TECHNICAL REPORT

A STUDY OF OPPORTUNITIES FOR RESEARCH ON MOTION SICKNESS

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OFFICE OF NAVAL RESEARCH  
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Technical Report  

A STUDY OF OPPORTUNITIES FOR RESEARCH  
ON MOTION SICKNESS  

by  

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FOREWORD

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This technical report was prepared for the Office of Naval Research and the Bureau of Medicine and Surgery, Department of the Navy, by the staff of the Life Sciences Research Office, FASEB, in accordance with the provisions of Contract No. N00014-72-C-0356.

We acknowledge the contributions of the numerous investigators and consultants who have assisted with this study. The report reflects the opinions expressed by participants in an ad hoc study group that met at Beaumont House, FASEB, on February 6-7, 1973, and other consultants. The report has been reviewed by these scientists and a judicious attempt has been made to incorporate the different viewpoints and opinions.

The authors accept responsibility for the contents of the report and the listing of the consultants' names in Section XI does not imply that they endorse the conclusions or recommendations.

C. Jelleff Carr, Ph.D.
Director
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SUMMARY

Motion sickness continues to be an operational and medical problem in the modern Navy and it is necessary to know more about the precise mechanisms underlying the causes of this disorder. Therefore, this study was undertaken to review work in this field and to identify new approaches to an understanding of the fundamental causes of motion sickness. The study includes a brief overview of present research and suggests possible applications of recent advances in a number of biomedical disciplines that provide opportunities for profitable research.

The study discusses the lack of a universally accepted definition of motion sickness, the need to investigate specific stimuli that evoke motion sickness, opportunities for fruitful studies on the anatomy and physiology of the vestibular apparatus of animals and man, and how evolving knowledge of the neurochemistry of the central and autonomic nervous systems may be applicable to understanding some basic considerations of motion sickness.

Despite extensive studies of the vestibular apparatus, aspects of the anatomy and physiology of this system are incompletely understood. New techniques are now available for additional investigation of the development and maturation of vestibular end-organs, structure and function of specific vestibular receptors, and the role of visual and other sensory cues in evoking the motion sickness syndrome. One of the most promising approaches to research on motion sickness may be the investigation of the role of neurohumoral transmitters during the period between stimulation and the generation of symptoms and signs. Circumstantial evidence strongly suggests that neurochemical substances may be active in perception of motion and development of symptoms and signs characteristic of motion sickness, particularly those with a short latency.

The phenomena of adaptation and habituation following repeated stimulation are discussed. It is suggested that the sophisticated methodologies utilized in the experimental study of response patterns to motion and in preselection of men be used to study individual differences per se. It is possible that investigations of this type will lead to the identification of some biochemical parameters that are correlated with the symptoms and signs which are well documented. Research workers in this field
are aware of the need for continued study of these phenomena as an approach to understanding the basic mechanisms involved in motion sickness.

The suggestions for future research set forth in Section IX may be useful to research administrators in identifying areas for emphasis in future years.
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I. THE PROBLEM

Periodic reassessment of a field of investigation is desirable to establish milestones of understanding and achievement but, more important, reevaluation often brings fresh ideas to bear upon old problems. The term "technology assessment" is popular to illustrate the application of concepts and techniques from varied fields to seek solutions to a problem. The present study was designed with these ideas in mind. The goal of this study was to review present research on motion sickness and to exploit advances in related disciplines that could improve the understanding of human responses to motion. The purpose was to delineate new opportunities for research on the nature of motion sickness and thus identify possible approaches to control this incapacitating disorder.

Prophylactic drug therapy for motion sickness introduced 30 years ago has been only partially successful in meeting the performance requirements of men in military situations. Extensive research investigations on motion sickness have elucidated many facets of motion as related to this clinical syndrome. Unfortunately, there is no clear understanding of the neurophysiological bases of motion sickness and even a pharmacologic explanation of the effectiveness of drugs is wanting. However, recent research on the finer neuroanatomy, neurophysiology, and biochemistry of the mechanisms involved in the functions of the central and autonomic nervous systems has developed new concepts that may elucidate the nature of this strange malady.

There are two facets to motion sickness, one related to causative factors and the second to the consequences of motion on man. Most research has been directed toward understanding and controlling the consequences of undesirable motion effects. Presumably knowledge of basic causes would lead to more productive studies on the control of consequences of motion. On the other hand, measuring those events within the sensory systems that trigger neurohumoral sequelae, presumably biochemical in nature, that elicit the undesirable effects in man remains a critical problem. This report addresses these latter issues.

The military services have high stakes at risk in seeking to control the adverse effects of motion on man. Naval operations involve new types of seagoing vessels and aircraft as well as traditional ship designs. Surface effects vehicles and hovercraft produce new patterns of motion.
affecting personnel. New generation aircraft including rotary-wing and vertical short takeoff-and-landing (VSTOL) aircraft introduce new problems in operator perception of true spatial motion (Joy, 1971; Welsh, 1971). The man-machine interaction in modern military equipment exposes man to special, more severe, and potentially more frequently encountered hazards. It is essential that these new types of equipment do not prove to be harmful to personnel and do not compromise their military effectiveness. One primary objective of the military biomedical program is maintaining and indeed, improving the performance of personnel by maximizing efficiency of the human sensory systems in military operations (Joy, 1971; Welsh, 1971).

Motion sickness is a persistent problem in the modern Navy. There is a continuing need to know more about the precise mechanisms, both physical and physiological, underlying motion sickness. Present studies are giving only partial answers to these questions and, at best suggest symptom suppression, not fundamental solutions. Therefore, it is appropriate to seek solutions to these problems by research on basic mechanisms. This research may not give immediate practical answers but the value of this approach has been proved in the past. The history of the biomedical sciences is laced with examples of serendipitous discovery that have led to a better understanding of causes of diseases and also a corresponding control of the effects of these maladies.
II. SCOPE OF THE STUDY

Preliminary discussions with research workers in universities and Navy laboratories revealed many facets of research on the causes, nature, and control of motion sickness.

From this background an agenda was developed for an ad hoc review group meeting convened at Beaumont, Federation of American Societies for Experimental Biology on February 6-7, 1973 (Section XI). The discussions of these scientists provided insight into the basic and applied aspects of motion sickness research and current programs. The scope of this report emerged from the discussions at the meeting and a review of pertinent current literature.

Emphasis was placed on recent work on motion sickness and investigations in related fields that provided useful approaches to future research. These included observations of the fine anatomic structure and neurophysiology of the vestibular system and the mechanisms underlying development of signs and symptoms following stimulation and during expression of the motion sickness syndrome. The biochemical and neurophysiological aspects of these responses were of particular interest. The interactions of vestibular output with the central nervous system and endocrine responses were explored. Discussion of the causes of individual differences in response to motion and in adaptation provided some insight into the essential nature of motion sickness. The importance of potential experimental approaches such as sensory deprivation was discussed.

It was not feasible to include all aspects of motion sickness research in the agenda. Vestibular modeling, prophylaxis and therapy, critiques of current techniques of study, and the effects of motion sickness on performance have been excluded from this study.

The scope of this study included exploration of present research on motion sickness and recent advances in related disciplines that might lead to a better understanding of the biological basis of human response to motion. The study provides a brief scientific assessment of the limits of current knowledge, evaluates the potential significance of recent advances in related fields, and identifies opportunities for future research.
III. BACKGROUND

A. OVERVIEW

The term motion sickness includes the symptoms of vague malaise, pallor, cold sweating, nausea, and vomiting. Its causes remain obscure but its significance on efficient human performance in the military situation is obvious. It interferes with effective crew performance on land, on sea, and in the air. Modern military vehicles, new hydrodynamic ships and high performance aircraft are capable of rapid linear and angular acceleration (Welsh, 1971). The performance of these machines may exceed the capacity of the operators and passengers to withstand the stress of real or apparent motion.

Most investigators agree that some form of sensory incongruity occurs prior to the onset of motion sickness. This conflicting sensory information may arise from other sensory modalities than the vestibular apparatus and can arise from within the vestibular system as well. Thus, both real or apparent motion may elicit the chain of events described as motion sickness. Usually, stimulation of the otoliths or semicircular canals initiates neural transmissions that result in responses to that motion. While there is little variation among individuals with respect to the interval between stimulation and response to motion, there is a recognized latency between stimulation and the onset of motion sickness that varies widely among individuals.

There is a wide range of individual variability in susceptibility to motion sickness and the ability to become adapted or habituated. The fundamental basis of these individual differences is incompletely understood. Reason (1969a) has suggested that individual differences in susceptibility reflect characteristic differences in the transduction of sensory intensity by the central nervous system. Guedry (1972) has speculated that differences are related to conditioning mechanisms during growth, which are, related, in turn to individual variability in rates of development of motor reactivity, personality and cognitive function during maturation.

Severe depression often occurs following prolonged motion sickness. Money (1970) has observed that the mechanisms involved in producing the depression may be similar to those of more prolonged mental disorders. It is noteworthy that little attention has been directed
to the mechanisms related to the depression of motion sickness although psychiatric depressions have been the subject of study for many years (Lehmann, 1966).

Extensive research in the past 30 years has shown that the types of motion inducing motion sickness are characterized by varying linear and angular accelerations of the vestibular apparatus and that a functional vestibular apparatus is required for development of motion sickness. More recently, the anatomic and neurophysiological pathways between vestibular end-organs and higher cortical centers have been investigated. Related studies have categorized patterns of response to motion under controlled experimental conditions, investigated individual differences in susceptibility to motion sickness, and evaluated human performance in environments that produce motion sickness.

The etiology and treatment of motion sickness have been reviewed by Baker (1966), Chinn and Smith (1955), and Tyler and Bard (1949). More recently Schadewaldt (1967) reviewed numerous aspects of seasickness, Money (1970) prepared a comprehensive review of investigations on all aspects of motion sickness, and Clark (1970) reviewed the literature on the psychological effects of vestibular stimulation and responses. Graybiel (1973) has collated much of the literature that deals with the responses of the vestibular system to weightlessness. This review also summarizes the test methodologies that have been evolved for evaluation of vestibular functions. All of these reviews provides an exhaustive bibliography of previous studies.

In recent years, a number of investigations have focused on the responses of the vestibular system and other sensory systems to the unnatural environmental situation encountered in space flight. Results have been reported in symposia on the role of the vestibular organs in the exploration of space sponsored by the National Aeronautics and Space Administration (Graybiel, 1973; NASA 1965, 1966, 1968, 1970, 1973) and a symposium sponsored by Aerospace Medical Research Laboratories (AMRL, 1963). Melville Jones (1971, 1972) has compiled the reports of the Canadian Defence Research Board from 1964 to 1971 on studies of sensory motor neurophysiology in the aerospace environment.

There is no unanimity of scientific opinion on a unified theory of causality of motion sickness. Experimental data are available that both support and refute several of the proposed theoretical explanations of man's response to complex motion. Continued development of basic explanations of the genesis and nature of the disorder such as those by
Graybiel (1969), Guedry (1972), Mayne (1969), Reason (1969a), and Steele (1961) are necessary as a background to further intensive and enlightening studies of this problem. The investigations during the past three decades have led to a renewed interest in theoretical considerations and explanations of basic processes involved in stimulus reception and response patterns (Graybiel, 1969; Guedry, 1972; Mayne, 1969; Reason, 1969a; Steele, 1961).

B. DEFINITION OF MOTION SICKNESS

The lack of a generally acceptable definition of motion sickness is related to the nature of the condition. It may be induced by a variety of stimuli that encompass real or perceived motion in at least one axis. Moreover, the response patterns evoked are nonspecific in that the symptoms show similarities to those which characterize many reactions to environmental stress or life-threatening situations. For these reasons, motion sickness is usually defined in terms that relate the stimulus to the evoked symptoms and signs.

The term motion sickness was introduced by Irwin (1881) to indicate seasickness as well as "sickness identical in kind" induced by various other motions. Despite the early introduction of the term, the pre-World War II literature contained few documented studies of the disorder (Tyler and Bard, 1949). Most definitions refer to a pattern of symptoms that is produced by perception of several types of real or apparent motion. The pattern progresses from apathy, drowsiness, and stomach awareness to pallor, cold sweating, nausea and vomiting. The range of causal stimuli is evident from the terms used to designate the disorder: swing sickness, seasickness, trainsickness, carsickness, airsickness, and spacesickness.

In his recent comprehensive review of the subject, Money (1970) stated the clinical description as:

"Motion sickness is a malady caused by certain kinds of motion. The signs and symptoms include malaise, pallor, cold sweating, nausea, and vomiting. Motion sickness is properly considered to be present whenever any of its signs and symptoms have been provoked by motion, although a few authors use the term only to specify frank vomiting caused by motion."
As with earlier definitions, it describes the condition in terms of responses and does not give any indication of the basic mechanisms involved in the disorder.

In an attempt to further delineate the effects of various stimuli and the functional relationships of responses, Graybiel (1969) suggested that two categories of responses were evident (Figure 1). The first (V-I Manifestations) involves stimulation of the vestibular system and higher cortical centers, which under normal circumstances receive vestibular neural output as well as that from other systems modulating the responses of the vestibular system and the neural responses. The second category (V-II Manifestations) includes epiphenomena that appear when vestibular organs are stimulated by unnatural conditions, and involve reception of vestibular stimuli by higher cortical centers not normally characterized as vestibular receiving areas. The symptomatology of motion sickness, as well as many other syndromes, is included in this second category.

Thus, Graybiel (1969) proposed that:

"Motion sickness is a clinical diagnostic term implying certain criteria have been met to ensure validity. Thus, a close temporal order of exposure to motion generating stressful accelerations and the appearance either of vomiting or some combination of such cardinal symptoms as nausea, pallor, sweating, increased salivation, and drowsiness, constitutes, respectively, a pathognomonic or valid diagnosis."

Implicit in this more detailed separation of the several stimuli and responses is an effort to more critically define each symptom in terms of both stimulus and each of the receptor and other systems involved in generation of the response (Figure 2).

Not all investigators accept this hypothesis; however, the schema does provide a logical categorization of the component parts of the stimulus receptor, and response systems in terms of physical input, neurophysiological throughput, and complex biological output that result in the condition, motion sickness.

The concepts presented in the schema do provide a framework within which opportunities for further research may be viewed in perspective. Obviously, further investigations into the basic aspects of motion sickness will result in modification or alteration of the diagram.
Sequence of possible events and processes underlying two categories of vestibular responses (V-I, natural vestibular stimulation; V-II vestibular stimulation by unnatural conditions) as proposed by Graybiel. (Modified from Graybiel, 1969).
Stimulus (input) and response (output) interrelationships that distinguish normal vestibular responses and reflex phenomena from epiphenomena such as motion sickness. (From Graybiel, 1972.)
IV. NATURE OF THE STIMULUS

A. REAL MOTION

Numerous experimental studies have shown that various types of motion can induce the responses that characterize motion sickness (Chinn and Smith, 1955). Studies of various forms of linear and angular acceleration suggest that, regardless of the type of motion, the specific stimulus is the changing acceleration of the head. With certain exceptions, acceleration of the individual or his head must change with time for the motion to be effective in causing motion sickness (Johnson et al., 1951; Money, 1970). There are certain changing accelerations, such as horseback riding, that do not cause motion sickness; accelerations that do not change relative to the individual, do not precipitate the condition.

It is important to recognize that motion in ships, airplanes, and some vehicles is exceedingly complex. For example, the motion of a ship may involve plunging, pitching, rolling, yawing and continuous forward motion (Sjoberg, 1970). An individual on a ship may move relative to the ship and his head may be in motion relative to his body. Such composite motions usually involve changing linear and angular accelerations. In general composite motion is more effective in producing motion sickness than any single component of that type of motion.

Because of these problems, investigators have used more controlled types of motion; for example, oscillating or rotating chairs, 2- and 4- pole swings, counter-rotating rooms, or have controlled motion of the subject and his head relative to the movement of the immediate environment. As noted previously, the only characteristic common to all experimental situations where motion sickness can be produced is varying acceleration of the head or labyrinths.

In a classic series of studies, Wendt and his associates (Alexander et al., 1945a, 1945b, 1945c, 1945d, 1947; Johnson and Wendt, 1955) used swings and other oscillating devices to investigate the specific characteristics of certain controlled motions that could be correlated with induction of motion sickness. They found that the individual influence of such variables as periodicity, acceleration, amplitude, and time, depended on the values of the other variables present at any instant. Subsequent studies of differing types of motion have confirmed and extended these
conclusions. In general, frequencies of 10 to 15 cycles per minute (cpm) are more effective in provoking motion sickness than higher or lower frequencies.

Implicit in the study of motion per se is the concept of establishing criteria for the prediction of motion sickness. If the causal motions could be characterized in detail, then operators of ships, vehicles, and aircraft could be alerted to the potential danger of deterioration in human performance under these specified conditions. Most authorities would agree that motion sickness results in reduced performance effectiveness. However, in a review of the effects of motion and motion sickness on performance, Baker (1966) noted the scarcity of documented reports on the effects of motion on human performance.

B. APPARENT MOTION

In the absence of actual movement of the body, external movement of the visual field may be perceived as apparent motion and may induce motion sickness. Although not conclusively proven, most investigators agree that in the absence of a functional vestibular system, visually perceived motion will not evoke motion sickness. This concept is based upon the assumption that visual stimulation initiates conditioned vestibular activity or motor responses in the head and neck. As suggested by Money (1970) in his recent review, the necessary experimental proof might be obtained from a study of the responses of labyrinthine-defective subjects to moving visual fields that do cause motion sickness in normal subjects.

C. RESEARCH OPPORTUNITIES

The dynamic responses of the semicircular canals have been studied extensively. The directional sensitivity exhibited by each of the three semicircular canals is known to be related to the orientation of the kinocilia on the cristae. However, the observed dynamic responses to high frequency stimulation are not in accord with theoretical expectations. There are a number of other derivations from theoretical expectations of canal responses that are considered to be adaptation effects, although this explanation is itself incomplete. The specificity of directional response of the utricle and saccule to various linear and angular accelerations have been studied (Benson et al., 1970); however, the dynamics of transduction
of linear accelerations by the maculae are poorly understood. There is a continuing need for further study of motions with varying frequency, amplitude, and duration to establish the dynamic responses of each vestibular receptor and their interactions.

There are two major impediments to such studies; accurate reproducible patterns of motion and valid and sensitive criteria for evaluating responses. More advanced models of motion simulators have been designed, more sophisticated models are technologically feasible, and more critical methods of evaluating vestibular responses are being developed (See Section VIII, A).

The difficulties of relating laboratory studies of controlled patterns of motion to patterns of motion on board maneuvering vessels or aircraft are well recognized. Equally difficult is the correlation of specific linear or angular accelerations within motion patterns and the development of motion sickness. For example, each vessel has its own characteristic responses to various sea conditions; roll and pitch vary with load, heading, and speed which in turn are related to sea directions. The actual force vectors experienced by the seaman are complex for he may or may not be in motion relative to the ship. Motion of personnel in vehicles and aircraft are similarly complex and depend on their acceleration, or that of their head, relative to the machine motion as well as these motions relative to that of the earth.

There is some knowledge of specific patterns of motion causing sickness, but relatively few studies have systematically related stimulus parameters to incidence of sickness. For example, vertical oscillations at 16 cpm at an acceleration level of 0.25 g are 20 times more liable to induce frank motion sickness than the same motion at 32 cpm at 0.65 g (Alexander et al., 1945d, 1947). Such data are scarce and knowledge on these aspects of motion are needed for incorporation in the design criteria for new air and sea craft.

Studies on incidence of motion sickness are currently underway using a design in which the level of acceleration and the frequency of vertical oscillation are varied independently. Research on the effects of angular acceleration in two axes (pitch and roll) simultaneous with vertical oscillations on incidence of motion sickness is planned as a consequence of these studies on controlled vertical oscillations.

There is a need for additional studies that focus on assessment of motion characteristics of ships, aircraft, and vehicles in relation to the effects of their patterns of motion on induction of motion sickness.
This information should be developed during the design and development of all equipment. Investigations are particularly necessary in the development of high performance sea and air craft where the performance capacity of the equipment may exceed that of the human operator thus negating the value of the engineering advances being built into the machine.

Knowledge of the range of possible motions of each type of craft is a prerequisite to evaluating responses of persons and their performance under such motion patterns. There is a further need for studies that relate patterns of motion, such as sea states or standard aircraft maneuvers to incidence of motion sickness and alterations in human performance.

In addition, the relationship of apparent motion to real motion in causation of motion sickness remains to be elucidated. Presently available evidence suggests that moving visual fields do not cause motion sickness in subjects lacking a functional vestibular system. This suggests that apparent motion produces motion sickness by stimulating the vestibular system. However, if the neurophysiological and biochemical mechanisms underlying motion sickness are similar in all susceptible species, it is possible that apparent motion produces motion sickness by different mechanisms in unconditioned and conditioned individuals. There is a need for further study of responses by labyrinthine-defective humans and experimental animals to visual stimulation known to precipitate motion sickness in normal subjects (See Section VI, D).

There is a further need to study the types and patterns of visual stimulation that can provoke motion sickness in normal subjects.
V. THE VESTIBULAR SYSTEM

A. ANATOMY AND PHYSIOLOGY

The structural organization and functional activities of the vestibular system have been described in considerable detail (Lim, 1969; NASA, 1970; Wersäll, 1972; Wersäll and Flock, 1965). The morphology and function of the semicircular canals are well known and the anatomy of the otolith system has been established, but several aspects of otolith function remain to be elucidated.

The following paragraphs are a brief overview of the anatomy and physiology of the vestibular system. It is not all-inclusive, but it does indicate gaps in current knowledge and explain why certain facets of the subject are related to a better understanding of motion sickness.

The vestibular system consists of two symmetrical halves on opposite sides of the head. Each portion is enclosed within the temporal bone and forms a part of the inner ear. The vestibular organs are located in the nonauditory, or posterior, labyrinth of the inner ear. Within the hollow canals or bony labyrinth of the petrous portion of the temporal bone, the membranous posterior labyrinth consists of three semicircular canals and the two components of the otolith system (utricle and saccule).

The anterior labyrinth and posterior labyrinth contain endolymph which circulates throughout both areas. Endolymph, like other intracellular fluids, is characterized by relatively high concentrations of potassium ions and low concentrations of sodium ions. The space between the membranous labyrinth and the bony labyrinth contains perilymph which has a relatively low potassium but high sodium ion content, similar to cerebrospinal fluid and the fluids of other extracellular body water compartments (Best and Taylor, 1966). The differences in sodium and potassium ion concentrations between the endolymph and the perilymph may be related to ionic potential differences associated with initiation or transmission of neural impulses within the sensory neuroepithelial cells, but this relationship is not fully understood.

Functionally, the vestibular system is analogous to an inertial guidance system consisting of angular and linear accelerometers. The left and right halves of the system must act in harmony for normal
vestibular functioning. Each lateral half of the vestibular apparatus is
a three dimensional structure that responds to, and in, each of the three
dimensions. The three semicircular canals function as angular acceler-
meters. The semicircular canals are arranged in three orthogonal planes,
each perpendicular to the other two. Each loop has an enlarged segment,
the ampulla, which contains the crista, a ridge of sensory neuroepithelium
surrounded at its base by secretory epithelial cells, and the cupula. The
latter, a gelatinous mucopolysaccharide structure, is supported on the
hair cells of the cristaæ. Movement of the endolymph initiates cupular
displacement which is transduced to neuronal signals by the hair cells.

The utricle, and probably the saccule, function as linear acceler-
meters and gravity receptors (Fluur, 1970). The maculae of the utricle
and saccule are neuroepithelial tissues that resemble the cristaæ structur-
ally. Each macula is covered by an otolithic membrane rather than a
cupula. Cilia of the hair cells extend into the gelatinous portion of the
otolithic membrane which also contains the otoconia. The otoconia,
crystals of calcium carbonate, have a specific gravity of approximately
3.0, contain organic substances (Lim, 1973a) and make up a significant
fraction of the mass of the otolithic membrane. Lindeman (1969) observed
that there is a distinct pattern of distribution of otoconia by size within
both the utricle and saccule. A change in gravitational force or linear
acceleration or deceleration results in pressure on the cilia by the otolithic
membrane. The weight of the otolithic membrane and otoconia bends the
cilia and results in an alteration in the rate of discharge of nerve impulses
from subserving hair cells.

It is generally held, but not conclusively proven, that displace-
ment of the cupula within each semicircular canal regulates the rate of
ampullary nerve discharge. Groen et al. (1952) have established a
direct relationship between cupular deflection and the neural signal in
primary afferent fibers originating in the ampullae of the canals. For
example, in the horizontal canal displacement of the cupula toward the
utricle enhances, and displacement away from the utricle inhibits, the
neural discharge rate relative to the spontaneous level of firing
(Wersäll, 1972). Within the utricle and saccule, discharge rates vary
with the direction and the pressure of the otolithic membrane on hair
cells. Several investigators (Fluur and Mellström, 1970; Spoendlin,
1965) have shown differential responses to electrical stimulation of
different areas of the utricular and saccular surfaces which, in part,
correspond with the directional sensitivity of the neuroepithelial cells
of the maculaæ. These and other observations suggest differential
patterns of nerve discharge within the hair cells on the maculaæ.
Impulses from the two types of sensory hair cells of the cristae and maculae are carried to the medulla by the vestibular portion of the 8th cranial nerve. These neuronal cells are bipolar. The cell bodies of these neurons are in the vestibular ganglion. The dendrites terminate synaptically in the two types of hair cells and the axons terminate in the 4 lobes of the vestibular nuclei of the medulla. A few axons extend to the flocculo-nodular lobe and the fastigial nuclei of the cerebellum. Several pathways, both ascending and descending, occur at this level.

Natural movements of the head, in any direction, stimulate at least one pair of receptors within the vestibular system. Excitation of receptor cells of the cristae of the semicircular canals or maculae of the otolithic organs produces nerve impulses that travel to higher brain centers via the 8th cranial nerve, vestibular nuclei and archeocerebellum. Under normal conditions, actual motion of the body also stimulates the proprioceptive and visual systems, but the primary receptors are thought to be those of the vestibular apparatus. Apparent motion of the visual field can substitute for vestibular stimulation in an individual with previous experience and will elicit the sensation of actual movement. Either vestibular or visual stimulation can produce motion sickness in conditioned individuals; however, vestibular stimulation alone is sufficient to induce the disorder. Observations in man and extensive studies of several animal species indicate that the absence of a functional vestibular system or bilateral sectioning of the 8th cranial nerve confers immunity to motion sickness (Money, 1970; Money and Friedberg, 1964).

B. RESEARCH OPPORTUNITIES

Despite critical studies of the vestibular apparatus in animals and man, many aspects of the anatomy and physiology of the system are incompletely understood. Because the vestibular end-organs are the primary receptors of all types of motion, additional study seems necessary because lack of knowledge concerning certain vestibular processes continues to impede progress in understanding motion sickness.

The following topical areas have been identified that require further investigation.
1. Development and Maturation of Vestibular Receptors

The development of the vestibular system from otic placode has been studied in some detail and the evolutionary aspects of differential development in vertebrates are fairly well elucidated (Titova, 1968; Wersäll and Flock, 1965). More recent studies, using transmission electron microscopy, X-ray diffraction techniques, and scanning electron microscopy have further clarified the fine structure of the vestibular end-organs (Carlström and Engström, 1955; Lim 1969, 1973a, 1973b; Wersäll, 1972). Similarly, Ross (1971) has used fluorescence microscopy of serial sections of the cochlea of several animal species to establish the pattern of nerve fiber distribution in the inner ear. Additional studies employing these techniques are needed to more critically detail the development and maturation of the vestibular end-organs (McCracken and Dodd, 1971).

The hair cells of the maculae and cristae exhibit a directional sensitivity. Groen (1961) suggested this property might be present in the embryonal placode prior to subsequent development of the specific vestibular end-organs. Evidence from other unrelated studies (Guedry, 1972) suggests that motion in early postnatal development might possibly be the stimulus for subsequent enhancement of directional sensitivity. Definitive investigation of directional sensitivity during early years would further elucidate the issue of hair cell orientation. Such studies would be most significant if anatomical differences could be related to observations of differences in response to motion (See Section VIII, C).

In a somewhat related field, several investigators (Erway et al., 1970, 1971; Purichia and Erway, 1972; Shrader and Everson, 1967) have shown that modification of the diets of pregnant experimental animals can alter the structure of the otoliths of the offspring. Diets deficient in manganese or zinc result in progeny in which otoliths are malformed or absent; diets containing excess manganese can lead to offspring with large numbers of otoconia. In addition, there is further evidence that otolith formation is influenced by those factors that alter calcium metabolism (Lim 1973b). The significance of these observations in relation to the early development of otoliths in the human remains to be investigated but may be associated with individual susceptibility to motion effects.

2. Structural Aspects of the Vestibular End-Organs

As noted previously, morphological investigations of the vestibular organs of experimental animals over the past two decades have provided sufficient information for correlation of structure with
function. Two types of sensory cells exist, one highly differentiated and the other more primitive (Wersäll and Flock, 1964). Both Type I and Type II cells are innervated by afferent and efferent fibers. There appears to be a need to extend these studies of cytoarchitecture of the sensory hair cells to further investigation of the structure of the cristae and maculae using the techniques of Lewis (1972), Lim (1973b), and Wersäll et al. (1971); and to further study of the interconnections of the nerve fibers associated with these receptors by methods employed by Grey and Barnes (1973), McCracken and Dodd (1971), and Ross (1971).

3. Functional Aspects of the Vestibular End-Organs

Almost all studies of vestibular responses to linear and angular accelerations (that is, evaluation of semicircular canal responses and otolithic responses) have been carried out with relatively simple stimuli, i.e., motion in one plane. Knowledge of the responses to these types of experiments is a necessary prerequisite to the understanding of responses to motion which result from movement with up to six degrees of freedom (Benson et al., 1970). In normal subjects, motion sickness can occur in situations where movement is simple or complex, but in any case is related to stimulation of one or more parts of the vestibular end-organs. A better understanding of vestibular responses to patterns of motion will clarify the interactions of specific stimuli with specific vestibular stimulation. This need is especially acute in regard to comprehension of thresholds and magnitude of responses to combined linear and angular acceleration (Johnson et al., 1967; Benson et al., 1970; Clark and Stewart, 1970) and to maintenance of equilibrium (Nasher, 1971).

Most investigators accept the concept, originally advanced by Steinhausen (1927), that the semicircular canals respond to angular acceleration as a "heavily damped torsion pendulum." During the past 46 years, numerous investigators have studied the contributions of the perilymph (Rejtö, 1939), endolymph (van Egmond et al., 1949) and ampulla wall (Dohlman, 1941) to angular displacement of cupula in response to head motion. Despite extensive study, there are few data on the rigidity of the cupula and ampulla walls. Anliker and van Buskirk (1971) have suggested that the ampulla wall offers little or no resistance to cupula displacement. Because this suggestion is partially in conflict with results of earlier studies, there is a need to reexamine the biomechanical properties of the ampulla wall. It is generally agreed that the endolymph is involved in cupula displacement; however, Dohlman and Kuehn (1973) have shown that the presence of spongy perilymphatic tissue, the occurrence of numerous fibers connecting the labyrinth and the perios- teum and the angle of the canal and ampulla serve to stabilize the
membranous system and prevent cupular deflection by movement of the perilymph. Additional investigations of this phenomenon should be undertaken.

Despite critical study of the ultrastructure of the vertebrate kinocilia and stereocilia, the problem of mechanoelectrical transduction by sensory hair cells is incompletely understood. In 1966, Lowenstein noted that most investigators assume that transduction is associated with the kinocilia. He pointed out that the cochlear hair cells have only stereocilia. In these sensory hair cells, the basal portion of the stereocilia are connected to the cuticular plate of the hair cell. These observations suggest that stereocilia do have a role in mechanoelectric transduction in the cochlear hair cells and could have a similar role in the vestibular system. These suggestions of Lowenstein (1966) should be studied because the exact mechanism of sensory cell stimulation is still the subject of considerable controversy.

Most investigators agree that the utricular macula responds to linear acceleration and possibly gravitational changes. The role of the saccular macula in transducing linear acceleration is less firmly established; some authorities suggest that a vestibular function is absent, while others have observed saccular response to linear acceleration (Fluur, 1970). Fluur and Möllström (1970) observed that electrical stimulation of certain discrete areas of the utricular or saccular neuroepithelia resulted in coordinated eye movements in alert cats and uncoordinated ocular responses in sleeping animals. It appears that further study of the role of the saccule in responses to stimulation by motion might be approached by animal studies of the interactions of the saccular response with that of other sensory receptors. Howland (1971) has proposed that both the otolithic organs and the semicircular canals of fish function as feedback loops on angular motion. These observations suggest that there are opportunities for further study of interactions of vestibular end-organs in animal models.

Fernandez and Goldberg (1971; Goldberg and Fernandez, 1971a, 1971b) have examined the discharge properties of first-order vestibular afferents of the semicircular canals of the squirrel monkey. They found that all neurons responded to angular acceleration in one direction by increased discharge and to acceleration in the other direction by decreased discharge. The response was always consistent with the morphological polarization of the hair cells in each of the three canals. Within each canal, they observed two types of neurons that could be differentiated on the basis of regularity or irregularity of discharge in response to angular acceleration. In regularly discharging units, the
greater the sensitivity to acceleration, the higher the resting discharge; this relationship was absent in irregularly discharging neurons.

In a subsequent study, Fernandez et al. (1972) have reported that otolithic first-order neurons respond to both pitch and roll. The magnitude of discharge was related to tilt angle trigonometrically. As with the neurons from semicircular hair cells, regular and irregular discharging units appear to be present in neurons from the hair cells of the otoliths. Morphological and physiological evidence suggested that regularly discharging units innervate Type II hair cells and irregularly discharging neurons innervate Type I hair cells.

Spoendlin (1966a, 1966b) reported that injection of streptomycin into the middle ear of cats produced degeneration of Type I hair cells but not Type II hair cells. After 7 days, the neuroepithelium consisted of Type II hair cells only; nerve endings and fibers of both types of sensory cells appeared unaffected by the treatment.

It would be worthwhile to combine the experimental techniques of Spoendlin with those of Fernandez and Goldberg (1971; Goldberg and Fernandez, 1971a, 1971b) in evaluating responses of motion sickness susceptible and resistant animals to linear and angular accelerations. Such experiments would be helpful in clarifying the role of the two types of hair cells, the two types of neurons and the responses of each in both the canals and otolithic organs.

Finally, it is noteworthy that other sensory systems characteristically possess two types of receptors, e.g., the rod and cone cells of the vertebrate retina and the inner and outer hair cells of the vertebrate cochlea. There is a need for further clarification of the afferent and efferent innervation processes of the two types of vestibular receptor cells (Sala, 1965). Recent studies of the structure and function of visual receptor cells may provide clues to other experimental approaches.
VI. OTHER SENSORY SYSTEMS

A. VISUAL STIMULATION

The eyes are the most active sensory receptors of the human body and unlike the vestibular end-organs and other sensory systems, the eyes are capable of moving independently. Thus, the eyes continually scan and monitor the visual frame of reference. Eye movement is essential to visual perception and also plays a role in perception of body acceleration (Guedry, 1965). Activities of the vestibular and visual systems are interconnected by neuronal tracts between the vestibular nuclei and the nuclei of the ocular nerves. These interconnections are responsible for the several types of nystagmic eye movement, a two component ocular motion useful in diagnosis of patterns of vestibular stimulation (Aschan et al., 1956; Guedry, 1966; Stahle, 1957, 1958).

Perception of body position and orientation results from integration of vestibular, visual and proprioceptive information. In general, visual perception that is in agreement with information from the vestibular end-organs and that of proprioceptive receptors is the normal condition. However, visual perception that is not in accord with vestibular and other sensory receptors usually promotes motion sickness (Money, 1970; Reason and Diaz, 1971).

The symptom pattern that characterizes motion sickness can be evoked by movement of the visual field without actual movement of the body. Although unequivocal proof is lacking, it seems logical that motion of the visual field results in vestibular stimulation or provokes conditioned adjustments in the vestibular centers because of experience. This concept is based on the existence of neuronal interconnections and repeated observations of the absence of motion sickness symptoms in labyrinthine-defective subjects exposed to various types of moving visual fields (Money, 1970).

B. PROPRIOEPTIVE STIMULATION

Changes in gravitational force in the normal vertical position also stimulate somatic proprioceptive cells. The relative importance of proprioceptive receptors has been demonstrated by experimental blockade of
sections of the dorsal roots in the cervical region of anesthetized animals. With proprioceptive impulses blocked, animals behave similarly to labyrinthectomized animals and do not become sick (Wolfson et al., 1965). However, when proprioceptive impulses are abnormal, e.g., in weightlessness, the occurrence of motion sickness appears to be more related to conditioning. As with visual stimulation, proprioceptive stimulation may suppress or augment the motion sickness syndrome depending on its agreement or conflict with vestibular stimulation, respectively.

C. AUDITORY STIMULATION

The inner ear consists of two interconnected portions, the anterior and the posterior labyrinth. Except for the saccule, the vestibular end-organs are found in the posterior portion, and the anterior labyrinth houses the saccule and the organ of hearing, the cochlea. The two sensory systems are closely linked anatomically and physiologically. While the production of endolymph in the utricle and semicircular canals may be independent from that of the saccule and cochlea, the endolymph circulates throughout the anterior and posterior labyrinths. In addition, the vestibular and auditory nerves join to form the major components of the 8th cranial nerve.

Harris (1972) has reviewed the effects of acoustical stimulation on the vestibular system and noted that many investigators have reported subjective responses such as disorientation, nausea, and giddiness in response to high intensity noise. Harris (1972) was unable to confirm the nystagmus and alteration of vertical perception reported by previous investigators, but he did find reductions in the quality of task performance involving maintenance of equilibrium during exposure to high noise fields.

Most studies suggest that auditory cues play a minor, but ill-defined role in the evolution of motion sickness. High intensity noise functions as an additional stressor and adversely affects human behavior (Carr and Fisher, 1971; Cohen, 1969).
D. OPPORTUNITIES FOR RESEARCH

It is generally recognized that critical analysis of visual and vestibular interactions resulting from combined visual and vestibular stimulation by means of nystagmography or subjective sensations is most difficult. It is evident that interactions of the two receptor systems occur at multiple levels. However, methods of monitoring nystagmic eye movements have been developed that are rapid, accurate, and experimentally quite useful and can be applied to the study of this subject (McNally, 1969; Montandon et al., 1969; Stahle, 1957, 1958).

It is possible that visual stimulation induces motion sickness by mechanisms other than interaction with vestibular receptors alone; for example, by interaction with higher brain centers that are also dependent on vestibular end-organ output (Money, 1970). Further accurate and reproducible investigations in this area are urgently needed. Because patterns of measured eye movement can be correlated with the type of motion stimulus, it would be of interest to compare the nystagmic responses of normal subjects to several patterns of actual motion, with and without visual stimulation, with the nystagmic movements induced purely by visual stimulation simulating identical patterns of motion. Crampton and Young (1953) have shown that normal subjects resistant or susceptible to motion sickness induced by motion, exhibit similar susceptibility to simulation by rotating visual fields. Similar studies that employ more sensitive criteria, e.g., changes in nystagmus (correlated with motion sickness) would be informative.

Money (1970) suggested that labyrinthine-defectives should be exposed to moving visual fields that induce motion sickness in nonmoving normal subjects. The suggested experiments might include labyrinthine-defective or other individuals who have lost vestibular function but have had sufficient experience to perceive motion. Previous studies showed that labyrinthine-defective subjects perceive actual or visually provoked motion, but do not become motion sick. More critical examination of early indicators of motion sickness are needed, e.g., changes in nystagmus patterns under these conditions (See Section VIII, A).

Dichgans et al. (1972) recently reported that subjects see a vertical line and sense body tilt in a direction opposite to that of a wide-angle visual display rotating around their line of sight. Displacement of the perceived vertical increases with speed of the moving display up to
a maximum of 15 degrees at 30 degrees per second. A similar phenomenon, the oculogravic illusion, occurs in subjects seated in the centrifuge or slow rotation room (Clark and Graybiel, 1968). In the latter situation, the direction of the gravity vector is shifted by centrifugal force. In the situation reported by Dichgans et al. (1972), the displacement of gravity in the vertical direction was induced by the movement of the visual field. In this case, there is no conscious conflict between visual and vestibular information concerning the actual vertical. Thus, the investigators concluded that perception of motion of the visual field was capable of modulating output from vestibular sensors of gravity. Because the maximum displacement appeared to be limited, they suggested that the constraint might be the output of otolithic and pressure receptors that sense gravity.

These experiments of Dichgans et al. (1972) have fundamental and practical significance. The results suggest that visual perception can modulate either otolithic signal output or efferent central nervous system signals relative to gravitational direction. In a practical sense, the techniques may provide an additional approach to evaluating visual, proprioceptive, and otolithic input into precipitation of the motion sickness syndrome (Dichgans and Brandt, 1973).

Harris (1972) reported that the performance demands of balancing the body by the feet on a rail was compromised during exposures to sound levels below those that resulted in subjective vestibular effects or nystagmus. These findings indicate that proprioceptive receptors are involved in labyrinthe control of equilibrium and suggest that acoustical stimulation may be secondary or incidental to the observed decrements in performance. These studies should be extended to include different sound spectra (including infra- and ultra-sound), frequencies, and exposure durations. The effects of high intensity steady-state and impulse noise on maintenance of equilibrium and precipitation of motion sickness must be explored further because modern military vehicles produce both types of sound.

Ornitz et al. (1973) have shown that both auditory and vestibular stimulation can increase the quantity, variability and clustering of spontaneous eye movement in rapid eye movement (REM) sleep. These observations are consistent with evidence from animal studies implicating the vestibular nuclei in control of eye movement during REM sleep (Pompeiano, 1967). The significance of interactions between vestibular and nonvestibular inputs to REM sleep is discussed in Section VIII; however
these studies indicate that auditory and vestibular stimulation may be more closely related at the receptor level. Additional study of this aspect of stimulus reception may prove to be useful (Johnson, 1973).

Lebovitz (1972) has proposed that the vestibular apparatus may be the receptor system for certain types of electromagnetic radiation, e.g., microwave radiation. He suggests that thermal gradients in the perilymph and endolymph induced by microwave radiation could stimulate vestibular neuronal responses. The possibility that microwave radiation stimulates the vestibular apparatus should be investigated. It may be important to evaluate microwave radiation as a further stimulus impinging upon the vestibular system of pilots, radar operators, and other personnel in situations where motion sickness can occur.
VII. CENTRAL NERVOUS SYSTEM ACTIVITIES

A. NEUROANATOMY

The major pathways connecting the vestibular end-organs with the vestibular nuclei, cerebellum, and other higher brain centers are fairly well elucidated. The anatomy of neural interconnections above the level of the vestibular nuclei has not been established in great detail, but it has been inferred from extensive studies of neurophysiology.

B. NEUROPHYSIOLOGY

The concept that motion sickness involves vestibular stimulation and central nervous system activity was probably recognized first by Irwin in 1881 and other early workers (Tyler and Bard, 1949; Wang and Tyson, 1954). These investigators explained activation of vestibular end-organs and implicated the cerebellum and cortical areas in the maintenance of equilibrium or vomiting induced by motion sickness. Since that time, the neuroanatomy of vestibular tracts has been studied in detail. In the past two decades, research in this area has focused on the neurophysiology and biochemistry of central nervous system activities.

Most investigators would agree that the reception, perception, and response to motion is mediated by the central nervous system through interconnections with the vestibular receptors and motor cerebral neurons. The interaction of the vestibular and central nervous system includes three interdependent activities: 1) activation of afferent neurons by mechanical stimulation of the hair cells, 2) inhibition of afferent impulses by efferent signals generated in the central nervous system in proportion to the afferent impulses, and 3) development of patterns of response (adaptation) within the higher brain centers when the afferent stimulation is repetitive (Groen, 1970; Sala, 1965).

One of the first pathways to be investigated was the mechanism of vomiting (Borison and Wang, 1953; Wang and Tyson, 1954). Animal studies established that the vestibular portions of the cerebellum are necessary for the vomiting associated with motion sickness. Further studies have shown that the chemoreceptive trigger zone in the floor of the fourth ventricle of the medulla is also necessary for induction of emesis (Borison and Wang, 1953; Wang and Chinn, 1954).
At the present time, evidence from studies on animals and man is sufficient to establish that the vestibular apparatus, the vestibular nuclei, the uvula and nodulus of the cerebellum, the chemoreceptive emetic trigger zone, the vomiting center, and the efferent peripheral nerves to the muscles of the thorax and abdomen are necessary for the vomiting reaction typical of motion sickness (Money and Wood, 1970). These authors suggest that neural connections to the eyes, viscera, and cerebral cortex are not absolutely necessary for development of motion sickness. From their review of previous investigations on neural mechanisms underlying motion sickness, they proposed an integrated scheme of interrelationships among the peripheral and central neural structures involved in the emesis classically associated with motion sickness (Figure 3). This scheme, and the reviews by Money (1970) and Money and Wood (1970), are relatively succinct summarizations of the current state of knowledge on the central nervous system structures and mechanisms involved in the emetic response in motion sickness.

Graybiel (1972) has developed a similar schema (Figure 2) that depicts motion sickness in terms of stimulation of the vestibular end-organs and patterns of response (symptoms and signs). This schema attempts to separate natural and unnatural stimulation in order to define each symptom in terms of both stimulus and particular responses.

If these diagrams (Figures 2 and 3) can be accepted as schematic representations of current understanding, then it seems evident that the greatest lack of factual information concerning motion sickness is associated with central nervous system activities and generation of early responses to vestibular stimulation.

C. NEUROCHEMISTRY

The delayed onset of vomiting after motion stimulation, the discovery of the role of the chemoreceptor trigger zone, and other evidence suggested that an "emetic chemical" might be produced in some region of the central nervous system (Money and Wood, 1970). Because of the inhibition of water diuresis, the presence of an antidiuretic substance in the urine of motion sick subjects (Taylor et al., 1957), and the occurrence of pallor and sweating, the hypophyseal region appeared to be the logical site of synthesis. However, Money and Wood (1970) did not observe changes in susceptibility to motion sickness in seven dogs
Neural mechanisms involved in motion sickness. Structures joined by the wide shaded lines are considered indispensible to the vomiting characteristic of motion sickness in dogs. (From Money and Wood, 1970).
after transbuccal hypophysectomy and partial hypothalamic destruction. They concluded that it was unlikely that hypophyseal hormones play a direct role in induction of vomiting in the normal animal.

However, Polis (1961) observed a significant increase in survival time of rats exposed to high linear acceleration stress after hypophysectomy. This increased tolerance was lost after several weeks. Adrenalectomized rats exhibited an initial loss of tolerance to acceleration, but this susceptibility tended to disappear later. In essence, although marked differences were evident early in the postoperative period, hypophysectomy and adrenalectomy together appeared to oppose the effects of either operation. Ultimately, rats with either or both operations tended to react to acceleration stress in a manner similar to that exhibited by control animals. Subsequent studies have related levels of nucleotides in the cerebral tissues to survival times of rats exposed to acceleration stress (Shmukler, 1972) (See p 57).

Giurgea et al. (1967) suggested that certain antimotion sickness drugs function by raising the level of γ-aminobutyric acid in the brain. In theory, motion would alter output of the vestibular centers of the cerebellum, resulting in a decrease in γ-aminobutyric acid, or in the presence of high concentrations of the substance, the output of vestibular cerebellar centers would be unable to affect the chemoreceptor trigger zone normally (Money and Wood, 1970). In limited studies of dogs treated with amino-oxyacetic acid to raise brain levels of γ-aminobutyric acid, Money and Wood (1970) concluded that the level of brain γ-aminobutyric acid probably plays little or no role in development of motion sickness.

Numerous studies have shown that levels of blood and urinary output of 17-hydroxycorticosteroids and catecholamines are increased in both susceptible and nonsusceptible subjects after exposure to motion (Colehour, 1965; Colehour and Graybiel, 1964, 1966; Goodall, 1962; Goodall and Berman, 1960; Goodall et al., 1964; Hickler et al., 1959; Sundin, 1958). In another study, no change in excretion of 17-hydroxycorticosteroids was found until the 8th to 10th day of living in the slow-rotation room (Graybiel et al., 1965). An increase in excretion of these corticoids is an expected consequence of anxiety, or stress; however, the basic mechanisms underlying alterations of blood levels or increased excretion of catecholamine derivatives and 17-hydroxycorticosteroids after exposure to accelerations producing motion sickness remain to be investigated.
D. RESEARCH OPPORTUNITIES

The anatomical tracts of the vestibular and central nervous system that are involved in motion sickness and the role of the chemoreceptive trigger zone and the vomiting center have been defined (Borison and Wang, 1953; Ito, 1970; Nyberg-Hansen, 1970; Sala, 1965). However, the neurophysiology and neurochemistry of central nervous system structures in motion sickness are known only indirectly; they have been inferred primarily from studies of symptom induction. Recent advances in neurophysiology and neurochemistry suggest numerous opportunities for research on central nervous system activities in motion sickness. Reevaluation of previous studies has revealed several opportunities for research on motion sickness utilizing the techniques and knowledge gleaned from related disciplines.

1. Organization of Neural Tracts

As noted previously, further investigation of neural pathways from the vestibular end-organs to centers within the central nervous system that modulate responses to real or apparent motion would be useful (Section V, B). The scanning electron microscope, together with the electron and optical microscope, and special staining techniques are being utilized to delineate the nerve pathways or sensory systems (Heimer, 1971). Use of fluorescent dyes, autoradiography and other chemical techniques developed in the past decade might assist in further elucidation of neuronal pathways active in the motion sickness syndrome.

Crain (1972) has reported that tissue culture techniques provide another approach to the study of organization and development of neural functions. Using cultures of several types of embryonic central nervous system explants, he has shown that the cultured tissues exhibit bioelectric discharges similar to normal tissues in vivo. Crain (1972) suggested that these techniques could provide insight into early behavioral development. These techniques might be applicable to the study of neural development in animals susceptible or resistant to motion sickness.

In an unrelated series of investigations, Gaze and Keating (1970; 1972; Keating and Gaze, 1970) have studied the development of neural tracts between the retina and optic tectum of the newt. They observed that normal or cut nerve fibers from the retina and from the optic tectum grow toward one another with remarkable individual nerve fiber specificity.
The concept of sensory cells and neurons with specific "labels" for each other is not new, but the experimental evidence of Gaze and Keating (1972) for systems of nerve fibers matching, even after surgical separation or alteration of eye location, is of fundamental significance. There is some indirect evidence that this phenomenon is present in vestibular nerve fibers. Wilson et al. (1972) have shown that much of the specific semicircular canal neural input to the vestibular nuclei is preserved and identifiable in neurons leaving the vestibular nuclei. Similarly, Llinas et al. (1971) found that Purkinje cells respond individually to inputs that arrive via several parallel fibers from vestibular neuroepithelia. If the specificity within the vestibular-cerebellar pathways (Llinas et al., 1971; Wilson et al., 1972) is developed during early growth and development by the systemic recognition of "labeled" neurons (Gaze and Keating, 1970, 1972; Keating and Gaze, 1970), it would help explain the behavioral observations of immunity to motion sickness in infants and the differential development of responses to motion evident in adults. Studies of the responses of young animals to motion following embryological manipulation of vestibular nerve fibers would be appropriate. It would be of interest to investigate the developmental changes within the vestibular organs of the flounder during eye migration (See Section VII, C).

2. Animal Models

It is essential that more definitive studies of the central nervous system activities be undertaken using animal models with pathways of information processing similar to those in man. Most studies have used the dog, cat, or other large mammals as animal models (Money, 1970). As more critical techniques are applied to the study of motion sickness, careful attention to selection of the proper animal models must be made. For example, Guedry and Collins (1967) have shown that the nystagmatic responses of man and cats to prolonged angular acceleration are basically dissimilar. These observations suggest that central nervous system suppression of primary vestibular reactions in cats is not the same as in man.

3. Cerebellar Activities in Motion Sickness

Because the cerebellum interacts with, or is connected to, almost all peripheral and central nervous pathways, it has been studied in detail. The overall inhibitory functions of the cerebellum have been determined from extensive neuroanatomical and neurophysiological studies (Eccles et al., 1967; Evarts et al., 1972; Fields, 1970; Fox and Snider, 1967).
Many investigators agree that future research should place additional emphasis on the importance of the cerebellum in the mediation of motion sickness. One possible key to the development of the motion sickness syndrome may be the ways in which this behavioral constellation is unique by comparison with other induced forms of vomiting and with other responses to motion. It may be more useful to study the emesis associated with motion sickness itself, rather than studying those features it shares with other forms of emetic behavior. Similarly, there is a need for additional research on patterns of real and apparent motion that provoke the full range of motion sickness symptoms including emesis, rather than responses to motion alone because these may involve separate central control processes (See Section IV).

There is a need to clarify more critically the role of the emetic chemoreceptor trigger zone in motion sickness. Studies should be undertaken to determine whether destruction of this receptor site eradicates only the vomiting symptom of motion sickness on the entire pathophysiological syndrome. It is recognized that this receptor site is located in a very compact region of the brain, but recent advances in microsurgery suggest that more precise and selective experimental lesions are now possible. Further research is required to establish how and where the chemoreceptor trigger zone fits into the chain of reflex transmissions within the vestibulo-cerebellar-reticular neural pathways that characterize the motion sickness syndrome.

In a recent review on the role of the cerebellum, Thach (1972) concluded that cerebellar output is involved in initiation and maintenance of some types of movement and posture and that discharges from specific cells in several loci are related to specific movements and postural changes. With respect to motion sickness, it is generally agreed that portions of the cerebellum are involved in more than the vomiting mechanism. Considerable circumstantial evidence supports the concept of the cerebellum as a center for monitoring and correlating input signals from various sensory systems and initiating, by feedback mechanisms, motor and other neuron activities which result in physiological and behavioral responses that characterize the symptoms and signs of motion sickness (Crampton and Gall, 1971; Eccles et al., 1967; Ito, 1970; Kennedy, 1970).

Thach (1972) concluded that more precise information on timing, coding, and plasticity of cerebellar neuronal circuits is needed. Timing refers to whether cerebellar output precedes and initiates or
follows and modifies the responses of target neurons. Coding refers to the specificity of pathways related to specialized motor pathways (See p 43) and plasticity involves similarity or differences in relationships between cerebellar output and motor systems during learning of a response and the actual response. It would appear that motion sickness per se is a condition which could be used as an experimental situation to investigate these questions concerning the role of the cerebellum in behavior.

4. Cerebral Involvement in Motion Sickness

Motion sickness can occur in the absence of a functional cerebrum, however the activities of the cerebral cortex can modify the responses to motion because of its inhibitory control over cerebellar and brainstem mechanisms (Money, 1970). Some of these pathways from the vestibular nuclei and cerebellum to the cerebrum are known (Blakemore et al., 1972; Gernandt, 1950; Snider and Lowy, 1970); however, analyses of these facets of central nervous system interactions in relation to development of motion sickness have not been investigated in detail. Understanding the neurophysiological interactions of higher cerebral centers may lead to clarification of the causes of certain types of motion sickness such as that induced by apparent motion.

Evidence from other disciplines indicates the basic functional cortical unit may be viewed as a multicellular column, block, or sheet of cells that are continuous from the surface to the white matter (Blakemore et al., 1972). The columnar subdivisions of the visual, auditory, and motor cortex have been studied in some detail; however, the topology of cerebral units active in early responses to motion and those which may be active in motion sickness have not been identified precisely.

The suggestion that motion sickness may occur is thought to increase the incidence; similarly, voluntary mental activity during exposure may prevent or prolong symptom development. Several studies have shown conflicting results of placebo effects in protection against motion sickness (Money, 1970). These observations are indicative of cerebral involvement in the ultimate expression of response patterns generated initially by stimulation of the vestibular, visual, and proprioceptive systems. Finally, adaptation and habituation to motion also includes cerebral functions (Wendt, 1965).
These aspects of involvement of higher brain centers in development of motion sickness are not unique to this particular condition. In a recent review of brain functions, Blakemore et al. (1972) suggested that there is a need for more neurophysiological studies of how programmed motor responses and sensory stimulation become related. Based on evidence from several lines of investigation, they suggest that the hippocampus may play a significant role in the programming of acquired sensory-response patterns. Exploration of this concept may give useful clues to increased understanding of central nervous system pathways functional in motion sickness.

5. Neurohumoral Transmitters

The recognized latency between stimulation and response as well as observations of incremental adaptation to motion suggest that production, destruction, or accumulation of a neurohumoral substance might be involved in eliciting motion sickness. Early attempts to identify possible metabolic breakdown products of such substances in body fluids provided few definitive leads for further study. However scientific exploration in neurochemistry has increased substantially in the past two decades. Within the broad context of the discipline of neurochemistry, many biochemical phenomena that contribute to the functional integrity of the nervous system and associated neurological disorders have been elucidated (Albers et al., 1972; Hall, 1972). For example, the basic physiological and biochemical properties of neurons appear to be quite similar in both invertebrates and higher vertebrates. Biosynthesis and a metabolic action of transmitter molecules, activation of postsynaptic membranes and the response to drug effects on nervous tissues have undergone relatively little evolutionary change from lower vertebrates to mammals (Schneider, 1973).

Much of the emphasis in these neurochemical studies has been directed at careful analysis of the processes of synaptic transmission. In order to understand signaling within the nervous system, it is essential to understand the mechanisms involved in mediation of nerve impulses by chemical transmitters at the synaptic junction. In addition, these discrete biochemical events of intercellular communication are important because the consequences of synaptic transmissions are the ultimate bases of behavior (Hall, 1972).

Within these advances in basic neurochemistry there are numerous opportunities for research on various facets of the motion sickness syndrome. The following examples of recent advances in
neurochemistry appear to be related to the underlying biochemistry of the central nervous system that may be altered by excessive exposure to motion.

a. Role of \(\gamma\)-aminobutyric acid. Notwithstanding the observations of Money and Wood (1970), a body of evidence supports the concept that \(\gamma\)-aminobutyric acid is a major inhibitory transmitter in the vertebrate central nervous system (Roberts and Hammerschlag, 1972). The basis of its action appears to be related to induction of altered membrane permeability to chlorine ions. This type of inhibitory effect has been found in preparations from neurons from the vestibular nuclei as well as other neurons within several parts of the cerebellum. The \(\gamma\)-aminobutyric acid system has been found in the retina, with highest activity in the sensory cells, in hippocampal pyramidal cells, and in the mammalian cortex (Roberts and Hammerschlag, 1972). These data suggest that the role of \(\gamma\)-aminobutyric acid in certain early responses of the central nervous system to motion should be reexamined.

b. Enzyme induction. Based on the observations of stepwise adaptation to motion (Borison (1970) and Graybiel (1970) suggested that enzyme induction might explain the course of adaptation. To date, little data supporting this concept have been collected. Whether or not the enzymes involved in synthesis of metabolism of these neurotransmitter substances are involved in the patterns of response that characterize motion sickness has not been investigated.

c. Biogenic amines. Nearly all of the neurohumoral transmitter chemicals are amines or amino acids. The most extensively studied substances are well-established transmitters, acetylcholine and norepinephrine and the related compounds; dopamine, serotonin, and histamine (Baldessarini, 1972; Hoskin, 1972; Snyder, 1972). However, glycine, glutamate, aspartate, acetylcholine, and noradrenaline are thought to function as neurotransmitters in excitatory and inhibitory tracts in the spinal cord (Roberts and Hammerschlag, 1972) and the cerebral cortex (Logan et al., 1972). The enzyme systems active in synthesis and metabolism of these substances have been studied in considerable detail.

Early studies of susceptible and resistant animals and man have established that differences in serum levels and urinary excretion of catecholamines and the related 17-hydroxycorticosteroids do occur in
response to motion (Colehour, 1965; Knoblock, 1965). Based on current understanding of the metabolism of biogenic amines in mediating synaptic transmissions at various levels within the nervous system, a reevaluation of the quantitative and qualitative aspects of their activity in relation to motion sickness would be appropriate. One or more of these substances may be the neurohumoral transmitter proposed by Borison (1970); in addition, detectable products of biogenic amine metabolism may serve as early indicators of central nervous system response to motion (See Section VIII, A).

As noted previously, little attention has been directed toward the mechanisms involved in the depression that occurs with motion sickness although psychiatric depressions have been the subject of study for many years (Lehmann, 1966). Recent studies indicate that metabolism of biogenic amines is important in several forms of depression (Eccleston, 1973). Money (1970) suggested that mechanisms underlying the depression observed in motion sick subjects might be similar to those of more prolonged mental depressive disorders. It is possible that altered patterns of biogenic amine metabolism found in psychiatric disorders may be analogous to changes produced in the motion sickness syndrome.

d. Prostaglandins. Several prostaglandins are known to be natural constituents of neural tissues and are released by brain cells following stimulation of afferent pathways. Cocconi et al. (1971) considered that the prostaglandins may function as mediators of synaptic transmission. However, the majority of available evidence suggests that they are more likely to function as modulating substances (Hinman, 1972; Ramwell, 1973; Ramwell and Shaw, 1971; Weeks, 1972). As such, the prostaglandins may have a role in the genesis of certain of the signs and symptoms that classically characterize the disorder.

Several mechanisms have been proposed to account for the reduction of norepinephrine release that occurs with repeated stimulation of adrenergic neurons. One concept involves prostaglandin activity. Hedqvist (1970) suggested that the release of norepinephrine was mediated by a negative feedback mechanism involving intracellular synthesis of prostaglandin E. Subsequently, evidence for this negative feedback system has been found in preparations of cerebellar neurons (Hinman, 1972), and other tissues (Pliskher and Green, 1973; Ramwell, 1973).
Polis et al. (1970) have shown that several prostaglandins injected into mice cause changes in plasma and brain phospholipids. The patterns of phospholipid alterations were similar to those induced by acceleration stress. Their results implicate prostaglandins in adaptive responses to stress by mobilization of stored energy necessary for motor and other activities involved in the reactions to stress.

These studies strongly suggest that prostaglandin metabolism in motion stressed animals and man would be a fruitful area for future research.

e. 3'-5'-adenosine monophosphate. The factors that affect impulse conduction by neurons are known to regulate formation and degradation of 3'-5'-adenosine monophosphate (cyclic AMP). In addition, interneuronal stimulation by release of neurohumoral substances initiates or modifies production of cyclic AMP in target cells (Robison et al., 1971).

Most investigators accept the concept proposed by Sutherland and colleagues (cf Liddle and Hardman, 1971) concerning the mechanisms of hormonal action. This concept holds that hormones are the first messengers, traveling from sites of synthesis to target organs or tissues. At the site of hormone action, they modify the intracellular concentrations of a second messenger. This latter substance initiates the metabolic activities that characterize the target tissue response to hormonal stimulation. Unless the target cells or tissues are continually exposed to the first messenger, the activity of the second messenger is short-lived because of enzymatic inactivation. Cyclic AMP is regarded as the classical example of the second messenger (Pastan, 1972).

There is little direct evidence to relate the metabolism of cyclic AMP to the development of motion sickness. However, the concept of primary and secondary messengers is certainly compatible with the initiation of responses to excessive vestibular stimulation. In addition, a number of indirect lines of evidence suggest that cyclic AMP activity could play a role in the recognized latency between stimulation and response, as well as incremental adaptation to motion.

For example, Siggins et al. (1973) found that direct application of norepinephrine to Purkinje cells alters the discharge patterns in a specific manner. The apparent effect is membrane
hyperpolarization caused by resistance to ion passage through the membrane. As a result of the hyperpolarization, neurons become less responsive to stimulation. Cyclic AMP, applied to Purkinje cells directly, mimicked the effects of norepinephrine. The investigators also observed increases in cyclic AMP activity in Purkinje cells when norepinephrine was applied or the neurons were stimulated. Similarly, catecholamines are known to stimulate cyclic AMP production in brain tissues (Klainer et al., 1962; Lake and Phillis, 1972). Greengard (cf Marx, 1972) has postulated that cyclic AMP regulates protein kinase systems at the synapse, which in turn are active in feedback mechanisms affecting inhibitory interneurons that secrete the neurohormone, dopamine. β-adrenergic blocking agents such as endogenous catecholamines, induce significant increases in plasma and urinary cyclic AMP levels (Liddle and Hardman, 1971). Finally, Sayers and Beall (1973) have reported that isolated cells from hypophysectomized rats required less adrenocorticotrophic hormone to induce the same level of cyclic AMP production than did cells from adrenal glands of control animals. This latter study suggests that both cyclic AMP production in endocrine gland cells and genesis of corticosteroids could be altered by changes in metabolism of the hypophyseal region (See Section VII, C).

These lines of evidence are unrelated to studies of motion sickness, but together they suggest that cyclic AMP metabolism may be involved in central nervous system activity initiated by vestibular stimulation. The interactions of biogenic amines, prostaglandins and cyclic AMP are not fully understood, but there is sufficient data to suggest that the neurochemistry of these compounds in motion sickness should be examined in detail in subjects exposed to motion.

f. Other transmitter substances. The possible existence of other specific neurochemicals or neurohumoral transmitters should not be overlooked. For example, Frank et al. (1970) reported that the pattern of aversive behavior in mice injected intraperitoneally with brain or liver homogenates of doner mice was similar to that displayed by donor animals after conditioning. They interpreted their results as evidence for transfer of a nonspecific stress-associated factor unrelated to memory. Bryant et al. (1972) have questioned this interpretation. Similarly, Goodman and Hiatt (1972) have reported the identification of a posterior pituitary gland factor that controls certain metabolic processes active in peristaltic contractions. They suggest the substance, coerin, is a hormone that controls gastrointestinal mobility in the bovine. Finally, Berl et al. (1973) have proposed that actomyosin-like molecules function in release of transmitter substances. They suggest that transmitter
release at sites of interaction between presynaptic vesicles and membranes is initiated by a contractile event which involves specific contractile proteins.

None of the above examples is directly related to the neurochemistry of motion sickness. However, they serve to point out that further exploration of central nervous system biochemistry may uncover substances or activities unique to the motion sickness syndrome.

6. **Other Aspects**

Irwin (1972) has stated that research on biochemical correlates of neural plasticity is hampered by several prevailing concepts within the field of neurophysiology. He suggests that future insights into the biochemical basis of brain functions are more likely to come from a comprehensive study of many biochemical processes and the way in which these relate to the overall anatomical, chemical, and cybernetic organization of the brain rather than too much emphasis on the synapse, nucleic acid metabolism, or cyclic AMP. The motion sickness state could be an excellent model system for such investigations.
VIII. RESPONSES TO MOTION PERCEPTION

Vestibular stimulation and central nervous system activities precede development of symptoms and signs of motion sickness. Excitation of autonomic nervous system processes accompany the onset of the disorder. With repeated stimulation and perception, adaptation and habituation occur, modifying the patterns of response to motion. These forms of reactions are all interrelated and exceedingly complex, leading to marked individual differences in susceptibility or resistance to motion sickness.

A. SYMPTOMS AND SIGNS

1. Background

The onset of motion sickness is characterized by a decline in subjective convictions concerning immediate health and welfare. Nausea is the most frequently reported symptom. Concomitantly, pallor and cold sweating develop, and vomiting occurs. These three signs are most frequently observed and are the usual diagnostic criteria used in both experimental and real life situations (Kennedy et al., 1968, 1971; Money, 1970; Reason and Graybiel, 1970).

Extensive clinical observation and experimental study have defined a broad array of signs associated with motion sickness including cardiovascular, respiratory, and gastrointestinal effects, changes in qualitative composition of body fluids, decreased body temperature, and other phenomena. Money (1970) has referenced these studies in his review on motion sickness. Investigations of biochemical changes in blood and urine during the onset of motion sickness have shown changes in glucose metabolism, electrolyte balance, and metabolism of corticosteroid hormones and their metabolites (Colehour, 1965; Knoblock, 1965). In general, entire patterns of metabolic and physiological alterations in body fluids are typical of responses to environmental stress.

Steele (1970) related symptomatology of motion sickness to maladaptation to the introduction of a novel inertial environment. He related the major symptoms to inadequate or inappropriate vascular or circulatory responses, resulting primarily from disturbances in central nervous system processing of sensory data.
Symptoms other than nausea and malaise include drowsiness, apathy, epigastric discomfort, headache, depression, fatigue, confusion, sensitivity to olfactory and gustatory stimuli, anxiety, anorexia, dizziness, indifference, and decreased performance efficiency.

In animal studies, induction of vomiting is the most frequently used criterion of motion sickness. In studies with human subjects, both objective measures such as pallor, sweating and emesis are used along with subjective estimates of onset or remission (Graybiel et al., 1968; Kennedy and Graybiel, 1965; Reason and Graybiel, 1970). In addition, controlled sequences of movements have served as a basis for developing techniques of assessing symptoms and signs (Kennedy and Graybiel, 1965; Miller and Graybiel, 1969, 1970). A quantifiable rating scale based on induction of malaise in a rotating chair has been shown to be correlated with susceptibility to motion sickness (Miller and Graybiel, 1970). Such techniques are useful in evaluating susceptibility or resistance of individuals, but they do not provide the direct information on early responses to motion that might provide clues to basic mechanisms that generate responses.

Nystagmus following vestibular stimulation has proven to be a reliable indicator of quantitative and qualitative activity of the vestibular end-organs (Wolfson et al., 1965). The movement of the eyes in nystagmus has an initial slow component in one direction and a second rapid motion in the opposite direction. For example, nystagmus to the right usually starts with ocular movement to the left and is followed by a rapid countermovement to the right.

The initial slow movement serves to maintain the eye position when the head moves relative to the earth and is due directly to stimulation of semicircular canal receptors by the angular motion of the head (Guedry, 1965). The second, fast component originates centrally (McCabe, 1965). The neural pathways involved in nystagmic eye movements are those known to interconnect the vestibular neuroepithelium, the vestibular nuclei, the medial longitudinal fasciculus and the oculomotor complex (Brodal, 1966). The quick secondary movement is monitored frequently; and Bergstedt (1961) has developed techniques for accurate recording of the slow component. Nystagmus in response to motion can be used as an early indicator of motion sickness in susceptible individuals. Techniques are available for critical assessment of nystagmic responses (Bergstedt, 1969; Honrubia, 1971a, 1971b, 1971c; Johnson et al., 1967; Stahle, 1958).
Schwab (1954) reported that pupillary constriction occurred during onset of motion sickness, although pupillary dilation usually is associated with frank motion sickness and emesis.

While pallor may precede sweating during development of motion sickness, the onset of sweating is recognized as an early indicator that can be monitored effectively (Crampton, 1955; McClure and Fregly, 1972; McClure et al., 1972; Parker, 1971). Graybiel et al. (1968) have suggested that the latency of onset may be a convenient diagnostic criterion of susceptibility. It is generally accepted that sweating of the volar or dorsal surface of the hands and feet occurs in response to arousal, whereas the sweating of other body surface areas usually occurs in response to thermal stimulation (McClure and Fregly, 1972). Regardless of experimental technique employed, palm or dorsal hand sweat responses are generally the most consistent early indicators (McClure et al., 1971).

Several investigators (McClure et al., 1971; Najayama and Takagi, 1959) have shown that the sweating response exhibits a pulsatile pattern, with increased and decreased flow rates that vary each 3 to 25 seconds. The pulsations are thought to be related to active sweat expulsion into sweat gland ducts as well as presecretory activity within the sweat gland.

The activities of the hypothalamic region are thought to be involved with initiation of autonomic responses such as sweating and pallor (Graybiel, 1969). Sympathetic adrenergic activity in the autonomic system can produce pallor and sweating and combinations of cholinergic blocking and norepinephrine activating agents are known to be effective antimotion sickness drugs (Wood and Graybiel, 1972). However, Money (1970) noted that the pallor associated with motion sickness has yet to be causally related to stimulation of autonomic activity. In addition, he suggested that available data are not inconsistent with the concept of a circulating chemical other than autonomic neurotransmitters.

2. **Research Opportunities**

The need to identify and select susceptible and resistant individuals has been the basis for development of several techniques for rating symptom and sign onset and remission (See Section VIII, C). It seems logical to suggest that investigations on signs with short latency after motion stimulation could provide clues to basic mechanisms.
a. **Biochemical signs.** The multiplicity of signs indicative of stress responses and the conflicting results of earlier studies of potential biochemical indicators of motion sickness have been factors in the apparent lack of research interest on early responses to motion. Recent advances in the development and automation of analyses of body tissues and fluids have greatly increased the efficiency and capacity of the biochemical laboratory (Moss et al., 1971). Much of the equipment, such as continuous flow analyses and computer assisted systems, was not available when components of body fluids were first analyzed in detail (Knoblock, 1965). The technological capacity to study many biochemical changes provides an opportunity to collect, store, and analyze the vast quantity of data that are necessary to correlate biochemical events with the signs associated with motion sickness.

b. **Central nervous system metabolites.** Production or elaboration of an emetic or other neurochemical entity as the first response of the central nervous system to motion has long been an attractive hypothesis. However, efforts to identify such metabolites have been unsuccessful. As noted previously (See Section VII, C), there is ample evidence from several disciplines to suggest the opportunity for further investigation of the role of corticosteroids and biogenic amines, \( \gamma \)-aminobutyric acid, prostaglandins and cyclic AMP in motion sickness.

Investigations of the biochemical responses of human subjects to vestibular stimulation in the slow-rotation room suggest numerous opportunities for further research (Colehour, 1965; Knoblock, 1965). It would be interesting to repeat these experiments using modern methods of clinical biochemistry. Furthermore, the experimental protocols might be modified to include analyses of body fluids before, during, and after real, apparent, or simulated motion.

In an early study of biochemical changes, Hamberger and Hyden (1949) observed quantitative and qualitative changes in nucleoproteins of the vestibular ganglion and Dieter's nucleus of the rabbit after exposure to angular acceleration. Based on current understanding these data were indicative of complex metabolic changes that are now known to occur in nerve cells (Albers et al., 1972).

At a more fundamental level, Roberts (1972), in reviewing results of a prolonged research effort on adrenocorticotropic hormone (ACTH) metabolism suggested a scheme that relates release of pituitary
adrenocorticotropic hormone following stress to the rapid rise in plasma corticosteroid levels that may activate adrenocortical steroidogenesis. It would be of interest to relate this concept of corticosteroid metabolism to the alterations of corticosteroid metabolism that characterize motion sickness.

Based on the concept that all physiological responses to stress have a common biochemical foundation, Polis et al. (1969) found that exposure to several stressors, including acceleration, were accompanied by significant increases or decreases in plasma phosphatidyl glycerol and seven other phospholipids. Equivalent changes were induced by prostaglandin E₁. In further related studies, Shmukler (1972) concluded that tolerance to acceleration stress in rats is dependent on maintenance of critical nucleotide levels in the brain.

Money (1970) noted that oligouria occurs regularly with motion sickness and appears to be associated with an identified circulating antidiuretic substance.

Pappenheimer et al. (1967) have shown that cerebrospinal fluid from sleep-deprived goats induces drowsiness when injected into another animal. It would be of interest to conduct similar studies with animals known to be resistant and susceptible to motion sickness. Labyrinthine-deficient animals could also be compared to normal animals and each group with each other, before and after exposure to quantified motion patterns.

In summary, circumstantial evidence strongly suggests that neurochemical substances may be active in perception of motion and development of symptoms and signs characteristic of motion sickness. These several aspects should receive additional attention for it is highly possible that such investigations will lead to the identification of biochemical correlates of symptoms and signs that are already well documented.

c. Cellular effects of motion. There has been considerable interest in the effects of weightlessness on biological systems from man to subcellular metabolic processes (Saunders, 1971). These studies on cellular systems, invertebrates, and plant material document specific cellular changes resulting from growth and development in the absence of gravitational force fields, during exposure to radiation, and under acceleration and vibrational stress. For example, although no significant
d. Pupillometry. Loewenfeld (1966) suggested that minute or transient alterations of the physiological state of an individual are especially evident at pupillary threshold response levels. In addition, these changes are a measure of a subject's autonomic nervous system balance. Measurement of changes in pupil diameter is a sensitive, reliable, and practical method with numerous applications in ophthalmology, neurology, and psychology. Techniques involving closed circuit television, infrared photography, and cinematography have been incorporated into pupillometry. It would be interesting to correlate other indicators of vestibular stimulation such as early nystagmus and motion sickness such as volar sweating, or malaise (as employed in diagnosis by Graybiel, 1969) with pupillary responses to various patterns of motion and acceleration. Furthermore, changes in pupillary response patterns might be early indicators of adaptation in the autonomic nervous system.

e. Other early indicators. Pompeiano (1970) and Ornitz (1970) have suggested that the relationship between rapid eye movement (REM) sleep and vestibular function should be studied more critically. The REM mechanism is thought to be triggered by a neurochemical substance that accumulates to a critical threshold level within a pontine center and is then released. Pompeiano postulated that the sensitivity of individuals to vestibular stimulation is inversely related to the duration of REM sleep and that the intensity of vestibular responses increase with REM deprivation.

It is generally accepted that females are more prone to motion sickness than males (Money, 1970). Age also affects susceptibility, with both sexes under 12 years of age and elderly more susceptible than young and middle age adults. In general, susceptibility decreases with increasing age from puberty to middle age. The sex difference is indicative of possible sex hormone influences after puberty; although even in
children under age 12, girls are more susceptible than boys. The age differences may be attributed to exposure, head position and adaptation (Money, 1970); however, the differential susceptibility of females and males should be examined more critically in view of the observations that few differences are evident in their responses to other forms of stress (Handler, 1970).

B. ADAPTATION AND HABITUATION

1. Background

Continuous or repetitive stimulation of any sensory modality, including the vestibular system, results in response decline. Such alterations in response are usually designated as the consequence of adaptation and habituation. It is well-known that repetitive exposure to motion normally results in a reduction in the severity of motion sickness; in fact, exposure to various patterns of motion is a useful therapeutic technique in controlling motion sickness. However, in a few individuals, responses are intensified rather than reduced. Because habituation and adaptation occur in a wide variety of natural and experimental conditions and because the processes are affected by many factors, the topic is one of the most controversial as well as most important issues in motion sickness research. A number of research programs on adaptive changes and habituation are currently active.

Most investigators agree (1) that adaptation or adaptive changes refer to the processes responsible for the decline in response with repeated stimulation and (2) that habituation refers to the processes that are involved in acquiring and retaining the adaptive changes. As noted by Money (1970) the response decline is real and measurable, but the mechanisms of adaptation and habituation have been studied only indirectly and are imperfectly understood. Groen (1965) and more recently, Guedry (1972) have suggested that central nervous system mechanisms rather than peripheral nervous system processes are responsible for the response decline in subjective effects of motion. Kennedy (1970) proposed that both adaptation and habituation have their basis in cerebellar activities. This concept is a modification of the thought that the cerebellum controls activity of the vestibular nuclei (Ito, 1970).

Reason (1969a) has explained adaptability in terms of two stages of central response. In the first, current sensory input is
matched to the neural record of previous exposures. The second stage
depends upon matching or mismatching of current input with data in the
neural store. If no incongruity in input and experience occurs, the
organism is already adapted. If there is a "mismatch," a series of
physiological and behavioral events occurs leading to either signal
matching and adaptation or to responses that characterize the signal
mismatch, i.e., motion sickness (Reason and Graybiel, 1972).

More recently, McClure (1972) proposed that stimulus
pattern determines the types of response decline. He suggested that
there are somewhat different response-decline phenomena associated
with continuous stimulation and with brief but repeated vestibular
stimulation.

Adaptation and habituation are topics of several current
studies, and the experimental work of the past several years has been
adequately reviewed and summarized by Clark (1970), Graybiel (1969),
Guedry (1972), McClure (1972), Money (1970), and Reason (1969a; 1969b).

2. Research Opportunities

There are a number of opportunities for research on adap-
tive changes and habituation that are currently being pursued; for example,
transference of adaptation phenomena (Dowd and Cramer, 1967; Reason
and Graybiel, 1969a, 1969b) and specific neural adaptation (Crampton
and Gall, 1971). The occurrence of motion sickness in astronauts returning
to earth after prolonged exposure (adaptation) to the absence of normal
gravitational force is a persistent reminder that additional research on
adaptation is required. Research investigators are aware of the need for
continued study of these phenomena as an approach to increased under-
standing of motion sickness.

C. INDIVIDUAL DIFFERENCES

1. Background

It is generally recognized that susceptibility to motion
sickness is an individual characteristic. Variation in symptom and
sign expression is both quantitative and qualitative. The effects of motion
on an individual probably form a continuum of slightly different responses
over a wide range. However, for reasons related to selection of individuals,
the patterns of response have been classified as resistance or susceptibility.
Dobie (1970) has shown that cupulometry cannot differentiate between sus-
ceptible and resistant individuals as had once been thought. Dobie's
Because motion sickness interferes with performance of military duties, prediction of susceptibility has been studied in considerable detail. Results of recent investigations, theoretical aspects, and usefulness of current selection procedures were topics discussed at a recent AGARD symposium on predictability of motion sickness in selection (1972). These topics are not included in this report, except where aspects of susceptibility prediction may provide clues to the fundamental basis of individual variation.

The classical orientation of biomedical research has been to derive from observational data generalizations that describe universal principles inherent in biological phenomena. Experiments and observations are made on individual organisms, and from these the investigator attempts to deduce those features that are common to all circumstances. Routinely, the investigator attempts to avoid consideration of individuals per se by studying large numbers of individuals and treating the observational data statistically, thus reducing inter-individual variations. This is often difficult in motion sickness studies because experimental constraints limit the number of subjects. Thus, the individual variation in immediate or prolonged responses to vestibular stimulation is often quite evident (Guedry, 1972).

Individual variability may also include intra-individual variation over time. In studies of animal or human response to motion, this second source of individual variation within the person from time to time is considered a consequence of adaptation or habituation. Because these two phenomena are ever present, the existence of some other basis of intra-individual differences over time can only be suggested.

The concept of variation is central to biometrics and statistical methods are useful in analysis of human biological variation (Vandenbark, 1966). It is generally assumed that variation means variability in data around a specific value. The usefulness of this approach for statistically delineating the range and patterns of responses in motion sickness has been hindered by the lack of a clearly defined endpoint short of emesis. However, several responses to motion such as nystagmus, sweating, time to emesis, or scores on the Motion Sickness Questionnaire, provide data that are amenable to statistical evaluation (Reason, 1969a).

Dubos (1969) has reported on the subtle effects of early influences of the environment on subsequent development of neural systems and behavior patterns in animals. There is considerable experimental evidence
supporting the concept that increased or decreased levels of early postnatal stimulation are factors in the development of sensory response patterns that characterize the adult (Schultz, 1965). This theory holds that the optimal range or level of variation to environmental stimuli within which the adult organism is capable of adapting is influenced significantly by the stimulation received at the neonatal stage. The fact that young animals and infants are immune or marginally susceptible to motion sickness makes this approach attractive.

Guedry (1972) has recently postulated that individual responses to whole body motion are developed early in postnatal maturaton. He points out that early in life, whole body motion is passive; later voluntary movements are a natural activity; and finally at maturity, voluntary whole body movements become partially subconscious responses. These changes in dominant types of motor activity are related to the development of peripheral and central nervous system pathways. Marshaling evidence from several fields, Guedry (1972) suggested that reactions to motion at several developmental stages are related to the stimuli which function as conditioning mechanisms. Ultimately, the stimuli that condition the responses of the individual are related to subsequent development of individual differences in motor reactivity, personality, and cognitive function. He postulated that differences in response to unnatural motion such as flight are a consequence of adaptation and habituation produced by exposure to natural motion.

Reason (1969a, 1969b) has approached the problem of individual differences on the basis of differences in perception of various types of periodic motion. He has postulated that individual differences in susceptibility to motion sickness reflect idiosyncratic variation in the initial strength of "neural mismatch" among sensory input signals, in the rate of adaptability, or in some complex function of both processes. Reason (1969a) has used the term "receptivity" to refer to the idiosyncratic way in which the central nervous system transduces stimulus energy and the term "adaptability" to indicate the rate at which an individual adjusts to sensory rearrangement. Reason and Graybiel (1972) reported experimental data that support the idea that both "receptivity" and "adaptability" contribute to individual variation in susceptibility to motion sickness. These data also suggest that the two processes are independent of one another within each individual. Adaptability appeared to be the more important in all subjects, but receptivity played a role in the final susceptibility of slow adapters.
These two approaches to the phenomena of individual differences in responses to motion are not inconsistent with one another. The basis of the "adaptability" suggested by Reason (1969a) could very well be the result of exposure to various types of motion and attendant feedback mechanisms that occur during early growth and maturation as postulated by Guedry (1972). Together these theoretical approaches to differential human susceptibility to motion sickness suggest that further insight into the fundamental nature of the disorder might be made through study of the development of individual differences.

2. Research Opportunities

A number of techniques are available for identifying individuals who can be classified as resistant or susceptible to various forms of motion sickness (Graybiel, 1973). For the most part, these tests have been developed as techniques of preselection, experimental study of response patterns, or adaptation to motion. Few studies have utilized these sophisticated methodologies to investigate individual differences per se. The concepts advanced by Reason (1969a) and Guedry (1972) could be explored further with the techniques of neurophysiology and neurochemistry (See Section VII).

a. Neurophysiology of maturation. The development of neural processes underlying individual differences in response to environmental stimuli during early maturation remains to be explored. Motion, as a stimulus, and motion sickness, as a response pattern, could be a useful model system for such studies. For example, Balázs (1973) has found that the majority of the cerebral cells of the rat are already formed at birth but that most of the cells of the cerebellum are produced postnatally. At birth, the cerebellum contains mainly Purkinje cells; other neurons including the stellato cells and granule cells are produced during the first few weeks after birth. The climbing fiber-Purkinje cell circuit is dominant in the immature cerebellum. As the other neurons are formed, mossy fiber circuits develop and the adult pattern of cerebellar activity becomes evident. Balázs (1973) has found that thyroid deficiency, inadequate nutrition, or corticosteroid treatment markedly alter the normal development of these neural pathways that coordinate motor activities related to equilibrium and posture.

A logical extension of these observations would be an investigation of differences in animal responses to various forms of motion under experimental conditions that would affect formation of neurons postnatally.
Based on a review of studies on schizophrenics and autistic children, Ornitz (1970) has concluded that central vestibular mechanisms are active in more than maintenance of equilibrium during maturation and growth. He suggested that the vestibular system plays a role in modulating the level of sensory input and level of motor output at times of intense excitation. These observations led Ornitz to consider that the characteristic symptoms were indicative of abnormal states of sensory and motor inhibition and absence of inhibition as the result of or associated with vestibular stimulation and response.

In a subsequent study, Ornitz et al. (1973) found that vestibular stimulation can increase the amount, variability, and clustering of spontaneous rapid eye movement during REM sleep in normal children. He concluded from these data that the vestibular system is involved in mediating the phasic activity of REM sleep. He postulated that the development of central vestibular control over phasic activity during REM sleep followed a maturational sequence and may be related to serotonin metabolism in the central nervous system.

These observations, together with the concept of Guedry (1972) concerning development of reactions to whole body motion during maturation, provide a basis for further investigation of the origin of individual patterns of response to motion. Indeed, motion during early development could be the stimulus for development of several processes of sensorimotor integration.

b. Autonomic nervous system activities. In general, the visceral organs are innervated by sympathetic and parasympathetic fibers and the innervations are reciprocating in the same viscus. In states of physiologic stress, widespread sympathetic discharge is recognized as a homeostatic phenomenon. Parasympathetic control is more discrete, usually localized, and concerned primarily with the functions of conservation and restoration of activity of specific organs such as the gastrointestinal tract and the cardiovascular system. In general, the sympathetic and parasympathetic systems are viewed as physiological antagonists. If one system inhibits a function, the other usually augments that function.

Extensive literature is available on the individual differences in the balance of the two branches of the autonomic nervous system (Hillarp, 1960; Wikler, 1957). Physicians concerned with the treatment of such diseases as peptic ulcer, spastic colitis, chronic pulmonary emphysema, and hyperexcitable emotional states recognize the clinical value of autonomic nervous system control by the proper selection of drugs to treat
these conditions. Pharmacotherapy of disease states related to an over-active sympathetic or parasympathetic nervous system is most effective, and a large number of drugs are useful because they selectively inhibit these structures. Thus, the sympathetic blocking drugs are effective in cardiac arrhythmias and the control of hypertension and the parasympathetic blocking agents are used to relieve the spasm of smooth muscle in pylorospasm and gastric hypermotility. The variability of individual responses to these drugs is large and the dosage must be titrated to the needs of each individual patient. These clinical observations support the view that people have different degrees of autonomic "tone" and as a consequence their responses to stressful situations differ (Cooper, 1967; McHugh, 1967; Stellar, 1960).

It is noteworthy that effective antimotion sickness drugs are categorized as autonomic drugs with an added effect on the central nervous system. Although a wide variety of drugs have been studied and some reported to be of limited value prophylactically in preventing motion sickness, their mechanism of action is not known (Douglas, 1970; Wood and Graybiel, 1972). Techniques are now at hand to study the degree of sensitivity of subjects to motion sickness, their individual level of autonomic balance, and their sensitivity to antimotion sickness drugs. It seems logical to investigate the possibility that people who are prone to motion sickness might have such attributes as a low pain threshold or a short attention span.

Studies should be undertaken to assess the level of autonomic balance in subjects by accurately measuring changes such as pupil diameter (Jasenski and Martin, 1967). Responses are complex but a definitive analysis with controls can be made. It would be informative to correlate these responses with other techniques for measuring individual sensitivity to motion. Pupillometry has been used effectively in evaluating an anticholinergic drug (Anonymous, 1968). Antimotion sickness drugs could be evaluated in a similar manner.

It is recognized that some individuals are prone to emotional imbalance, e.g., diarrhea, crying, vomiting, as a result of stressful situations. What is their degree of sensitivity to autonomic drugs as measured by pupillometry and is there any correlation with their sensitivity to motion? In a similar vein, is motion sickness a manifestation of the organism to the stress of motion, as tears from pain or laughter from pleasure? It seems logical to suggest that activities of the autonomic nervous system could be operative in the neural mismatch hypothesis proposed by Reason (1969a), particularly in the development and expression of "receptivity" (Reason and Graybiel, 1972).
c. Neurochemical differences. The identification of populations of susceptible and resistant individuals provides a basis for further study of quantitative and qualitative aspects of biochemical measures of response (See Section VII, C). These types of studies could be conducted with animals or human subjects selected on the basis of behavioral response patterns.
IX. RECOMMENDATIONS FOR FUTURE EMPHASIS

A number of research needs and opportunities for future research emphasis have been identified from a review of studies on motion sickness and investigations in related biomedical disciplines. It is not possible to assign priorities to specific research areas because this study covers a number of diverse fields. It is recognized that additional research on mechanisms underlying motion sickness will be costly. However, these costs must be weighed against the rising expenses of equipment and increasing investment in training qualified personnel.

A. NATURE OF THE STIMULUS

There are few systematic studies that have related the quantifiable parameters of real and apparent motion causing sickness to the incidence of motion sickness and the attendant diminution of human performance. There is a need to continue laboratory studies on:

- Angular accelerations and motions in one or more planes; and,
- Linear accelerations and motions.

There is a persistent need to relate knowledge on controlled patterns of motion to information on motion characteristics of ships, aircraft and vehicles, and further, to relate these types of stimuli to the induction of motion sickness. Knowledge of the range of possible motions of each type of craft is a prerequisite to evaluating responses of persons and their performance under such motion patterns.

These types of studies are particularly necessary in the development of high performance air and sea craft where the performance capacity of the machine may exceed that of the human operator, thus negating the value of the engineering advances being built into the machine.

(See Section IV, C, p 22)
B. THE VESTIBULAR AND OTHER SENSORY SYSTEMS

Despite critical studies of the vestibular apparatus in animals and man, many aspects of the anatomy and physiology of the system are incompletely understood. The understanding of motion sickness requires additional study of the specific receptors that respond to various types of accelerations and motion. The following topical areas should be investigated further:

- Development and maturation of vestibular end-organs;
- Structure and function of specific vestibular receptors; and,
- The role of visual and other sensory systems in response to motion and their interactions with the vestibular system in the development of motion sickness.

(See Section V, B, p 27 and Section VI, D, p 35)

C. CENTRAL NERVOUS SYSTEM ACTIVITIES

The anatomical tracts of the vestibular and central nervous system that are involved in motion sickness and, the existence of the chemoreceptive trigger zone and the vomiting center have been determined. However, the neurophysiology and neurochemistry of central nervous system structures in motion sickness are known only indirectly; they have been inferred primarily from studies of symptom induction. Advances in neurophysiology and neurochemistry indicate numerous opportunities for research on central nervous system activities in motion sickness, including:

- Organization of neural tracts, particularly (1) those interconnecting the vestibular end-organs with the chemoreceptive trigger zone and the vomiting center, and (2) those involved with development of adaptation;
- Further identification of cerebellar and cerebral activities in the development of motion sickness;
The role of neurohumoral transmitters in those neural tracts known to be involved in responses to motion and induction of motion sickness; and,

Investigation of the role of specific substances such as \( \gamma \)-aminobutyric acid, the several biogenic amines, prostaglandins, and cyclic AMP as early indicators of nervous system responses to vestibular stimulation.

(See Section VII, D, p 43)

The pharmacology of antimotion sickness drugs was outside the scope of this study. However, many investigators concur that there is a need to explore the mechanisms of drug action because this approach could provide opportunities for additional study of the physiological and biochemical basis of motion sickness.

D. RESPONSES TO MOTION PERCEPTION

It seems logical to suggest that investigations on signs with short latency after motion stimulation could provide clues to basic mechanisms. Circumstantial evidence strongly suggests that neurochemical substances may be active in perception of motion and development of symptoms and signs characteristic of motion sickness. It is possible that such investigations will lead to the identification of biochemical correlates of symptoms and signs that are already well documented.

Adaptation and habituation occur with repeated stimulation and perception and modification of patterns of response result from these processes. There are a number of opportunities for research on adaptive changes and habituation that are currently being pursued; for example, transference of adaptation phenomena and specific neural adaptation. There is a need for additional support for investigations of these phenomena as an approach to increased understanding of motion sickness.

A number of techniques for identifying individuals who can be classified as resistant or susceptible to various forms of motion sickness have been developed as techniques of preselection, experimental
study of response patterns or adaptation to motion. Few studies have utilized these sophisticated methodologies to investigate individual differences \textit{per se}. The existence of individual differences in resistance or susceptibility to motion sickness should be exploited as a research approach, including:

- Study of early influences of environmental stimuli on development of neural systems and behavior patterns;

- Investigation of changes in quantifiable responses to controlled vestibular, visual, and other stimuli during early childhood and adolescence; and

- Possible correlation of neurochemical and neurophysiological differences in susceptible and resistant individuals with the development of susceptibility or resistance and "adaptivity" or "resistivity" during growth to maturation.

(See Section VIII, p 55, 60, and 63)
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XI. CONSULTANTS

ON

A STUDY OF OPPORTUNITIES FOR RESEARCH

ON MOTION SICKNESS

AD HOC STUDY GROUP MEETING

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A STUDY OF OPPORTUNITIES FOR RESEARCH ON MOTION SICKNESS

Technical Report

Kenneth D. Fisher, and C. Jelleff Carr

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This study was undertaken to review work in this field and to identify new approaches to an understanding of the fundamental causes of motion sickness. It includes a brief overview of present research and suggests possible applications of advances in a number of biomedical disciplines that provide opportunities for research. The study discusses the lack of a universally accepted definition of motion sickness, the need to investigate specific stimuli that evoke motion sickness, opportunities for studies on the anatomy and physiology of the vestibular apparatus of animals and man, and how evolving knowledge of the neurochemistry of the central and autonomic nervous systems may be applicable to understanding some basic considerations of motion sickness. New techniques are now available for investigation of the development and maturation of vestibular end-organs, structure and function of specific vestibular receptors, and the role of visual and other sensory cues in evoking motion sickness. One of the most promising approaches may be the investigation of the role of neurohumoral transmitters during the period between stimulation and the generation of symptoms and signs. The phenomena of adaptation and habituation are discussed. It is suggested that the methodologies utilized in the experimental study of response patterns to motion and in preselection of men be used to study individual differences per se. It is possible that investigations of this type will lead to the identification of some biochemical correlates of symptoms and signs which are well documented. Research workers are aware of the need for continued study of these phenomena.
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