ingestion of the 2 percent sucrose solution (7.0 ± 0.9 ml per hour compared to 7.1 ± 1.2 ml per hour). This suggests that purines do not suppress food intake because of a nauseating or a general tranquilizing effect.

The results of this study show that the purine inosine not only suppresses feeding known to be related to the diazepam receptor, but also suppresses food deprivation–induced feeding, insulin-induced feeding, and spontaneous nocturnal feeding. Since the effective purines appear to be only those shown to interact with the benzodiazepine receptor, and since the benzodiazepines modulate satiety (*9*), it appears likely that inosine may be an endogenous modulator of satiety acting through the benzodiazepine receptor.

A number of nutrients including carbohydrates, proteins, and fats have been postulated to regulate ingestive behaviors (*27*). On the basis of our study it seems that a purinergic model of appetite regulation can be considered along with the glucostat, aminostat, and lipostat models of appetite regulation.

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Diazepam Impairs Lateral Position Control in Highway Driving

Abstract. *Nine expert drivers operated an instrumented vehicle in tests over a highway at night after being treated with diazepam (5 and 10 milligrams), a placebo, and nothing. They reacted to 10 milligrams of diazepam with increased lateral position variability. Potentially dangerous impairment was inferred from the reactions of some subjects.*

Recent evidence indicates that 20 to 30 percent of drivers in Europe and North America regularly use prescribed psychotropic drugs and that these drivers become involved in serious traffic accidents at a rate five to ten times that of nonusers (*1*). By far the most frequently prescribed drugs are benzodiazepine tranquilizers, of which the most popular is diazepam (Valium or Stesolid). Laboratory, driving simulator, and closed-course driving tests have provided contradictory results but occasionally the suggestion of an adverse diazepam effect on skills and judgment related to actual car driving (*2*). Two studies undertaken in the real environment relied upon post-test observer ratings for demonstrating adverse effects of diazepam on driving in urban or suburban traffic (*3*). The authors of both reports indicated that single observer reliability and interobserver agreement were less than desired. In addition, neither report indicates what performance changes the observers noted in deriving their more-or-less general ratings.

Our study was designed to measure diazepam's effects on aspects of highway driving performance. Test conditions were controlled, and performance was measured objectively. The major purpose was to determine whether single, moderate doses of diazepam impair the driver's fundamental road-tracking ability during uninterrupted high-speed travel. We reasoned that if drivers lose this ability to any significant extent, they can hardly be expected to cope adequately with superimposed task demands.

Subjects were nine healthy, male police driving instructors (ages 24 to 34 years). They were familiar with the road on which they were tested as the result of patrol and teaching duties. Further familiarization with the road, test vehicle, and procedures was provided individually in a preliminary rehearsal. Subjects were informed of the general nature of the experiment, though not of the drug used. Only one recalled having used a prescribed psychotropic drug (diazepam, for 2 weeks, 3 years earlier). Subjects' activities were controlled on test days. They had slept normally, engaged in light work and then fasted for 4 hours before they arrived.

Subjects undertook a 1-hour driving test under five separate conditions, 1 to 3 weeks apart: (i) 10-mg diazepam treatment (D-10), (ii) 5-mg diazepam treatment (D-5), (iii) placebo control (P), (iv) no-tablet control (N), and (v) early-morning control (M). Driving tests began during evening hours (2000 to 2200 hours, with the time constant for a given subject), except in condition M, when the test began at 0100 hours. The order of conditions was different for eight subjects, but one order was inadvertently replicated for the ninth. Drugs and placebo were administered 1 hour before the tests according to a double-blind procedure. Tests were scheduled on consecutive weeknights during the months October to December, but were postponed in

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the event of fog, rain, snow, road icing, or strong wind (> 8 m/sec). The test consisted of operating a specially instrumented vehicle (Volvo 145 Express) twice around a 50-km highway circuit. The subject was accompanied by an experimenter who had access to redundant controls. The highway was part of the Netherlands primary road system and consisted of two traffic lanes (width, 3.6 m) in each direction, divided by a wide median shoulder with barrier and bordered by an outside shoulder (3.8 m). The road was level, generally straight and traversed a rural area. Traffic on the circuit was generally moderate to light and offered no impediment to uninterrupted travel at normal highway speeds.

Subjects were generally instructed to drive in the right traffic lane, except when passing slower vehicles. Different specific instructions were given at the beginning of each circuit. On one circuit, the subject was told to concentrate on maintaining speed at the posted limit (100 km/hour) while allowing his lateral position to vary normally within the delineated lane boundaries. On the other, he was to drive as straight as possible while maintaining his preferred speed between 80 and 120 km/hour. Order of instructions alternated between subjects but was constant for the same subject across conditions. The purpose of the two instructions was to determine whether potential drug effects could be overcome by greater concentration. Recordings of speed and lateral position were made on previously selected, straight highway segments, 1 to 9 km apart. Five of these were in one direction on the circuit, four in the other. Separate recordings were 32 seconds long, during which time the vehicle traveled 844 to 1111 m, depending on speed. The subject was led to believe that recordings were continuous. Lateral position was measured by an electrooptical transducer mounted behind the vehicle (*4*). It scanned road surface luminance laterally for 3.5 m, of which 3.0 m extended beyond the right side of the vehicle. The greater luminance of the right lane line was the reference for measuring the distance between the center line of the vehicle and the lane boundary as an analog voltage. An electrotachometer attached to the transmission out of the gearbox provided a voltage analog of speed. Both signals were sampled at 4 Hz, digitized, and stored in a microprocessor (LSI-11/Vo2) disk file. Separate recordings were later analyzed to yield mean and standard deviations (S.D.'s) of lateral position and speed. Each statistic was averaged by instructions and conditions. A measurement of subjective arousal during a test was obtained on an interval scale according to a standardized method (*5*).

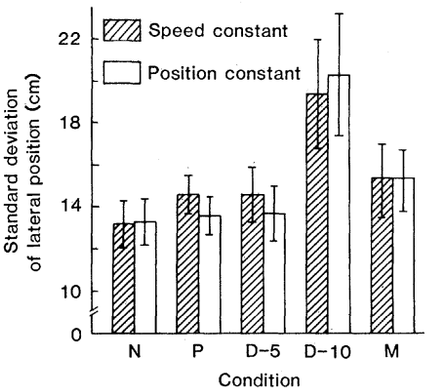

Fig. 1. Average (±1 standard error) standard deviations of lateral position in each condition (*N*, no tablet; *P*, placebo; *D-5*, 5 mg of diazepam; *D-10*, 10 mg of diazepam; *M*, early morning) and for both instructions.

Similar measurements of speed and lateral position were obtained in conditions N, P, and D-5. Usually a difference less than 2 percent separated means of variables measured in these conditions, and never did the difference exceed 6 percent. Mean subjective arousal was "normal," that is, near the midpoint of the scale. In D-10, however, the subjects' average lateral variability rose (Fig. 1). For eight of the nine subjects, lateral variability in D-10 was higher than in any other condition. Analyses of variance with a priori mean-pair comparisons confirmed the significance of these differences between D-10 and each of the other conditions (with condition N, $F = 7.26$, $P < .03$; with P, $F = 5.93$, $P < .05$; with D-5, $F = 6.08$, $P < .04$; with M, $F = 11.40$, $P < .01$; d.f. = 1, 8). Neither instructions nor order of instructions had any significant effect on lateral variability.

Striking elevations in lateral variability were occasionally measured in D-10 for certain subjects. Standard deviations in the range 40 to 52 cm were repeatedly obtained on separate highway segments for two individuals, and once for a third (*6*). No value exceeding 35 cm was ever obtained from any subject in another condition.

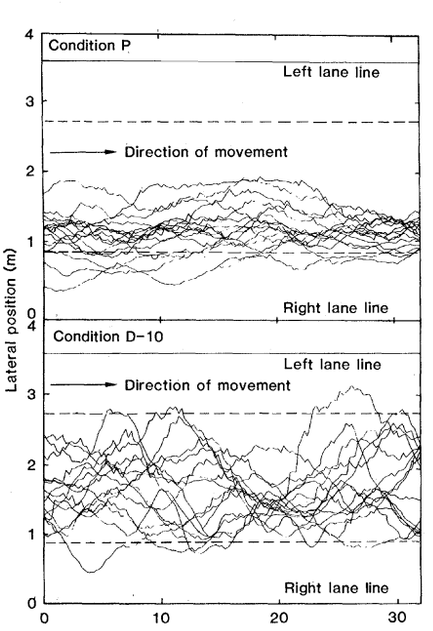

Fig. 2. Vehicle midline position over separate 32-second trials for the most extreme subject in conditions P and D-10. The ordinate scales show the midline distance from the right lane line and dashed lines indicate the limits of midline positions that contain vehicle wheels within lane boundaries.

Figure 2 shows the actual recordings of the vehicle's midline for the extreme subject over successive recording periods in conditions P and D-10. The horizontal dashed lines indicate the limits of the vehicle's midline beyond which the left or right wheels would cross respective lane boundaries. The subject occasionally drove on the right shoulder in P, but never approached to within 1 m of the left boundary. Yet in D-10, his lateral variability was so much greater that he frequently approached the adjacent traffic lane. Indeed he allowed the vehicle to travel beyond left boundary on four occasions, as far as 50 cm and for about 2 percent of the traveled distance. The other extreme subject made two excursions beyond the left boundary, to a distance of 30 cm, for about 1 percent of the traveled distance.

Subjects who showed a marked rise in lateral variability from condition P to D-10 likewise experienced something of the same from condition N to M. These changes may be independently attributed to the respective effects of diazepam and sleep deprivation. The correlation between lateral variability changes from P to D-10 and from N to M across all subjects was significant (Pearson's $r = .84$, $P < .05$). Changes in lateral variability were also inversely related to interval-scale changes in subjective arousal [from P to D-10, $r = -.79$; from N to M, $r = -.81$ ($P < .05$)].

Mean speed and speed variability did not vary significantly between conditions. Mean speed was affected by instructions, as the subjects complied precisely with the instruction to maintain a constant speed (overall mean ± S.D. = 100.0 ± 1.9 km/hour) but drove significantly faster [$F(1, 8) = 97.86$; $P < .01$) attempting to maintain a constant position (111.0 ± 5.4 km/hour).

We did not attempt to measure concentrations of diazepam in the blood, but previous studies (*7*) have shown that a single 10-mg oral dose will, after 1 to 2 hours, produce concentrations similar to those in patients following a typical dosage regimen of 5 mg, three times daily. This does not imply that short- and long-term diazepam effects will necessarily be the same because of equivalent blood concentrations, nor that healthy volunteers will react like patients in any case. We cannot conclude from our results that diazepam will render all drivers, and particularly habitual diazepam users, unable to operate a motor vehicle safely. Patients possessing less driving skill than our subjects, however, might be expected to react even more adversely when beginning diazepam therapy. If they eventually adapt to long-term treatment in ways reducing the diazepam effect upon driving performance, their impairment would pass. Until this can be demonstrated, however, it would be prudent to assume that many diazepam users are impaired to some degree.

The measured impairment was confined to a loss of the subjects' ability to control the lateral position of the vehicle during high-speed travel on straight roads. It was apparent for most subjects in conditions D-10, but to widely different degrees. In two subjects, and possibly three, impairment reached levels that might rightfully be called dangerous. Their standard deviation of lateral position exceeded that associated with the containment of lateral movement within lane boundaries [about 35 cm (*8*)], and their movement extended into adjacent lane and shoulder areas. Because these excursions appeared involuntary, one might assume that their control ability had diminished below that required to operate safely on normal roads. Volitional effort, which allowed the subjects to comply with speed instructions, was apparently insufficient to overcome the effect of diazepam on lateral variability.

The correlation between changes in lateral variability from control conditions to D-10 and M may provide some clue about the mechanism of the diazepam effect. Performance changes in both cases were accompanied by a corresponding drop in subjective arousal. Those individuals whose performance deteriorated with the normal loss of arousal that accompanies prolonged wakefulness showed even greater impairment accompanying loss of arousal after the 10-mg diazepam treatment. The lability of the arousal process might therefore be the individual mitigating factor that determines the drug's effect on driving performance. If so, one would expect to find similarly adverse effects of diazepam on driving performance in all situations characterized by low task demands and monotony but perhaps not under more challenging and stimulating circumstances.

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6. This third subject allowed the vehicle's standard deviation of lateral position to reach 45 cm once near the end of his D-10 condition. He thereupon chose to terminate the experiment, saying that he could no longer operate safely. Although informed beforehand of this possibility and encouraged to exercise the same option, both of the other extreme subjects continued driving until the scheduled end of D-10, in spite of poorer performance.
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8. Assuming a Gaussian lateral position distribution, nearly all variability would be contained within a range of 6 S.D. (plus vehicle width of 150 cm). Thus, when S.D. = 35 cm, full lateral range would be about 360 cm, the lane width.
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Electroencephalogram Tests for Brain Dysfunction: A Question of Validity

Ahn *et al.* reported (*1*) that abnormal electroencephalogram (EEG) patterns are much more common in abnormal children than in normal children, and concluded that "Measurement of these EEG parameters may offer a brief, reliable, and economic method for rapid examination of children who, because of consistent behavioral problems or learning difficulties, are considered at risk for brain dysfunction or disorder." However, the data reported by Ahn *et al.* do not support their proposed clinical application of EEG technology.

First, it is necessary to examine the normal and abnormal groups compared by Ahn *et al.* (*1*). Group 1 was composed of U.S. children of normal intelligence and school achievement. Group 2 was composed of Barbados children, also of normal intelligence and achievement. Group 3 was composed of children examined in a pediatric neurology service, with intelligence and school achievement information unavailable. Group 4 was composed of children with IQ's between 65 and 84 and Wide Range Achievement Test scores below 90 in language or arithmetic skills or both. Group 5 was composed of children with IQ's above 85 but with below-normal school achievement by the same definition as group 4. Thus EEG data were examined for two groups of normal children, one group of neurological patients, one group that could as well be called dull-normal as learning disabled, and one group of learning-disabled children.

By their more stringent criterion of abnormality (two or more EEG parameters different at $P < .01$ from the developmental norm), Ahn *et al.* (*1*) find that 4 percent of group 1, 2 percent of group 2, 48 percent of group 3, 46 percent of group 4, and 47 percent of group 5 children have abnormal EEG records.

These data do not indicate the validity of the EEG test for discriminating between children with and without brain dysfunction or disorder. Validation of a test of brain dysfunction would require showing a higher proportion of abnormal EEG's in a group known to have a higher rate of brain dysfunction than in a group known to have a lower rate of brain damage (*2*). But Ahn *et al.* (*1*) do not present any independent evidence that rates of brain damage are higher in their three abnormal groups than in their two normal groups. For example, it would be helpful to know what proportion of the children in group 3 were having neurological problems, and what the reason is for believing that the children in group 4 have brain dysfunction of any kind.

More troublesome still is that the three abnormal groups show almost exactly the same percentage of abnormal EEG's

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