tions. Furthermore, since studies in vitro have shown that bag cell hormone regulates activity of neurons in the abdominal (*5*), buccal, and pedal (*30*) ganglia, it may be possible to examine the hormonal control of neuronal circuits in vivo that mediate the different behavioral components of egg laying.

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14. Spikes from bag cells within a cluster are synchronous (*2*) and it has been suggested that this synchrony is due to electrical coupling (*4*).
15. Bag cell neurites extend less than halfway up the connectives, yet electrical stimulation of the connectives near the pleural ganglia can evoke bag cell responses whereas stimulation of other nerves does not (*4*).
16. Injection of bag cell extract in the whole animal can cause eggs to appear in the small hermaphroditic duct within 1 minute. [R. E. Coggeshall, *J. Morphol.* **132**, 461 (1970)]. Some animals do not lay eggs when injected with bag cell extract, indicating that the extract is not always sufficient to trigger egg laying. This is probably because of the absence of eggs in the ovotestis of some animals (W. P. Aspey and J. E. Blankenship, unpublished observations). In addition to the peripheral effect, bag cell extract also has central effects on abdominal ganglion neurons (*5*).
17. Neuroendocrine cells generally have longer spike durations than conventional neurons. For review, see L. H. Finlayson and M. P. Osborne, *Adv. Comp. Biochem. Physiol.* **6**, 165 (1975).
18. A preliminary report of some of these findings has appeared: F. E. Dudek and H. M. Pinsker, *Soc. Neurosci. Abstr.* **6** (1976).
19. Most previous studies of egg laying in *Aplysia* have been carried out on *A. californica*. The identified neurons in the abdominal ganglion of both species have similar electrophysiological and anatomical characteristics [J. E. Blankenship and R. E. Coggeshall, *J. Neurobiol.* **7**, 383 (1976); (*8*, *9*)].
20. Egg quantity was measured as the volume of displaced seawater. For the 46 animals in this study, the average amount of eggs laid preoperatively was 3.34 ± 1.08 ml per day.
21. In the double and single cut groups, the free ends of the cut nerves were tied off. In single cut animals, there was no obvious difference between those with the left ($N = 3$) and those with the right ($N = 2$) connectives intact. Postoperative observations were conducted blind. Only animals who survived at least 4 days after surgery were included. Postoperative mortality was approximately equal for the four groups: one of seven mock operated, one of five single cut, five of 19 double cut, and two of 15 deganglionated animals died before we completed 10 days of postoperative observation.
22. The occasional egg laying in the deganglionated and double cut animals was probably the result of a peripheral mechanism triggered by the buildup of eggs in the ovotestis (F. E. Dudek, J. S. Cobbs, H. M. Pinsker, in preparation). The evidence for this hypothesis is as follows: (i) normal animals tend to lay more eggs after they miss a day or two, suggesting that eggs gradually build up in the ovotestis; (ii) the deganglionated and double cut animals who laid eggs postoperatively usually did so in large amounts (Table 1); and (iii) those deganglionated and double cut animals who failed to lay eggs spontaneously after 10 to 12 days after the operation were injected with bag cell extract and typically laid extremely large amounts of eggs (Table 1). F. Strumwasser, F. R. Schlecte, and S. Bower [*Fed. Proc. Fed. Am. Soc. Exp. Biol.* **31**, 405 (1972)] found that deganglionated animals can show normal egg-laying behavior when injected with bag cell extract.
23. Cutting both connectives near the pleural ganglion may have had some deleterious (trophic) effect on the bag cell neurites instead of, or in addition to, removing orthodromic input. However, a neurotrophic effect on bag cells would probably require several days to impair egg laying, whereas the double cut animals stopped laying eggs immediately after surgery. Other evidence (*15*) supports the hypothesis of a descending orthodromic input.
24. For recording from vertebrate nervous systems in vivo, see M. I. Phillips, Ed., *Brain Unit Activity During Behavior* (Thomas, Springfield, Ill., 1973). For recording from arthropods in vivo, see H. Aréchiga and C. A. G. Wiersma, *J. Neurobiol.* **1**, 71 (1969); J. J. Wine and F. B. Krasne, *J. Exp. Biol.* **56**, 1 (1972). For recording from mollusks in vivo see K. R. Weiss, J. Cohen, I. Kupfermann, *Brain Res.* **99**, 381 (1975); A. Gelperin and D. Forsythe, in *Simpler Networks and Behavior*, J. C. Fentress, Ed. (Sinauer, Sunderland, Mass., 1976); H. M. Pinsker, J. Cobbs, J. E. Kanz, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **35**, 769 (1976); *Soc. Neurosci. Abstr.* **6**, 353 (1976); J. Cobbs and H. M. Pinsker, *ibid.*, p. 342.
25. The intense stimulation of the connective required to trigger the bag cells (*4*) often produced side effects in the intact animal such as inking and massive contractions. Intrasomatic and extracellular studies in vitro (*8*) indicated that electrical extrasomatic stimuli to the bag cells could also initiate an afterdischarge. Although stimulus artifacts obscured the direction of spike conduction during the stimulus train, after it was terminated the spikes typically propagated from distal neurites along the ipsilateral connective toward the bag cell somata. These brief extrasomatic stimuli probably directly activated an intrinsic mechanism of the bag cells for repetitive firing. This suggests that the putative neuronal input might also trigger this intrinsic mechanism rather than driving individual bag cell spikes.
26. Animals were rejected if no spikes from conventional (non–bag cell) axons were recorded from the connective when the animal was stimulated mechanically. Several animals were monitored simultaneously, and records of bag cell activity were kept on FM tape and on a pen recorder.
27. We observed a few cases of egg laying in animals from which we had not previously recorded bag cell activity. In these animals, we stimulated the connective maximally but were unable to record bag cell activity; this indicated that our electrode was misplaced.
28. The longest latency from onset of spontaneous bag cell activity to the appearance of eggs was between 137 and 167 minutes (this animal's discharge is shown in Fig. 2A1). When behavioral observations were made at shorter intervals to get a more accurate measure, the mean latency ($N = 7$) was 29.9 ± 5.3 minutes.
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31. This research was supported, in part, by grants NS 11255-03 and NS 12223-01 to H.M.P. and by grant NRC A0395 to F.E.D. We thank J. Cobbs for invaluable help in the experiments; A. Gelperin, D. Forsythe, and I. Kupfermann for advice concerning the cuff electrodes; and W. Aspey, J. Blankenship, R. E. Coggeshall, W. D. Willis, Jr., and C. Taylor for criticism of an early draft of this report.

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Motion Sickness: An Evolutionary Hypothesis

Abstract. *Since the occurrence of vomiting as a response to motion is both widespread and apparently disadvantageous, it presents a problem for evolutionary theory. An hypothesis is proposed suggesting that motion sickness is triggered by difficulties which arise in the programming of movements of the eyes or head when the relations between the spatial frameworks defined by the visual, vestibular, or proprioceptive inputs are repeatedly and unpredictably perturbed. Such perturbations may be produced by certain types of motion, or by disturbances in sensory input or motor control produced by ingested toxins. The last would be the important cause in nature, the main function of the emesis being to rid the individual of ingested neurotoxins. Its occurrence in response to motion would be an accidental by-product of this system.*

Current knowledge about motion sickness has been reviewed by Money (*1*). In summarizing the explanatory problem presented by the condition, Money and Myles (*2*) described it as "an evolutionary anomaly. . . . There is no survival value in experiencing nausea, or in vomiting, when exposed to motion, and so it is surprising that the powerful central mechanism of vestibulo-gastric illness arose in many different species." Motion sickness is disabling, unpleasant, and common. The central component is vomiting and the most frequently reported accompaniments are pallor, sweating, and nausea. To those who suffer from it, it is highly disadvantageous. Why then should it occur?

Two explanations have been advanced (*1*–*3*). The first, which attributes the condition to conflict between sensory inputs, was recently restated by Reason and Brand (*3*) who argue that "situations which produce motion sickness are all

characterized by a condition of *sensory rearrangement* in which the motion information signalled by the vestibular receptors, the eyes, and the non-vestibular proprioceptors, is at variance with the kinds of inputs that are expected on the basis of past experience . . . there appear to be two kinds of rearrangement responsible for motion sickness. One is . . . between the eyes and the vestibular receptors. The other is . . . between the semicircular canals and the otoliths." The second explanation attributes motion sickness to overstimulation. But this would not explain why stimuli such as those produced by riding on horseback do not, while riding on a camel or an elephant may produce the condition, and some mild stimuli, such as slow-rotation rooms, are effective. Money notes that both explanations attempt to find something noxious in the stimulus, but that even if this were so the occurrence of motion sickness would be no less of an evolutionary puzzle since vomiting does not make the stimulus less noxious.

There are two main ways in which to frame an evolutionary explanation of a phenomenon. First, it might in some way be beneficial to the species. But the vomiting response to motion has no apparent survival value and in some situations, for example, survivors on ocean rafts, has certainly contributed to many deaths. Second, the phenomenon may be a neutral side effect of a beneficial gene or genes. But motion sickness is both widespread in humans and occurs in a wide range of species, including horses, monkeys, sheep, some species of birds, and even codfish, but not rabbits or guinea pigs. It is implausible that a nonbeneficial pleomorphic effect would be manifested in so extensive a range of genetic contexts. Furthermore, the syndrome implies the existence of direct or indirect pathways between the visual and vomiting centers which represent a biological investment that is difficult to think of as arising as an accident. The condition is also so obviously disadvantageous that, if there were no positive reason for its presence, natural selection should have acted strongly to eliminate it, at least in species naturally exposed to passive movement such as arboreal animals or those that live in or venture into water. No wonder Money concludes that a "major advance in etiology is required before the essential nature of the sickness is revealed and vomiting is seen to be a logical response to motion in a healthy animal" (*1*).

The object of the present report is to redefine the nature of the situation that triggers the condition and on this basis to suggest an evolutionary explanation for its occurrence.

At almost every moment of waking life an animal must organize its movements in relation to a spatial framework. If it has a flexible neck it must do so in relation to at least three distinguishable sources of spatial information (disregarding auditory information). Its location in physical space is indicated by proprioceptive inputs, mainly derived from trunk and limbs, vestibular inputs, which specify the position of the head, and visual inputs, which establish a visual framework. These senses may be regarded as establishing three spatial reference systems, which require to be continuously coordinated with one another. Perceptual adaptation (*4*) may be taken to represent effects of the mechanisms by which these systems are constantly coordinated with and calibrated against one another. We may assume that incongruities, failures of correlation between one type of input and another, must constitute an immediate challenge to realign the conflicting systems. Such failures of correlation may arise and be responded to gradually, as when the limbs grow larger with the passage of the years, or acutely, as when one plunges into water. But every movement must involve continuous reference to and coordination between these systems. For example, turning to focus on a target glimpsed in the periphery of vision may involve visually guided eye movements, a head movement, perhaps mainly under vestibular guidance, and proprioceptively controlled compensatory or associated body movements. Failure of the attempt would constitute a challenge to examine the adequacy of each of these control systems and the mechanisms correlating them. More specifically, we may suppose there are mechanisms for relating visual and vestibular information, and for correlating information about the position of the head and that of the body.

The first suggestion follows from this analysis. It is that the trigger for motion sickness consists not in movement, or any particular class of movements per se, but in the occurrence of repeated challenges to redetermine the relations of the eye-head (*5*) or the head-body systems, or both. Such challenges would arise when the individual is placed in a situation in which, because it is unfamiliar or because it exceeds his adaptational capacity, one type of input is repeatedly misleading in what it predicts for another, and this affects some skilled motor performance such as fixation or maintaining head position. Thus the traveler in a boat or car may have an irregular series of impulses injected into the path representing the trace of his body or head position. Each of these impulses may demand modification or interruption of an eye movement, if he is attempting to fixate or track a target visually.

This suggestion is similar to the sensory conflict theory (*3*) but differs in that the trigger is seen to lie not in a conflict between the present pattern of input and past experience, but in the occurrence of a situation in which two closely coupled spatial reference systems (visual and vestibular, or vestibular and proprioceptive) must both be consulted continuously and in parallel in order to perform a motor task (which may be the control of eye position), but irregular or unpredictable perturbations are introduced into the previously established correlation or calibration between the two systems.

Why should this cause gastrointestinal disturbance? All species must have been under continuous evolutionary pressure to develop protections against ingesting or ingested toxins. There are three obvious levels of defense: rejection by taste, emesis provoked by effects on the stomach lining or by stimulation of appropriate chemoreceptors after absorption, and emesis evoked by early or minimal physiological disturbances produced by absorbed toxins. The second suggestion made here is that since the systems involved in controlling movement, including eye movements, and determining the location of the body in space are complex, almost continually in action and highly susceptible to even a minor degree of disruption, they constitute an ideal warning system for detecting early central effects of neurotoxins, where these have not activated more basic levels of defense. Naturally occurring toxins which affect the nervous system are likely to alter sensory inputs or motor coordination, or both. Even a minor degree of impairment of sensory (vestibular) input or of the coordination of eye muscles would produce mismatches between the systems. An emetic response to repeated such mismatches would be an advantageous adaptation for an unspecialized feeder which might ingest neurotoxins in vegetation or carrion. It is unfortunate that unusual or sophisticated situations, such as vehicular travel, should so often provide a stimulus of the same sort in man. But the syndrome which we may identify as "motion sickness" in the latter instance, "food-poisoning" in the former, would have the

same biological function in each case.

If this suggestion is correct, motion sickness is an adaptive response evoked by an inappropriate stimulus. It will be elicited by any situation which generates repeated challenges to the highly skilled and continuous information-processing activity responsible for maintaining the alignment between two closely coupled spatial reference systems.

A number of features of motion sickness support this hypothesis. The importance of the coordination between vestibular and proprioceptive sensation is attested by the finding that the movements of the head relative to the body caused by vehicular motion are larger in more susceptible subjects (*1*). If the head is held fast the amount of sickness falls. With few exceptions (for example, conditioned sickness) vestibular stimulation is necessary for motion sickness to occur. The disorder is not found when the vestibular system has been destroyed or the eighth nerves cut.

There is also evidence for the importance of the eye-head system. Movement of all or a large part of the field of vision without movement of the body can cause sickness. The ineffectiveness of movement of a small part of the field indicates that it is shift in the visual framework relative to that provided by other sensory systems that is the important factor. Movement of the visual field does not induce sickness when the labyrinths are defective, a disturbance of correlation between visual and proprioceptive inputs being ineffective alone. It is probable that proprioceptive and visual systems are at best only loosely coupled in the absence of vestibular information, and disparities do not lead to readjustive efforts or, if they do, since these might normally occur via recalibration in relation to the vestibular input in each case, they do not function as early warning signs of toxic effects.

Infants and young puppies appear not to be susceptible. This is consistent with the explanation offered since young mammals are fed on milk or preselected food which is unlikely to be toxic, and are often subject to random and unpredictable movements when they are carried. It may also be predicted that the condition should be rare in species with highly specialized or limited diets, or which are very tolerant of the toxins which may occur in their diets.

Vomiting, and the defecation and salivation which may also occur, are consistent with a reaction designed to eliminate toxins. But why do nausea and malaise occur? The answer may be that when an animal encounters a toxic substance it should not only eliminate it, it should also avoid it in future. There is now considerable evidence that gastrointestinal disturbance occurring some hours after ingesting a food and produced in various ways can cause a conditioned aversion to the tastes and smells experienced (*6*). This suggests that the subjectively unpleasant aspects of motion sickness, the nausea and malaise, may occur because they contribute to this process of aversive conditioning. A common symptom of motion sickness is unusual sensitivity to repulsive sights or odors, suggesting sensitization of previous aversive conditioning. The marked depression sometimes experienced may be part of the same phenomenon, but it might also be a precautionary adaptation, in view of the excitatory effects sometimes produced by ingested toxins.

Finally, one may note that other types of anomalous vomiting, such as that consequent on a head injury, raised intraocular pressure, or severe pain, may have analogous explanations: these conditions may activate the same or other toxin early warning systems.

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Refractoriness in Female Lizard Reproduction: A Probable Circannual Clock

Abstract. *Postreproductive* Cnemidophorus uniparens *maintained under free-running conditions of constant darkness for 7 months became reproductive at the same time as controls exposed to a long photoperiod. This lizard exhibits a pause in reproductive activity (refractory period) commencing in late summer in nature and terminating in mid-December in captivity. Both groups terminated refractoriness and started reproducing simultaneously in December despite maintenance of the experimental group in darkness since September. These results confirm the hypothesis that the refractory period in this lizard is under endogenous control.*

A distinctive feature of certain temperate lizards is an interval, like that shown by birds (*1*), following termination of breeding in nature, during which gonadal development cannot be stimulated experimentally by photothermal manipulation. Such a refractory period was first noted in lizards by Mayhew (*2*) and has subsequently been confirmed for several other species (*3–7*). Refractoriness commences more or less in late summer and terminates spontaneously in the laboratory approximately during November and December, after which warm temperature stimulates gonadal development regardless of photoperiod. Although light was previously considered the principal cue for lizard reproduction (*2, 8*), Tinkle and Irwin (*3*) revealed that in the lizard *Uta stansburiana*, photoperiod is not essential for timing the female reproductive cycle. Results with other temperate species (*4–7*) have confirmed Tinkle and Irwin's findings. In at least one of these species (*Cnemidophorus uniparens*), refractoriness is not at the level of the gonad but apparently at the hypothalamo-hypophysial level (*9*); the refractory period in this species is apparently under endogenous control (*10*). Although photothermal alterations do not seem to change timing of the reproductive cycle in these species, it is not clear what effect extended free-running conditions (all light or all dark and constant temperature) may have on the duration of the refractory period. Here we test the effects of prolonged darkness and warmth on reproductively refractive parthenogenetic lizards *C. uniparens* to further elucidate probable control of the refractory period.

Animals were collected between 6 and 10 June 1973 in Sierra County, New Mexico. They were housed in groups of three in 56-liter terraria and exposed to a photothermal regime of 14 hours of light and 10 of darkness (LD 14 : 10). Heat and light were provided by a 125-watt reflector lamp (General Electric) located 35