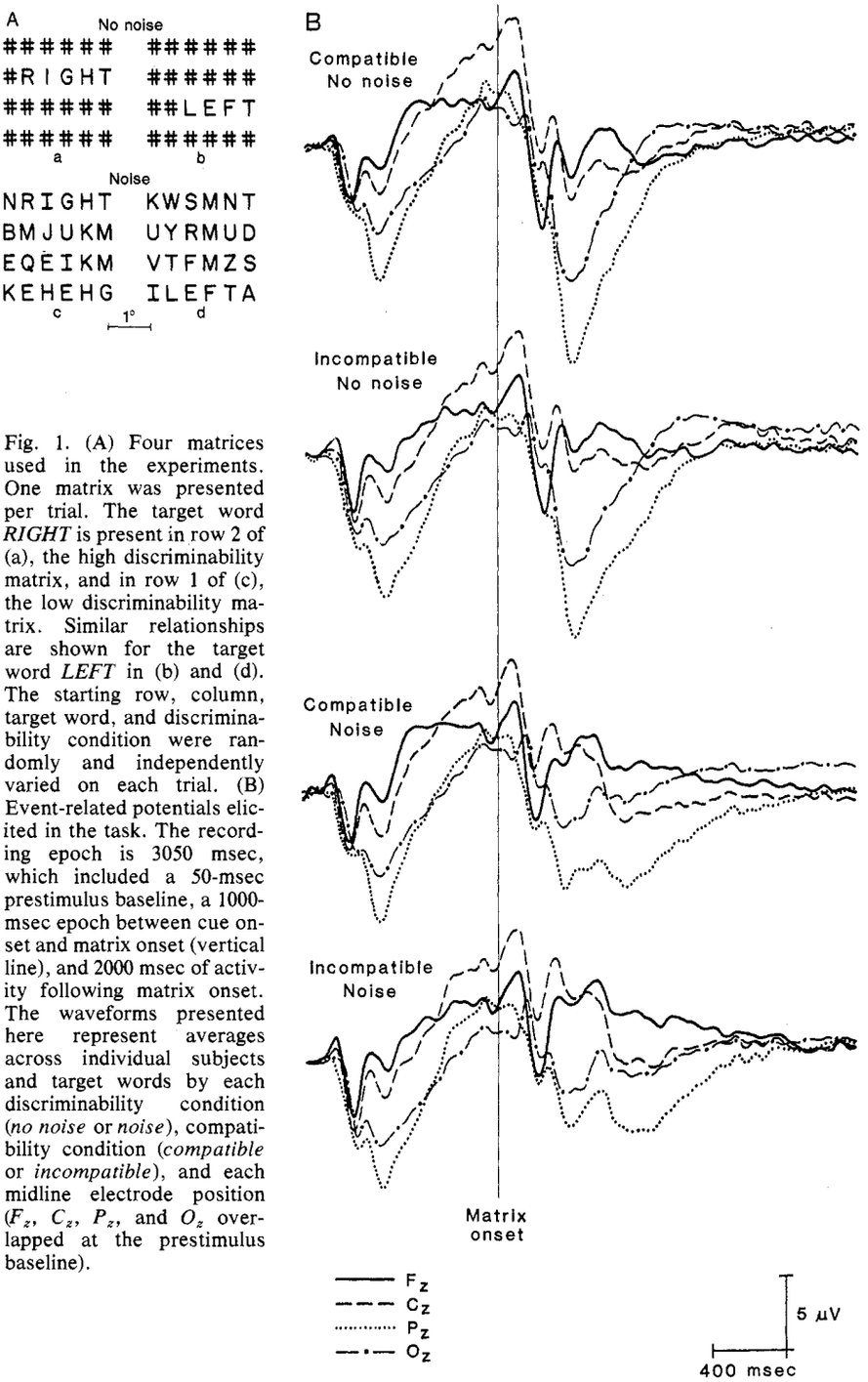

Fig. 1. (A) Four matrices used in the experiments. One matrix was presented per trial. The target word *RIGHT* is present in row 2 of (a), the high discriminability matrix, and in row 1 of (c), the low discriminability matrix. Similar relationships are shown for the target word *LEFT* in (b) and (d). The starting row, column, target word, and discriminability condition were randomly and independently varied on each trial. (B) Event-related potentials elicited in the task. The recording epoch is 3050 msec, which included a 50-msec prestimulus baseline, a 1000-msec epoch between cue onset and matrix onset (vertical line), and 2000 msec of activity following matrix onset. The waveforms presented here represent averages across individual subjects and target words by each discriminability condition (*no noise* or *noise*), compatibility condition (*compatible* or *incompatible*), and each midline electrode position (F_z, C_z, P_z, and O_z overlapped at the prestimulus baseline).

right button (right thumb) was now appropriate for LEFT, and the left button for RIGHT. The stimulus-response mapping, discriminability condition, target word, and position of the target within the matrix were selected randomly on each trial. Each possibility was equally probable, and each was chosen independently of the others.

Stimulus discriminability and stimulus-response compatibility have been demonstrated to have additive effects on mean RT (*9*). In a preliminary experiment, we established that this relationship holds in the specific conditions of our laboratory. The effects of discriminability and stimulus-response compatibility on mean RT and the percentage of correct responses were additive (*10*).

In the main experiment, RT and electrophysiological measures were obtained simultaneously (*11*). Stimulus discriminability and stimulus-response compatibility were again found to have additive effects on reaction time (*12*). The mean RT's for the "no noise" trials were 624 msec for compatible responses and 716 msec for incompatible responses. For the "noise" trials, the mean RT's were 891 msec and 981 msec for the compatible and incompatible responses, respectively. Thus the difference between mean RT's due to discriminability was 266 msec, and the difference due to compatibility was 91 msec.

The electroencephalogram (EEG) data for each artifact-free single trial were sorted on the basis of subject, electrode position, target word, discriminability condition, compatibility condition, and correctness of response. The EEG epochs within each sorting bin were averaged. Two sets of averages were obtained, those in which the epochs were aligned by matrix onset, and those in which the epochs were aligned by the subject's response (*13*). Figure 1B shows the ERP's averaged across subjects, and target words, for the midline electrode positions. The matrix elicits an ERP in which a large positive potential is prominent at the parietal electrode site. On the basis of its scalp distribution and latency, we identify this positive potential as the P300 (*14*).

To quantify the latency of P300, we subjected each single trial waveform obtained from the parietal electrode site to low-pass filtration (− 3 dB at 3.52 Hz) to attenuate EEG activity outside of the bandwidth of P300. The latency of the largest positive peak between 200 and 1500 msec after the onset of the matrix was measured for each trial and used as an estimate of P300 latency. Figure 2 depicts the mean P300 latency estimates

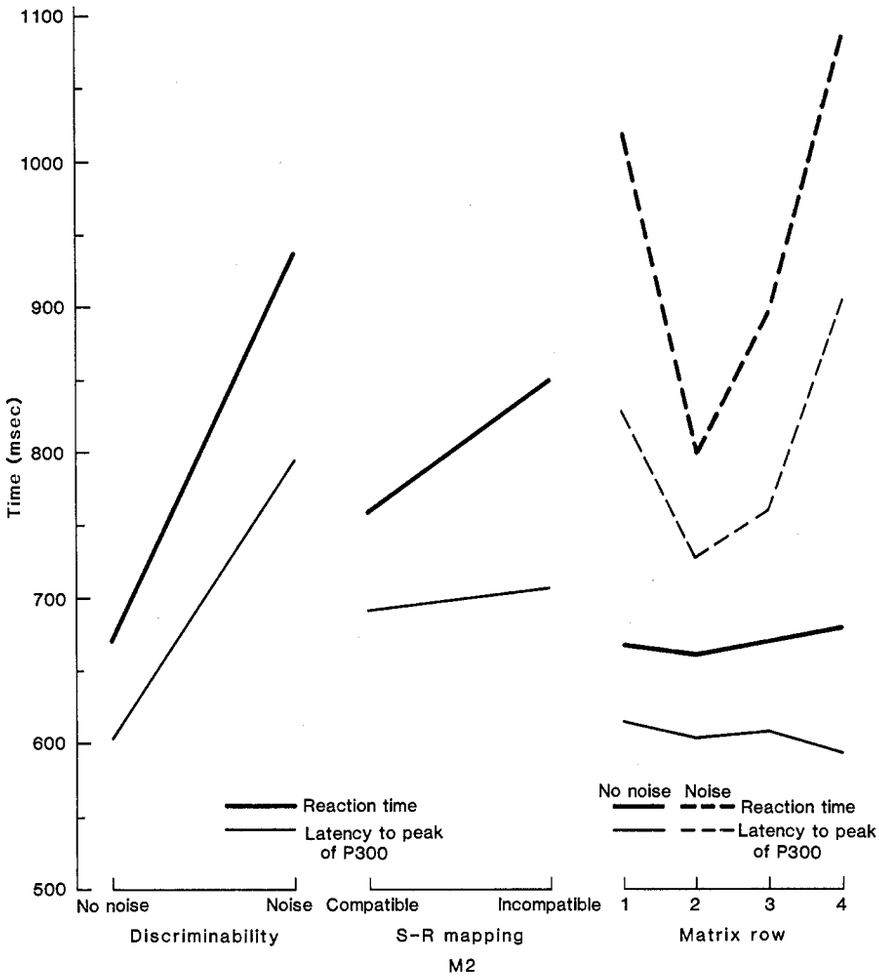

Fig. 2. The mean reaction times (thick lines) and P300 latencies obtained from single-trial measurement (thin lines) for each experimental factor. The main effects of discriminability condition are shown in the left panel. The main effects of stimulus-response compatibility are shown in the middle panel. The interaction of discriminability and matrix row is depicted in the right panel.

and the mean RT's plotted against the experimental variables. The mean P300 latency for the "no noise" trials was 589 msec for the compatible response and 617 msec for the incompatible response. For the "noise" trials, these values were 792 msec and 796 msec. The P300 latency difference of 191 msec due to the discriminability factor was statistically significant [$F(1, 12) = 94.4$, $P < .0001$]. The 16-msec difference associated with the stimulus-response compatibility factor was not statistically significant [$F(1, 12) = 1.6$, $P < .228$]. The variance of the P300 latency was not affected by any experimental variable.

Additional support for our hypothesis is displayed in the right panel of Fig. 2. The position of the target word within the matrix had a large effect on mean RT. Targets in either the top or bottom rows were associated with much longer RT's than targets in the middle rows. This effect, however, was restricted to the "noise" trials (*15*). According to the additive factors model, this interaction of stimulus discriminability and target position indicates that a common stage is affected by both variables. Therefore, P300 latency should also be affected by target position. This prediction is supported (*16*) by the similarity of the patterns of RT and P300 latency in Fig. 2 (*17*).

These data confirm the proposition that P300 latency is sensitive to the duration of stimulus evaluation processes and relatively insensitive to response selection processes, whereas RT is strongly influenced by both. Thus, P300 latency can serve as a metric in the study of mental chronometry. We emphasize that our results do not bear on the nature of the process manifested by P300 [see (*4*)]; we only assert that this process is contingent on stimulus categorization.

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7. These assumptions reflect the serial-successive progression of processing stages inherent in the additive-factors model. Other models predict that all processes are active concurrently, although contingent upon each other's output. See, for example, J. L. McClelland, *Psychol. Rev.* **86**, 287 (1979).
8. Each matrix was composed of four rows and six columns of characters arranged as a square which subtended approximately 2.5°. One target word was presented on each trial, written horizontally, and appearing with equal probability in any of the four rows. The starting column of the target word was also randomly chosen and varied among columns 1 and 2 for RIGHT and columns 1, 2, and 3 for LEFT.
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11. Fifteen male students (right-handed, ages 19 to 32 years) participated. The matrix was exposed for 400 msec. The cue-to-matrix onset interval was 1000 msec with the cue's exposure duration set for 750 msec of the interval. The scalp EEG was recorded from six silver–silver chloride scalp electrodes (F_z, C_z, P_z, O_z, C_3, and C_4, according to the 10/20 system) referenced to linked mastoids. Electrodes placed above and to the side of the right eye were used to record the electrooculogram (EOG) in bipolar fashion. The EEG was amplified by a Van Gogh polygraph with a 1/2 amplitude upper cutoff of 35 Hz and with a 10-second time constant. The EOG was amplified with an upper cutoff of 15 Hz and with a 1-second time constant. Both the EEG and EOG were digitized at 5 msec per point for a period of 3.5 seconds beginning 50 msec prior to the cue stimulus and continuing until 2450 msec after the onset of the stimulus matrix. These data were stored on digital tape along with a record of the stimulus conditions and reaction time for that trial. Of the total trials, 17.8 percent were not used either because the subject failed to respond within 2000 msec, or because of eye movement artifact in the EEG.
12. The grand mean RT was 805 msec. The mean RT for "noise" trials was 266 msec longer than for "no noise" trials [$F(1, 12) = 166.6$, $P < .0001$]; the mean RT for incompatible stimulus-response mappings was 91 msec longer than for compatible mappings [$F(1, 12) = 84.5$, $P < .0001$]. Equivalent values were obtained when trials marked for eye movement artifacts were included in the analysis. "Noise" trials were associated with higher RT variance than "no noise" trials [$F(1, 12) = 32.1$, $P < .0001$]. There was a nonsignificant trend for more RT variance in the incompatible than compatible trials. Subjects performed correctly on 91.7 percent of the trials.
13. The response-aligned waveform data will be described elsewhere.
14. The large positivity seen in the "no noise" waveforms is probably a composite of two potentials: one maximum in amplitude over the centroparietal scalp sites and the other maximum in amplitude over the parieto-occipital scalp sites. The former potential we identify as P300. In the "noise" trials, these potentials are dissociated in time as the latency of the P300 component increases. On some percentage of the trials, the earlier positive component may have been used to estimate P300 latency. As this component appears relatively fixed in latency, these trials would add a fixed component to the distributions of P300 latency. It is unlikely that this affected our conclusions. The absence of any significant changes in the variances of the P300 latency distributions suggests that it is unlikely that such misreadings occurred more often in some conditions. [For more details see (*10*).]
15. The mean RT's obtained for each matrix row (from the top) were 843, 730, 783, and 883 msec [$F(3, 36) = 27.1$, $P < .0001$]. This row effect strongly interacted with stimulus discriminability [$F(3, 36) = 23.5$, $P < .0001$] because it was not present in the "no noise" trials.
16. The mean P300 peak latencies for each matrix row were 721, 665, 684, and 748 msec [$F(3, 36) = 7.9$, $P < .0004$]. As for RT, the row effect interacted with stimulus discriminability [$F(3, 36) = 11.0$, $P < .0001$] and was not present in the "no noise" trials.
17. For all experimental factors, the change in mean RT is greater than the change in mean P300 latency. This result is readily apparent in the differing slopes of P300 and RT in Fig. 2. See (*10*) for a discussion of these differences and their potential relevance to the assumptions underlying the additive-factors model.

18. This research was supported by the Office of Naval Research under contract N00014-76-C-0002, with funds provided by the Defense Advanced Research Projects Agency, and by the Air Force Office of Scientific Research, Bolling Air Force Base, Washington, D.C., under contract F49620-79-C-0233, and the Air Force Systems Command, Wright-Patterson Air Force Base, Ohio, under contract F33615-79-C-0512. We thank E. F. Heffley and C. C. Wood for helpful comments on this report.

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21 April 1980; revised 28 July 1980

Cyclophosphamide-Induced Spermatogenic Effects Detected in the F_1 Generation by Behavioral Testing

Abstract. *Fischer 344 male rats were treated with cyclophosphamide (10 milligrams per kilogram of body weight) for 5 weeks and subsequently mated to females previously treated with saline or cyclophosphamide. The F_1 progeny of the cyclophosphamide-treated males exhibited behavior deficits when compared to controls. These data could indicate a chemically induced genetic effect manifested by behavioral alterations.*

Chemical mutagens induce a variety of sperm abnormalities. These may be detected at the chromosome level, for example, in Y chromosome nondisjunction (*1*), or at the cellular level, in which morphological aberrations of sperm heads (*2*) or aspermia may be observed (*3*). The genetic transmission of some of these effects has been reported (*4*), but no attempt has been made to correlate these cytological findings with any behavioral anomalies in the F_1 generation although Brady *et al.* noted a "gametotoxic" effect in rats treated with lead (*5*). We report evidence of behavioral aberrations in the F_1 generation of cyclophosphamide (CP)-treated male rats. These results suggest that the behavioral test system devised provides a sensitive and new end point to evaluate the genetic effects of mutagens in vivo. The use of this phenotypic end point in studying mutagenic agents may closely parallel the results one would expect to find in the human population after exposure to a mutagen.

A total of 30 female and 20 male adult Fischer 344 rats (*6*) were injected intraperitoneally with either 10 mg of CP per kilogram of body weight or a 0.9 percent saline solution. The animals were injected daily for 5 days, allowed to rest for the next 2 days, and then treated again for a total period of 5 weeks (*7*). Beginning 3 days after the last injection, the animals were housed in cages with a ratio of two females to one male per cage for about 2 weeks. The males were then switched to another cage according to the same breeding scheme for two additional weeks. The crosses used in the breeding scheme were as follows: saline-treated males and females (saline × saline, controls), saline-treated males with CP-treated females (saline × CP), CP-treated males with saline-treated females (CP × saline), and CP-treated males and females (CP × CP).

During breeding the animals were weighed at weekly intervals, and the dates of birth of all litters were recorded. Twelve live pups (three litters) were born from the CP × CP matings; 41 pups (nine litters) from the CP × saline group; 82 pups (ten litters) from the saline × saline group (35 of these control pups were randomly chosen for study in this report); no pups were born from the saline × CP matings (*8*). Thirteen animals (three from the CP × CP group and ten from the CP × saline) died postpartum.

One case of gross morphological abnormality occurred in the offspring from CP-exposed parents. One male pup of a CP × CP mating was born with a single eye. This condition was associated with a low body weight, compared to the littermates, which persisted to adulthood. Because of the low number of pups surviving for 1 day in some of the CP × CP and CP × saline litters, pups from the different breeding groups were fostered to females so as to provide an average nursing litter size of eight pups.

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