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THE AUTONOMIC NERVOUS SYSTEM AND MOTION SICKNESS

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1 INTRODUCTION

An elementary description of the autonomic nervous system is presented, followed by a brief description of motion sickness. Finally, changes in the autonomic nervous system with motion sickness are described. More details concerning the autonomic nervous system are found in Chapter 3, and Chapter 5 provides further information about the neural basis of nausea and vomiting.

2 BASIC DESCRIPTION OF THE AUTONOMIC NERVOUS SYSTEM

2.1 Definition of the Autonomic Nervous System

A vertebrate "nervous system" is usually understood to include peripheral sensory (afferent) nerves, a brain and spinal cord, and peripheral motor (efferent) nerves. The term *central nervous system* (CNS) refers to the brain and spinal cord, and *peripheral nervous system* refers to all the neural structures outside the CNS. The term *autonomic nervous system* is normally used to refer discretely to certain specific neural pathways that are only peripheral in location and only motor in function. These autonomic pathways are efferent from the brain and spinal cord to three specific kinds of effectors: smooth muscle, cardiac muscle, and glands. The autonomic nervous system usually refers specifically and exclusively to these peripheral motor pathways to smooth muscle, cardiac muscle, and glands. Some authorities define the autonomic nervous system in this way,[6,120,130] and others do not provide definitions but characterize the autonomic nervous system in terms of its parasympathetic and sympathetic parts, describing both of the parts as exclusively peripheral and efferent and visceral.[17,27,50] The autonomic nervous system (ANS) could logically be renamed the *peripheral motor pathways to the viscera* (PMPV) or *efferent autonomic pathways* (EAP), but reviewers, like dictionary writers, should be historians rather than law givers and we shall refrain from inventing new terms. "In German one speaks of *das viszerale Nervensystem*, in French of *le system vegetatif*."[17] Nevertheless, the autonomic nervous system is not a nervous system.

Some authorities use the term *autonomic nervous system* to include also certain afferent pathways from the viscera and certain central mechanisms,[83] but most do not. Other authorities define the ANS as comprising "all the neurons lying completely outside the central nervous system,"[38] a definition that is consistent with the original classification proposed by Langley in 1921. This classification excludes any afferent pathways and any central mechanisms, but includes[128] the enteric neurons which lie completely within the walls of the gut. We shall exclude the enteric neurons from the definition because it is probably best to use the term ANS in the way it is actually used most of the time, to refer only to the parasympathetic and sympathetic pathways (peripheral visceral efferent pathways). We shall refer to other mechanisms specifically as required.

These peripheral efferent pathways to smooth muscle, cardiac muscle, and glands do deserve a special name, because they have special characteristics. Of all the peripheral motor pathways, only the autonomic pathways have a synapse located between the CNS and the effector, and only the autonomic pathways include neurons that are located completely outside the CNS. Unlike other motor fibers, the motor fibers that contact smooth muscle, cardiac muscle, and glands belong to neurons the cell bodies and processes of which lie entirely outside the CNS; the cell bodies of these neurons are located in autonomic ganglia (outside the CNS). "Neither somatic motor neurons, whose cell bodies lie within the spinal cord, nor primary sensory neurons, whose axons project into the spinal cord or brain stem, can be considered autonomic."[38]

2.2 Automaticity of the ANS

Autonomic pathways usually function with autonomy, with independence from voluntary control, and hence the origin of the term. It should be understood, however, that special feedback training can confer the ability to exert some voluntary control of activity in some of the autonomic pathways.[18,65,84,118] It is also important to note that, although the autonomic nervous system functions with considerable independence from voluntary control, it does not function with autonomy from the rest of the body. The autonomic nervous system is fully integrated with the rest of the body, and is controlled by the brain and spinal cord. Control of the autonomic nervous system is based on information about the environment and the body, including information provided by afferent nerves from the viscera.

The body has, of course, some motor pathways that are *not* autonomic but are nevertheless independent of conscious volition most of the time. Major respiratory muscles, such as the diaphragm and the intercostal muscles, are striated muscles innervated by somatic (not autonomic) nerves and they function independently of voluntary control most of the time. The moving of air in and out of the lungs is not an autonomic function even though it is usually done without participation of conscious volition. Similarly, the external eye muscles are striated muscles that are innervated by somatic motor fibers in cranial nerves 3, 4, and 6, and these fibers are influenced constantly by "automatic" neural mechanisms that receive inertial and gravitational information from the vestibular apparatus of the inner ear, and visual information from the retina. These nerve fibers can of course be controlled readily by conscious volition, as in making saccadic eye movements. The *torsional* eye movements (rotational displacements of the eye about the optic axis) that are routinely produced reflexly during tilt of the head in roll[15,30] cannot be produced voluntarily except by people who have received special training. The tensor tympani muscles and the stapedius muscles of the middle ears are also fast striated muscles that are innervated by somatic, not autonomic, nerves; these nerves also are controlled independently of conscious volition, by the acoustic reflex (although some people can contract and relax the middle ear muscles voluntarily).

Probably all the muscles that are normally controlled voluntarily (striated muscles innervated by somatic neurons) are occasionally controlled automatically, i.e. reflexly, as in postural reflexes, flexion reflexes, and shivering. In general, striated muscle is controlled both by conscious volition and automatically. In contrast, smooth muscle, cardiac muscle, and glands receive only autonomic motor nerve supplies and are controlled automatically almost always. There are, of course, those rare people who have had biofeedback training and have learned how to change some autonomic activity voluntarily.[18,21,119] Also, autonomic activity is routinely influenced by voluntary activity. For example, when visual fixation is voluntarily changed from far to near, changes occur in the autonomic control of two smooth muscles in the eye, the ciliary muscle and the iris, so that clearer vision is achieved.

2.3 Parasympathetic and Sympathetic Divisions of the ANS

Understanding the autonomic changes associated with motion sickness requires a basic understanding of the differences between the parasympathetic and the sympathetic divisions of the ANS. The parasympathetic pathways are also called the cranio-sacral pathways because they exit the CNS in the cranium and in the sacral part of the spinal cord (in cranial nerves 3, 7, 9, and 10, and from spinal cord sacral segments 2, 3, and 4); the sympathetic pathways are also called thoracico-lumbar pathways because they exit the CNS from spinal cord segments thoracic 1 to lumbar 3.

All the junctions of the parasympathetic fibers with their effectors are "cholinergic," i.e., one of the major neurotransmitters at the effector is acetylcholine; most, but not all, of the junctions of the sympathetic fibers with their effectors are "adrenergic," i.e., one of the major neurotransmitters at the effector is norepinephrine. Three of the sympathetic junctions are exceptional; the sympathetic junctions at the sweat glands and at the piloerector muscles, and also the sympathetic junctions that *dilate* blood vessels with sympathetic stimulation, are actually cholinergic.

Autonomic nerve endings at effectors may secrete many other neurotransmitters in addition to acetylcholine (ACh) and norepinephrine (NA). Other such neurotransmitters include "adenosine 5'-triphosphate (ATP), 5-hydroxytryptamine (5-HT), dopamine, and a number of peptides, notably neuropeptide Y (NPY), vasoactive intestinal polypeptide (VIP), enkephalin, somatostatin, cholecystokinen, substance P (SP), and calcitonin gene-related peptide (CGRP)."[11] At most, if not all, autonomic effector junctions a *mixture* of two or more (reportedly, up to six) transmitters is secreted. Certain mixtures or "codings" are commonly found. "The predominant 'codings' are: sympathetic nerves, NA, ATP, and NPY; parasympathetic nerves, ACh and VIP."[11] Also, at some autonomic effectors there are two or more different kinds of receptors for a single neurotransmitter, so that blockers that are effective for some receptors do not necessarily block receptivity in other receptors.

Most autonomic effectors are supplied by fibers of both the parasympathetic system and the sympathetic system. In such dually innervated effectors, the influence of the two systems are often opposite. For example, an *increase* in action potential frequencies in the *parasympathetic* fibers to the heart tends to slow the heart rate, and a *decrease* tends to speed up the heart rate; an *increase* in action potential frequencies in the *sympathetic* fibers to the heart tends to speed up the heart rate, and a *decrease* tends to slow the heart rate.

Another important difference between the parasympathetic and the sympathetic systems is that the sympathetic system controls secretions by the adrenal medulla, which secretes into the bloodstream the major transmitter of the sympathetic system, norepinephrine, together with epinephrine; the secretion is roughly 20% norepinephrine and 80% epinephrine but the proportions are different in different circumstances.[39,50] These secretions have the effect of mimicking, all at once, increases in activity in most of the sympathetic pathways. The parasympathetic system has no comparable endocrine gland.

A large number of the sympathetic pathways can be activated all at the same time as part of a "stress response," whereas large numbers of the parasympathetic pathways cannot be activated all at the same time. With alarm or stress (often because of a conscious perception), the "stress" or "fight-or-flight" responses become evident. These responses include *conscious sensations* (sometimes fear or anger), *endocrine responses*, and *the autonomic response*. The autonomic response is an en bloc activation of a large part of the sympathetic nervous system, an increase in action potential frequencies in a large number of the sympathetic neural pathways. This increase in sympathetic activity causes, among other things, a rise in the heart rate, an increase in the strength of contractions of the heart, a rise of blood pressure, an increase in circulating red blood cells as they are released from the spleen (not quantitatively important in humans), a blood shift out of the skin and abdominal organs and into skeletal and cardiac muscle, decreased digestive activity, increased

secretions by sweat glands, increased diameters of bronchioles, increased diameters of the pupils, and an increase in circulating epinephrine and norepinephrine; the increase in circulating epinephrine has a variety of effects, including increases in blood glucose and blood fatty acids.

2.4 Other Distinguishing Characteristics of the ANS

Autonomic pathways are different from somatic motor pathways not only in their automaticity but also in the *function* of the basal or "tonic" activity: at rest, there is a basal frequency of action potentials along the autonomic pathways to smooth muscle, cardiac muscle, and glands, and some of the important adjustments in autonomic control are made by *decreasing* the frequencies of action potentials from that basal level. There is also tonic activity, at rest recumbent, in the somatic motor nerves to striated muscle, but this is maintenance activity rather than controlling activity, and important adjustments in the functional control of these muscles do not involve decreases from the resting levels of activity (with the occasional, and arguable, exception of the external anal sphincter).

Another difference between autonomic motor pathways and somatic pathways is that somatic pathways innervate only one kind of effector (striated muscle) using only one kind of neurotransmitter (acetylcholine) at the effector, whereas autonomic pathways innervate a variety of effectors using a variety of neurotransmitters. Autonomic fibers are also smaller in diameter, conduct at slower speeds, and use generally lower frequencies of action potentials.

Parts of the autonomic nervous system will react to an isolated small stimulus such as a puff of wind, a light touch, a flash of light, or a sound. Stimuli that consist of specific meaningful patterns can provoke in the autonomic nervous system certain specific and meaningful responses. A flash of light might cause changes in the autonomic nervous system that result only in a small, brief increase of heart rate, but an appropriate *pattern* of optical stimuli can cause changes in the autonomic nervous system with the result that the diameter of the pupil and the focus of the eye are altered to produce clearer vision. A pattern of optical stimuli that reveals a large, angry grizzly bear running at the observer can provoke autonomic responses that include large increases in heart rate and blood pressure, increases of blood flow to skeletal muscles, increased diameter of the bronchioles, etc.

Similarly, a brief vestibular stimulation can also cause small discrete autonomic changes.[123] However, stimulating the vestibular system over a period of time can provoke motion sickness, a syndrome that includes a variety of large changes in the autonomic nervous system. The autonomic changes in motion sickness can be seen as appropriate to a poisoning situation that involves vomiting. The autonomic responses to single, small vestibular stimuli have no particular relationship to the autonomic changes that occur when motion sickness is provoked, just as the autonomic responses to single flashes of light have no particular relationship to the autonomic changes that occur when the eye reports a charging grizzly bear.

3 MOTION SICKNESS

3.1 Definition and Essential Nature

Motion sickness is a sickness caused by motion. Motion sickness is: the signs and symptoms of the sickness caused by motion. Motion sickness appears to be a poison response caused by unnatural motion acting on the vestibular system.[101,103] Motions of the

body can act on the vestibular apparatus and thereby on the central vestibular mechanisms to generate motion sickness. Motions of visual fields apparently cause motion sickness[26,69,90,113,124] "by stimulating the vestibular system,"[100] by acting through central connections to the central vestibular mechanisms.[13] In many motion sickness situations there is probably a combined action of several different kinds of information about orientation and motion: information from the vestibular apparatus,[63,68] from the eyes,[90,124] from proprioceptors,[76] and from memory.[110,116]

Various aspects of motion sickness have been reviewed recently.[7,8,12,23,28,29,94,96,122] Motion sickness never occurs in people or animals who lack vestibular function,[63,68] and susceptible animals become absolutely nonsusceptible to all forms of motion sickness after bilateral surgical removal of the vestibular apparatus.[105,121] People lacking vestibular function are nonsusceptible even to the motion sickness caused by purely visual stimuli.[13] The vestibular system is necessary for motion sickness. Also, discrete stimulation of the vestibular system is sufficient to cause motion sickness in normal people who are at rest with the eyes closed.[100] Discrete vestibular stimulation can give rise to a group of signs and symptoms that looks like a poison response.

Motion sickness is not a sickness in the normal sense of the word; it is the usual response of normal people to certain kinds of abnormal motion stimuli. In motion sickness the problem is the response to the stimulus, and failure to respond will completely eliminate the problem. This is unlike trauma or low temperatures or low oxygen pressures or bacterial infection, where the problem is not the response and failure of the body to respond would *not* eliminate the problem. Motion sickness is an inappropriate response to a stimulus.

Essentially all normal people can be made motion sick if the stimulus is appropriate and lasts for a long enough time, but there are important differences in individual susceptibility. Differences in individual susceptibility are determined by a variety of characteristics,[49] some of them genetic,[1,4] and the degree of motion sickness experienced in a given situation can be determined by special circumstances,[40] by the activities skills or strategies of an individual in the motion environment,[147] by perceptual style,[49] by the functional capacity of the vestibular apparatus of the inner ear,[63,68] by habituation,[24,45,88,125] medications,[86,129,144,145] psychological influences,[31,49,67,99,114] or special biofeedback training.[5,18,19,65,134]

The vomiting of motion sickness is one of several known kinds of inappropriate vomiting, "inappropriate" because the stomach is emptied even though there is no poison in it. Inappropriate vomiting can occur in the morning sickness of pregnancy,[140] in response to emotional stress,[10,44] severe physical pain,[10] radiation,[8] mechanical irritation of abdominal viscera,[10] or physical exercise that is extremely vigorous and prolonged.

In many cases there is little understanding of the essential nature of inappropriate vomiting, but in the case of motion sickness it is now understood[16,135] that the vestibular system plays an important role in the vomiting response to certain poisons as well as in the vomiting response to motion. In animals after bilateral surgical removal of the vestibular apparatus, the emetic response to motion is lacking[121] and also the emetic response to certain poisons is grossly defective.[104] Since the vestibular system functions in both the vomiting response to certain poisons and the vomiting response to certain motions, it is reasonable to think (1) that the vestibular mechanism that functions in the vomiting response to poisons arose as a biological protective mechanism, and (2) that certain unnatural motions can stimulate that protective mechanism to produce the poison response that is called motion sickness. This is much more reasonable than assuming that there are two different emetic mechanisms in the vestibular system (one for poisons, and a separate one for motions). The essence of motion sickness seems to be that certain unnatural motions stimulate, inappropriately, a protective mechanism.

3.2 Motion Sickness as a Poison Response

If there is only one emetic mechanism in the vestibular system, then the sensitivity of that mechanism in a given individual might be expected to determine the individual's sensitivity both to emetic poisons and to motion. The individuals who are more susceptible to emetic poisons might be expected also to be more susceptible to motion sickness. In one study,[107] positive evidence of this was found: persons who were more susceptible to motion sickness were also more susceptible to the nausea and vomiting of drugs that have emetic side effects. Seventy-seven cancer patients who were found by questionnaire to be susceptible to motion sickness were "matched to cancer patient controls without previous motion sickness by sex, age, type and dose of chemotherapeutic drug received, and antiemetic medication." It was found that the cancer chemotherapy produced, in the patients with a history of motion sickness, significantly "more frequent, severe, and longer-lasting nausea and vomiting than controls."[107] This evidence suggests that there is only one emetic mechanism in the vestibular system.

The sensitivity to the nausea and vomiting side effects of drugs and the sensitivity to motion are possibly both determined by the same protective mechanism. The results from the experiment with chemotherapeutic drugs[107] resemble the results from the experiment that tested experimental animals before and after labyrinthectomy:[104] the animals that were more susceptible to the vomiting of drugs (the preoperative animals) were also more sensitive to motion sickness, and the animals less sensitive to the vomiting of drugs (the postoperative animals) were also less sensitive to motion sickness.[104] It has been found also in rats, using kaolin ingestion (pica) as the index of sickness, that sensitivity to motion correlates with sensitivity to emetic poisons.[53] The failure of labyrinthectomized rats to develop conditioned taste aversions 19 days postoperatively[112] is another indication of the involvement of the vestibular system in poison responses (although they recovered the ability to acquire conditioned taste aversions 29–30 days postoperatively).

Authorities in the field of poisoning[2,115] apparently do not make lists of the "basic" or "physiological" responses to poisoning, perhaps because of their primary concern about the differential determination of which poison is present and how to counteract it. There are different direct effects of different poisons and also different bodily responses to different poisons. However, poisoning authorities do recognize that some "non-specific" reactions to poisoning occur. "Nausea and vomiting are probably the most common nonspecific alimentary symptoms of poisoning."[115] A list of the signs and symptoms of motion sickness is perhaps a list of nonspecific reactions to poisoning.

"Motion sickness is possibly the purest and simplest poison response available for study, because it can be produced for study without the complicating presence of a poison. It is produced by a motion stimulus that masquerades as a poison."[103] Unnatural motion seems to activate a poison response mechanism, and as a result the body inappropriately inflicts on itself malaise, anxiety, nausea, and other conscious sensations, and also pallor, cold sweating, vomiting, endocrine responses, and autonomic responses (not necessarily in that order). It is of course possible that an otherwise-harmless dose of an emetic such as apomorphine could provoke the same collection of signs and symptoms, not by provoking each sign or symptom individually but by simply turning on a poison-response mechanism so that the body then inflicts on itself the whole poison-response syndrome. Such a poison response to a harmless dose of apomorphine would be just as "inappropriate" as the poison response in a motion sickness episode and, as in motion sickness, failure to respond would completely eliminate the problem.

3.3 The "Two Phenomena" of Motion Sickness

Motion sickness appears to be a poison response that includes two major phenomena: (1) emptying of the stomach, and (2) a stress response. This "two-phenomena" concept can accommodate all the known signs and symptoms of motion sickness. The emptying of the stomach includes the vomiting and some accompanying conscious sensations. The stress response includes most of the endocrine responses and autonomic responses and some accompanying conscious sensations. It is reasonable to describe motion sickness as including a stress response because the endocrine phenomena of motion sickness and the autonomic phenomena of motion sickness, together, do comprise an easily recognized stress response.[18,34,70-75,97,113] Presumably, all or most emetic poison responses include a stress response as well as the emptying of the stomach; perhaps the stress response improves the chances of surviving some kinds of poisons. It is known that experimental animals lacking stress response mechanisms are much more likely to die when exposed to any one of a variety of stresses.

Presumably motion sickness is stressful *only* because the poison response includes a stress response; that is, if the poison response that is motion sickness included only a program for producing stomach emptying and no program for producing a stress response, the stomach would be emptied without any stress being experienced. It is only because the poison response includes a stress response that motion sickness is experienced as stressful.

In motion sickness situations both parts of the poison response, the emptying of the stomach and the stress response, are "inappropriate": the stomach is emptied in the absence of a poison, and a stress response occurs in the absence of a stress. No one suggests that there is a poison present in the stomach with motion sickness, but sometimes it is suggested that there is a stress present. There have been many attempts to see something noxious or stressful in the motions that elicit motion sickness, but such attempts have been remarkably unsuccessful.[100] This is not surprising, since most such motions are not stressful; failure to respond to the motions completely eliminates the problem. It is a new and different use of the word *stress* to argue that a physical stimulus such as a motion is a sickness-causing stress when simple failure of the nervous system to respond would completely eliminate the problem. Other kinds of physical stresses cause problems that cannot be eliminated by simple failure to respond. For example, the problems caused by the physical stresses of cold, heat, dehydration, bacterial infection, radiation, anoxia, etc., are not eliminated by simple failure to respond.

The problem in motion sickness is not a stress; the problem is the inappropriate response to the motion. In fact, some provocative motions are clearly and obviously not stressful, except for causing motion sickness. The most common provocative motions, the motions of ships in moderate seas, are not noxious, not injurious, not a threat to the calibration of the vestibulo-ocular reflex, not frightening, not stressful in any way to adults who do not respond inappropriately, and not stressful even for babies before the age of mobility;[100] such babies eat and sleep and smile happily in these environments. To vomit and to generate a stress response in reaction to these motions is remarkably inappropriate.

A poison response includes a stress response, and therefore vomiting as part of a poison response is a stressful experience, but vomiting that is not part of a poison response does not have to be accompanied by stress. As reported by a psychiatrist specialist in eating disorders,[148] vomiting that is not part of a poison response is sometimes not a stressful experience. Some bulimics who vomit voluntarily do not find that the vomiting itself is stressful, although many feel guilty about it afterwards. Some bulimics look forward to vomiting and consider it something positive, and some learn to vomit spontaneously, without mechanical inducement. There seems to be no reason to assume that emptying of the stomach per se *has* to be stressful.

On rare occasions the stress response seems to be missing from motion sickness. Some unusual test subjects exposed to provocative motion vomit after brief exposure and are ready to continue the testing because they do not find it stressful to vomit.

One common view of motion sickness is that the unnatural motion produces the stomach-emptying phenomena (nausea and vomiting) and that the stomach-emptying phenomena are stressful, causing the stress response. This seems unlikely since, as suggested above, there is no reason to assume that a simple emptying of the stomach has to be stressful. Also, in some people the parts of motion sickness that comprise a stress response are well developed before vomiting or nausea occurs. It seems unreasonable to say that the stress response is caused by the nausea in those individuals who have the stress response before the nausea.

The reverse view of motion sickness is also common; this view suggests that the motion causes a stress response (an "unbalance" of the autonomic nervous system) and that the stress response then causes the stomach-emptying phenomena. This also seems unlikely since, as suggested above, the motion is not usually stressful except for its ability to cause motion sickness. Moreover, most stress responses do not cause nausea or stomach emptying: sky divers and sprinters, for example, experience stress and have extremely high heart rates but they seldom, if ever, vomit or experience nausea from the stress. Anecdotally, several hundred sprinters and several hundred skydivers have been observed before, during, and after the events, and not a single one was seen vomiting.[149] Furthermore, in some people the nausea appears before any signs of a stress response. It seems especially unreasonable to say that the nausea is caused by the stress response in those individuals who have the nausea before the stress response.

Specific evidence of the sequence of events in motion sickness might be of interest. Although conscious perception of abdominal changes is often the first indication of motion sickness in strongly provocative test situations,[48,82] parts of the stress response in fact appear before the start of nausea in some people. One important part of the stress response, the two- or threefold increase in blood flow in skeletal muscle,[126] occurs in some subjects *before* any report of nausea[127] and is therefore unlikely to be caused by the nausea or other stomach-emptying phenomena in these subjects. On the other hand, in some other subjects the nausea is well developed before the increase in muscle blood flow occurs and it is therefore unlikely that the change in muscle blood flow causes the nausea in these subjects. Two other parts of the stress response, pallor and cold sweating, also occur in some subjects before any perceived nausea and in other subjects only after nausea is perceived.[52,55,64,126] One major study found a "remarkable consistency of pallor detected prior to the report of nausea,"[22] and another major study[82] found that autonomic [stress response] effects "preceded [nausea] onset in very few individuals."

Overall, there is no preponderance of evidence for thinking either that the stomach-emptying phenomena occur before the stress response or that the stress response occurs before the stomach-emptying phenomena. It seems that the stomach-emptying phenomena and the stress response are produced at about the same time; there is no evidence that one causes the other.

The autonomic phenomena associated with emptying of the stomach cannot be used as indicators of whether the stress response precedes or follows or occurs at the same time as the stomach emptying, because these autonomic phenomena are themselves "stomach-emptying" phenomena rather than "stress response" phenomena. While considering the sequencing of events in motion sickness, however, it should be mentioned that the change of gastric motility with motion sickness, the gastric tachyarrhythmia, "typically precedes the first reports of nausea by 2 to 3 minutes."[70]

3.4 The Signs and Symptoms of Motion Sickness

The major signs and symptoms of motion sickness are listed below. Autonomic signs are included here but some of them are described more fully in Section 4.

3.4.1 Stomach-Emptying Phenomena

3.4.1.1 Conscious Sensations

- Abdominal sensations such as awareness and discomfort[47,52]
- Malaise, drowsiness[47]
- Nausea[70,100,124]
- Sensations of vomiting taking place (visual, auditory, proprioceptive, and tactile sensations of vomiting taking place)

The origin of nausea is not known, and nausea is sometimes assumed to be the conscious awareness of unusual activity in the central mechanisms of vomiting.[100] It is now known, however, that vomiting can occur without consciousness of nausea, in bulimics[148] and astronauts in space,[133] and it seems that the assumption about awareness of unusual activity in the central mechanisms is not a valid one; that is, the central mechanisms of vomiting seem to be capable of functioning without provoking the conscious sensation called nausea. One caution: it might be that the culture of astronauts makes it difficult for them to experience or report nausea,[102] or to acknowledge on-going symptoms of motion sickness.

When the stomach is present and innervated, certain stimuli to it can elicit nausea. Nevertheless, it is clear that the stomach is not the only elicitor of nausea, because "human subjects with total gastrectomy not infrequently experience nausea."[25] Nothing that the stomach might do is necessary for nausea, and since motion sickness does occur in gut-denervated animals it seems unlikely that the sensation nausea in motion sickness is triggered primarily from the stomach. It seems possible that the sensation of nausea in motion sickness is generated in the brain as part of a poison response. It is also possible that the nausea of motion sickness results from the increased plasma levels of the antidiuretic hormone AVP[54,132] that occur with motion sickness. The vomiting of motion sickness in dogs is not impeded or delayed by the surgical removal of the pituitary gland, however, and this procedure removes a major source of AVP and produces polyuria.[106] Furthermore, nausea in humans can be provoked without any increase of plasma AVP, by giving ipecacuanha.[108]

3.4.1.2 Vomiting

- Increased Plasma Antidiuretic Hormone, i.e., AVP[23,32,36,70,71,131,146] — Plasma levels of AVP are increased up to 20 or 30 times the pre-motion levels.
- Salivation — In most people, measured salivation flow is decreased with motion sickness.[41-43] In most squirrel monkeys, the measured salivation flow is increased.[59-61] In some people, just before vomiting, there is a brief but strong increase in salivation.
- Decreased motility of the stomach and changes in the electrogastrogram.[77,79,80,124,133]
- Decreased motility of the upper small intestine.[80,93,95,133]
- Giant Retrograde Contraction — A single, strong retrograde peristaltic wave from the mid-small intestine to the gastric antrum.[77-79]
- Phasic contractions of pylorus and small intestine.[80]

- Elevation of cardia of stomach into thorax, and relaxation of lower esophagus.
- Adjustments of body posture.
- Retching, i.e., special coordinated contractions of the respiratory muscles and muscles of the abdominal wall.[95]
- Closure of the glottis, elevation of the soft palate.
- Compression of stomach by abdominal wall and diaphragm; relaxation of diaphragmatic hiatus.[78,95,141]
- Opening of the mouth.
- Expulsion of vomitus.
- Repetitive swallowing.

Motion sickness in dogs often includes, before vomiting, defecation, urination, and obvious drooling.[105] In squirrel monkeys there is marked foaming at the mouth, chewing motions of the jaw,[142,143] licking,[14] and a motionless trance-like state that occurs invariably in some experimental conditions but not[142,143] in others. There is also visible salivation in cats, both in motion sickness and in other poison responses.[87]

The massive increases of plasma antidiuretic hormone (AVP) are likely related to the stomach-emptying phenomena, rather than to the stress response. The evidence is convincing. Increased levels of AVP are thought to be closely associated with nausea.[150] When large doses of AVP are injected in humans, "Increased intestinal activity is likely to cause nausea, belching, cramps, and an urge to defecate."[54] Vomiting as well as nausea is very common after administration of AVP to humans.[132] Increases of AVP are known to be absent in some vomiting situations but present in some other vomiting situations,[108] and present also in "anaesthetized man or experimental animals" in which "traction on the intestines consistently resulted in very large increases in plasma antidiuretic activity."[117]

Increases of plasma AVP probably play some role in the nausea and vomiting of motion sickness[32,36,70,71] although it is difficult to say how important this role might be. The tendencies of AVP to cause cramps and the urge to defecate are possibly counteracted in human motion sickness by the stress response phenomena, but in dogs motion sickness often does include defecation.

Also, "in the course of many studies in both rats and human volunteers, we were impressed with how rarely pain or other obvious stresses ... had any discernible effect on plasma AVP."[117] In rats, the researchers[117] were surprised to find that "none of the three stresses employed — light ether anesthesia, water immersion, or pain — had any detectable effect at any time on plasma AVP even though all three resulted in very large increases in plasma corticosterone ..." It seems clear that the increases in plasma AVP with motion sickness are *not* part of the stress response and that they *are* part of the vomiting response; these AVP increases would help to prevent dehydration and loss of blood pressure[39] in prolonged vomiting situations.

There are several possible influences of AVP in motion sickness. These include the antidiuresis of motion sickness, the sensation of nausea, the vomiting, the facial pallor, and the increased blood flow in skeletal muscle. It is also possible that AVP increases the rate of selective transfer of water from saliva into the blood vessels of the tissues of the mouth. Several AVP antagonist medications have been tested for their influence on motion sickness in squirrel monkeys, and one of them abolished emesis in all six of the animals tested.[14]

The central and peripheral mechanisms of vomiting have been well reviewed recently (see References 9, 77, 80, 81, 93, 95, 98, 141; see also Chapter 5 in this book). A few minutes before vomiting, the motility of the stomach and duodenum decreases markedly and following this decrease of motility some contents of the upper half of the small intestine are

emptied back into the stomach by a single powerful retrograde peristaltic contraction called the RGC, retrograde giant contraction.[80] The RGC "begins at mid small intestine and propagates retrograde to the gastric antrum."[79] This giant contraction consists of a long, continuous portion of the gut that is contracted to a small diameter, a length of some 70 cm, and the 70-cm area of small diameter travels along the gut from mid small intestine to the gastric antrum of the stomach.[151] The emptying, or partial emptying, of the upper small intestine into the stomach would tend to move any poison to the stomach where vomiting could remove it, and also the acidic stomach contents would tend to be neutralized by the intestinal contents so that damage to the esophagus during vomiting would be less likely.[77]

Following the RGC there are "post-RGC phasic contractions occurring in the stomach and small intestine."[79] These phasic contractions are especially prominent in the lower small intestine, and serve to "move the contents of the lower small intestine into the colon in a stripping fashion."[77] Of course, absorption of a poison from the colon into the blood stream is much less likely than from the small intestine, and this movement into the colon can be considered protective.

Overall, it seems that the RGC empties the upper half of the small intestine into the stomach, and the phasic contractions empty the lower half of the small intestine into the colon. These two actions would do much to stop the absorption of the contents of the gut and would therefore be protective against poisons in the gut.

The lower esophageal sphincter relaxes and the lower half of the esophagus relaxes, and the cardia of the stomach is drawn through the diaphragmatic hiatus into the thorax by contraction of the upper esophagus. Apparently the "acute angle" between the stomach and the esophagus is thereby altered and the "fundic reservoir above the gastroesophageal junction is eliminated."[77] Movement of stomach contents into the esophagus is facilitated. The lower half of the esophagus passively accepts vomitus, which moves in and out of the lower half of the esophagus with retching.

The glottis closes,[9] and the soft palate rises. "Vomitus expulsion occurs at the end of retching as a single maximal [and prolonged] contraction of the rectus abdominis and diaphragmatic dome, while the diaphragmatic hiatus relaxes."[78] "The external (inspiratory) muscles also co-contract with the diaphragm and abdominal muscles during vomiting."[95] Apparently, the positive pressure in the abdomen and the negative pressure in the thorax moves the vomitus from the stomach to as high as the top third or so of the esophagus (the body of the stomach is a passive sac that is squeezed by the striated muscles of the diaphragm and the abdominal wall). The upper esophageal sphincter (UES) relaxes.

The top half, or more,[81] of the esophagus in dogs (top quarter in humans) is striated muscle and is an active participant in ejecting the vomitus. The "cervical esophagus about 5–10 cm from the UES contracts. This cervical esophageal contraction propagates orad at about 10 cm/s,...The cervical esophageal retrograde contraction may represent one of the primary differences between retching and vomiting and may be responsible for projectile vomiting."[78] Another crucial difference between retching and vomiting is, apparently, the relaxation of the hiatal area of the diaphragm.[77] The striated muscle of the pharynx is also active in ejecting the vomitus.

The head is lowered, the mouth opens, the tongue protrudes, and the vomitus is expelled. After expulsion of vomitus the pharynx is cleared by repetitive swallowing. The stomach slowly returns to its normal position.

The very active role of the esophagus in vomiting is noteworthy. Rupture of the esophagus while vomiting, with fatal outcome, has been reported.[66]

The peripheral neural mechanisms of vomiting are further described in Section 4.1.2 below. The central mechanisms of vomiting are described in Chapter 5 (by Miller and Grélot).

3.4.2 Stress Response

3.4.2.1 Conscious Sensations

- Anxiety, or distress, or dread[70,82,124]

Motion sickness produces no sensation of anger, but there is a dread or anxiety that is perhaps related to fear, and there is a tendency to contemplate *exclusively* the motion sickness, and to contemplate it with apprehension. There is a striking absence of inclination to daydream or to think of business, politics, sports, romance, or anything except the sickness. People suffering severe motion sickness in a laboratory just do not spontaneously think about baseball games or the stock market, and they do not smile or laugh. It is reasonable to think that in operational situations a motion-sick person might be delinquent in maintaining attention and vigilance to tasks, especially "background" tasks such as eliciting crew cooperation, checking fuel levels, and making radio reports.

The anxiety of motion sickness is distinguishable from the nausea of motion sickness.[82] The changes in consciousness and behavior that indicate anxiety or dread are not simply nausea and not simply an awareness that vomiting is impending. These changes are utterly unlike the changes in a bulimic who has no nausea but knows that voluntary vomiting is impending (and who looks forward to it). The victim of motion sickness is possessed by a remarkable anxiety/distress/dread.

3.4.2.2 Endocrine Responses

- Increased plasma ACTH[72,73]
- Increased plasma cortisol[32,70,71]
- Increased plasma epinephrine[22,23,70-72,74,75,146]
- Increased plasma norepinephrine[70-72,74,75]
- Increased plasma thyroid hormones, a tiny increase indirectly detected[51]
- Decreased plasma thyroid stimulating hormone[51]
- Increased plasma growth hormone[32]
- Increased plasma prolactin[32]
- Increased plasma beta endorphin, anticipatory and after vomiting[70,71]

The plasma levels of the classic stress response hormones, epinephrine, norepinephrine, ACTH, and cortisol, are all elevated with motion sickness. Plasma levels of growth hormone, prolactin (in both males and females), and beta endorphin also rise in response to various stresses in humans,[97] and they do rise also in motion sickness. Plasma levels of thyroid stimulating hormone are reported to be decreased by stress in animal studies and to be unchanged or increased by stress in humans,[97] but they were found to be decreased in humans by motion sickness.

Note also that the massive increase of plasma antidiuretic hormone (AVP) with motion sickness is *not* listed here as part of the stress response. The increased plasma AVP is better considered part of the vomiting response and is listed as such, above.

The nausea of motion sickness is what concerns the motion-sick person, and it is probably for that reason that there is a popular tendency to consider the nausea as the real motion sickness and the other phenomena as accompanying changes that might or might not *correlate* well with "the motion sickness." It should be noted that the stress response phenomena are real and are part of motion sickness regardless of the correlation with the nausea.

3.4.2.3 Autonomic Responses

The autonomic parts of the stress response are part of Section 4.

4 CHANGES IN THE AUTONOMIC NERVOUS SYSTEM WITH MOTION SICKNESS

There are autonomic changes associated both with the emptying of the stomach and with the stress response of motion sickness. The autonomic changes associated with emptying the stomach include important increases in the level of activity in the parasympathetic pathways, as well as possible increases in the sympathetic pathways.

The autonomic changes associated with the stress response appear to be, predominantly, increases in activity in the sympathetic pathways and/or decreases in activity in the parasympathetic system. The two exceptions, both indications of increased parasympathetic activity, are (1) an increase in variability of the intervals between heart beats in squirrel monkeys,[58,62] although a different measure of variability in these intervals in humans decreases,[70] and (2) a small decrease in the dark field focus distance with motion sickness in humans.[35] The more prominent autonomic changes with the stress response of motion sickness are indicative of increased sympathetic activity: pallor, cold sweating, and increased blood flow to skeletal muscle.

The changes in heart rate and blood pressure with motion sickness are of small magnitude, even with severe motion sickness. Many stress responses have peculiarities, however, and the small magnitudes of these changes are perhaps just the idiosyncrasies of the stress response of motion sickness. In general, the stress responses from different kinds of stress resemble each other[34,50] but they are not identical.[3,97,113,138] It would be reasonable to expect some differences between the responses to heat stress, cold stress, psychological stress, exercise stress, fear, anger, revulsion, and poisoning stress. One experimental study found, for example, that heart rate increased with motion sickness but decreased with the revulsion evoked by viewing a film showing battlefield surgical operations.[113] The reason for the modest cardiovascular part of the stress response of motion sickness could be the high plasma level of AVP with motion sickness. High levels of AVP can substantially reduce both heart rate and blood pressure.[108,132]

The changes described below are probably caused primarily by the autonomic nervous system, but it has not been ruled out that some of the changes are related to other, possibly hormonal, influences. Although the remarkable pallor of motion sickness is usually ascribed to increases in activity in the sympathetic neural pathways, a role of the antidiuretic hormone AVP in the production of the pallor has not been ruled out.

4.1 ANS Changes Associated with Emptying of the Stomach

4.1.1 Salivation

There seems to be no compelling evidence on which to base the assignment of salivation changes to either the "emptying of the stomach" part or the "stress response" part of motion sickness. We shall locate it here as part of the emptying of the stomach, for the reason that salivation is closely related to gastric function.

Investigation has revealed that in humans there is a *perceived increase* of salivation with motion sickness in most subjects[42] but actually a *measured decrease* of salivary flow rate in most subjects.[42,43] There is also a surprising increase in the sodium concentration of saliva with motion sickness,[42,43] surprising because an increased concentration of sodium is an indication of an increased rate of secretion of saliva.[50] The concentration of salivary sodium

in motion sickness has been found to increase also in squirrel monkeys, but in this species the measured flow rate of saliva does tend to increase with motion sickness, as would be expected when the concentration of sodium increases.[58,59]

It has been suggested that the measured *decrease* of flow rate in motion-sick humans[42,43] could be the result of an increased activity in the *sympathetic* division of the autonomic nervous system[41,43,50] or a decreased activity in the parasympathetic division[39,43,50] or both. The measured *increase* of flow rate in motion-sick squirrel monkeys is probably the result of increased activity in the *para*sympathetic division of the autonomic nervous system.[58,59] In dogs the increase of salivation immediately before apomorphine vomiting has been shown to be driven by the parasympathetic system.[37]

The decreased salivary flow rates with motion sickness in humans seem to be unlike the situation in cats, dogs, and monkeys who drool visibly or foam at the mouth with motion sickness. It is possible, however, that with motion sickness in these animals the salivary flow rate remains unchanged but the animals decrease the rate of swallowing. The *perceived* increase of salivation (in the face of a measured decrease) in humans could also be caused by a decrease in the normal rate of swallowing[42] with motion sickness. A decreased rate of swallowing in a poisoning situation might have protective value, since it could reduce the amount of poison swallowed.

It seems possible that the rate of swallowing is decreased and the rate of absorption of water into the tissues of the mouth is increased in motion sickness. If so, then the measured concentrations of salivary constituents in the mouth would presumably increase. In fact, it has been reported that the concentrations of the salivary constituents measured, sodium, potassium, and proteins, do increase with motion sickness.[43,58,59-61] In prolonged vomiting situations an increased rate of absorption of water into the tissues of the mouth, possibly under the influence of AVP, would perhaps tend to protect against dehydration: more of the water in saliva would be returned to the blood, instead of being either lost out the mouth directly (if swallowing is inhibited), or swallowed and then lost in vomitus.

In some human subjects there is a brief but strong increase in salivation, with swallowing, and sometimes with "pressure" sensations localized to the salivary glands themselves, immediately before vomiting; this latter phenomenon seems closely related to the vomiting, but it is seldom reported in motion sickness and it is perhaps separate from the changes in salivation that occur earlier, before vomiting is imminent. The earlier changes in salivation are the ones reported in the motion sickness literature. In dogs given apomorphine it has been reported that there is increased salivation[37] and increased frequency of swallowing[81] starting 2 min or so before vomiting.

4.1.2 *Gastrointestinal Motility*

The major control of functional gastrointestinal motility is by the parasympathetic part of the ANS. The sympathetic part of the ANS appears to influence gastrointestinal motility only moderately and in a general way, with an overall inhibiting and relaxing effect.

Surface electrodes on the abdomen of humans can record the electrical activity of the wall of the stomach, the electrogastrogram or EGG.[70,71,124] The EGG changes with motion sickness. The basic electrical rhythm of the EGG is 3 cycles per minute, but with the onset of motion sickness a "tachyarrhythmia" occurs: the frequency of the EGG increases to 4-9 cycles per minute,[71,146] and also the magnitude of the EGG voltage decreases. The muscular activity of the stomach decouples from the electrical activity when the frequency increases in motion sickness, and the increased frequency of the EGG is actually accompanied by a marked *decrease* of the tonus and motility of the stomach.

The initial inhibition of motility of the stomach and small intestine that occurs with motion sickness is imposed by inhibitory parasympathetic fibers from the vagus nerve.[141] These inhibitory fibers are thought to be the same fibers that provide the inhibitory phases

of normal motility.[98] The inhibition/relaxation is mainly in the proximal part of the gastrointestinal tract, i.e., in the antrum of the stomach and in the duodenum and "proximal jejunum."[98] The inhibitory fibers that provide this initial inhibition are parasympathetic but their neurotransmitter is thought not to be acetylcholine. The fibers have been referred to as "non-adrenergic, non-cholinergic inhibitory vagal system."[141] Transection of the vagus nerve at the diaphragm prevents this initial inhibition, except possibly in the antrum of the stomach.[79,80,141]

The giant retrograde contraction that follows the initial inhibition is also driven by parasympathetic fibers from the vagus nerve. This GRC is eliminated by cutting the vagus nerve[81,98] and is also eliminated by atropine,[79,80,98] although one report suggests that it is not eliminated by atropine.[141]

The phasic contractions that follow the GRC are also driven by parasympathetic fibers from the vagus nerve. These contractions are also eliminated by transection of the vagus nerve.[78]

Presumably the elimination of the prodromal gastrointestinal changes would prevent the emptying of the top half of the small intestine into the stomach before vomiting, so that animals lacking these prodromal activities would vomit without removing any ingested material that had gained access to that part of the small intestine. With these prodromal changes eliminated, vomiting nevertheless occurs apparently normally; the stomach contents are expelled.[78-80] In fact, dogs with the entire sympathetic and parasympathetic nerve supplies to the gut severed are able to vomit in an apparently normal way after exposure to motion.[137]

4.1.3 The Esophagus

Neither the pharyngoesophageal actions in vomiting, nor the expulsion of vomitus, is altered by vagal blockade at the cervical level. "Therefore, vagal reflexes of thoracic or abdominal origin or efferent fibers of the recurrent laryngeal nerves do not control these pharyngoesophageal motor responses."[78] Since the pharynx and the upper part of the esophagus are *striated* muscle, the ANS is not involved in their motor control. No doubt the pharyngoesophageal motor contributions to the expulsion of vomitus are controlled by somatic nerves. This is what would be expected of a fast strong response that needs precise timing to be effective (striated muscle, somatic nerves). The pharyngoesophageal contractions are presumably timed to coordinate with the other contractions controlled by somatic nerves (the contractions of the diaphragmatic dome and the abdominal wall). It has been suggested[80] that the central mechanism of vomiting "may consist of two functionally distinct parts that are activated sequentially: one controlling the gastrointestinal responses and the other the somatomotor responses." In fact, the striated part of the esophagus, and the pharynx, as well as the abdominal wall and the diaphragm, would be controlled by the "somatomotor" part of the central mechanism (not via the ANS).

4.2 ANS Changes Associated with the Stress Response

4.2.1 Heart Rate

The cardiovascular changes in motion sickness[18-22,46,82] are generally in the same directions as in well-known stress responses, but in motion sickness some of these changes are surprisingly small[57] and some are transient.[126,127] In some studies the heart rate increased with motion sickness and in some studies it did not; in some studies a low heart rate or an unchanged heart rate is reported.[100] Transient changes in heart rate could be missed in studies[56] that stop the motion and measure the heart rate by feeling it with the experimenter's fingers. The required head movements of some motion sickness experiments, when

performed in a motionless environment, are actually sufficient to produce increases in heart rate although of course no motion sickness is provoked.[82] Such increases should not be attributed to motion sickness.

The investigators who do observe increases in heart rates with motion sickness[20,22,57,82] appear to be using more severe levels of motion sickness than investigators who observe no increases,[46,82] and it seems likely that increases in heart rate occur but only with the more severe levels of the sickness. Investigators who stop the motion stimulus before the appearance of the more severe sicknesses do not see any increases in heart rates.[82] The increases of heart rate with more severe motion sickness, as recorded during the motion by electrocardiograph (not afterwards using fingers and a stopwatch), appear to be real.[20,82,113]

With moderate or severe levels of nausea, the observed increases of heart rate are statistically significant in some studies, although they do not occur in all the subjects, and the magnitudes of the increases are only 5 to 15 or so beats per minute.[20,82] This modest increase of heart rate with motion sickness, 5 to 20%, is much less than the 100% or so found in swimmers just before a competitive swim sprint,[89] or the 150 to 199% increase produced by skydiving or fast running in non-experts, or the 40 to 99% or so increase in astronauts prior to rocket launch into orbit.[82] Considering the level of misery and anxiety being suffered by victims of severe motion sickness, it is surprising that the increase of heart rate is not greater. Apparently there have been no comprehensive studies of heart rate during the frank vomiting of motion sickness, although there is some indication that it does increase.[56]

It is possible that the heart rate with motion sickness would be more typical of stress response situations (higher) if high plasma levels of AVP were not generated by motion sickness. It is not clear that the levels of AVP in motion sickness are sufficiently high to influence heart rate, but it is known that high levels of plasma AVP cause substantial decreases of heart rate and coronary blood flow.[132] The decreases of heart rate after injection of large doses of AVP in humans are roughly 15%. Perhaps it is relevant that stimulation of the area postrema inhibits heart rate in some species.[33] Also, when apomorphine was administered to normal humans,[108] nausea and vomiting was provoked and plasma AVP rose dramatically and mean arterial pressure *fell* significantly; in people with diabetes insipidus however, the apomorphine provoked the nausea and vomiting but of course no rise in plasma AVP, and in these people the fall in blood pressure was smaller and not statistically significant. When ipecacuanha was given to the subjects,[108] nausea and vomiting were provoked but no rise in plasma AVP occurred, and with ipecacuanha the blood pressure and the pulse rate both *rose* significantly.

Increased activity in the sympathetic division of the ANS can cause increased heart rates, and the modestly increased heart rates with motion sickness can be considered part of a stress response.

4.2.2 *R-R Interval*

The measure of interest here is the variability in the interval between heart beats. The R-R interval (RRI), the duration of the interval between heart beats, is more variable when the *para*sympathetic system is more active in controlling the heart, and less variable when the sympathetic system is more active in controlling the heart.[136] In a study of 52 human subjects exposed to a rotating optokinetic drum that provoked motion sickness, it was found that the RRI variability *decreased* (that is, the pulse became steadier) with motion sickness.[57,70] Specifically, "the mean successive differences of R-R intervals" decreased with motion sickness. Considering this result together with the observed gastric tachyarrhythmia and increased skin conductance levels with motion sickness, a small mean increase in pulse rate in the subjects, and other evidence, it was suggested that "high sympathetic nervous system activity plays an important role in the appearance of ... symptoms of motion sickness."[57]

On the other hand, in motion sickness tests of five normal squirrel monkeys it was found that the variability of the RRI *increased* with motion sickness.[62] The measure of variability of the RRI in the monkeys was "the coefficient of variance (CV) of mean R-R intervals," not the same measure of variability as in the study of humans,[57] but the finding must be given careful attention for the reason that it is tempting to ignore it because it is an exception to the generalization.

It is an exception to the generalization that the stress response of motion sickness consists only of increases in the sympathetic influences and/or decreases in the parasympathetic influences. However, the measure of variability employed, CV of RRI, is a sensitive measure that is possibly more appropriate for detecting variability in RRI than mean successive differences of RRI intervals which could be confounded by beat frequency. The CV of RRI was also validated pharmacologically in 11 monkeys: a drug that reduces the parasympathetic influence, atropine, produced a decrease in the CV, and a drug that increases beta-adrenergic (sympathetic) influence, isoproterenal, similarly produced a decrease in the CV; both of these results suggest that the CV measure is a valid one. Two drugs that might be expected to *increase* the CV, carbachol ("stimulates the parasympathetic nerve system") and propanolol (produces "beta-adrenergic blockade") did not produce significant changes in the CV,[62] but significance is often technically difficult to achieve with small test populations. The motion sickness tests in the five monkeys, with increased CV of mean RRI, seem to be valid indicators of increased *para*sympathetic influence on the heart with motion sickness in this species.

Surprisingly, in the same study[62] three monkeys with unilateral labyrinthectomy were exposed to the motion sickness stimulation and all three showed *decreased* CV of the RRI, the *same* sort of result as found in the study[57] of humans. Unilaterally labyrinthectomized animals might be expected to be somewhat less susceptible to motion sickness than normals, but if they do get motion sickness, presumably the sickness should be similar to that of normal animals although perhaps less severe. The findings in the three unilaterally labyrinthectomized monkeys therefore appears to contradict the findings in the five normal monkeys. In this monkey study there was, unfortunately, no mention of the behavior of the heart *rate* with the motion sickness. A later study by some of the same investigators[58] confirmed the increased CV of RRI in squirrel monkeys with motion sickness but, as in the earlier study, no information was provided about heart rates. The later article also confirms their view that there is an increased influence of the parasympathetic system on the salivary glands with motion sickness in squirrel monkeys. Salivary responses are presumably part of the stomach-emptying part of motion sickness and do not suggest anything about the stress response of motion sickness.

The stress response of motion sickness in squirrel monkeys, in its cardiac RRI manifestation, is exceptional. In these monkeys the increase of RRI variability with motion sickness is not characteristic of a typical stress response. Increased activity in the sympathetic division of the ANS can cause decreased variability of the RRI, and in humans the decreased variability of the RRI with motion sickness can be considered part of a stress response.

4.2.3 Blood Pressure

Several studies of blood pressure in motion sickness have found no large changes.[64,82,126,127] Blood pressure tends to vary with motion sickness, but it "can rise or fall in response to motion in both susceptible and nonsusceptible individuals."[100] Even two subjects who had their blood pressure measured "through a needle inserted into the brachial artery"[64] did not show clear directions of changes in blood pressure with motion sickness.

Since the blood flow in skeletal muscle can increase markedly in motion sickness, and since no corresponding loss of blood pressure is observed, therefore either the cardiac output increases (unlikely since the pulse rate increases are small) or there is a decreased

blood flow elsewhere in the body (probably in skin and, more importantly, in viscera).[126,132] There is presumably an increase of peripheral resistance in skin and viscera that balances nicely the decrease of peripheral resistance in skeletal muscle.

Absence of a large increase in blood pressure is not typical of a stress response. The enormous increase of blood flow in skeletal muscle with motion sickness can be expected to be a powerful reducer of blood pressure in motion sickness, and could explain the failure of blood pressure to rise with motion sickness. Also, the large increases of plasma AVP with motion sickness could explain the failure of blood pressure to rise. It is known that large doses of AVP injected into humans cause substantial decreases in cardiac output, decreases in coronary blood flow, and substantial decreases in heart rate.[132] Since AVP does decrease coronary blood flow,[132] it would be prudent for people with heart disease to avoid conditions in which motion sickness could occur. Plasma AVP in motion sickness increases to 20–30 times the normal levels.

4.2.4 Blood Flow in Skeletal Muscle

With moderate-to-severe motion sickness there is a two- to threefold increase in the blood flow through the forearm.[126,127] There is also an increase in the total limb volume with motion sickness. This was measured in 46 human subjects exposed to head movements while rotating at 30 rpm, and it was found that the rate of flow of blood through the forearm increased two to three times in susceptible subjects.[126,127] The blood flow was measured by venous occlusion plethysmography (the venous return from the arm is blocked with a pressure cuff and the rate of swelling of the arm is measured). The measurements were done repeatedly without interrupting the motion stimulus, and the subjects called for cessation of the stimulus when they thought that emesis was imminent.

Thirty-two of the subjects stopped the stimulus before five minutes had elapsed, and in all of these 32 subjects all of the measurements showed at least some increase in forearm blood flow, compared to the pre-motion flow. "Although there were some exceptions, the magnitude of the change in forearm blood flow correlated with the severity of the symptoms, and it was often possible, by observing the blood flow recordings, to predict when the subject would signal that he would vomit if stimulation were not discontinued."[126] Since the human forearm is 85% muscle by volume, the results are taken to be an indication of increases in skeletal muscle blood flow generally. The blood flow in the calf of the leg of one subject was found to increase similarly. One study did not find the increase in forearm blood flow, possibly because a lesser degree of motion sickness was provoked.[82]

Increased activity in the sympathetic division of the ANS can cause increased blood flow in skeletal muscle, and the increased blood flow in skeletal muscle with motion sickness can be considered part of a stress response.

4.2.5 Blood Flow in Skin and Blood Content of Skin

The hallmark facial pallor, the pasty or greenish face of people suffering from motion sickness, is presumably caused by a lack of red color in the face, a decreased presence of red blood in the skin. The pallor is apparently caused by a reduction in the amount of blood present in the skin rather than a reduction in the rate of flow of blood through the skin, and measurements of blood flow in human fingers did not reveal any decrease during motion sickness,[82] although earlier studies found decreases of finger pulse volume with motion sickness.[22,113] With motion sickness onset there is actually a brief flushing of the face in some people,[52,111] but the flushing is usually replaced by pallor as the sickness continues. In most people the pallor then persists for as long as the sickness lasts. In one study the "onset of pallor, as detected on the color films, occurred before the report of nausea in all but 3 of 14 cases."[22]

The spectacular decrease in the amount of blood in the skin of the face, the remarkable pallor, is exactly what would be expected from a very strong increase in activity in the sympathetic nervous system, and the shunting of blood out of the skin is thought to be beneficial in stressful situations because more blood would be available to skeletal muscle and less blood would be lost if the skin were broken. The extreme degree of pallor seen in motion sickness, however, is seldom seen in response to other stresses, seldom in athletes even during extremely vigorous exercise. People who exercise to the point of exhaustion and nausea will sometimes exhibit facial pallor, but sprinters and skydivers just do not look like people suffering from motion sickness, even though they have heart rates that suggest a strong stress response.

It is puzzling that motion sickness seems to produce such an extreme sympathetic effect on the blood vessels of the skin of the face (constricting them) and on the blood vessels of skeletal muscle (dilating them), but such a modest effect on the heart rate and blood pressure. A possible explanation of the extreme change in the skin is that the massive increase in plasma AVP also constricts the blood vessels in skin. At higher levels of AVP, "Circulation in the skin and the gastrointestinal tract is markedly reduced"[39] and "After the injection of large doses of vasopressin, marked facial pallor as a result of cutaneous vasoconstriction is commonly observed."[54]

In motion sickness the plasma levels of AVP can reach 20 or even 30 times normal levels. If 20 or 30 times normal levels can be called a "large dose," then the hallmark pallor of motion sickness might be considered partly the result of the body's release of AVP into the bloodstream. At this time it is reasonable to think that *both* the sympathetic nervous system and the plasma AVP play roles in causing the remarkable pallor of motion sickness.

With motion sickness in spaceflight it has been reported that the pallor is much less than with motion sickness on Earth, possibly because the fluid shift caused by weightlessness keeps blood in the skin of the face.[102] In colder environmental temperatures there is probably more pallor with motion sickness than in warmer environmental temperatures. "Environmental temperature affects the degree of pallor but not the time of its onset."[22]

Increased activity in the sympathetic division of the ANS can cause pallor, and the pallor of motion sickness can be considered part of a stress response.

4.2.6 Cold Sweating or Increased Skin Conductance

"Cold sweating is the sweating that occurs without an adequate thermal stimulus,"[55] and this kind of sweating is a prominent sign of motion sickness. In an experiment in which motion sickness is provoked by head movements on a rotating platform, "A sweat response can be obtained from the palmar aspect of the hand during the initial few head movements...This response is maximal on the first one or two head movements and quickly declines with continuation of the stimulus. At a varying time interval after the commencement of head movements, a distinct sweat response occurs on the dorsal aspect of the hand and arm, independent of the palmar response."[92] The initial brief palmar sweating is "arousal" sweating, and the more extensive later sweating is "thermal" (but inappropriate) sweating.[92]

The sweating with motion sickness is sweating without an adequate thermal stimulus, but the environmental temperature retains an important influence. With motion sickness "more sweating took place at the 94° than at the 84° environmental temperature."[22] It was further found that as "the temperature was lowered increased amounts of vestibular stimulation were required to evoke the sweat response,"[91] and with environmental temperatures of 65°F or below there was little or no sweating in most subjects even though the nausea criterion was reached. Sweating or increased skin conductance with motion sickness is a consistent finding.[20-22,55,57,91,113,114]

Increased activity in the sympathetic division of the ANS can cause sweating, and the sweating of motion sickness can be considered part of a stress response.

4.2.7 Decrease in the Dark Field Focus Distance

Motion sickness has been found to increase the refractive power of the lens and thereby decrease the dark field focus distance of the eye.[35] The increase of refractive power was less than 0.5 diopters, a small fraction of the 60 diopters that is the total refractive power of the normal relaxed eye and a small fraction of the 10 diopters that is the maximum possible *change* in focus that can be achieved (in young people) by voluntary accommodation. In a normal eye, focused on infinity when relaxed, a maximum effort at near vision can increase the refractive power of the lens by roughly 10 diopters in a 20-year-old (and zero diopters in a 50-year-old: approximately 1/3 of a diopter of accommodative power is lost per year, with aging, starting from childhood). An increase of 0.5 diopters, and the corresponding decrease in the focus distance, is not insignificant.

An increase in the accommodative power of the lens of the eye is achieved by an increase in the activity of the parasympathetic fibers to the ciliary muscle and a resulting increase of contraction of the ciliary muscle.[50] The observed decrease in the dark field focus distance with motion sickness is therefore an indication of an increase in parasympathetic activity, and such an increase is exceptional in the stress response of motion sickness. The autonomic parts of the stress response of motion sickness are predominantly increases in sympathetic activity and/or decreases of parasympathetic activity. In the context of a stress response, the increase in parasympathetic activity to the ciliary muscle of the eye, and the resulting decrease in dark focus distance, must be considered paradoxical.

It has been pointed out[35] that motion sickness is not the only stress that provokes a decrease in the dark field focus of humans. "Two subjects were made angry by insulting remarks directed to them while their accommodative level was being tracked in complete darkness. In both cases a rise in accommodative level, lasting for several minutes, occurred; in one instance the rise exceeded 1 [diopter]."[139] It might be that the peculiarity of an increase of the parasympathetic activity to the ciliary muscle, in the stress response of motion sickness, is not so much a peculiarity of motion sickness as it is a peculiarity of the optical accommodative responses of humans to stresses in general. The parasympathetic fibers to the ciliary muscle exert the major control of focus distance; the sympathetic fibers to the ciliary muscle are in fact incapable of exerting any strong influence on focus distance since "they supply very weak innervation to the ciliary muscle."[50]

The optical accommodative response of a human to a near object usually occurs as part of a "near response" or "triad response" that includes, in addition to a decrease in the focus distance, a convergence of the eyes (directions of gaze move together more), and a decrease in the size of the pupils. The sympathetic fibers to the iris are much more influential than the sympathetic fibers to the ciliary muscle, and it would be interesting to find out whether the pupil shows an increase of sympathetic activity in motion sickness. Whether the other two parts of the human "near response" (pupillary constriction, and convergence) occur with motion sickness has apparently not been investigated.

In a different species, rabbits, exposed to a different stress, the expected *decreases* of accommodative power (and increases of focus distances) in response to stress were found; in this species the expected decrease of parasympathetic activity with stress seems to have occurred. When, in dim light, "rabbits were startled by a sudden tap on the nose (the most convenient stimulus), by having their heads sharply raised and lowered or turned side to side, or by being suddenly jostled about, or upon hearing a sudden noise such as the slamming of the door, they immediately"[109] showed *decreases* in accommodative power of the lens (increases of focus distance). These changes lasted 2 to 5 min and on average were 1 diopter.

5 SUMMARY AND CONCLUSIONS

Motion sickness can be seen as a poison response that occurs, inappropriately, in response to certain kinds of motion. The signs and symptoms form two groups, (1) stomach-emptying phenomena and (2) stress response phenomena. It is sometimes postulated that the stomach emptying phenomena of motion sickness are stressful and cause the stress response; it is also postulated sometimes that the stress response of motion sickness causes the stomach-emptying phenomena. In fact, the available evidence does not support either of these (mutually exclusive) etiological postulates. The evidence suggests that motion acts on the vestibular system to trigger a poison response, and that the poison response provides both the stomach emptying and the stress response.

The stress response of motion sickness includes changes of conscious sensations (including distress or dread), endocrinological changes (increased plasma levels of norepinephrine, epinephrine, ACTH, cortisol, etc.), and autonomic changes. The autonomic changes of the stress response of motion sickness seem to be the result of increases of activity in the sympathetic pathways: pallor, cold sweating, increased blood flow in skeletal muscle, and a modest increase in pulse rate.

The stomach-emptying phenomena include a suppression of upper gastrointestinal motility, followed by the emptying of the upper half of the small intestine into the stomach and the lower half into the colon (thereby preventing the further absorption of most substances). Then retching and vomiting empty the stomach. Conscious sensations of nausea, and sensations of vomiting, also occur. Another prominent stomach-emptying phenomenon of motion sickness is an increase in the concentration of the antidiuretic hormone AVP in the circulating blood, an increase up to 30 times the normal circulating concentration. There is evidence that the high levels of AVP in motion sickness prevent the strong increase of arterial blood pressure that typically does occur with stress responses but does not occur in motion sickness. The AVP would also give some protection against water loss in prolonged vomiting situations.

The autonomic phenomena of stomach emptying are, of course, controlled mostly by the parasympathetic pathways. Controversies about whether sympathetic or parasympathetic responses are dominant in motion sickness can probably be resolved by noting that the stress response of motion sickness involves increases in sympathetic activity whereas the stomach-emptying phenomena of motion sickness involve increases in parasympathetic activity.

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