MOTION SICKNESS

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INTRODUCTION

The excellent review on motion sickness by Tyler and Bard in 1949 (358) thoroughly discussed the manifold aspects of the etiology and treatment of this condition. Recently, Borison and Wang (52) have presented, with equal competence, the broader, but related subject of vomiting. Other summaries of specific aspects of motion sickness have recently appeared in the literature (14, 73, 102, 154). No attempt will be made, therefore, in the present review to discuss in detail material already presented so adequately. Instead, we shall concentrate upon certain recent advances in the mechanism and treatment of motion sickness and shall lean heavily upon the references cited for much of the background material.

The first recognition of motion sickness is lost in antiquity. As Fonssagrives (131) has so aptly commented, seasickness was born the day a novice sailor set foot upon a ship. Certainly, centuries before the Christian era it was well known, as evidenced by allusions in the writings of Homer and Hippocrates. The early literature on the incidence and treatment of seasickness from the period of the Roman Empire to the 17th Century has been carefully compiled and reported by Pezzi (304). Realization that the malaise and nausea of sea travel are merely generalized responses to certain characteristic forms of motion is generally attributed to Irwin (193) who, in 1881, coined the term "motion sickness." It seems probable, however, that the similarity between seasickness and the disturbances caused by other forms of travel must have been apparent to observing travelers and physicians long before this time. Motion sickness has been reported after most forms of travel, including car, train, ship, airplane, wagon, and camel, as well as after participation in various amusement park or testing devices (Barany chair, swing, etc.). The term "kinetosis" is preferred by some investigators (347) to include motions having repeated accelerated and decelerated linear and rotary components.

SYMPTOMS OF MOTION SICKNESS

The usual symptoms of motion sickness include anorexia, drowsiness, pallor, epigastric awareness, malaise, cold sweat, nausea, vomiting and retching. Salivation, headache, increased intestinal peristalsis, fatigue, and mental depression may also occur. The sequence, number and intensity of symptoms may vary considerably depending upon the individual and the kind and severity of motion experienced. This variation has posed a perplexing problem to investigators desirous of firm criteria as indices of motion sickness. Many of the symptoms are subjective sensations and virtually impossible to quantitate. For example,

some persons with no obvious symptoms will complain of severe nausea, whereas others, demonstrating all overt symptoms of motion sickness, will deny being nauseated.

Hemingway (172) has shown that cold sweating is a reliable indication of incipient motion sickness under well controlled conditions. Thermal sweating, however, vitiates this measurement and the need for galvanometric equipment makes it impractical in any large-scale or field study. Cardiovascular and respiratory changes during motion sickness have been amply reported in the older literature. Over-ventilation may occur in individuals suffering from motion sickness (321, 322). It is probable that the dizziness, tingling, and disorientation after motion sickness may, in some cases, depend upon such respiratory hyperactivity. Such a case is described by Pumphrey *et al.* (311), who reported tetany in an individual following hyperventilation and repeated vomiting. Such respiratory changes, however, are by no means an invariable concommitant of sickness. In this connection, the alkalosis from hyperventilation should not be confused with the ketosis and alkalosis occasionally reported from excessive vomiting and reduced food intake as has been reported by Marrack (262).

Prior to World War II, changes in blood pressure and pulse rate during motion sickness were widely accepted and contributed to the concept of "vagotonia" and "sympathicotonia" advanced by Eppinger and Hess in 1917 (109). Proponents of this theory divided susceptibles into those demonstrating a hyperactivity of the sympathetic nervous system (sympathicotonics) and those with an excessively active parasympathetic system (vagotonics). Therapy was predicated on an improvement of the autonomic balance (183). These terms have now largely fallen into disuse with the realization that changes in blood pressure and pulse, after exposure to motion, are indistinguishable between susceptible and nonsusceptible individuals (171, 353).

Facial pallor frequently serves as an indication of approaching nausea and vomiting. Unfortunately, it is merely a suggestive symptom rather than a definite indication of sickness. Furthermore, such change in color becomes apparent only in persons having relatively little pigment.

Other physiological and biochemical measurements have been equally unreliable in detecting changes attributable to motion sickness. Cipriani and Morton (92) failed to detect any electrocardiographic, electroencephalographic, respiratory, or blood pressure changes after swinging volunteers. More recent studies in seasickness indicate that the alpha rhythm of the electroencephalogram may be activated and the dominant wave frequency slowed (80) but these changes are neither constant nor typical enough to have diagnostic value.

No consistent change in blood constituents (Ca, glucose, P, Na, K, O_2 saturation and CO_2) after motion sickness has been demonstrated (120) although some evidence exists that glucose concentration may rise moderately and inorganic phosphate concentration fall whether or not the subject gets sick (275). Presumably, this is related to sympathetic stimulation. Since many of the symptoms of motion sickness suggest cholinergic activity, acetylcholine content

and cholinesterase activity in blood of swing-sick dogs were analyzed. No significant change could be demonstrated (37).

The unsatisfactory status of the above physiological and biochemical measures in detecting motion sickness leaves vomiting as the only simple, objective criterion. For this reason, the effectiveness of prophylaxis or therapy is generally based upon a decrease in emesis, with the full realization that vomiting is not a necessary consequence of motion sickness, and that a vomiter may suffer less distress than a person who does not progress to this point. The utility of this criterion is amply vindicated by the numerous drug studies in which it has been used.

The gastrointestinal movements during vomiting are discussed in detail by Borison and Wang (52). Suffice it to say here, that the once prevalent concept of pylorospasm and reversed peristalsis of stomach and esophagus largely has been abandoned. On the contrary, now it is believed that gastric distension occurs from loss of gastric tone, followed by generalized contraction of the duodenum and abdominal musculature (192, 232, 313, 380).

INCIDENCE OF MOTION SICKNESS

Dog and man seem the animals most susceptible to motion sickness. Tyler and Bard (358) speculated that this may be related to the absence of adequate stimuli in their normal habitat. However, other animals more acrobatically inclined are not immune; approximately 15 per cent of a group of cats vomited when swung through an angle of 90 degrees on a swing with a 14.5 feet (4.42 meters) radius (286), whereas dogs under similar circumstances had a sickness rate of approximately 75 to 80 per cent (88, 274, 286). Horses, cows, monkeys, poultry, and songbirds have been reported susceptible to seasickness (60, 69, 124) although data on the incidence are unavailable. It has even been claimed that trained seals en route from England to America, and fish being conveyed to the New York Aquarium from the Galapagos Islands became seasick (60). The criteria of seasickness are not indicated! In our hands, monkeys have been completely resistant to swinging for periods of one to two hours (88). Morton (274) was also unsuccessful in producing swing sickness in monkeys.

Human seasickness. A precise estimate of the incidence of motion sickness in man is obviously impossible, for it will vary with the type, severity and duration of motion. It will vary with the age and experience of the population selected, with the criteria employed and, possibly, with a variety of uncontrollable environmental factors. Reports of the incidence of seasickness range from 0.8 per cent on large ocean liners (254) to almost 100 per cent in certain combat landing operations (358). A more realistic value would appear to be the estimate by Schwab (330) that 40 per cent of any population group are susceptible to seasickness on sudden exposure to rough weather at sea. In our own experience, the incidence of seasickness among young military personnel during ten separate transatlantic crossings in naval transports ranged from 15.7 to 59.6 per cent, with an average of 31.5 per cent. These values represent

cases of frank vomiting and were obtained from over 1,000 men receiving placebos during mild to turbulent crossings. In a series of over 3,000 subjects in small landing craft, Tyler (355, 356) reported seasickness rates from 11 to 60 per cent. Of these, approximately 2 to 30 per cent had severe nausea or vomiting. The exposure time was one to three hours.

Airsickness. The incidence of airsickness shows a similar variation depending upon the persons tested, intensity of turbulence, type of plane, and duration of flight. In pressurized commercial aircraft, only 0.6 per cent of all passengers carried became sick (374). Figures are not available for the incidence in non-pressurized commercial aircraft, but they are also quite low since rough weather is generally avoided and flights are of short duration. The incidence of sickness in military planes has been thoroughly reviewed by Tyler and Bard (358) and by Hemingway (174). In the early stages of World War II, the aviation student received his first flying in the form of 10 hours of dual instruction at college training detachments. During this initial training period, sickness occurred in approximately one of each 40 flights. Eleven per cent of the trainees were sick on at least one of their ten flights. As would be expected, the incidence decreased with experience, from 5.7 per cent on the first flight to 1.1 per cent on the tenth flight (177). In primary training, the incidence was somewhat higher (13.1 per cent) (174) probably because of the more rigorous flying duties required. Among the eliminees, approximately twice as many (19.8 per cent) were airsick as among those who graduated (10.8 per cent). Greenberg (159) questioned veterans upon their return from combat tours. He found the overall incidence of airsickness of these men during their training period to be 25.7 per cent. In combat, however, the incidence was only 5.4 per cent, and the rate of interference with performance of duty during combat was very low—0.3 per 1,000 man missions.

Navigator trainees were more susceptible than other crew members. Of 380 students studied 65.7 per cent were airsick one or more times and the overall airsickness on 4,534 man missions was 15.6 per cent (230). Green (157) reported that over half of 176 navigator-bombardiers became sick at least once during their training. This is in contrast to an average incidence of all personnel of only 17 per cent. The values reported are higher than those of other surveys since Green included relatively mild symptoms which are ordinarily not considered as airsickness. McIntyre and Gardiner (241) found airsickness in 33 per cent of navigator trainees. Other reports confirm the relatively high incidence among navigator trainees (19, 63, 221). The higher susceptibility of navigator trainees seems the resultant of several factors: inclusion of candidates eliminated for airsickness from pilot training, longer training flights than for other crew positions, and greater visual and postural disturbances attendant upon the necessary duties.

As might be expected, the transportation by air of large numbers of troops inexperienced in flying causes considerable airsickness when moderate turbulence is encountered. In a flight of only 2½ hours duration at low altitude (250 to 500 feet) in a C-54 airplane, 24.6 per cent vomited (87). This coincides with the

conclusion of Littauer and Bruger (225) that flights in excess of 2½ hours can be expected to make one-fourth of the passengers sick. In gliders, notoriously sensitive to atmospheric variations, Park (292) reported 35 per cent sickness during maneuvers, and Littauer (224) up to 80 per cent in a 5-hour flight. Johnson and Mayne (200) claimed that a 30-minute glider flight was sufficient to produce 60 per cent sickness under normal summer conditions.

At the USAF School of Aviation Medicine, mild to moderate evasive tactics in a C-47 aircraft have been employed during the past five years as a technique in the screening of potential airsickness prophylactics. The incidence of vomiting among the placebo group has approximated 50 per cent during a 60-minute test flight. Under closely comparable conditions, Johnson and Mayne (200) report 41 per cent to have become sick. During maneuvers, from 15 to 20 per cent of untreated paratroopers have been shown to become airsick while being transported to their drop zone in 30 to 90 minutes (75, 78). Winfield (375), on the other hand, claims no cases resulted in 20-minute flights among paratroopers during training.

Under less turbulent conditions, sickness among airborne troops diminish accordingly. During maneuvers on an exceptionally smooth flight lasting approximately one hour, only 3.6 per cent became airsick (229). Under somewhat similar conditions during more recent maneuvers (Operation Long Horn, 1952), 6.8 per cent of 486 controls vomited during a smooth flight of approximately 1,000 miles (75).

Other forms of motion sickness. No reliable data are available on the incidence of car sickness, train sickness, or sickness on various other conveyances. Rudat (320) estimated that 3 to 4 per cent of all persons become sick on train or car.

In addition to these forms of travel sickness, motion sickness has also been reported on various devices employed for entertainment or specifically designed for experimental purposes. From perusal of many thousands of questionnaires, we feel that a surprisingly large proportion of the population has found the term "amusement" devices somewhat of a misnomer.

The swing was widely adopted during the war as a simple experimental device to estimate the susceptibility of various population groups to motion and to test the effectiveness of medications. Sickness can regularly be induced in 20 to 30 per cent of unselected subjects by swinging for 20 minutes through an arc of 120° to 150° (173, 345). With more prolonged swinging, rates of vomiting as high as 57 per cent have been obtained (284). With flying personnel known to be susceptible to airsickness, from 58 to 65 per cent became swing sick (174).

Other devices of varying complexity have been developed for the study of motion sickness. Elevators (336, 337), rockers (91, 308, 309), rotating chairs (347) and "wave machines" (3) have all been employed. The most elaborate is the wave machine employed by Wendt and his coworkers in which velocity, acceleration or amplitude could be varied independently. The effect of each component on the production of nausea has been investigated systematically by this group in a series of fundamental studies which will be discussed in more detail in a later section. Spiegel and his coworkers (347) were able to produce

nausea and vomiting in 75 per cent of unselected subjects within 8 minutes with their rotating-tilting machine. Here, the head of the subject was tilted either in the sagittal or the frontal plane while he was being rotated in a Barany-like chair. This gyroscopic precession (imposing one angular velocity upon another) has been noted by several other investigators as an effective stimulus for the production of nausea and vertigo (201, 206, 239).

Susceptibility. The susceptibility of an individual to motion sickness cannot be predicted prior to his exposure to the appropriate motion. It is common knowledge that some individuals may be prostrated by turbulence which is completely without effect upon their neighbors. Attempts to explain these differences on the basis of racial, psychological, physiological, or biochemical differences have been unrewarding. Although certain rough generalizations have been made, it can be stated categorically that for any specific case the susceptible person cannot be differentiated from the resistant except by exposure to the motion in question.

To our knowledge, there are no data to support the contentions that Englishmen, Chinese, and Malayans have a high resistance to seasickness (60) or that Frenchmen, Jews (60), Filipinos and Puerto Ricans (2) are readily susceptible. Such generalizations appear to be purely subjective impressions.

Bohec (cited by Brooks (60)) claimed that the insane, hypertensive, feverish, and tabetic were relatively immune. No basis for these statements is given. His further statement that rope walkers, acrobats, dancers, deaf mutes, and young children are resistant seems more likely. Individuals participating in jobs requiring delicate balance or controlled movements either would adapt or seek other employment. Further, such acrobats and athletes early learn the importance of visual orientation during rapid spins and other maneuvers. The immunity of persons with inner ear damage is well authenticated (195, 337), and has been confirmed experimentally (336, 337). The resistance of young children (under age 2) to motion has been attested by numerous workers (358), although no controlled study has ever been made on this matter. It seems probable that the lowered sickness rate among infants is mainly attributable to the large proportion of time they are in a reclining position. Further, it is hard to differentiate motion sickness in the infant from other disturbances which are apt to be blamed as the culpable factors. Puppies, however, have been found resistant to elevator movements (337) and to swinging (37). Bakwin (25) claims that carsickness is more common in children (over 2) than in adults, but that seasickness or airsickness is less common. No explanation for this anomalous position is apparent; nor are any quantitative data cited. Cone, a pediatrician with considerable experience as a ship's physician, maintains that the incidence of seasickness among children is much higher than is commonly assumed (93). Certainly, there is no question that the susceptibility to seasickness drops sharply between young adulthood and middle age. In a survey of over 5,000 subjects studied during transatlantic crossings, Chinn *et al.* (77) reported a steady decline in seasickness with age, ranging from 31 per cent vomiting at age 17 to 19 years to 13.2 per cent vomiting at age 30 to 39. Persons over the age of 40 showed an

increase to 17.4 per cent but the series was too small to have any statistical significance. Noble (284) contends that susceptibility to swing sickness increases above the age of 40, but this conclusion also is based on rather limited data. The general increase in resistance to seasickness as one ages may reflect adaptation through greater sailing experience or a general decreased physiological sensitivity. In opposition to the statement that greater experience may be the decisive factor, is the observation that seasickness similarly declines with age even when persons making their first sea voyage are alone considered (77). Women have been reported to be more prone than men to airsickness (217).

An extensive literature has accumulated in an attempt to correlate various somatic, physiological or psychological factors in determining susceptibility to motion sickness. Wendt and his coworkers have been especially active in this field. The results have been consistently and disappointingly negative. Wendt (10, 370) could find no significant correlates among over 200 tested. These included cold pressor test, breath holding capacity with positive and negative pressure, dermographia, reaction to tilt table, reaction to injection of methacholine, data on respiratory pattern, pulse rate, blood pressure, skin temperature, forehead sweating, salivation, and many others. There was no difference in response between susceptible and nonsusceptible persons. This lack of correlation for many of these and other variables has been amply confirmed in other laboratories. Kirkner (207) reported that relative palmar resistance drop was not related to motion sickness susceptibility. Electroencephalographic tracings of normal and susceptible individuals were indistinguishable (196, 223). No differences in blood composition (38) or type of stomach (231) could be detected between those who became sick and those who did not.

As already discussed, the once prevalent idea that abnormal sensitivity of the autonomic system, especially of the parasympathetic, predisposed towards sickness has been largely discarded. Attempts to identify certain psychiatric or personality traits among motion susceptible persons have been inconclusive. Bond (50) reported that the great bulk of susceptible individuals gave evidence of considerable emotional maladjustment. MacPhee and Pennington (249) also believed that chronic motion sickness is correlated with emotional instability. However, when the Minnesota Multiphasic Personality Inventory was used as an index, no significant relationship could be established between neurotic tendency and motion susceptibility (382). It seems probable that the underlying cause in significant numbers of chronic motion sickness sufferers may be of psychoneurotic origin. However, since most susceptible persons eventually adapt themselves to motion, the reviewers do not believe that personality disturbances are of great importance. Additional studies in this area are needed.

SELECTION OF PERSONS RESISTANT TO MOTION SICKNESS

Selection of persons resistant to motion sickness and, especially to airsickness, has been attempted by several methods: 1) questionnaire, 2) labyrinthine function tests, 3) use of a swing or other device, and 4) testing under actual sailing

or flying conditions. An excellent discussion of the validity and shortcomings of each can be found in the review of Hemingway (174).

Questionnaire. The simplest method of selection is through the use of a questionnaire to elicit the individual's previous experience with motion of various types and his response to this motion. An accurate history has been shown to have fair predictive value (40, 99). There are two inherent shortcomings of such a procedure: 1) many individuals have had insufficient experience with rough motion to know how they will react, and 2) completely honest answers are difficult when the examinee believes his assignment may depend on his response. This was especially true with aviation student candidates.

Labyrinthine testing. As will be discussed in more detail later, the labyrinth has been implicated in motion sickness since the latter part of the 19th Century. It is natural, therefore, that tests of vestibular function early would be suggested for the screening of motion susceptible individuals. During the early stages of World War II, all United States pilot candidates having motion sickness history of any kind were required to undergo a Barany Chair test. McDonough and Thorner (233) found only 10 aviation cadets of 644 tested who were judged abnormal by this test. Later studies on part of these men indicated that two-thirds had been airsick one or more times and 5 per cent had been eliminated for airsickness. They concluded that the Barany Chair was of no value as a selection device. Spiegel, Henny and Wycis (346) proposed for selection their rotating-tilting machine. Other workers (62, 163, 277) could detect no correlation between the response to cold caloric stimulation and sensitivity to motion sickness unless the reaction was unusually marked. More recent advocates of vestibular testing, however, claim remarkably sensitive selection of susceptible persons by their technique. Evrard (110) based his selection upon the time required for a candidate to assume a modified Romberg position (one foot in front of the other, eyes blindfolded) after sudden stopping of a rotating chair in which eight revolutions were made in 10 seconds. However, Schuster (334) using this technique, was unable to detect any difference between those sensitive or resistant to swing sickness. DeWit (102) used a turning room rather than a chair and determined the duration of nystagmus after sudden cessation of turning. This is considered a reflection of the time required for the cupula to return to a position of rest. By plotting the duration of nystagmus against the logarithm of the speed of rotation, a straight line is obtained. DeWit found chronically seasick individuals to have much steeper "cupulograms," *i.e.*, nystagmus persists longer for any given rotary impulse. These individuals also displayed a somewhat lower threshold for nystagmus (2.5° per sec.) compared with normal controls (3° per sec.). The threshold is claimed to measure the sensitivity of the vestibular apparatus and the steepness of the curve, the degree of habituation to labyrinthine stimuli.

Artificial motion device. The utilization of a swing, elevator, or roll and pitch machine has been the technique most widely investigated for predictive value. The most critical analysis of this procedure was made by Hemingway (176) using a swing. Of 348 unselected individuals, 28 per cent became sick during a

routine test. Of 107 eliminees from flight training 90 per cent became swing sick. Other workers have found a similar correlation between a history of motion sickness and sickness induced on a swing or other device (8, 62, 115, 197). Individuals becoming airsick became swing sick as well. However, many persons may become swing sick without ever developing airsickness (176). Noble (284) has stated that swing tests tend to overrate the number of susceptible persons. If a single swing test were taken as the criterion for selection, Hemingway (174) has shown that 11 per cent of men not susceptible to airsickness would be eliminated. Conversely, the test would not select 15 per cent of the individuals who would become airsick. Further, approximately four persons in five will become adapted to motion. This group would not be detected by a single swing test. These difficulties point up the objection to any of the single screening techniques advanced; namely, that those who will overcome their motion sickness through experience are not differentiated from those who are doomed to remain susceptible. Hemingway (174) suggested a modified swing test in which the ability of swing sick individuals to adapt to motion would be compared with their ability to overcome sickness. Joekes (197) demonstrated that less than three per cent of persons originally swing sick failed to adapt on subsequent trials. Brown *et al.* (62) demonstrated that adaptation to swinging can be developed when persons are repeatedly exposed at intervals of one to seven days. Susceptibility returned after a two-weeks' rest. Incidentally, there is no evidence that such adaptation on a swing confers any protection against airsickness (152).

The hazards of misclassification inherent in the use of any stimulus or motion different from that encountered during normal travel has emphasized actual operational conditions as the best selection procedure.

Ship or plane. Hemingway (176) studied 198 airsick students throughout their first ten flights. A rapid fall in airsickness was noted during the first five flights. Only one of every four persons sick on his first flight became sick on the fifth. During the fifth to tenth flight, the incidence of airsickness continued to fall, although much more slowly. Those sick after this time may represent the chronic sufferers. No simpler method for their detection has yet been demonstrated. An interesting objective test for this purpose was proposed by Goehring and Schwab (152). Injections of neostigmine intramuscularly induced nausea and vomiting among a high percentage of chronic seasickness sufferers, whereas it had no effect in 45 of 50 persons with little history of motion sickness. Other investigators, however, could make no distinction between resistant and sensitive personnel by this technique (42). Other attempts to implicate acetylcholine or cholinesterase as factors in sensitivity to motion have been inconclusive (23, 37, 234, 255, 276). DeWit (102) has attempted to classify susceptible persons on the basis of vasolability as indicated by oscillations of blood pressure measured in the central retinal artery after swinging. The group reported was small.

ETIOLOGY OF MOTION SICKNESS

Characteristics of motion. The most obvious approach in determining the underlying factors of motion sickness is to analyze accurately the characteristic mo-

tions producing sickness and to evaluate their relative importance. Such attempts have been made for many years. It is a matter of common experience that certain types of motion are rarely nauseating despite large vertical or rotary accelerations: horseback riding, running, motorcycling, etc. Further, violent seas are not necessarily more distressing than less turbulent conditions. It is only natural that ship movements would be the first to be examined. Quix (314) cites data published in 1910 (202) describing such movements as a resultant of the wind and wave interaction. Unfortunately, as clearly pointed out by Morales (272) and by Handford and coworkers (167), correlation of ship movements with their disturbing sequelae is an extremely difficult task. Not only is the investigator faced with the intricate complex of the various motion components (pitch, roll, heave) continuously varying in intensities, but he must further contend with the constant migration and changing activities of the subject himself. These obstacles are emphasized by Handford *et al.* (167) who reported such an attempt in a naval transport utilizing 638 subjects. No significant correlatives could be obtained. These authors recommended that either smaller vessels be employed where a small group of subjects could be under complete control, or the ship's movements be simulated and their effects studied under laboratory conditions.

Progress along this latter approach has already been made. Using the swing and the more complex "wave machine" the effect of varying amplitude, frequency, duration, etc. on the incidence of motion sickness has been determined. Cipriani (90) determined the accelerative forces acting upon the subject during the swinging act. Radial acceleration was greatest at the low point of the arc. The effective difference between this point and the end of the arc constituted the principal stimulus upon the vestibular system. Fraser and Manning (134), using human subjects, and Noble (283) using dogs, varied the radius and frequency of the swinging. They found that an increase in accelerative force tends towards increased swing sickness, but that no additional effect was apparent beyond a certain point. Similarly, for any given accelerative force (arc of swing) there was an optimum frequency. The greater response to composite movements has already been indicated by Spiegel on the Barany chair (347), by Kerr and Frank on the centrifuge (206), by McIntyre on the swing (239), and by Johnson and coworkers (201) on the swing and aircraft.

Wendt and coworkers undertook a comprehensive analysis of the characteristics of nauseating motion to establish their hypothesis that the time characteristic of a motion, rather than its intensity, is the relevant feature. The reader is referred to this impressive series of reports for details of their experimental design and findings (3, 4, 5, 6, 9).

In this review, only a brief summary is appropriate. Using human subjects, under closely controlled conditions, the Wesleyan investigators varied, or controlled, these aspects of the waves: 1) the rate of work during exposure period (wave energy x wave frequency), 2) the energy per wave, 3) the time per wave (cycling rate) and 4) the acceleration-level and wave-form. They found that the rate of work, considered independently of the character of the wave, was not a significant variable. The incidence of sickness could be altered by varying the

character of the wave, even though the rate of work was kept constant. Each of the other variables contributed to the ability of the wave to induce sickness and each depended for its ultimate effect upon its interrelation with the other factors. Tremendous differences in nauseating properties were detected among waves having the same energy content. Thus, waves having cycles of 16 per minute at 0.25 g. acceleration level were roughly 20 times as nauseating per unit of energy as those with 32 cycles per minute and 0.65 g. level.

VESTIBULAR FACTORS AND MOTION SICKNESS

The relationship between vestibular stimulation and motion sickness has been established and documented by an overwhelming bibliography extending back almost a full century. Sjöberg (337) credits the pioneer work on the vestibular apparatus by Purkinje (312), Flourens (310), Ménière (266), Goltz (155), Breuer (57, 58), Mach (236) and Brown (61) as establishing a firm foundation for the recognition of its role during motion. Apparently, Irwin (193) and Palasne de Champeaux (290) independently and simultaneously in 1881 recognized the role of labyrinthine stimulation in seasickness and its relationship to Ménière's disease. The next year James (195) reported the failure of some deaf mutes to show distress after exposure to rotation or rough seas. This observation was rapidly confirmed and extended (211, 268, 269, 306), so that by the start of the twentieth century the importance of the labyrinth in seasickness and rotary vertigo was clearly recognized by Corning (96, 97) in 1901. The crucial experiment demonstrating the indispensability of the labyrinth for the production of motion sickness was apparently reported in 1903 by Kreidl at a scientific meeting in Kassel (212). He found that animals with their 8th nerve cut or with bilateral labyrinthectomy could no longer be made sick by artificial ship movements. This vital observation was confirmed by Sjöberg in 1929 (336), by McNally, Stuart and Morton in 1942 (248), by Babkin and Bornstein in 1946 (21), and by Johnson in 1945 (199). The early literature on the labyrinthine physiology is both exhaustive and exhausting. Omission of pertinent experimental conditions, comparison of data obtained under different circumstances, and the failure to distinguish between velocity and acceleration, have led to a tangle almost beyond unsnarling. As Sjöberg (337) complained, the difficulties of bringing order into this vast and chaotic literature are almost insurmountable.

Once receptors in the labyrinth had been implicated beyond doubt, it next became necessary to evaluate the relative importance of each sense organ within this structure. As is well known, these receptors consist of the cristae of the semicircular canals which respond primarily to angular acceleration and sensory epithelium or maculae of the otolith organs sensitive to linear acceleration. Ironically, the very similarities between the symptoms after rotation and those of motion sickness, which led to the recognition of labyrinthine involvement, were responsible for delaying realization of the role of the otolith organs. Early workers believed that simulation of the semicircular canals and their receptors adequately explained the symptoms of motion sickness (26, 65, 69, 123, 124). Gradually, however, it was realized that certain observations of motion sickness

could not be reconciled with such a concept. First, there is incontrovertible evidence that motion sickness may be produced on elevators and other devices giving *only* linear acceleration. Although early workers (64, 208, 252) believed these movements also stimulated the semicircular canals, it is now generally agreed that the canal receptors can be affected only by angular acceleration. Thus, stimulation of the cristae could not be the sole cause of *all* motion sickness although it is still conceivable that they play a vital role in those forms of motion where angular acceleration is common, such as seasickness. Even this point has been seriously questioned, however, on the grounds: 1) that the angular acceleration aboard ships is generally below the threshold of semicircular canal stimulation and, 2) that nystagmus, which results from such stimulation is absent. A summary of the analyses of linear and angular accelerations produced aboard ship during normal and violent seas has been carefully compiled by Sjöberg (337) together with his own calculations. He concludes that this angular acceleration is generally less than 2° per sec. per sec. Quix and Werndley (315) quoted by DeWit (102) estimated the maximal accelerations in heavy rolling to be from 3 to 5° per sec. per sec. and during pitching 2° per sec. per sec. Since the threshold for semicircular canal stimulation has been reported from 2 to 5° per sec. per sec. (102, 235, 314, 337) it is apparent that adequate stimulation would occur only under very turbulent conditions or in a very sensitive subject.

The failure to observe nystagmus during seasickness is added evidence that the stimulation of the semicircular canals during rolling and pitching is inadequate to account for the development of seasickness. Oriel (288a) could detect no evidence of nystagmus in some 5,000 seasick persons. Similarly, to our knowledge, there has been no report of nystagmus during airsickness, carsickness, trainsickness, etc. It may well be as Sjöberg (337) has cautioned, that small eye movements may occur during a high sea which are not visible to the unaided observer. This contention arises from the detection by Fleisch (129) of small reflex eye movements in the rabbit imperceptible to the naked eye. Whether nystagmus is absent or imperceptible, however, would not seem to weaken seriously the argument that cristae stimulation plays a secondary role in the etiology of motion sickness. Other workers maintain that nystagmus should not be taken as an inevitable indication of cristae stimulation (347). Since rolling movements of the ships have a relatively small amplitude, only small oscillations of the cupula would result. These may be inadequate to evoke ocular reflexes, but sufficient to produce other symptomatology.

Evidence in favor of otolith involvement has steadily accumulated. In fact, the sites have been more specifically identified as the utricular maculae since the saccule has been absolved from participation in labyrinthine static or kinetic reflexes (247, 358). Again, it should be pointed out that simple up and down movements, which could only act upon the otoliths, effectively produce motion sickness. Further, in contrast to angular acceleration, the magnitude of linear accelerations developed during pitching and heaving, and even in rolling, is many times the receptor organ threshold. The threshold value for linear accelerations is approximately 0.01 g (102, 358) whereas the actual forces developed on

ship, airplane, swing, etc. may be 100 or more times this value. Few travelers will dispute the statement that pitch or heave in a ship is the most distressing motion. In fact, persons still become sick in ships with twin keels or suspended cabins designed to prevent roll (358) but not pitch and heave.

Perhaps the most convincing demonstration of the importance of utricular stimulation in producing motion sickness, is the effect of head positioning. The relief obtained by a motion sick individual upon reclining constitutes probably the oldest and best treatment discovered for this ailment. Although various explanations have been offered to explain this relief, it now seems probable that the underlying mechanism is the shifting of the utricular maculae to less vulnerable positions. This explanation was first suggested by Quix (314). During World War II, Canadian workers systematically studied the effect of body and head position on the incidence of swing sickness and arrived at similar conclusions. Howlett, Wardill and Brett (191) produced no sickness with supine and only 18 per cent with prone subjects. When the men were supine, but with their heads dangling, 68 per cent became sick. In sitting position 61 per cent were sick. However, when they remained in the same sitting position but tilted their head backward, none became sick. This demonstrates that head position and not body position is the important factor. Essentially, similar results were obtained by other investigators (241, 259, 260). The significance and interpretation of much of this work has recently been questioned by Johnson *et al.* (201) who found a surprisingly high correlation between motion sickness and head movements. Persons showing the greatest head movements while on a swing or plane were the most susceptible. Head immobilization under these circumstances produced a striking resistance in both man and animals. The authors point out that Manning (256) was unable to make any person sick on a spring accelerator when the subject's head was fixed, whereas Wendt (371) and McEachern *et al.* (235) reported considerable motion sickness when they performed the same experiment without head fixation. Further, the finding of Alexander *et al.* (9) that certain frequencies on his wave machine are the most nauseating is in harmony with the concept that this frequency may represent a harmonic with that of the subject's head. The results of Howlett *et al.* (191) also are questioned for the head positions resulting in least sickness (supine, prone) also are those in which the head would be expected to be most nearly immobile.

These results are in conformity with the findings of early workers that head movement on a rotating chair increased the nauseating capabilities of this treatment (123, 162). Conversely, Fischer and Wodiak (125) were able to prevent or decrease nausea in susceptible subjects by head fixation. The decision whether the relationship between head position and motion susceptibility depends upon otolith orientation or the precessional effect of head movements must await further experimentation. It would be most informative to repeat the experiments of Howelett, Wardill and Brett (191) with the head immobilized in each of the various positions. From the data now available, it would seem that linear accelerations or stimulation of the utricular maculae are generally the principal stimuli. The superimposition, however, of even small angular accelerations

greatly magnifies the nauseating potentialities (238, 283). The relative importance of angular versus linear acceleration is a fascinating question but essentially an academic one since motion leading to sickness generally contains both components.

CENTRAL NERVOUS PATHWAY

The nervous pathway through which labyrinthine stimulation evokes nausea and vomiting has never been completely traced. Careful plotting of this route is not only of great physiological interest but, also, of obvious practical importance in the selection or development of effective medication.

In the onset of motion sickness, it is apparent that the central and autonomic nervous systems are repetitively bombarded with impulses along afferent pathways not only from the vestibular organ, but, also, from other sources such as the optic, proprioceptive and visceral systems. The importance of these latter stimuli are not minimized, but since motion sickness can be prevented by interruption of vestibular impulses (bilateral labyrinthectomy, sectioning of 8th nerve) this pathway deserves primary emphasis. The involvement of the autonomic system has already been mentioned and is manifest by the pallor, sweating, dizziness, etc. which are so prominently evident in motion sickness. Bo and Livan (45) claim to have traced sympathetic fibers originating in the utricular maculae and running to the sympathetic vascular plexus, *i.e.*, to the stellate ganglion.

In the central nervous system, the stations at present recognized include the vestibular receptors in the cerebellum, a chemoceptive zone located in the superficial region of the medulla, and the emetic center. Ablation of each of these areas confers resistance to motion sickness on otherwise susceptible dogs. Experimental support for this statement is summarized below.

Cerebellum. The role of the cerebellum in motion sickness was first examined by Kreidl (210). This prolific early investigator stated that animals could still be made "seasick" by his experimental device after extirpation of the cerebrum and of the cerebellum. Unfortunately, the original report is unavailable so we can only speculate on the completeness of the cerebellar removal. Since subsequent work (27, 28, 366) has established beyond reasonable doubt that the cerebellum is indeed essential for the development of motion sickness it seems probable that significant portions of the key cerebellar structures must have remained following surgery. Bard and his collaborators (28) removed the entire cerebellum of a dog susceptible to swing sickness and retested it upon the swing during the next seventeen months. In fifteen trials with exposures of 1 or 2 hours, the dog failed to vomit. Additional dogs became resistant after removal of the nodulus, uvula, and pyramis, whereas ablation of the entire vermis or of the pyramis together with minor damage to the uvula did not alter the animal's sensitivity to motion. These workers conclude that the nodulus and uvula were involved in the genesis of motion sickness and, possibly, the lingula and flocculi. That the medulla was not damaged in these experiments is manifest by the persistent sensitivity of these animals to apomorphine.

In an attempt to pinpoint more closely the vital cerebellar zone, Wang and Chinn (366) repeated and extended these crucial experiments of Bard *et al.* (28). They confirmed the nonessential nature of the pyramis and vermis, but were unable to localize with certainty the vital structure. When the nodulus or the uvula alone was destroyed, the animals occasionally showed resistance or an increased threshold to swinging. Removal of both structures, however, provided complete immunity. Thus, nine dogs invariably vomiting within 25 minutes had nodulus plus all or part of the uvula destroyed. In 39 one-hour swingings after surgery, no vomiting resulted in 38 cases and delayed (46 minutes) vomiting in the remaining instance.

Emetic trigger zone. The concept of a "vomiting center" sensitive to apomorphine and certain other chemical agents has long been accepted by neurophysiologists and clinicians alike. The meticulous studies of Wang and Borison (52, 364) however, have demonstrated convincingly that the emetic mechanism consists of two anatomically close but functionally separable units in the medulla oblongata: a) the emetic center located in the region of the fasciculus solitarius and underlying reticular formation; and b) a chemosensitive trigger zone located in the superficial region of the medulla, dorsolateral to the vagal nuclei. It is the latter structure which is the site of action of many so-called central emetic agents (apomorphine (362), morphine (367), cardiac glycosides (53), etc.) Animals with bilateral destruction of this zone are resistant to large doses of these agents, although their emetic center is intact, as can easily be demonstrated by oral cupric sulfate or other gastrointestinal stimulation. Destruction of the emetic center by radon implantation confers complete resistance against all emetic stimuli (363).

This emetic trigger zone has been found important in the mediation of motion sickness. Ten of 12 dogs in whom this area had been ablated failed to vomit after long exposure to swinging (365). Two of the dogs remained sensitive to motion. The cause of such occasional failures is unknown. A possible explanation is that the medullary mechanism for motion sickness involves a larger area of the area postrema than is necessary for apomorphine emesis. Resistance to apomorphine would not then represent a complete trigger zone ablation. The correct explanation must await further studies. Whatever it is, there is no question that the medullary trigger zone must be a normal station in the genesis of motion sickness.

The importance of a chemosensitive zone in motion sickness has interesting and far-reaching implications. Does the trigger zone respond to a chemical elaborated in significant amounts during motion? Do other emetic agents or treatments act in similar manner? In this connection, attention is again called to the scattered experiments attempting to implicate acetylcholine in motion sickness (38, 42, 152, 255). The similarity of many of the symptoms during motion sickness with those induced by acetylcholine, the effectiveness of many anticholinergic agents against motion sickness and the strong anticholinesterase activity of certain emetics (apomorphine, morphine, etc.) all suggest possible

involvement of this ubiquitous chemical. A re-evaluation of the role of acetylcholine in vomiting may be profitable.

Cerebrum. At least in dogs, the cerebral cortex has been shown to have little or no role in the etiology of motion sickness. Bard and his collaborators (28) prepared a decerebrate dog, as well as dogs with a variety of cortical ablations. In every instance, the operated animals showed normal sensitivity to swinging. The cortical destruction included bilateral temporal lobectomy, removal of both frontal poles, and removal of all neocortex except both frontal poles. Babkin and Schachter (22) prepared a dog with the cortex of both hemispheres removed. The dog, with one exception, was resistant to prolonged swinging. Since histological examination of this brain was not reported, possible damage to essential cerebellar or medullary structures cannot be excluded. It is difficult to conceive of decortication conferring immunity to swinging when total decerebration does not.

NON-LABYRINTHINE STIMULI IN MOTION SICKNESS

In summary, the main pathway of impulses originating in the labyrinth has been plotted, at least in general terms, as proceeding by way of the 8th nerve to the vestibular nucleus, then traversing the vestibular portion of the cerebellum (probably nodulus and uvula), stimulating the chemosensitive trigger zone in the medulla and, finally, reaching the emetic center itself. This route is reasonably direct and well charted. There are, however, other byways in which the development of motion sickness is evoked or abetted by non-labyrinthine factors. These factors can roughly be grouped as constitutional, visual, proprioceptive, or psychological. The concept that the susceptible individual differs physiologically or constitutionally from the resistant person has already been discussed and will not be considered further at this point other than to reiterate the conclusion that no significant differences have been proved.

Visual stimuli. That purely visual stimuli may evoke nausea and other visceral changes is a matter of common experience. The illusion of motion when a vehicle passes alongside one's own is known to all and under some circumstances may produce symptoms typical of motion sickness. Similarly, disorientation is believed to be a major cause in airsickness and seasickness when the individuals are unable to maintain visual contact with the ground or horizon. This might account, for, or be a contributing factor to, the increased susceptibility to motion of pilots riding as passengers (20, 157), of navigators and radio operators (174), or pilot trainees during acrobatics (128), and of troops crouching on landing craft (355). Allard (11), on the contrary, found four dogs to vomit within 11 to 22 minutes in the swing before and in 40 to 120 minutes after blindfolding. On the swing, subjects blindfolded, with eyes closed, or in an enclosed cabin, became more susceptible to the motion (261). These findings leave in doubt the old injunction repeated by Fischer (124) for the relief of nausea at sea, namely, close the eyes. In this connection, it would be interesting to study the relative incidence of seasickness among blind persons. It is known that such persons become seasick but no data are available on the frequency. Armstrong (20) contends that vertigo will result when conflicting sensory impressions from two or

more organs of equilibration are present in consciousness. He believes vision may inhibit vestibular vertigo if the eye can fix an object and allow a correct orientation in space. This principle has been utilized by dancers, skaters, gymnasts, etc. who jerk their heads around rapidly during a spin and, except for this short period of turning, keep their heads fixed upon a point of reference. Even experienced personnel may become nauseated if this is not done. The role of other ocular disturbances in the development of motion sickness has not been established. Flack (126) believed seasickness to induce ocular muscle imbalance. He stated further that persons in whom such imbalance is not induced or aggravated do not suffer from seasickness. An increase of ocular imbalance after swinging, especially among susceptible individuals, also was reported by Best *et al.* (37). This was not confirmed by Howlett and Brett (190) who, in fact claimed the reverse. Livingston (226) could find no correlation between purely visual stimuli and susceptibility to airsickness, nor could Mayou (265) detect any significant visual changes.

Visceral displacement. The sensation of deep discomfort, so familiar to all who have experienced turbulence aboard ship or plane, has stimulated much discussion on the role of visceral displacement. Although various abdominal supports have been advocated, as will be discussed briefly later, no convincing evidence has ever been presented that visceral movements or their sequelae are of importance in the development of motion sickness. As Tyler and Bard (358) point out, the jolting motions of horseback riding or of various strenuous sports or activities do not produce nausea although they are much more severe than conditions encountered even under turbulent exposures.

Other miscellaneous factors which have been implicated by early workers, but which have been shown to have little or no effect, include hypoxia (133), elevated temperatures (175, 250, 258), and alterations in blood distribution (358).

Psychic factors. By far the most controversial question in the entire field is the importance of the psychic factor in the genesis of motion sickness. Few subjects precipitate more heated discussions or have more ardent partisans. The controversy lies not so much in the recognition of psychic factors as contributory causes, but rather in their relative importance. It may be admitted at the outset that the development of sickness in some cases seems explicable only by assuming a strong psychological basis. This would include those instances where persons become sick on motionless vehicles or even upon thinking of sea or air travel. On the other hand, there are also numerous cases of sickness where no element of apprehension, fear, suggestibility or emotional disturbance can be discovered. Further, as has been demonstrated repeatedly, animals easily can be made sick with little danger of conditioning. These clear-cut extremes, unfortunately, comprise a relatively small proportion of the total who become sick in any given occasion and leave adequate space for areas of violent disagreement. In general, earlier authors have considered psychic effects as major determinants, whereas the present trend is to assign to them considerably less importance.

Tyler and Bard (358) classified the arguments in favor of a psychogenic basis

as follows: 1) that susceptible individuals show emotional instability or neurotic traits, 2) that apprehension and fear precipitate motion sickness; 3) that disagreeable sights and odors are responsible; 4) that individuals show conditioning and may become sick without motion; 5) that mental or physical activity decreases susceptibility; 6) that emergencies may restore seasick individuals to health; and 7) that placebos are effective in preventing motion sickness. Each of these points has been taken up in detail and discussed critically by Tyler and Bard (358). Since relatively little pertinent material has appeared since this review was published in 1949, no purpose would be served by repeating the discussion at this time. We shall content ourselves with summarizing the general conclusions and referring the reader to their article for a more comprehensive treatment.

There is undoubtedly a strong tendency among the laity and physicians alike to suspect emotional instability or neurotic traits in motion-susceptible individuals. Further, there is no question that many susceptible persons have, in fact, psychiatric disturbances. Since chronically seasick or airsick persons in the military service are generally referred for psychiatric interview, this group may well seem to be disproportionately large. On the other hand, it is also an undisputed fact that many persons with neurotic trends or disturbed family relations are not susceptible to motion. The crucial point is whether a significantly higher proportion of motion-susceptible persons display such tendencies than do motion-resistant individuals. A definite answer to this question must await psychological studies specifically oriented towards this end. From the data available, however, no striking distinctions are apparent between the two groups.

Fear and apprehension in sea- and airsickness, especially the latter, still are viewed by many persons as playing a prepotent role. This is apparent in the frequent scorn and condescension shown by the immune, as well as in the embarrassment and feelings of guilt of the sufferer. The prevalence of this view was evidenced in a questionnaire by Thorner (350) in which 187 Air Force stations reported some airsickness. In the opinion of the flight surgeons at those bases, apprehension was perhaps the most important factor. This contention was supported by Levy (220) who attributed all cases of airsickness to apprehension with tenseness in the air. Similarly, Poppen (307) states flatly that airsickness is "practically always an unsatisfactory rationalization of fear." This strong emphasis appears exaggerated. It is difficult to reconcile such statements with the development of motion sickness in animals, with the relative infrequency of nausea and vomiting in the absence of motion during periods of equal or greater fear and terror, with the effectiveness of the swing in producing sickness despite almost complete absence of fear, and with occasional reports that sudden danger actually seemed to cure motion sickness. Additional evidence against the role of fear is the report that epinephrine injection produced no increase in frequency of nausea or vomiting in response to vestibular stimulation (105). A more moderate view appears appropriate, namely, that fear and apprehension may increase somewhat the incidence of motion sickness but that they are relatively minor factors so far as the over-all incidence is concerned. It is the im-

pression among medical personnel that airsickness is more prevalent in paratroop organizations than in other airborne, non-jumping, units. It would be interesting to test this impression by flying paratroopers on a routine mission in which half would jump in the usual manner but the other half in the same plane would participate only as passengers.

The aggravating effect of unpleasant sights and odors to persons already affected by motion is unquestioned, as is the fact that some highly susceptible persons may become conditioned to motion. No data are available to determine the proportion of total susceptible individuals falling into these categories. It is believed to be small.

The contention that mental and physical activities prevent or ameliorate motion sickness by their psychological effects is questionable. In the first place, physical activities, such as walking the deck, produce changes in positional and visual stimuli which may give benefit in some cases; secondly, there is no evidence that mental activity *per se* has any effect in relieving motion sickness. In fact, as already mentioned, navigators are among the most prone to develop airsickness despite their constant preoccupation with maps, calculations and instruments.

The final evidence offered in support of the importance of psychological factors has been the alleged protection afforded by inert substances given as placebos. On this score, the literature is conflicting. No significant protection by placebo administration could be demonstrated against swing sickness (118, 294, 295, 297) or airsickness (222, 340). Noble, Sellers, and Best (287) maintained that placebos afforded definite protection of the order of 20 to 30 per cent in sea trials when compared with untreated individuals. Tyler and Bard (358) sharply question these results since no information is given on the selection, distribution, supervision or duties of each group. Tyler, in a somewhat similar study, using unselected troops in small landing craft, could detect no difference between those receiving placebos and those without any medication whatever (355).

In summary, there can be little doubt that the labyrinthine stimulation is by far the most important factor in the genesis of any form of motion sickness. Other factors, including psychological, must be placed in decidedly subordinate categories. These latter factors may aggravate an already existing illness or, in isolated instances, may even constitute the primary causes of motion sickness. Attempts to overcome or minimize their effects, therefore, are desirable, and, in many instances may be profitable. The major effort, however, in any concerted attack upon motion sickness must be directed toward blocking or dulling labyrinthine stimulation or the transmission of these impulses to higher centers.

PROPHYLACTIC AND THERAPEUTIC MEASURES

There is no ailment, with the possible exception of the common cold, or hiccoughs, for which the general populace and the medical profession alike have prescribed with greater assurance and originality. The remedies have been selected on the basis of hearsay, personal experience, accident, or often apparently occult revelation. The treatments are generally uncontrolled, frequently amusing,

and occasionally ingenious. The recommendations range from cuffs about the neck for control of cerebral blood flow to corsets for abdominal support, from gastronomic heroics to Spartan self restraint, from ingestion of herbs to injections of vitamins.

For the most part, the treatments have been empiric or based upon theories which have since been largely abandoned. Apart from certain medications to be discussed shortly, the one persistent recommendation that is pertinent today is for the sufferer to assume a supine or prone position. This treatment has not only survived the years, but has received a solid theoretical and experimental base. Other treatments have been less fortunate.

Binders. The binding of certain body areas to prevent vascular engorgement or visceral displacement was first suggested by Keraudren in 1812 (205). Genée (143) recommended a binder around the neck to compress the jugular veins and keep the brain hyperemic. In more recent times, Sjöberg (337) placed dogs in plaster casts and reported them to be more resistant to motion, while a number of authors (66, 101, 143, 203, 219, 307) advocated the use of abdominal binders to decrease motion sickness in human beings. Still more recently, Allard (11) tightly bound the abdomens of four dogs and reported a delay in the onset of vomiting when they were swung. Other workers (92) found the binders to be ineffective.

Dietary measures. The most popular area for self expression has been in the prescription or restriction of dietary items. They were generally communicated to early clinical journals as letters to the editor. Included in this category is the one culled by Tyler and Bard (358) specifying soup made of horseradish and rice seasoned with red herring and sardines, as well as another, cited in a recent editorial (15), composed of salt and vinegar which was prepared in error by one person and drunk accidentally by a second. It was reported to have given instant relief. Abstention or indulgence in tobacco or in alcoholic beverages were impartially prescribed, depending upon the adviser's predilection. There is no good evidence to indicate that susceptibility to sea- or airsickness can be modified by fasting or eating (7). Overindulgence or any practice leading to gastrointestinal distress under ordinary conditions will, of course, increase the person's vulnerability on the plane or ship.

Physical therapy and psychotherapy. The physical condition of an individual is not a determining factor in his susceptibility and attempts to increase resistance by physical training exercises have proved fruitless (251). Gibson, Manning, and Kirkpatrick (146) were able to reduce susceptibility after an eight-week active physical training period, but they included vestibular training as well. Psychotherapy has been little more successful despite claims to the contrary (34, 60, 307). The favorable reports are inadequately controlled; improvement has by no means been clearly established, and factors of adaptation, head position, vision, and even of drug therapy have been largely ignored. An evaluation of the effectiveness of psychological supports with the above factors under adequate control, remains to be done.

Adaptation. The ability to adapt to motion has been pointed out repeateldy.

Some investigators have attempted to take advantage of this process to increase resistance in susceptible individuals. The relative resistance of professional dancers, acrobats, and divers has already been noted. This is probably due, in part at least, to adaptive processes, as well as to visual orientation, discussed earlier. The decreased susceptibility after repeated exposures on the swing (62, 257) and in the air (174) have been graphically demonstrated. Adaptation to swing sickness, however, does not confer protection against airsickness (145).

Miscellaneous. Other measures recommended for the prevention and cure of motion sickness include breathing exercises (237), warm salt water baths (34), oxygen inhalation (51, 106, 369), ultraviolet irradiation (368), and packing the external ear canals with cotton (218).

DRUGS FOR PROTECTION AGAINST MOTION SICKNESS

It has been stated that "everything that can be swallowed has been claimed to cure motion sickness" (15). Prior to World War II, the great bulk of such claims was based, in large part, on the personal experiences of ship surgeons and other travelers. These reports are of little value beyond historical interest. They were largely subjective impressions based upon the response of a few subjects. Controlled experiments under standardized conditions were practically unknown. The military requirements for effective medications stimulated investigators to utilize larger numbers of subjects and a more systematic approach, so as to screen the ever-increasing list of compounds deemed worthy of test.

Methods of testing. Two general types of subjects have been employed for routine drug testing: 1) known susceptible subjects, and 2) large groups of unselected individuals. The latter procedure has been found the more satisfactory and most studies have utilized this technique. It has the advantage of being more amenable to statistical treatment, of easing the procurement of subjects, and of avoiding the complications of adaptation to motion.

Testing of human subjects under field conditions, *i.e.*, aboard ship or plane, must ultimately be employed for the evaluation of any medicament. Such testing requires large numbers of subjects, because of inherent variability in the weather and in ship and plane movements. For this reason, the swing, vertical accelerometers, and other devices already described, have been widely used for preliminary screening. With these devices, rigidly standardized conditions can be easily and readily invoked, necessitating fewer subjects. It has generally been felt that drugs effective against one type of motion sickness will be active in preventing other types. This may well be true in many cases. Recent studies, however, have pointed out the hazard of this assumption (82). Thus, three compounds, hyoscine, diphenhydramine, and N(α-methyl-β-dimethylaminoethyl) phenothiazine (lergigan®), which have afforded marked protection against both sea- and airsickness were tested against swing sickness. In confirmation of frequent reports (342), hyoscine afforded significant protection. Neither of the others displayed any protection whatsoever. This finding is disconcerting when it is realized that many compounds have been eliminated from further consideration

on the basis of negative swing tests. Further, it weakens considerably the usefulness of artificial devices in the testing of anti-motion sickness drugs.

Still more hazardous is the use of animals for drug evaluation. Noble (282, 285) screened an extensive series of potential preventives by using susceptible dogs on the swing. Atropine, hyoscine, and hyoscyamine were completely ineffective in the dog despite their usefulness in man. Similarly, of the compounds mentioned above (hyoscine, lergigan®, diphenhydramine) none was able to protect susceptible dogs on the swing (82). Conversely, chlorpromazine has been reported to give excellent protection to dogs against swing sickness (94) but to be ineffective in man against seasickness (166). This indicates that one may err in both directions if protection of dogs against swing sickness is used as a criterion of activity in man against sea- or airsickness. Many excellent prophylactics might be overlooked and ineffective drugs would be recommended.

Attempts to correlate the ability of a drug to combat motion sickness with its anti-nauseant properties against other emetic agents have been unrewarding. Many effective compounds, to be discussed later, have been reported active against the nausea and vomiting encountered in pregnancy and Ménière's disease, or caused by radiation or by the administration of substances such as the general anesthetic agents, morphine, apomorphine, nitrogen mustard and others. However, many other preparations show an unexpected selectivity in relieving emesis induced by one of these conditions but not by motion sickness or *vice versa*. One must be careful, therefore, to attribute protective or therapeutic properties only to those compounds which have been tested on relatively large numbers of human subjects under conditions of actual flight or sailing. Until these conditions are fulfilled, the value of a drug, regardless of its performance under other circumstances, must be considered as suggestive, but not convincing.

A useful formula for comparing the effectiveness of various treatments was introduced by Holling, McArdle and Trotter (187). This expresses the percentage of susceptible persons under the experimental conditions who were protected by the treatment employed. The per cent becoming sick in the experimental group is subtracted from the per cent sick in the control group and the difference divided by this latter value (per cent of controls sick). The quotient is then multiplied by 100 to convert to a percentage value. This value affords a basis of comparison for drugs tested under varying conditions. With moderate turbulence, the calculations compensate for minor differences in the sickness rate in different experiments. Use of this formula for tests during very mild or very rough weather, however, may be very misleading. To take extreme examples, it is conceivable that the weather might be so rough that practically everyone, medicated or not, became sick. The apparent degree of protection under these circumstances would be very low. On the other hand, under mild conditions, it is equally conceivable that a few susceptible unmedicated subjects might become sick while no person receiving the drug would be affected. The rate of protection in this case would be 100 per cent. Comparison under such widely divergent conditions would strongly bias the interpretation. In general, an effective medication will protect at least 50 per cent of otherwise susceptible persons when 20 to 50 per cent of the control group becomes sick.

A systematic consideration of motion sickness medicaments is rendered difficult by the numerous mixtures that have been used empirically, frequently without first determining the effectiveness of the individual components. Witts in 1941 (367) compiled a list of proprietary seasickness remedies available at that time. Over 40 preparations were included, 70 per cent of which were mixtures containing from two to seven components. As Smith (342) has commented, it is questionable whether this tendency to employ mixtures has aided materially in the search for effective remedies. Most of the preparations tested prior to and during World War II were parasympatholytic drugs or central nervous depressants. Vitamins and central nervous stimulants were occasionally employed. During the past few years, the antihistamine series and related drugs have been widely explored.

Parasympatholytic drugs. Since many of the symptoms of motion sickness are similar to those evoked by acetylcholine or by stimulation of the parasympathetic system, it is not surprising that parasympatholytic drugs were among the first tried. They have remained popular through the years. The belladonna alkaloids were suggested in 1869 (13) and atropine was first employed in 1880 (30). Although atropine, hyoscine, hyoscyamine and related preparations were widely used before World War I as constituents of various proprietary preparations, no controlled evaluations were attempted until 1942. Since then, there has been abundant proof that the belladonna alkaloids are effective prophylactics in man against air-, sea-, and swing sickness. Smith (342) in 1946, reviewing the work done during the war years, listed over 80 separate experiments in which one or more of the belladonna alkaloids were employed on mechanical devices, in the air, or on the sea. The most important of these alkaloids are atropine, hyoscine, and hyoscyamine. The terminology of these compounds is rather confusing. Hyoscyamine exists as the *d* and the *l* isomers. The levo form is stated to be more powerful in the peripheral autonomic effects and is the commercial preparation. Both forms have similar central nervous system effects (156). Atropine is a mixture of equal parts of these isomers. Hyoscine is closely related to hyoscyamine and also may exist as the *d* or *l* isomer. The levo form has been used almost exclusively and is generally implied when the specific form is not stated. Its official designation by the United States Pharmacopeia is scopolamine and by the British Pharmacopeia, hyoscine.

Atropine and *l*-hyoscyamine in 1.0 mg. doses have given good protection against sea- (187) and swing sickness (345). Only a single report is available on the use of *d*-hyoscyamine (187) for the prevention of motion sickness. In this instance 2.0 mg. was used on 34 subjects at sea. The protection was not significant and the authors concluded that *l*-hyoscyamine is largely responsible for the effectiveness of atropine. The small series of subjects employed makes such a conclusion hazardous.

By far the most work has been done with *l*-hyoscine (scopolamine). There is no convincing evidence that hyoscine is superior to atropine or hyoscyamine, but it is generally believed to produce fewer side effects (343). This fact, plus the wealth of clinical and experimental reports have led to the adoption of hyoscine as a standard with which new or potentially effective drugs can be compared.

The intensive testing of dozens of compounds and mixtures during the war failed to uncover any preparation superior to hyoscine in effectiveness or safety. Even with the introduction of an entirely new series of effective drugs during the past few years, hyoscine must still be considered as one of the most effective and most versatile compounds available.

As already reported, hyoscine, as well as its relatives in the belladonna family, is ineffective in preventing swing sickness in dogs (82, 285). In man, on the other hand, it has repeatedly demonstrated its value against swing sickness (284, 293, 332, 345), seasickness (148, 149, 182, 186, 187, 228, 267) and airsickness (49, 85, 222, 340, 341, 349). The dose of hyoscine hydrobromide generally used has been 0.65 mg. to 0.75 mg. although results from 0.4 to 1.2 mg. have been reported. Glaser and Hervey (148, 149) used 1.0 mg. and found hyoscine to be significantly superior to all other drugs tested in preventing seasickness. Chinn and Milch (79) have shown a similar high degree of protection against airsickness with this dose. In addition, hyoscine has been combined with other medicaments in numerous experimental or commercial preparations. In many instances, it is safe to say, all or much of the effectiveness could be attributed to the hyoscine component. Three preparations, in particular, should be cited, which, although largely discarded at present, appear frequently in the older literature: Vasano®, a proprietary mixture of hyoscine and hyoscyamine camphorates; the Royal Canadian Navy Research Unit Preparation (RCN Remedy) containing niacin plus hyoscine and hyoscyamine; and the Army Motion Sickness Preventive (MSP) which contained hyoscine, atropine and amytal. Later, the Canadian workers preposed a new preparation termed "Canadian Motion Sickness Remedy —National Research Council Formula" containing hyoscine, hyoscyamine, and the thiobarbiturate V-12 (ethyl-β-methylallylthiobarbituric acid). Each of these mixtures has afforded good protection against motion sickness (29, 116, 119, 187, 228, 284, 287, 293, 295, 339, 340, 355) but there is no evidence to indicate that any of them is superior to hyoscine alone. This statement also can be repeated for the numerous empirical mixtures in which hyoscine is combined with other atropine-like compounds or with parasympatholytic drugs, vitamins, central nervous stimulants, central nervous depressants, or local anesthetics. The testing of these mixtures is reviewed adequately elsewhere (342, 358). The ability of this heterogenous group of preparations, under a variety of conditions and experimenters, to afford consistent protection, is indirect but convincing evidence of the utility of hyoscine.

Hyoscine aminoxide, a partial oxidation product of hyoscine, has been reported to have one-third of hyoscine's activity in Parkinson's disease but only one-sixth of its toxicity (98). This favorable ratio prompted its trial against air- and seasickness. It was found effective in 2.0 mg doses against both air- (85, 87) and seasickness (76), but the side effects were at least as frequent and severe as might be expected for an equivalent dose of hyoscine alone. This will be discussed later, when side effects are considered in more detail.

Atropine and scopolamine are well known to have two main actions in the body: 1) upon the central nervous system, and 2) upon smooth muscle and secre-

tory glands innervated by postganglionic cholinergic nerves. Synthetic substitutes for the belladonna alkaloids generally have less effect upon the central nervous system. For this reason, they have been used extensively as antispasmodics of smooth muscle, especially of the gastrointestinal tract. These synthetic antispasmodics have been consistently ineffective against motion sickness. Pavatrine®, homatropine, benzoyloscine, benzoyltropine, syntropan® and atropine methyl nitrate (eumydrine®) have been tested on the swing or ship (342). Demerol®, related chemically to this series was also tested on the swing (345). The results, although promising in a few cases, were based on uncontrolled observations or on small numbers of subjects so that the findings must be considered inconclusive.

More recent synthetic antispasmodics have been subjected to a critical evaluation aboard ship and in amost every instance have proved without value in preventing seasickness. These include methantholine (banthine®) bromide (75) dicyclomine (bentyl®) hydrochloride (75), β-diisopropyl-aminoethylxanthene-9-carboxylate methabromide (probanthine®) (75), and hyoscine N bromobutylate (buscopan®) (75). Phenyl-n-propyl-N-methyl-4-piperidylidenemethane (Schering 1667) gave slight but significant protection (75). The findings with these compounds are strong evidence that the anti-spasmodic activity of parasympatholytic drugs bears little relationship to their anti-motion sickness effectiveness. Rather, their action upon the central nervous system seems the determining factor. This will be discussed later.

Largely as a result of the now discarded concept of an imbalance between the sympathetic and parasympathetic systems as the causative factor in motion sickness, numerous other drugs affecting the autonomic nervous systems have been advocated. No evidence can be found that the various parasympathomimetic agents, such as muscarine, pilocarpine, physostigmine, acetylcholine and metacholine, had any beneficial effects (376). From the symptomatology of motion sickness, it would be expected that these compounds would aggravate, rather than palliate, the condition.

Similarly, drugs minimizing or depressing the effect of the sympathetic system have been employed. We have been unable to locate any report on the use of epinephrine for the treatment of motion sickness although Witts (376) lists it as an ineffective remedy. It has been given to normal individuals to determine whether it facilitated vestibularly induced nausea and vomiting, as might be expected if fright were a factor in the genesis of motion sickness. In physiologically effective doses, it was completely without effect (105). Ephedrine had negligible protection against airsickness in gliders (292). Similarly, *d*-desoxyephedrine showed a relatively low degree of protection against seasickness (187). Amphetamine sulfate has been employed with indifferent success. Blackham listed it as one of the best treatments (along with bromides, cocaine, chloral hydrate and ephedrine) (44). Hill (184) found improvement in 39 per cent, but no control data were reported. No or poor protection with amphetamine against air- (189, 292) and swing sickness (62, 332, 338) were obtained by United States and Canadian workers alike. Numerous mixtures have been used which contain amphet-

amine (342), and more recently dextroamphetamine (86). Since these preparations contain other active ingredients, it is difficult to evaluate the possible effect of this analeptic. There is no evidence that the protection against motion sickness is greater than would have resulted in its absence.

Of the sympathetic blocking agents, ergotamine tartrate was used rather widely in early proprietary remedies. There is no evidence that it has afforded any significant protection. Recently, White (372), reported that the synthetic sympatholytic N-(2-chloroethyl) dibenzylamine hydrochloride (dibenamine®) increased the vomiting threshold to apomorphine in the dog. This prompted the trial of a similar agent against seasickness (77) N-phenoxisopropyl-N-benzyl-beta-chloroethylamine hydrochloride (dibenzyline®), which reportedly caused fewer side effects (246). This compound gave no protection; if anything, it increased the incidence of vomiting above that of the placebo group ($P = 0.08$).

The involvement of the central nervous system in the genesis of motion sickness and the use of drugs to modify central activity have intrigued investigators from the very beginning. Most of such investigations have dealt with central depressants. There are, however, some reports on the use of central nervous stimulants as well. Amphetamine, which has already been discussed in connection with sympathomimetic drugs is of course a central stimulant as well. Caffeine and strychnine were common constituents of seasickness remedies (Boot's seasickness remedy, Roberts seasickness granules, Cafinal compound, Mothersill's seasickness remedy, Thallason, etc.) (376). Their main purpose seems to have been the combatting of depressant effects of other constituents in the formula rather than any direct effect in preventing seasickness.

Central nervous depressants. Central nervous depressants were among the first medicaments attempted to prevent motion sickness and have remained popular throughout the years. This probably can be attributed to one's obvious resistance to motion while sleeping or heavily sedated. Early workers employed bromides (185, 279), chloral hydrate (279), chlorbutanol and similar preparations (360, 376). With the development of barbiturates, these compounds rapidly replaced the other hypnotics and sedatives and were incorporated widely in various proprietary remedies. Bruns (66), in 1926, employed diallylbarbituric acid and Bohec (48), in 1930, recommended phenobarbital (together with bellafoline). Since then barbiturates of short (332), moderate (245, 281, 332), and long (29, 187, 339) duration of action were all tried with indifferent success. The most exhaustive studies on this group of drugs were conducted by Noble and his coworkers. He found a number of a large series of barbiturates to prevent swing sickness in dogs (285). These included neonal, pentobarbital, phenobarbital, and barbital in that order of effectiveness. In human beings, however, only ethyl-β-methylallylthiobarbituric acid (V-12; mosidal®) demonstrated marked protective effect (281). There was no relation between the anti-motion effect of barbiturates and their hypnotic potency. In fact, many thiobarbiturates actually produced central nervous system stimulation (209). These compounds were considered, therefore, as a means of minimizing sedation. Unfortunately, many compounds of greater anti-motion sickness potency in dogs had to be excluded

from human testing because of their toxicity. A few other thiobarbiturates of low toxicity were tested in human beings: ethyl-(1-methylbutyl)-thiobarbituric acid (V-5); ethylisoamylthiobarbituric acid (V-7); ethyl-n-butylthiobarbituric acid (V-8); and n-butyl-(1-methylallyl)-thiobarbituric acid (V-9) (284, 295, 297). These were largely ineffective even when the largest tolerated dose was used. V-12 alone or in combination with other medication was tried extensively during the war with conflicting results. The Canadian workers, in general, reported preparations containing V-12 to be highly effective against both swing sickness and seasickness. Noble (284) reported V-12 in doses of 315 mg. to be more effective on the swing than various belladonna mixtures. Further, he reported that V-12 combined with hyoscine or with hyoscine plus hyoscyamine gave still better protection. Parker (293), however, found V-12 less effective than hyoscine (0.8 mg.) or than a hyoscine-hyoscyamine mixture. Neither he nor Smith (339) could detect any superiority of a V-12-hyoscine mixture over that of hyoscine alone. Tyler (355, 356) found V-12 alone, V-12 with hyoscine, or with hyoscine plus hyoscyamine protected persons at sea. This protection was less than that with hyoscine alone. More recently, Chinn *et al.* (77) tested V-12 in sea trials and could detect no protection in doses of 150 mg. given three times daily. The first dose was given just before sailing. Noble (286) has recommended that V-12 be given for a day prior to exposure to motion. Whether the ineffectiveness of V-12 in this case can be attributed to the failure to medicate for 24 hours prior to sailing cannot be said. The utility of this compound is markedly reduced if such a procedure is necessary.

Since both belladonna alkaloids and certain barbiturates afford protection under appropriate conditions, attempts to obtain still greater benefit by their combination were inevitable. There have been two such mixtures which have enjoyed considerable support: 1) the Motion Sickness Preventive, Army Development type (MSP) containing amytal® (130 mg.), hyoscine hydrobromide (0.22 mg.) and atropine sulfate (0.16 mg.) and 2) the "Canadian Motion Sickness Remedy", National Research Council Formula containing 0.1 mg. hyoscine hydrobromide, 0.3 mg. hyoscyamine hydrobromide and 130 mg. V-12. The most extensive trials have been with the first mixture (MSP). It was developed before the World War II by Barrow who also reported its first field test in 1943 (29). This, and subsequent trials at sea, demonstrated conclusively that MSP afforded significant protection against seasickness (228, 355, 356). Its effectiveness against airsickness was less notable although unquestionably significant (18, 340). On the swing, the protection was statistically not significant (339). However, the test group was very small and there is no reason to believe that a larger series would not yield results comparable to those obtained on the sea or in the air.

The Canadian Motion Sickness Remedy has not been field-tested to our knowledge. It was recommended largely on the basis that certain individuals responded to V-12 but not to the belladonna alkaloids, and *vice versa* (284). One must certainly concede that this preparation should give good protection. As pointed out earlier, the mixture of hyoscine and hyoscyamine has almost invariably done so.

This has occurred whether a barbiturate was present (117, 284), or absent (116, 284, 293, 295). In regard to the salient point in this consideration, as to whether the remedy is more effective than the belladonna alkaloids given alone, there is a greater division of opinion. Noble (284) maintains that the combination of small doses of V-12 and hyoscine gave greater protection than either component alone. When optimal doses of hyoscine or hyoscyamine are used there is no evidence that mixtures containing barbiturates (284, 293, 339, 355) increase the protection afforded. The possibility remains that each component of a mixture may be given in dosage lower than that required for optimal protection when given alone. This would not increase the effectiveness of the mixture in preventing motion sickness but might reduce the incidence or severity of side effects. Controlled studies with the Canadian Motion Sickness Remedy or with other mixtures containing barbiturates must be conducted before one can ascribe to these preparations any superiority over hyoscine given alone. Despite the impressive literature on barbiturates and their continued use in many proprietary preparations, their present role in motion sickness treatment must be considered of little importance.

Vitamins. The ever expanding areas of vitamin therapy coupled with the empiric search for motion sickness treatment made it almost inevitable that vitamins be tested for effectiveness. It is not surprising therefore that thiamine, niacin and pyridoxine have been examined. More surprising is the fact that numerous vitamins remain untested.

Thiamine was ineffective against swing sickness when given in 10 (339) or 15 (284) mg. doses. Niacin alone in doses of 100 to 150 mg. failed to give significant protection against swing sickness (284, 293, 332). Because of its dilating effect on peripheral vessels, however, many investigators have added it to the belladonna alkaloids in an attempt to increase their concentration in the brain. It was combined with hyoscine and hyoscyamine in 1943 and the mixture ("R. C. N. Remedy") was widely tested by the Royal Canadian Navy Research Unit. This mixture has given significant protection whenever it has been tested against swing sickness (284, 293), seasickness (228, 296, 355), or airsickness (340). Niacin has been incorporated into other mixtures containing hyoscine plus amphetamine (234, 295), hyoscine, hyoscyamine and amytal® (284), and hyoscine, hyoscyamine, V-9 and amphetamine (296). In each instance the preparation has been effective, but there has been no evidence to show that niacin played any role.

The widespread use of pyridoxine in other conditions of nausea and vomiting (pregnancy, irradiation sickness, Ménière's disease, etc.) stimulated its trial in motion sickness. On the swing, doses of 100 or 200 mg. given one hour before swinging gave no protection whatever (339). Thuer (351) reported that pyridoxine was ineffective against seasickness. Recently, however, Benkendorf has given a large series of seasick patients 50 mg. of pyridoxine with success (33). Of 500 seasick patients receiving pyridoxine by mouth, a third were reported to have marked improvement and another third mild improvement. Of 2500 patients given pyridoxine by rectal suppository 90 per cent showed improvement. A

small series (90) of patients receiving rectal suppositories as placebo treatment were not improved. The criteria of sickness and of improvement were not reported. The large series and the striking response, however, indicate that a re-evaluation of pyridoxine is in order. Voss (361) has recently reported its effectiveness in airsickness.

Antihistamines. In 1949, Gay and Carliner made their now famous report on the effectiveness against seasickness of dimenhydrinate (dramamine®) (140, 141). They administered 100 mg. dramamine® upon embarkation and 400 mg. daily for at least 48 hours to 134 soldiers during a rough North Atlantic crossing. The protection afforded was spectacular. Not one of the 134 men vomited or became nauseated and only two men complained of dizziness. The results obtained with dramamine® given therapeutically were equally striking. Of 389 men who received dramamine® after becoming seasick, complete relief was reported by 372 (95.6 per cent). The use of placebo treatment in 59 seasick individuals resulted in 38 failures (64.4 per cent). The design of the experiment was sharply criticized by Tyler and Bard (358) on the basis of: 1) the heterogeneous distribution aboard the ship of the subjects receiving dramamine® or placebo treatment, and 2) the failure to include a known prophylactic (*e.g.*, hyoscine) with which to compare the effectiveness of dramamine.

Despite the validity of these criticisms, the work of Gay and Carliner stimulated a new burst of activity in a field which had remained essentially dormant since the close of the war. The effectiveness of dramamine® in preventing seasickness was rapidly and repeatedly confirmed (1, 80, 89, 139, 291, 310, 323, 326, 333, 379). An incidental consequence of the sudden widespread use of this compound, has been the confusion created by the numerous proprietary names employed. The literature has become replete with references to amosyt®, gravol®, suprimal®, chlornautine®, novamin®, vomex A®, and others, all referring to dramamine®. In addition, mixtures containing other substances as well have been making their appearance, each, of course, with a separate name.

As might be expected, dramamine® also affords significant protection against airsickness (81, 264, 335, 348, 349, 381). Against swing sickness, the results are somewhat equivocal. Diamant (103) tested its effectiveness at a dose level of 1.5 mg. per kg. against swing sickness in 38 subjects. It was reported "very effective" in only 12 per cent. The criterion of effectiveness is not known. On the other hand Strickland *et al.* (349) could detect no difference between placebo and dramamine® in protecting swing-susceptible persons. In this connection, Chinn and Plotnikoff (82) found no difference between placebo and diphenhydramine (benadryl®) in protecting against swing sickness. Benadryl® and dramamine® are very closely related as will be discussed shortly.

Despite the overwhelming evidence that dramamine® is indeed an effective medicament in motion sickness, it cannot be considered superior to other available drugs. Dramamine® first was compared directly with a known anti-motion drug by Strickland *et al.* (349) in the airplane. In this study, when 100 mg. dramamine® was given one hour before flight, 33 per cent of the subjects became airsick. When 0.65 mg. hyoscine was similarly administered to subjects in the

same aircraft, only 20.4 per cent became sick. This difference is not statistically significant. The finding that dramamine® is not superior to hyoscine against airsickness was confirmed by Boland and Grinstad (49). Against seasickness, also, no significant difference in protection was apparent between dramamine® and either hyoscine (80, 166), or any of several other preparations (77) to be discussed later.

Dramamine® is the 8-chlorotheophylline salt of beta dimethylaminoethylbenzohydryl ether. Benadryl® is the hydrochloride of the same base. This close chemical similarity suggested (280) that their pharmacological actions should also be the same, since 8-chlorotheophylline in the quantity contained in the former should have little effect (158). This prediction was confirmed by comparing the effectiveness of dramamine® and benadryl® in equivalent doses against airsickness (81) and seasickness (80, 379). No difference in their ability to protect susceptible persons could be detected. The protective properties of dramamine® and benadryl® stimulated considerable speculation for it raised the interesting possibility that anti-motion sickness efficacy might be related to antihistamine potency. This hypothesis was rapidly disproved by the demonstration that many strong antihistamines afford no protection against motion sickness. Thus, phenindamine tartrate (thephorin®) (80), methaphenilene hydrochloride (diatrin®) (76), N-(methyl-β-dimethylethyl)-phenothiazine hydrochloride (isophenergan®) (77); N-(β-dimethylaminoethyl) phenothiazine hydrochloride (lisergan®) (77), and N-diethylaminoethylphenothiazine hydrochloride (diparcol®) (77) all failed to protect against seasickness. Further, chlorprophenpyridamine maleate (chlortrimeton®) and doxylamine (decapryn®) gave little or no protection in the air (85). Chinn and coworkers failed to detect any protection against seasickness with pyranisamine maleate (neoantergan®) (80) or with synopen (77) despite isolated reports to the contrary (31, 227, 351). Thus, no correlation appears to exist between antihistamine potency and motion sicknesss protection.

Despite the failure of some antihistamines to be effective prophylactics against motion sickness, a large number from this group have afforded excellent protection. Diphenhydramine (benadryl®) has already been mentioned. Additional studies have invariably confirmed the striking protection offered by this compound against seasickness (76, 77, 166). As already noted, it has failed to protect against swing sickness (82). Its diethyl analogue β(-diethylaminoethylbenzhydryl ether) also has given significant protection against seasickness (77, 215). Preliminary studies by McKay (242) with prophenpyramine (trimeton®) maleate had indicated promising protection against airsickness. This was confirmed in more extensive tests not only for airsickness (75, 79) but for seasickness as well (241). Antazoline (antistine®) hydrochloride also has been reported to have protected several susceptible children (181) and to have given good results after intramuscular injection (46). Still another antihistamine of different chemical structure protecting against seasickness is 1-dimethylamino-2(2′benzyl-p-chloro)-phenoxyethane hydrochloride (Lilly 01780) (166).

Perhaps the most interesting group of antihistamines used against motion sick-

ness has been the phenothiazine derivatives. The most widely tested member of this series has been promethazine (phenergan®, lergigan®). It has been found effective both as the hydrochloride and as the chlorotheophylline salt. It apparently was used first by Beaumont in 1949 (31) in conjunction with anthisan® (pyranisiamine maleate) suppository. Although the protection was attributed to the latter preparation, it now seems probable that most of the effectiveness came from the promethazine. Ambrus and Ambrus (12) reported that with phenergan® "in almost every case we saw good results", but no data were shown. The usefulness of promethazine has since been repeatedly confirmed (75, 76, 77, 79, 86, 87, 108, 148, 149, 168).

Some confusion has arisen concerning the exact structure of phenergan® and its relation to lergigan®. According to the respective pharmaceutical firms phenergan® and lergigan® are N-(methyldimethylaminoethyl)-phenothiazine hydrochloride. The methyl group in the former compound is said to be on the carbon beta to the phenothiazine nucleus whereas the latter has the methyl group on the alpha carbon. The purest preparations supplied by both firms give essentially the same motion sickness protection. Infrared spectrograms of both compounds were identical (77); the melting point of the mixture was not depressed (317). It seems probable, therefore, that both preparations represent the same compound. The isomer tentatively designated as "Isophenergan" has been found completely inactive (77).

Glaser and Hervey (148) compared phenergan® with benadryl® and with hyoscine against seasickness. Men were placed in rubber boats in a swimming pool and subjected to artificial waves. Phenergan® gave good protection, slightly better than benadryl® but not as good as 1.0 mg. hyoscine. In aircraft, also, 1.0 mg. hyoscine was found superior to 25 mg. phenergan® (79). As Bethell (39) has pointed out, phenergan® is slowly absorbed and maximum effectiveness may not have resulted in these tests. One of the most striking aspects of the effect of phenergan® has been its long duration of action. The frequently confirmed long acting antihistamine effect was pointed out by Halpern in the original investigations of this compound (164). Approximately 20 hours are required for the effectiveness of phenergan® to be reduced by half when measured against intradermal histamine wheal response (24). Similar duration of effectiveness was noted against motion sickness. Medication twice daily gave good protection against seasickness but once daily was ineffective (77).

Other phenothiazine derivatives have been found effective: N-diethylaminopropylphenothiazine hydrochloride (parsidol®) (77); pyrathiazine (pyrrolazote®) hydrochloride (77); and N-(β-methyl-β-trimethyl ammonium)-ethylphenothiazine methosulfate (multergan®) (77) all give significant protection against seasickness. Pyrathiazine has also been tested and found effective against airsickness (75). The failure of isophenergan to protect against seasickness has already been mentioned. Similarly N-(β-dimethylaminoethyl)-phenothiazine hydrochloride (lisergan®) (77), N-diethylaminoethylphenothiazine hydrochloride (diparcol®) (77) and chlorpromazine (thorazine®) (166) have failed to protect against seasickness. Bénitte (32) recommends lisergan® because of its low hypnotic effect.

He presents no data, however, to indicate its effectiveness. The marked changes in effectiveness resulting from slight chemical differences make this group of compounds a very interesting one. It would seem profitable to test a series of them against motion sickness in an attempt to derive some basis for relating chemical structure to effectiveness. The failure of chlorpromazine to protect was especially interesting, for this compound has prevented swing sickness in dogs (74, 94) as well as emesis in man under a variety of stimuli. This again points up the danger of predicting effectiveness in human beings on the basis of animal data.

Antihistamines which have recently attracted considerable interest are members of the piperazine series. Thus far, three have been tested, *i.e.*, the hydrochlorides of cyclizine (marezine®), chlorcyclizine (perazil®, diparalene®) and meclizine (bonamine®), postafene®). All three preparations were shown effective against both sea- (76, 77, 80, 166) and airsickness (75, 79, 87, 111). All had approximately equal effectiveness against seasickness. In the air, perazil® seemed least effective (87) although the compounds have not been compared directly. The most striking feature of the effect of these piperazine derivatives has been the long duration of action. Perazil® has proved effective when given twice daily (77, 79, 80, 166) and bonamine® is active for at least 24 hours (77, 166). Marezine® has not been given less frequently than three times daily. The action of bonamine® is especially noteworthy. It has been reported to protect guinea-pigs against a histamine aerosol given several days later (273). Given 24 hours prior to take-off, it has protected soldiers and airmen (75, 79) against airsickness. Given once daily it will protect against seasickness (77). Recent work suggests that its duration of action may be even longer, since a single 50 mg. capsule given before sailing afforded protection comparable to that obtained with other medications given 3 times daily for the first two to three days of the crossing. In this connection, however, it should be remembered that resistance to motion rapidly develops aboard ship and the ability of a drug to tide one over the critical first 24 hours may give protection for the entire trip. Another compound of somewhat similar structure to the piperazines, N-phenyl-N-benzyl-4-amino-1-methylpiperidine (soventol®), has recently been reported as effective against motion sickness (104).

The independent action of two distinct groups of drugs, the belladonna alkaloids and the antihistamines, stimulated trials of various combinations in the hope that an even more effective preparation could be devised. Chinn and Oberst (81) combined the usual dose of benadryl® (50 mg.) with that of hyoscine (0.65 mg.) and reported the mixture to be more effective than either component alone. Since side effects were correspondingly increased the advantage of the mixture was somewhat lessened. A mixture containing half the usual doses of each constituent (25 mg. benadryl® and 0.35 mg. hyoscine) has also been employed. This has given approximately the same protection as the full dose of either component alone with somewhat fewer side effects (76, 86, 87). Hyoscine aminoxide (scopodex®) (1.0 mg.) also has been combined with benadryl®. Against airsickness (87) and seasickness (76) it afforded somewhat less protection than

was obtained with the hyoscine-benadryl® preparations. Hyoscine has also been combined with the antihistamines trimeton® (72, 243), or phenergan® (149). The protective effect in these cases was not demonstrably greater than that of hyoscine alone.

Central nervous stimulants (caffeine, *dl*-amphetamine, *d*-amphetamine) have been added to effective motion sickness preventives in attempts to control the sedation produced. From the rather limited data available, the inclusion has not impaired the effectiveness of the prophylactic on the swing (103) aboard ship (160) or in the airplane (86).

Miscellaneous substances. A variety of other preparations have been tried throughout the years with rather unimpressive results. Bulbocapnine was believed to cause central inhibition without general depression (23), so it was used on susceptible dogs in the swing. In 19 tries, it prevented vomiting for the entire test (60 to 95 min.). In four cases, vomiting was delayed and in the remaining six it was ineffective. Berggren (35, 36) found it to decrease rotary nystagmus in both rabbit and man. Birren, *et al.* (41) however, could not confirm this in dogs and maintained that there was no rationale for the use of bulbocapnine. The powerful side effects of this compound would seem to preclude its use even if moderate protection could be demonstrated.

Recommendations for glucose and alkali were common in older literature (127, 140, 253). Hasegawa (169, 170) reported that no person receiving sodium bicarbonate intravenously became seasick. He makes the rather startling suggestion that this treatment dissolved the otolithic crystals, affording protection in this manner. Sodium nitrite (302), magnesium sulfate (305), potassium chloride (121, 122) and salts of ammonium and strontium (122) have been recommended. A colloidal preparation of cerium oxalate (perenesin®) was especially popular prior to World War II with several reports attesting to its effectiveness (59, 178, 213, 214). Digitalis (142), combinations of oleander, *Adonis vernalis*, *Convallaria majalis* (142) and extracts of the Mary thistle (*Silybum marianum* L.) (216) have all been employed.

Side effects. To this point the various drugs have been discussed primarily from the point of view of their effectiveness against motion sickness. As with any other drug, however, the practical value is not determined by its effectiveness alone. The incidence and severity of side effects are equally important factors. This is especially true in the Armed Services where the greatest demands on an individual may be invoked immediately after sea or air transport. It is vital that the drug not impair the person's ability to perform his task. Should one prescribe anti-motion sickness drugs and risk side effects or should he refuse such medication and risk varying degrees of incapacitation from sea or airsickness? This is the dilemma faced by the naval or flight surgeon and is one for which no firm answer can be given. Additional data are badly needed, not only to decide whether a given medication impairs performance but also to learn about its influence on behaviorial or personality traits such as aggressiveness, initiative, etc.

In large doses, hyoscine and other belladonna alkaloids have undesirable side

effects. The peripheral effects include decreased sweating and salivary flow, cycloplegia and cardiac acceleration. Centrally, large doses may produce disorientation, excitement and even hallucinations, giving way to a secondary depression. Single doses of hyoscine, required to produce such central changes, would rarely be given except by accident. Keil (204) produced accommodative defects and lowered visual efficiency by administering hyoscine in doses greater than 1.5 mg. This is approximately twice the dose usually employed. No significant deleterious effects on vision could be detected in either Air Force (340) or Navy (222) navigation students when the smaller dose was administered. The decreased sweating after hyoscine did not measurably handicap men working under conditions of extreme heat (187). The principal symptoms from the dosage ordinarily employed (0.6 to 1.2 mg.) is dryness of the mouth and most workers employing hyoscine have commented on this complaint (352). Glaser and Hervey (148) claimed that 1.0 mg. hyoscine hydrobromide gave few side effects when it was used against seasickness. It seems likely that the effects of motion itself made it difficult to select those symptoms attributable to the drug, for in a more recent study Glaser (147) compared the side effects of various anti-motion sickness drugs without exposing the subjects to motion. He found that a single dose of 1.0 mg. hyoscine hydrobromide significantly increased complaints of drowsiness, headache, nausea, giddiness, blurred vision and flushing of the face, as well as of dryness of the mouth. Over 90 per cent of the subjects had dry mouth and about half felt giddy. The drug was considered unpleasant by 65 per cent of those taking it, considerably more than for any of the other drugs under study (placebo, promethazine (25 mg.) and diphenhydramine (25 mg.)). Glaser felt that the side effects of the drugs were proportional to their effectiveness against seasickness and that side effects may be inevitable if powerful medication is required.

Little significant effects on performance could be detected by the various tests employed. After 0.5 mg. hyoscine hydrobromide, no deterioration in psychomotor performance or intelligence could be detected either at ground level or at a simulated altitude of 18,000 feet (344). Comprehensive studies on psychological efficiency by Payne *et al.* (300) revealed less impairment by hyoscine hydrobromide (0.65 mg.) than by any other motion sickness preventive tested. These workers compared the response to a battery of 32 separate tests after the administration of hyoscine hydrobromide (0.65 mg.), dimenhydrinate (100 mg.), diphenhydramine (50 mg.) or a mixture of diphenhydramine (50 mg.) plus hyoscine hydrobromide (0.65 mg.). The tests were selected to allow evaluation of the following processes: visualization, integration, number manipulation, coordination, and spatial relations which in turn were believed relevant to performance of pilot and navigator duties. All drugs were shown to affect measurements of navigator ability more than of pilot ability. Hyoscine was less disturbing than the others and the diphenhydramine-hyoscine mixture was the most disturbing. Subsequent studies, more closely simulating the duties of the pilot and navigator, confirmed these findings. There were no significant effects of hyoscine upon an exacting and perceptual-motor task related to piloting although

the mixture of diphenhydramine plus hyoscine produced significant impairment (299). Similarly, the least decrement upon navigation performance was apparent after hyoscine ingestion. The subject's ability was tested by a four-hour aerial map reading mission and a three-hour ground celestial trainer mission (301).

Although a single moderate dose of hyoscine or its relatives apparently does not produce marked side effects or performance decrement, there is some evidence that periodic administration may cause more serious effects. Thus, when 0.75 mg. hyoscine hydrobromide was given three times daily (80), the incidence of blurred vision and dry mouth was high. Further, one case of auditory hallucinations (among 88 subjects) was observed after 36 hours of medication. The dangers of the continued administration of hyoscine-like drugs were emphasized on another field study (76) when hyoscine aminoxide (scopodex®) was employed. This compound has been reported to have approximately one-third the pharmacological activity of hyoscine with only one-sixth its toxicity (98). Accordingly 2 mg. were given three times daily. Within 24 to 36 hours, over half the subjects complained of dry mouth and blurred vision and approximately one-fourth reported nightmares. More seriously, 11 of the 96 subjects suffered hallucinations and one became quite manic. These alarming symptoms lasted from 24 to 36 hours. Reducing the scopodex® dosage to 1 mg. three times daily (together with 25 mg. benadryl®) failed to evoke hallucinations, although dry mouth and blurred vision remained high. Glaser (147) contends that "fears of cumulative poisoning by hyoscine . . . in the present dosage are unfounded and that some tolerance . . . may be acquired within a few days." He recommends, however, that 1.0 mg. hyoscine hydrobromide be given only for the original dose and subsequent doses be reduced to 0.5 mg. three times daily. The effectiveness of this regimen remains to be tested. As discussed above, 2.25 mg. daily in 3 divided doses gave good protection but considerable side effects (80), whereas 0.75 (80) or 1.0 mg. (166) given twice daily were ineffective.

Corey and Webster (95) using somewhat smaller doses of hyoscine hydrobromide (0.65 mg. initially plus 0.32 mg. every 6 hours) could detect no untoward symptoms except sleepiness, dryness of mouth and throat, and decreased lachrymation. Marksmanship was somewhat poorer in the hyoscine group. Tyler (357), on the contrary, claimed that marksmen receiving Army Motion Sickness Preventive containing hyoscine and atropine together with amobarbital (amytal®) actually improved their firing. This is probably attributed to the amobarbital since amobarbital alone significantly improved marksmanship (354). Further, the Royal Canadian Navy remedy containing hyoscine, hyoscyamine and niacin was without effect as was the thiobarbiturate V-12.

As would be expected, drowsiness is the most frequent complaint with preparations employing the usual barbiturates. The dosage contained is below that ordinarily required for hypnosis. A single report has been found of a fatal poisoning with the Army Motion Sickness Preventive (132). In this instance, it was estimated that 30 tablets had been taken. Death was attributed to the amobarbital (approximately 2 grams) although 6 mg. hyoscine hydrobromide and 5 mg. atropine sulfate also were present.

Among the thiobarbiturates, many apparently effective preparations were abandoned because of disagreeable or dangerous side effects (287). Although V-12 was considered among the least toxic of the effective thiobarbiturate, Noble, *et al.* (287) cautioned against overdosage or administration for more than five days in any week because of the danger of liver damage.

By far the most common side effect of the antihistamines used in motion sickness prophylaxis has been sedation. In their original report, Gay and Carliner (140) claimed that not one of the 300 men receiving 400 mg. dramamine® daily experienced any "untoward side effects." It is probable that sedation was not placed in this category, for numerous reports attest to the marked depression induced with even smaller amounts of dramamine (43, 103, 244, 335). In fact, dramamine has been shown to compare favorably with clinically employed doses of barbiturates in causing drowsiness (288). Similarly, drowsiness has been a major complaint when benadryl®, perazil®, (112), pyrolazote® (112), trimeton® (112), phenergan® (112), 2-benzhydryl oxyethylamine hydrochloride (288), and parsidol® (288) were used. Preliminary studies with multergan®, bonamine® and 1-dimethylamino-2-(2′-benzyl-p-chloro)-phenoxyethane hydrochloride (Lilly 01780) indicate that these preparations exert relatively little sedative action (288).

Apart from sedation, the most common complaints related to the use of the antihistamine series are symptoms associated with anti-cholinergic activity: dry mouth, blurred vision, dizziness, fatigue. Phenergan® has the greatest anticholinergic activity of any of the compounds mentioned (164). Some workers (68, 147) contend that protection against motion sickness depends upon the hyoscine-like activity of the compound so that these side effects are inevitable in any effective preparation. This point of view will be discussed shortly.

SITE AND MECHANISM OF ACTION OF DRUGS

The mode by which the various preparations exert their protective action remains unknown. In all fairness, this statement can be extended to include all anti-emetic drugs. Until the site and mechanism of action can be elucidated, new drugs will continue to be selected on a trial and error basis rather than by any systematic procedure. As stated earlier, both the autonomic and central nervous system may transmit different impulses to the vomiting center. Decreasing the sensitivity anywhere along these pathways should be reflected by an increased resistance to motion sickness.

Vestibular action. Many workers believe the primary action of a number of drugs is upon the peripheral vestibular structures. Dramamine® has relieved the vertigo of labyrinthine origin (138, 378) as well as the vestibular reactions after labyrinthine fenestration (71). Furthermore, its successful use in Ménière's syndrome has been reported (16). Action upon the semicircular canals and the otolith organs has been claimed, although supporting evidence is still somewhat controversial. Fermin *et al.* (113, 114) believed it acted first upon the otolith system and in larger doses upon the semicircular canals. With doses from 25 to 70 mg. per kg., the otolith reflexes of rabbits were abolished or attenuated, but

those from the semicircular canals persisted. With still larger doses (80 mg. per kg.) all labyrinthine reflexes could be abolished. This was confirmed further by demonstrating that 80 mg. per kg. prevented symptoms of vestibular disturbance after unilateral labyrinthectomy. Similarly, other authors have reported little effect upon reflexes from the semicircular canals with doses ordinarily employed. Oral administration of 200 mg. dramamine® did not alter the duration of nystagmus or vertigo in normal human subjects (47, 377). The response of dogs (263) and guinea-pigs (179) after rotation was also unaffected by the administration of dramamine. Bromnautine®, identical with dramamine except for the substitution of bromine for chlorine in the theophylline nucleus, had no effect on first rotatory nystagmus in large doses (151). On the contrary, experiments have been reported indicating a reduced sensitivity to both caloric and rotatory stimulation. Gutner *et al.* (161) found dramamine® (100 mg.) to be the only drug tested to prolong the onset and to shorten the duration of nystagmus after a caloric test. Benadryl®, 8-chlortheophylline, aminophylline, hyoscine and secobarbital were all ineffective as was a mixture of benadryl® and chlortheophylline. Essentially the same results were obtained by Monnier and Laue (271) in rabbits. They found that dramamine® significantly decreased the intensity of nystagmus whereas hyoscine, pyrrolazote®, benadryl®, beta o-methoxyphenylisopropylmethylamine (orthoxine®) and 8-chlortheophylline alone were ineffective. The 8-chlortheophyllinate of pyrrolazote® and orthoxine® inhibited the vestibular apparatus similarly to dramamine®. Boenninghaus (47) and DeWit (102) also have reported that dramamine® modifies post rotational nystagmus. DeWit (102), however, believed the effect to be central since only the duration of response was altered by dramamine® and not the intensity of angular acceleration required to produce nystagmus. Atropine acted in the same manner.

The opposing reports on the ability of dramamine® to combat induced nystagmus suggest that this action cannot be its sole or major contribution in preventing motion sickness. The apparent discrepancies may eventually be reconciled on the basis of species differences, dosage administered and sensitivity of test procedures. The action of other effective anti-motion sickness preparations (bonamine®, trimeton®, phenergan®) on the peripheral labyrinthine structures is not known. There is no reason to believe, however, that they will differ markedly from those reported.

The effect of anti-emetic drugs on various sites in the vestibular nerve tract and brain centers is relatively unexplored. Gutner *et al.* (161) employed galvanic stimulation of the mastoid area as a test of the integrity of this pathway. The amount of current required to cause the subject to tilt was taken as an index of vestibular activity. Over twice the current was required to reach this endpoint after dramamine® ingestion, but no increase was observed after any of the other drugs employed (hyoscine, benadryl®, seconal, 8-chlortheophylline, aminophylline). The blood pressure drop resulting after stimulation of the 8th nerve was abolished by the antihistamine lergigan® (phenergan®) (144).

Action on cerebellum. Since the vestibular portion of the cerebellum is in the afferent pathway to the emetic center, drugs acting upon this site would be

expected to demonstrate some protection against motion sickness. Unfortunately, tests are not available to determine specific depression of this area, so that there is no method of evaluating this factor at present.

Action on medulla. The next known station in the pathway is the chemoceptive emetic trigger zone of Wang and Borison (364). Depression of the sensitivity of this site can be detected by changes in its threshold to apomorphine (362), cardiac glycosides (53), and other chemical emetics (367). Drugs raising these thresholds would be expected to afford some protection against motion sickness. Unfortunately, the available data lend relatively little support to this assumption. Mitchell (270) claimed dramamine® gave complete protection to usual emetic doses of apomorphine in 13 of 15 cats, and there was a delay in vomiting in the two unprotected animals. Benadryl®, an equally effective anti-motion sickness medicament, however, protected in only two of 12 trials. Goethe (153) also reported protection against apomorphine by dimenhydrinate. Schmidt *et al.* (329), on the contrary, could detect no protection with either compound in the cat. Chen and Ensor (72) found that benadryl® and dramamine® in large doses reduced (but did not prevent) vomiting in dogs after apomorphine. This has been confirmed by Paul (298) and by Boyd and Boyd (54) with toxic or near toxic doses. Cook and Toner (94) obtained a slight (but not statistically significant) decrease in the frequency of vomiting after 20 mg. benadryl® per kg. body weight. A similar reduction in vomiting episodes has been reported when large doses of the antihistamines phenergan®, isothazine®, neoantergan®, thiazinamon®, and benadryl® were given 30 minutes before the subcutaneous injections of apomorphine (107). The greatest reduction in vomiting was produced by isothazine®. It is interesting that this compound was ineffective against seasickness (77). When doses more in line with human usage were administered White and coworkers (373) found benadryl® or dramamine® to afford protection. They found 1 mg. benadryl® per kg. and 2 mg. dramamine® per kg. to protect dogs against 30 microg. apomorphine per kg. given subcutaneously. (The report states 30 mg. per kg., but this is obviously a typographical error.) All other workers agree that neither dramamine® nor benadryl® in moderate doses altered the emetic responses to apomorphine in cats (54) or dogs (54, 82, 278, 329). In addition, other compounds of related pharmacological activity were shown to be ineffective: diphenhydramine 8-bromotheophyllinate (54), promethazine hydrochloride (54, 82), methapyrilene hydrochloride (54) and methapyrilene 8-chlorotheophyllinate (54).

As stated earlier, other compounds also stimulate the trigger zone (morphine, digitalis, etc.). Clinically, dramamine® has been reported to relieve dramatically the nausea and vomiting following morphine medication (319). Experimentally, however, it failed to provide any protection (136). It has been claimed (70) that digitalis-induced vomiting in pigeons can be prevented by a variety of antihistamines including neoantergan®, antistine®, phenergan®, thephorin®, pyribenzamine® and the chlor- and bromtheophylline salt of this last compound. In complete opposition is the report of Moser *et al.* (278) who could find no inhibition of vomiting with any of the antihistamines tested (benadryl®, dramamine®, neoantergan® and phenergan®).

That many motion sickness preventives act by depressing the chemoceptive trigger zone in the medulla, is an attractive hypothesis. Reluctantly one must conclude that the bulk of evidence to date is not in support of such a concept. The possibility is reduced still further by the failure of chlorpromazine to protect man against seasickness (166). This amazingly versatile compound is the only one to our knowledge which has been shown unequivocally to raise the apomorphine threshold in the dog (55, 56, 94, 100, 150). It also protects against other agents or treatments shown to act on the chemoceptive emetic trigger zone: ergot (hydergine) (56, 150), morphine (56), radiation (83), and swinging (94). The difference in the response of man and dog exposed to motion after chlorpromazine emphasizes again the hazards of relying too heavily upon animal studies in the testing of anti-motion sickness drugs. The possibility of anatomic and pharmacologic differences in the emetic chemoreceptor trigger zone of man and dog should be explored. Such differences are known to exist between dogs and cats. Thus, the emetic dose of apomorphine in cats is 1000 times higher than in dogs (52) and chlorpromazine is ineffective in the former species (56).

The emetic center, located in the region of the fasciculus solitarius and the underlying lateral reticular formation, is the ultimate target for afferent volleys regardless of their origin. The sensitivity of this structure is reflected by the animal's threshold to oral cupric sulfate. Neither labyrinthectomy, nor cerebellar lesions, nor trigger zone ablations affect the emetic dose of this compound. Most dogs will vomit after 40 mg. cupric sulfate given by mouth and practically all after 80 mg. There is no convincing evidence that any of the anti-emetics in the usual clinical doses will significantly raise this threshold. Thus, chlorpromazine in doses of 2 mg. per kg. had no effect upon the cupric sulfate threshold of dogs (150). Only a slight central depression was obtained with even larger doses. Phenergan® in doses of 25 mg. or less orally will protect man against motion sickness, but the injections subcutaneously in dogs of many times this amount (10 mg. per kg.) did not increase resistance to cupric sulfate (84). In fact, even large doses of barbiturates (20 mg. sodium pentobarbital per kg.) only occasionally raised the emetic threshold to cupric sulfate (84). Moser *et al.* found dramamine to have no effect on cupric sulfate vomiting (278). The frequent reports, therefore, that anti-emetic agents act by depressing the vomiting center (32, 194, 318) must be considered as unsubstantiated.

The possibility of vomiting being initiated by other neuronal loci, cephalad to the brain stem, cannot be ignored. Hess (180) produced vomiting in unanesthetized cats by electrical stimulation of the diencephalon. Penfield and Welch (303) evoked nausea, retching movements and a desire to vomit when the supplementary motor area in the mesial surface of the cerebral cortex was stimulated. In effective doses most anti-motion sickness drugs cause significant central depression. Moreover, there is the rough parallelism between the effectiveness of preparations against motion sickness and against paralysis agitans (Parkinson's disease) which is generally believed a disturbance of higher centers. The belladonna alkaloids, benadryl® (67, 137, 325), trimeton® (137), artane® (331), and phenergan® (137) have all proved effective against both disorders. The correlation is not complete, for some anti-Parkinson drugs (diparcol®, thephorin®,

decapryn®, etc.) seem to provide no protection against motion sickness. Conversely, at least one compound protecting against seasickness (Lilly 01780) (166) was of no value in treating Parkinson's disease (137). Nevertheless, the similarity is striking and suggests some connection. Atropine, artane®, benadryl®, and especially hyoscine prevented the postural tremors induced by lesions in the subthalamus or midbrain reticular formation (359). These compounds are, of course, also effective motion sickness prophylactics. Since compounds active in both conditions possess significant anticholinergic activity, it seems possible that antagonism to acetylcholine is an important factor in each case. All compounds preventing motion sickness have significant anticholinergic activity, with the possible exception of bonamine® (289). However, many active anticholinergic compounds are completely ineffective against either motion sickness or Parkinson's disease. Methantholine (banthine®) (77), probanthine® (77), hyoscine bromobutylate (buscopan®) (77) and prantal® (76) were without effect in protecting against seasickness despite their antagonism to acetylcholine. It is significant, however, that each of these compounds is a quaternary ammonium derivative and that such compounds are singularly lacking in effects upon the central nervous system (17). This, of course, is the objective when their peripheral action is desired and explains, to a large extent, the popularity these preparations enjoy in reducing stomach motility and secretion since large doses are required for the production of central effects. Of all the quaternary ammonium derivatives tested against motion sickness, only multergan® has demonstrated any protective action and this was somewhat less than that of other effective agents. The failure of these compounds to protect despite their parasympathetic blocking action is additional evidence of the secondary role of the autonomic system in the etiology of motion sickness. On the other hand, anticholinergic agents derived from tertiary amines may have very marked central effects which disappear upon quaternization (327). Among the compounds tested for protection against seasickness the ineffectiveness of buscopan®, a quaternary derivative of hyoscine is another indication of this tendency.

The importance of central rather than peripheral antagonism of acetylcholine is further suggested by the interesting studies of Himwich and his coworkers on forced circling movements after injection of various anticholinesterases (135). When diisopropylfluorophosphate (DFP) or other powerful anticholinesterases are injected into the carotid artery, the animals circle in a direction opposite to the side of injection: to the left when the right artery was used and to the right if the left carotid was employed. Typical convulsive patterns become evident in electroencephalographic tracings. These convulsive cortical seizures can be prevented or cured if benadryl®, dramamine®, hyoscine, atropine or phenergan® are given (198, 328). Similar antihistamines with less anticholinergic activity, *i.e.*, thephorin®, antistine®, pyribenzamine®, neoantergan® and chlortrimeton®, were ineffective. None of the latter has demonstrated significant anti-motion sickness protection. The apparent parallelism has prompted the suggestion (76) that the forced circling technique be utilized as a rough screening procedure for effective motion sickness prophylactics. Its usefulness for this purpose and for

selection of anti-Parkinson drugs merits investigation. From these reports, it seems likely that the central antagonism of acetylcholine or related substances plays a major role in preventing motion sickness. The exact site or sites of these antagonisms cannot be given with any assurance. It is believed, however, that the primary areas must be subcortical in view of the findings reported earlier in this review; namely, completely decerebrate dogs can be made motion-sick; strong central depressants are poor prophylactics unless given in large doses; counteraction to central depression by an analeptic does not destroy protection; and some effective prophylactics have only slight or no depressant action.

For centuries, the selection of prophylactic agents against motion sickness has been empiric. As in all areas of medicine, this procedure has been productive but inefficient. The gradual elucidation of the mechanism of motion sickness, and of emesis in general, should allow more rapid progress in drug development.

REFERENCES

1. Adams, J. C. L.: "Dramamine" and sea-sickness. Brit. Med. J., 2: 947, 1950.
2. Albrecht, F. K.: A therapeutic evaluation of benzedrine sulfate in treatment of seasickness: Results in 100 cases. Med. Clin. North America, 27: 1652–1658, 1943.
3. Alexander, S. J., Cotzin, M., Hill, C. J., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. I. The effects of variation of time intervals between accelerations upon sickness rates. J. Psychol., 19: 49–62, 1945.
4. Alexander, S. J., Cotzin, M., Hill, C. J., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. II. A second approach to the problem of the effects of variation of time intervals between accelerations upon sickness rates. J. Psychol., 19: 63–68, 1945.
5. Alexander, S. J., Cotzin, M., Hill, C. H., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. III. The effects of various accelerations upon sickness rates. J. Psychol., 20: 3–8, 1945.
6. Alexander, S. J., Cotzin, M., Hill, C. J., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. IV. The effects of waves containing two acceleration levels upon sickness. J. Psychol., 20: 9–18, 1945.
7. Alexander, S. J., Cotzin, M., Hill, C. J., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. V. Incidence of sickness at various hours of the day. J. Psychol., 20: 19–24, 1945.
8. Alexander, S. J., Cotzin, M., Hill, C. J., Jr., Ricciuti, E. A. and Wendt, G. R.: Wesleyan University studies of motion sickness. VI. Prediction of sickness on a vertical accelerator by means of a motion sickness history questionnaire. J. Psychol., 20: 25–30, 1945.
9. Alexander, S. J., Cotzin, M., Klee, J. B. and Wendt, G. R.: Studies of motion sickness. XVI. The effects upon sickness rates of waves of various frequencies but identical acceleration. J. Exper. Psychol., 37: 440–448, 1947.
10. Alexander, S. J., Helmick, J. S., Hill, C. J., Jr. and Wendt, G. R.: A second experimental comparison of autonomic responses in individuals susceptible and non-susceptible to motion sickness. Civ. Aero. Ass. Div. Res., Aug. 1946.
11. Allard, A.: Le mal de l'air. Bruxelles méd., 32: 327–334, 1952.
12. Ambrus, J. L. and Ambrus, C. M.: Motion-sickness and anti-histamines. Lancet, 1: 326, 1950.
13. Anonymous: Sea-sickness. Lancet, 2: 258, 1869.
14. Anonymous: Recent studies on the treatment of motion sickness. Editorial. Ann. Int. Med., 35: 1383–1389, 1951.
15. Anonymous: Motion sickness. Editorial. Brit. Med. J., 2: 553–554, 1952.
16. Anonymous: Ménière's syndrome. Queries and Minor Notes. J.A.M.A., 141: 500, 1949.
17. Anonymous: Parasympathetic depressants—anticholinergic agents. Res. Today, 10: 31–51, 1954.
18. Anonymous: Surgeon General's Office U. S. Army. Prevention of motion (air-)sickness in airborne troops. Comm. Aviat. Med., N.R.C., Rep. No. 285, 1944.
19. Anonymous: Rep., U.S. Nav. Air Training Station, Pensacola, Fla., cited by Hemingway (174).
20. Armstrong, H. G.: Principles and practices of aviation medicine. Williams and Wilkins, Baltimore, 3rd ed., 1952.
21. Babkin, B. P. and Bornstein, M. B.: The effect of swinging and of binaural galvanic stimulation on the motility of the stomach in dogs. Rev. canad. biol., 2: 336–349, 1943.
22. Babkin, B. P. and Schachter, M.: Proc. 2nd Meet. Ass. Comm. Med. Res., N.R.C. Canada, Rep. No. C 4059, Oct. 7, 1943.
23. Babkin, B. P., Dworkin, S. and Schachter, M.: Experimental motion-sickness and attempts at therapy. Rev. canad. biol., 5: 72–86, 1946.
24. Bain, W. A., Broadbent, J. L. and Warin, R. P.: Comparison of anthisan (mepyramine maleate) and phenergan as histamine antagonists. Lancet, 2: 47–52, 1949.
25. Bakwin, H.: Motion sickness in children. J. Pediat., 35: 390–393, 1949.
26. Bárány, R.: Versuche zur Erklärung der Seekrankheit. Monatsschr. Ohrenh., 44: 723, 1910.

27. BARD, P.: Comm. Aviat. Med., N.R.C., Rep. No. 485, Sept. 1945.
28. BARD, P., WOOLSEY, C. N., SNIDER, R. S., MOUNTCASTLE, V. B. AND BROMILEY, R. B.: Delimitation of central nervous mechanisms involved in motion sickness. Fed. Proc., 6: 72, 1947.
29. BARROW, L. L., CONN, H. F. AND WILLIAMS, S. C.: A report of the comparative study of motion sickness remedies on troops at sea. Bull. Subcomm. Motion Sickness, 55–59, 1943.
30. BEARD, G. M.: The treatment of sea-sickness: its relation to medical etiquette on shipboard. Brit. Med. J., 2: 362 1880.
31. BEAUMONT, F. K.: Antihistaminic drugs and sea-sickness. Brit. Med. J., 2: 1472–1473, 1949.
32. BÉNITTE, A. C.: Le mal des transports. Bull. internat. serv. san., 25: 235–249, 1952.
33. BENKENDORF, L.: Über die Behandlung der Seekrankheit. Deutsche med. Wchnschr., 78: 393–394, 1953.
34. BENNETT, R. A.: Seasickness and its treatment. Brit. Med. J., 1: 752–754, 1928.
35. BERGGREN, S.: Experimentelle Untersuchungen über den Einfluss des Bulbocapnins auf den vestibularen Nystagmus. Acta oto-laryng., 11: 200–215, 1927.
36. BERGGREN, S.: Über den Einfluss des Bulbocapnins auf spontanen Nystagmus beim Menschen. Acta oto-laryng., 13: 233–240, 1929.
37. BEST, C. H., SELLERS, E. A., PARKER, J. AND STEPHENSON, N. R.: Proc. Conf. Motion Sickness, N.R.C. Canada, Aug. 28, 1942.
38. BEST, C. H., SELLERS, E. A. AND STEPHENSON, N. R.: Investigations into chemical factors concerned in the production of motion sickness. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix A.
39. BETHELL, M. F.: Prevention of seasickness with hyoscine, benadryl and phenergan. Lancet, 2: 888, 1951.
40. BIRREN, J. E., FISHER, M. B. AND STORMONT, R. T.: Evaluation of a motion sickness questionnaire in predicting susceptibility to seasickness. U. S. Nav. Med. Bull., 45: 629–634, 1945.
41. BIRREN, J. E., STORMONT, R. T. AND PFEIFFER, C. C.: An evaluation of the potentiality of bulbocapnine as a motion sickness preventive. Nav. Med. Res. Inst., Project X278, Rep. No. 3, Aug. 16, 1944.
42. BIRREN, J. E., STORMONT, R. T. AND PFEIFFER, C. C.: Nav. Med. Res. Inst., Project X278, Rep. No. 4, Feb. 26, 1945.
43. BJERVER, K. AND GOLDBERG, L.: Central effects of antihistamine compounds and their use in motion sickness. Acta physiol. scandinav., 25: Suppl. 89, 10–11, 1951.
44. BLACKHAM, R. J.: Sea-sickness. Brit. Med. J., 2: 163–167, 1939.
45. BO, M. D. AND LIVAN, M.: Sulla innervazione vegetativa della macula utriculi umana. Arch. ital. otol., 63: 456–462, 1952.
46. BOCK, E.: Personal communication to Goethe and Köbke (154).
47. BOENNINGHAUS, H. G.: Die Beeinflussung des experimentell ausgelösten Nystagmus und Schwindels durch Vomex A. Ztschr. Laryng. Rhin. Otol., 31: 558–564, 1953.
48. BOHEC, J.: Sur un nouveau traitement du mal de mer par les alcaloides totaux de la belladone et leur association avec la phényl-éthyl-malonylurée. Presse méd., 38: 21–22, 1930.
49. BOLAND, J. D. AND GRINSTAD, A. D.: Comparison of scopolamine hydrobromide and dramamine in the treatment and prevention of airsickness. J. Aviation Med., 22: 137–145, 1951.
50. BOND, D. D.: Psychiatric analysis of forty subjects made sick by a swing. USAF Sch. Aviat. Med., Project No. 149(1), July 31, 1943.
51. BOOTHBY, W. M., MAYO, C. W. AND LOVELACE, W. R., II.: One hundred per cent oxygen. Indications for its use and methods of its administration. J.A.M.A., 113: 477–482, 1939.
52. BORISON, H. L. AND WANG, S. C.: Physiology and pharmacology of vomiting. Pharmacol. Rev., 5: 193–230, 1953.
53. BORISON, H. L. AND WANG, S. C.: Locus of the central emetic action of cardiac glycosides. Proc. Soc. Exper. Biol. & Med., 76: 335–338, 1951.
54. BOYD, E. M. AND BOYD, C. E.: Antihistamines and apomorphine-induced vomiting. Canad. J. Med. Sc., 31: 320–325, 1953.
55. BOYD, E. M., CASSELL, W. A. AND BOYD, C. E.: Prevention of apomorphine-induced vomiting by (dimethylamino-1-n-propyl-3)-N-(2-chloro) phenothiasine hydrochloride. Fed. Proc., 12: 303, 1953.
56. BRAND, E. D., HARRIS, T. D., BORISON, H. L. AND GOODMAN, L. S.: The antiemetic activity of 10-(α-dimethylaminopropyl)-2-chlorophenothiasine (chlorpromasine) in dog and cat. J. Pharmacol. & Exper. Therap., 110: 86–92, 1954.
57. BREUER, J.: Über die Funktion der Bogengänge des Ohrlabyrinths. Med. Jahrbücher Wien, 4: 72–124, 1874.
58. BREUER, J.: Beiträge zur Lehre vom statischen Sinne. (Gleichgewichtsorgan, Vestibularapparat des Ohrlabyrinths.) Med. Jahrb. d. k. k. österr. Staates, Wien, 5: 86–156, 1875.
59. BREYER, H.: Vorteile von Peremesin bei der Behandlung der Seekrankheit. Therap. Gegenw., 80: 46, 1939.
60. BROOKS, M.: Seasickness. U. S. Nav. Med. Bull., 37: 469–480, 1939.
61. BROWN, A. C.: On the sense of rotation and the anatomy and physiology of the semicircular canals of the internal ear. J. Anat. and Physiol., 8: 327–331, 1874.
62. BROWN, G. L., MCARDLE, B. AND MAGLADERY, J. W.: Interim report on clinical investigations with airsickness. Brit. Flying Personnel Res. Comm., Rep. No. 410 (a), Jan. 1941.
63. BROWN, R. B., BRETT, J. R. AND HOWLETT, J. G.: Swing sickness and a history of motion sickness in relation to airsickness. Ass. Comm. Aviat. Med. Res., N. R. C. Canada, Rep. No. C2504, May 18, 1943, Appendix A.
64. BROWN, T. G.: Die Atembewegungen des Frosches und ihre Beeinflussung durch die nervösen Zentren und durch das Labyrinth. Arch. ges. Physiol., 130: 193–218, 1909.
65. BRUNS, O.: Untersuchungen über die der Seekrankheit zugrunde liegenden Störungen und über die Therapie dieses Zustandes. Med. Klin., 10: 1093–1095, 1914.

66. Bruns, O.: Wesen und Bekämpfung der See- und Luftkrankheit. München. med. Wchnschr., 73: 977–979, 1926
67. Budnitz, J.: The use of benadryl in Parkinson's disease. A preliminary report of 8 cases. New England J. Med. 238: 874–875, 1948.
68. Burn, J. H.: Pharmacological action of antihistamine compounds. Brit. Med. J., 2: 691–693, 1950.
69. Byrne, J.: On the physiology of the semicircular canals and their relation to seasickness. J. T. Dougherty, New York 1912.
70. Camiscasca, L. and Vecchiati, R.: Sul meccanismo di asione di alcuini moderni medicamenti antinausea. Oto-rino-laring. ital., 19: 364–372, 1951.
71. Campbell, E. H.: The effectiveness of dramamine in relieving the vestibular reactions following the labyrinthine fenestration operation. Laryngoscope, 59: 1261–1272, 1949.
72. Chen, G. and Ensor, C. R.: The influence of diphenhydramine HCl (Benadryl) on apomorphine-induced emesis in dog. J. Pharmacol. & Exper. Therap., 98: 245–250, 1950.
73. Chinn, H. I.: Motion sickness in the military service. Mil. Surgeon, 108: 20–29, 1951.
74. Chinn, H. I.: Unpublished data.
75. Chinn, H. I., Gammon, W. R. and Frantz, M. E.: Prevention of airsickness among airborne troops. J. Appl. Physiol., 5: 599–602, 1953.
76. Chinn, H. I., Handford, S. W., Cone, T. E., Jr. and Smith, P. K.: The effectiveness of various drugs for the prophylaxis of seasickness. Am. J. Med., 12: 433–439, 1952.
77. Chinn, H. I., Handford, S. W., Smith, P. K., Cone, T. E., Jr., Redmond, R. F., Maloney, J. V. and Smythe, C. M.: Evaluation of some drugs in seasickness. J. Pharmacol. & Exper. Therap., 108: 69–79, 1953.
78. Chinn, H. I. and Jenkins, R. T.: Unpublished data.
79. Chinn, H. I., Milch, L. J. and Dugi, A. J.: Comparison of various drugs against airsickness. J. Appl. Physiol., 6: 257–259, 1953.
80. Chinn, H. I., Noell, W. K. and Smith, P. K.: Prophylaxis of motion sickness. Arch. Int. Med., 86: 810–832, 1950.
81. Chinn, H. I. and Oberst, F. W.: Effectiveness of various drugs in prevention of airsickness. Proc. Soc. Exper. Biol. & Med., 73: 218–219, 1950.
82. Chinn, H. I. and Plotnikoff, N. P.: Evaluation of various techniques for screening antimotion sickness drugs. J. Appl. Physiol., 5: 393–394, 1953.
83. Chinn, H. I. and Sheldon, G. I.: Effect of chlorpromazine on emesis after radiation. Proc. Soc. Exper. Biol. & Med., 86: 293–295, 1954.
84. Chinn, H. I. and Sheldon, G. L.: Unpublished data.
85. Chinn, H. I., Strickland, B. A., Oberst, F. W., Wilks, S. S. and Tinkham, M.: Evaluation of some drugs in motion sickness. J. Aviation Med., 21: 424–429, 1950.
86. Chinn, H. I., Strickland, B. A., Jr., Waltrip, O. H. and McGeary, J. D.: Prevention of airsickness during training flights. U.S. Armed Forces Med. J., 4: 1609–1612, 1953.
87. Chinn, H. I., Waltrip, O. H. and Massengale, H. W.: Further studies on the effectiveness of various drugs against airsickness. J. Aviation Med., 22: 535–539, 1951.
88. Chinn, H. I. and Wang, S. C.: Unpublished observations.
89. Christiansen, M.: Sma erfaringer om sjøyge. Ugesk. laeger, 112: 86–87, 1950.
90. Cipriani, A.: Analysis of the forces encountered on the simple swing used in the study of motion sickness. Proc. Comm. Seasickness. N. R. C. Canada, Nov. 27, 1942, Appendix C.
91. Cipriani, A. and McEachern, D.: Proc. Conf. Motion Sickness, N. R. C. Canada, Rep. No. C2246, Nov. 27, 1942.
92. Cipriani, A. and Morton, G.: Studies of blood pressure, electrocardiograms and respiratory tracings in volunteers. Motion sickness. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix I.
93. Cone, T. E., Jr.: Personal communications.
94. Cook, L. and Toner, J. J.: The antiemetic action of chlorpromazine, SKF No. 2601-A (RP-4560). J. Pharmacol. & Exper. Therap., 110: 12, 1954.
95. Corey, E. L. and Webster, A. P.: Effects of scopolamine on marksmanship. Comm. Aviat. Med., N. R. C. Rep. No. 268, Nov. 1, 1943.
96. Corning, J. L.: The nature and treatment of vertigo. J.A.M.A., 36: 722–727, 1901.
97. Corning, J. L.: The suppression of rotary vertigo: its bearing on the prevention and cure of seasickness. New York Med. J., 80: 297–299, 1904.
98. Co Tui and Debruille, C.: The comparative toxicity and effectiveness of scopolamine hydrobromide ($C_{17}H_{21}O_4N \cdot HBr$) and scopolamine aminoxide hydrobromide ($C_{17}H_{21}O_5N \cdot HBr$). Am. J. Pharm., 117: 319–326, 1945.
99. Cotzin, M., Hill, C. J., Jr. and Wendt, G. R.: Studies of motion sickness. IV. The prediction of airsickness and of laboratory motion sickness by means of a personal history questionnaire. OGMCM-534, Final Rep., April 17, 1946.
100. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M. and Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3 (diméthyl amino-3-propyl)-10 phénothiazine (4,560 R.P.). Etude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle. Arch. Internat. pharmacodyn., 92: 305–361, 1953.
101. Dennos, P. H.: Seasickness. J.A.M.A., 86: 319–324, 1926.
102. De Wit, G.: Seasickness (motion sickness), a labyrinthological study. Acta oto-laryng., Suppl., 108: 1–56, 1953.
103. Diamant, H.: Antihistaminpreparat vid rörelsesjuka. Nord. med., 48: 1321–1324, 1952.
104. Donisch, W.: Personal communication to Goethe and Köbke (154).

105. DORCUS, R. M.: Influence of physiologically effective doses of epinephrine on vestibularly induced nausea Civ. Aero. Ass., Rep. No. 5, 1942.
106. DUBOIS, R.: Sur le mal de mer. Compt. rend. Soc. biol., 90: 407–408, 1924.
107. DUCROT, R. AND DUCROT, P.: Étude comparative de l'action anti-émétique de quelques antihistaminiques de synthèse. Compt. rend. Soc. biol., 145: 356–368, 1951.
108. ENGQUIST, S.: Ett nytt svenskt sjöskjukemedel. Svenska Läkartidn., 47: 1464–1467, 1950.
109. EPPINGER, H. AND HESS, L.: Vagotonia. A clinical study in vegetative neurology. Translated by Kraus, W. M. and Lellitte, S. E. Nervous and Mental Disease Publishing Co., New York 1917.
110. EVRARD, E.: Une nouvelle épreuve de déséquilibration provoquée. Application á la sélection des aviateurs et aux recherches sur le mal de l'air. Méd. aéro., 7: 399–410, 1952.
111. EVRARD, E.: Prévention et traitement du mal de l'air par un nouvel antihistaminique; premiers résultats expérimentaux. Bruxelles méd., 33: 173–184, 1953.
112. FEINBERG, S. M., MALKIEL, S. AND FEINBERG, A. R.: The antihistamines—their clinical application. Year Book Publishers, Chicago 1950.
113. FERMIN, H., DEINSE, J. B. VAN AND HAMMELBURG, E.: De werking van dimenhydrinaat op het labyrinth. Nederl. tijdschr. geneesk., 94: 3036–3041, 1950.
114. FERMIN, H., DEINSE, J. B. VAN AND HAMMELBURG, E.: The effect of dimenhydrinate upon the labyrinth. (An experimental study.) Acta oto-laryng., 38: 543–549, 1950.
115. FIELDS, W. S.: Induced motion sickness in naval ratings. Proc. Conf. Motion Sickness, N. R. C., Aug. 28, 1942, Appendix D.
116. FIELDS, W. S.: Therapeutic trials with barbiturates and vasano compounds. Proc. Conf. Motion Sickness. N. R. C. Canada, June 16, 1943, Appendix K.
117. FIELDS, W. S.: Further therapeutic trials with belladonna alkaloids. Proc. Conf. Motion Sickness. N. R. C. Canada, 1943, Appendix L.
118. FIELDS, W. S.: Proc. 6th Meet. Subcomm. Seasickness, N. R. C. Canada, Rep. No. C 4032, 1943.
119. FIELDS, W. S., CAMPBELL, B. A. AND PENFIELD, W.: Clinical drug trials, V-1, drug X, Vasano (second report). Proc. Comm. Seasickness, N. R. C. Canada, Nov. 27, 1942, Appendix E.
120. FIELDS, W. S., MEAKINS, J. C. AND MCEACHERN, D.: Blood chemistry studies in motion sickness. Proc. Conf. Motion Sickness, N. R. C., Proj. NM2, Aug. 28, 1942, Appendix E.
121. FIELDS, W. J. AND PENFIELD, W.: Preliminary therapeutic experiments. Motion Sickness. Proc. Conf. Motion Sickness, 1942, Appendix F.
122. FISHER, L.: Seasickness and internal ear stimulation. New York Med. J., 106: 542–546, 1917.
123. FISCHER, M. H.: Experimentelle Untersuchungen über Nausea und ihre pharmakologische Bekämpfung. Ztschr. ges. exper. Med., 61: 608–626, 1928.
124. FISCHER, M. H.: Die Seekrankheit. Handbuch der normalen und pathologischen Physiologie, 15: part 1, 495–516. Springer, Berlin 1930.
125. FISCHER, M. H. AND WODAK, E.: Zur Verminderung (Verhütung) der Nausea bei Vestibularisreizung. München. med. Wchnschr., 69: 400, 1922.
126. FLACK, M.: Note on sea-sickness. Brit. Med. J., 1: 176–177, 1931.
127. FLACK, M.: Airsickness and seasickness. Proc. Roy. Soc. Med., 24: 635–641, 1931. (United Service Section 13–19).
128. FLAHERTY, T. T.: Airsickness during acrobatics. U.S. Nav. Med. Bull., 40: 902–906, 1942.
129. FLEISCH, A.: Das Labyrinth als beschleunigungsempfindendes Organ. Arch. ges. Physiol., 195: 499–515, 1922.
130. FLOURENS, P.: Expériences sur les canaux sémicirculaires de l'oreille. Paris 1828.
131. FONSSAGRIVES, J. B.: Traité d'hygiène navale ou de l'influence des conditions physiques et morales dans lesquelles l'homme de mer est appelé á vivre et des moyens de conserver sa santé. J. B. Baillière, Paris 1856.
132. FOUCAR, F. H., GORDON, B. J. AND KAYE, S.: Fatal poisoning from motion sickness preventive (containing amytal, barbital preparation). J.A.M.A., 131: 971–972, 1946.
133. FRASER, A. M.: Ass. Comm. Aviat. Med. Res., N. R. C. Canada, Rep. No. C 2644, Oct. 10, 1944.
134. FRASER, A. M. AND MANNING, G. W.: Effect of variation in swing radius and arc on incidence of swing sickness. J. Appl. Physiol., 2: 580–584, 1950.
135. FREEDMAN, A. M. AND HIMWICH, H. E.: DFP: Site of injection and variation in response. Am. J. Physiol., 156: 125–128, 1949.
136. FREESE, H. B., BIANCHI, R. G. AND HAMBOURGER, W. E.: Morphine—induced emesis in dogs treated with β-dimethylaminoethylbenzohydrylether-8-chlorotheophyllinate (dramamine). Fed. Proc. 9: 274, 1950.
137. GAIR, D. S. AND DUCEY, J.: Chemical structure of substances effective in treatment of Parkinsonism. Arch. Int. Med., 85: 284–298, 1950.
138. GAY, L. N.: Prophylactic and therapeutic control of vestibular disturbances with dimenhydrinate. J.A.M.A., 145: 712–715, 1951.
139. GAY, L. N : A subsequent report on dramamine. The prophylactic and therapeutic control of motion sickness and vestibular disturbances. Mil. Surgeon, 108: 324–331, 1951.
140. GAY, L. N. AND CARLINER, P. E.: The prevention and treatment of motion sickness. I. Seasickness. Bull. Johns Hopkins Hosp., 84: 470–487, 1949.
141. GAY, L. N. AND CARLINER, P. E.: The prevention and treatment of motion sickness. I. Seasickness. Science, 109: 359, 1949.
142. GELLER, W.: Die Seekrankheit und ihre Behandlung. Klin. Wchnschr., 19: 1310–1313, 1940.
143. GENÉE, R. W.: Die Bekämpfung der Seekrankheit durch ständige passive Hyperämie des Gehirns. München. med. Wchnschr., 71: 166–167, 1924.
144. GERNANDT, B. E. AND SCHMITERLÖW, C. G.: Some observations concerning the mode of action of the antihist-

aminic drug "Lergigan" (N-(α-methyl-β-dimethyl aminoethyl)phenothiazine hydrochloride) in motion sickness. Brit. J. Pharmacol., 8: 181–186, 1953.
145. Gibson, W. C., Manning, G. W. and Cohen, E.: Value of a simple swing in acclimatization to airsickness. Proc. Ass. Comm. Aviat. Med., Rep. 25, Feb. 1944, Appendix G.
146. Gibson, W. C., Manning, G. W. and Kirkpatrick, B.: Effect of active vestibular training on motion sickness. Proc. Conf. Motion Sickness. N. R. C. Canada, June 16, 1943, Appendix I.
147. Glaser, E. M.: Experiments on the side effects of drugs. Brit. J. Pharmacol. 8: 187–192, 1953.
148. Glaser, E. M. and Hervey, G. R.: The prevention of seasickness with hyoscine (scopolamine), benadryl and phenergan. Lancet, 2: 749–753, 1951.
149. Glaser, E. M. and Hervey, G. R.: Further experiments on the prevention of motion sickness. Lancet, 1: 490–492, 1952.
150. Glaviano, V. V. and Wang, S. C.: Dual mechanism of anti-emetic action of chlorpromazine. Fed. Proc., 13: 358, 1954.
151. Gley, P. and Delor, J.: Action de la bromnautine sur les réflexes labyrinthiques et pathogénie du mal de mer. Compt. rend. Soc. biol., 146: 530–531, 1952.
152. Goehring, H. D. and Schwab, R. S.: The use of the swing, the injection of prostigmine and caloric stimulation of the labyrinth in the estimation of susceptibility to chronic seasickness. U.S. Nav. Hosp., Chelsea, Mass., Rep. Oct. 1943.
153. Goethe, H.: Experimentelle und klinische Nausea - Therapie mit β-Dimethyläthylaminobenzhydryläther-1,3-dimethyl-8-chlorxanthin (Vomex A). Medisinische, 1953: 720–721.
154. Goethe, H. and Köbke, P.: Die Therapie der Seekrankheit. Ztschr. Tropenmed. Parasitol., 4: 265–281, 1953.
155. Goltz, F.: Ueber die physiologische Bedeutung der Bogengänge des Ohrlabyrinths. Arch. ges. Physiol., 3: 172–192, 1870.
156. Goodman, L. and Gilman, A.: The pharmacological basis of therapeutics. Macmillan Co., New York 1941.
157. Green, D. M.: Airsickness in bomber crews. J. Aviation Med., 14: 366–372, 1943.
158. Green, D. M., Bridges, W. C., Johnson, A. D., Lehmann, J. H., Gray, F. and Field, L.: Xanthine studies: 1) effects of aminophyllin, 1,3 diethyl 8 bromoxanthine and 1,3 dimethyl 8 chloroxanthine on cardiac output. Fed. Proc., 8: 296, 1949.
159. Greenberg, R. J.: Incidence of airsickness in AAF training and combat. A medical evaluation program. AAF AS M 43, Sch. Aviat. Med., Project 467, Rep. No. 3, 1945.
160. Gulli, O.: Reisesyke og dens behandling. Tidsskr. norske laegefor., 71: 762–764, 1951.
161. Gutner, L. B., Gould, W. J. and Batterman, R. C.: Action of dimenhydrinate (Dramamine) and other drugs on vestibular function. Arch. Otolaryng., 53: 308–315, 1951.
162. Guttich, A.: Beitrag zur Physiologie des Vestibularapparates. Beitr. Anat. etc. Ohr., 7: 1–18, 1913.
163. Hallpike, C. S. and Fitzgerald, G. M.: Pathology of airsickness. Brit. Flying Personnel Res. Comm., Rep. No. 334, 1941.
164. Halpern, B. N.: Recherches sur une nouvelle série chimique de corps doués de propriétés anti-histaminiques et anti-anaphylactiques: les dérivés de la thiodiphénylamine. Arch. internat. pharmacodyn., 74: 314–333, 1947.
165. Hamilton, H.: Sodium amytal—its value in seasickness. California & West. Med., 36: 317–318, 1932.
166. Handford, S. W., Cone, T. E., Jr., Chinn, H. I. and Smith, P. K.: Drugs preventing motion sickness at sea. J. Pharmacol. & Exper. Therap., 111: 447–453, 1954.
167. Handford, S. W., Cone, T. E., Jr. and Gover, S. C.: A ship's motion and the incidence of seasickness. Mil. Surgeon 113: 157–167, 1953.
168. Harper, J.: Prevention and treatment of travel sickness with promethazine chlorotheophyllinate. Lancet, 1: 1141–1143, 1951.
169. Hasegawa, T.: Prevention of motion sickness by intravenous injection of sodium bicarbonate. Arch. Otolaryng., 50: 708–715, 1949.
170. Hasegawa, T.: Prevention of motion sickness by intravenous injection of sodium bicarbonate. Jap. Med. J., 431–438, 1949.
171. Hemingway, A.: Results on 500 swing tests for investigating motion sickness. AAF Sch. Aviat. Med., Project 31, Res. Rep. No. 2, Nov. 5, 1942.
172. Hemingway, A.: Cold sweating in motion sickness. Am. J. Physiol., 141: 172–175, 1944.
173. Hemingway, A.: Cardiovascular changes in motion sickness. J. Aviation Med., 16: 417–420, 1945.
174. Hemingway, A.: Review: Survey of research on the problem of airsickness in the Army Air Forces. AAF Sch. Aviat. Med., Project 381, Res. Rep. No. 1, April 20, 1945.
175. Hemingway, A.: Environmental temperature and swing sickness. J. Aviation Med., 17: 86–88, 1946.
176. Hemingway, A.: Selection of men for aeronautical training based on susceptibility to motion sickness. J. Aviation Med., 17: 153–163, 1946.
177. Hemingway, A. and Green, E. L.: Airsickness during early flying training. J. Aviation Med., 16: 409–416, 1945.
178. Herrmann, E.: Über die Behandlung des Erbrechens mit Peremesin. Pharm. Zentralhalle, 76: 456–457, 1935.
179. Hertz, F. and Riskaer, H.: Effects of antihistamines on vestibular function in guinea-pigs. With description of a new apparatus for recording head deviation during rotation test. Acta pharmacol. et toxicol., 9: 109–116, 1953.
180. Hess, W. R.: Vegetative Funktionen und Zwischenhirn. Helvet. physiol. et pharmacol. acta, Suppl. 4, 1947.
181. Heuilly, F.: Emploi d'un antihistaminique de synthèse (antistine) comme préventif du mal des transports. Soc. Méd. Nancy, June 15, 1950.

183. HILL, I. G. W. AND GUEST, A. I.: Prevention of seasickness in assault craft. A report of experiments under tropical conditions. Brit. Med. J. 2: 6–11, 1945.
183. HILL, J.: The care of the sea-sick. Brit. Med. J., 2: 803–807, 1936.
184. HILL, J.: Benzedrine in sea-sickness. Brit. Med. J., 2: 1109–1112, 1937.
185. HILL, J.: The treatment of sea-sickness. Practitioner, 138: 297–306, 1937.
186. HOLLING, H. E.: Travel sickness. Pharm. J., 112: 130–140, 1951.
187. HOLLING, H. E., MCARDLE, B. AND TROTTER, W. R.: Prevention of seasickness by drugs. Lancet, 1: 127–129, 1944.
188. HOUGHTON, E.: "Dramamine" and seasickness. Brit. Med. J., 2: 947, 1950.
189. HOWLETT, J. G.: A method of investigating the usefulness of drugs in airsickness and its application in two experiments. Med. Selection Board, No. 6, Dec. 3, 1942.
190. HOWLETT, J. G. AND BRETT, J. R.: Proc. Conf. Motion Sickness. N. R. C. Canada, Aug. 28, 1942, Appendix R.
191. HOWLETT, J. G., WARDILL, T. E. M. AND BRETT, J. R.: The effect of position on the incidence of swing sickness. Proc. Conf. Motion Sickness, N. R. C. Canada, Rep. No. C 2507, June 16, 1943.
192. INGELFINGER, F. J. AND MOES, R. E.: The activity of the descending duodenum during nausea. Am. J. Physiol., 136: 561–566, 1942.
193. IRWIN, J. A.: The pathology of seasickness. Lancet, 2: 907–909, 1881.
194. JAQUENOUD, P. AND MERCIER, Y.: L'effet anti-émétique des anti-histaminiques. Anesth. et analg., 9: 493–509, 1952.
195. JAMES, W.: The sense of dizziness in deaf mutes. Am. J. Otol., 4: 239–254, 1882.
196. JASPER, H. H. AND MORTON, G.: Electroencephalography in relation to motion sickness in volunteers. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix J.
197. JOKES, A. M.: Correlation of swing with airsickness in air gunners with addendum on adaptation tests. Brit. Flying Personnel Res. Comm., Rep. No. 475, July 1942.
198. JOHNS, R. J. AND HIMWICH, H. E.: A central action of some antihistamines. Correction of forced circling movements and of seizure brain waves produced by the intracarotid injection of diisopropylfluorophosphate (DFP). Am. J. Psychiat., 107: 367–372, 1950.
199. JOHNSON, W. H.: N. R. C. Canada, Progr. Rep. N. M. 20, 1946.
200. JOHNSON, W. H. AND MAYNE, J. W.: Stimulus required to produce motion sickness. Restriction of head movements as a preventive of airsickness. Field studies on airborne troops. J. Aviation Med., 24: 400–411, 1953.
201. JOHNSON, W. H., STUBBS, R. A., KELK, G. F. AND FRANKS, W. R.: Stimulus required to produce motion sickness. 1. Preliminary report dealing with importance of head movement. J. Aviation Med., 22: 365–374, 1951.
202. JOHOW, H.: Hilfsbuch für den Schiffbau. Springer, Berlin 1910, p. 437.
203. KEEVIL, J. J.: Benzedrin in seasickness. J. Roy. Nav. Med. Serv., 74: 219–222, 1938.
204. KEIL, F. C.: The effect of oral doses of hyoscine (scopolamine) on visual efficiency. AAF Sch. Aviat. Med., Res. Rep. 157 (1), June 2, 1943.
205. KERAUDREN, A., cited by Irwin, J. A.: The literature of sea-sickness. Med. Record, 43: 617–619, 1893.
206. KERR, W. AND FRANKS, W. R.: 1942; cited by Johnson *et al.* (201).
207. KIRKNER, F. J.: Psychophysiological studies of motion sickness and airsickness. J. Comp. & Physiol. Psychol., 42: 273–285, 1949.
208. KLEYN, A. DE AND VERSTEEGH, C.: Labyrinthreflexe nach Abschleuderung der Otolithenmembranen bei Meerschweinchen. Arch. ges. Physiol., 232: 454–465, 1933.
209. KNOEFEL, P. K.: Stimulation and depression of the central nervous system by derivatives of barbituric and thiobarbituric acids. J. Pharmacol. & Exper. Therap., 84: 26–33, 1945.
210. KREIDL, A., cited by Fischer (124).
211. KREIDL, A.: Beiträge zur Physiologie des Ohrlabyrinths auf Grund von Versuchen an Taubstummen. Arch. ges. Physiol., 51: 119–150, 1892.
212. KREIDL, A.: Verhandl. Ges. d. Deutschen Naturforscher u. Ärzte. Kassel 1903, cited by Quix (314).
213. LANGE, J.: Peremesin, ein giftfreies Mittel gegen Erbrechen (besonders Schwangerschaftserbrechen, See-, Luft-, Eisenbahnkrankheit, etc.). München. med. Wchnschr., 80: 1327–1328, 1933.
214. LANGE, J.: 10 Jahre kolloides Cer-oxalat (Peremesin). München. med. Wchnschr., 90: 749, 1943.
215. LARSEN, V.: Bidrag til β-disetylaminoacetylbenzhydrylaethers (Rigidyl) farmakologi. Ugesk. laeger, 112: 750–753, 1950.
216. LECLERC, H.: Emploi du chardon marie comme préventif de la naupathie. Presse méd., 46: 1220, 1938.
217. LEDERER, L. G.: Conf. Motion Sickness, Nat. Acad. Sci., Rep. Sept. 9, 1950.
218. LEMON, A. E.: Treatment of seasickness. J.A.M.A., 73: 104, 1919.
219. LEVEN, G. AND LEVEN, R.: Le mal de mer et son traitement. Presse méd., 40: 237–238, 1932.
220. LEVY, T.: Observations on air sickness. Mil. Surgeon, 93: 147–151, 1943.
221. LILIENTHAL, J. L.: Nav. Sch. Aviat. Med., N. A. T. B., Pensacola, Fla., Project X-252, Rep. No. 1, May 1944.
222. LILIENTHAL, J. L.: The effect of hyoscine on airsickness. J. Aviation Med., 16: 59–68, 1945.
223. LINDSLEY, D. B. AND WENDT, G. R.: Investigation into the relationships of the electroencephalogram to motion sickness susceptibility. Div. Anthrop. and Psychol., N. R. C., Dec. 1944, Appendix B.
224. LITTAUER, D. I.: Min. 6th Meet., N. R. C., Subcomm. Motion Sickness, p. 69, 1943.
225. LITTAUER, D. I. AND BRUGER, M. H.: Hq. Airborne Comm., Rep. to Office Surgeon General, March 1, 1944.
226. LIVINGSTON, P. C.: Apparatus for investigating visual reactions in relation to airsickness. Brit. Flying Personnel Res., Rep. No. 463, May 1942.
227. LOZANO DE LAMO, E.: Tratamiento antihistamin del mareo. Medicina Clinica, 16: 276–278, 1951.

228. Luykx, H. M. C.: Motion sickness preventives. Comm. Aviat. Med., N.R.C., Rep. No. 306, April, 1944.
229. McDonough, F. E.: Comm. Aviat. Med., N.R.C., Rep. No. 102, Nov. 1942.
230. McDonough, F. E.: Comm. Aviat. Med., N.R.C., Rep. No. 181, July 1943.
231. McDonough, F. E.: Roentgenographic studies of gastrointestinal motility observed in swing test subjects. USAF Sch. Aviat. Med., Rep. No. 102 (2), July 15, 1943.
232. McDonough, F. E. and Schneider, M.: The effect of motion on the roentgenographic appearance of the stomach and small bowel. Gastroenterology, 2: 32–45, 1944.
233. McDonough, F. E. and Thorner, M. W.: Regulation Barany and swing tests in navigation cadets. AAF Sch. Aviat. Med., Project 100, Res. Rep. No. 1, Dec. 23, 1942.
234. McEachern, D. and Lehmann, P.: Comm. Motion Sickness, Summary of Rep., Sept. 9, 1942.
235. McEachern, D., Morton, G. and Lehman, P.: Seasickness and other forms of motion sickness. I. A general review of the literature. War Med., 2: 410–428, 1942.
236. Mach, E.: Physikalische Versuche über den Gleichgewichtssinn des Menschen. Sitzungsber. K. Wien. Akad. Wiss., Abt. III, 68: 124, 1873.
237. McIntosh: Personal communication to McEachern *et al.* (235).
238. McIntyre, A. K., cited by Tyler and Bard (357).
239. McIntyre, A. K.: Austral. Flying Personnel Res. Rep. F. R. 10, cited by Johnson *et al.* (201).
240. McIntyre, A. K.: Notes on airsickness. Brit. Flying Personnel Res. Comm., Rep. No. 358i, Nov. 1943.
241. McIntyre, A. K. and Gardiner, I. D. R.: Effect of antimalarial drugs on susceptibility to motion. R.A.A.F. Personnel Res. Comm., Rep. No. 73, 1943.
242. MacKay, E. M.: Personal communication.
243. MacKay, E. M.: Stanford Med. Bull., in press.
244. MacKay, R. A. and Ferguson, J. K. W.: Influence of certain anti-motion-sickness drugs on psychomotor and mental performance. J. Aviation Med., 22: 194–195, 1951.
245. McLaughlin, F. L.: Nembutal in seasickness. Canad. Med. A. J., 32: 544–545, 1935.
246. McLean, R. A., Fendrick, A. J., Macko, E. and Fellows, E. J.: Studies on N-phenoxyisopropyl-N-benzyl-beta-chloroethylamine, an orally effective adrenergic blocking agent. J. Pharmacol. & Exper. Therap., 101: 26–27, 1951.
247. McNally, W. J. and Stuart, E. A.: Physiology of the labyrinth reviewed in relation to seasickness and other forms of motion sickness. War Med., 2: 683–771, 1942.
248. McNally, W. J., Stuart, E. A. and Morton, G.: Proc. Conf. Motion Sickness. N.R.C. Canada, Rep. No. C 748, Aug. 28, 1942.
249. MacPhee, H. M. and Pennington, L. A.: The identification of cases of chronic motion sickness during military screening examinations. J. Social Psychol., 23: 61–64, 1946.
250. Magladery, J. W.: Brit. Mil. Personnel Comm., Rep. No. 330, 1944.
251. Magladery, J. W.: Interim report of investigations into airsickness in gliders. Brit. Mil. Personnel Comm., Rep. No. 56, 1942.
252. Magnus, R.: Körperstellung; experimentell physiologische Untersuchungen über die einzelnen bei der Körperstellung in Tätigkeit tretenden Reflexe, über ihr Zusammenwirken und ihre Störungen. Springer, Berlin 1924.
253. Maitland, T. G.: Seasickness. Practitioner, 129: 251–266, 1932.
254. Maitland, T. G.: Heath cruises and prophylaxis in sea-sickness. Practitioner, 133: 146–155, 1934.
255. Manning, G. W.: Choline esterase activity in relation to airsickness. Ass. Comm. Aviat. Med. Res., N.R.C. Canada, Rep. No. C 2513, May 1943.
256. Manning, G. W.: N.R.C., Canada, Rep. No. C2649, 1943.
257. Manning, G. W.: Acclimatisation to swing sickness. Proc. Ass. Comm. Aviat. Med. Res., Feb. 25, 1944, Appendix F.
258. Manning, G. W. and Stewart, W. G.: Ass. Comm. Aviat. Med. Res., N.R.C., Canada, Rep. No. C 2426, Dec. 1942.
259. Manning, G. W. and Stewart, W. G.: Ass. Comm. Aviat. Med. Res., N.R.C., Canada, Rep. No. C 2510, June 1943.
260. Manning, G. W. and Stewart, W. G.: Proc. Conf. Motion Sickness. N.R.C., Canada, Rep. No. C 2511, June 16, 1943.
261. Manning, G. W. and Stewart, W. G.: Effect of body position on incidence of motion sickness. J. Appl. Physiol., 1: 619–628, 1949.
262. Marrack, J. R.: Ketosis in sea-sickness. Brit. Med. J., 1: 178–179, 1931.
263. Mason, M. M.: Dramamine and the vestibular apparatus in dogs. Am. J. Vet. Res., 13: 549–554, 1952.
264. Maycock, R. and Morant, G. M.: Trials of dramamine as a preventive for airsickness. Brit. Flying Personnel Res. Comm., Memo 20, Feb. 1951.
265. Mayou, B.: Visual problems in connection with airsickness. Brit. Flying Personnel Res. Comm., Rep. No. 464, 1942.
266. Ménière, P.: Maladies de l'oreille interne offrant les symptômes de la congestion cérébrale apoplectiforme. Gas. méd. Paris, 16 (3me sér.): 88–89, 1861.
267. Merrell, M.: Analysis of Dr. David B. Tyler's experiments in motion sickness remedies by individual boats. Comm. Aviat. Med., N.R.C., Rep. No. 408, 1945.
268. Minor, J. L.: Freedom of deaf-mutes from sea-sickness: Its bearing upon the theory of sea-sickness and its treatment. Memphis J. Med. Sc., 1: 252–254, 1889.
269. Minor, J. L.: Seasickness: its cause and relief. New York Med. J., 64: 522–523, 1896.

270. MITCHELL, L.: Dimenhydrinate vs. diphenhydramine. Science, 112: 154, 1950.
271. MONNIER, M. AND LAUE, H.: Technik der Elektronystagmographie zur Analyse des vestibulären Drehnystagmus beim Tier. (Pharmakologische Prüfung der Wirksamkeit von Antihistaminica-Chlortheophyllin-Verbindungen.) Arch. exper. Path. u. Pharmakol., 217: 82-90, 1953.
272. MORALES, M. F.: Motion sickness: Physical considerations regarding its etiology. In: Human factors in undersea warfare. N.R.C., Washington, D. C., 1949, pp. 399-414.
273. MORREN, H., TROLIN, S., DENAYER, R., GRIVSKY, E. AND MARICQ, J.: Nouvelles substances antihistaminiques à action prolongée: les 1-4 heurs (aralcoyl) pipérazines. Bull. Soc. Chim. Belg., 60: 282-295, 1951.
274. MORTON, G.: Susceptibility of animals to induced motion sickness. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix K-1.
275. MORTON, G., CIPRIANI, A. AND MCEACHERN, D.: Mechanism of motion sickness. Arch. Neurol. & Psychiat., 57: 58-70, 1947.
276. MORTON, G. AND MCEACHERN, D.: Experimental studies on the susceptible individual. Motion sickness. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix O.
277. MORTON, G., MCNALLY, W. J. AND STUART, E. A.: Caloric vestibular tests in relation to susceptibility to motion sickness. Proc. Conf. Motion Sickness, Aug. 28, 1942, Appendix H.
278. MOSER, C. E., HARRISSON, J. W. E., AMBERS, J. L. AND LEONARD, C. A.: A note on the effect of antihistamine drugs on experimental vomiting. J. Am. Pharm. A. (Scient. Ed.), 40: 115, 1950.
279. MOXEY, V.: The treatment of sea-sickness. Brit. Med. J., 2: 1040-1041, 1924.
280. NICKERSON, M.: Dramamine. Science, 111: 312-313, 1950.
281. NOBLE, R. L.: Motion sickness. Rep. Ass. Comm. Army Med. Res., Oct. 17, 1944.
282. NOBLE, R. L.: Methods of assaying motion sickness preventives on dogs. Canad. J. Res., Sect. E, 24: 226-234, 1945.
283. NOBLE, R. L.: Observations on various types of motion causing vomiting in animals. Canad. J. Res., Sect. E, 23: 212-225, 1945.
284. NOBLE, R. L.: Treatment of experimental motion sickness in humans. Canad. J. Res., Sect. E, 23: 10-20, 1946.
285. NOBLE, R. L.: The effect of barbiturates and other substances on motion sickness in dogs. Canad. J. Res., Sect. E, 26: 283-294, 1948.
286. NOBLE, R. L.: Motion sickness: With special reference to airsickness. Practitioner, 160: 453-458, 1948.
287. NOBLE, R. L., SELLERS, E. A. AND BEST, C. H.: The treatment of motion sickness (a review of therapeutic studies sponsored by the National Research Council of Canada). Canad. Med. A. J., 56: 417-424, 1947.
288. NOELL, W. K., CHINN, H. I. AND HABERER, C. E.: Unpublished data.
288A. ORIEL, G. H.: The treatment of sea-sickness. Lancet, 2: 1146-1147, 1927.
289. P'AN, S. W.: Personal communication.
290. PALASNE DE CHAMPEAUX, E. P.: Contribution à l'étude des symptômes, du diagnostic et de la pathogénie de la maladie de Ménière. Quelques réflexions sur les rapports du mal de mer et de la maladie de Ménière. Thèse de Paris, 1881.
291. PALMER, J. M.: "Dramamine" and seasickness. Brit. Med. J., 2: 946-947, 1950.
292. PARK, J.: Airsickness in gliders. Brit. Flying Personnel Res. Comm., Rep. No. 510, 1943.
293. PARKER, J. M.: Motion sickness studies at H.M.C.S. York. 4th Meet. Comm. Nav. Med. Res., Ottawa, Feb. 16, 1945, Appendix O.
294. PARKER, J. M. AND FIELDS, W. S.: Proc. 3rd Meet. Ass. Comm. Nav. Med. Res., N.R.C. Canada, Rep. No. C 4069, 1944.
295. PARKER, J. M., FIELDS, W. S. AND SELLERS, E. A.: Therapeutic trial conducted in Montreal and Toronto. Proc. Conf. Motion Sickness, N.R.C. Canada, Rep. No. C 4036, 1943, Appendix M.
296. PARKER, J. M., FIELDS, W. S., SELLERS, E. A. AND BEST, C. H.: Report on sea trials with RCN experimental seasickness Remedy No. 1. RCN Med. Res. Unit, 1943.
297. PARKER, J. M., SELLERS, E. A. AND STEPHENSON, J. R.: Proc. 2nd Meet. Ass. Comm. Nav. Med. Res., N.R.C. Canada, Rep. No. C 4037, 1943.
298. PAUL, R., cited by Boyd and Boyd (54).
299. PAYNE, R. B. AND HAUTY, G. T.: The effect of motion sickness preventives upon certain perceptual motor components of the pilots' task. USAF Sch. Aviat. Med., Project 21-1601,0004, Rep. No. 3, May 1953.
300. PAYNE, R. B., MOORE, E. W. AND BETHURUM, J. L.: The effect of certain motion sickness preventives upon psychological efficiency. USAF Sch. Aviat. Med., Project 21-32-019, August 1952.
301. PAYNE, R. B., OSIER, D. R. AND TOMLINSON, P. A. S.: The effects of certain motion sickness preventives upon navigator proficiency. USAF Sch. Aviat. Med., Project 21-1601-0004, Rep. No. 1, May 1953.
302. PEARCY, J. F. AND HAYDEN, D. B.: Preliminary report on sodium nitrite therapy in seasickness. J.A.M.A., 90: 1193, 1928.
303. PENFIELD, W. AND WELCH, K.: The supplementary motor area of the cerebral cortex. Arch. Neurol. & Psychiat., 66: 289-317, 1951.
304. PEZZI, G.: La cura del mar di mare attraverso i tempi. Ann. Med. Nav. Roma, 56: 630-638, 1951.
305. POCH, J. M.: Sulfato de magnesio y mal de mer. Día Médico, 13: 798-800, 1941.
306. POLLAK, J.: Ueber den "galvanischen Schwindel" bei Taubstummen und seine Beziehungen zur Funktion des Ohrenlabyrinthes. Arch. ges. Physiol., 54: 188-208, 1893.
307. POPPEN, J. R.: Seasickness. Etiology and treatment. U. S. Naval Med. Bull., 37: 463-469, 1939.
308. POZERSKI, E.: Appareil pour l'étude de l'influence des oscillations rythmiques sur les animaux de laboratoire. Compt. rend. Soc. biol., 85: 702-704, 1921.

309. Pozerski, E.: Sur les troubles produits chez le chien par les oscillations rythmiques. Compt. rend. Soc. biol., 85: 760–770, 1921.
310. Proosdij-Hartsema, E. G. van: Dimenhydrinaat bij misselijkheid als symptoom van enige aandoeningen. Geneesk. tijds., 28: 41–46, 1950.
311. Pumphrey, R. E., Kun, J. R., Johnson, M. A. and Day, A. L.: Unusual conditions aggravated by seasickness. Report of two cases. U. S. Nav. Med. Bull., 46: 742–743, 1946.
312. Purkinje, J. E.: Beiträge zur näheren Kenntnis des Schwindels aus heautognostischen Daten. Med. Jahrb. Wien, VI, 2. St., 79–125, 1820.
313. Quigley, J. P., Bavor, H. J., Read, M. R. and Bropman, B. L.: Evidence that body irritations or emotions retard gastric evacuation, not by producing pylorospasm but by depressing gastric motility. J. Clin. Invest., 22: 839–845, 1943.
314. Quix, F. H.: Le mal de mer et le mal des aviateurs. Monogr. otorhino-laryng. internat., 8: 825–912, 1922.
315. Quix, F. H. and Werndley, L. U. H. C.: Trans. Roy. Neth. Acad. Sc., 1931, cited by DeWit (102).
316. Reynolds, T. T.: On the nature and treatment of seasickness. Lancet, 1: 1161–1163, 1884.
317. Roeing, I.: Personal communication, 1952.
318. Rubin, A. and Metz-Rubin, H.: Effect of dramamine upon post operative nausea and vomiting. Surg., Gynec. & Obst., 92: 415–418, 1951.
319. Rubin, A. and Winston, J.: The role of the vestibular apparatus in the production of nausea and vomiting following the administration of morphine to man. Clinical and experimental data, including the effects of dramamine and bensedrine. J. Clin. Invest., 29: 1261–1266, 1950.
320. Rudat, W.: Die Bewegungskrankheiten—Ätiologie und Therapie. Deutsches Med. J., 3: 345–346, 1952.
321. Rushmer, R. F.: Overventilation in subjects during the swing test. USAF Sch. Aviat. Med., Project No. 133 (1), May 1, 1943.
322. Rushner, R. F.: Hyperventilation in flying personnel. AAF Sch. Aviat. Med., Project No. 162, Res. Rep. No. 1, Sept. 16, 1943.
323. Rust, S. M. and Fosbery, F. W. A.: Prevention of sea-sickness. Brit. Med. J., 2: 98, 1949.
325. Ryan, G. M. S. and Wood, J. S.: Benadryl in the treatment of Parkinsonism: Results in forty cases. Lancet, 1: 258–259, 1949.
326. Santesson, G.: Det nya sjösjukemedlet-β-dimetylamino-etylbenshydryleter-8-klorteofyllinat (Amosyt). Svenska Läkartidn., 46: 2492–2496, 1949.
327. Schallek, W. and Smith, T. H. F.: Electroencephalographic analysis of side effects of spasmolytic drugs J. Pharmacol. & Exper. Therap., 104: 291–298, 1952.
328. Schiff, M., Esmond, W. G. and Himwich, H. E.: Forced circling movements (adversive syndrome) correction with dimenhydrinate (dramamine). Arch. Otolaryng., 51: 672–677, 1950.
329. Schmidt, C. D., Sata, E., Brieger, K. R. and Borison, H. L.: The effects of dimenhydrinate (Dramamine) and diphenhydramine (Benadryl) on apomorphine-induced emesis. J. Pharmacol. & Exper. Therap., 106: 412–413, 1952.
330. Schwab, R. S.: Chronic seasickness: Neurological, psychiatric and naval aspects. U. S. Naval Med. Bull., 40: 923–936, 1942.
331. Schwab, R. S. and Tillman, W. R.: Artane in the treatment of Parkinson's disease. A report of its effectiveness alone and in combination with benadryl and parpanit. New England J. Med., 241: 483–485, 1949.
332. Sellers, E. A., Parker, J. M. and Stephenson, N. R.: Motion sickness experiment. N.R.C. Canada, Nov. 27, 1942, Appendix F.
333. Shaw, C. C.: Dramamine trials in the United States Navy. Mil. Surgeon, 106: 441–449, 1950.
334. Shuster, D. W.: Personal communication.
335. Simon, S. W. and Seyler, L. E.: Dramamine in pilots. J. Aviation Med., 20: 371 and 379, 1949.
336. Sjöberg, A. A.: Experimental studies of the eliciting mechanism of sea-sickness. Preliminary communication. Acta oto-laryng., 13: 343–347, 1929.
337. Sjöberg, A. A.: Experimentelle Studien über den Auslösungsmechanimus der Seekrankheit. Acta oto-laryng., Suppl., 14: 1–136, 1931.
338. Smith, P. K.: Effect of bensedrine on swing sickness. AAF Sch. Aviat. Med., Rep. No. 113 (1), Aug. 9, 1943.
339. Smith, P. K.: Effect of various substances on swing sickness. Proc. Soc. Exper. Biol. & Med., 63: 209–210, 1946.
340. Smith, P. K.: The effectiveness of some motion sickness remedies in preventing air sickness in Air Force navigation students. J. Aviation Med., 17: 343-345, 1946.
341. Smith, P. K.: Use of hyoscine hydrobromide for the prevention of airsickness in flexible gunnery students. J. Aviation Med., 17: 346-347, 1946.
342. Smith, P. K.: Present status of drugs for use in motion sickness with particular reference to airsickness. AAF Sch. Aviat. Med., Project No. 468, June 14, 1946.
343. Smith, P. K.: Treatment of airsickness with drugs. Am. J. Med., 4: 649–652, 1948.
344. Smith, P. K. and Hemingway, A.: Effect of hyoscine (scopolamine) on swing sickness and on performance. AAF Sch. Aviat. Med., Res. Rep. No. 111 (1), 1943.
345. Smith, P. K. and Hemingway, A.: Effect of some atropine-like drugs on swing sickness. Proc. Soc. Exper. Biol. & Med., 63: 206–208, 1946.
346. Spiegel, E. A., Henny, G. C. and Wycis, H. T.: Changes of cerebral circulation induced by labyrinthine stimulation. Am. J. Physiol., 142: 589–593, 1944.
347. Spiegel, E. A., Oppenheimer, M. J., Henny, G. C. and Wycus, H. T.: Experimental production of motion sickness. War Med., 6: 283–290, 1944.

348. Strickland, B. A., Jr. and Hahn, G. L.: The effectiveness of dramamine in the prevention of airsickness. Science, 109: 359–360, 1949.
349. Strickland, B. A., Jr., Hahn, G. L. and Adler, H.: Studies on airsickness. J. Aviation Med., 21: 90–97 and 163, 1950.
350. Thorner, M. W.: Questionnaire analysis of the problem of airsickness as it is met with in stations in the continental U. S. Sch. Aviat. Med., Project 83, Rep. 1, 1942.
351. Thuer, W.: Reisekrankheit, Erfahrungen mit Synopen (Geigy) bei Seekrankheit. Schweiz. med. Wchnschr., 82: 312–315, 1952.
352. Tonndorf, J. R., Hyde, R. W., Chinn, H. I. and Lett, J. E.: Absorption from nasal mucous membrane: systemic effect of hyoscine following intranasal administration. Abstrs. Comm. XIX. Internat. Physiol. Congress, Montreal, 1953, pp. 830–831.
353. Trotter, W. R.: Sea-sickness. Practitioner, 157: 45–49, 1946.
354. Tyler, D. B.: Summary of findings of the studies on motion sickness fatigue, and prolonged wakefulness. OEM cm-282, Comm. Aviat. Med., Rep. No. 505, 1945.
355. Tyler, D. B.: The influence of a placebo, body position and medication on motion sickness. Am. J. Physiol., 146: 458–466, 1946.
356. Tyler, D. B.: Comm. Aviat. Med., N.R.C., Final Rep., 1946.
357. Tyler, D. B.: Effect on marksmanship of some motion sickness preparations containing barbiturates and hyoscine. J. Appl. Physiol., 1: 737–742, 1949.
358. Tyler, D. B. and Bard, P.: Motion sickness. Physiol. Rev., 29: 311–369, 1949.
359. Vernier, V. G. and Unna, K. R.: Effects of anti-Parkinsonian drugs on tremor monkeys. Fed. Proc., 12: 376, 1953.
360. Voll, R.: Heutige Kenntnisse über die Seekrankheit. Diss. Hamburg, 1938, cited by Goethe and Köbke (154).
361. Voss, W.: Beitrag zur Prophylaxe gegen Luftkrankheit. Medizinische, 1: 879–881, 1953.
362. Wang, S. C. and Borison, H. L.: The vomiting center: A critical experimental analysis. Arch. Neurol. & Psychiat., 63: 928–941, 1950.
363. Wang, S. C. and Borison, H. L.: The vomiting center: Its destruction by radon implantation in dog medulla oblongata. Am. J. Physiol., 166: 712–717, 1951.
364. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides. Gastroenterology, 22: 1–12, 1952.
365. Wang, S. C. and Chinn, H. I.: Experimental motion sickness in dogs. Functional importance of chemoceptive emetic trigger zone. Am. J. Physiol., 178: 111–116, 1954.
366. Wang, S. C. and Chinn, H. I.: Unpublished data.
367. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydergine in dogs. Fed. Proc., 12: 378, 1953.
368. Waters, H.: A case of air sickness treated by ultraviolet radiation. Brit. J. Actinotherapy, 5: 173, 1930.
369. Weiss: Über die Behandlung der Seekrankheit mit Sauerstoffinhalationen. München. med. Wchnschr., 73: 1658, 1926.
370. Wendt, G. R.: Studies of somatic, physiological and psychological correlates of motion sickness. Civ. Aero. Ass. Div. Res., Aug. 1945.
371. Wendt, G. R.: N.R.C., Final Rep., Dec. 1945.
372. White, J. M.: Personal Communication.
373. White, J. M., Freedman, D., McCawley, E. L. and Gray, W. D.: Effect of certain dialkyl-substituted amino alkyl bearing compounds on apomorphine-induced emesis. Fed. Proc., 9: 325, 1950.
374. Whittingham, H. E.: Medical aspects of air travel. I. Environment and immunization requirements. Brit. Med. J., 1: 557–558, 1953.
375. Winfield, R. H.: Medical aspects of selection and training of parachute troops. Report on problem of airsickness in parachute troops. Brit. Flying Personnel Res. Comm., Rep. No. 277, March 27, 1941.
376. Witts, L. J.: Remedies for seasickness and airsickness. Brit. Flying Personnel Res. Comm., Rep. No. 318, June 1941.
377. Winston, J., Rubin, A., Lewis, J. S. and Rehberger, J. M.: The effect of dramamine upon cochlear function and the vestibular responses to turning in normal subjects. Ann. Otol., Rhin. & Laryng., 59: 622–630, 1950.
378. Witteman, L. A.: A new treatment for vertigo. Eye, Ear, Nose & Throat Monthly, 28: 272–273, 1949.
379. Wright, W. L.: Effectiveness of newer drugs in seasickness. U. S. Armed Forces Med. J., 1: 570–577, 1950.
380. Wolf, S.: The relation of gastric function to nausea in man. J. Clin. Invest., 22: 877–882, 1943.
381. Yetwin, I. J.: Dramamine for prevention of airsickness in airborne troops. Mil. Surgeon, 107: 453–455, 1950.
382. Zwerling, I.: Psychologic factors in susceptibility to motion sickness. J. Psychol., 23: 219–239, 1947.