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Chapter 27

Motion sickness

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Abstract

Over 2000 years ago the Greek physician Hippocrates wrote, "sailing on the sea proves that motion disorders the body." Indeed, the word "nausea" derives from the Greek root word *naus*, hence "nautical," meaning a ship. The primary signs and symptoms of motion sickness are nausea and vomiting. Motion sickness can be provoked by a wide variety of transport environments, including land, sea, air, and space. The recent introduction of new visual technologies may expose more of the population to visually induced motion sickness. This chapter describes the signs and symptoms of motion sickness and different types of provocative stimuli. The "how" of motion sickness (i.e., the mechanism) is generally accepted to involve sensory conflict, for which the evidence is reviewed. New observations concern the identification of putative "sensory conflict" neurons and the underlying brain mechanisms. But what reason or purpose does motion sickness serve, if any? This is the "why" of motion sickness, which is analyzed from both evolutionary and nonfunctional maladaptive theoretic perspectives. Individual differences in susceptibility are great in the normal population and predictors are reviewed. Motion sickness susceptibility also varies dramatically between special groups of patients, including those with different types of vestibular disease and in migraineurs. Finally, the efficacy and relative advantages and disadvantages of various behavioral and pharmacologic countermeasures are evaluated.

SIGNS AND SYMPTOMS

The primary signs and symptoms of motion sickness are nausea and vomiting. The aversive nature of nausea and vomiting due to motion sickness was exploited in historic times both as an unusual form of punishment (Reason and Brand, 1975) and also as a strange type of therapy (Harsch, 2006). Other related symptoms include stomach awareness, sweating and facial pallor (sometimes called "cold sweating"), increased salivation, sensations of bodily warmth, dizziness, drowsiness (also denoted as the "sopite syndrome"), sometimes headache, and unsurprisingly, loss of appetite and increased sensitivity to odors. The importance and negative impact on performance of "sopite" are often underestimated (Lackner, 2014). Yawning has been shown to be a behavioral marker for the sopite syndrome and consequent reduced task performance (Matsangas and McCauley, 2014).

A typical motion sickness questionnaire is shown in Table 27.1, which lists the more frequent symptoms, excluding vomiting and facial pallor. This is an adaptation of the simulator sickness questionnaire (Kennedy and Fowlkes, 1992). The occurrence of oculomotor symptoms (such as eye strain, difficulty focusing, also headache) is relatively higher in situations where visual mismatches may be the provoking stimulus, such as in simulators and virtual-reality systems, as opposed to motion sickness due to whole-body accelerative stimuli such as during ship motion. Headache is provoked more by visual than real motion, even when the real motion is twice as provocative as visual motion in terms of nauseogenicity (Bijveld et al., 2008). For a more rapid assessment, the following global sickness rating scale has proved reliable and useful: 1 = no symptoms; 2 = initial symptoms of motion sickness but no nausea; 3 = mild nausea; 4 = moderate nausea; 5 = severe nausea and/or retching; 6 = vomiting (Golding et al., 2003).

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Table 27.1

Symptom questionnaire for motion sickness (excludes facial pallor and vomiting)

Do you have any of the following symptoms right now? (tick boxes)				
	0	1	2	3
	None	Slight	Moderate	Severe
General discomfort				
Fatigue				
Headache				
Eye strain				
Difficulty focusing				
Increased salivation				
Sweating				
Nausea				
Difficulty concentrating				
Fullness of head				
Blurred vision				
Dizziness (eyes open)*				
Dizziness (eyes closed)*				
Vertigo				
Stomach awareness				
Burping				

*Illusory feelings of motion.

Physiologic responses associated with motion sickness may vary between individuals. These include autonomic changes such as sweating and vasoconstriction of the skin causing pallor (less commonly, skin vasodilation and flushing in some individuals), with the simultaneous opposite effect of vasodilation and increased blood flow of deeper blood vessels, changes in heart rate which are often an initial increase followed by a rebound decrease, and inconsistent changes in blood pressure (Benson, 2002). Gastric stasis occurs for the stomach and increased frequency and reduced amplitude of the normal electogastric rhythm (Stern et al., 1985; Koch, 2014). The drop in stomach fundus and sphincter pressure correlates with the nausea of motion sickness (Schaub et al., 2014). A host of hormones are released, mimicking a generalized stress response, amongst which vasopressin is thought to be most closely associated with the time course of motion sickness (Eversmann et al., 1978). The observation of cold sweating suggests that motion sickness may disrupt

aspects of temperature regulation (Golding, 1992). This notion is also consistent with the observation that motion sickness reduces core body temperature during cold-water immersion, accelerating onset of hypothermia (Cheung et al., 2011).

Although motion sickness is unpleasant in its own right, under some circumstances it may have adverse consequences for performance and even for survival. Motion sickness preferentially causes decrements on performance of tasks that are complex, require sustained attention, and offer the opportunity of the person to control the pace of effort (Hettinger et al., 1990). Simple tasks and overlearned tasks are less susceptible to performance decrements caused by motion sickness, whereas novel tasks and cognitive tasks involving spatial orientation processing are particularly vulnerable (Gresty and Golding, 2009). For pilots and aircrew, motion sickness can slow training in the air and in simulators and even cause a minority to fail training (Benson, 2002). Approximately 70% of novice astronauts will suffer some degree of space sickness in the first 24 hours of flight. Although vomiting in space is doubtless unpleasant, the possibility of vomiting while in a spacesuit in weightlessness is potentially life-threatening, consequently precluding extravehicular activity for at least the first 24 hours of spaceflight (Heer and Paloski, 2006). For survival at sea, such as in in liferafts, sea sickness can reduce survival chances by a variety of mechanisms, including reduced morale and the "will to live," failure to consistently perform routine survival tasks, dehydration due to loss of fluids through vomiting (Benson, 2002), and possibly due to the increased risk of hypothermia (Cheung et al., 2011).

PROVOCATIVE CIRCUMSTANCES

There is a potential for motion sickness to be caused in a wide range of situations – in cars, tilting trains, funfair rides, aircraft, weightlessness in outer space, virtual reality and simulators (Table 27.2). The classic provocative environment is at sea, as observed by the Greek physician Hippocrates over 2000 years ago, "sailing on the sea proves that motion disorders the body." Indeed, the word nausea derives from the Greek root word *naus*, hence nautical, meaning a ship. The general term motion sickness embraces sickness provoked by a wide variety of environments, car sickness, air sickness, space sickness, sea sickness, cinerama sickness, simulator sickness. Interestingly, sound cues can be added to this list, since vection (illusory self-motion) can be induced using moving (rotating) auditory cues in the laboratory. However, auditory-induced vection is much weaker than equivalent visually induced vection and, unlike visual motion, auditory cues for implied motion are unlikely to produce significant sickness, except for the most susceptible individuals (Keshavarz et al., 2014).

Estimates for incidence rates of motion sickness vary widely, partly due to individual differences in susceptibility and also because superficially similar transport environments can vary dramatically in terms of their motions and consequent nauseogenicity. For example, although air travel in small planes that can encounter low-altitude air turbulence can provoke motion sickness in about 25% of passengers, flights in large airliners have incidence rates of less than 1% (Murdin et al., 2011). Long-distance coach journeys can cause some symptoms of motion sickness in over

Table 27.2

Provocative stimuli for motion sickness

Context	Examples of provocative stimuli for motion sickness
Land	Cars, coaches, tilting trains, skiing, riding camels, elephants, funfair rides
Sea	Boats, ferries, survival rafts, divers' lines undersea
Air	Transport planes, small aircraft, hovercraft, helicopters, parabolic flight
Space	Shuttle, spacelab
Optokinetic*	Wide-screen cinemas, microfiche-readers, "haunted swing," simulators, virtual reality (head mounted display, HMD), rotating visual drums or spheres, pseudo-Coriolis, reversing prism spectacles
Laboratory†	Cross-coupled (Coriolis) stimuli. Low-frequency translational oscillation (vertical or horizontal), off-vertical axis rotation (OVAR), counterrotation, **g** excess in human centrifuges, auditory vection (a very weak stimulus)
Associated‡ stimuli	Emetic toxins, chemotherapy, postoperative nausea and vomiting (PONV), extreme arousal (fear increases/fight decreases)

*Optokinetic stimuli are classed separately since they do not need additional physical transportation of the person under all definitions, although some might be also classed under Laboratory.

†Laboratory stimuli evoking motion sickness are simply refined elements of those provocative stimuli found in the outside world.

‡Associated stimuli are included to indicate the basic evolutionary functions served by nausea and vomiting.

a third of passengers (Turner and Griffin, 1999b) and a quarter of co-drivers became motion sick in rally cars (Perrin et al., 2013). In an extensive survey of cruise ships, motion sickness was the most common reason for physician consultations; the incidence was 4.2 per 1000 person/days, being higher than for infections or injuries (Schutz et al., 2014). Incidences can be much higher in small boats and rough seas. In liferafts, incidence rates of over 50% vomiting have been observed after 1 hour of moderate sea motion (Benson, 1999).

Cinerama sickness has long been known to affect a small percentage of the population, with less than 6% having any symptoms at all (Golding, 2006a), but the widespread introduction of new visual technologies may pose more of a problem. Technologies such as virtual reality and three-dimensional (3-D) stereoscopic video films may provoke more motion sickness than 2-D films. Although one study found only low levels of sickness, with no clear differences between viewing 2-D versus 3-D video (Pölönen et al., 2013), the majority of studies suggest that the new 3-D visual technologies are more provocative of motion sickness and pose a problem for some viewers (Bos et al., 2013; Naqvi et al., 2013; Solimini, 2013).

MECHANISMS AND THEORIES FOR MOTION SICKNESS

Mechanisms

The generally accepted explanation of the "how" or mechanism of motion sickness is based on some form of sensory conflict or sensory mismatch between actual versus expected invariant patterns of vestibular, visual, and kinesthetic inputs, as predicted by an "internal model." A key observation leading to the understanding of this concept is that the physical intensity of the stimulus is not necessarily related to the degree of nauseogenicity (Golding, 2006b). For example, with optokinetic stimuli, the motion is implied, but not real. A person sitting at the front in a wide-screen cinema experiences self-vection and cinerama sickness, but there is no physical motion of the body in the real world. The vestibular and somatosensory systems are signaling that the person is sitting still, but the visual system is signaling illusory movement or self-vection. Consequently, the generally accepted explanation of the "how" of motion sickness is based on some form of sensory conflict or sensory mismatch.

Sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual, and kinesthetic inputs (Claremont, 1931; Reason and Brand, 1975). These also include intravestibular conflicts between rotational accelerations sensed by the semicircular canals and linear-translational accelerations (including gravitational), sensed by the otolith organs. A variety of detailed hypotheses have been developed to explain the exact nature of sensory conflict or sensory mismatch (e.g., Oman, 1990; Benson, 1999). Benson (2002) categorized neural mismatch into two main types: (1) conflict between visual and vestibular inputs or (2) mismatch between the canals and the otoliths. An even more simplified model was proposed by Bos and Bles (1998). They postulated that there is only one conflict: between the subjective expected vertical and the sensed vertical. However, despite this simplification, their underlying model is necessarily complex and finds difficulty in accounting for the observation that motion sickness can be induced by types of optokinetic stimuli which pose no conflict concerning the earth-vertical (Bubka et al., 2006). Most models of motion sickness also incorporate integrator and decay systems in which the rate of accumulation of "sensory conflict" is processed by leaky integrators with different time constants (Oman, 1990). This process can be below conscious experience until a threshold is reached signaling the onset of overt symptoms and the awareness of the beginning of motion sickness (Golding and Stott, 1997a).

The "rule of thumb" model originally advanced by Stott (1986) is not the most elegant in theoretic terms, but arguably is still the most practical. This model proposes a set of simple rules, which, if broken, will lead to motion sickness:

1. Visual-vestibular: motion of the head in one direction must result in motion of the external visual scene in the opposite direction.
2. Canal-otolith: rotation of the head, other than in the horizontal plane, must be accompanied by appropriate angular change in the direction of the gravity vector.
3. Utricle-saccule: any sustained linear acceleration is due to gravity, has an intensity of 1 **g**, and defines "downwards."

In other words, the visual world should remain space-stable, and the sustained force vector is gravity, which should always point down and average over a few seconds to 1 **g**.

In some environments there may be only one provocative stimulus. At sea it is the low-frequency "heave" motion of the vessel that provokes sea sickness. However in many environments multiple stimuli and conflicts may be involved. For example, air sickness in a pilot produced by the flight of an agile military aircraft may be due to up to five sources (Golding, 2006b). Flying through air turbulence produces low-frequency translational oscillation of the aircraft, which may cause air sickness. In addition, during aircraft turns there may be provocation from the four following sources: visual-vestibular mismatches as the pilot senses "down" to remain through the axis of the body but the external visual world to be tilted;

sustained changes in the scalar magnitude of gravitoinertial force (GIF) due to centripetal acceleration; cross-coupling (Coriolis) due to head movements during rotation of the aircraft if the turn is tight enough; and also the **g**-excess illusion if the pilot tilts the head during increased GIF.

In virtual-reality systems and simulators, self-vection, retinal slip, and poor eye collimation may be an important provocative stimulus, but phase lag between real motion and the corresponding update of the visual display may be equally or more important. Compensatory vestibulo-ocular reflexes (VORs) to head movements are as fast as 10 ms; consequently, visual update lag disparities not much longer than this may be easily detectable by subjects. If visual display update lags are much longer than this, they may provoke sickness, since it has been shown that virtual-reality sickness has been induced with update lags as short as 48 ms (Golding, 2006b).

Low-frequency translational motion is a major source of motion sickness in land vehicles, ships, and aircraft, and has been sufficiently well described to provide engineering design parameters (exposure time, acceleration, frequency) for standards regulated by the International Standards Organization (ISO 2631, 1997). The frequency weighting function is of theoretic as well as applied interest. Laboratory experiments (O'Hanlon and McCauley, 1974; Golding et al., 2001) and ship motion surveys (Lawther and Griffin, 1988) have shown that nauseogenicity increases as a function of exposure time and acceleration intensity, as might be expected, but, more unusually, that nauseogenicity peaks at the low-frequency motion of around 0.2 Hz. Such low-frequency motions are present in transportation in ships, coaches, aircraft flying through air turbulence, and on camels and elephants, all of which can provoke motion sickness.

This frequency relationship also explains why some forms of transport are not provocative; for example people do not experience horse sickness. During horse riding, walking, running, and riding off-road trail bikes, the frequencies are higher than 1 Hz. Consequently, although these motions can be quite severe (capable of bruising the person), they are not nauseogenic (Golding, 2006b). Hypotheses for the frequency dependence of nauseogenicity of translational oscillation are a phase error in signaling motion between canal-otolith and somatosensory systems (Von Gierke and Parker, 1994; Benson, 1999), or a frequency-dependent phase error between the sensed vertical and the subjective or expected vertical (Bos and Bles, 1998). It has also been proposed that a zone of perceptuomotor ambiguity around 0.2 Hz triggers sickness, since at higher frequencies imposed accelerations are usually interpreted as translation of self through space, whereas at lower frequencies imposed accelerations are usually interpreted as a shift in the main force vector, i.e., tilt of self with respect to the assumed gravity vertical (Golding et al., 2003; Golding and Gresty, 2005). The region of 0.2 Hz would be a cross-over between these two interpretations and, thus, a frequency region of maximal uncertainty concerning the correct frame of reference for spatial orientation. More recently, Gresty et al. (2011) proposed a related ecologic explanation, that this frequency tuning of motion sickness is related to mechanical limitations on human body motion. This proposes that a cause of motion sickness may be difficulty in selecting appropriate tactics to maintain body stability at vehicle motion *ca.* 0.2 Hz, between whole-body GIF alignment seen at lower frequencies versus lateropulsion seen at higher frequencies.

Although the physiologic mechanisms are still not fully known, understanding of the brain mechanisms which underpin sensory conflict and motion sickness has progressed greatly. In a series of elegant experiments, Oman and Cullen (2014) have identified brainstem and cerebellar neurons whose activity corresponds to what might be expected of putative sensory conflict neurons. The pathways that integrate vestibular and emetic gastrointestinal signals that produce nausea and vomiting are being elucidated (Yates et al., 2014). The concept of a discrete brainstem area postrema "vomiting center" has been superseded by the picture of a network of nuclei, including the nucleus tractus solitarius (NTS) and the medullary reticular formation. It seems that the same brainstem areas mediate vomiting and nausea irrespective of the triggering mechanism, whether motion or toxins. These brainstem areas not only include the NTS but also the dorsolateral reticular formation of the caudal medulla (lateral tegmental field), and the parabrachial nucleus, which act together to integrate signals that lead to nausea and vomiting (Yates et al., 2014). The NTS is the terminus of many visceral afferents and it also receives efferent projections from the area postrema. The NTS is now known to relay signals to the emesis pattern generator. In addition, neurons in the vestibular cerebellum, including the fastigial nucleus, are influenced by visceral afferents. Galvanic vestibular stimulation in the cat has been shown to produce patterns of neural activation revealed by c-fos labeling, some of which correlate with overt signs of motion sickness, others of which show no such relationship but may relate to covert affective aspects such as nausea (Balaban et al., 2014). The onset of visually induced nausea in humans has been studied with functional magnetic resonance imaging (fMRI) (Napadow et al., 2013a). Increased activity preceding nausea was found in the amygdala, putamen, and dorsal pons/locus coeruleus, whereas, with onset

of nausea, activity was observed in a broader network, including insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices. Strong nausea was associated with sustained anterior insula and midcingulate activation, suggesting a closer linkage between these specific regions within the brain circuitry subserving nausea perception (Napadow et al., 2013a).

Why does motion sickness exist?

By contrast with the "how" of motion sickness, (i.e., the mechanisms), for which there is some consensus concerning sensory conflict, there are widely differing opinions concerning the "why" of motion sickness, or even if it is a useful question to ask. The primary functions of the vestibular system are spatial orientation, maintenance of balance, and stabilizing of vision through VORs. Additional vestibular functions have been proposed to explain the "why" of motion sickness. These hypotheses can be classified broadly into: poison detector; vestibular cardiovascular/autonomic reflex; disorientation/motor warning; and nonfunctional evolutionary maladaptation.

The poison or toxin detector hypothesis states that the vestibular system can act as a toxin detector. Thus, the evolutionary purpose of what we call motion sickness is postulated to be the same as for any emetic response, which is to protect the organism from the toxic effects of potentially harmful substances that it may have ingested (Treisman, 1977). The toxin detector hypothesis proposes that the brain has evolved to recognize any derangement of expected patterns of vestibular, visual, and kinesthetic information as evidence of central nervous system malfunction and to initiate vomiting as a defense against a possible ingested neurotoxin. In other words, it provides a backup to the main toxin detector system of chemoreceptors of the afferent vagal nerves and the chemoreceptor trigger zone of the brainstem.

To summarize this hypothesis, motion sickness in pedestrian humans or other animals is simply the inadvertent activation of this ancient defense reflex by the sensory conflicts induced by the novel altered visual and force environments of sea, air, land transport, space, and virtual reality (Golding, 2006b). This evolutionary-based hypothesis is consistent with the observation that motion sickness is evolutionarily well preserved, from humans down to the level of the fish (ironically, fish can become sea sick during aquarium transport) (Reason and Brand, 1975). It is also consistent with the observation that people who are more susceptible to motion sickness are also more susceptible to toxins, chemotherapy, and postoperative nausea and vomiting (PONV) (Morrow, 1985; Golding, 1998). There have also been further attempts to test the toxin detector hypothesis by seeing whether individual differences in bitter taste sensitivity and aversion, which reflects activity of one part of the primary toxin detector system, correlates with motion sickness susceptibility, thought to reflect activity in the hypothetical backup toxin detector system. However, unlike the well-proven associations of motion sickness susceptibility with chemotherapy sickness or PONV, these bitter-taste studies have provided contradictory results. Positive correlations (Sharma et al., 2008), negative correlations (Benson et al., 2012), or no significant correlations (Golding and Tayyaba, 2014) for bitter-taste sensitivity with motion sickness susceptibility have been reported. Finally, perhaps the most convincing evidence is that the toxin detector hypothesis has been experimentally tested in animals. This demonstrated that emetic responses to challenges from emetogenic toxins were significantly reduced after bilateral vestibular ablation (Money and Cheung, 1983).

The vestibular cardiovascular/autonomic reflex hypothesis is based on the observation that tilt stimulation of the otolith organs, which transduce linear accelerations, provokes a pressor response (increased blood pressure and cardiac output) mediated via vestibular-cardiovascular projections (Yates et al., 1998). It has been proposed that motion sickness is caused by the inappropriate activation of such vestibular-cardiovascular reflexes. The general concept is that the vestibular and visual systems influence autonomic control for the purpose of maintaining homeostasis during movement and changes in posture. Thus, motion sickness arises from an aberrant activation of neural pathways that serve to maintain a stable internal environment (Yates et al., 1998).

A somewhat similar, but nonfunctional, explanation has been proposed by Balaban (1999): that motion sickness might be regarded as referred visceral discomfort after activation of vestibular autonomic reflexes due to the convergence of vestibular and autonomic afferent information in the brainstem and cerebellum. The vestibular-cardiovascular reflex hypothesis has a good historic pedigree in the 19th-century concept of "cerebral anemia" as the cause of motion sickness (Nunn, 1881). Although some support is provided by the observation that cerebral hypoperfusion preceded nausea during GIF variation induced by centrifugation (Serrador et al., 2005), the situation is unclear, since there is considerable overlap between sick and nonsick individuals' pressor responses to motion sickness induced by the GIF variation of parabolic flight (Schlegel et al., 2001).

The importance of the vestibular-cardiovascular reflexes in maintaining blood pressure may be limited, at least in humans. Bilateral labyrinthectomized patients' pressor responses to rapid tilts are only minimally slower than normal subjects (<500 ms) (Radtke et al., 2003), and these patients do not appear to be fainting frequently

as they adjust their posture during everyday activity as they walk around, lie down, and stand up. Moreover, although not a formal disproof, this hypothesis does not predict the relative nauseogenicity of the various gravity-referenced and body-referenced directions of motions that would be expected to alter blood pressure (Golding et al., 1995, 2003).

The disorientation/motor warning hypothesis postulates that motion sickness is a punishment system which has evolved to discourage development of perceptual-motor programs that are inefficient or cause spatial disorientation (Guedry et al., 1998). In other words, this system has evolved to discourage self-exposure to circumstances causing disorientation or motor instability. An extension of this hypothesis is that prostration caused by motion sickness reduces the likelihood of injury or vulnerability to predators (Bowins, 2010). Recent variants of this last idea postulate that motion sickness evolved to discourage risky activity in ancestral fish that were suffering vestibular malfunction (Thornton and Bonato, 2013), or that proto-hominids would avoid looking for food in swaying trees that might threaten security; thus tending to survive (Knox, 2014). However an unanswered difficulty with all disorientation/motor warning hypotheses is: why would evolution select such slow-onset negative reinforcers such as nausea and vomiting, rather than the readily available rapid warning systems of fear and pain?

The most reductionist approach is the evolutionary maladaptation hypothesis (Oman, 2012). Evolution is not perfect: an example of evolutionary maladaptation is the co-location of the entries to the respiratory airways and the esophagus in many land animals, which makes them susceptible to death by choking. From the perspective of the evolutionary maladaptation hypothesis, motion sickness is just an unfortunate consequence of the physical proximity of the motion detector (vestibular) and vomiting circuitry in the brainstem. It is just bad luck. Oman (2012) has stated that adaptive hypotheses for motion sickness such as the toxin detector hypothesis are "naïve 'just-so' stories" (Oman, 2012, p. 125), the reference being to the children's stories by the author Rudyard Kipling providing amusing and fanciful explanations for differing animal characteristics, for example, such as how the elephant got its trunk, the leopard its spots. Oman (2012), to support his critique, notes: (1) that every symptom of motion sickness does not exactly match up with those evoked by food poisoning; and (2) that bilateral vestibular ablation does not totally prevent vomiting to all toxins, as observed by Money and Cheung (1983). However, these two criticisms, although valid, are not decisive. Criticism 1, about patterns of symptoms, is limited, since it is known that, apart from nausea and vomiting, there is no exact profile of symptoms. Symptoms vary considerably for many reasons, among different individuals, among different types of poisoning, and among different types of provocative motion stimuli. Criticism 2, that bilateral vestibular ablation does not abolish vomiting to all emetogenic poisons, misses the point that the toxin detector hypothesis for motion sickness does not claim this. The toxin detector hypothesis only postulates that the vestibular system provides a useful backup to the main toxin detector system of chemoreceptors of the afferent vagal nerves and the chemoreceptor trigger zone of the brainstem.

To summarize, all of the above hypotheses remain in contention to provide explanations for the "why" of motion sickness. If motion sickness is just a random and complicated evolutionary maladaptation, then it has been remarkably well preserved across species, from fishes to humans, and, by implication, over many millions of years. At present, the balance of evidence would seem to favor either the functional explanation of the toxin detector hypothesis or the "bad luck" evolutionary maladaptation hypothesis.

PREDICTORS OF MOTION SICKNESS SUSCEPTIBILITY

Concept of motion sickness susceptibility

Any concept of individual differences in motion sickness susceptibility must acknowledge the multifactorial nature of motion sickness susceptibility itself. At least three processes are thought to be at work: initial sensitivity to motion, rate of natural adaptation, and the ability to retain protective adaptation in the longer term (Reason and Brand, 1975). Moreover, correlations among various types of motion challenges are not high (Lentz, 1984), implying differential sensitivity in individuals to different types of motion. For example, the correlation between individual susceptibility to translational versus cross-coupled (Coriolis) motion can sometimes be very low (Golding, 2006b). Factor analysis of self-report questionnaires, designed to assess susceptibility to motion sickness, suggests the existence of independent latent susceptibilities to different types of provocative environments, usually forming factors that might be termed transportation by land, air, sea, or funfair rides (Golding, 1998). This might seem to contradict the notion of a general motion susceptibility dimension. Nevertheless, these apparently contradictory views can be argued to both be true, i.e., general motion susceptibility factors and specific factors both exist. Other limitations are imposed by the test–retest reliability of response to a motion challenge, which may be estimated from repeated exposures in the laboratory to be around $r = 0.8–0.9$ (Golding, 2006b).

Motion Sickness Susceptibility Questionnaires (MSSQs: sometimes called Motion History Questionnaires) enable a rapid estimate to be made of an individual's susceptibility. A typical questionnaire is shown in Table 27.3, and this has been validated to predict motion sickness to motion stimuli in the laboratory and in transport environments (Golding, 2006a). An overall indicator of susceptibility may be calculated as the MSSQ score = (total sickness score) × (18) / (18 – number of types not experienced). This formula corrects for differing extent of exposure to different motion stimuli in individuals. For the normal young adult population, the median MSSQ score is 11.3, where higher scores indicate greater susceptibility, and vice versa. More details are given in the original reference (Golding, 2006a).

Genetics

Individuals vary widely in their susceptibility, but nearly all people can be made motion-sick given a sufficiently provocative stimulus. Lackner (2014) has suggested that susceptibility in the general population varies by a vast range: about 10 000–1. There is a large genetic contribution to the individual differences in susceptibility. Monozygotic and dizygotic twin studies indicate that the heritability of motion sickness is high, at around 70%, in childhood and declines through puberty and the early adult years to around 55% (Reavley et al., 2006). This decline of heritability with age may be due to differing experiences between each individual twin of a pair of twins to provocative environments as they grow older and to the consequent differential habituation. In shrews, selective breeding for high versus low motion sickness susceptibility strains has shown the importance of genetic determinants for motion sickness and that this extends to anesthesia-induced emesis, indicating some common mechanisms under genetic control (Horn et al., 2014). Multiple genes are probably involved. But the nature of the genes involved is not yet clear. One example is the observation that a single-nucleotide polymorphism of the alpha2-adrenergic receptor increases autonomic responses to stress in humans and also contributes to individual differences in autonomic responsiveness to provocative motion (Finley et al., 2004). However, it is unclear whether this is a marker for motion sickness susceptibility or simply a general marker for autonomic reactivity. There is evidence for Chinese hypersusceptibility to motion sickness, and this may provide some indirect evidence for a genetic contribution to such differences (Stern et al., 1993; Klosterhalfen et al., 2005).

A recent large-scale genome study has isolated 35 single-nucleotide polymorphisms (SNPs) associated with motion sickness (Hromatka et al., 2015). Genetic variants associated with motion sickness pointed to roles for inner-ear development, neurologic processes, and (more surprisingly) glucose homeostasis. Several of these SNPs displayed sex-specific effects, with up to three times stronger effects in women. This study also suggested that PONV and migraines may share underlying genetic factors with motion sickness. The latter finding is of course consistent with the known comorbidities of motion sickness.

General predictors

Sex and age are the two main predictors of individual susceptibility in the general population. Surveys of transportation by sea, land, and air indicate that women are more susceptible to motion sickness than men, although it must be emphasized that this sex difference is an overall trend with considerable overlap. Women show higher incidences of vomiting and a higher incidence of symptoms such as nausea (Kennedy et al., 1995). Large-scale surveys of passengers at sea indicate a 5:3 female-to-male risk ratio for vomiting (Lawther and Griffin, 1988). This difference in vomiting suggests that the increased susceptibility in women is likely to be objective and not due to differential subjective reporting of symptoms. The elevated susceptibility in women does not seem related to extra habituation to greater ranges of motion environments experienced by risk-taking males (Dobie et al., 2001), nor to gender-biased differential self-selection between males and females, e.g., when volunteering for laboratory motion sickness experiments (Flanagan et al., 2005). Moreover, this sex difference is not exclusive to humans because, in animals, such as *Suncus murinus*, females show significantly more emetic episodes and shorter latencies to emesis in experimental exposures to motion (Javid and Naylor, 1999).

The cause of greater motion sickness susceptibility in women has been suggested to involve the female hormonal cycle. Susceptibility varies over the menstrual cycle, peaking around menstruation. But this cannot fully account for the greater susceptibility in females, because the magnitude of fluctuation in susceptibility across the menstrual cycle is only around one-third of the overall difference between male and female susceptibility (Golding et al., 2005). The elevated susceptibility of females to motion sickness or, indeed, to PONV or chemotherapy-induced nausea and vomiting (Morrow, 1985; Golding, 1998), may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the fetus to harmful toxins during pregnancy, or subsequently through milk. Elevated susceptibility in females may be "hard-wired," but capable of upregulation, albeit variably, by hormonal influences during the menstrual cycle and even further during pregnancy.

Table 27.3

Motion Sickness Susceptibility Questionnaire Short-form (MSSQ-Short)

This questionnaire is designed to find out how susceptible to motion sickness you are, and what sorts of motion are most effective in causing that sickness. Sickness here means feeling queasy or nauseated or actually vomiting.

Your childhood experience only (before 12 years of age): for each of the following types of transport or entertainment, please indicate:

1. As a child (before age 12), how often you felt sick or nauseated (tick boxes):

	Not applicable – never traveled	Never felt sick	Rarely felt sick	Sometimes felt sick	Frequently felt sick
Cars					
Buses or coaches					
Trains					
Aircraft					
Small boats					
Ships, e.g., Channel ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big dippers, funfair rides					
	t	0	1	2	3

Your experience over the last 10 years (approximately): for each of the following types of transport or entertainment, please indicate:

2. Over the last 10 years, how often you felt sick or nauseated (tick boxes):

	Not applicable – never traveled	Never felt sick	Rarely felt sick	Sometimes felt sick	Frequently felt sick
Cars					
Buses or coaches					
Trains					
Aircraft					
Small boats					
Ships, e.g., Channel ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big dippers, funfair rides					
	t	0	1	2	3

Adapted from Golding (2006a).

Infants and very young children 2 than two years old are immune to motion sickness. However, they have no difficulty vomiting. Motion sickness susceptibility usually begins from perhaps around 6–7 years of age, although sometimes susceptibility may onset before this (Reason and Brand, 1975), and peaks around 9 years (Turner and Griffin, 1999a; Henriques et al., 2014). The reasons for this are uncertain. Puberty begins later (around 10–12 years) than the age for onset of motion sickness susceptibility. This implies that sex hormonal changes *per se* are not a direct explanation for the onset of motion sickness susceptibility. Another possibility is that the perceptuomotor map is still highly plastic and not fully formed until around 7 years of age. Most theories of motion sickness propose that this perceptuomotor map provides the "expected" invariant patterns for detecting possible sensory mismatches in the relationships between vestibular, visual, and kinesthetic inputs, i.e., the "internal model (see section above on mechanisms). Following the peak susceptibility, there is a subsequent decline of susceptibility during the teenage years toward adulthood around 20 years. This doubtless reflects habituation. Although it is often stated that this decline in susceptibility continues in a more gradual fashion throughout life toward old age, the evidence is somewhat limited, given that older people may avoid motion environments if they know that they are susceptible. Indeed, longitudinal evidence from individuals who have been studied objectively in the laboratory suggests that, toward older age, susceptibility may increase in a minority of individuals.

A multiplicity of other possible predictors of susceptibility have been examined over the years, with relatively few being found to be of significance. Cross-sectional surveys show that individuals with high levels of aerobic fitness appear to be more susceptible to motion sickness, and longitudinal experiments show aerobic fitness training increases motion sickness susceptibility (e.g., Cheung et al., 1990). The reasons are unclear, with one suggestion being that a more reactive autonomic nervous system (including hypothalamic–pituitary–adrenal axis) in aerobically fit individuals may sensitize them. Psychologic variables such as mood may modify susceptibility in contradictory directions: state variables, such as extreme fear or anxiety conditioned to motion, may contribute indirectly to motion sickness susceptibility, although, by contrast, extreme arousal "fight or flight," such as observed in warfare, may suppress motion sickness (Reason and Brand, 1975). Personality trait variables such as extraversion or neuroticism do not strongly predict motion sickness susceptibility, with only minor correlations being observed between extraversion or similar personality traits with reduced susceptibility (Reason and Brand, 1975; Gordon et al., 1994) and higher levels of trait anxiety associated with increased susceptibility (Paillard et al., 2013).

Reliable physiologic markers for predicting individual motion sickness susceptibility have proved elusive. Otolith asymmetry between left and right labyrinths, as measured during parabolic flight, has been proposed as an indicator of susceptibility for space sickness (Diamond and Markham, 1991). However in a more general sense, individual variation in sensory thresholds to angular or translational accelerations does not seem to relate to susceptibility in any obvious fashion. Although motion sickness produces profound autonomic changes, baseline autonomic characteristics are unlikely to provide useful predictors for motion sickness susceptibility (Farmer et al., 2014). Similarly, although motion sickness can cause postural instability, the evidence that individual differences in postural stability or perceptual style (e.g., Riccio and Stoffregen, 1991) are major predictors of motion sickness susceptibility seems limited (Golding and Gresty, 2005; Diels and Howarth, 2013; Lackner, 2014). Shorter time constants of the central vestibular velocity store have been suggested to correlate with reduced motion sickness susceptibility (Dai et al., 2011; Lackner, 2014), but others have found no evidence of such a relationship (Golding and Gresty, 2005; Furman et al., 2011). In an attempt to resolve this apparent contradiction, it has been proposed that it may not be the absolute duration of the time constant *per se*, but the ability to modify readily the time constant that may be a candidate marker for success in motion sickness habituation (Golding and Gresty, 2005). In a similar vein, reduced thresholds for cervical vestibular-evoked myogenic potentials (cVEMPs) predict future habituation to sea sickness, the suggestion being that cVEMP at lower thresholds indicates that the individual has broader dynamic range in which the reflex can respond and adapt to a wider array of stimulus amplitudes (Tal et al., 2013). Individual differences in brain white-matter structure revealed by fMRI may relate to nausea susceptibility (Napadow et al., 2013b).

Special groups: blindness, vestibular disorders, and migraine

Blind or blind-folded normally sighted individuals can be made motion-sick using real physical motion, although obviously optokinetic stimuli (Table 27.2) will be ineffective. Blind individuals, ranging from congenital to late-acquired blindness, are as susceptible to motion sickness as sighted individuals with eyes closed, and their range of susceptibility tends to be comparable to normal-sighted people when exposed to provocative cross-coupled motion (Graybiel, 1970).

Certain groups with medical conditions may be at elevated or reduced risk. Individuals who have complete bilateral loss of labyrinthine (vestibular apparatus) function appear to be immune to motion sickness. However, this may not be absolutely true under all circumstances, since some bilateral labyrinthine-defective individuals are still susceptible to motion sickness provoked by visual stimuli designed to induce self-vection during pseudo-Coriolis stimulation, i.e., pitching head movements in a rotating visual field (Johnson et al., 1999). When well-characterized patients with complete bilateral vestibular failure were exposed to highly provocative off-vertical-axis rotation (OVAR), a few showed minor symptoms of motion sickness (Murdin et al., 2015). This may have been due to residual vestibular function or, more probably, due to aversive sensations of whole-body motion and visual disturbances, since the OVAR was performed in the light.

The reason for the elevated motion sickness susceptibility in migraineurs (without overt vestibular disease) is not known (Murdin et al., 2015). It has been proposed that there may be a genetic link caused by defective calcium ion channels shared by the brain and inner ear, leading to reversible hair cell depolarization, producing vestibular symptoms, and that the headache might just be a secondary phenomenon (Baloh, 1998). An alternative hypothesis is that it may be due to altered serotonergic system functioning (Brey, 2005; Drummond, 2005). Support for this possibility was provided by the observation that the serotonin 1B/1D agonist rizatriptan provided significant antimotion sickness effects in migraineurs (Furman et al., 2011). However, rizatriptan did not provide significant protection against exposure to more provocative vestibular stimulation, suggesting that the role of rizatriptan in this context is more likely to be as a modulator of susceptibility rather than a direct blocker of motion sickness.

It is possible that there are several underlying and overlapping mechanisms for this link, including pain pathways and autonomic reactivity (Cuomo-Granston and Drummond, 2010). The complexity of any association between migraine and motion sickness is illustrated by Bosser et al. (2006), who surveyed the general population (i.e., unselected for severe migraine, by contrast with migraineurs requiring medical help or attending migraine clinics). This survey demonstrated the expected significant bivariate association between elevated motion sickness susceptibility and migraine. However, when these data were reanalyzed using multivariate techniques, the existence of any independent association of motion sickness with migraine disappeared and was replaced by other more important predictors, such as syncope and autonomic reactivity (Bosser et al., 2006). Patients with vestibular migraine are especially susceptible to motion sickness (Boldingh et al., 2011; Paillard et al., 2013; Murdin et al., 2015). Patients with Menière's disease seem to have elevated motion sickness susceptibility compared to controls, but not as elevated as patients with vestibular migraine, as suggested by a telephone survey (Sharon and Hullar, 2014). The data from a much larger-scale survey of Menière's disease patients versus healthy controls would appear to confirm this overall elevated susceptibility for Menière's patients (unpublished data of the author).

An overview of the motion sickness susceptibility of some special patient groups is given in Figure 27.1 from studies using both validated self-report motion sickness susceptibility questionnaires and nauseogenic OVAR (Paillard et al., 2013; Murdin et al., 2015). In Figure 27.1, compared with controls, patients with bilateral vestibular loss were either completely resistant to motion sickness or had very low symptom scores. Unilateral vestibular loss (UVL) also decreased susceptibility, but to a lesser extent than bilateral vestibular loss; however, it should be noted that these were "compensated" UVL patients, i.e., patients who had adapted to sensory conflict caused by the loss of vestibular function on one side, since in the acute phase the usual observation is that UVL patients may be more sensitive to motion. Patients with vestibular neuritis or benign paroxysmal positional vertigo showed no overall difference in susceptibility compared to controls. But, within this broad picture, many individuals had up- or downregulated their sensitivity to motion in response to their disease. Vestibular migraine led to greatly elevated susceptibility. Patients attending migraine clinics, but without vestibular migraine, had equivalent elevations of susceptibility.

MAL DE DÉBARQUEMENT

Mal de débarquement is the sensation of unsteadiness and tilting of the ground when a sailor returns to land. Whittle (1689) provided an early description of *mal de débarquement*, after the landing and during the advance of the troops of William of Orange in Torbay in 1688:

> *As we marched here upon good Ground, the Souldiers would stumble and sometimes fall because of a dissiness in their Heads after they had been so long toss'd at Sea, the very Ground seem'd to rowl up and down for some days, according to the manner of the Waves.*

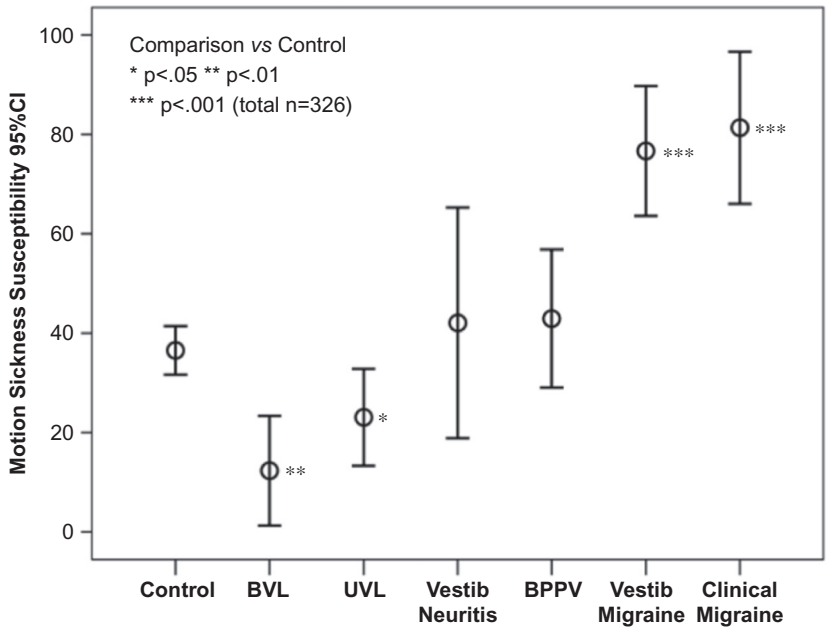

Fig. 27.1. Motion sickness susceptibility scores are shown for patient groups together with significances of comparison with age-equivalent healthy controls. The 95% confidence interval (CI) is smaller for controls as a consequence of larger numbers. Motion sickness susceptibility for Menière's disease is probably similar to migraine groups. BVL, bilateral vestibular loss; UVL, unilateral vestibular loss; BPPV, benign paroxysmal positional vertigo. See text for details. (Data source: combined from Paillard et al., 2013, Murdin et al., 2015, and data on file.)

A similar effect is observed in astronauts returning to 1 **g** on earth after extended time in weightlessness in space. *Mal de débarquement* can lead to motion sickness, but symptoms usually resolve within a few hours as individuals readapt to the normal land environment. Individuals susceptible to *mal de débarquement* may have reduced reliance on vestibular and visual inputs and increased dependence on the somatosensory system for the maintenance of balance (Nachum et al., 2004). It has long been known that view of a stable horizon reference can increase resistance to motion sickness (see next section), but provision of an artificial horizon failed to have any effect on *mal de débarquement* (Tal et al., 2014).

In a small minority of individuals, symptoms persist for months and years and can be troublesome. Patients with persistent *mal de débarquement* syndrome exhibit impaired postural stability but do not exhibit differences in intracortical excitability compared to controls (Clark et al., 2013). Customized vestibular exercises have been proposed as a treatment (Murdin et al., 2011). Some temporary relief can be obtained by re-exposure to motion, but this is not a viable treatment. Standard antimotion sickness drugs appear ineffective, but benzodiazepines appear to offer some relief (Cha, 2009). It has been suggested that repetitive transcranial magnetic stimulation can reduce symptoms for persistent *mal de débarquement* syndrome (Cha et al., 2013).

BEHAVIORAL COUNTERMEASURES

Behavioral countermeasures to motion sickness may be broadly classified into habituation versus more immediate short-term behavioral modifications, such as changes in body posture and visual attention. Habituation offers the surest countermeasure to motion sickness but, by definition, is a long-term approach. Habituation is superior to antimotion sickness drugs, and it is free of side-effects (Cowings and Toscano, 2000). The most extensive habituation programs, often denoted "motion sickness desensitization," are run by the military, where antimotion sickness medication is contraindicated for pilots because of side-effects, including drowsiness and blurred vision. These programs have success rates exceeding 85% (Benson, 1999; Lucertini et al., 2013), but can be extremely time consuming, lasting many weeks. Critical features include: (1) the massing of stimuli (exposure at intervals greater than a week almost prevents habituation); (2) use of graded stimuli to enable faster recoveries and more sessions to be scheduled, which may help avoid the opposite process of sensitization; and (3) maintenance of a positive psychologic attitude to therapy (Yen Pik Sang et al., 2005). Whether or not antimotion sickness drugs are of any practical use in this context is debatable. For example, although some studies appear to show that antimotion sickness drugs can improve the rate of adaptation (Lackner and Graybiel, 1994;

Cohen et al., 2008), other studies in both the laboratory (Wood et al., 1986) and at sea (Van Marion et al., 1985) have shown that, although antimotion sickness medications may speed habituation compared to placebo in the short term, in the longer term they are disadvantageous. This is because, when the antimotion sickness medication is discontinued, the medicated group relapses and is worse off than those who were habituated under placebo.

Habituation, itself, is often stimulus-specific, producing the problem of lack of generalization and transfer of habituation from one type of motion to another. For example, tolerance acquired to car travel may confer no protection to sea sickness (Murdin et al., 2011). Thus, to foster transfer, it is useful to use as wide a variety of provocative motions as possible. The studies by Kaufman (2005) underline the specificity of habituation to different types of motion, with different anatomic patterns of neuronal functional changes (presumably reflecting learning) in the vestibulo-olivo-cerebellar network to different classes of provocative stimuli. Neural structures such as the amygdala as well as areas such as the nucleus tractus solitarius are thought to be important in processes of induction of and habituation to motion sickness (Nakagawa et al., 2003; Pompeiano et al., 2004).

The scope of applications of habituation training is diverse, e.g., to reduce motion sickness produced by short arm rotors intended to provide artificial gravity in future space flight (Young et al., 2003). Research continues to optimize habituation approaches (Cheung and Hofer, 2005; Stroud et al., 2005). On a positive note, although stimulus specificity of motion habituation may be a problem for some people, some generalization of habituation acquired from one type of stimulus to another can be demonstrated. Exposing subjects to visual-vestibular interaction in the laboratory reduces their sensitivity to motion sickness during travel in buses, for example (Dai et al., 2011). Similarly, a controlled trial demonstrated that optokinetic training gave improvements in reducing sea sickness in 71% of those treated versus 12% of controls (Ressiot et al., 2013).

Immediate short-term behavioral counter measures include reducing head movements, aligning the head and body with GIF (Golding et al., 2003; Wada et al., 2012), or lying supine (Golding et al., 1995). Consistent with the general observation that reducing head movements can reduce motion sickness, movement restraint of head, shoulders, hips, and knees reduced motion sickness induced by playing a video game while standing (Chang et al., 2013). However, such protective postures and restriction of movement may be incompatible with task performance under many circumstances. It is usually better to be in active control, i.e., to be the driver or pilot, rather than a passenger (Rolnick and Lubow, 1991), a finding replicated in the laboratory (Golding et al., 2003). Similarly, enhanced perceptions of control and predictability appear to reduce motion-induced nausea (Levine et al., 2014). In a different context, exertion of control reduced motion sickness induced by playing video games on a tablet computer (Stoffregen et al., 2014).

Avoidance of tasks such as reading in a moving vehicle that enhance visuovestibular conflict is often recommended. The importance of this may be gauged by the observation that up to a quarter of co-drivers became motion-sick in rally cars if they were reading a book or sitting in the back seat (Perrin et al., 2013). Stroboscopic illumination protected against motion sickness for backseat military helicopter personnel, perhaps because it reduces retinal slip and visual-vestibular conflicts (Webb et al., 2013). Although galvanic vestibular stimulation (GVS) can cause vertigo and nausea, the opposite effect has been proposed, i.e., that it may provide a novel, modulatory countermeasure for motion sickness. GVS synchronous with the visual field may normalize electrogastrographic and autonomic responses and reduce motion sickness during flight simulation (Cevette et al., 2012). The mechanism perhaps involves reducing visual-vestibular conflicts. Obtaining a stable external horizon reference is helpful (Turner and Griffin, 1999b; Bos et al., 2005). However, although a direct view out of a car window reduced sickness, a real-time video display of the view ahead failed to reduce sickness in rear-seat car passengers (Griffin and Newman, 2004). Standing with a wider stance width and view of the horizon may reduce postural instability and motion sickness at sea (Stoffregen et al., 2013).

Controlled regular breathing has been shown to increase motion tolerance to provocative motion, being approximately half as effective as standard antimotion sickness drugs, yet rapid to implement and free of side-effects. The mechanism by which controlled breathing has its effect is uncertain but may involve activation of the known inhibitory reflex between respiration and vomiting (Yen-Pik-Sang et al., 2003a,b). Supplemental oxygen may be effective for reducing motion sickness in patients during ambulance transport. By contrast, it does not alleviate or prevent motion sickness in individuals who are otherwise healthy. This apparent paradox is explained by the suggestion that supplemental oxygen may work by ameliorating a variety of internal states in ill patients that sensitize for motion sickness, rather than blocking motion sickness directly (Ziavra et al., 2003). Some report acupuncture and acupressure to be effective against motion sickness (Bertalanffy et al., 2004). However, well-controlled trials find no evidence for their value (Bruce et al., 1990; Miller and Muth, 2004). Anecdotally, modification of diet has been said to alter susceptibility to motion sickness. Unfortunately,

the evidence is contradictory; for example, one study suggested that protein-rich meals inhibit motion sickness (Levine et al., 2004), whereas another study drew the opposite conclusion, that any meal of high-protein or dairy foods 3–6 hours prior to flight should be avoided to reduce air sickness susceptibility (Lindseth and Lindseth, 1995).It has been suggested that ginger (main active agent gingerol) acts to calm gastrointestinal feedback (Lien et al., 2003), but conflicting reports of its effect on motion sickness indicate that any such effects are weak (Palatty et al., 2013). For habitual smokers the temporary abstinence and consequent withdrawal from nicotine provide significant protection against motion sickness (Golding et al., 2011). Indeed, this finding may explain why habitual smokers are at reduced risk for PONV, whereas nonsmokers have elevated risk. The other main PONV risk factors are female sex, greater motion sickness susceptibility, and previous episodes of PONV. The unavoidable temporary nicotine withdrawal perioperatively and the consequent increased tolerance to sickness may explain why smokers have reduced risk for PONV (Golding et al., 2011).

Placebo effects can be strong but very variable (Lackner, 2014). Combining positive verbal instructions and placebo can promote reductions in motion sickness (Horing et al., 2013). Providing pleasant (or unpleasant) scents had no effect on motion sickness sensitivity, although the reverse effect occurred, since motion sickness enhanced sensitivity to odors (Paillard et al., 2014). By contrast, another study claimed pleasant odors alleviated motion sickness (Keshavarz et al., 2014). In an unpublished study several years ago the present author used pleasant odors to prevent motion sickness of participants in parabolic flight; at the initial stages of motion sickness some alleviation occurred, but at higher levels of motion sickness the pleasant odor became aversive and exacerbated symptoms. The contradictory nature of such findings suggests that the effect of pleasant odors is likely to be weak and of little practical use as a countermeasure for motion sickness. Listening to pleasant music can reduce motion sickness elicited by cross-coupled motion (Yen-Pik-Sang et al., 2003a), a finding replicated with visually induced motion sickness (Keshavarz and Hecht, 2014).

PHARMACOLOGIC COUNTERMEASURES

The majority of drugs currently used against motion sickness were identified and proven over 40 years ago (Wood and Graybiel, 1969). They may be divided into the categories: antimuscarinics (e.g., scopolamine), H_1 antihistamines (e.g., dimenhydrinate), and sympathomimetics (e.g., amphetamine). Combinations, e.g. scopolamine + dexamphetamine, are highly effective, since both drugs combine their different antimotion sickness properties and their respective side-effects of sedation and stimulation cancel each other out. Commonly used antimotion sickness drugs are shown in Table 27.4. However, these drugs, alone or in combination, are only partially effective. The more recently developed potent antiemetics are not effective against motion sickness, including D_2 dopamine receptor antagonists and 5-HT_3 antagonists used for side-effects of chemotherapy (Levine et al., 2000) or neurokinin NK_1 receptor antagonists (Golding, 2006b). This is probably because their sites of action may be at vagal afferent receptors or the brainstem chemoreceptor trigger zone, whereas antimotion sickness drugs act elsewhere.

All antimotion sickness drugs can produce unwanted side-effects, drowsiness being the most common; promethazine is an example (Cowings and Toscano, 2000). Scopolamine may cause blurred vision in a minority of individuals, especially with repeated dosing. The combination amphetamine + scopolamine (so-called "scopdex") is probably the most effective, with the fewest side-effects, at least for short-term use. This is because both scopolamine and amphetamine have antimotion sickness activity and act through different pathways so they have additive efficacy, while their side-effects of sedation and stimulation cancel each other out. For legal reasons (drug abuse potential) the scopdex combination is no longer available apart from specialized military use. Unfortunately, new atypical stimulants such as modafinil have been shown to be of no use as a replacement for amphetamine in the treatment of motion sickness (Hoyt et al., 2009). Some drugs, such as transdermal scopolamine or the calcium channel antagonist cinnarizine, are significantly less sedating than others (Gordon et al., 2001).

Oral administration must anticipate motion since motion sickness induces gastric stasis, consequently preventing drug absorption by this route (Stewart et al., 2000). Injection overcomes the various problems of slow absorption kinetics and gastric stasis or vomiting. Transdermal delivery offers the advantage of providing protection for up to 72 hours with low constant concentration levels in blood, thus reducing side-effects. The slow onset time (6–8 hours) of transdermal scopolamine can be offset by simultaneous administration of oral scopolamine, enabling protection from 30 minutes or so onwards (Nachum et al., 2001). Unfortunately, there may be variability in absorption via the transdermal route, which alters effectiveness between individuals (Gil et al., 2005). Chewing gum formulations offer the prospect of motion sickness prophylaxis with reduced side-effects compared to tablets, due to a more sustained release (Seibel et al., 2002). Buccal absorption is effective with scopolamine but an even faster route is via nasal

Table 27.4

Common antimotion sickness drugs

Drug	Route	Adult dose	Time of onset	Duration of action (hours)
Scopolamine	Oral	0.3–0.6 mg	30 minutes	4
Scopolamine	Injection	0.1–0.2 mg	15 minutes	4
Scopolamine	Transdermal patch	One	6–8 hours	72
Promethazine	Oral	25–50 mg	2 hours	15
Promethazine	Injection	25 mg	15 minutes	15
Promethazine	Suppository	25 mg	1 hour	15
Dimenhydrinate	Oral	50–100 mg	2 hours	8
Dimenhydrinate	Injection	50 mg	15 minutes	8
Cyclizine	Oral	50 mg	2 hours	6
Cyclizine	Injection	50 mg	15 minutes	6
Meclizine	Oral	25–50 mg	2 hours	8
Buclizine	Oral	50 mg	1 hour	6
Cinnarizine	Oral	15–30 mg	4 hours	8

Adapted from Benson (2002).

scopolamine spray. Although not yet available for routine use, with higher (alkaline) pH-buffered formulations to promote absorption, peak blood levels may be achieved in 9 minutes (Ahmed et al., 2000), and this route has been shown to be effective against motion sickness (Simmons et al., 2010).

Research into new antimotion sickness drugs includes re-examination of old drugs such as phenytoin, as well as the development of new agents. The range is wide, including phenytoin, betahistine, chlorpheniramine, cetirizine, fexofenadine, benzodiazepines, and barbiturates, the antipsychotic droperidol, corticosteroids such as dexamethasone, tamoxifen, opioids such as the μ-opiate receptor agonist loperamide, neurokinin NK_1 receptor antagonists, vasopressin V_{1a} receptor antagonists, *N*-methyl-D-aspartate antagonists, 3-hydroxypyridine derivatives, 5-HT_{1a} receptor agonists such as the antimigraine triptan rizatriptan, selective muscarinic M_3/m5 receptor antagonists such as zamifenacin and darifenacin (for review, see Golding, 2006b). So far, none of these drugs has proven to be of any major advantage over those currently available for motion sickness (Golding, 2006b). The reasons are various and include relative lack of efficacy, complex and variable pharmacokinetics, or in those that are effective, unacceptable side-effects. A possible candidate for an effective antimotion sickness drug with fewer side-effects might be a selective antagonist for the m5 muscarinic receptor (Golding and Stott, 1997b).

Future development of drugs with highly selective affinities to receptor subtypes relevant to smotion sickness should aim to produce an antimotion sickness drug of high efficacy and with few side-effects. The elucidation of neurophysiologic mechanisms and pharmacologic mapping of brain regions and pathways associated with motion sickness may provide the grounds for the rational development of more effective medication in the future.

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