of the anesthetic block (6, 7). These currents were also not influenced by internal anesthetics (Fig. 2C). This is in contrast to the effects of external anesthetics, which cause a marked alteration of the steady-state current-voltage relation for ACh-induced current (6, 7).

To determine whether the anesthetics reached the internal membrane surface, the voltage-activated sodium current was examined in two myoballs. At a holding potential of -80 mV, a 30-msec pulse to -40 mV elicited an inward sodium current. In the absence of anesthetic compounds, the sodium current was not affected by stimulating at a frequency of 1 Hz. However, 20 minutes after the addition of 1 mM QX-314 to the internal solution, the sodium current exhibited a use-dependent block, decreasing by about one-third in response to 30 pulses at 1 Hz. Extracellular 1 mM QX-314 was without effect on the current through the sodium channel. A use-dependent inhibition of sodium current by internal QX-314 was reported previously (9).

It is possible that an asymmetry of surface potentials could explain the asymmetrical effects of QX-314 and QX-222 on the ACh channel. If the extracellular negative surface potential is greater than the intracellular surface potential, it could concentrate the cationic anesthetic at the outer mouth of the ACh channel, thus increasing its effectiveness when applied externally. If the extracellular surface charge density is about 0.002 electron charge per square angstrom (10), then the surface potential can be calculated by use of the Grahame equation (10, 11). The calculated extracellular surface potential, -41 mV, would increase the concentration of the monovalent cation from 0.1 mM in the bath to 0.5 mM at the outer membrane surface. This concentration is still less than the intracellular concentration, 1 mM. In spite of the fact that the intracellular concentration is greater, these anesthetics have no effect when applied intracellularly. It seems to us, therefore, that asymmetry of surface potential cannot explain this result.

Extracellular anesthetics appear to block channels by hopping over an extracellular barrier and binding to an intrachannel site within the transmembrane electrical field. Apparently the blocker is unable to hop over an even larger intracellular barrier to reach the inside of the cell. If the blocker could be driven by voltage over an intracellular barrier, the block would be relieved at sufficiently negative potentials by a "punchthrough" mechanism (12), which has not

been observed for the ACh channel (6, 7). The large intracellular barrier may prevent access of internally applied anesthetics to the binding site. It is conceivable that the intracellular barrier is the selectivity filter of the channel (2). Regardless of the mechanism of action of anesthetics, it is clear from these experiments that the channel is not a symmetrical structure. Our data are in agreement with recent morphological evidence showing that the ACh receptor-channel complex has an asymmetrical structure within the lipid bilayer (13).

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References and Notes

1. T. M. Linder and D. M. J. Quastel, J. Physiol. (London) 281, 535 (1978); P. R. Adams, Biophys. J. 25, 70 (abstr.) (1979); P. H. Barry, P. W. Gage, D. F. Van Helden, J. Membr. Biol. 45, 245 (1979).
2. R. Horn and M. S. Brodwick, J. Gen. Physiol. 75, 297 (1980).
3. The internal solution consisted of 85 mM sodium aspartate, 155 mM sucrose, 5 mM sodium-Hepes (pH 7.3), 1 mM NaCl, and 2 mM EGTA. The Ringer solution contained 85 mM sodium aspartate, 150 mM sucrose, 5 mM sodium-Hepes (pH 7.4), and 1.5 mM CaCl₂.
4. P. R. Adams, J. Physiol. (London) 268, 271 (1977); R. E. Sheridan and H. A. Lester, J. Gen. Physiol. 70, 187 (1977).
5. J. H. Steinbach and C. F. Stevens, in Frog Neurobiology: A Handbook, R. Llinás and W. Precht, Eds. (Springer-Verlag, New York, 1976), p. 33; P. R. Adams and B. Sakmann, J. Physiol. (London) 283, 621 (1978).
6. P. R. Adams, J. Physiol. (London) 268, 291 (1977).
7. P. Ascher, A. Marty, T. O. Neild, ibid. 278, 207 (1978); E. Neher and J. H. Steinbach, ibid. 277, 153 (1978); H. A. Lester, M. E. Krouse, M. M. Nass, N. H. Wasserman, B. F. Erlanger, Nature (London) 280, 509 (1979).
8. P. R. Adams, J. Physiol. (London) 268, 291 (1977).
9. G. R. Strichartz, J. Gen. Physiol. 62, 37 (1973); M. D. Cahalan, Biophys. J. 23, 285 (1978).
10. C. A. Lewis, J. Physiol. (London) 286, 417 (1979).
11. D. C. Grahame, Chem. Rev. 41, 441 (1947). We used the free activity of sodium ions in our calculation. This was measured in our solutions by a glass sodium electrode (Microelectrodes, Inc.).
12. R. J. French and J. B. Wells, J. Gen. Physiol. 70, 707 (1977).
13. M. W. Klymkowsky and R. M. Stroud, J. Mol. Biol. 128, 319 (1979); D. S. Wise, A. Karlin, B. P. Schoenborn, Biophys. J. 28, 473 (1979).
14. We thank P. Adams, R. Klebe, K. Lee, C. Stevens, and R. Tsien for advice and comments; V. Bonnefil for technical assistance; and B. Takman for his gifts of QX-314 and QX-222. Supported by NIH grants NS-13778, CA-19017, and NS-12961.
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Preserved Learning and Retention of Pattern-Analyzing Skill in Amnesia: Dissociation of Knowing How and Knowing That

Abstract. Amnesic patients acquired a mirror-reading skill at a rate equivalent to that of matched control subjects and retained it for at least 3 months. The results indicate that the class of preserved learning skills in amnesia is broader than previously reported. Amnesia seems to spare information that is based on rules or procedures, as contrasted with information that is data-based or declarative—"knowing how" rather than "knowing that." The results support the hypothesis that such a distinction is honored by the nervous system.

Amnesia, a neurologic syndrome characterized by a deficit in the formation of new memories, can exist independently of other cognitive impairment. The deficit is global, affecting both verbal and nonverbal material irrespective of modality (1). In particularly severe amnesia, as exhibited, for example, by the noted case of H.M. (2, 3), the impairment has been described as "forgetting the incidents of daily life as fast as they occur" (2, p. 15).

Amnesic patients have nonetheless been reported to learn and remember certain perceptual-motor skills, including tracking and mirror tracing (4–7), frequently at a rate comparable to that of control subjects (6, 7). Yet these same patients had little or no recollection of having previously performed the task.
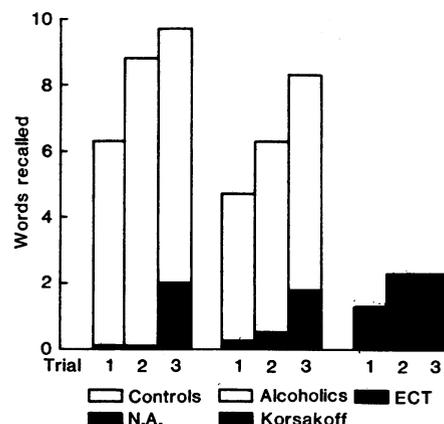

Fig. 1. Anterograde amnesia for ten word pairs presented three times. After each presentation, subjects saw the first word of each pair and tried to recall the second.

They have also been reported to increase the speed with which they perform maze-learning tasks, despite their failing to learn the appropriate sequence of turns (6, 8). In addition, work with normal subjects has dissociated kinesthetic-motor memory from spatial and verbal memory on the basis of differences in forgetting rates and in susceptibility to interference (9). These data have suggested that perceptual-motor information might enjoy a special neurologic status that could be responsible for the sparing of perceptual-motor skills in amnesia.

We now report that the class of preserved learning skills in amnesia extends beyond perceptual-motor tasks. Amnesic patients were able to acquire a mirror-reading skill that minimized perceptual-motor involvement and were able to retain it for more than 3 months. In three consecutive daily sessions and in a fourth session 13 weeks later, eight amnesic patients learned to read mirror-reflected words at a rate equivalent to that of matched control subjects. The mirror-reading task was selected because of its dependence on pattern-analyzing rather than perceptual-motor skills (10–12). The subjects learned the mirror-reading skill despite amnesia for the words that had been read and with negligible recollection of having previously performed the task.

We tested N.A., who has been amnesic for verbal material since sustaining a stab wound to the diencephalon in 1960

(13); four patients with chronic alcoholic Korsakoff syndrome; three patients tested 6 to 9 days after a prescribed course of bilateral electroconvulsive therapy (ECT) for relief of depressive illness (14); and control subjects for N.A. and for the Korsakoff patients (15). All patients were severely amnesic as assessed by formal tests of new learning ability and by their inability to remember day-to-day events (Fig. 1) (16).

Subjects saw cards presented by mirror-reflection in a tachistoscope, each card displaying three low-frequency nouns with eight to ten letters; for example, they saw

bedraggled–capricious–grandiose

Subjects were asked to read each word triad aloud and to press a button when finished. The button press stopped a millisecond timer and terminated the trial. Subjects read five blocks of ten word triads on each of three consecutive days and also on a fourth day approximately 13 weeks later. For each block of ten triads, half were common to all blocks (repeated) and half were unique (nonrepeated). By analyzing separately the performance for the nonrepeated and the repeated word triads, we evaluated the ability to acquire the rules or procedures necessary for mirror reading, and also evaluated the ability to benefit from frequent repetition of specific words.

All amnesic patients learned the pattern-analyzing skill (nonrepeated word triads) (Fig. 2) [main effect of block number: $F(4, 28) = 12.65, P < .001$; main effect of test day: $F(2, 14) = 14.63, P < .01$; linear component: $F(1, 5) = 179.72, P < .001$]. Indeed, N.A. and the Korsakoff patients learned at a rate equivalent to that of their matched controls (17).

For all subjects, the learning curves for the repeated triads were similar to but steeper than those for the nonrepeated triads [$F(1, 18) = 101.14, P < .001$], which reflected the facilitatory effect on reading speed of remembering the specific words that were repeated from block to block. This facilitatory effect was smaller for the amnesic patients than for the control subjects (18), which illustrates that, despite learning the mirror-reading skill normally, amnesics were poor at remembering which words they had read. This dissociation can be appreciated most clearly in Fig. 3. For performance on nonrepeated word triads, which depends only on the rules or procedures involved in mirror reading, there was no forgetting between sessions by either the amnesic patients [$t(6) < 1, P > .3$] or by the controls [$t(10) < 1, P > .3$]. For performance on repeated

Fig. 2. Acquisition of a mirror-reading skill during three daily sessions, and retention 3 months later. The ability to mirror read unique (nonrepeated) words was acquired at a normal rate by amnesic patients. The ability of amnesic patients to mirror read repeated words was inferior to the control rate because amnesic patients, unlike control subjects, could not remember the specific words that had been read.

word triads, which depends in addition on memory for the specific words that were repeated from block to block, only the amnesic patients showed marked forgetting [$t(6) = 2.78, P < .02$].

The striking deficit in memory for specific items exhibited by the amnesic patients was also illustrated by their poor performance on a recognition memory test administered after day 3 of testing (19). For the nonrepeated words, recognition d' was amnesics, 0.36 ± 0.1; controls, 1.46 ± 0.2 [$t(18) = 3.07, P < .01$]; for the repeated words, recognition d' was amnesics, 1.97 ± 0.4; controls, 3.79 ± 0.1 [$t(18) = 4.24, P < .001$]. Upon being questioned, none of the amnesic patients reported that words had been repeated during the task, even though by the end of session 4 the set of repeated words had been presented 20 times. All of the control subjects reported spontaneously that words were frequently repeated.

The finding of intact acquisition and retention of mirror-reading skill in amnesic patients adds to the set of learning skills known to be preserved in amnesia, and suggests that the class of preserved learning skills may be considerably broader than was previously thought. The traditional view has held that the role of motor information is crucial in determining which tasks amnesics can learn. This view is based on the premise that motor information enjoys a special neurologic status and is thereby spared in amnesia. However, amnesic patients have recently been found to be impaired in a test of short-term kinesthetic-motor memory (20), which indicates that motor performance is not uniformly spared in amnesia. Moreover, amnesic patients can learn skills that are apparently not perceptual-motor in nature, including the present pattern-analyzing skill. Thus, there have been reports of numerical rule learning (21) and eyeblink conditioning (22) in amnesic patients, and anecdotal observations (23) that amnesic patients are often good at learning testing procedures even when they fail on the tests (24).

If, as Kolers suggested (11, 12), acquiring reading skills involves the learning of encoding operations or procedures rather than the remembering of specific results of these operations, amnesic patients seem to provide a clear example of this distinction. Amnesic patients can apparently learn the encoding rules or procedures for acquiring skills, but can remember little or nothing of the information that results from applying them.

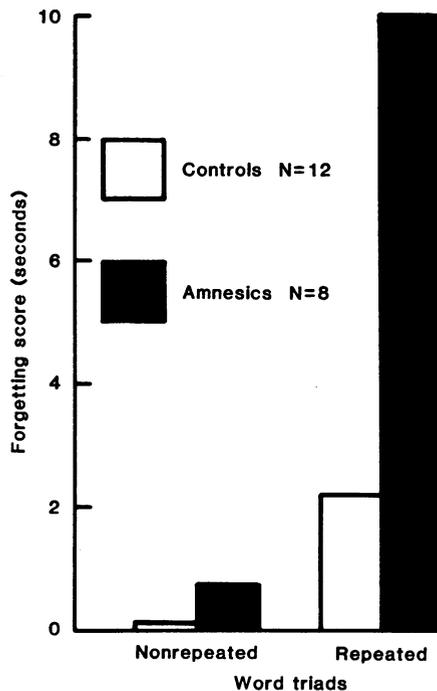Whether a task can or cannot be learned in amnesia seems to depend on the na-

Fig. 3. Forgetting between sessions as measured by the difference in reading time between the last block of each session and the first block of the subsequent one. The interaction of the subject group by type of word was significant [$F(1, 18) = 6.08, P < .03$)].

ture of the information and not on the extent of motor involvement demanded by the task. We propose that perceptual-motor and pattern-analyzing skills belong to a class of operations governed by rules or procedures; these operations have information-processing and memory characteristics different from those operations that depend on specific, declarative, data-based material. Although the distinction we have drawn between these classes of information may not permit all tasks to be sharply dichotomized, it should prove useful in predicting what is affected or spared in amnesia. This distinction between procedural or rule-based information and declarative or data-based information, which is reminiscent of the classical distinction between "knowing how" and "knowing that," has been the subject of considerable discussion in the literature of cognition and artificial intelligence (25). The experimental findings described here provide evidence that such a distinction is honored by the nervous system.

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References and Notes

1. B. Milner, Clin. Neurosurg. 19, 421 (1972); G. Talland, Deranged Memory (Academic Press, New York, 1965); L. R. Squire, in Electroconvulsive Therapies: Biological Foundations and Clinical Application, W. B. Essman and P. Abrams, Eds. (Spectrum, Jamaica, N.Y., 1980).
2. W. B. Scoville and B. Milner, J. Neurol. Neurosurg. Psychiatry 20, 11 (1957).
3. B. Milner, S. Corkin, H.-L. Teuber, Neuropsychologia 6, 215 (1968).
4. S. Corkin, ibid., p. 255.
5. B. Milner, in Physiologie de l'Hippocampe (Centre National de la Recherche Scientifique, Paris, 1962).
6. D. N. Brooks and A. Baddeley, Neuropsychologia 14, 111 (1976).
7. N. Cohen and L. R. Squire, Soc. Neurosci. Abstr. 4, 256 (1978).
8. S. Corkin, Neuropsychologia 3, 339 (1965).
9. M. I. Posner, Science 152, 1712 (1966); J. Exp. Psychol. 75, 103 (1967); _____ and A. F. Konick, Organ. Beh. Hum. Perform. 1, 71 (1966).
10. In a series of studies of the ability of normal subjects to read geometrically inverted text (11, 12), Kolers found excellent acquisition and long-term retention of pattern-analyzing operations "that are directed at the surface lexical features of the text" and that can be distinguished from memory for the results of these operations, "the semantic or other grammatical content of text that is the subject of most contemporary studies" (11).
11. P. A. Kolers, Cognit. Psychol. 7, 289 (1975); in Levels of Processing in Human Memory, L. Cermak and F. I. M. Craik, Eds. (Erlbaum, Hillsdale, N.J., 1979).
12. _____, Science 191, 1280 (1976).
13. H.-L. Teuber, B. Milner, H. G. Vaughan, Neuropsychologia 6, 267 (1968); L. R. Squire and P. C. Slater, ibid. 16, 313 (1978); L. R. Squire and R. Y. Moore, Ann. Neurol. 6, 503 (1979).
14. The patients had received a series of seven to ten bilateral treatments. B. Cronholm and C. Blomquist [Acta Psychiatr. Scand. 34, 18 (1959)] and B. Cronholm and J.-O. Ottosson [Br. J. Psychiatry 109, 251 (1963)] found anterograde amnesia 1 week after a series of two to seven and a series of three or four bilateral treatments, respectively.
15. Six normal control subjects were matched to N.A. for age (control mean, 38.8 years; N.A., 42 years), subtest scores on the Wechsler Adult Intelligence Scale (WAIS) (information: 21.7 versus 22; vocabulary: 60.0 versus 66), and educational background (14.8 years versus 13 years). Six alcoholic control subjects were matched to the Korsakoff patients for age (48.5 years versus 51.0 years), WAIS subtest scores (information: 17.2 versus 17.5; vocabulary: 50.7 versus 46.3), and educational background (10.7 years versus 12.2 years).
16. Their deficit was also observed in delayed recall of prose material. After a 15-minute delay, N.A. and the Korsakoff patients could remember none of the material learned 15 minutes earlier, and the ECT patients recalled an average of 2.1 segments. By contrast, the six control subjects recalled 6.8 segments and the alcoholic control subjects recalled 4.7 segments after the same delay.
17. N.A.'s reading time fell outside the 95 percent confidence interval for only 3 of the 20 blocks and never during the final 8 blocks. For Korsakoff patients and their alcoholic controls, there was no main effect of subject group [$F(1, 18) = .02, P > .3$] and no interaction of subject group with either block number [$F(4, 32) < 1, P > .3$] or test day [$F(3, 24) < 1, P > .3$].
18. For both the amnesic patients and the control subjects, we calculated for each block the ratio between reading time per repeated word triad and reading time per nonrepeated word triad. Compared with amnesic patients, control subjects benefited more rapidly from the repeated word triads [main effect of subject group: $F(1, 18) = 18.17, P < .001$; interaction of subject group by block number: $F(4, 72) = 3.72, P < .01$; interaction of subject group by test day: $F(3, 54) = 3.86, P < .03$] and to a greater extent (lowest value of ratio attained: amnesics, .30; controls, .15; average value of ratio attained: amnesics, .48; controls, .31).
19. Each subject inspected a list of words which included the 15 repeated words, 45 nonrepeated words, and 60 distracter words and marked those words that could be remembered from the 3 days of testing.
20. L. Cermak and B. Uhly, Percept. Mot. Skills 40, 275 (1975). Cohen and Squire (6) studied delayed lever-movement reproduction in the absence of

visual cues. In a procedure that separated distance cues and end location cues, both amnesic patients and control subjects accurately reproduced movements in a no-delay condition, but the amnesic patients were impaired relative to controls after delays of 12 and 60 seconds.

21. F. Wood, thesis, Duke University (1974); B. T. Volpe, W. Hirst, M. S. Gazzaniga, *Soc. Neurosci. Abst.* 5, 1079 (1979).
22. L. Weiskrantz and E. K. Warrington, *Neuropsychologia* 17, 187 (1979).
23. S. Corkin (4) referred to this phenomenon as "sparing of testing habits" after M. Glickstein and R. W. Sperry [*J. Comp. Physiol. Psychol.* 53, 322 (1960)].
24. It is not yet clear how the performance of amnesic patients on numerical rule learning or classical conditioning compares with the performance of control subjects. Only when amnesic patients perform as well as controls is it possible to argue conclusively for preserved learning or memory in amnesia. Good, but not normal, performance by amnesic patients could occur because some methods of testing yield good performance in all subjects [L. R. Squire, *Neuropsychologia* 18, 369 (1980)] and not because the

aspect of memory under study is preserved in amnesia. Thus, reports of good performance by amnesic patients on incomplete figures [E. Warrington and L. Weiskrantz, *Nature (London)* 217, 972 (1968)] or partial information [*ibid.* 228, 628 (1970); *Neuropsychologia* 12, 419 (1974)] do not necessarily mean that these tasks demonstrate preserved function. Amnesic patients often do rather well in recognition memory tasks compared with free recall tasks, but the advantage of recognition memory over free recall applies to control subjects as well [G. Talland, *Deranged Memory* (Academic Press, New York, 1965), p. 231].
25. T. Winograd, *Understanding Natural Language* (Academic Press, New York, 1972); in *Representation and Understanding*, D. Bobrow and A. Collins, Eds. (Academic Press, New York, 1975).
26. Supported by the Medical Research Service of the Veterans Administration, by National Institute of Mental Health grant MH24600, and by NIMH Mental Health Clinical Research Center grant 1P50 MH 30914.

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dark cycles. This suggestion is supported by the finding that food deprivation can induce analgesia, which is markedly attenuated by naloxone (4). Related to this point are several studies implicating endogenous opioid systems in the modulation of food intake. Central injections of opioid peptides increase food intake in the rat (7), while opiate antagonists decrease food intake (8). Also, the cyclicity in adrenal responsiveness to adrenocorticotropic hormone (ACTH) is primarily a function of food intake patterns (9). In view of these findings, we explored the hypothesis that diurnal fluctuations in pain sensitivity are entrained by circadian patterns of food intake.

The subjects were 24 adult male hooded rats individually housed and maintained on a 12-hour light-dark cycle. They were randomly assigned to one of two experimental groups. In the first group (group A), free access to food was given only during the light phase of the cycle; in the second group (group B), only during the dark phase (10). Water was always freely available.

After an 8-day period of adaptation to the restricted feeding schedule, the animals were tested for pain sensitivity by the tail-flick method. The latency of tail flicking in response to a thermal stimulus of fixed intensity was determined for each rat during the first 2 to 4 hours of both the light and dark phases (11). The food availability schedules for the two groups were then reversed, and the animals were tested again 8 days later.

The results of this experiment clearly indicate that food availability can significantly alter pain sensitivity and that this effect is largely independent of the light-dark cycle. Pain thresholds were uniformly elevated after food deprivation, regardless of the phase of the cycle (Fig. 1A). A within-subjects, repeated-mea-
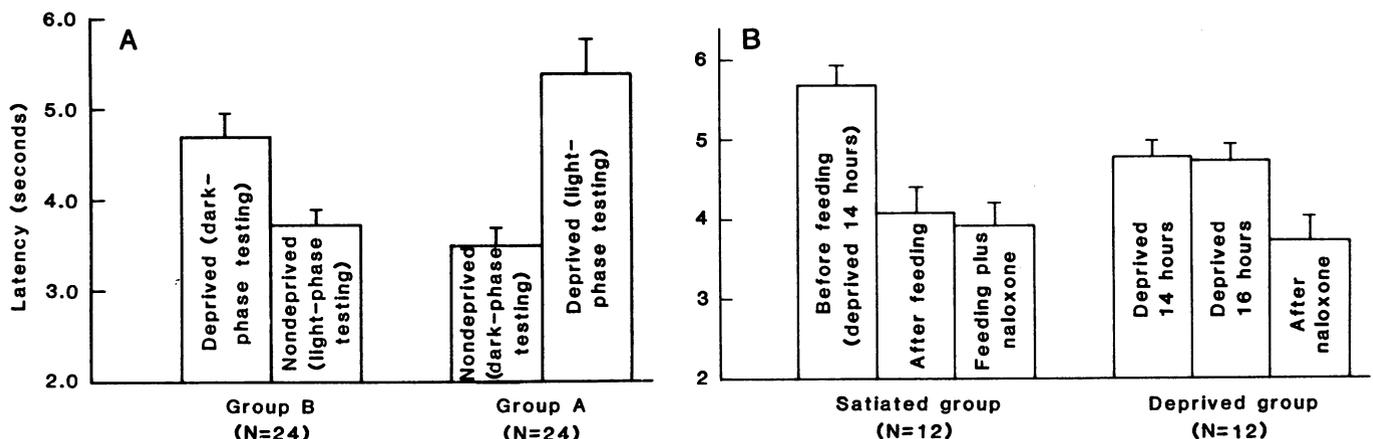
Mediation of Diurnal Fluctuations in Pain Sensitivity in the Rat by Food Intake Patterns: Reversal by Naloxone

Abstract. *Rats maintained on a 12-hour light-dark cycle were tested for pain sensitivity after being deprived of food during either the dark or the light phase of the cycle. Diurnal fluctuations in pain sensitivity were observed. The fluctuations followed food intake patterns rather than a natural circadian rhythm, with food deprivation producing a decrease in pain sensitivity. The analgesic response produced by this mild food deprivation was strongly attenuated by naloxone or feeding, suggesting that endogenous opioid systems may be related to patterns of food intake.*

Diurnal variations in pain sensitivity have been demonstrated repeatedly in rats (1, 2). These variations are attenuated or abolished by the opiate antagonist naloxone, suggesting that the phenomenon is mediated by an endogenous opioid system (3, 4). Strong support for this suggestion is provided by the finding that fluctuations in pain sensitivity are closely paralleled by alterations in levels of endogenous opioids in the rat brain (5). It has been assumed that this diurnal cyclicity in pain sensitivity reflects the circadian rhythm common to other pituitary hormone concentrations (1). We now present evidence suggesting that diurnal fluctuations in pain sensitivity reflect patterns of food intake rather than a circadian rhythm.

Researchers reporting diurnal rhythms in pain sensitivity and endogenous opioid concentrations used standard light-dark cycles in conjunction with unrestricted feeding (1, 2). However, since rats given this liberty feed predominately at night (6), the possibility exists that pain sensitivity cycles are entrained by food intake patterns rather than light-

Fig. 1. (A) Effects of light-phase or dark-phase food availability on tail-flick latency in food-deprived and nondeprived rats. Verticle bars represent the standard errors of the mean. (B) Effects of feeding and naloxone administration on tail-flick latency. Since the results for both light phases are comparable, the data are collapsed for illustration. Vertical bars represent the standard errors of the mean.