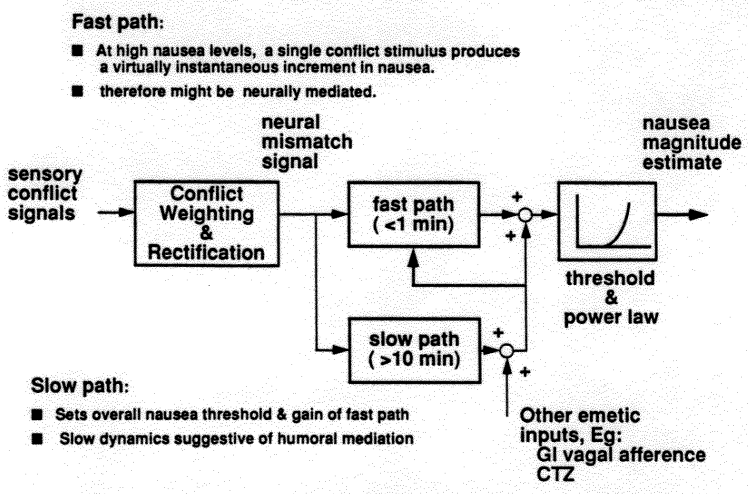

FIG. 4. Schematic diagram of revised model for nausea path symptom dynamics.

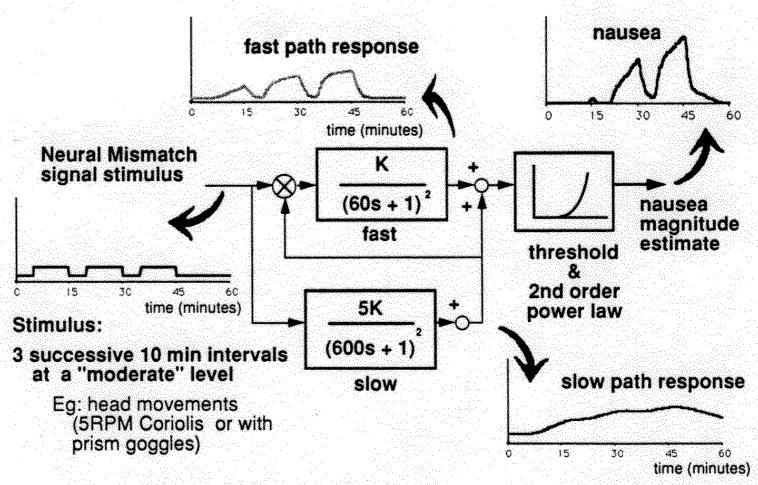

FIG. 5. Mathematical model for nausea path symptom dynamics. Insets show results of a computer simulation.

their relationship to the threshold element requires some explanation. In the past, many authors have assumed that sensory conflict coupling to symptom pathways is a temporary ("facultative") phenomenon. However, the author has argued (Oman 1982) that some level of subliminal sensory conflict coupling must be present in normal daily life because conflict signals seem to be continuously functionally "averaged" at subliminal levels, probably by the same mechanisms or processes that determine the intrinsic dynamics (latency, avalanching tendency, recovery time, etc.) of symptoms and signs when conflict exceeds normal levels. The output pathways probably consist functionally of dynamic elements followed by a threshold, and not the reverse, as would be the case if the linkage were temporary.

In the model, both fast and slow pathways represent neural or humoral processes that act to continuously accumulate (i.e., low pass filter or "leaky" integrate) weighted, rectified conflict signals. One block (the "fast path") has a relatively short characteristic response time and the other (the "slow path") a relatively long one. In the model simulations shown in the insets of Fig. 5, the fast path is a second-order low pass block with 1-min time constants; the slow path is a similar block with 10-min time constants. Second-order or higher block dynamics are required so that model predictions show characteristic

overshoot when the conflict stimulus is turned off. The slow path block normally has a higher gain (by a factor of about five) than the fast path, and at the beginning of stimulation is functionally the more important element. Slow path output acts together with other classes of fast-acting nauseogenic inputs (e.g., vagal afference from the gut or emetic drug stimulation) to bias the threshold of nausea response. In this model, the slow path block output also acts as a multiplicative factor on fast path response gain. When prolonged stimulation has raised the slow path output, the response of the fast path becomes much larger, as shown in the Fig. 5 simulation. Thus, the revised model mimics the much magnified response to incremental stimulation which we observe experimentally in long duration sickness. (In the 1982 version of this model, increased response sensitivity at high symptom levels was a consequence only of the time invariant power law magnitude estimation characteristic at the output of the model. This earlier model failed to adequately simulate the rapid rise and fall of sensation at high sickness levels).

The fast and slow dynamic elements in the model presumably describe the kinetics of either the orientation–emetic linkage mechanisms or the dynamic properties of the emetic centers themselves. The dynamic operators may approximate the action of some humoral diffusion or active transport process, or could be the intrinsic dynamics exhibited by a network of vomiting center neurons to direct neural or humoral conflict signal stimulation. For example, vestibular conflict neurons might work in synergistic pairs, somewhat as vestibular afferent neurons do, and project to neurons (perhaps in area postrema, AP) associated with nausea perception and vomiting. If the synapses were excitatory and had the character that a burst of conflict neuron activity produced a prolonged (e.g., 1 min) depolarization, "leaky integrator" dynamics would result. Carpenter et al. (1990) have described a class of AP neurons that respond qualitatively in this fashion to a variety of directly applied neurotransmitter agents. They attribute the long lasting depolarization of these neurons to a second messenger mechanism. Slow path dynamics might be associated with a potentiation of the fast path synaptic pathway by a third agent circulating from the hypothalamus–pituitary or diffusing through the ventricles. This slow path is presumably characterized by much slower response times. This speculative interpretation is mentioned here primarily to illustrate the kinds of physiological mechanisms that might be involved.

Conclusions

Because the contemporary conflict theory can account for the known forms of motion sickness, and for the role of active movement alleviating symptoms in some circumstances and causing them in others, there is strong circumstantial evidence that conflict neurons actually exist in the CNS. However, so far relatively few animal experiments have been conducted with the specific objective of identifying a "conflict" neuron or the emetic linkage process. The search has been largely limited to the vestibulo–ocular pathways in the brainstem and cerebellum. Recent experiments indicate that the cortex and limbic system are major sites for spatial orientation information processing. Real progress may be limited until orientation research focuses on these areas. Also although sensory conflict signals are probably neurally coded, as discussed in the previous section, conflict linkage mechanisms may involve humoral information transmission. If so, a search for the emetic link using classical anatomical or microelectrode techniques will of course be unsuccessful, and it is perhaps not particularly surprising that the link has not yet been found.

Another problem is that until motion sickness research entered the quantitative "as if" modelling phase, it has not been possible to suggest what functional criteria are imposed by the conflict theory which could be exploited by physiologists to recognize conflict neurons or the sensory mismatch signal experimentally. This paper represents a first attempt. Based on the discussion in previous sections, we can suggest the following.

(*i*) Conflict signals are error signals in CNS control pathways subserving posture and movement. Conflict coding is probably neural and conveys relatively high bandwidth signed information concerning the instantaneous difference between actual and motorically anticipated sensory input. Conflict signals are postulated to exist for at least the vestibular modalities, and it can be argued (see above) that they exist within the visual and (or) proprioceptive sensory modalities as well. In alert, behaving animals, the signals should be small during normal active movements and momentarily large when unexpected obstacles or disturbance forces are briefly encountered. As the animal recognizes and corrects for the disturbance, the conflict increase should extinguish. If the conflict process can be driven experimentally, conflict signals should produce behaviors suggestive of disorientation and may trigger corrective motor responses. Long duration direct stimulation of vestibular conflict processes should trigger motion sickness signs. Sustained, unpredictable, exogenous movement should produce prolonged sensory conflict and symptoms. Sensory rearrangements (e.g., visual distortion via prism goggles) should produce conflict that is reduced in magnitude as sensory–motor learning proceeds via internal model updating. These signals (or their combination, the neural mismatch signal) probably play some causal role in triggering sensory–motor learning. In general, the size of sensory conflict signals should be related to previous sensory–motor experience under identical sensory rearrangement conditions. When the rearrangement stimulus is removed, increased conflict signals of opposite sign should be observed. Antimotion sickness drugs probably have little effect on conflict signal size.

(*ii*) Efference copy signals that encode and subtractively completely cancel anticipated sensory inputs may not be found because their functional effect could be distributed along parallel pathways, as noted earlier.

(*iii*) The neural mismatch signal represents the putative common influence exerted on the emetic brain by conflict signals occurring in various sensory modalities. The signal may not be neurally coded. It should increase in magnitude with sensory conflict, regardless of the sign of the associated conflict. If the dynamics of the fast and slow path mechanisms originate in multiple diffusion and (or) transport processes, it may not be possible to directly experimentally find a single entity corresponding to the neural mismatch signal, but only signals corresponding to the output of the fast and slow path model elements.

The model presented here captures many of the known characteristics of motion sickness in at least semiquantitative fashion. However, the model has certain limitations that should be noted. The model posits an observer that is mathematically linear. Although recent experimental data certainly are consis-

tent with the notion that the CNS functions as an observer, there is some evidence that sensory cues are evaluated in nonlinear ways. Also, the model can only mimic, but not predict, the adaptation process. The model for symptom dynamics does not (yet) incorporate elements that account for observed autogenous "waves" of nausea at high symptom levels, nor the decrease in nausea immediately after emesis occurs. Models for response pathways mediating other physiologic responses such as pallor, skin temperature, and stress hormone changes have not yet been attempted.

Mathematical characterization of the dynamic characteristics of symptom pathways is a difficult "black box" system identification problem. The model described above was based only on the character of responses to exogenous motion and sensory rearrangements. The possibility of a secondary contribution by abdominal afferents due to visceral motion needs to be more completely explored. Much can potentially be learned from the study of dynamic responses to other classes of emetic inputs and from studying the influence of behavioral (e.g., biofeedback) and pharmacological therapies.

Acknowledgements

Supported by NASA–Johnson Space Center grant NAG9-244. The author is indebted to Dr. J. T. Reason, who in 1977 asked: "Isn't there some way to reconcile the Neural Mismatch model with the Kalman Filter approach?" and to Dr. R. Sivan, whose suggestion led to an answer. Dr. O. L. Bock made many contributions to our early experiments and models for human symptom dynamics. A major role in subsequent experiments was played by W. J. C. Cook, B. W. Ragues, and J. C. Eagon. The experiments were conducted under protocols approved by the MIT Committee on the Use of Humans as Experimental Subjects.

BARD, P., WOOLSEY, C. W., SNIDER, R. S., MOUNTCASTLE, V. B., and BROMLEY, R. B. 1947. Delimitation of central nervous system mechanisms involved in motion sickness. Fed. Proc. Fed. Am. Soc. Exp. Biol. **6**: 72.

BARON, S., and KLEINMAN, D. L. 1968. The human as an optimal controller and information processor. NASA Contract. Rep. CR-1151.

BOCK, O. L., and OMAN, C. M. 1982. Dynamics of subjective discomfort in motion sickness as measured with a magnitude estimation method. Aviat. Space Environ. Med. **53**: 773–777.

BORAH, J., YOUNG, L. R., and CURRY, R. E. 1978. Sensory mechanism modelling. U.S. Air Force Aeronaut. Syst. Div. Tech. Rep. AFHRL TR 78-83.

BORISON, H. L., and BORISON, R. 1986. Motion sickness reflex arc bypasses the area postrema in cats. Exp. Neurol. **92**: 723.

BRIZZEE, K. R., and NEAL, L. M. 1954. A reevaluation of the cellular morphology of the area postrema in view of recent evidence of a chemoreceptive function. J. Comp. Neurol. **100**: 41.

CARPENTER, D. O. 1990. Neural mechanisms of vomiting. Can. J. Physiol. Pharmacol. **68**: This issue.

CHINN, H. I., and SMITH, P. K. 1955. Motion sickness. Pharmacol. Rev. **7**: 33–82.

CLAREMONT, C. A. 1931. The psychology of seasickness. Psyche, **11**: 86–90.

CRAMPTON, G. H., and DAUNTON, N. G. 1983. Evidence for a motion sickness agent in cerebrospinal fluid. Brain Behav. Evol. **23**: 36–41.

EAGON, J. C. 1988. Quantitative frequency analysis of the electrogastrogram during prolonged motion sickness. MD thesis, Harvard–MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA.

EVERSMANN, T., GOTTSMANN, M., UHLICH, E., ULBRECHT, G., VON WERDER, K., and SCRIBA, P. C. 1978. Increased secretion of growth hormone, prolactin, antidiuretic hormone, and cortisol induced by the stress of motion sickness. Aviat. Space Environ. Med. **49**: 53–57.

GRAYBIEL, A. 1975. Angular velocities, angular accelerations, and coriolis accelerations. Chap. 7. *In* Foundations of space biology and medicine. Vol. II, Book 1. NASA/USSR Academy of Sciences, Washington, DC.

GRAYBIEL, A., WOOD, C. D., MILLER, E. F., and CRAMER, D. B. 1968. Diagnostic criteria for grading the severity of acute motion sickness. Aerosp. Med. **39**: 453–455.

GUEDRY, F. E. 1965. Psychophysical studies of vestibular function. *In* Contributions of sensory physiology. Vol. 1. *Edited by* W. D. Neff. Academic Press, NY. pp. 63–135.

——— 1968. Conflicting sensory orientation cues as a factor in motion sickness. Fourth Symposium on the Role of the Vestibular Organs in Space Exploration. NASA (Spec. Publ.) SP-187. pp. 45–51.

——— 1978. Visual counteraction of nauseogenic and disorienting effects of some whole body motions — a proposed mechanism. Aviat. Space Environ. Med. **49**: 36–41.

HEIN, A., and HELD, R. 1961. A neural model for labile sensorimotor coordinations. Biol. Prototypes Synth. Syst. **1**: 71–74.

HELD, R. 1961. Exposure history as a factor in maintaining stability of perception and coordination. J. Nerv. Ment. Dis. **132**: 26–32.

HENN, V., COHEN, B., and YOUNG, L. 1980. Visual vestibular interaction in motion perception and the generation of nystagmus. Neurosci. Res. Program Bull. 18, No. 4.

JAMES, W. 1882. The sense of dizziness in deaf mutes. Am. J. Otol. **4**: 239–250.

JANOWSKY, D. S., RISCH, S. C., ZIEGLER, M., KENNEDY, B., and HUEY, L. 1984. A cholinomimetic model of motion sickness and space adaptation syndrome. Aviat. Space Environ. Med. **55**: 692–696.

KALMANN, R. E. 1960. Contributions to the theory of optimal control. Biol. Soc. Mat. Mex. **5**: 102–119.

KALMAN, R. E., and BUCY, R. S. 1961. New results in linear filtering and prediction theory. Trans. ASME, Ser. D: J. Basic Eng. **83**: 95–108.

KOHL, R. L. 1985. Endocrine correlates of susceptibility to motion sickness. Aviat. Space Environ. Med. **56**: 58–65.

MELVILL JONES, G. 1974. Adaptive neurobiology in space flight. Proceedings of the Skylab Life Sciences Symposium. Vol. 2. NASA TMX–58154.

MILLER, A. D. 1988. Motion-induced nausea and vomiting. Chap. 5. *In* Nausea and vomiting: recent research and clinical advances. *Edited by* R. K. Harding, J. Kucharczyk, and D. J. Stewart. CRC Press, Cleveland.

MILLER, A. D., and WILSON, V. J. 1983*a*. Vestibular-induced vomiting after vestibulocerebellar lesions. *In* Mechanisms of motion induced vomiting. Brain Behav. Evol. **23**: 26–31.

———1983*b*. Vomiting center reanalyzed: an electrical stimulation study. Brain Res. **270**: 154–158.

MILLER, A. D., TAN, L. K., and SUZUKI, I. 1987. Control of abdominal and expiratory intercostal muscle activity during vomiting; role of ventral respiratory group expiratory neurons. J. Neurophysiol. **57**: 1854–1866.

MONEY, K. E. 1970. Motion sickness. Physiol. Rev. **50**: 1–39.

OMAN, C. M. 1978. A sensory motor conflict model for motion sickness. Workshop III presentation. Space Motion Sickness Symposium, November 16, 1978, NASA Johnson Space Center, Houston, TX.

——— 1982. A heuristic mathematical model for the dynamics of sensory conflict and motion sickness. Acta Oto-Laryngol. Suppl. 392.

——— 1987. Spacelab experiments on space motion sickness. Acta Astronaut. **15**: 55–66.

OMAN, C. M., and COOK, W. J. C. 1983. Dynamics of skin pallor in motion sickness as measured using an infrared reflectance technique. 54th Annual Aerospace Medical Association Meeting, May 1983, Houston, TX.

OMAN, C. M., COOK, W. J. C., REGE, O., SAPIRSTEIN, J., and NICHOLS, T. 1986. Time course of skin pallor in motion sickness. Abstracts of 7th International Man in Space Symposium, February 13, 1986, Houston, TX.

RAGUE, B. W., and OMAN, C. M. 1987. Use of a microcomputer system for running spectral analysis of EGG's to predict the onset of motion sickness. Proceedings of the 9th Annual Conference on IEEE Engineering Med. Biol. Soc. (Boston), **1**: 87–90.

REASON, J. T. 1969. Motion sickness: some theoretical considerations. Int. J. Man-Mach. Stud. **1**: 21–38.

——— 1978. Motion sickness adaptation: a neural mismatch model. J. R. Soc. Med. **71**: 819–829.

REASON, J. T., and BRAND, J. J. 1975. Motion sickness. Academic Press, London.

STEELE, J. E. 1968. The symptomatology of motion sickness. Fourth Symposium on the Role of the Vesticular Organs in Space Exploration. NASA (Spec. Publ.) SP-187.

STEVENS, S. S. 1957. On the psychophysical law. Psychol. Rev. **64**: 153–184.

TYLER, D. B., and BARD, P. 1949. Motion sickness. Physiol. Rev. **29**: 311–369.

VON HOLST, E. 1954. Relations between the central nervous system and the peripheral organs. Br. J. Anim. Behav. **2**: 89–94.

WANG, S. C., and BORISON, H. L. 1950. The vomiting center: a critical experimental analysis. Arch. Neurol. Psychiatry, **63**: 928–941.

WANG, S. C., and CHINN, H. I. 1953. Vestibular reflex pathway in experimental motion sickness in dogs. Abstracts of the XIX International Physiological Congress, Montreal. pp. 868–869.

——— 1954. Experimental motion sickness in dogs: functional importance of chemoreceptive emetic trigger zone. Am. J. Physiol. **178**: 111–116.

——— 1956. Experimental motion sickness in dogs: importance of labyrinth and vestibular cerebellum. Am. J. Physiol. **185**: 617–623.

WILPIZESKI, C. R., LOWRY, L. D., and GOLDMAN, W. S. 1986. Motion-induced sickness following bilateral ablation of area postrema in squirrel monkeys. Laryngoscope, **96**: 122.

WONHAM, W. H. 1968. On the separation theorem of stochastic control. SIAM J. Control, **6**: 312–326.

YOUNG, L. R. 1970. On visual vestibular interaction. Proceedings of the 5th Symposium on the Role of the Vestibular Organs in Space Exploration. NASA (Spec. Publ.) SP 314.