NAMRL-1182

PERCEPTION OF BODY POSITION AND SUSCEPTIBILITY TO MOTION SICKNESS AS FUNCTIONS OF ANGLE OF TILT AND ANGULAR VELOCITY IN OFF-VERTICAL ROTATION

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NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY

June 1973

Prepared for the
NATIONAL AERONAUTICS
AND
SPACE ADMINISTRATION

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NASA Order T-81633
Biomedical Research Office, Johnson Space Center
NASA Order T-5904B
Office of Life Sciences

Released by

Captain N. W. Allebach, MC USN
Officer in Charge

4 June 1973

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Naval Aerospace and Regional Medical Center
Pensacola, Florida 32512

INTRODUCTION

Constant-speed rotation of a subject about his longitudinal axis which has been slightly tilted with respect to gravity produces an unusual and ever-changing pattern of stimulation (2, 3). The effect can be illustrated by considering the subject stationary in an upright position, and having an acceleration vector rotate around him at an off-vertical angle of incidence equal to the chair's tilt. This mode of stimulation has proven to be highly effective in evoking symptoms that characterize motion sickness and, theoretically at least, provides adequate stimulation to the otolith and other gravireceptor organs, but probably not to the semicircular canals. This technique may therefore offer a simple, precise, and highly controllable method of grading a subject's susceptibility to motion sickness from otolithic stimulation and may complement those susceptibility tests in which the semicircular canals are the initial or primary etiological factor (8, 9).

Evidence from testing a few subjects highly resistant to motion sickness had indicated that a greater provocative effect was derived from increasing the off-vertical angle from 10° to 20° at various rotational rates, but the relative change in effectiveness was not explored (2, 3). In these earlier studies the method of grading susceptibility utilized a schedule of ever-increasing rotational rates, which often unnecessarily prolonged the test duration and frequently caused a very rapid rise in symptomatology when the adequately stressful rate was finally reached (2, 3). As a result, great care had to be exercised to prevent the overshoot of a preselected endpoint of mild severity, termed Malaise IIA (M IIA) by Graybiel et al. (4) and based on a numerical scale formulated by those authors. In addition, the original test method exposed the subject to periods of incremental increases in the vestibular stressor level. Low levels of stressor stimulation were usually initially compensated, and in the process might have served as training toward increasing adaptation, an undesirable factor when determining baseline and relative measurement of susceptibility among subjects.

The purpose of the present study was to explore: (a) the change in provocative effect of varying the rate of rotation from 2.5 rpm to 45 rpm about a slight (10°) off-vertical axis, and (b) by using a velocity within the range of maximum effectiveness, to measure the relationship between motion sickness susceptibility and varying degrees of off-vertical tilt from 2.5° to 25°.

PROCEDURE

SUBJECTS

Four young Navy enlisted men, ranging in age from 19 to 21 years, who had previously demonstrated motion sickness susceptibility to off-vertical rotation volunteered as subjects. Each was found to be healthy by a comprehensive Navy medical examination, given prior to his acceptance as a research subject, and remained so during the experimental procedure, as reported daily in his pre-examination

questionnaire (8). Functional tests of the semicircular canals (5) and otolith organs (6,7) plus those of postural equilibrium (1) proved further that those specific systems were functioning well within normal limits.

METHOD

A standard Stille rotating chair, Model RS-3, mounted on a motor-driven tilt base served as an off-vertical rotation (OVR) chair (Figure 1). The degree of tilt relative to the gravitational upright was registered on a large protractor scale. The subject's head was centered over the axis of rotation and held rigidly against the headrest by an adjustable strap across his forehead. A seat belt further secured him to the chair. His eyes were covered with a small padded goggle which did not interfere with an observer's being able to note facial flushing, pallor, and sweating. The combined weight of the subject and the chair superstructure was statically balanced in a 20° off-vertical position to ensure constant speed rotation ($\pm$ <0.1%) during the OVR tests. The chair was then returned to upright and accelerated at 5°/sec^2 until the selected terminal velocity was reached. After no less than 60 seconds' duration the chair was quickly tilted at 5°/sec to the selected tilt position and off-vertical rotation was continued until moderate malaise (M IIA) (4) was manifested or the time limit of 60 minutes had elapsed. If the malaise endpoint was reached, the chair was quickly tilted to the upright, which immediately abolished the stressor stimulus, and decelerated at 5°/sec^2.

Initially, the effect of the chair velocity in an off-vertical position was tested by exposing each subject to a schedule of several test velocities (2.5, 5.0, 10.0, 15.0, 20.0, 30.0, 40.0, 45.0 rpm), while maintaining in each case a 10° tilt of the rotational axis from upright. Each subject was tested twice, once in the clockwise and once in the counterclockwise direction of rotation, at each velocity. This procedure was followed by one in which the same subjects were tested once at each of the several tilt angles (2.5, 5.0, 7.5, 10.0, 15.0, 20.0, and 25.0 degrees) during a constant velocity of 17.5 rpm. That value, based upon an ongoing analysis of results from the first half of this study, was selected as representing the best estimate of a single rate of rotation that would produce a nearly maximum provocative effect. The scheduled order of presentation of each velocity and tilt angle was randomized not only for each subject, but also among subjects. Although the overt symptoms of M IIA (4) quickly disappeared, at least 24 hours separated the individual trials.

RESULTS

Tolerance of off-vertical rotation as reflected by the duration required to evoke M IIA is plotted for the four subjects in Figure 2 as a function of chair velocity (rpm). It was possible to draw an average subject-response curve (solid line of Figure 2) only between 10 rpm and 25 rpm since the M IIA endpoint was not reached at the other velocities by all subjects. This curve section was, however, extended in an idealized fashion (dotted lines) in both directions in Figure 2 to portray the marked general changes in response throughout the entire range of test velocities. SC, the most

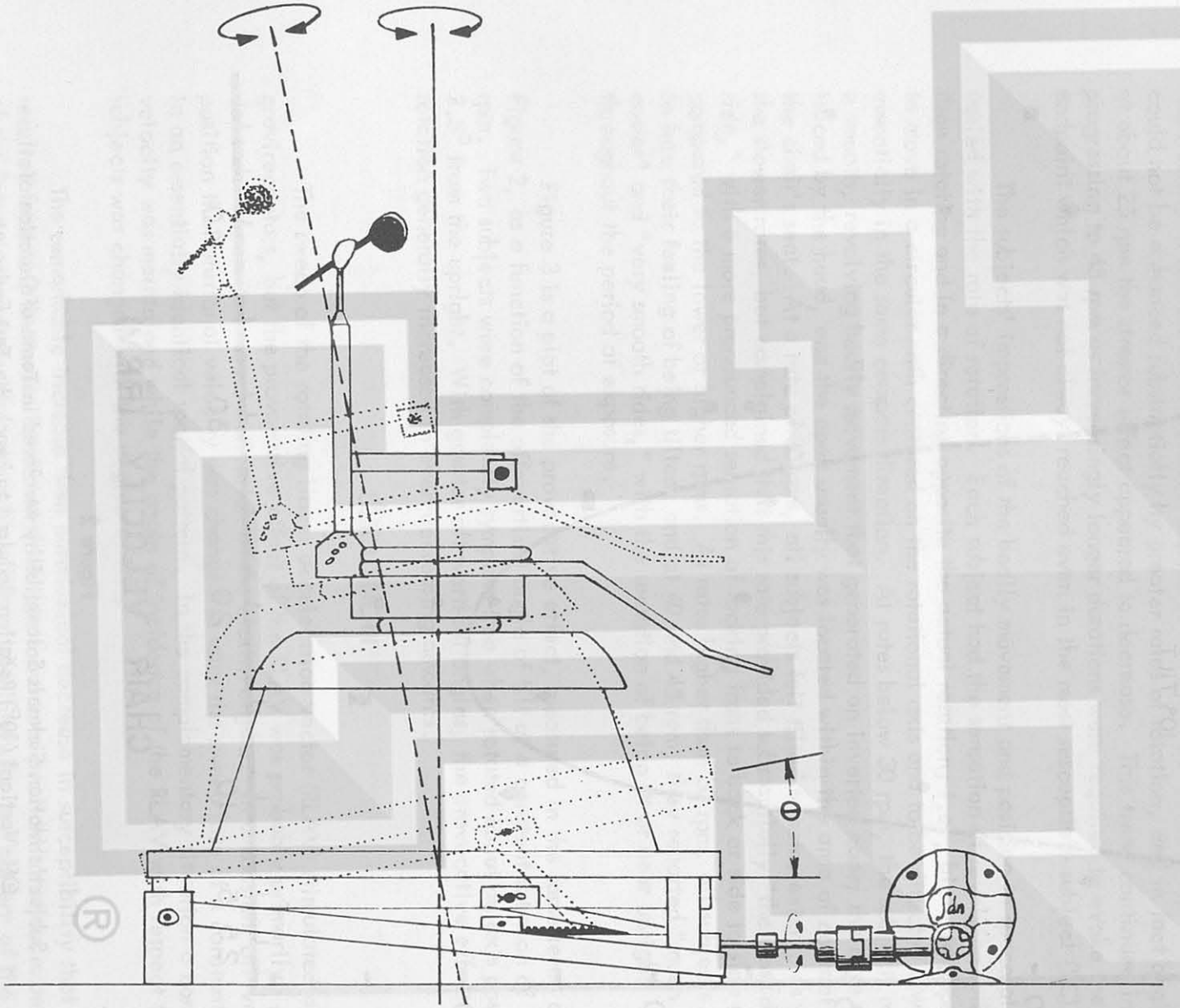

Figure 1

Off-Vertical Rotating Chair Device

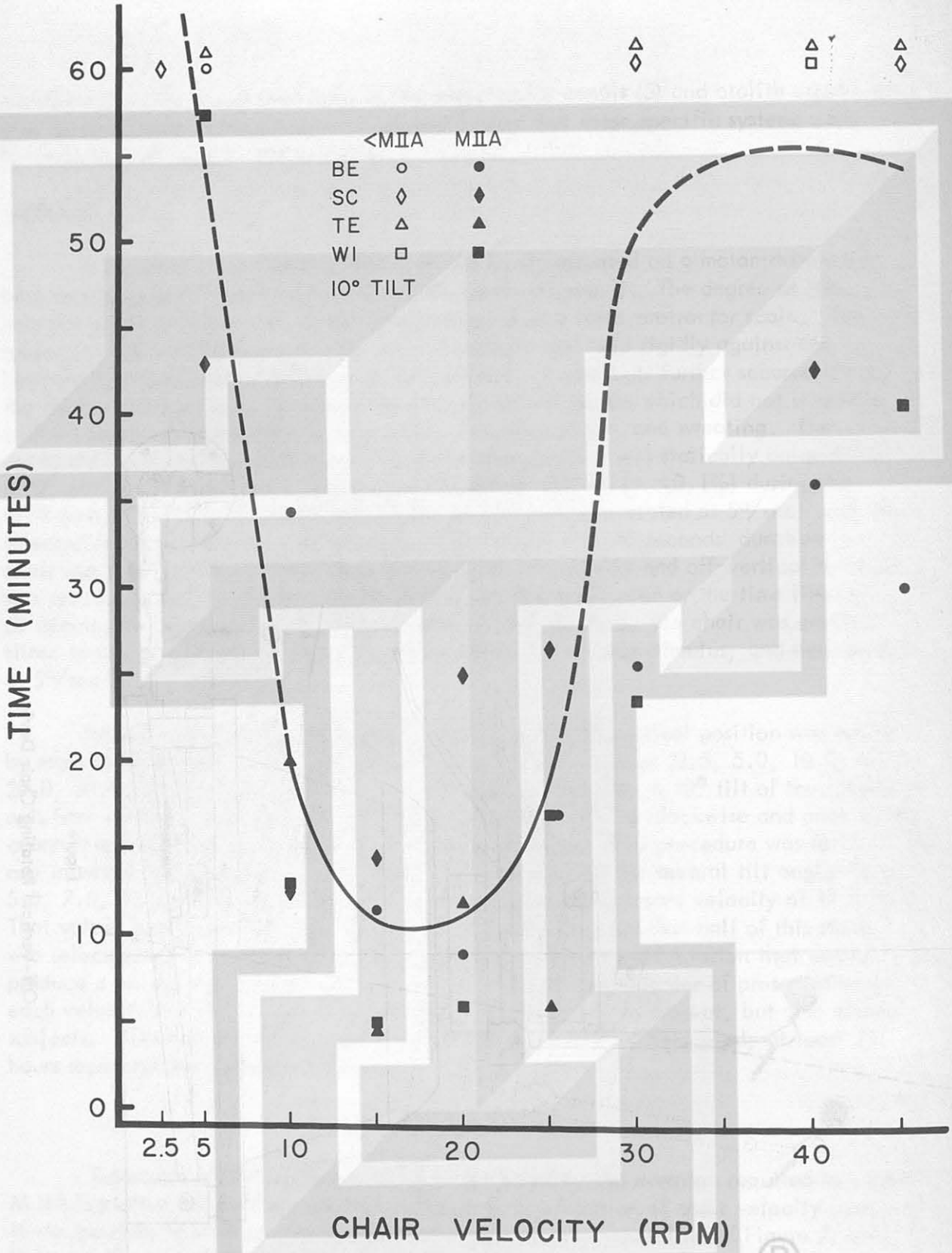

Figure 2

Subject's Motion Sickness Susceptibility Measured in Terms of Duration of Off-Vertical (10°) Rotation Required to Reach the Test Endpoint (Malaise IIA (M IIA) or 60 minutes) As a Function of Rotational Rate (rpm)

susceptible subject, reached the endpoint criterion (Malaise IIA) with an average of 43 minutes' exposure at 5 rpm but remained symptomless throughout the 60-minute maximum test period at 2.5 rpm. With 5 rpm subjects TE and BE were unaffected and subject WI reached M IIA just prior to the end of the test. Increasing the velocity from 5 rpm to 10 rpm evoked the endpoint in all subjects, three within 20 minutes. An even greater provocative effect was found at 15 rpm and 20 rpm, with all subjects manifesting M IIA within 15 minutes' exposure. The provocative effect, however, could not be enhanced substantially by greater rates of rotation, and in fact beginning at about 25 rpm the stressor effect appeared to decrease. This trend continued in progressing to 45 rpm as increasingly longer durations were required to evoke the endpoint which was not always reached even in the most susceptible subject (SC).

The subjects' impressions of the bodily movement and position in space also varied with the rate of rotation. Each subject had the sensation of revolving rather than rotating and in a direction opposite the actual rotation; i.e., his head appeared to move in a circular path centered on the rotational axis and to be directed always essentially in the same compass direction. At rates below 30 rpm, the subjects reported a smooth, revolving bodily movement that generated an inverted cone; the base was traced by the head, and the apex usually was located within the area of contact with the chair's seat. At a rate of 30 rpm, all subjects felt tilted to some extent, as with the slower rates, but complained that this rate provided substantially "the most difficult ride," with a more pronounced sensation of rocking front to back or side to side as compared to the lower or higher rpms. At rates higher than 30 rpm, all subjects began to lose their feeling of being tilted, and at 40 and 45 rpm, they reported "much easier" and "very smooth rides," with the sensation of being at or near upright throughout the period of exposure.

Figure 3 is a plot of the provocative effect, measured in the same terms as Figure 2, as a function of the off-vertical angle of tilt at a constant rotation of 17.5 rpm. Two subjects were completely symptom free when rotated about an axis positioned 2.5° from the upright. With greater off-vertical angles, the provocative effect of rotation generally increased in ever-decreasing amounts.

DISCUSSION

The sweep of the rotating linear acceleration vector (RLAV) stimulated all gravireceptors, but the provocative effect of the RLAV was probably primarily dependent upon its unusual activation of the otolith organs. In a constant off-vertical position the rotational velocity was changed to vary the sweep rate of a constant force in an essentially identical spatial pattern. In the complementary situation a constant velocity was maintained while the angle of incidence of the RLAV with respect to the subjects was changed with the degree of tilt.

The remarkable increase then paradoxical decrease in susceptibility that resulted from step increases in off-vertical rotational rate provided another example of the importance of the frequency as well as of the intensity and pattern of the stimulus

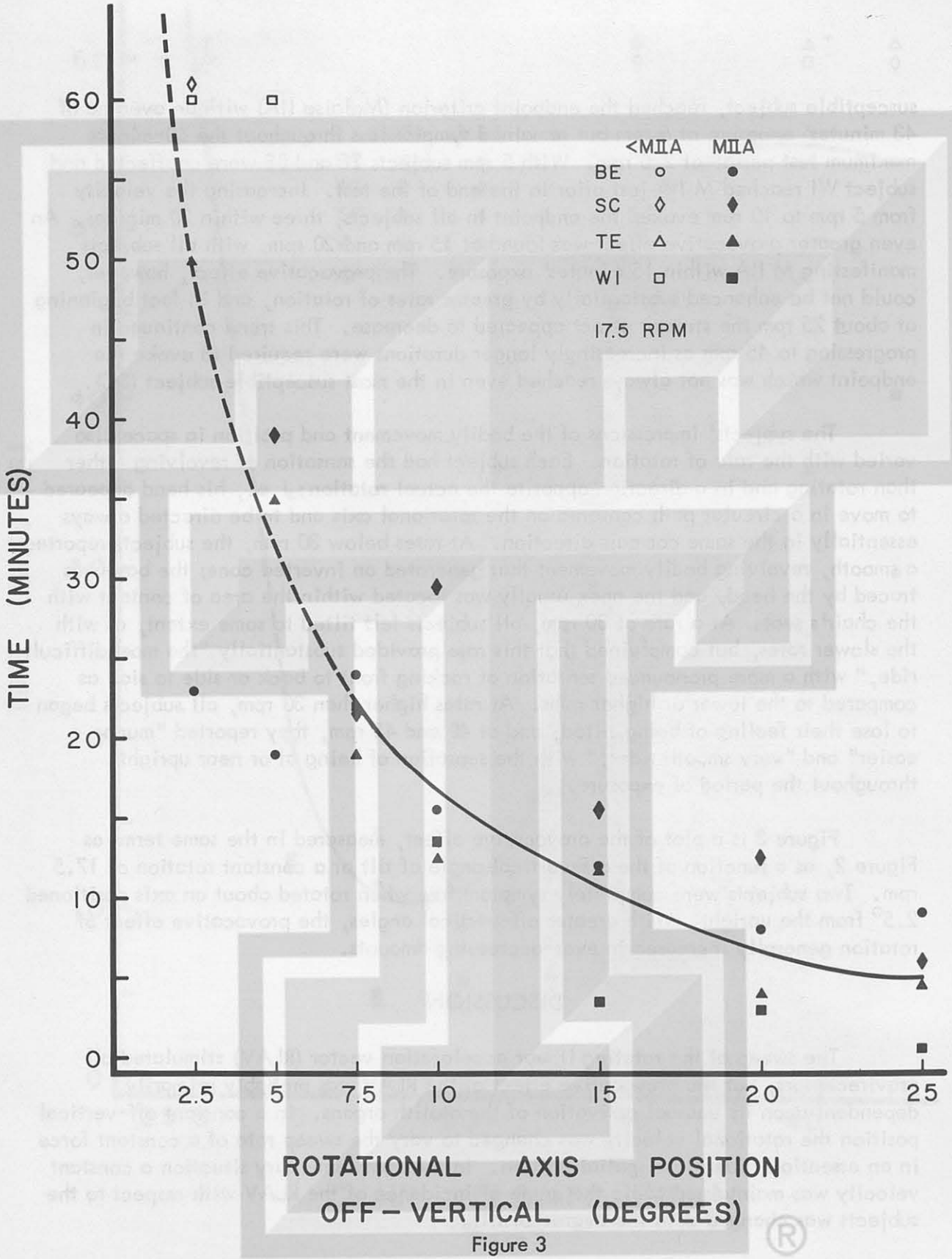

Figure 3

Subject's Motion Sickness Susceptibility Measured in Terms of Duration of a Constant Rotational Rate (17.5 rpm) Required to Reach the Test Endpoint (Malaise IIA or 60 minutes) as a Function of Off-Vertical Placement of the Rotational Axis

in the production of motion sickness. Wendt (10) found, for example, that a medium-frequency linear wave motion of 16 to 22 cpm was most effective in making men sick, but that there was a sharp decrease at subsequent higher frequencies. At the low rotational rates used in our study, normal physiological conditions were approximated and, as expected most subjects experienced little or no vestibular stressor effect. The slight increase in the provocative effect at 45 rpm from that seen at 40 rpm, and the extent to which the more rapid rotational rates failed to eliminate the evocation of motion sickness symptomatology in part of the subjects, may indicate the possible contribution of nonotolithic proprioceptors which were also stimulated by the RLAV. It is noteworthy, however, that the most susceptible subject (SC) who reached the Malaise IIA endpoint even at 5 rpm was symptom free at 30 rpm and at higher rates of rotation.

Figure 4 displays on a logarithmic scale the response data of Figure 3 within the range of off-vertical angles that was found effective in evoking M IIA in all subjects. The excellent empirical fit of these data with a straight line indicates that the stressor value of a relatively slow constant speed (17.5 off-vertical rotations per minute) varies directly with the axis tilt angle in accordance with Fechner's law. The nonotolithic receptors, which are also responsive to these experimental conditions, represent secondary stressor influences since they, per se, cannot evoke motion sickness (3,9). The primary genesis of the changes in the provocative effect as a function of off-vertical displacement of the rotational axis (RLAV angle) must therefore be vestibular. More specifically, this effect very likely involves the bizarre activity of cilio-otolith elements that would tend to respond slavishly to the everchanging direction of the acceleration vector sweep. If such otolithic activity was the basis for the Fechnerian relationship found, then it would follow that the stressor effect under our test conditions is in direct proportion to the integrated change in the amount of deformation of the macular sensory hairs, coded in logarithmic terms.

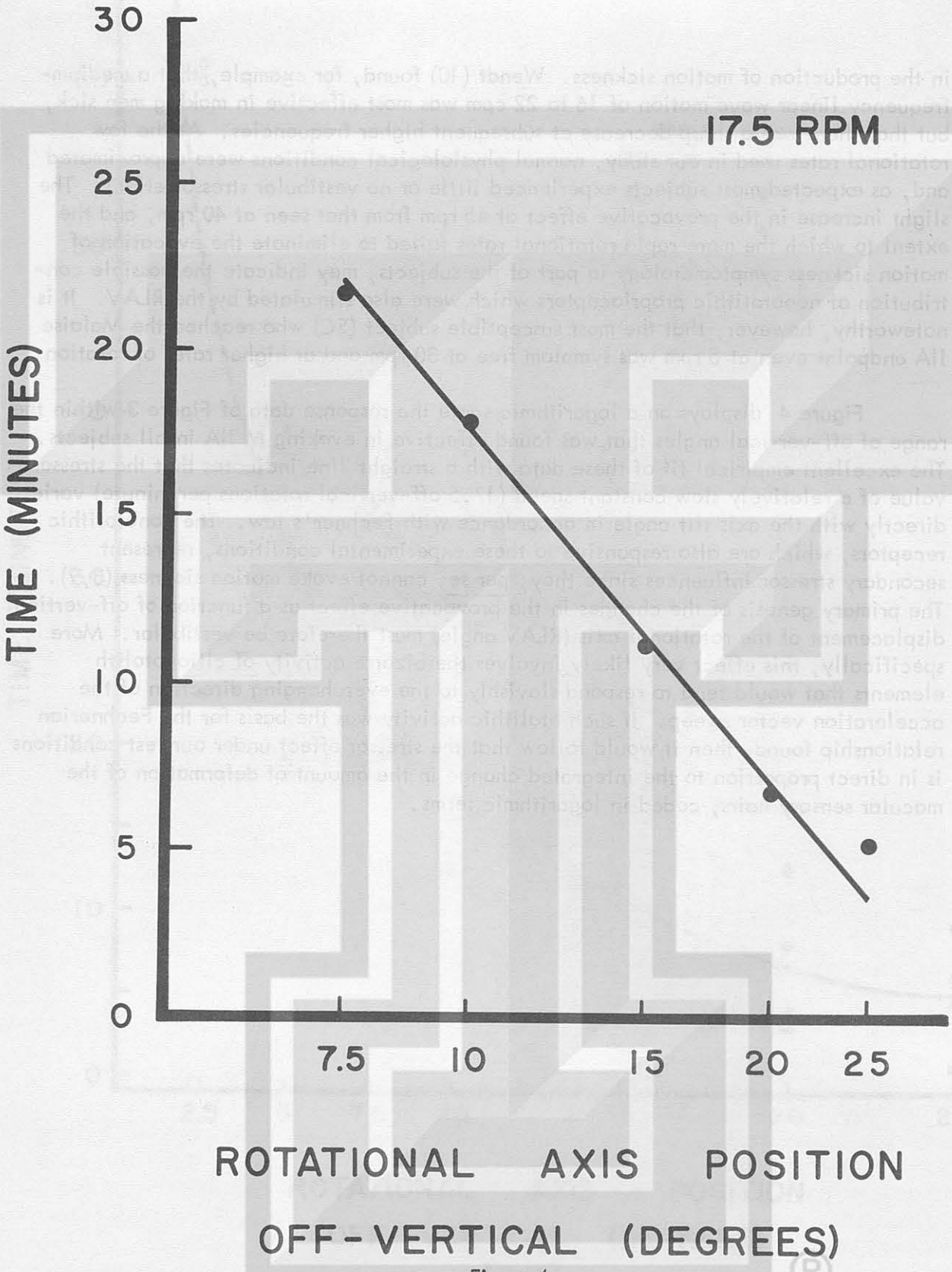

Figure 4

Data of Figure 3 Expressed as a Linear Relationship Between Duration of Exposure Required to Evoke Malaise IIA and Logarithmically Scaled Off-Vertical Position of Axis of Constant Speed Rotation (17.5 rpm)

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Unclassified

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*
Naval Aerospace Medical Research Laboratory
Pensacola, Florida 32512

2a. REPORT SECURITY CLASSIFICATION
Unclassified

2b. GROUP
N/A

3. REPORT TITLE
PERCEPTION OF BODY POSITION AND SUSCEPTIBILITY TO MOTION SICKNESS AS FUNCTIONS OF ANGLE OF TILT AND ANGULAR VELOCITY IN OFF-VERTICAL ROTATION

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*
N/A

5. AUTHOR(S) *(First name, middle initial, last name)*
Earl F. Miller II, and Ashton Graybiel

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
4 June 1973	10	10

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
NASA Orders T-81633 and T-5904B	NAMRL-1182
b. PROJECT NO.	
c.	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d.	

10. DISTRIBUTION STATEMENT
Approved for public release; distribution unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Prepared for the National Aeronautics and Space Administration	N/A

13. ABSTRACT

Four normal subjects manifested little or no susceptibility to motion sickness in a chair device tilted 10° off-vertical and rotated at 2.5 rpm or 5 rpm; with further rate increases the end-point of mild symptoms was always reached and within increasingly shorter durations. Susceptibility was maximal at either 15 rpm or 20 rpm but with higher rotational rates declined rapidly, reaching a plateau of relatively low susceptibility at 40 rpm and 45 rpm; furthermore, at these higher velocities, the subjects began to lose their sensation of being tilted off-vertical. Two subjects were asymptomatic when the chair was tilted 2.5° off-vertical and rotated at 17.5 rpm; with greater angles of tilt susceptibility of all subjects increased in ever-decreasing amounts.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Motion sickness						
Otolith organs						
Vestibular organs						
Body image						
Off-vertical rotation						

NAMRL-1168

THRESHOLDS FOR THE PERCEPTION OF ANGULAR ACCELERATION AS INDICATED BY THE OCULOGYRAL ILLUSION

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Prepared for the
NATIONAL AERONAUTICS
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NASA Order T-81633
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NASA Order T-5904B
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Released by

Captain N. W. Allebach, MC USN
Officer in Charge

11 June 1973

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SUMMARY PAGE

THE PROBLEM

To measure thresholds for perception of angular acceleration as indicated by the oculogyral illusion in 300 normal subjects and in 4 subjects with bilateral labyrinthine defects.

FINDINGS

A motorized chair with precise servo controls provided clockwise or counterclockwise rotation of the subject about his vertical axis at rates that varied in accordance with one of 24 extended trapezoidal-shaped profiles. Each profile consisted of four phases: 20 sec of constant positive acceleration, 25 sec at constant (terminal) velocity, 20 sec of constant negative acceleration, and 25 sec at zero velocity. Acceleration ranged in logarithmic progression from 0.02 to 6.00°/sec^2. The threshold response to clockwise and counterclockwise acceleration was determined by a double-staircase method and was defined as the lowest of the 24 accelerations at which the subject could perceive the oculogyral illusion in three out of four or four out of six trials ($\geq$ 67 per cent). This illusion was perceived as an apparent rightward or leftward movement of the visual target in the direction of acceleration. The target was a narrow collimated line of light contained within a goggle device and therefore fixed in relation to the subject.

The method provided a brief and reliable (ρ = .70) means of measuring the thresholds. The great majority of the subjects revealed no substantial directional preponderance (CW vs CCW threshold). Threshold frequency distributions for the two directions of rotation were similar and ranged in rate (deg/sec^2) from 0.020 to 0.950 with means of 0.146 (CW) and 0.152 (CCW). The threshold of response (deg/sec^2) in more than half the normal subjects was less than 0.10, in over three-fourths was less than 0.20, in over 90 per cent was less than 0.30, and in 100 per cent was less than 1.00. None of the labyrinthine-defective subjects perceived the illusion at the highest acceleration (6.00°/sec^2) employed.

INTRODUCTION

The oculogyral illusion may be perceived by a person passively exposed to angular acceleration as apparent motion (in the direction of turn) of visual objects that are fixed relative to him (8). The illusion has its genesis in the semicircular canals and a knowledge of cupuloendolymph mechanisms, the role of adaptation effects and the influence of secondary etiological factors are all essential for predicting its behavior under different stimulus conditions (1,2,6,9). Studies have shown that its perception under ideal test conditions yields lower threshold values than other canal response indicators: the manifestation of nystagmus, and the sensation and aftersensation of rotation (1,3,5,7,16). Indeed the thresholds of the illusion are so low that their measurement is limited by the precision of the rotating device. A highly sophisticated servo-controlled device, the Rotating Litter Chair (RLC), was developed expressly for determining with this indicator any changes in cupular thresholds of response that might occur during the prolonged weightless Skylab missions (14). The purpose of this report is to evaluate the RLC and a relatively short method for determining the thresholds of perception of the illusion in a large sample of normal subjects and in four deaf persons with severe bilateral labyrinthine defects.

PROCEDURE

SUBJECTS

Three hundred normal healthy men, ranging in age from 17 to 49 years, served as test subjects; most (261) of these subjects were less than 26 years of age. This group was comprised of 203 pilots or pilot trainees, 44 enlisted personnel, and 53 civilians. Each had demonstrated normal otolith and semicircular canal function, as indicated, respectively, by ocular counterrolling (11,12) and caloric response (10). In addition, four deaf individuals with severe bilateral labyrinthine defects, as defined in Table I, served in determining non-labyrinthine influences upon the perception of rotation.

APPARATUS

Rotating Litter Chair

The rotating litter chair (RLC) (Figure 1) is a relatively lightweight (~145 lb) motor-driven rotational chair device that is described elsewhere in detail (14). A servo-controlled d-c brush-type motor is programmed to rotate automatically a seated subject at any one of 24 velocity versus constant time (90 sec) profiles (Figure 2) within extremely narrow limits of precision (Table II). The 24 extended trapezoidal-shaped profiles yielded in progressive logarithmic steps a range of constant accelerations from $0.02^{\circ}/sec^2$ (step 1) to $3.00^{\circ}/sec^2$ (step 23); two log units of acceleration separated steps 23 and 24. The man-supporting superstructure and motor of the RLC are directly coupled to eliminate gear slack and perceptible vibration and therefore meet the physiological requirement of eliminating small performance errors that are normally within the sensitivity range of the delicate vestibular organs.

Table I

Clinical Findings in Four Deaf Subjects with Bilateral Labyrinthine Defects

Subj.	Age	Deafness Etiology	Age of Onset (yrs)	Hearing R	Hearing L	Caloric Response* R	Caloric Response* L	Date of Clinical Tests	Counterrolling Index†
GR	48	Mastoiditis	12	Nil	160 dB	Negl.	Negl.	1967	60
GU	22	Meningitis	4 $\frac{1}{2}$	$\geq$ 145 dB	$\geq$ 145 dB	Negl.	Negl.	1967	89
MY	26	Meningitis	8	None	None	None	None	1967	99
PE	33	Meningitis	12	None	None	Negl.	Negl.	1967	77

*Negligible or no observable nystagmus when tympanum irrigated with water at a temperature of 11° C or less.
†Calculated as one-half the sum of the eye roll measured in minutes of arc at the 50° rightward and leftward tilt positions.

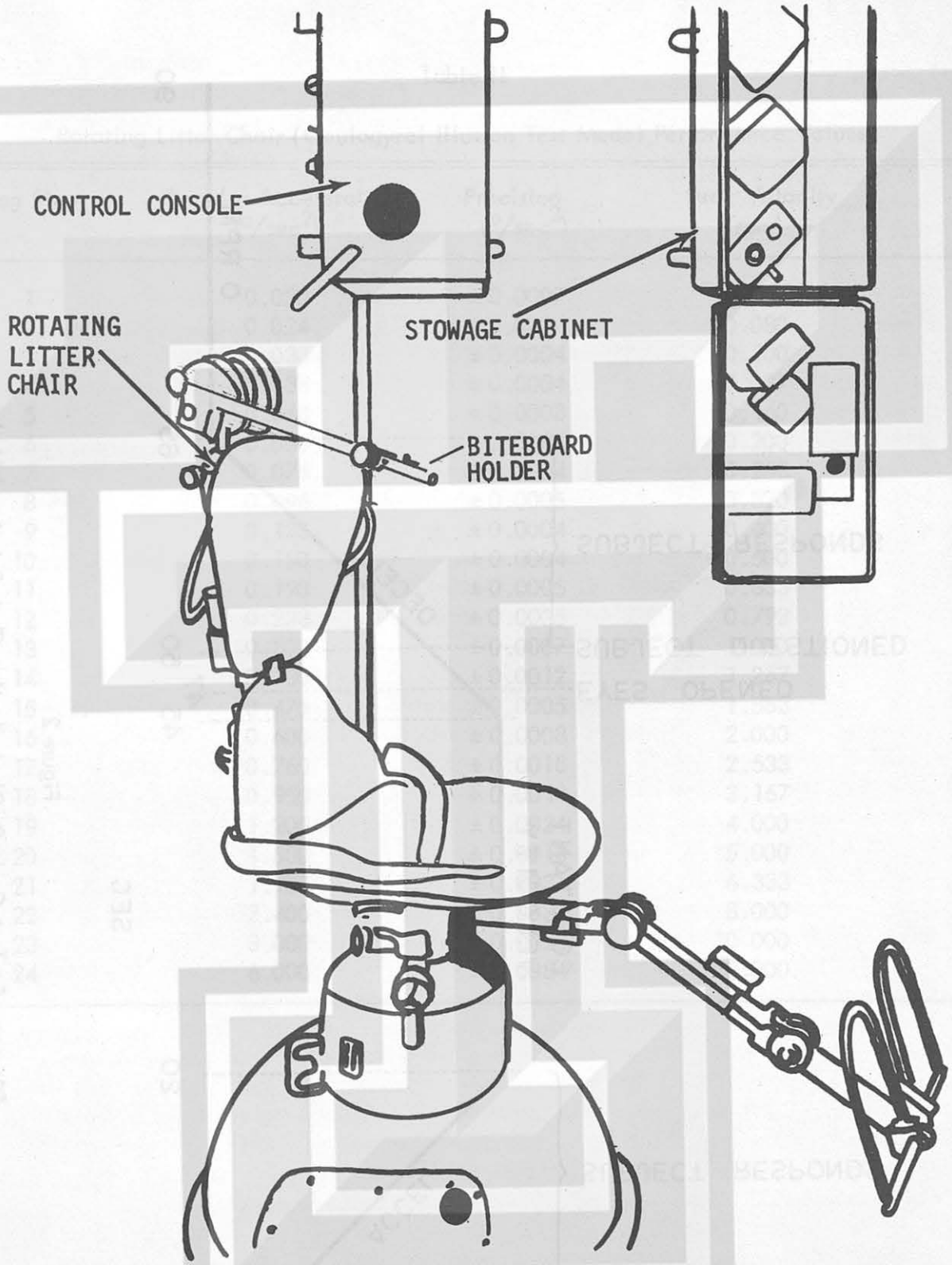

Figure 1

Diagram of the Rotating Litter Chair and Ancillary Equipment, Including the Control Console and Stowage Cabinet for the Vestibular Test Goggle and Biteboards

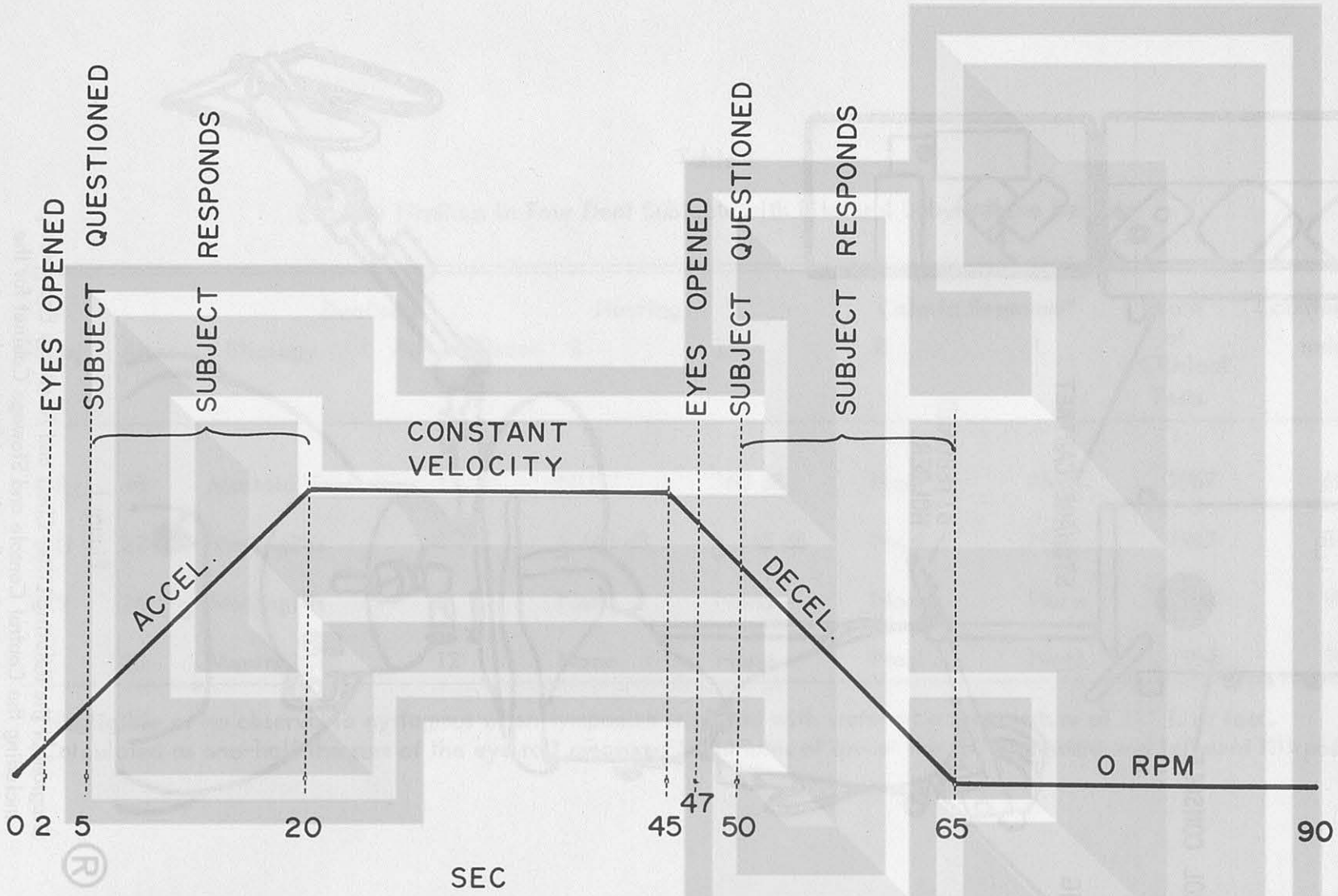

Figure 2

Diagram of a Test-Cycle Profile Indicating Chair Rotational Mode and Experimental Activity as a Function of Time

Table II

Rotating Litter Chair (Oculogyral Illusion Test Mode) Performance Values

Log Step	Angular Acceleration ($^{o}/sec^{2}$)	Precision ($^{o}/sec^{2}$)	Peak Velocity (rpm)
1	0.020	± 0.0007	0.067
2	0.024	± 0.0004	0.080
3	0.030	± 0.0004	0.100
4	0.038	± 0.0004	0.127
5	0.048	± 0.0008	0.160
6	0.060	± 0.0004	0.200
7	0.076	± 0.0004	0.253
8	0.096	± 0.0005	0.320
9	0.120	± 0.0004	0.400
10	0.150	± 0.0004	0.500
11	0.190	± 0.0005	0.633
12	0.238	± 0.0005	0.793
13	0.300	± 0.0007	1.000
14	0.380	± 0.0012	1.267
15	0.475	± 0.0005	1.583
16	0.600	± 0.0008	2.000
17	0.760	± 0.0018	2.533
18	0.950	± 0.0018	3.167
19	1.200	± 0.0024	4.000
20	1.500	± 0.0018	5.000
21	1.900	± 0.0036	6.333
22	2.400	± 0.0030	8.000
23	3.000	± 0.0028	10.000
24	6.000	± 0.0084	20.000

Vestibular Test Goggle

The vestibular test goggle (VTG), described in detail elsewhere (13), is a self-contained device worn over the subject's eyes (Figure 3). The collimated line-of-light target, the only thing visible to the subject, is self-illuminated by a radioactive source (tritium gas, 100 millicuries, AEC license Number 09-06979-03) contained in the goggle. Two knurled knobs permit the target to be rotated 360° about its center and moved vertically, from a straight-ahead position, ± 20° about the center of rotation of the viewing right eye; the left eye is occluded by being covered with a portion of the goggle. The device is held on the face by its attachment to a biteboard assembly which, in turn, is secured by an adjustable support connected to the RLC (Figure 4). The distance between the ocular and occlusal planes is adjusted so that the subject's visual axis in its primary position is essentially in the "horizontal" plane containing the optic axis of the target system. The target was found to be completely visible to all subjects having a wide range of interpupillary distances; so, no means of lateral adjustment was incorporated in the goggle.

METHOD

The subject's fitness for testing was determined by a questionnaire (Appendix A). The oculogyral illusion was demonstrated at the time of the biteboard fitting by having the subject observe the apparent movement of the test-goggle target during gentle side-to-side head movements.

The subject was then secured in a seated position within the RLC, and his biteboard and the VTG were affixed to the support mechanism of the chair. He engaged the biteboard with his teeth and donned the VTG by tilting his head forward 20°. The target viewed by his right eye was adjusted so that it appeared vertical and straight ahead. The purpose of the fixed head tilt was to place the "plane" of the lateral canals closer to the plane of rotation.

A sound source for signalling the normal subject was situated directly over his head, which eliminated it as a cue to the chair's rotational direction; the labyrinthine-defective subject was signalled by lightly tapping the top of his head. The rotational chair was located in a test cubicle, which permitted this area to be darkened and thereby removed any possible influence of any small openings between the goggle's padding and the face. During testing, auditory directional cues were effectively removed by having the normal subject wear earphones. All subjects used hand-held, color-coded lights to signal, when requested, the direction of apparent movement of the target. After one of the 24 acceleration rates was selected on the basis of the predetermined test schedule and subject performance, the program start switch of the RLC was pressed. After 2 seconds of constant positive acceleration, the subject was signalled to open his eyes; after 5 seconds' accumulative time, he was signalled again to judge whether the target appeared to move rightward or leftward, or to remain stationary. If the subject did not respond after 15 seconds' accumulative time, a third signal was given. If no response was received within 20 seconds' accumulative

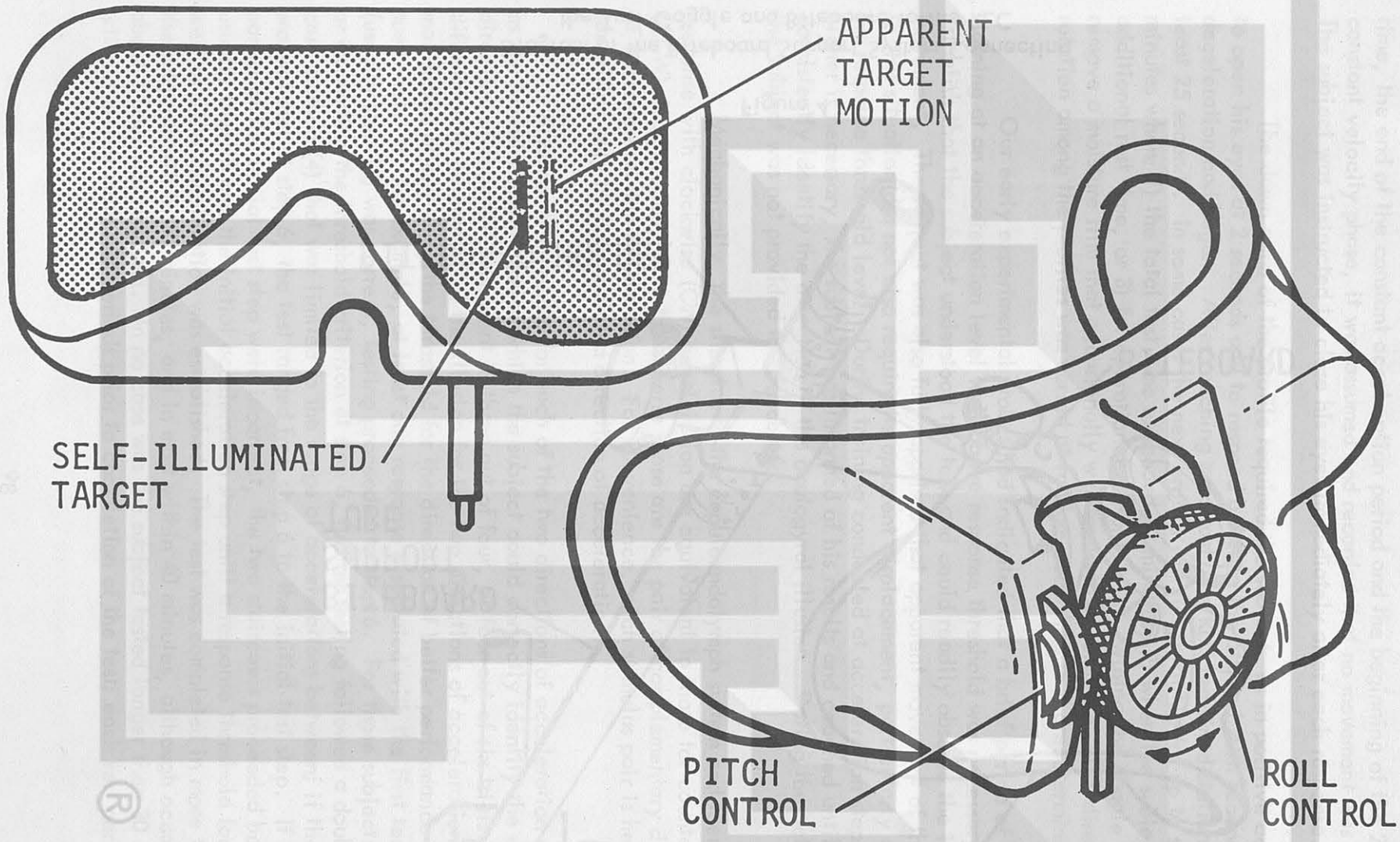

Figure 3

Diagram of the Vestibular Test Goggle (VTG). At Top a Rear View of the Goggle Illustrates an Apparent Rightward Movement of the Line-of-Light Target as Viewed by the Right Eye. The Bottom Half-Front View Shows the Knurled Knobs for Adjusting the Roll and Pitch Positions of the Target.

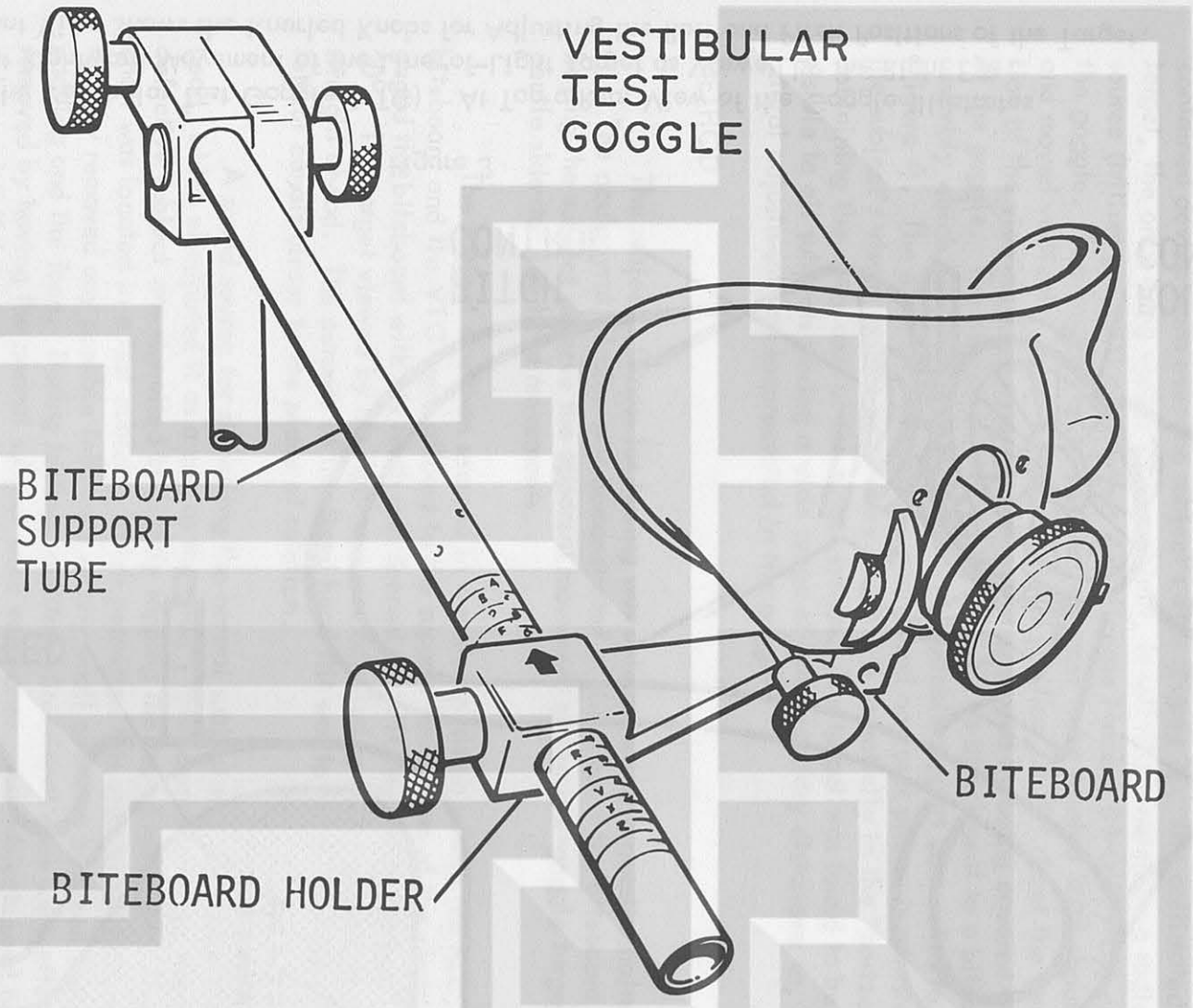

Figure 4

Diagram of the Biteboard Support System Connecting
the Test Goggle and Biteboard to the RLC

time, the end of the constant acceleration period and the beginning of the 25-second constant velocity phase, it was assumed and recorded that no movement was perceived. The subject was instructed to close his eyes immediately after each response.

The down ramp of the profile required the subject, as in positive acceleration, to open his eyes at 2 seconds and to respond between the 5th and 20th second after deceleration had begun. After reaching zero rpm, the RLC remained stationary for at least 25 seconds. In some cases the next profile was not initiated for up to several minutes when: 1) the total test time exceeded 30 minutes, 2) when the subject requested additional rest time, or 3) for operational reasons, e.g., wiping the goggle lens to remove a moisture film that occasionally was found to accumulate. The direction of rotation among the profiles was varied at random according to a predetermined schedule.

Our early experimental probes had indicated that a brief period of feedback training at an acceleration level well above response threshold was necessary to establish that the subject understood the task and could readily observe the illusory movement. The subject was also fully apprised that apparent movement of the target in this situation did not also require its apparent displacement, particularly at or near his response threshold level. During training conducted at acceleration step 12, or higher if necessary, the subject was informed of his results and coached until he could consistently identify the direction of the oculogyral illusion. During the actual test, the subject was not provided this feedback.

Mechanically, the stimulus to the cupuloendolymph system and therefore its response with clockwise (CW) acceleration are equivalent to those for counterclockwise (CCW) deceleration, as in the reverse sense are the pair of complementary directions of acceleration and deceleration. For convenience, each stimulus pair is henceforth identified only by its associated direction of acceleration.

A response threshold for each of the two directions of acceleration was defined as the lowest acceleration at which the subject could correctly identify the expected direction of apparent movement in three out of four, or four out of six trials. When a difference in perception of the illusion for the two directions of acceleration was manifested at any step, the threshold for the direction of better performance was pursued first. If, for example, at least one response associated with the first test profile (usually step 12) was correct, testing proceeded to step 6. For those subjects meeting or exceeding the threshold criterion at step 6, further testing followed a double-staircase method (4) that was limited to the range of accelerations between; if the criterion was not met at step 6, the test ranged from step 6 to the initial test step. If both responses at the initial test step were incorrect, the two staircases proceeded between usually step 15 and the initial acceleration step until a response threshold for CW as well as CCW acceleration was established. The test was completed in more than half the subjects within 30 minutes, and in most within 40 minutes, although occasionally about 1 hour was required. In no case was the subject tested longer than 30 minutes without one or more rest periods prior to completion of the test; each rest period of about

5 minutes was instituted with the subject remaining in the RLC but with his head removed from the goggle and biteboard support.

The oculogyral illusion threshold of each normal subject was measured by this procedure on two different occasions, separated by at least 24 hours, in order to determine test-retest reliability.

RESULTS AND DISCUSSION

The large number of trials and long test periods often covering many days or weeks that are typical in measurements of a response threshold were avoided in this study without apparent undue compromise in sensitivity or reliability by using 24 logarithmic step levels of accelerative stimuli. On a linear basis this schedule introduces ever-increasing increments of acceleration among the progressive test steps with the result, desirable from a practical point of view, that differentiability among individuals decreases as an indirect function of threshold level.

Directional preponderance, i.e., a difference in threshold for CW and CCW acceleration, was not manifested in 35 per cent, was less than $0.1°/sec^2$ in 84 per cent, and less than $0.2°/sec^2$ in 94 per cent of the normal subjects; the remaining subjects revealed a preponderance that ranged from 0.2 to $0.7°/sec^2$. Furthermore, a moderately high correlation ($\rho = .72$) was found to exist between data obtained with CW and CCW acceleration. A substantial directional (CW vs CCW) preponderance in the OGI threshold response would therefore not be the expected result in a normal individual. A follow-up investigation of the small number of subjects who demonstrated relatively large directional preponderances was not conducted, but a study of unilaterally labyrinthectomized individuals gave some evidence that an acute unilateral vestibular disturbance may cause a preponderance (15).

The individual thresholds for CW and CCW acceleration were averaged to obtain a single measure of test-retest reliability which proved also to be moderately high ($\rho = .70$). This level of reliability and the brief test period required make the method feasible as a clinical-type test of semicircular canal function. The large sample of normative data offers a substantial basis for comparing the OGI thresholds of response of individuals with possible vestibular disfunction.

Frequency distributions of the oculogyral illusion threshold values among all the normal subjects for CW and CCW acceleration are presented in Figure 5. The distributions were similar for the two directions of angular acceleration and ranged in terms of rate (degrees per second per second) from 0.020 to 0.950, with means of 0.146 (CW) and 0.152 (CCW), a median of 0.096 (CW, CCW), and modes of 0.096 (CW) and 0.076 (CCW). These same distributions expressed in terms of cumulative frequency are given in Figure 6. The distributions on a linear scale are skewed right: More than half the individual thresholds fell below $0.10°/sec^2$; over three-fourths were less than $0.20°/sec^2$; over 90 per cent less than $0.30°/sec^2$; and 100 per cent less than $1.00°/sec^2$. These findings compare well with those of Clark and Stewart (2) who found that the OGI thresholds of their 32 subjects ranged from $0.04°/sec^2$ (close to the lower limit of their

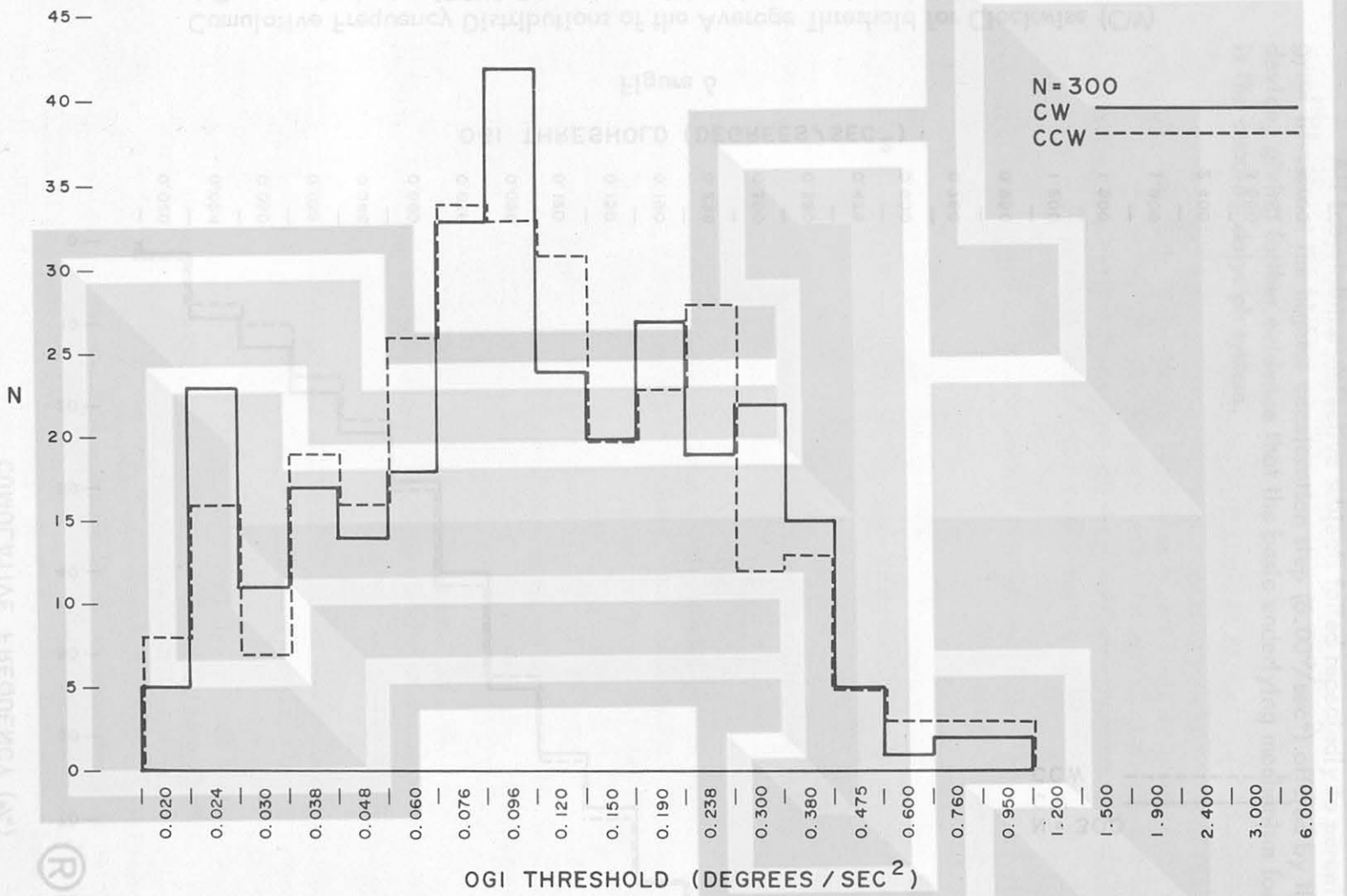

Figure 5

Frequency Distribution of the Oculogyral Illusion Threshold for Clockwise (CW) and Counterclockwise (CCW) Directions of Acceleration Among 300 Normal Subjects

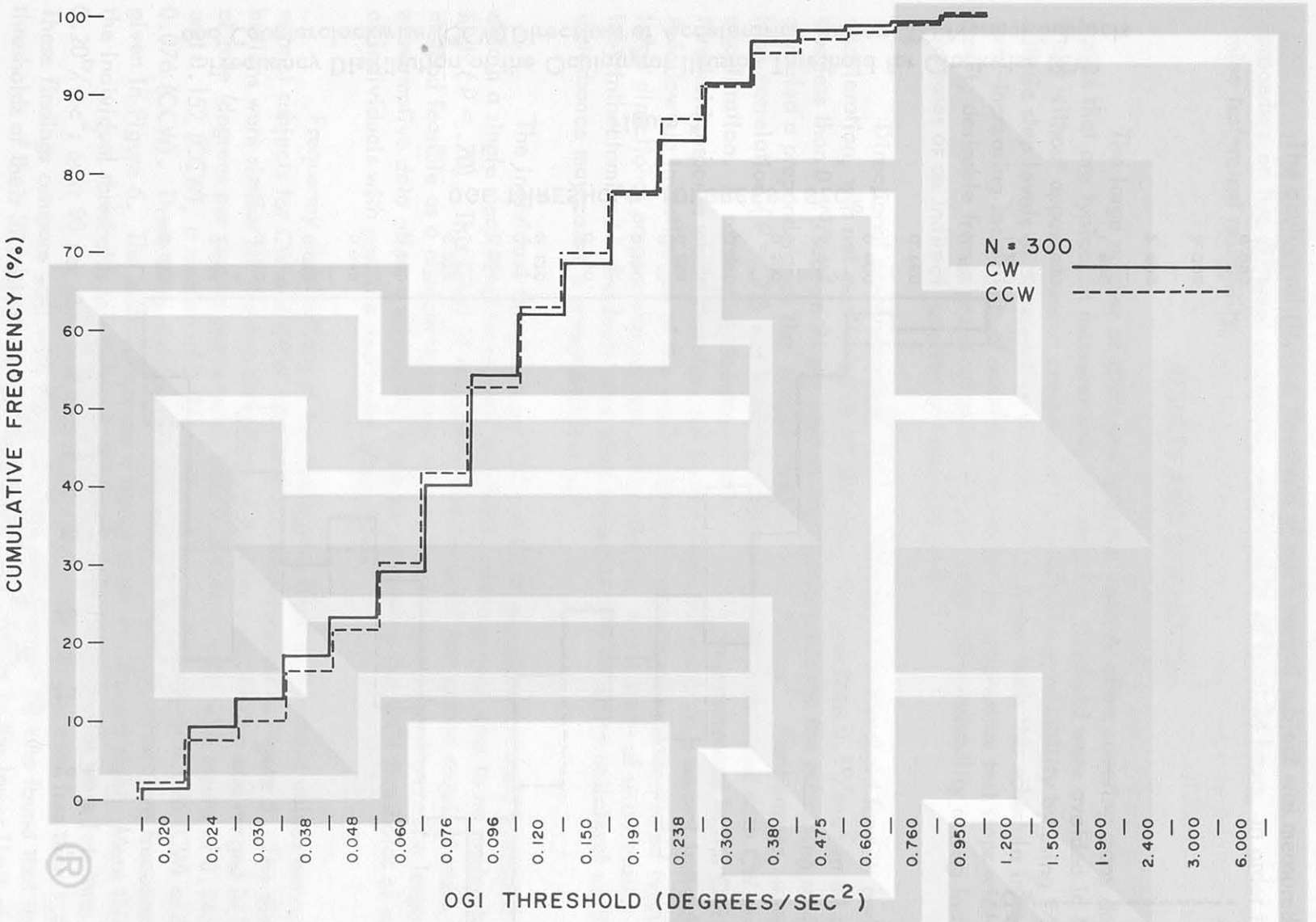

Figure 6

Cumulative Frequency Distributions of the Average Threshold for Clockwise (CW) and Counterclockwise (CCW) Directions of Acceleration Among 300 Normal Subjects

device) up to 0.28°/sec^2, and confirm their conclusion that normal healthy adult men have semicircular canals that are highly sensitive to accelerative stimulation.

All labyrinthine-defective subjects failed repeatedly to perceive the oculogyral illusion at the highest acceleration step (6.00°/sec^2) offered by the RLC test device, giving further evidence that the basic underlying mechanism for this illusion is the cupuloendolymph system.

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APPENDIX A

Subject's Pre-experimentation Questionnaire

Name/Number	Date Time
Last First Middle Initial	
Have you been well throughout the past week? YES NO	
Are you free of all major health complications? (e.g., heart disease, diabetes, back trouble, etc.) YES NO	
Are you in your usual state of fitness today? YES NO	
If no to one or more of the above questions, specify problem and include severity, time course, where localized, etc.	
How much alcohol have you consumed during the past 24 hours? (No. and kinds of drinks)	
How much tobacco in past 3 hours? Cigarette(s) Cigar(s) Pipe(s) full	
Have you taken drugs or medicine of any kind in past 24 hours? YES NO	
If yes, were they? Analgesic (aspirin) Sedative or tranquilizer Antimotion sickness remedy (anti-histamine) Other, including eye and ear drop medications	If name of drug(s) is known, please list below: _____ _____ _____
How many hours sleep did you get last night?	Was this sufficient? YES NO
How anxious are you regarding your participation in these tests? NOT MINIMAL MODERATE GREAT VERY GREAT	
How many hours since your last meal?	
How many cups of fluid have you had in the past 2 hours?	
Have you served as a subject in any rotational test within the past 48 hours? YES NO	
If yes, endpoint reached.	

Unclassified
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*
Naval Aerospace Medical Research Laboratory
Pensacola, Florida 32512

2a. REPORT SECURITY CLASSIFICATION
Unclassified

2b. GROUP
N/A

3. REPORT TITLE

THRESHOLDS FOR THE PERCEPTION OF ANGULAR ACCELERATION AS INDICATED BY THE OCULOGYRAL ILLUSION

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*
N/A

5. AUTHOR(S) *(First name, middle initial, last name)*
Earl F. Miller II, and Ashton Graybiel

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
11 June 1973	16	16

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
NASA Orders T-81633 and T-5904B	NAMRL-1168
b. PROJECT NO.	
c.	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d.	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Prepared for the National Aeronautics and Space Administration	N/A

13. ABSTRACT

The semicircular canal threshold, as measured by the perception of the oculogyral illusion, was determined by a double staircase procedure among 300 normal and 4 labyrinthine-defective subjects. A motorized chair with precise servo controls rotated the subject in a CW or CCW direction at rates varying in accordance with one of 24 extended trapezoidal-shaped profiles: 20 sec of constant acceleration, 25 sec at constant (terminal) velocity, 20 sec of constant deceleration and 25 sec at zero velocity. Accelerations ranged in logarithmic progression from 0.02 to 6.00°/sec^2. The illusion appeared as rightward or leftward movement of the visual target in the direction of acceleration. The target, a narrow collimated line of light, was contained within a goggle device worn by the subject and therefore fixed in relative position to him.

The method provided a brief and reliable (ρ = .70) threshold measurement. The majority of normal subjects revealed no substantial directional preponderance (CW vs CCW threshold). Threshold frequency distributions for the two directions of acceleration were similar and ranged in rate (deg/sec^2) from 0.20 to 0.950 with means of 0.146 (CW) and 0.152 (CCW), a median of 0.096 (CW, CCW), and modes of 0.096 (CW) and 0.076 (CCW). The threshold of response (deg/sec^2) in more than half the normal subjects was less than 0.10, in over three fourths was less than 0.20, in over 90 per cent less than 0.30, and 100 per cent less than 1.00. None of the labyrinthine-defective subjects perceived the illusion at the highest acceleration (6.00°/sec^2) employed.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Illusions						
Semicircular canals						
Vestibular apparatus						
Perception						
Vestibular tests						
Rotation						
Acceleration effects						
Deafness						

Environmental Biology and Medicine, 1973, Vol. 2, pp. 91-138

SPACE MISSIONS INVOLVING THE GENERATION OF ARTIFICIAL GRAVITY*

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Abstract—The present account deals chiefly with the role of the vestibular organs in space exploration, which is important both from the operational and theoretical viewpoint. With regard to the former, the prevention of reflex vestibular disturbances and motion sickness poses a problem if a portion of the spacecraft is rotated to generate artificial gravity. The transition into weightlessness, exposure in a rotating environment, and sudden transitions between the two all pose not only somewhat different problems but also problems that vary in their significance for a given space flyer. The two vestibular organs are affected very differently on transition into weightlessness. The six semicircular canals are virtually gravity independent, while the four otolith organs are freed from the constant stimulus of gravity, something that cannot be achieved under terrestrial conditions; this unique response provides a unique opportunity for scientific investigation. Prevention of vestibular side effects eventually gets down to selection, adaptation, and possibly the use of drugs.

The generation of artificial gravity represents permanent alleviation of an otherwise continuous potential hazard: the weightless space vehicle. Use of the word *alleviation* applies only to the first generation of spacecraft. It is feasible to go far beyond minimal requirements by providing a range of G-loadings, not possible under terrestrial conditions, that not only will have practical benefits but also be objects of high scientific interest. With the advent of a space shuttle, and consequent reduction of stress incidental to launch and return, the limiting factor regarding fitness for space travel will be the conditions aloft. If the radius of the rotating portion of the space vehicle is sufficiently great to keep the angular velocity low, these limiting conditions, insofar as the biologically effective force environment is concerned, will have advantages far outweighing disadvantages.

In regard to the weightless vehicle, it is not yet known if countermeasures, which do not involve the generation of artificial gravity, will ensure general fitness comparable to that under terrestrial conditions. But we do know that the maintenance of such a comparable state of general fitness will make great and continuous demands on the astronaut's or astroscientist's time [1-8], and that illness aloft, making exercise impossible, could pose a hazard.

A great deal of discussion has been devoted to the interdigitating trade-offs involved in the attempt to decide if there is need to generate artificial gravity. A classic experiment would be to have a group of persons live in the weightless, nonrotating portion of a space vehicle, and another group in the rotating portion, both for extended periods of time and at different subgravity levels. The immediate availability of artificial gravity would provide not only experimental stations to study the ameliorative effects of previous exposure to weightlessness, but also "insurance" in case of emergency need. Until such a definitive experiment can be conducted, however, facts must be gathered piecemeal under less than ideal conditions in the rotating spacecraft. The major areas of interest in such exploratory experiments, which will influence design and consequently affect decisions, center around habitability, work conditions, and man's health and general fitness [9, 10, 11]. Parallel experiments must be conducted in the weightless spacecraft, to determine the cost and effectiveness of countermeasures in preventing zero-G asthenia and the difficulties in carrying out a wide variety of tasks under weightless conditions [12-15].

The intent of this article is to present background information relative to generating artificial gravity by rotating a portion of the space vehicle, with particular attention to the role played by the vestibular organs. On space missions where artificial gravity is generated by this means, the semicircular canals and otolith apparatus (collectively termed the vestibular organs) play an important role. These organs of equilibrium have evolved to ensure proper orientation under the two-dimensional gravitoinertial force environment on Earth. Under the unique conditions in the weightless, and especially in the rotating environment, the vestibular organs may not only furnish inadequate or inappropriate information, but also, under unusual conditions, may cause reflex vestibular disturbances and motion sickness.

MAN'S BIOLOGICALLY EFFECTIVE FORCE ENVIRONMENT

In this section, the concept will be developed briefly of man's biologically effective force (BEF)

*Research conducted under sponsorship of Office of Advanced Research and Technology, NASA Order L-43518.

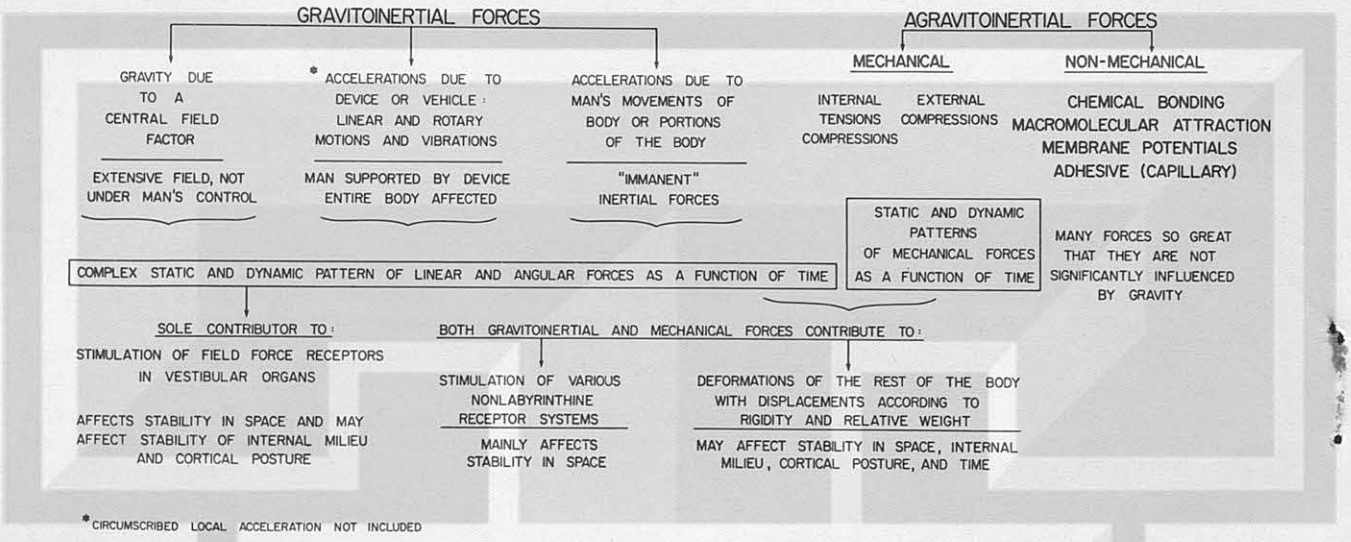


FIGURE 1. Man's Biologically Effective Force Environment under Terrestrial Conditions.

environment in relation to life activities under terrestrial conditions, and its general usefulness illustrated in connection with the unique force environments in aerospace flight. The need for a common basis, in discussing and comparing these forces, is best exemplified by comparing "life" in a weightless spacecraft with that on Earth. A comprehensive analysis and synthesis will not be attempted; this would entail a considerable undertaking, and even then be incomplete. The purpose here is to set forth major guidelines which point to further exploitation for practical or theoretical purposes.

Man's gravitoinertial force environment has its genesis at once in gravity due to a central field factor, and the inertial forces generated by the motions of "machine," or man, or both (Fig. 1). Under ordinary living conditions on Earth, gravitational force may be regarded as a constant and the only force of sufficient magnitude to affect total body weight significantly. This is the force to which man has become adapted throughout evolutionary development and to which he is accustomed through experience. The addition of mutually perpendicular lines to the vector, representing gravitational upright, forms the spatial frame of Earth reference. When man is exposed in conveyances and devices that generate accelerations or change his position with respect to the gravitational or gravitoinertial vertical, he is subjected to unnatural stimulus conditions that may range far beyond physiologic limits. These accelerations generate an external force field that, along with gravity, comprises the total *external* force field.

The inertial forces generated by the active motions of the body or its parts may be regarded as "immanent" forces, inasmuch as they do not contribute to the external force field but combine with it. These immanent forces are either of small magnitude or short duration, and are significant partly because they are associated with motions that change the position of the body with regard to the other components in the force environment, and partly because these forces are sufficient to stimulate specialized sensory receptors that provide information about body statics and dynamics. Combined gravitational, inertial, and immanent accelerative forces constitute a complex, dynamic pattern that varies as a function of time.

Although the equivalence of gravitational and inertial mass is the unifying principle underlying the gravitoinertial force concept, this simplicity gives way to great complexity when the structural and functional characteristics of the body are taken into account. The body lacks uniformity, and a state of mechanical equilibrium in all parts of the body is never reached. Stimulation of the vestibular organs in an unusual manner (even if the strength of the stimulus is small) may cause far-reaching disturbances after "amplification" in the central nervous system.

The agravitoinertial forces are far more difficult to identify and measure, in terms of a common unit, than the accelerative forces. The forces assume great importance in a weightless environment, and a dichotomy may be drawn between the agravitoinertial forces of mechanical origin and those of

nonmechanical origin (Fig. 1). For the latter, further distinctions are possible, ranging between forces so great at one extreme that absence of gravitational force is of no practical consequence, and the other extreme when its influence is felt. All these mechanical forces are generated by tensions and compressions and, along with gravitoinertial forces, contribute to bodily deformations and to stimulation of nonvestibular mechanoreceptors.

Weightlessness

Under natural terrestrial conditions, the force of gravity due to a central field factor is only part of our biologically effective force (BEF) environment; hence it is important to distinguish between weightlessness per se and man active in a weightless spacecraft. This difference, which may be great, will be determined mainly by the role played by mechanical forces that are effective in countering the null-gravity state.

An effort to analyze the BEF environment in a weightless spacecraft is shown in Figure 2. Gravitoinertial forces are generated mainly by the motions of man and machine, although even in orbital space flight man will be exposed to a scalar gravitational potential, however small, and to a gravitational force while his mass is countersupported. Immanent accelerations generated in the course of man's work and housekeeping activities contribute little to his "apparent weight," but are important, since they stimulate sensory receptors (directly and indirectly) and thus contribute to the information flow to the nervous system.

The preservation of man's well-being in a weightless spacecraft depends heavily on the agravitoinertial forces, of mechanical or nonmechanical origin. An analysis of the latter should be made in terms of their effectiveness at different organizational levels in the body. A table might be prepared to indicate the forces operant at different levels; e.g. molecular, intracellular, cellular, and tissue levels. Cytochemical reactions involve forces (thermodynamic, bioelectric, and chemical) so great that they are "gravity independent." An extreme example of gravity independence is the requirement, in differential centrifugation of body fluids and cells, for using levels of force measured in thousands of G units. Under ordinary living conditions, bone

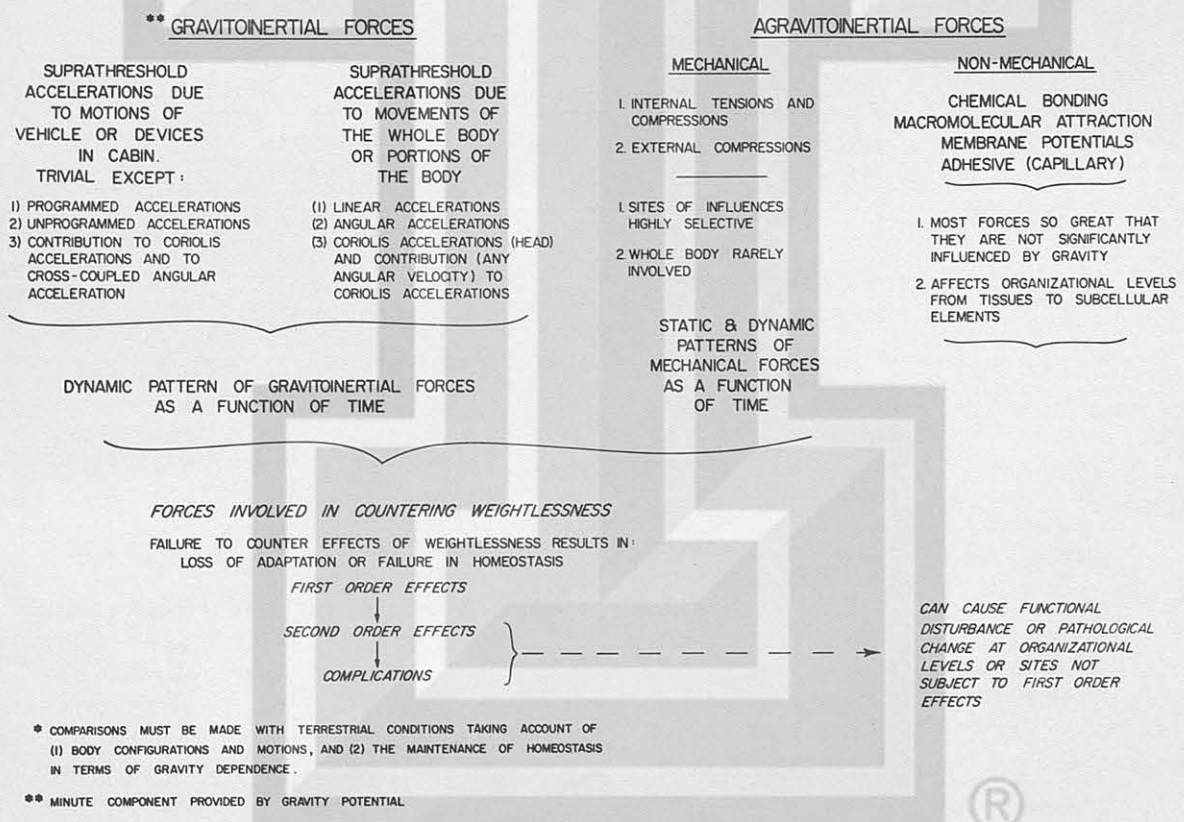


FIGURE 2. Man's Biologically Effective Force Environment in Near-Weightlessness.*

is a gravity-dependent tissue, at least in many portions of the body; however, the marked difference in gravity dependence between, for example, the os calcis and skull is not fully explained. Blood considered as a tissue is gravity-independent, but as part of the circulatory system it is gravity-dependent.

The different organizational levels in cells and tissues at which gravity dependence appears as an influence has not been investigated systematically. This information is important, however, for two related reasons: first, to point out where preventative measures become necessary in the absence of gravity, and second, to point out the possibility of important alterations in the systems not primarily affected by weightlessness. The latter circumstance is demonstrated in findings of Soviet scientists on two properly nourished dogs tethered in a weightless spacecraft for 3 weeks [16]. Not only were the expected changes revealed, but also alterations at organizational levels down to fragmentation of DNA molecules in a few cells [17]. If the alterations leading to the death of monkey Bonnie (Biosatellite III) were a consequence of weightlessness, then the experiment constitutes an outstanding example of primary effects leading to second and higher order effects, as shown in Figure 2 [18]. Inasmuch as molecular forces are gravity independent, these changes in the DNA could not have been a primary effect of weightlessness, but must have been a second or higher order effect.

The *nonmechanical* forces just described are largely out of man's control; hence, agravitoinertial *mechanical* forces assume great importance in a weightless environment since they are under man's control to a great extent, and can be utilized in the prevention of zero-G asthenia.

When man is free-floating or lightly restrained in a weightless vehicle, agravitoinertial mechanical forces are minimal and, although important for the maintenance of homeostasis in the milieu interieur, are nevertheless of trivial value in the maintenance of musculoskeletal fitness. No further experience is needed to state categorically that man's general fitness would deteriorate rapidly in the absence of mechanical forces generated by physical exercise.

Certain comparisons between voluntary activity under terrestrial and weightless conditions are shown in Figure 3. On Earth, under conditions of bed rest and especially when asleep, man is unable

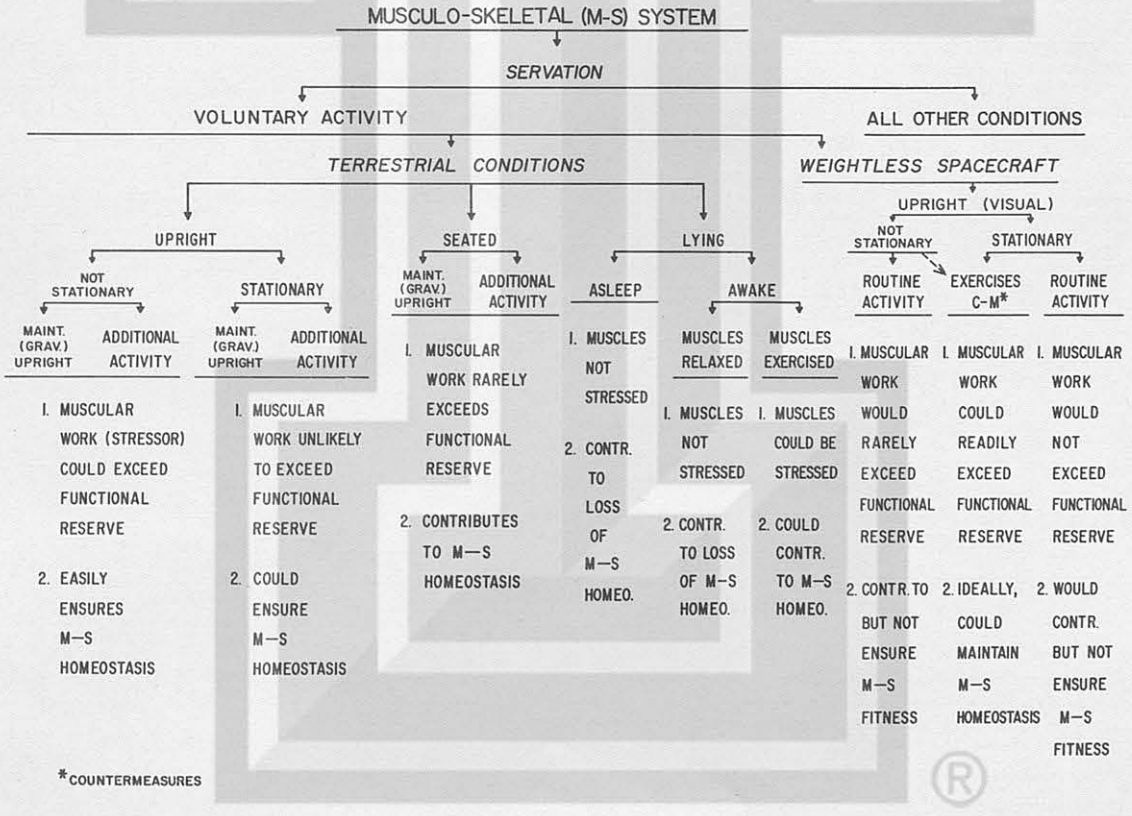


FIGURE 3. Voluntary Activity under Terrestrial and Weightless Conditions.

to maintain stability or homeostasis in the muscular and skeletal systems. In other words, to ensure homeostasis, these systems require greater stress. This is accomplished to a considerable extent by sitting and standing; periods of exercise are also beneficial. Thus, musculoskeletal homeostasis, even under ordinary living conditions, is not preserved during bed rest but requires physical work. In carrying out muscular work, many other systems are called into play. For example, the cardiorespiratory system also resembles the musculoskeletal system in that a homeostatic state over a period of time is ensured by periods of increased stress, compensating for periods of decreased stress which, if long continued, would lead to loss of fitness. Briefly summarized, man must exercise to remain fit even under terrestrial conditions; this is best accomplished when he is in the upright position so that the gravitational load, although spread unequally, is influenced by body height and mass.

In weightlessness, preservation of musculoskeletal homeostasis presents a problem in that the periods of decreased stress or understressing are more severe than on Earth; therefore, compensation requires periods of overstressing, with stress either of greater magnitude or of longer duration. These countermeasures could present problems; one would be failure to ensure that the stress, represented on Earth by the antigravity component of musculoskeletal work, is properly compensated. Moreover, other systems called into play during muscular work aloft, such as the cardiovascular system, may not have all the benefits accorded under terrestrial conditions. A prime example would be the loss of hydrostatic effect on body fluids. Therefore, it is highly desirable to obtain systematic measurements on the effects of these activities in countering the weightless state.

Proposals have been made to generate artificial gravity in space flight by means of small [19] or large [20, 21] on-board centrifuges, or by rotating the major portion of the spacecraft [22, 23]. Only the last will be considered here since it is the best means of preventing the most significant biomedical problems. In anticipation of this possibility, Earth-based simulators have been built [24-30], and it is important to compare major characteristics of these two rotating environments.

Slowly Rotating Room Environment

In a slowly rotating room constrained to rotate about the Earth vertical axis, a person carrying out various activities is subjected to complex changes in the gravitoinertial force environment. It is necessary to take into account not only the forces acting at man's center of gravity but also the separate consequences of head and limb motions, with and without whole body motions.

Figure 4 illustrates the forces acting on the subject's mass when he is recumbent and when seated. Centrifugal force derives from $r\omega^2$ where r = radius and ω = angular velocity. The angle ϕ represents the change in direction of the gravitoinertial upright from the gravitational upright. With the subject moving with or against the direction of rotation or toward or away from the center of rotation, Coriolis forces must be taken into account as well as the changes in centripetal force. The fundamental law relating the time rate of change of a vector, measured by an observer in space rotating with respect to the reference space, may be expressed mathematically by the vector equation:

$$\left(\frac{d\bar{V}}{dt}\right)_r = \left(\frac{d\bar{V}}{dt}\right)_m + (\bar{\omega}_{rm} \times \bar{V})$$

where

$(d\bar{V}/dt)_r$ = change in velocity vector with respect to the reference space

$(d\bar{V}/dt)_m$ = change of velocity vector with respect to moving space

$(\bar{\omega}_{rm} \times \bar{V})$ = change of velocity vector due to rotation of moving space

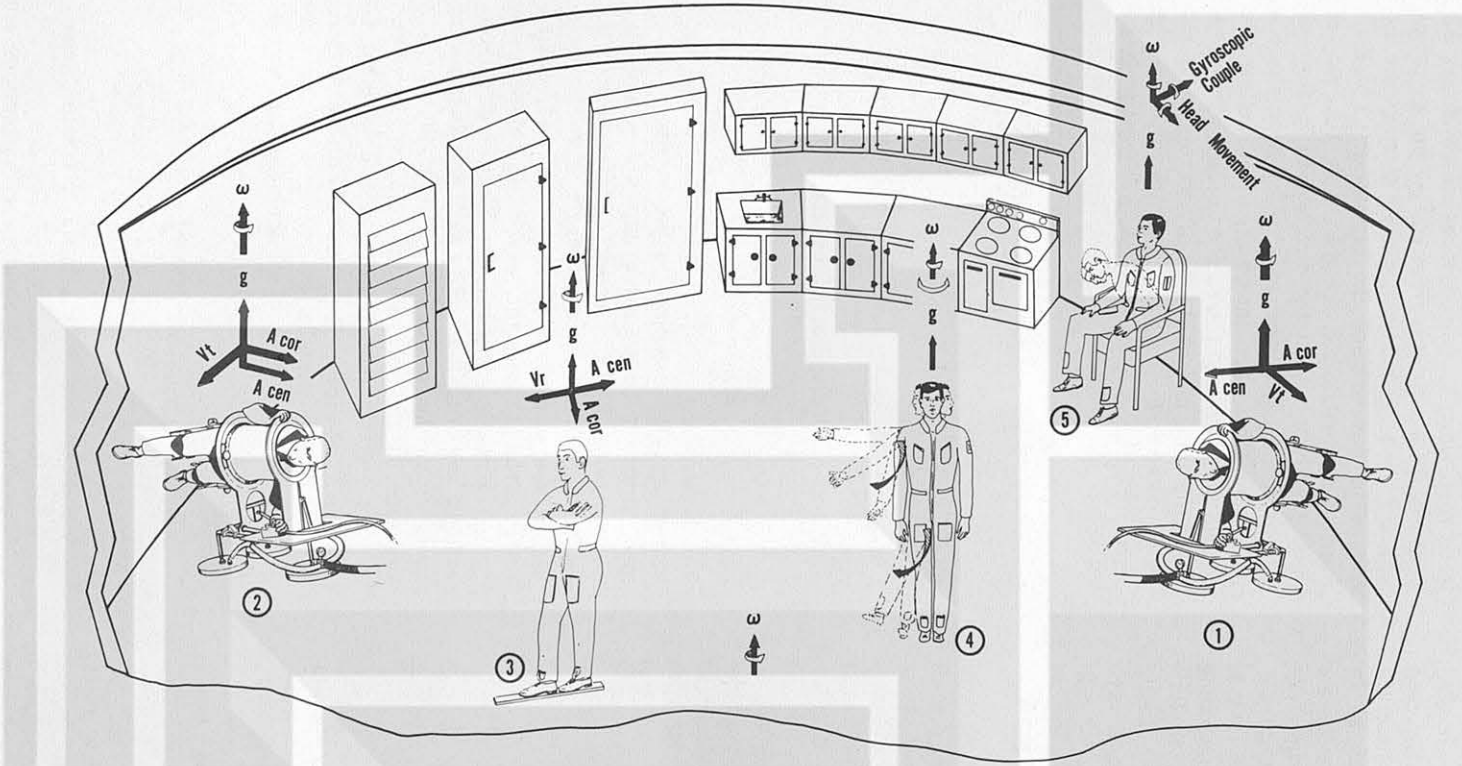
This acceleration or force vector may manifest itself in two ways to a subject in the rotating environment. First, it adds to the apparent weight of a body moving in the direction of rotation and subtracts from the apparent weight when it moves against the direction of rotation. Second, when a body moves toward the center of rotation, the Coriolis force is exerted in the direction of rotation at right angles to the body's motion; when moving away from the center of rotation, the force is opposite to the direction of rotation. A motion parallel to the axis of rotation will generate no Coriolis acceleration. The value of Coriolis acceleration in G-units for a body moving perpendicularly to the axis of rotation in a spinning system may be determined by:

$$F_{(Coriolis)} = 0.00651 \ VN$$

where:

V = velocity of body relative to rotating vehicle in feet per second

N = vehicle rate of rotation in revolutions per minute



g = Acceleration Of Gravity
A cen = Centripetal Acceleration
A cor = Coriolis Acceleration
Vt = Tangential Velocity
Vr = Radial Velocity
ω = Angular Velocity Of Rotating Room

Legend: Crewmen 1 and 2, in articulated molds supported by air-bearing devices, are "walking on the wall," simulating the orientation in a rotating spacecraft. Crewman 2 walking in the direction of rotation becomes somewhat heavier because his angular velocity, hence centripetal acceleration, is increased and sums with the Coriolis accelerations generated. Crewman 1 walking opposite to the direction of rotation becomes somewhat lighter because his centripetal acceleration is decreased and the Coriolis accelerations must be subtracted. Crewman 3 walking toward the periphery of the room is exposed to increasing levels of centripetal acceleration and constant levels of Coriolis accelerations. Crewman 4, standing, is demonstrating two phenomena: first, as he moves his arm or leg sideways, a tendency to veer backward, the so-called "giant-hand" effect; second, as he makes (rotates) his head move in the plane of the room's rotation, cross-coupled angular accelerations and illusions are not generated, a so-called "free movement." Crewman 5 is making a head movement out of the plane of rotation which does generate cross-coupled angular accelerations producing characteristic illusions described.

FIGURE 4. Responses to the Force Environment in a Rotating Room. (Drawing courtesy of Dr. D. B. Cramer)

For any motion not exactly perpendicular to the axis of rotation, the component of the velocity that is perpendicular is used to determine the Coriolis force; hence, the value must be multiplied by the sine of the angle between the angular rotation rate vector and the velocity vector. Figure 5 illustrates the Coriolis force in G-units for various rates of movement perpendicular to the axis of rotation at different rates of rotation. The combined Coriolis and centripetal forces influence the ataxia exhibited by subjects.

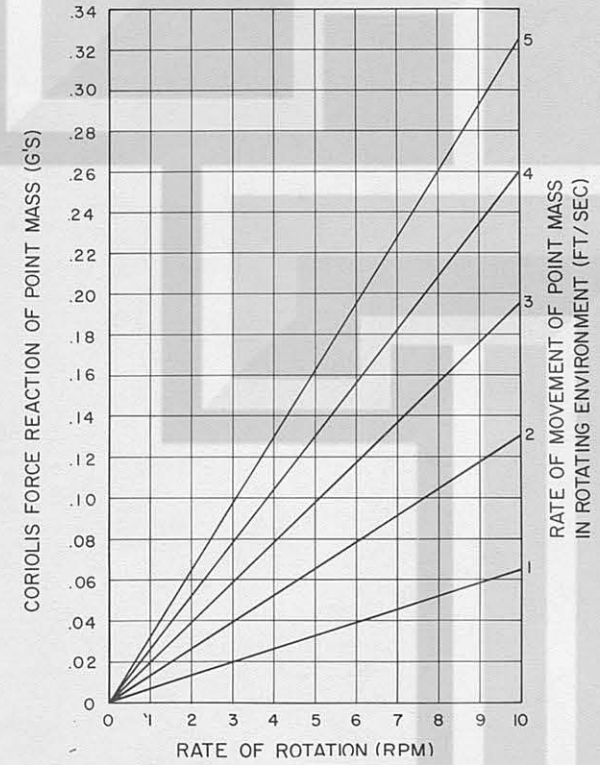


Figure 5. Coriolis Force Reaction of a Mass Moving in a Rotating Environment. (Force in pounds = Earth gravity weight × G units)

It is apparent, from Figures 5 and 6, that a person walking against the direction of spin will experience a slight decrease of apparent weight, and a slight increase when walking with the direction of rotation. Also, moving toward the center, the Coriolis force would be in the direction of spin, and walking toward the periphery, the direction would be reversed.

The above analysis is oversimplified because the motions of the limbs and head need not conform to the motions of the center of gravity; moreover, the motion of the center of gravity itself is complex

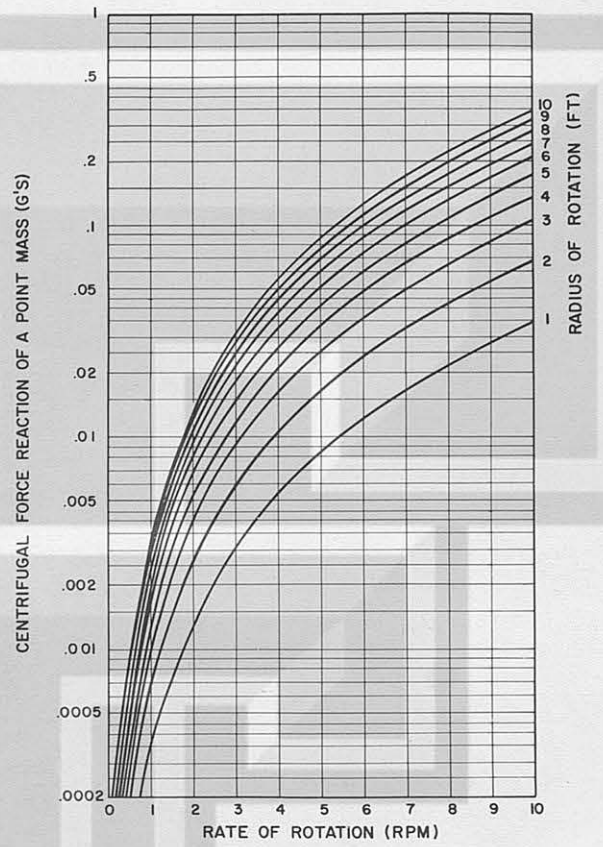


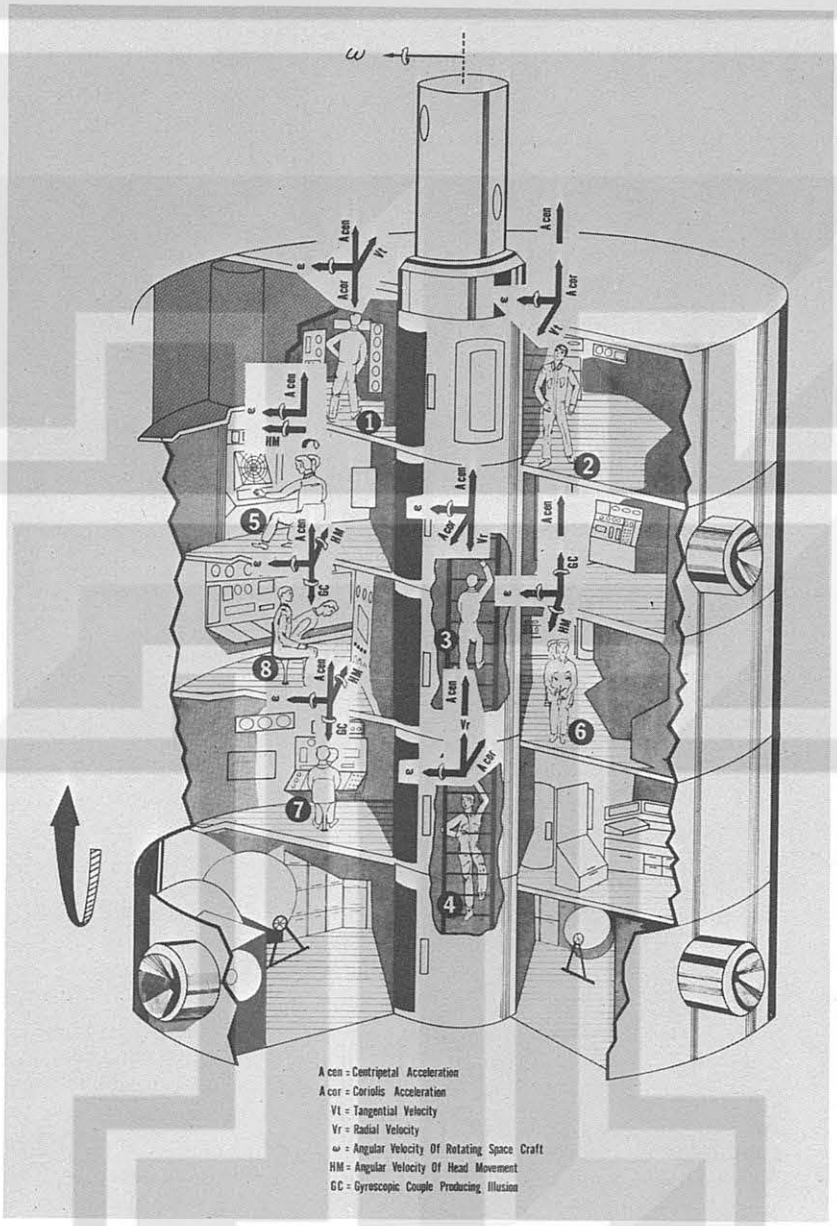
Figure 6. Centrifugal Force Reaction of a Mass in a Rotating Environment. (Force in pounds = Earth gravity weight × G units)

[31, 32], although the motions normal to the Earth horizontal would not generate a Coriolis acceleration.

The cross-coupled angular accelerations (to be noted later) constitute an abnormal stimulus pattern in the case of the semicircular canals. These accelerations, generated by simultaneous rotation of the head about two axes, may also properly be termed Coriolis accelerations, but this designation has led to confusion. When these accelerations are above threshold, reflex vestibular disturbances result and may be followed by motion sickness. They are of great practical importance, therefore, in dealing with rotating environments. Cross-coupled angular accelerations per se are independent of the distance from the center of rotation of the room and, indeed, of the level of G-loading within the ranges to be encountered in rotating environments.

Rotating Spacecraft Environment

In a rotating spacecraft (Fig. 7), as pointed out in connection with Figure 1, when dealing with



Legend: Crewman 1 is walking in a direction opposite to rotation; hence his weight is decreased. Crewman 2 is walking in the direction of rotation, hence his weight is increased. Crewman 3 is descending the ladder, thereby experiencing an increase in weight proportional to the lengthening of his radius; the Coriolis acceleration resulting from his descent will tend to keep him against the ladder. Crewman 4 ascending the ladder will experience a decrease in weight, and the Coriolis acceleration, because he is on the opposite side of the ladder compared with crewman 3, will also tend to keep him against the ladder. Crewman 5 is moving his head from the upright to his right shoulder which is in the plane of rotation, hence cross-coupled angular accelerations are not generated and there are no illusions. Crewman 6 is making the same head movement as crewman 5, but the plane is now perpendicular to the plane of rotation, and cross-coupled angular accelerations are generated, resulting in charcteristic illusions. Crewman 7 is making the same motion as crewman 6, but the illusions are reversed because he is facing in the opposite direction. Crewman 8 facing the center and bending forward generates forces similar to crewman 7. Note the important differences between responses in the SRR (Fig. 4) and spacecraft.

FIGURE 7. Responses to the Force Environment in a Rotating Spacecraft. (Drawing courtesy of Dr. D. B. Cramer)

impulse accelerations and the forces they generate, the minute gravitational potential has little or no physiological significance. Moreover, in a slowly rotating room man's orientation when standing is parallel, or almost parallel, to the axis of rotation; in the spacecraft his long axis when standing is perpendicular to the axis of rotation.

In the absence of gravity, Coriolis forces naturally constitute a larger fraction of the "apparent weight" than in the slowly rotating room (Fig. 4). This has practical significance in terms of postural stability and locomotion, which will be discussed below.

THE VESTIBULAR SYSTEM

In primitive fish, the ear, which has acoustic and nonacoustic sensory organs, developed in association with the hindbrain. The organ of hearing long remained rudimentary, and evolutionary development of the acoustic system had to await expansion of the primitive forebrain in higher vertebrates. In contrast, the nonacoustic portion of the ear, containing otolith organs and semicircular canals, developed early, for these organs were essential to equilibrium. When the cerebellum appeared, which was an outgrowth of the hindbrain, the basic componentry of the vestibular system was nearly complete. Thus, in viewing the phylogenetic "scale" from fish to man, the essential structure and cardinal function of the vestibular system remain unchanged.

The otolith apparatus and semicircular canals are uniquely constructed to sense linear and angular accelerations, convert this energy into electrical impulses, and, mainly through influencing motor behavior, aid in orientation to the upright and eye-head-body coordination. Under natural stimulus conditions, behavioral responses to which the vestibular system contributes are characterized by automaticity, reliability, and egality among members of a species or subspecies. There is little if any awareness of vestibular influences when man is engaged in natural activities, because sensory inputs from vestibular organs are destined mainly for lower portions of the central nervous system. Consequently, we are not familiar through personal experience, as in vision or hearing, with the functions subserved. Indeed, it was not generally recognized until the turn of the century that these were organs of equilibrium rather than hearing.

Concerted efforts have been made only recently to study the vestibular system comprehensively, which have been aided by the new techniques of morphologists, neurophysiologists, psychophysiologists, and others. Much of the basic work was done on marine forms and lower vertebrates, but more recently subhuman primates have been used. Few behavioral studies have been conducted, and in most of them, intact animals were not used. In some respects, behavioral studies are easier to carry out on man than on animals, and have the advantage of using the definitive experimental subject. Under natural stimulus conditions, the experimenter has poor control over the stimulus and is further limited in finding specific, reliable, response indicators; consequently, almost all human experiments depend on using an unnatural stimulus that elicits a response that is always unnatural and usually abnormal. This is done for the purpose of manipulating and measuring the stimulus to semicircular canal or otolith, or both, and to evoke specific measurable responses. The investigator gains advantages that are offset to a greater or lesser degree by individual differences in susceptibility to a disturbing stimulus, and individual differences in the rate of acquisition and decay of adaptation effects. Despite these difficulties and gaps in our knowledge, a considerable body of information on man is available.

Space flights provide greater opportunities than problems for investigation of the vestibular organs. Transition into weightlessness abolishes the gravitational stimulus to the otolith apparatus similar to closing the eyes or entering a sound-free anechoic chamber. Thus it creates for the human or animal subject an experimental condition that is impossible to achieve on Earth yet essential to round out investigations of the otolithic system. The elegance of transition into weightlessness as an experimental procedure can only be appreciated in light of the profound disturbances associated with attempts to ablate these organs through surgical or other means. The weightless spacecraft offers a unique scientific opportunity to investigate relations between the otolithic apparatus, on the one hand, and canalicular and nonotolithic somatic sensory systems (touch, pressure, kinesthesis), on the other.

Problems referable to the vestibular organs have appeared under stimulus conditions in the weightless spacecraft; to generate artificial gravity by rotating the spacecraft, major problems must be solved. Such problems arise mainly from the rapid transitions in and out of rotating environments, which disturb the vestibular system without allowing sufficient time for adaptation. Consequences are vestibular side effects that include visual and postural disturbances and motion sickness symptomatology. The vestibular mechanisms underlying the appearance and disappearance of these manifestations are compli-

cated. Some understanding of these mechanisms is essential, therefore, not only for the prevention of side effects but also for the proper evaluation of trade-offs involved in making decisions regarding whether to generate artificial gravity and, if so, the design of rotating spacecraft.

The End Organs

The paired end organs are situated in hollowed channels in the petrous portion of the temporal bone (Fig. 8) [33]. Within the bony labyrinth, the membraneous labyrinth is surrounded by perilymph and filled with endolymph. Thus the sensory receptor mechanisms are protected from effects of superimposed body weight by the bony labyrinth and, by virtue of contained fluids, from effects of accelerations. Exceptions to the protections are displacements due to differences in specific weight among fluid and solid tissues, and displacement due to inertial lag in fluid-filled circular ducts which resemble a torus.

This "protection" is illustrated by findings on animal subjects exposed to high-peak and sustained linear acceleration [34-36]; data derived from tests of squirrel monkeys at a wide range of linear accelerations are shown in Table 1. Immediately after exposure to sustained accelerations at levels *below* 60 G [34], none demonstrated abnormal eye motions and only a few manifested slight ataxia. Moreover, none sustained any damage to the vestibular organs, as revealed by histologic study of the gross and fine structure. At 60 G and above, fragmentation appeared in the otolithic zone.

The Otolith Apparatus

The four otolith organs appear as thickened portions, or macular plates, on the inner walls of the paired utricle and saccule (Fig. 9). These four curved macular plates together occupy (not

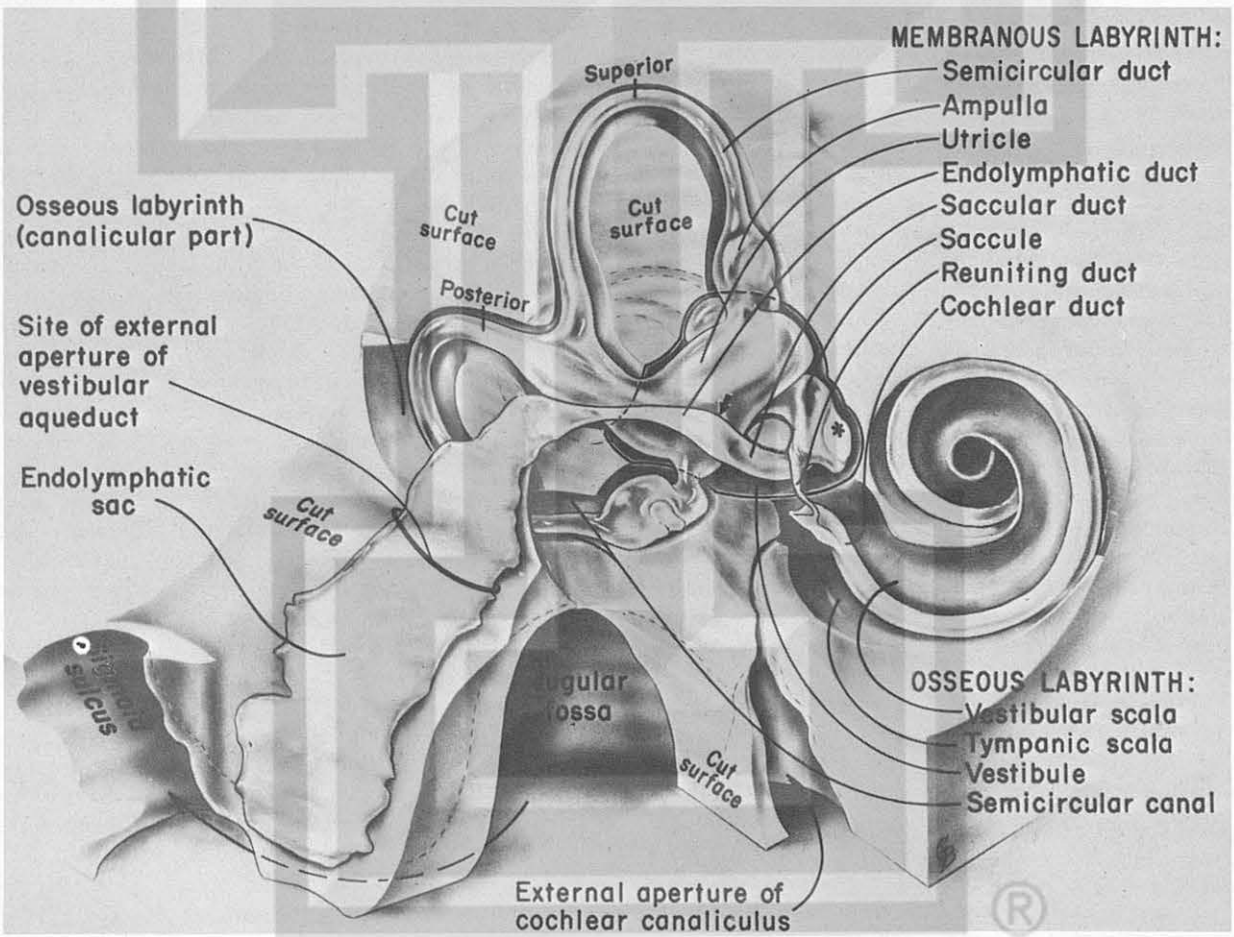


FIGURE 8. Reconstruction of the Membranous Labyrinth and Related Anatomy [33].

[p, peak-g exposure; +++, severe; ++, moderate; +, slight; ±, questionable; —, negative]

g-level	Number of animals	Ataxia		Spontaneous eye movement
		Floor	Bar	
20.....	2	—	—	—
30	3	±	±	—
40	2	+	—	—
50	3	+	+	—
60	4	++	++	—
75	2	+	+	—
80	1	±	—	±
100	3	++	++	±
125	3	++	++	±
150	6	+++	+++	+
175	4	+++	++	+
200	6	+++	++	+
		—	—	—
200 p.....	1	—	—	—
250 p	1	+	++	+
300 p	1	—	+	+
350 p	3	++	+++	+
400 p	3	++	+++	++
450 p	4	++	+++	±
500 p	1	+++	+++	++

counting overlap) a significant portion of an imaginary sphere [37]. A cross section of the saccular macula of a squirrel monkey, similar to that in man, is shown in Figure 10, and a sketch of the zonal structure is shown in Figure 11 [38].

The otolithic membrane contains otoconia (Fig. 12) [39], concretions of calcium carbonate with a specific weight of about 2.71, embedded in a gelatinous material. This membrane is the only tissue within the bony labyrinth that differs considerably from the specific gravity of the lymph fluids. The hairlike projections of the sensory cells protrude into the cupular membrane on which the otolithic membrane rests. Movement of the otolithic membrane relative to these sensory "hairs," or cilia, constitutes the effective stimulus to the organ (Fig. 13) [39].

The sketch in Figure 14 was drawn from electronmicrographs of the sensory epithelium of the utricular macula of the squirrel monkey [40]. Two types of hair cells, each with two types of cilia, are depicted. Each cell has 60 to 70 sterocilia and one kinocilium laid out in strict geometrical arrangement. It is considered likely that the kinocilium plays the major role in energy transfer. In different regions of the macula, kinocilia are polarized in different directions (Fig. 15); hence, a shearing force in one plane will result in kinocilia moving in different directions with reference to the kinociliar pole [41].

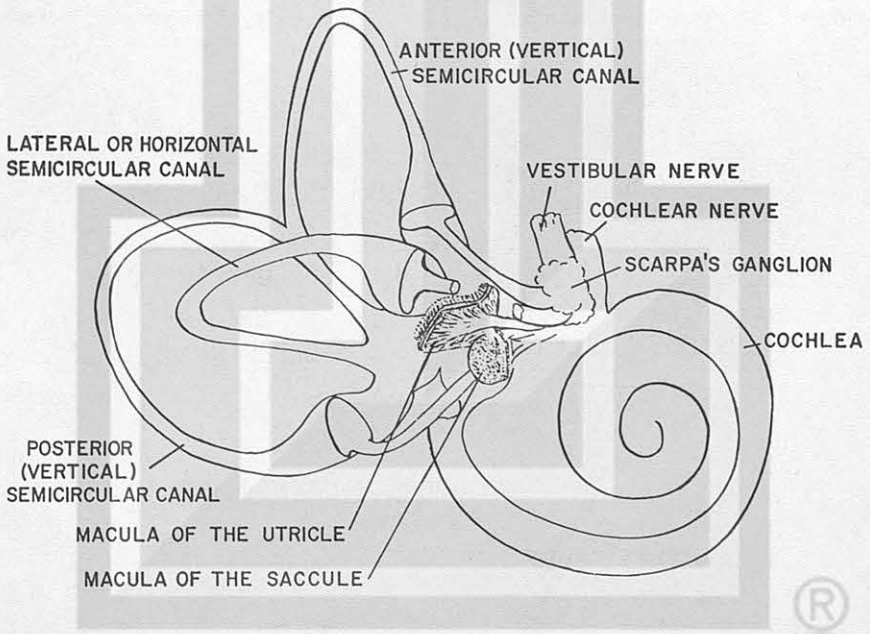


FIGURE 9. Labyrinth of Left Ear as Viewed from the Medial Aspect.

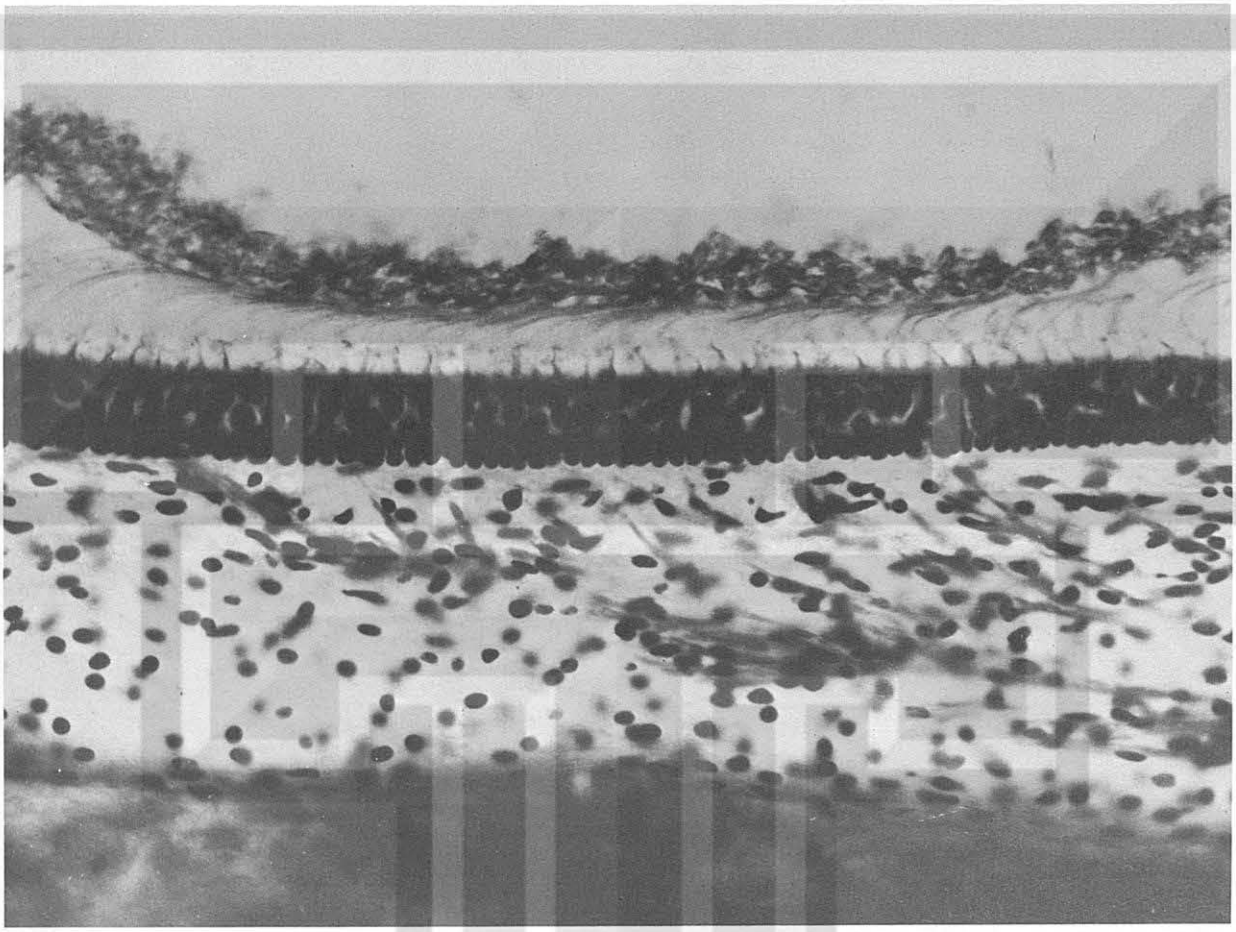


FIGURE 10. A View of Macula Saccula from a Squirrel Monkey [38]. Zonal structure is clearly seen.

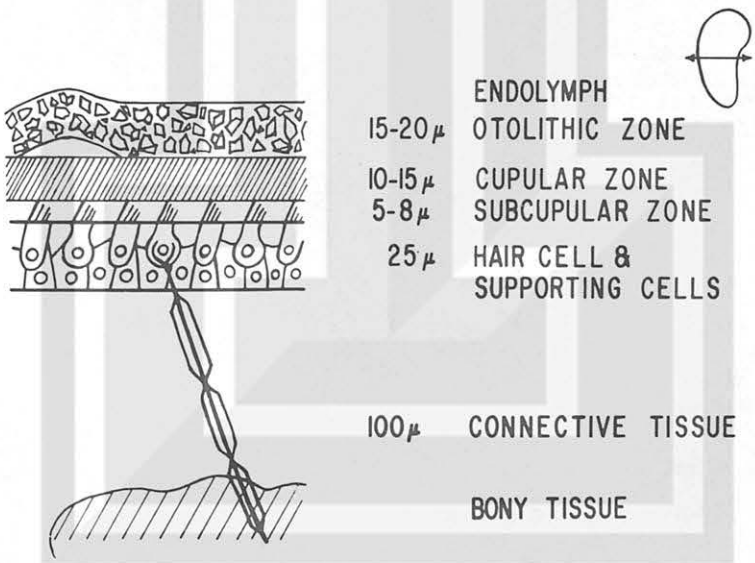


FIGURE 11. Schematic of the Zonal Structure of the Macula Sacculi in the Squirrel Monkey [38].

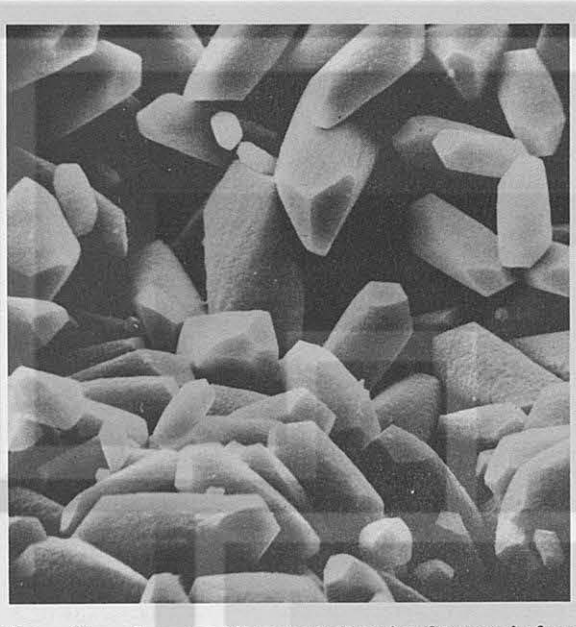


Figure 12. Scanning Micrograph Showing Statoconia from the Macula Utriculi in the Cat [39].

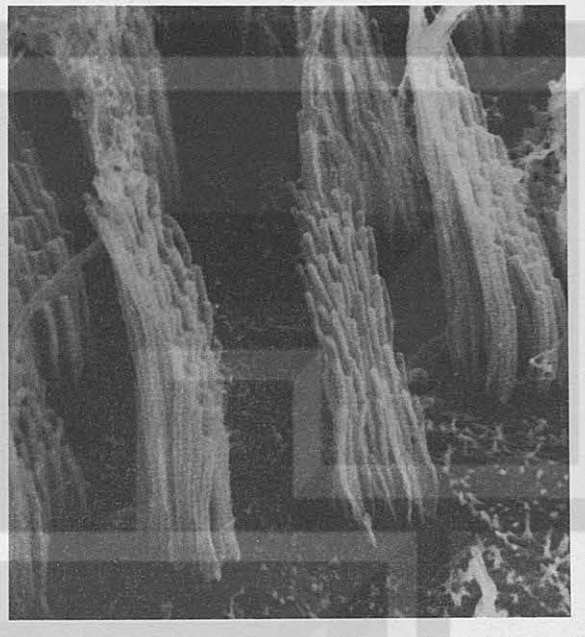


Figure 13. Bundles of Sensory Hairs at the Periphery of the Macula Utriculi in the Chinchilla [39].

It is generally agreed that the receptors in the otolith organs are stimulated by changes in their position relative to the direction of gravity, and by linear and Coriolis accelerations. The "power train," constituting the cilia-otolith mechanism, is initiated by a displacement between the otolithic membrane and the membrane supporting the hair cells [42]. The result is mechanical deformation of the cilia (kinocilium) which, in turn, causes chemical changes affecting the generation of bioelectricity (nerve action potentials). After a suprathreshold stimulus, the resting spike discharge is altered in its temporal and spatial patterning, constituting the propagated discharge which, traveling along nerve fibers to the central nervous system, is the means by which otolith sensory inputs affect behavior. Most receptor cells have a resting discharge, but some do not. Typical responses are shown in Figure 16 [43]; deviation toward or away from the kinociliar pole has opposite effects. In some cells, stimulation may result in abolition of the resting discharge.

There is proof of a tonic otolith influence even in the absence of impulse accelerations (ocular counterroll) and when the head is apparently fixed with respect to the gravitoinertial vector (oculogravic illusion). Presumably, this tonus has its genesis in the cilia-otolith mechanism. Two possibilities must be considered. First, there are continual, slight (unavoidable) changes in position of the

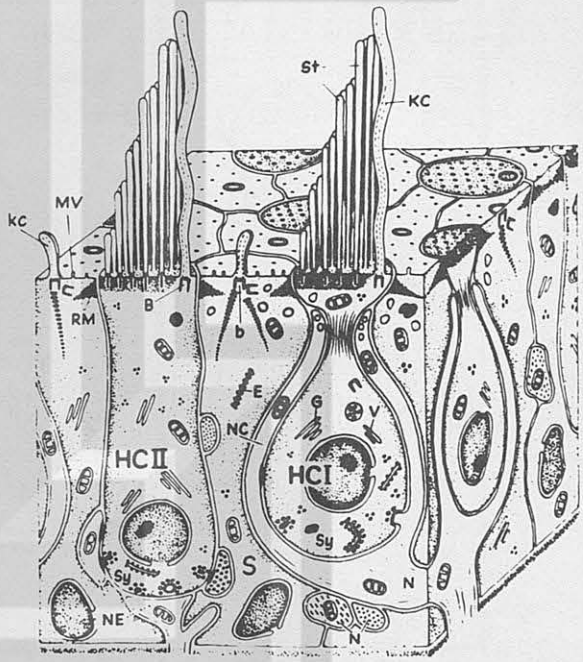


Figure 14. Schematic of an Area from a Vestibular Sensory Epithelium with the Two Types of Haircells (HCI and HCII). KC, kinocilia; St, stereocilia [40].

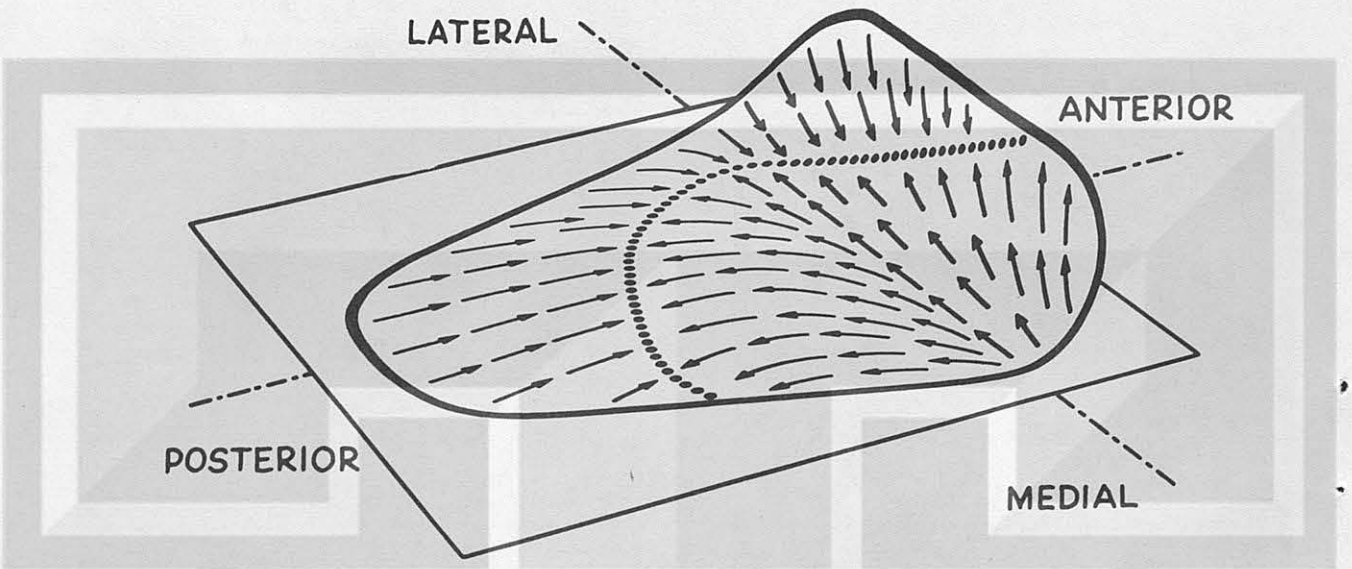


FIGURE 15. Schematic of Polarization Pattern of Sensory Cells in Macula Utriculi of Guinea Pig [41].

Arrows indicate the direction of polarization showing how it spreads fanlike from one side of macula up to a certain line beyond which polarization is reversed. Kinocilia on either side of this dividing line are facing each other.

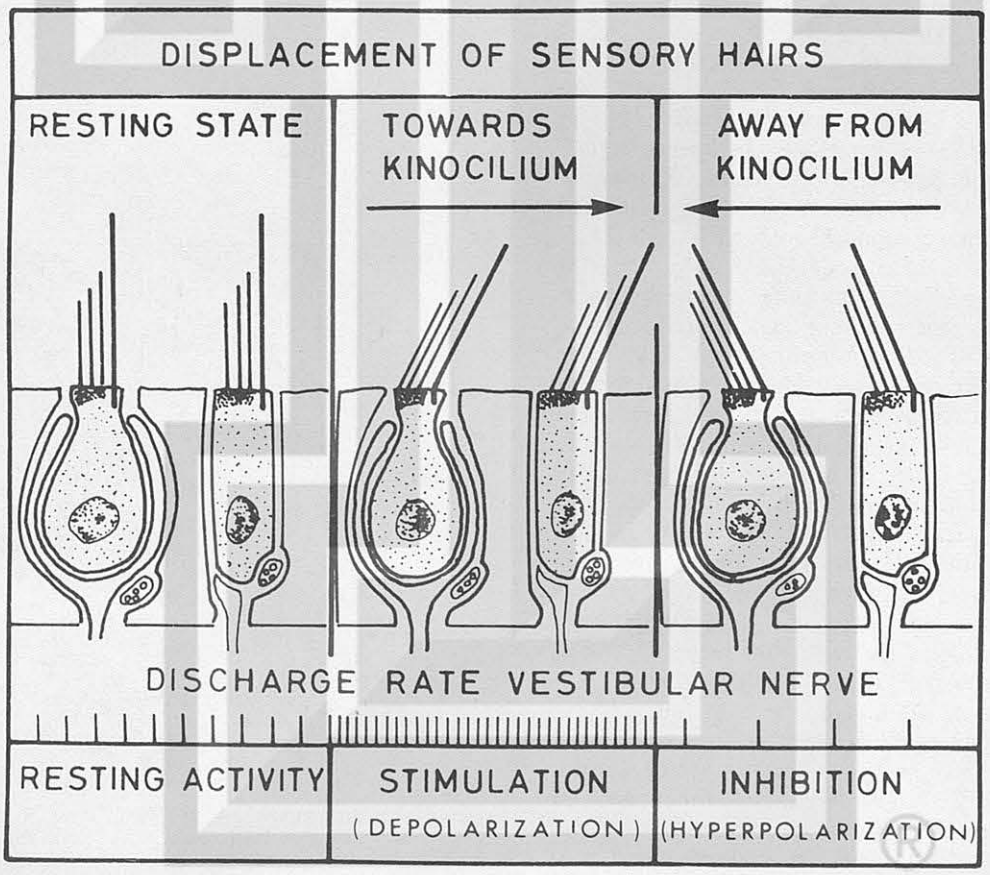


FIGURE 16. Electrical Discharge Rate of the Hair Cells as a Function of Displacement of the Sensory Hairs [43].

macular plates with respect to the gravity vector, constituting in effect an accelerative stimulus making the otolith organs act as accelerometers. Second, receptor units fire continually in response to the weight of the otoconia, in which case the otolith apparatus reacts both as an accelerometer and a static pressure transducer. Several recent reports deal with modeling of the input-output relations of the otolith apparatus under both static and dynamic conditions [44-46].

The Semicircular Canals

The gross structure of the semicircular ducts is quite different from that of the otolith organs, although the sensory epithelium is similar.

The so-called "semicircular" canals actually form a complete circuit by virtue of their connections with the utricle (Fig. 8). One extremity of each canal is dilated to form the ampulla; a cross section of a horizontal canal ampulla in the squirrel monkey is shown under low magnification in Figure 17 [38]. The crista is a transverse ridge of tissue covered with the sensory epithelium containing sensory receptor cells similar to those in the macular plates.

Kinocilia in the hair cells are uniformly polarized; in the horizontal canals they are toward the utricle (utricular pole) and in the vertical canals toward the opposite pole. Cilia extend into the cupula, and this structure completes a fluid-tight gate across the ampulla. The cupula is hinged at the crista and free to move back and forth, from its position in the capillary dome, in response to movements of the endolymph. According to Groen [47], the motion of the cupula is frictionless, and during these motions the seal remains fluid-tight.

Clockwise rotation of the canal about an axis at right angles to the plane shown in Figure 17 would result in an inertial lag of the endolymph, causing the cupula to be displaced counterclockwise. This cupula-endolymph mechanism has been likened to a heavily damped torsion pendulum. Its dynamics may be expressed by a second-order differential equation relating angular deviation of the cupula to angular acceleration normal to the plane of the canal. The power train transforming angular acceleration forces to electrical energy in the semicircular canals is apparently quite different from the corresponding mechanisms in the otolith organs. Moreover, gravity, which plays a major role under natural stimulus conditions in the cilio-otolith system, may be neglected.

Head motions under natural conditions generate a high angular acceleration with the onset of rotation, angular in character, followed by a very brief period of rotation approaching constant velocity, and ending with another transient acceleration of opposite sign. Although the acceleration and deceleration magnitude may be different, the time-integral of angular acceleration at the onset and offset are equal (area under the curves). Thus, under most natural conditions, it is thought that the end organ responds as an integrating accelerometer.

The orientation of the six semicircular canals with reference to the coordinate planes of the head is shown in Figure 18. It will be noted that, although the three canals on one side lie approximately in mutually perpendicular planes, only the horizontal canals lie close to one of the coordinate planes of the skull, the superior and posterior canals deviating by 45 degrees from the sagittal and frontal planes. Although the two "horizontal" canals are coplanar, this plane lies at a 20 to 30 degree angle to the horizontal plane of the head, open above, as viewed from the front. When man is upright, by flexing the head forward in the "ape position," the horizontal canals are approximately coplanar with the Earth horizontal. Rotary motions in the horizontal plane generating impulse angular accelerations would stimulate the horizontal pair of

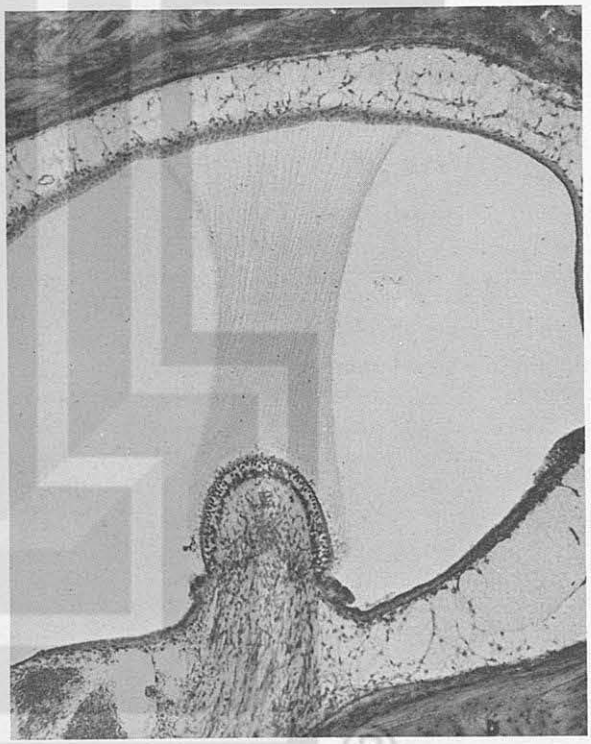


Figure 17. Crista-Cupula System of Horizontal Canal from Squirrel Monkey [38].

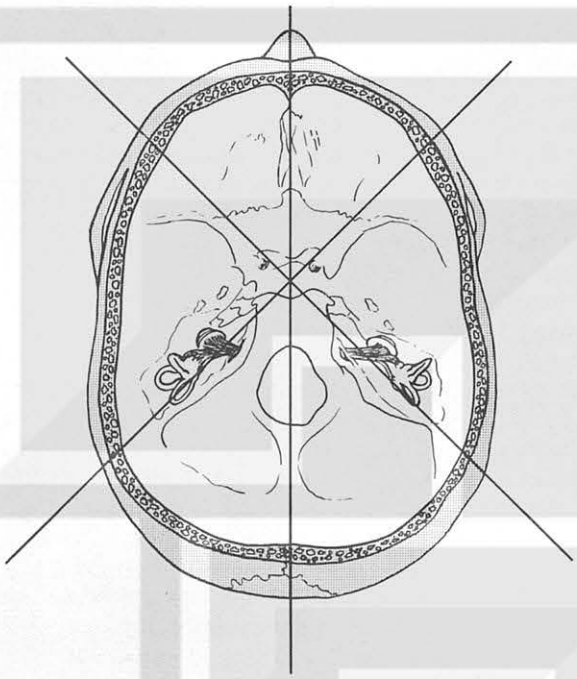


Figure 18. Orientation of Semicircular Canals (enlarged) as Viewed in the Skull from Above.

canals, although not maximally. Rotation in the sagittal and frontal planes would generate angular accelerations in planes almost 45 degrees from the planes of vertical (superior and posterior) canals. The operational significance is evident when a pilot's canals are stimulated during pitch, roll, and yaw of an aircraft [48, 49]. The full significance of differences in orientation between horizontal and vertical canals with reference to the head awaits elucidation.

A sizable and important body of information deals with input-output relations of the semicircular canals [50-57], mainly the horizontal pair of canals. Models based on man's responses to stimulation of the horizontal pair of canals conform closely [58-62] to theoretical predictions. Some discrepancies may be explained on the basis of a "central inhibitory mechanism" [63] and "pattern centre interference" [64]. Attempts to extend the scope of mathematical description of function of the three pairs of canals and to develop models have been less successful than for the horizontal pair of canals.

Central Nervous System (CNS) Connections

This section summarizes briefly the exceedingly complex vestibular reflex mechanism, and points out some of the important functional neuroanatomical relations. Figure 19 indicates the principal nervous pathways [65] and some additional features are shown in Figure 20 [66].

Afferent impulses from sensory receptors in the canals and otolith organs are propagated along first-order neurons that terminate in the vestibular nuclear complex, cerebellum, and reticular formation. According to one authority [67], some primary fibers reach the motor nuclei of the extraocular muscles, although this was not verified in a later investigation [68]. These terminations are sites of origin for monosynaptic vestibular pathways and receiving sites for reciprocal or outside influences. The widespread distributions of these neuronal chains and networks, along with the less well-known efferent fibers terminating in the receptor cells of the canals and otolith organs, constitute the reflex vestibular system.

The vestibular nuclear complex is the chief center of the vestibular system with regard to both anatomical organization and functional control. The vestibular nuclei have important reciprocal linkages with the cerebellum and reticular formation; they send out major projections that ascend, descend, and cross the neuraxis, and contain sites for interconnection with other sensory systems and other neural mechanisms coordinating reflex activity [69-76].

There is evidence that vestibular activity reaches areas to which specific tracts have not yet been identified anatomically. Representation in the cerebral cortex of the brain has been established by means of the evoked potential method [77-79]. Connections between the vestibular system and visceral nervous system have been demonstrated, using electrophysiological methods on animal subjects [80-82] and behavioral indicators for man exposed to unusual periodic accelerations.

The vestibular system, concerned almost entirely with control of movement, is subject to strong modulating influences. Specific control over afferent impulses may be in the nature of gating mechanisms subserved by efferent vestibular fibers [83-86]. The cerebellum contributes greatly to the fine control of movement and exercises a strong tonic inhibitory control over vestibular reflexes. Cortical influences are also mainly inhibitory, as are those originating in the reticular formation [87, 88].

Extensive connections of the vestibular system with motor nuclei of the extraocular muscles deserve special attention. In the cat, stimulation of a branch of the vestibular nerve supplying a single canal may result in conjugate deviation of the eyes

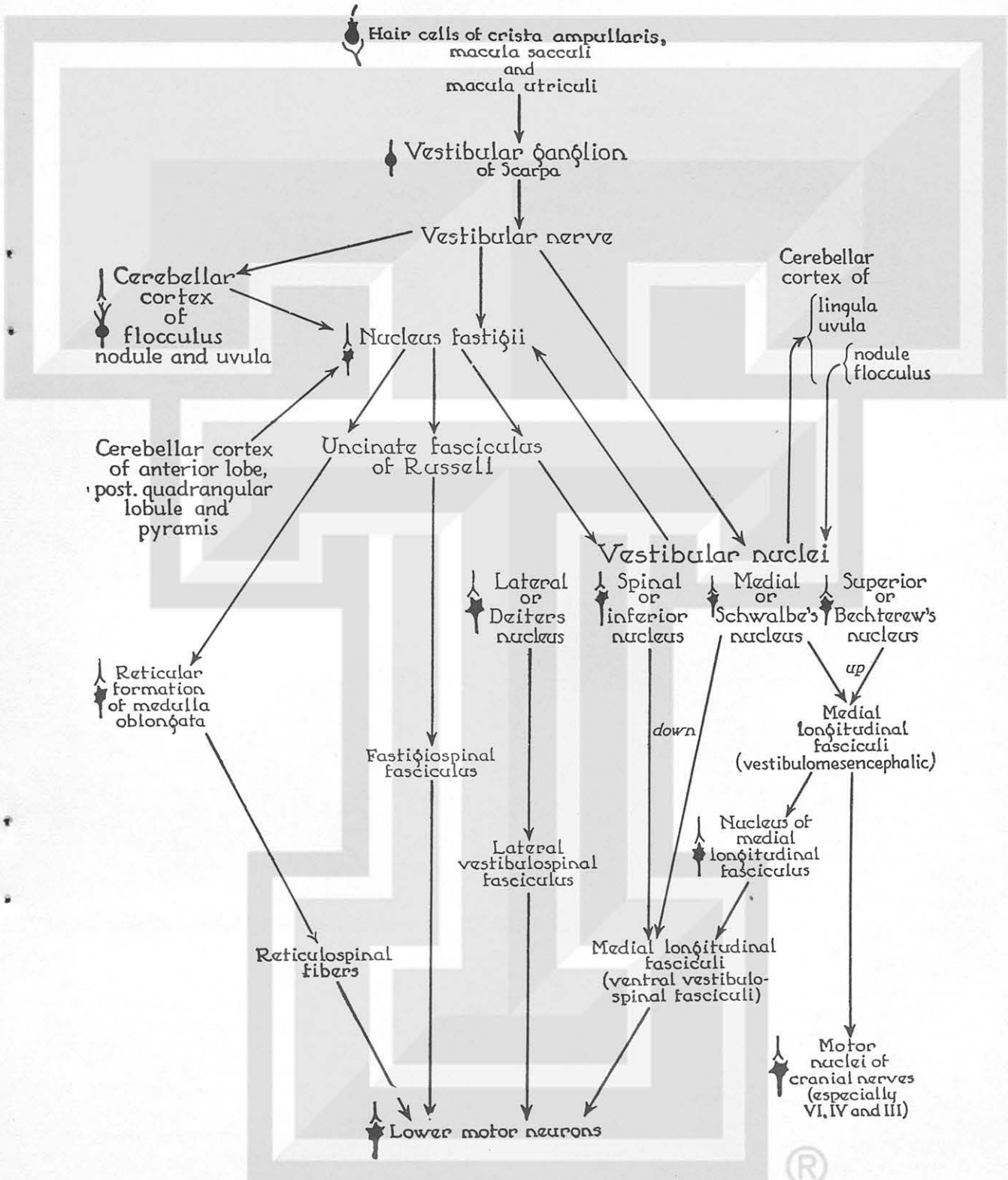
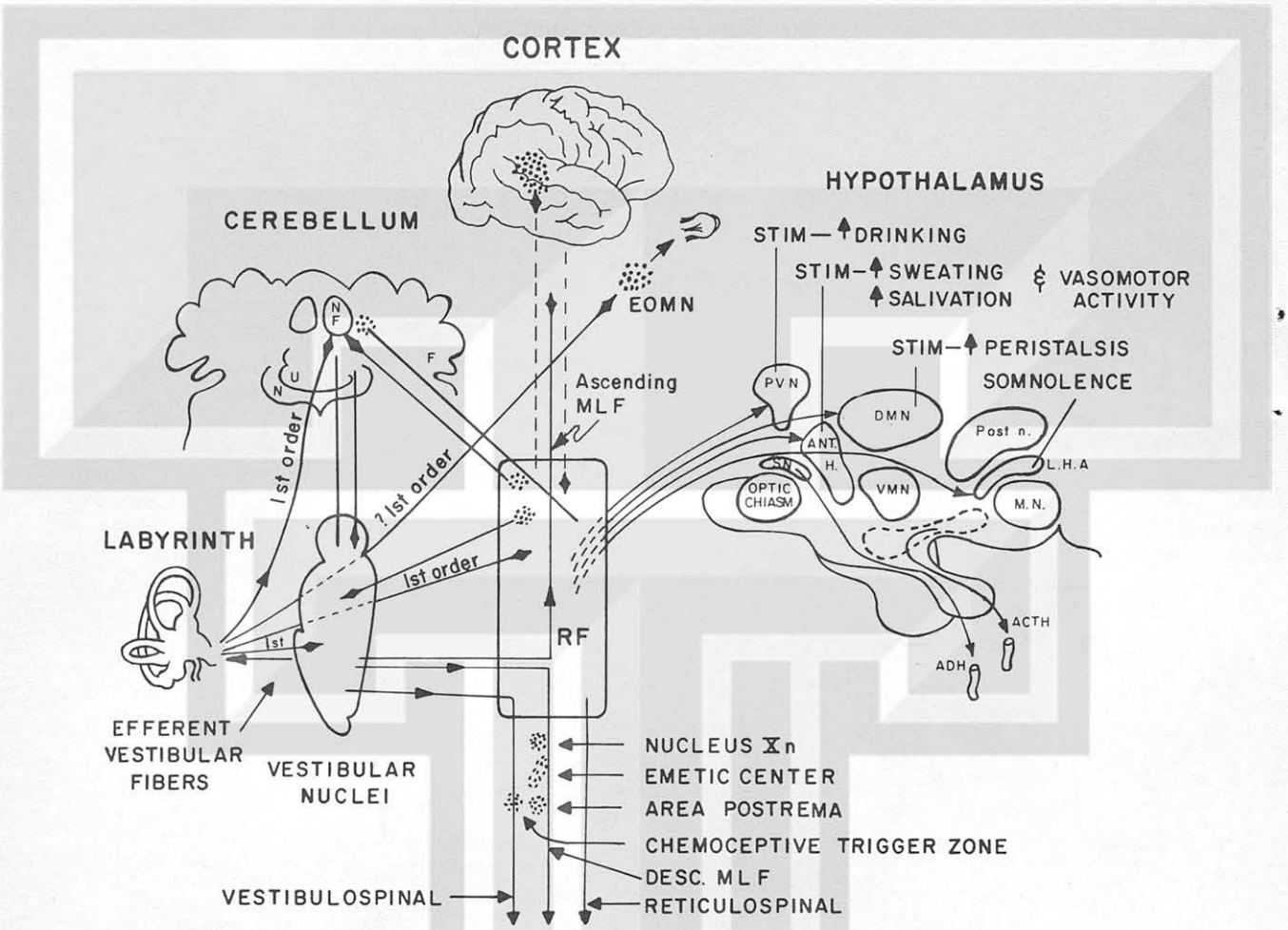


FIGURE 19. Vestibular or Equilibratory System [65].



NF	Fastigial nucleus	MLF	Medial longitudinal fasciculus	DMN	Dorsomedial hypothalamic nucleus
U	Uvula	RF	Reticular formation	VMN	Ventromedial hypothalamic nucleus
N	Nodulus	PVN	Paraventricular nucleus	Post N.	Posterior nucleus
F	Flacculus	SN	Supraoptic nucleus	L.H.A.	Lateral hypothalamic area
EOMN	Extraocular motor nuclei	Ant. H.	Anterior hypothalamic area	M.N.	Medial nucleus

FIGURE 20. Possible (abnormal) Irradiation of Vestibular Activity (dotted lines) Following a Strong Coriolis Acceleration. (First order refers to effects) [66]

[89]. Such movement, involving agonists and antagonists, implies that messages with highly specific physiological "meanings" are sent to the extraocular motor nuclei. The close relationship between the vestibular system, on the one hand, and vision and the control over eye motions, on the other, has a firm foundation in the underlying neuroanatomical relations.

Extensive connections, some of them monosynaptic [76], also exist between some of the vestibular nuclei and the spinal cord, particularly to those portions controlling movements of the head and trunk. These underlying neuroanatomical relationships provide the foundation for the powerful control the vestibular system exerts on coordinated movements of eyes, head, and trunk.

Reciprocal influences between canalicular and otolithic inputs and integration between right and left vestibular inputs are of great importance; some of the anatomical pathways and sites of interaction have been identified and studied in detail. The benefits of the advantages of having paired organs

must lie in synergism effected in the central nervous system, since loss or even damage to one labyrinth results in not only loss of servation but also in severe vestibular disturbances. These disturbances that may be severe in man would be fatal to many animals; they are in sharp contrast to the little or no disturbance following unilateral loss of visual or auditory function. Since vestibular influences do not reach the neocortex to any great extent, the possibility of right-left differences based on learning would be negligible, which is a matter of practical significance.

Vestibular Input-Output Relations

An effort to identify important elements determining vestibular input-output relations is shown schematically in Figure 21. In this framework, the vestibular organs play either the essential role or a contributory role in a multitude of responses under different stimulus conditions. At the bottom of the chart there is a brief categorization of circumstances giving rise to normal or abnormal vestibular responses. Emphasis here will be mainly on the responses elicited in normal persons under natural terrestrial conditions or on exposure in

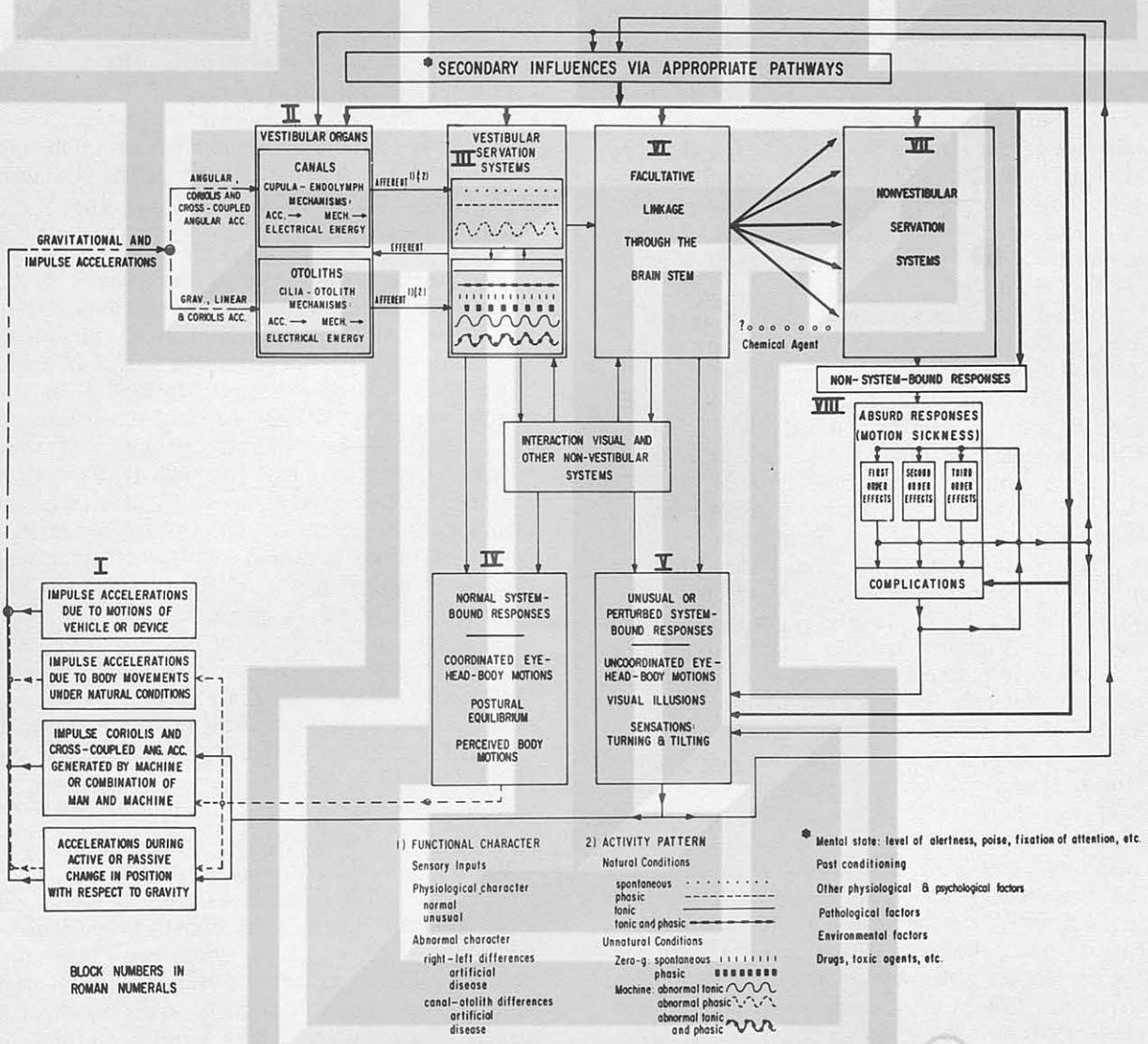


FIGURE 21. Conceptual Framework of Important Elements and Their Interactions Underlying System-Bound Vestibular Disturbances and Nonsystem-Bound Disturbances (Motion Sickness).

unusual gravitoinertial force environments (shown in Block I of Fig. 21). Man's motions, especially those involving rotation of the head, make a very important contribution to stimulus patterns. The cupula-endolymph and cilio-otolith mechanisms (Block II) have been discussed in the section on end organs. It is important to recall that mechanical events interposed between cessation of the accelerative stimulus and discharge of afferent impulses may be greatly prolonged in the canal, depending on antecedent events, giving rise to "illusory" aftereffects.

The canalicular and otolithic systems are shown (in Block III) as separate and interacting, although the combining term "vestibular system" is commonly used since the central nervous system pathways of the two components have not been fully traced; behavioral responses often represent a "combined" effect. The arrow (between Blocks II and III) indicates the efferent or return flow of impulses to the end organs, thus closing a loop; this efferent vestibular activity is under intensive study. Morphological evidence is on a firm basis [84, 86, 90], but man's functional role is uncertain. Likely it will prove inhibitory, which has been shown in the frog [91].

Natural and representative unnatural canalicular and otolithic activity patterns are shown under *Activity Pattern* at the bottom of Figure 21. Interactions between the canalicular and otolithic systems have been demonstrated under abnormal stimulus conditions [92-95], and between vestibular and nonvestibular systems (notably vision) [96-98]. A listing of typical secondary influences is shown. When man is engaged in natural activities under terrestrial conditions, the main chain of events involves those in Blocks I to IV of Figure 21. The loop is closed by virtue of (1) gravity, (2) man's motions generating immanent accelerations, and (3) changes in position of the otolith apparatus with regard to direction of the gravitational or gravitoinertial vertical and gravity. Vestibular influences find expression mainly through articulating motor effector systems concerned with postural stability [99] and stabilization of the retinal image [100], which are termed "normal system-bound responses."

In unnatural gravitoinertial force environments, the canals or otolith organs or both are stimulated in an unusual manner (Fig. 21, *Activity Pattern*), eliciting vestibular side effects that may fall into two categories, system-bound and nonsystem-bound responses. The former mainly comprise reflex phenomena such as nystagmus (Block V). The latter constitute an epiphenomenon elicited by certain repetitive stimuli which not only disturb the vestibular system but allow vestibular influences to stimulate cells outside the system (Block VIII). These responses include the symptomatology of motion sickness. Certain aspects of these input-output relations will be discussed in detail below. It is important here to point out distinguishing characteristics of system-bound and nonsystem-bound responses and the principal means of their relationship.

The multitudinous system-bound responses that can be elicited under unnatural stimulus conditions range from near-normal to grossly abnormal and defy easy categorization. It is helpful to keep in mind the approximate location of a specific response in the broad spectrum (since in general, the greater the departure from normality the greater the individual difference in susceptibility, acquisition, and decay of adaptation effects). This approach to classification is made difficult by the fact that the same phenomenon evoked by a threshold or suprathreshold stimulus may fall into the spectral extremes. The term reflex vestibular disturbance (RVD) designates the entire range, except in some instances at the near-normal end.

In general, RVD reflects instability of the vestibular system. Typical manifestations include nystagmus, the oculogyral illusion, eye-head-body incoordination, and postural disequilibrium. Systematic studies reveal characteristics of the various responses that may be observed or inferred. In general, these responses manifest: (1) short latencies typical of reflex phenomena; (2) maximal responses to the initial stimulus; (3) modulation by secondary influences; (4) little evidence of temporal perseveration on cessation of the stimulus (explicable exceptions here); and (5) a response decline indicating the effect of adaptation. When stimulus patterns have the potential for precipitating motion sickness (as well as RVD), these symptoms may be avoided, for example, by short exposure, making it possible to elicit reflex vestibular disturbances as "isolated" vestibular responses. Much of the following discussion, however, applies only to motion sickness [101-106].

Typical overt symptoms of motion sickness are well-known. Systematic studies reveal the characteristics of (1) delayed appearance of symptoms after onset of the stressful stimuli; (2) gradual or rapid increase in severity of symptoms; (3) modulation by secondary influences; (4) perseveration after sudden cessation of stimuli; and (5) response decline, indicating recovery. Further abstractions reveal great individual differences in susceptibility and in acquisition and decay of adaptation; transfer of adaptation effects; learning; and conditioning.

The appearance of symptoms always indicates that the adaptive capacity of the vestibular system has been exceeded. Indeed, even prior to the appearance of overt responses it can be demonstrated that the individual's susceptibility has arisen. Moreover, the order of appearance of symptoms is affected by the strength of stressful stimuli and length of exposure. Secondary etiologic influences, categorized in Figure 21, are always present, tending either to raise or lower susceptibility. Vision plays an important role. A pilot, for example, free of symptoms in the cockpit, may experience motion sickness in the navigator's closed compartment. Mild symptoms of motion sickness have disappeared under the influence of experimenter-directed tasks that may have preempted central nervous system pathways used by irradiating vestibular influences. Covert factors may come into play, which include defects, disease, and functional disturbances not diagnosed or wrongly considered unimportant. Examples are personality defects, making a person unwilling or unable to cope with functional disorders of vestibular origin, prodromal stages of disease, and undiagnosed vestibular disease or functional disorder.

Little is known concerning the precise nature of the facultative linkage. The fact that irradiating vestibular activity is demonstrably open to modulating influences points to the use of common pathways in the brainstem reticular formation. This common meeting ground between somatic and visceral systems is essential, not only for coordination at the reflex level, but also to provide voluntary control over otherwise autonomic responses. The unusual (but not unique) characteristic of the vestibular linkage is the readiness with which vestibular activity may get "out of bounds" and elicit widespread responses that include typical symptoms of motion sickness. There is a long delay at times between the onset of stimulation and appearance of motion sickness, which suggests that a chemical linkage may also be involved.

Recovery during continual exposure to stress is complicated. At some point in time, the tendency toward restoration of homeostasis in nonvestibular systems exceeds the influences having a contrary tendency. At another point in time, nonvestibular systems are freed from vestibular influences (adaptation in the vestibular system and disappearance of any neurohormones released). Then restoration takes place spontaneously through homeostatic events and processes, not only in the systems responsible for first-order effects, but in all systems involved in higher order effects and complications. Curves depicting the time course of adaptation in the vestibular system, the disappearance of vestibular influences, and the restoration in nonvestibular systems tend to overlap and have not been clearly defined. Thus, engagement and disengagement between the vestibular and nonvestibular systems is difficult to follow, but interesting to study.

Investigations dealing with reflex vestibular disturbances and motion sickness in man may be directed to the solution of an operational problem, or to the accumulation of facts, the synthesis of which would be applicable to any operational problem.

Nonvestibular mechanoreceptors may be stimulated by mechanical and gravitoinertial forces, but the vestibular organs are stimulated only by gravitoinertial forces. (This was pointed out in connection with Figures 1 and 2.) These differences become important on transition into weightlessness; in addition, the two vestibular organs are affected very differently, as summarized in Figure 22. Presumably, when the astronaut is at rest with head fixed, there would be physiological deafferentation of the otolith apparatus, with consequent loss of its tonic discharge but retention of a spontaneous or resting discharge [107, 108], analogous to the difference between eyes-open and eyes-closed. There would be no corresponding effect on the semicircular canals. Rotations of the head would provide stimulus to the canals the same as under terrestrial conditions. However, the transient linear accelerations generated might or might not constitute an adequate stimulus to the otolith apparatus, and, if adequate, the information would neither be useful for orientation to the upright nor concordant with the canalicular input. Thus, among vestibular receptors and nonvestibular mechanoreceptors, the canals alone are stimulated essentially the same with natural movements of the head (body) under terrestrial and weightless conditions. The otolith organs encounter a unique stimulus condition with the lifting of the stimulus due to nullification of gravity.

Inversion Illusion

From the operation viewpoint, the astronaut may experience the inversion illusion, motion sickness, and, probably, the loss of the A and E phenomenon, and rotary autokinesis.

In space flight, some cosmonauts have experienced the inversion illusion on making the transition into weightlessness [8, 109]. The phenomenon is probably dependent on physiological deafferentation of the otolith receptors, which is suggested by the observation in parabolic flight that some normal

CANALICULAR SYSTEM — GRAVITY INDEPENDENT

	RESTING DISCHARGE							PHYSIOLOGICAL STIMULUS CONDITIONS						ARTIFICIAL STIMULUS CONDITIONS		
	GENESIS	MAINT. NEURAL CONN 2ND NEUR	MAINT. NEURAL CONN BEYOND 2ND N.	MODULATED BY OTO. APPARATUS	TONUS	AFFECTS R-L V. BALANCE	INC. SUSC. TO CNS FUNCT. DIST.	STIM—ULUS	SENSORY INPUT	MOD. OTO. OUTPUT	MOD. BY OTO. OUTPUT	AFFECTS R—L VESTIB. BALANCE	INC. SUSC. TO CNS DIST.	CORIOLIS ACC.	ANGULAR ACC.	LINEAR ACC. & CONSTANT ROTATION WITHIN CRITICAL RANGE
EARTH	BIOCHEM. GRAVITY INDEPENDENT	YES	YES	YES	PROB-ABLY	YES	?	INERTIAL ANGULAR & CORIOLIS ACC.	PHASIC	YES	YES	NO	YES	ABNORMAL RESPONSE V-I + V-II POSSIBLE	RESPONSE THRESHOLDS $0.04°/SEC^2$	MAY CONSTITUTE AN ADEQUATE STIMULUS
SPACECRAFT	BIOCHEM. GRAVITY INDEPENDENT	YES	YES	YES	PROB-ABLY	YES	?	THE SAME	PHASIC	YES	YES & MAY AFFECT BE-HAVIORAL RESP.	?	YES	IND. SUSC. V-I + V-II MAY BE DIFFERENT	RESPONSE THRESHOLDS MAY WELL BE DIFF.	SHOULD BE DIFFERENCES (QUANT.) AT LEAST. IMP. TO INVESTIGATE

OTOLITHIC SYSTEMS — GRAVITY DEPENDENT

	RESTING DISCHARGE		PHYSIOLOGICAL STIMULUS CONDITIONS					ARTIFICIAL STIMULUS CONDITIONS	
	PRESENCE	GENESIS	STIMULUS DUE TO GRAVITY: PROOF	STIMULUS DUE TO GRAVITY: SENSORY INPUT	STIMULUS DUE TO CHANGE IN POSITION OF HEAD IN GRAVITATIONAL FIELD: DURING CHANGE	STIMULUS DUE TO CHANGE IN POSITION OF HEAD IN GRAVITATIONAL FIELD: HEAD FIXED IN NEW POSITION	STIMULUS DUE TO IMMANENT INERTIAL LINEAR ACC.	RESPONSE THRESHOLDS TO STIMULATION	SUPRATHRESHOLD LEVELS OF STIMULATION
EARTH	INFERRED	CHEM→ EL. ACT.	OCULAR COUNTERROLL, OCULOGRAVIC ILLUSION A&E* & PERCEPT. UPRIGHT VARY AS FUNCTION OF g LOADING	TONIC: MODULATES REFLEX ACTIVITY AND CANALICULAR INFLUENCE	DYNAMICS NOT INVESTIGATED IN SYSTEMATIC FASHION	FEW SYSTEMATIC STUDIES. SERVATION DECREASES WITH LARGE DEPARTURES FROM UPRIGHT	PROBABLY LESS IMP. THAN CANALS FOR MAINTAINING POSTURAL UPRIGHT IN MAN	VARY WITH DEPARTURES FROM GRAV. UPRIGHT OR GRAVITOINERTIAL UPRIGHT	ESTABLISHMENT OF GRAVITOINERTIAL VERTICAL OTHER THAN IN LONG BODY AXIS CHARACTERIZED BY A "LAG" AND A "MAGNITUDE" EFFECT (OVERCOMPENSATION AT LEVELS GREATER THAN 1.2 g UNITS)
SPACECRAFT	DEMONSTRATED IN PARABOLIC FLIGHT	GRAVITY INDEPENDENT	? NO A&E C-ROLL PERCEPT. UPRIGHT * A&E MUELLER & AUBERT PHENOMENA	NO INPUT	NOT POSSIBLE		MAINLY TRANSIENTS SHOULD BE MEASURED. STIMULUS THRESHOLDS MAY BE AFFECTED BY LOSS OF g LOADING. PROBABLY EFFECTIVE IN STIMULATING OTO. SYSTEM	HAS NOT BEEN INVESTIGATED CAREFULLY BUT THERE ARE REPORTS OF "INCREASED SENSITIVITY" BEHAVIORAL SIGNIFICANCE IN TERMS OF GRAVITOINERTIAL UPRIGHT NECESSARILY DIFFERENT	THE ABSENCE OF THE EARTH'S STANDARD OF GRAVITY WILL HAVE EFFECT OF EXAGGERATING THE INFLUENCE OF VECTORS NOT IN ACCORD WITH BODY OR VISUAL UPRIGHT. POSSIBLE EFFECTS ON ORIENTATION AND SUSCEPTIBILITY TO MOTION SICKNESS

FIGURE 22. Certain Differences between Life on Earth and in a Weightless Spacecraft with Reference to the Canalicular and Otolithic Systems.

subjects, but no labyrinthine-defective (L-D) subject, experienced the illusion [110].

The problem of motion sickness experienced in orbital flight and in the weightless phase of parabolic flight is discussed in a subsequent section. Not easily explained are the great individual differences in susceptibility to motion sickness in weightlessness, resulting not only from normal stimulation of the canals but also from cross-coupled angular accelerations that would result from head motion in a rotating vehicle. It would appear that some persons have unusually low and some unusually high susceptibility. Thus, the subgravity level is a parameter that must be taken into account as well as the angular velocity. The curves describing susceptibility to motion sickness as a function of subgravity level can be determined from experiments in parabolic flight, but require validation under actual space flight stimulus conditions. The U.S. experience with regard to motion sickness in space missions has recently been reviewed in detail [111], and the Soviet experience is also a matter of record [2, 8, 112, 113].

A and E Phenomena

Wade [114] has recently reviewed the literature dealing with visual orientation to the upright (and how it is influenced by body position with reference to the gravitational vertical) and has analyzed the contributory role of postural mechanisms in terms of the otolith, neck, and trunk systems. In brief, it is readily demonstrated that when man is upright, orientation of a visual target to the gravitational vertical and horizontal, in the absence of visual cues to the upright, is accurate and that with rightward or leftward tilt, a bias appears first in a gradual displacement of the visual vertical to the opposite side of the gravitational vertical, the Müller [115] or E effect; after tilting through 65 degrees the bias reverses and eventually is displaced toward the same side, the Aubert [116] or A effect.

In Figures 23-A and 23-B, the curves demonstrate differences between normal and L-D subjects, respectively, in perceiving A and E effects, which clearly point to contributory influence of the otolith apparatus [117]. Some evidence that this

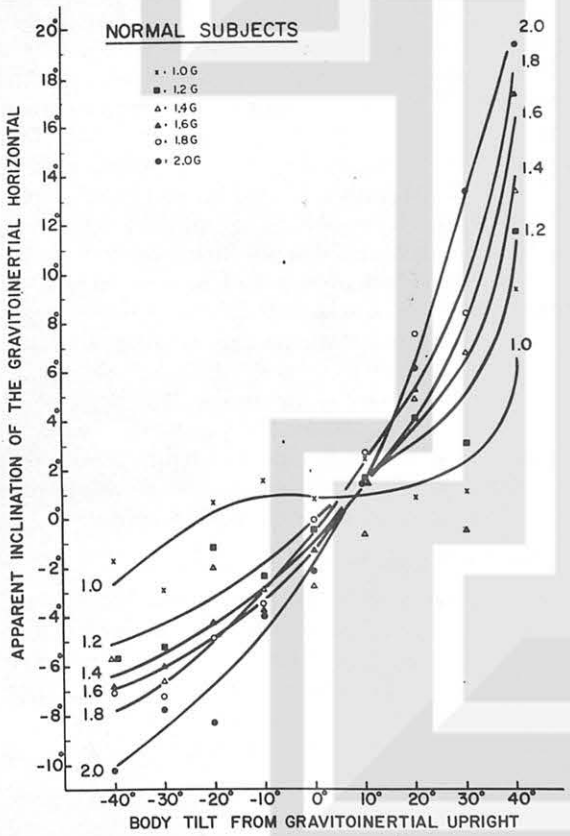


Figure 23-A. Change in E-Phenomenon as a Function of Increasing g Level in Normal Subjects [117].

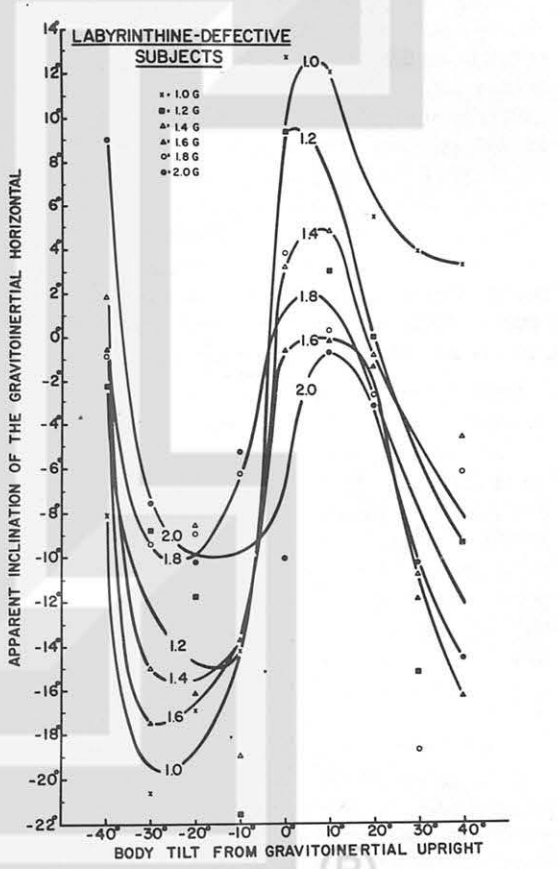


Figure 23-B. Change in E- and A-Phenomena as a Function of Increasing g Level in L-D Subjects [117].

bias is lost in weightlessness was demonstrated in Gemini flights V and VII [118], suggesting that under terrestrial conditions it is dependent on otolithic and nonotolithic gravireceptors. In the Gemini flights there was no evidence of perception of rotary autokinesis, which is probably related to the A and E phenomena. Rotary autokinesis is perceived both by normal and L-D subjects under terrestrial conditions [119].

Theoretically, it is not an overstatement that the role of the vestibular organs will never be fully elucidated without conducting experiments in the weightless spacecraft. Only in the weightless space laboratory will it be possible to: (1) investigate the role of tonic otolithic activity due to gravity; (2) uncouple otolithic and nonotolith mechanoreceptor influences; and (3) investigate an elegant example of vestibular disturbance due to deafferentation rather than an abnormal pattern of otolithic stimulation.

VESTIBULAR PROBLEMS AND GENERATION OF ARTIFICIAL GRAVITY

The "vestibular problem" is one to be considered, among others, to determine vehicle design criteria. Those who are concerned include: (1) specialists knowledgeable in regard to other human element problems; (2) engineers who must ensure inertial stability of the vehicle, taking into account "cost"; (3) astronauts who must assume partial responsibility in self-prevention of vestibular side effects, and, along with astroscientists, participate as subject or observer in validation experiments; (4) biomedical personnel in charge of long-range and specific-mission plans; and (5) investigators conducting ground-based supporting experimentation.

With regard to trade-offs in reaching a compromise regarding the design of a rotating space vehicle, laboratory studies have indicated that vestibular side effects tended to increase as a log function of angular velocity (generating cross-coupled angular accelerations) and that other physiological side effects are the result of short-radius and high-angular velocities. Thus, it seems that the approach to the compromise involves relative weighting factors assigned to the cross-coupled angular acceleration, Coriolis accelerations, and subgravity level (short-radius effects would not be involved if the other conditions were satisfied).

Limitations in simulating novel stimulus conditions, such as those involved in making sudden transitions between rotating and nonrotating portions of a space base, force an extension of ground-based studies to include validation of observations and experiments conducted aloft. The astronaut necessarily plays the key role in this integration. As the subject he can serve as his own control in validating studies; as the on-board experimenter, he is essential in conducting experiments and making observations aloft; as the astronaut, he has responsibilities in preventing vestibular side effects during the mission. Prevention involves taking charge rather than responding to events, and requires close cooperation between the astronaut in the space base and the biomedical representatives in the ground-based control center, during the period of adjustment.

Ground-based activities involving the astronaut center around individualization of the problem in preventing vestibular side effects and the astronaut's somewhat complementary roles of subject and on-board experimenter. Major elements of the activities include selection (or secondary selection), instruction, preflight adaptation, monitoring his progress during the mission, and postflight assessment. For the astroscientist, who does not double as an astronaut, considerations are somewhat different. He would not be under the same time-load stress as the astronaut prior to launch, and, presumably, there would be little restriction in terms of participation in prelaunch assessment, indoctrination, and adaptation. Since his tasks aloft would not include items critical for life support, rapid adjustment to stimulus conditions would not be necessary, which in turn would permit greater freedom in the selection process. The direction of the ground-based experimental program would be determined largely by findings obtained under space flight conditions.

The operational objective of concern here is the prevention of vestibular side effects. This eventually reduces to the selection process, adaptation, education, and experience, and the use of various countermeasures including drugs. The sections to follow will be organized around various vestibular "tests," during which the astronaut will become indoctrinated and the biomedical staff will acquire the information necessary to make decisions.

Vestibular Assessment in Astronauts

Distinction among functional, provocative, and simulation tests is useful, although somewhat arbitrary. Only simulation tests will be discussed in detail here, mainly because they comprise the most important tests for assessing astronauts, and partly because some of the material is not readily accessible elsewhere.

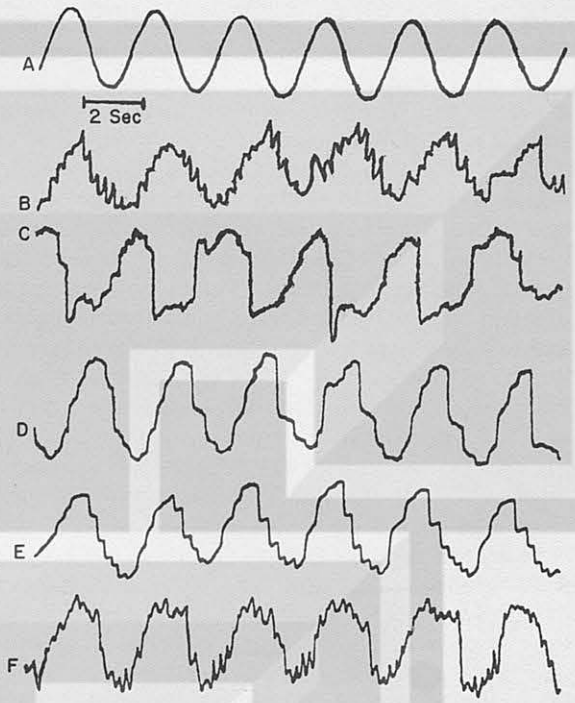
Functional Tests

According to evidence, functional test scores within the normal range have no value in predicting individual differences in susceptibility to reflex ves-

tibular disturbances and motion sickness [112, 113, 120]. They are valuable, nevertheless, from the clinical standpoint (ruling out overt and, if possible, cryptic defect or disease), and from the standpoint of making comparative measurements, with the astronaut serving as his own control. The reliability of most vestibular tests is not high when compared with vision or hearing tests; hence, there is need or desirability for repeated measurements on astronauts who serve as experimental subjects. Functional tests should be used in the selection of aviators, astronauts, and subjects for vestibular experimentation.

Clinicians have described batteries of tests [103, 121-124] which might be referred to for details, but nearly all batteries include tests for spontaneous and positional nystagmus, a modified Hallpike test. Some clinicians use a visual-tracking "pendulum test," which will be described briefly.

Eye motions are recorded while the subject "tracks" an oscillating target. Displacement and frequency of the pendulum device can be varied. Normal persons begin to have difficulty in tracking the target with displacements greater than 20 degrees and a frequency greater than 0.8 Hz (oscillation time = 1.2 sec), which is declared by the appearance of saccadic perturbation in the record. The testing procedure can be exploited by using one eye for fixation. Typical results are shown in Figure 24.



A. normal tracking movement
B. congenital nystagmus
C. acoustic neuroma on left side
D. lesion vestibular nuclei
E. basilar impression
F. posttraumatic nystagmus

Figure 24. Eye Movements Recorded during Pendulum Test.

Tests of canal function. Thermal stimulation consists of delivering a jet of water of known temperature, at a predetermined rate and volume, against the eardrum. The head is positioned so that the horizontal paired canals are vertical. Differences in specific weight of endolymph at body temperature and that portion of the canal influenced by the irrigating water cause displacement of the cupula. Thermal stimulus to one ear is grossly abnormal because of the disturbance created in the delicate right-left synergistic mechanisms underlying normal canalicular function. Each horizontal canal can be stimulated individually (vertical canals also can be stimulated), which is a great advantage. The nystagmic response may be observed, but nystagmographic recordings are recommended for objectivity and to provide better opportunity for analysis.

With the well-known Hallpike test [125], irrigating temperatures of 30° and 44°C are used. While nausea may be induced in highly susceptible persons, the great advantage is in determining what is termed right-left labyrinthine and directional preponderance. The threshold caloric test [126], used routinely, has advantages for screening purposes and comparative measurements; the subject serves as his own control, and the vestibular disturbance is brief and recovery quick. Irrigating temperatures just below body temperature usually suffice; if not, decreases by steps are made until a response is obtained. If irrigating temperatures below 35°C are required to elicit a response, some abnormality should be suspected.

Angular acceleration thresholds. Rotating devices have been fabricated that provide not only stimulus of a physiological character (albeit unusual), but also may have excellent performance characteristics, including preprogramming. The most sensitive indicator is the oculogyral illusion, but "sensations" and nystagmus are also used routinely.

The oculogyral illusion is a form of apparent motion that has its genesis in the cupula-endolymph mechanism and may be viewed under many different circumstances [127]. In measuring "thresholds," one of the favorable conditions is a dimly lighted three-dimensional target viewed in darkness and fixed with regard to the subject. Expected apparent motion is in the direction of acceleration.

Clark and Stewart [128] reported that the mean threshold for the perception of the oculogyral illusion was found to be $0.11^{\circ}/sec^2$ in 32 normal subjects when they were exposed to rotation in the vertical axis for 10 seconds.

Tests of otolith function. Ocular counterrolling, described in detail by Miller [129], has the advantage of not disturbing the vestibular system; hence, it qualifies as a test to be conducted under near-normal stimulus conditions. Values obtained with different degrees of rightward and leftward tilt describe curves that can be examined for left-right symmetry. The "index" values (one-half the sum of the maximal left and right roll), obtained in a group of 550 presumably normal persons and 10 labyrinthine-defective (L-D) subjects, are shown in Figure 25 [130]. The rare instances when values fall below 120 seconds of arc are unexplained.

A variety of other tests are available, but none is recommended as a substitute for ocular counterrolling; sometimes a second test is desirable if facilities for counterrolling are not available. The other tests include (1) the oculogravic illusion test [96], (2) elicitation of compensatory eye motions by exposing a subject to horizontal oscillations on a horizontal swing or other device [131], and (3) elicitation of nystagmus in a device that rotates the subject about an axis other than Earth vertical, or revolves him in a counterrotating capsule or room that exposes him to a rotating linear acceleration vector [132-135].

The oculogravic illusion deserves brief mention since it is perceptible in a rotating environment. When a person is subjected to change in direction of the gravitoinertial vertical with reference to himself, this is rightly interpreted as body tilt away from the upright; the visual framework tends to tilt concordantly which has been termed the oculogravic illusion [96]. It is mainly dependent on the integrity of the otolith system, although nonvestibular proprioceptors may contribute to its perception. When a person views an objectively vertical luminous line in the dark, it will appear to tilt when the direction of the resultant force vector has inclined about 1.5 degrees from the Earth vertical. The observer's estimates of the tilt correspond closely to the change in direction of the resultant vector, up to about 30 degrees; beyond this the subject increasingly overestimates the angular change. Figure 26 shows estimates of the illusion by normal and L-D subjects under dry and head-out water immersion conditions on a human centrifuge [136]. Greater individual variation in the settings was made by the L-D compared to the normal subjects, but the contribution of (mainly) nonotolith gravireceptors under dry conditions in the case of the L-D subjects is evident. Water immersion simulated the weightless conditions to some extent with regard to nonotolith, but not to otolith receptors.

Postural equilibrium test battery. A limitation of postural equilibrium tests is that many systems, in addition to the vestibular reflexes, are challenged;

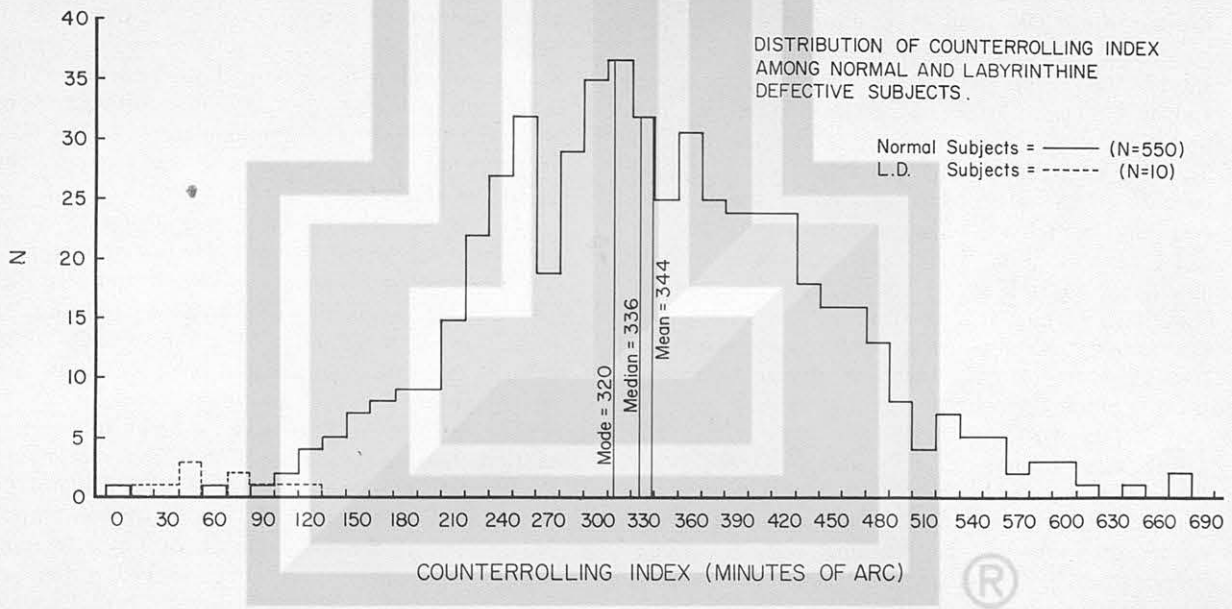


FIGURE 25. Distribution of Counterrolling Index among Normal and Labyrinthine-Defective Subjects [130].

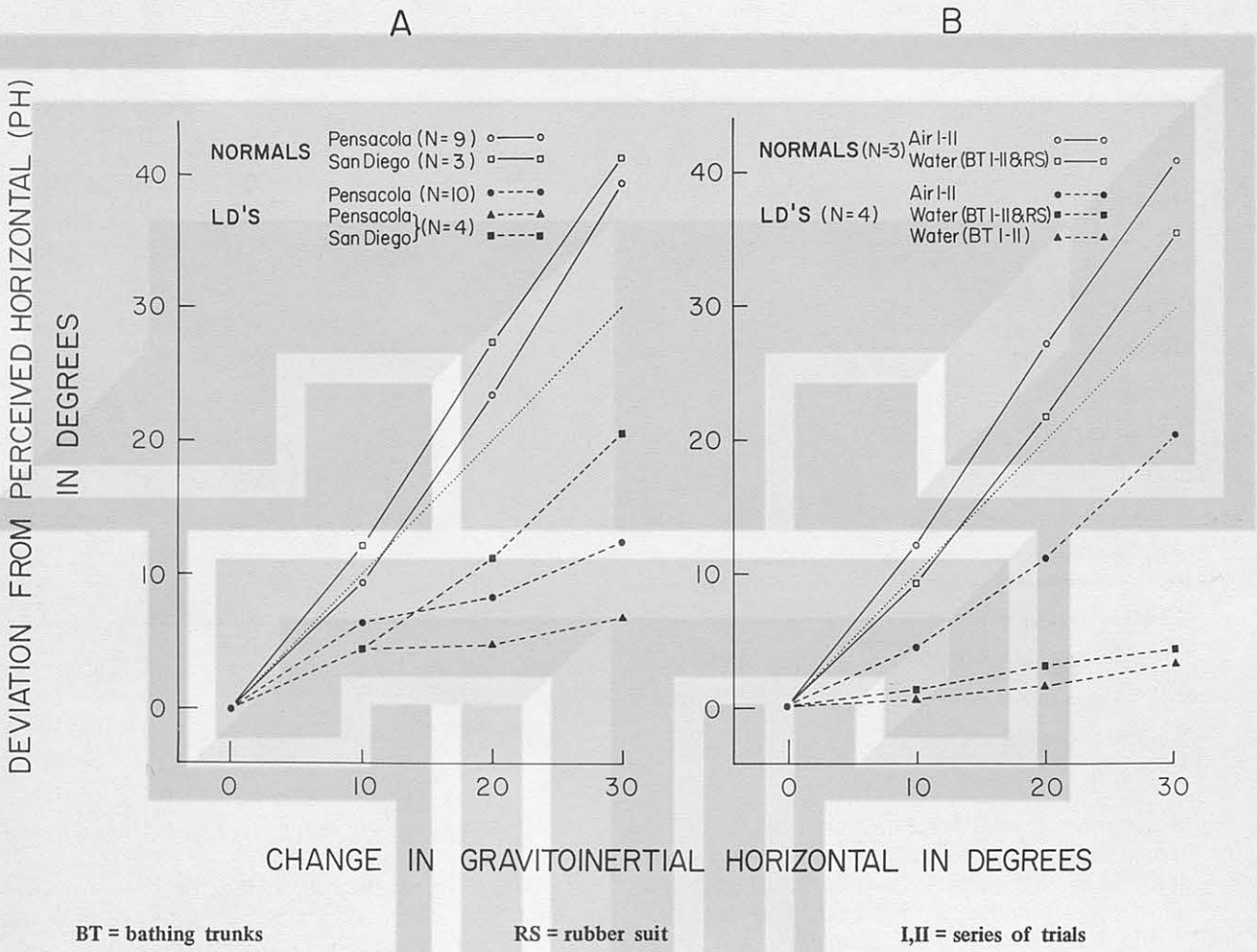


FIGURE 26. Comparison between Mean Settings of a Target Line to the Horizontal of Extrapersonal Space Made by Normal and Labyrinthine-Defective Subjects under Wet and Dry (air) Conditions [136].

however, a distinct advantage is the testing of natural behavioral mechanisms. Findings in subjects with partial loss of vestibular function [137] suggest that postural equilibrium is more dependent upon canalicular than on otolithic function. A useful test battery, described in detail by Graybiel and Fregly [138], requires the subject to stand or walk in the stringent position of body erect, arms folded against chest, and wearing flat-heeled leather-soled shoes. Test items that constitute this battery are:

Sharpened Romberg (SR): Stand on floor, eyes closed, feet in heel-to-toe position. Maximum score, 240.

Walk eyes open (E/O): Walk heel-to-toe, eyes open, on rail ¾-inch wide. Maximum score, 15.

Stand eyes open (E/O): Stand heel-to-toe, eyes open, on ¾-inch rail. Maximum score, 180.

Stand on leg, eyes closed (SOLEC): First right leg (SOLEC-R), then left leg (SOLEC-L). Maximum score, 150.

Walk a straight line heel-to-toe on floor (WALEC). Maximum score zero.

The scores are normalized in percentile equivalents; some comparative scores are shown in Table 2. Scores below the 6th percentile are regarded as abnormal, and above the 40th, in the typical normal range. In general, improvement in scores suggests normality, and its absence, abnormality.

Provocative Tests

Provocative tests are important in evaluating a person's susceptibility to reflex vestibular disturbances and to motion sickness. In addition, they may measure his ability to cope with such disturbances, either with or without the aid of countermeasures, including the use of drugs. Factors of etiologic significance may be introduced, in addition

Table 2. Group Differences in the Percentage of Abnormal Ataxia Test Battery Scores

Subject groups	N	Walk E/O (%)	Stand E/O (%)	Stand E/C (%)	SR (%)	SOLEC-R (%)	SOLEC-L (%)	WALEC (%)
Normals	240[a]	1	5	4	7	3	4	3
Patients with vertigo	76[b]	18	26	22	37	23	35	29
Congenitally deaf	3	0	0	33	67	33	67	67
Head injury deaf	5	60	60	80	60	80	80	40
Unilat. labyr.-defect.	11	18	18	18	64	46	64	100
Ménière's patients	4[c]	25	50	75	100	100	100	100
Bilat. labyr.-defect.	26	72	96	96	100	100	100	100

[a]N = 198 on SOLEC-R and SOLEC-L; N = 147 on WALEC

[b]N = 31 on SOLEC-R and SOLEC-L; N = 38 on WALEC

[c]N = 3 on SOLEC-L and WALEC

to the gravitoinertial force environment, to simulate more completely the anticipated operational conditions, or to explore their roles in affecting an individual's susceptibility to novel circumstances.

The distinctions between provocative and simulation tests are: primarily, duration, and second, specificity in terms of the global exposure conditions. Thus, the predictive value of provocative tests is less than that of simulation tests. Validity of the findings, in the case of functional tests, is compromised if the subject is either suffering from active disease involving the vestibular systems, or has not compensated completely from permanent injury that is no longer active.

In conducting and interpreting the results of provocative tests, difficulties are encountered and precautions must be taken, which bear some relationship. Difficulties originate in: (1) individual differences in susceptibility to a given test; (2) intra-individual differences in susceptibility with exposure to different gravitoinertial force environments; (3) preternaturally high susceptibility if sufficient time has not elapsed between exposures; (4) adaptation as an inevitable consequence of every test, with considerable individual variation in the rate of acquisition and of loss of adaptation; and (5) expressing the results in absolute values. There would be a great advantage in using normalized scores and standardized techniques.

There are advantages in the use of provocative tests, such as the low "cost" (in terms of time and equipment), making a "test battery" feasible; individual testing is practicable; and their value in studying vestibular mechanisms and in evaluating countermeasures. While a great number of provocative tests are in use, only a few that are relevant to space flight operations will be described.

The dial test. A standardized test, known as the dial test, was devised for determining susceptibility to motion sickness in the slow rotation room (SRR). Stressful Coriolis accelerations are generated by simultaneous rotations of room and subject. Five dials are placed so that the subject is required to move his head and trunk to five different extreme positions to set the needle at a given number on each dial. This maximizes the rotation of the head out of the plane of the room's rotation. A "sequence" consists of setting the five dials in accordance with a tape recording, one every 6 seconds, followed by a rest period of 6 seconds. The subject continues the task, usually with eyes open, until a definite end point is reached, usually MIII (severe malaise) (Table 3 [139]), or (usually) until 20 sequences or 100 settings have been made.

Table 3. Diagnostic Categorization of Different Levels of Severity of Acute Motion Sickness [139]

Category	Pathognomonic 16 points	Major 8 points	Minor 4 points	Minimal 2 points	AQS* 1 point
Nausea syndrome	Vomiting or retching	Nausea+ II, III	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing/Subjective warmth ⩾ II
Cold sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Headache ⩾ II
Central nervous system					Dizziness: Eyes closed ⩾ II ; Eyes open III

Levels of Severity Identified by Total Points Scored

Frank Sickness (S)	Severe Malaise (M III)	Moderate Malaise A (M IIA)	Moderate Malaise B (M IIB)	Slight Malaise (M I)
⩾ 16 points	8-15 points	5-7 points	3-4 points	1-2 points

*AQS = Additional qualifying symptoms. +III = severe or marked, II = moderate, I = slight.

If the original rate of rotation (e.g., 7.5 rpm) is too stressful, the velocity is reduced, or increased if the original rate is too weak. With few exceptions, normal persons reach the end point at a velocity between 5 and 20 rpm. Results are scored in terms of angular velocity, number of head motions, and level of symptom (e.g., 10 rpm, 78, MIII, respectively).

The Coriolis sickness susceptibility index. This modification of the dial test uses a rotating Stille or litter chair. The subject makes standardized head motions, usually with eyes closed [140]. Angular velocities higher than those in the SRR are required to reach the same end point. The method of scoring is a noteworthy feature of this test, which yields a single value, the "index," enabling the investigator to make comparisons among subjects.

Off-vertical rotation test. In contrast with the dial and Coriolis sickness susceptibility tests, which mainly "disturb" the canalicular system, a rotating linear-acceleration vector mainly stresses the otolithic system. The off-vertical rotation (OVR) test is one of many and may be scored in "duration," which has some, but not all, advantages of an index.

The device consists of a rotating chair (Fig. 27 [141]) mounted on a platform that can be tilted by a handcrank or electric motor. The degree of tilt

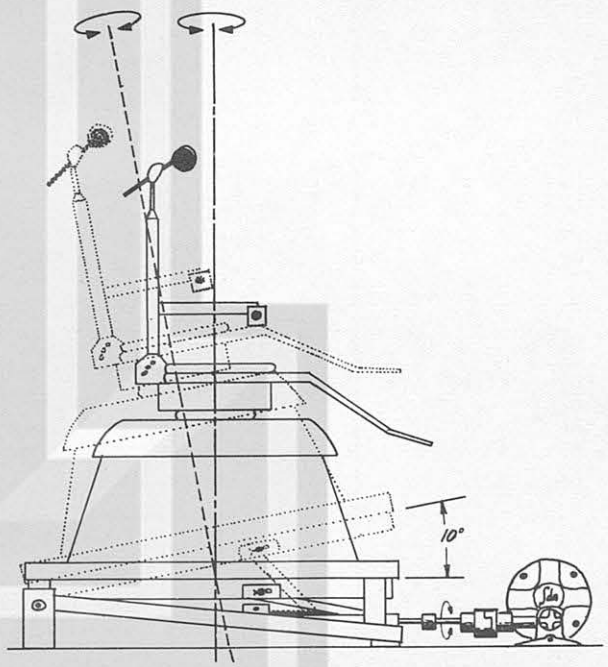


Figure 27. Off-Vertical Rotating Chair Device [141]. (Slide mechanisms for positioning subject not shown)

can be read from a large protractor. The subject's head is held rigidly against the headrest by adjustable straps across his forehead; it is centered precisely over the center of rotation, with smooth rotation ensured by proper counterbalancing. The rotation, programmed on a time axis, involves periods of acceleration at $0.5°/sec^2$ for 30 seconds, followed by periods of constant velocity for 6 minutes, until either the end point is reached or 6 minutes completed at 25 rpm, the cutoff point. In effect, this program represents unit increases of 2.5 rpm every 6.5 minutes after the initial step. The end point can be expressed in terms of elapsed time at terminal velocity, as total elapsed time at terminal velocity, or as total elapsed time, which serves as an index of susceptibility to motion sickness. With each revolution of the OVR device, the subject continually changes position in regard to the gravitational upright. Thus, receptors in the paired maculae of utricle and saccule and nonvestibular proprioceptors are continually exposed to an unusual stimulus pattern.

The findings from OVR tests in a group of healthy men, most of them attached to a naval air station, are shown in Figure 28 [141]. All but 12 reached the predetermined end point (MIIA) at a 10-degree tilt; all but five of the remainder reached it only when the angle of tilt was increased to 20 degrees. Thus, scores ranked 95 subjects in terms of their susceptibility to this unusual gravitoinertial force environment and demonstrated that five were not highly susceptible.

Plots comparing susceptiblity to motion sickness are shown in Figures 29 and 30, with scores obtained in testing the function of the semicircular canals and otolith organs [141]. It appears that no significant relationships were found between functional test scores and susceptiblity to motion sickness. However, it should be noted that when extreme values are compared, susceptibility is higher in subjects with low rather than high oculogyral illusion threshold test values, and susceptibility is lower in subjects with high rather than low values for the counterrolling index.

Simulation Tests

An effort to predict susceptibility to vestibular side effects under the novel conditions in a rotating space base poses problems, some of which are pointed out in Figure 31. The slow rotation room (SRR), used to simulate the angular velocity, is

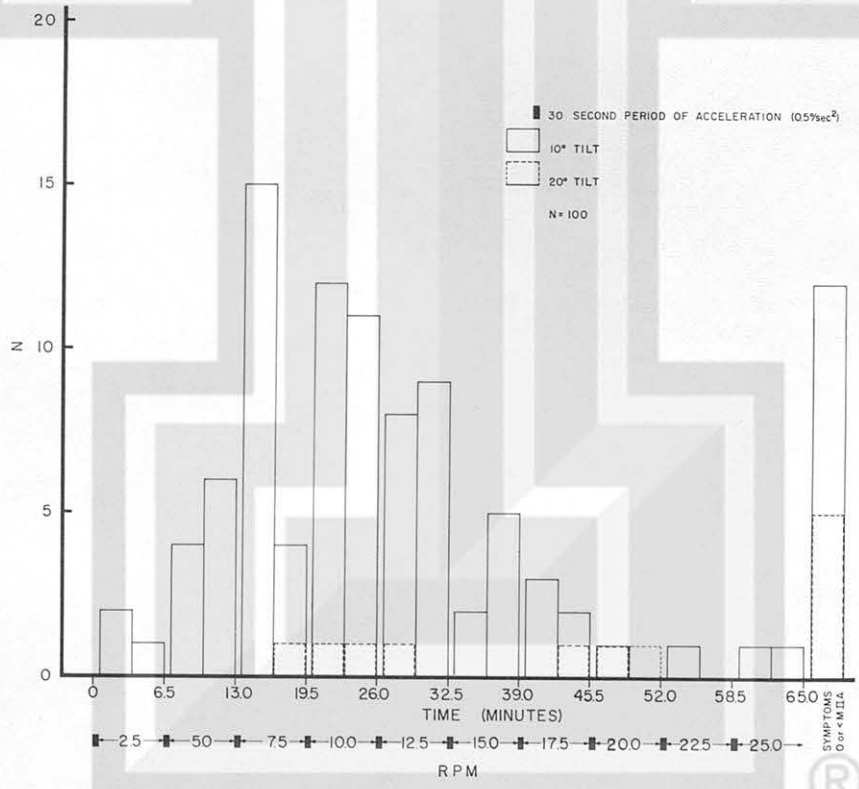


FIGURE 28. Susceptibility Index in Subjects Exposed to Off-Vertical Rotation According to Programmed Stress Indicated on Abscissa [141].

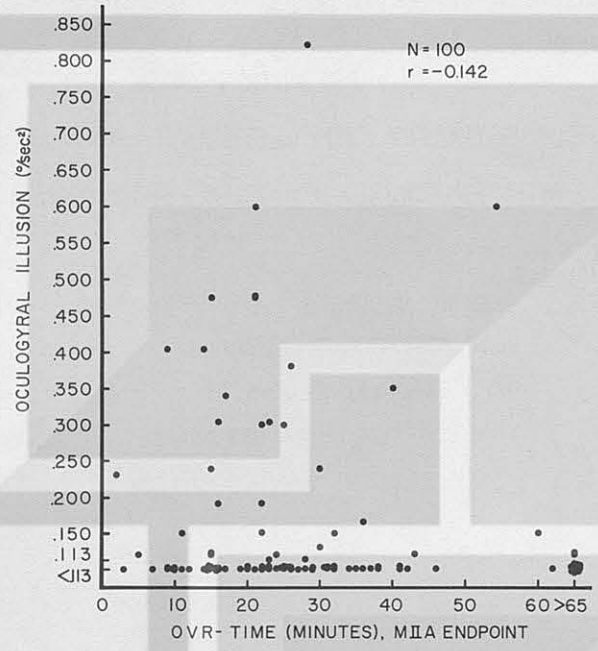


Figure 29. Comparison of Motion Sickness Susceptibility with Scores on Test of Semicircular Canal Function (the oculogyral illusion) [141].

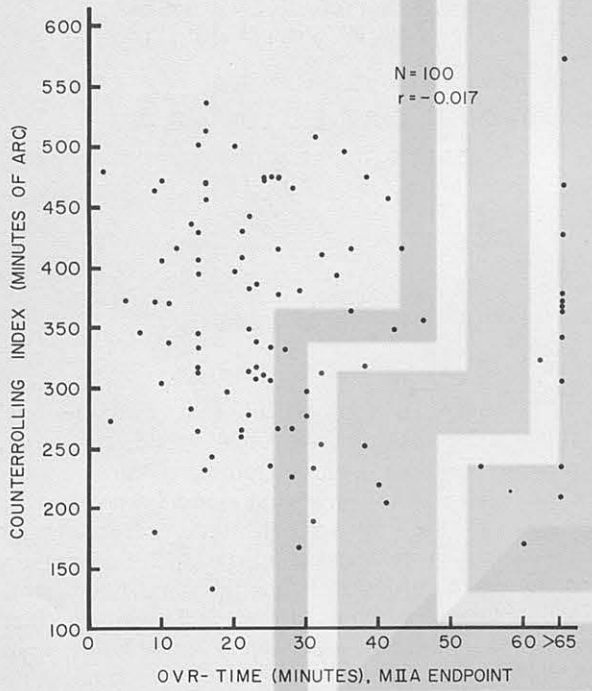


Figure 30. Comparison of Motion Sickness Susceptibility with Scores on Test of Otolith Function (counterrolling index) [141].

completely enclosed and provides for prolonged exposures and sudden transitions between rotating and nonrotating states. The SRR fails to simulate space-base conditions in notable aspects of weightlessness, subgravity levels, man's orientation when upright in regard to the axis of rotation, and the Coriolis forces while walking and handling objects. Stated another way, the SRR provides a very useful simulation device for the important study of effects of cross-coupled angular accelerations (except for fractional subgravity levels and man's orientation in regard to the axis of rotation).

The SRR is useful in demonstrating the qualitative aspects of the role of vestibular organs in postural equilibrium and in walking. However, nonvestibular factors play a greater role. The necessary use of small rotating devices poses limitations in terms of visual reference, length of exposure, and postural equilibrium. Parabolic flight offers the opportunity to study the effects of weightlessness and fractional subgravity levels for brief periods. Orbital flights, prior to the establishment of a space base, offer the opportunity to use small or even fairly large rotating devices for validating ground-based experimental findings, and prolonged exposure is advantageous for the study of adaptation effects.

It is convenient, although somewhat arbitrary, to distinguish between experiments designed to elicit responses whose geneses are mainly in the vestibular system, and those designed to prevent such responses by means of stepwise incremental increases in the stressful stimuli.

The following studies, selected for operational relevance, were conducted for the most part either in the SRR or in parabolic flight.

Slow rotation room (SRR). A series of experiments was carried out in the SRR to determine any differences in susceptibility to vestibular side effects, dependent upon man's orientation to the axis of rotation, and if adaptation effects acquired in one orientation mode transferred to the other. A unique feature of this experiment was that subjects could walk on the "wall" of the circular SRR, and carry out tasks while horizontal in relation to the Earth vertical [142]. This was made possible by using air-bearing supports and custom-fitted articulated fiber glass molds.

Four subjects participated in two different experiments involving adaptation to the stimulus conditions, with the room rotating at 4 rpm for either 4 or 5 days. One pair of subjects, initially in the horizontal mode, was changed to vertical near the middle of the perrotation period when symptoms of motion sickness had disappeared; in

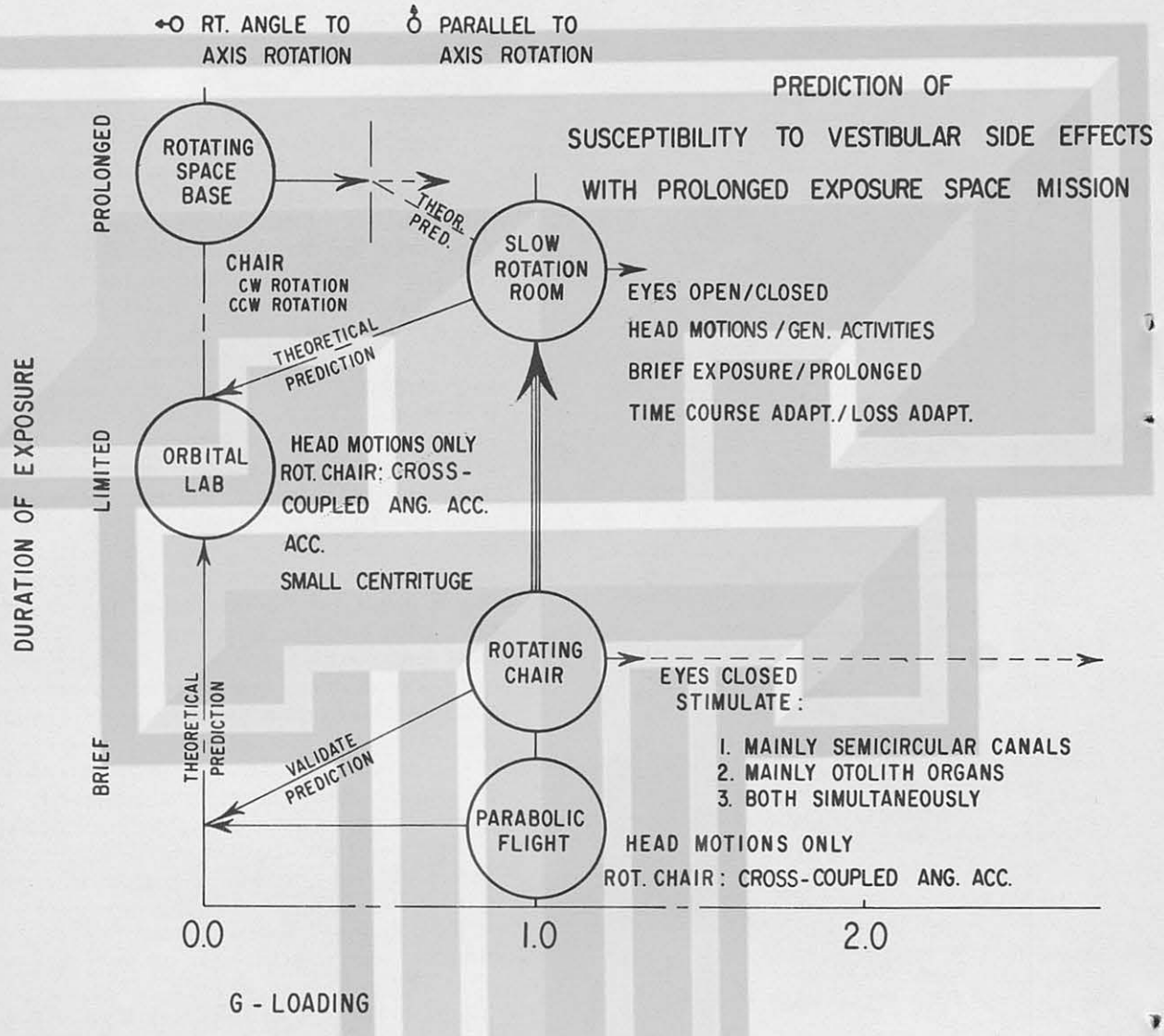


FIGURE 31. Problems in Predicting Vestibular Side Effects in Rotating Space Base.

the second experiment, they began in the vertical mode. The order was reversed for the second pair. When in the horizontal mode, subjects spent approximately 6 hours a day in the airbearing device, 6 to 10 minutes upright, and the remainder of the time recumbent on a bunk.

The findings, summarized in Figure 32, indicate no significant difference in susceptibility in the two modes, and that transfer of adaptation is excellent. On cessation of rotation only mild symptoms of motion sickness were manifested. A byproduct of the experiment was a demonstration of important differences between motion sickness and postural disequilibrium during adaptation to the rotating environment and subsequent return to the stationary. In the start-horizontal mode, adaptation ensuring freedom from symptoms of motion sickness on change to the vertical mode did not prevent ataxia. In the start-vertical mode, adaptation resulted in a great decrease in ataxia; this adaptation perseverated throughout the finish-horizontal mode and as long as 36 hours afterward. This implied that dynamic processes underlying postural homeostasis involved muscular activities largely rendered static when subjects were in the horizontal mode.

In the light of this experiment, earlier studies on prolonged exposures in the SRR were reviewed, particularly manifestations of motion sickness on

cessation of rotation. In this area, an experiment where four subjects were exposed at 10 rpm over a period of 12 days was notable [143]. Despite the severe symptoms experienced, especially in the first half of the perrotation period, manifestations of motion sickness on cessation of rotation were trivial or absent.

Adaptive capacity tests, used to measure individual differences in the rate of acquisition and decay of adaptation in a rotating environment, have recently been investigated. Qualifying as simulation tests, they measure at once susceptibility to reflex vestibular disturbances and motion sickness and ability to adapt and retain adaptation effects. Repeated exposures are required to measure retention of adaptation effects, and the best schedule is yet to be determined. These tests have various options [144-146], but all rely on exposure to stepwise increases in stressful accelerations.

The findings from one of these tests are summarized with the aid of Table 4 [145]. Ten young subjects executed controlled head (and body) motions at each of ten 1-rpm increases in velocity of the slow rotation room. Eight discrete head motions at 2-second intervals comprised a sequence, and 4 seconds elapsed between sequences. At the end of each head motion the subject responded with a yes or no; yes indicated that he experienced one or more reflex vestibular disturbances or symptoms of motion sickness. The adaptation criterion, a negative response during three sequences, determined the point at which the angular velocity of the SRR was increased by 1 rpm. The number of head movement sequences required by subjects at different step increases is shown in Table 4. There were great individual differences in performance: four of the 10 subjects experienced motion sickness and dropped out; one at 5 rpm, two at 6 rpm, and one at 10 rpm. One subject required only nine sequences (72 head motions) to reach 10 rpm, which were made at velocities below 3 rpm. At the other extreme, one subject required 390 sequences (3120 head motions) to achieve the adaptation criterion at 10 rpm.

This type of procedure stands at some point between brief susceptibility tests and incremental adaptation tests designed to prevent reflex vestibular disturbances and motion sickness. Tests of adaptive capacity are, however, the best available for re-

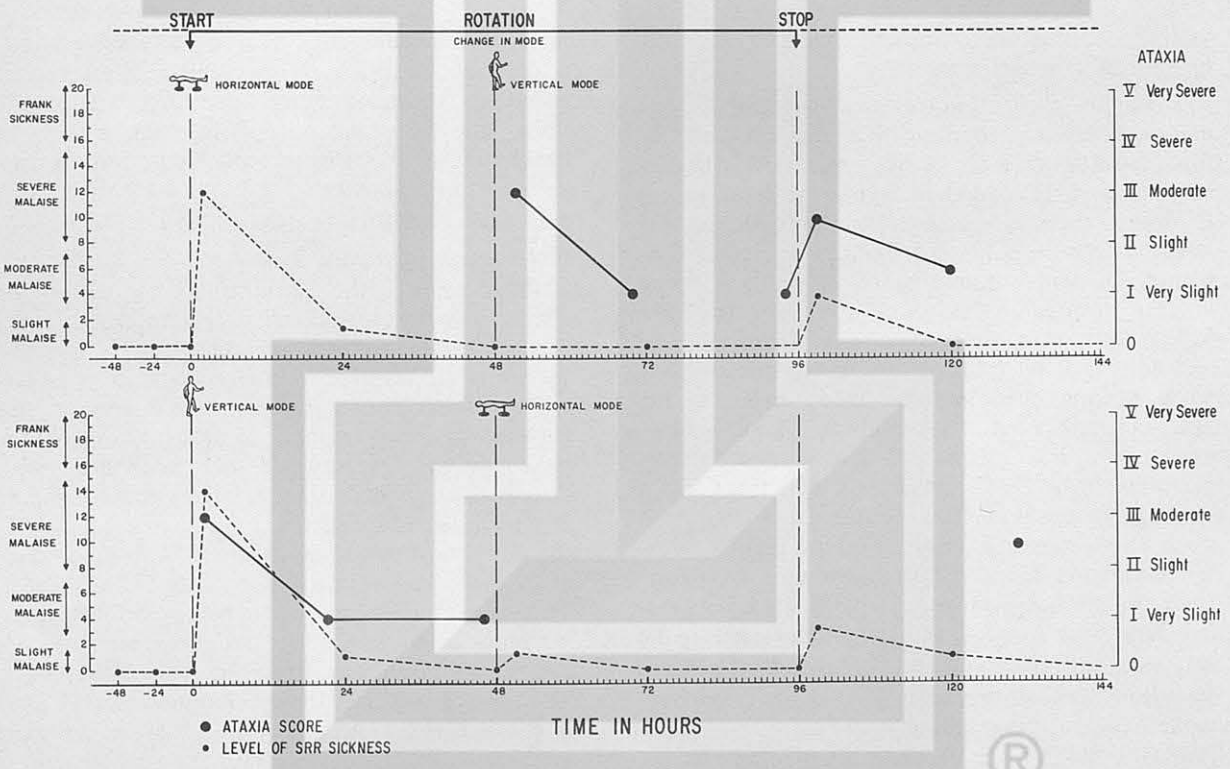


FIGURE 32. Approximate Mean Changes in Level of Symptoms of Motion Sickness and in Postural Disequilibrium in Four Young Healthy Subjects Exposed to Sudden Changes in Body Orientation during Continual Rotation at 4 rpm.

Table 4. Number of Movement Sequences Prior to Achieving Adaptation Criterion at Each rpm*[145]

Subject	1	2	3	4	5	6	7	8	9	10 rpm
RE	0	1	2	9	10	20	33	64	94	157
TA	0	2	3	2	3	9	10	5	8	8
HA	1	2	4	4	7	11	18	34	48	22
JE	5	4	0	0	0	0	0	0	0	0
HU	0	1	2	1	1	2	4	5	6	6
DI	0	0	0	2	2	2	2	3	3	4
HE	0	0	0	0	0	0	3	15	31	T(45)
JA	0	0	1	12	6	T(23)				
SY	8	7	1	1	1	T(10)				
WE	23	44	33	22	T(225)					

*This value represents the total number of movement sequences executed at each rpm less the three movement sequences, eliciting negative sensation, which constituted the adaptation criterion.

**T indicates that rotation was terminated without achieving the adaptation criterion. The figures in parentheses show the number of sequences completed prior to termination.

vealing individual differences in ability to cope with operational stimulus conditions.

Parabolic flight. Studies on susceptibility to motion sickness in the weightless phase of parabolic flight have been mainly of two types [147]. In one, subjects were restrained in their seats and required to make standardized head motions during the weightless phase only. The findings, summarized in Figure 33, demonstrate that of the subjects tested in this manner, six were asymptomatic, five experienced symptoms only when making head motions, and one showed increased susceptibility when making head motions as compared to the head restraint (control) condition. These findings agree with those of Soviet investigators utilizing parabolic flights [148, 149] and with the findings on astronauts [111] and cosmonauts [8] who experienced motion sickness in orbital flight.

The second kind of experiment used a rotating chair device. Subjects were required to make standardized head motions similar to those used in the dial test, but with eyes blindfolded. Each subject served as his own control, and comparisons were made between susceptibility under terrestrial conditions and that during parabolic flight, using similar periods of rotation and nonrotation. Findings summarized in Figure 34 [147] indicate a significant increase in susceptibility aloft in some subjects and a decrease in others. When subjects were ranked according to susceptibility under terrestrial conditions, the higher the susceptiblity, the greater the likelihood of an increase aloft (with some exceptions to this generality).

Prevention of Vestibular Side Effects

Incremental Adaptation Tests

Programming the acquisition of adaptation effects is to be recommended only in that it is the best means to an end. A number of factors and trade-offs are involved, although the basic operation is to establish new integrative patterns in the nervous system in response to changes in the stimulus conditions. One objective is to keep the nervous system busy coping with the largest possible change in stimuli, short of eliciting unwanted responses. In the absence of any response, there is no other guide as to the nervous system being fully tasked; that is, operating at high efficiency. In practice, however, responses are often delicate indicators, which, if not present spontaneously, may be evoked cautiously. The degree of provocation required serves as a monitor. It is important that only those experienced in these kinds of tests can task the nervous system to the limit without risk. The smaller the experience, the greater the margin of safety required.

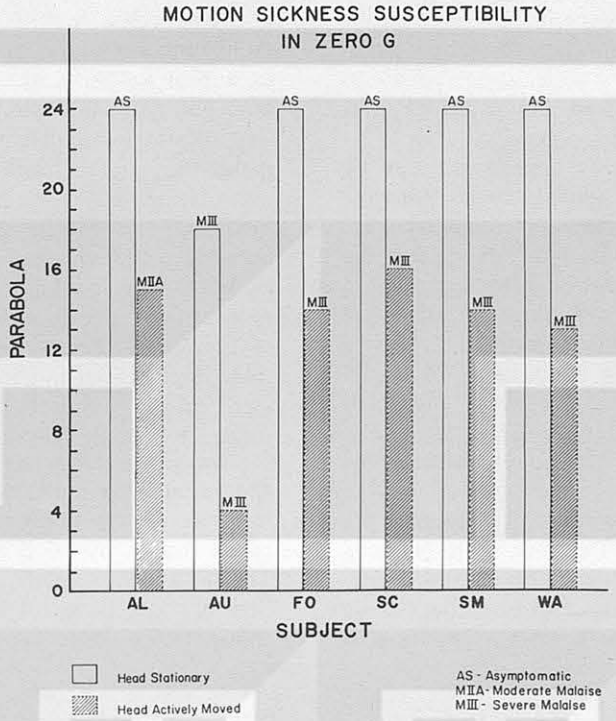


FIGURE 33. Effect of Active Head Movement Relative to the Restrained Condition upon Sickness Susceptibility among Six Susceptible Subjects, Measured in Terms of the Number of Parabolas Required to Provoke Severe Malaise [147].

O* = no symptoms, except in subject HA who experienced moderate malaise (M IIA) on his first test at O g.
M III = severe malaise

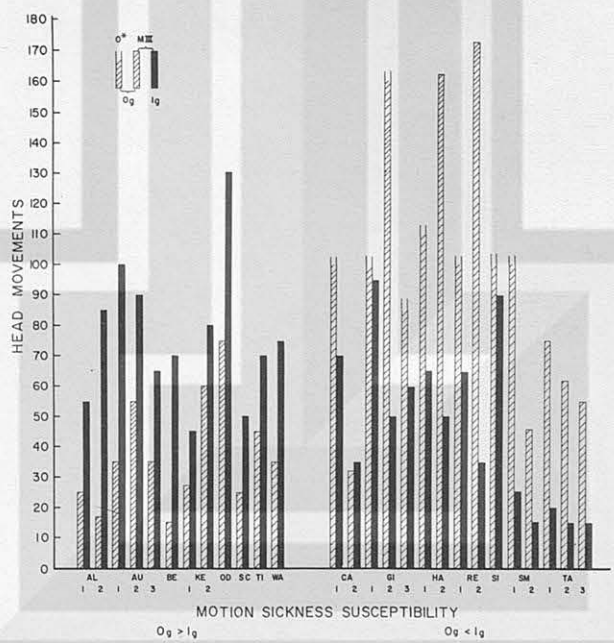


FIGURE 34. Comparison of Coriolis (motion) Sickness Susceptibility in 15 Subjects Measured in Weightlessness and under Terrestrial Conditions [147].

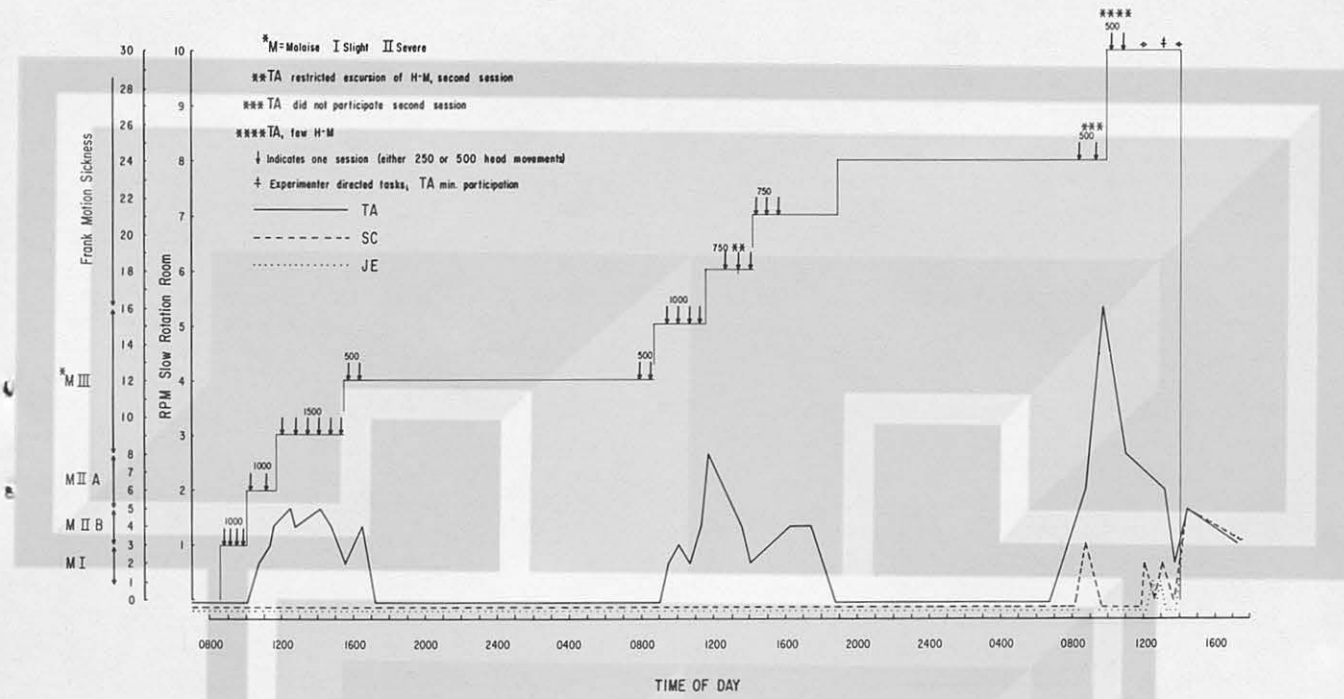


FIGURE 36. Stress Profile in the SRR and Manifestations of Motion Sickness in Three Healthy Subjects Exposed to Rotation for over 2 Days [151].

motions made at each step (each up-down counting as one motion), and the level of the subjects' symptoms. One subject, TA, who was quite susceptible, became very drowsy at 2 rpm, experienced epigastric discomfort at 5 rpm, and minimized or refrained from making head motions at the higher rpm. The two remaining subjects had mild symptoms at terminal velocity, which became more severe on cessation of rotation. TA resorted to the use of an antimotion sickness drug. Noteworthy features of the experiment were the inability of TA to keep up with the schedule; symptoms resulting from inadequate adaptation in the other two subjects; and increased symptoms in all subjects on cessation of rotation.

The findings in a similar test, (but with more head motions at the higher angular velocities) are shown in Figure 37 [151]. Symptoms of motion sickness were trivial, except those of subject RO, which were very mild at 8 rpm and 9 rpm and on cessation of rotation. Complaints were minimal on cessation of rotation except for ataxia, which was aggravated by head motions. These findings confirm inferences drawn from earlier studies, demonstrating that the time required to effect adaptation can be greatly shortened by controlling head motions and angular velocity, and with an adaptation schedule. The problems were greater at relatively high compared with relatively low velocities and except for one instance, there were no problems when the unit increase was 1 rpm.

The findings stimulated intensive studies on: (1) the best way to execute a discrete head-body motion; (2) spacing between the head motions; (3) size of unit increases in velocity; (4) number of head motions as a function of 1-rpm increases in angular velocity; and (5) individual differences in rate of acquisition and decay of adaptation effects (mentioned above).

The findings in another report [146] can be briefly summarized with the aid of Figure 38. The adaptation schedule was the same for all three subjects who participated and the procedure was essentially the same as that which has been described in connection with Table 4. On Day 1, while rotating counterclockwise, subjects made 40 head movement sequences at 2 rpm, 50 at 3 rpm, 70 at 4 rpm, 90 at 5 rpm, and 110 at 6 rpm. While rotating, the subjects were then transferred to carrying out highly stressful, generalized activities in an attempt to evoke motion sickness. Their performance indicated that the head motions had produced substantial protection against reflex vestibular disturbances and motion sickness. On Day 2, the head movement sequences executed by the subjects were 130 at 7 rpm, 150 at 8 rpm, 180 at 9 rpm, and 80 at 10 rpm. Again the subjects were transferred to generalized activities with performance similar to

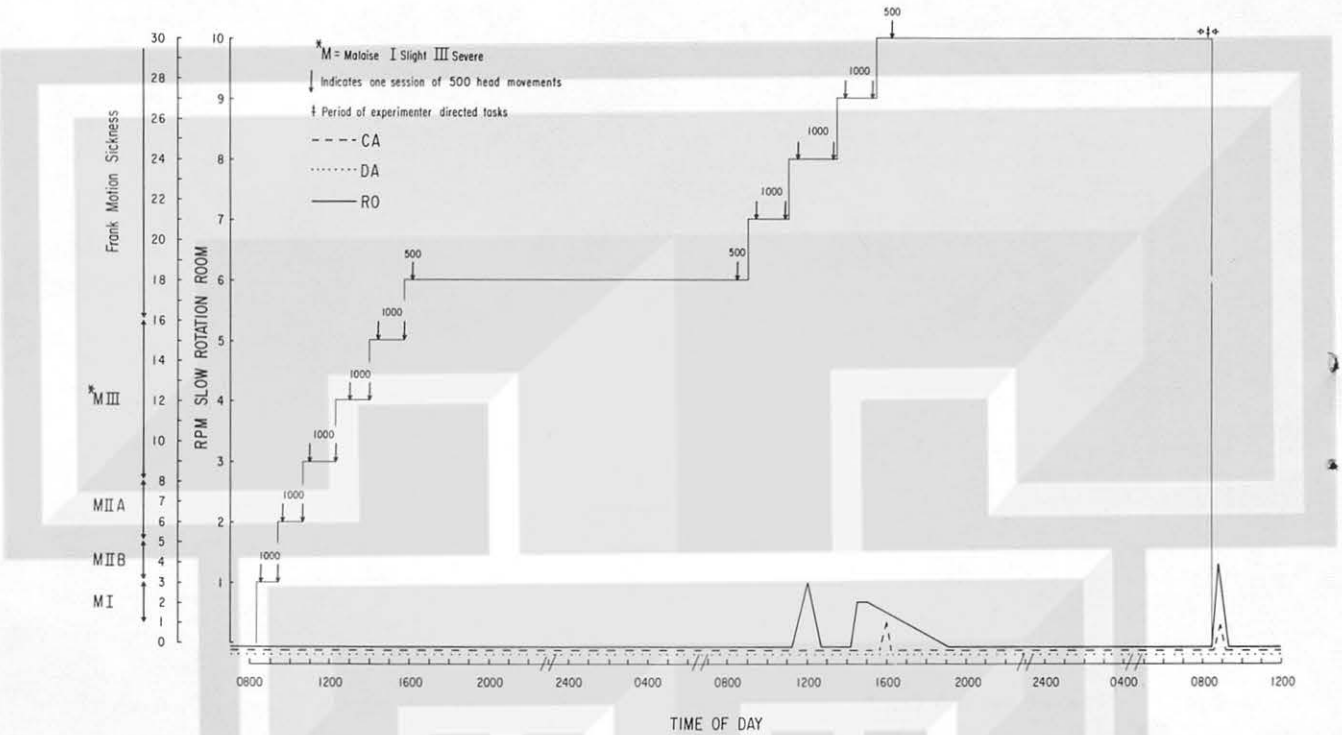


FIGURE 37. Stress Profile in the SRR and Manifestations of Motion Sickness in Three Healthy Subjects Exposed to Rotation for about 2 Days [151]. (The large number of head motions accounted for the rapid adaptation)

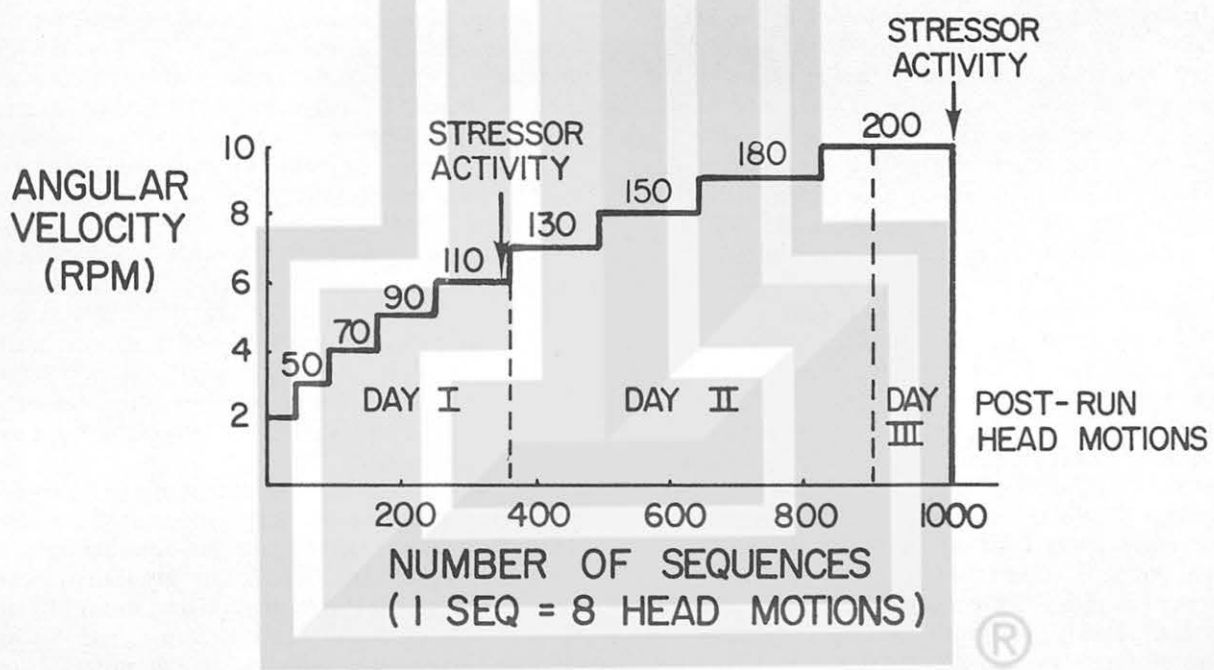


FIGURE 38. Stimulus Profile for a 3-Day Adaptation Schedule on the SRR [146].

that on Day 1. On the morning of Day 3, after 120 head movement sequences at 10 rpm, the room was brought to a stop, and the subjects executed the same head motions as during rotation. There were no symptoms of motion sickness, and all reflex effects quickly disappeared.

The three subjects in this 3-day experiment executed an incremental adaptation test before and after participation in the experiment. The findings are in Figure 39. This test is also identical to the incremental adaptation test described in connection with Table 4. Noteworthy are: (1) the small number of affirmative responses 6 hours after the 3-day experiment ended; (2) that weekly exposures led to increasingly better performance; and (3) that when subjects were rotated in the opposite direction (clockwise), performance was far better than on the first preexperimental test, indicating transfer of adaptation effects acquired during counterclockwise rotation. Again, findings support the conclusion that sudden transfers between the rotating and non-rotating environments are not only feasible in the SRR, but also that adaptation effects may not decay rapidly and, with weekly practice, be retained and improved.

Postural Equilibrium

Postural disequilibrium appears as an undesirable side effect in a rotating environment. However, the cross-over point is soon reached in a spacecraft when benefit is greater than handicap, since postural stability when lying, sitting, and even standing, requires only small levels of centripetal force. The difference between getting about in a weightless and rotating vehicle cannot be compared precisely, short of experience aloft, because of the shortcomings of simulation studies. This raises the extremely important question whether ataxia, used here in the broad sense of man's instability in carrying out tasks, might be the chief factor determining the level of artificial gravity to be generated. If comfort and efficiency are the guiding principles, ataxia may play a big role; if physical fitness is the goal, the

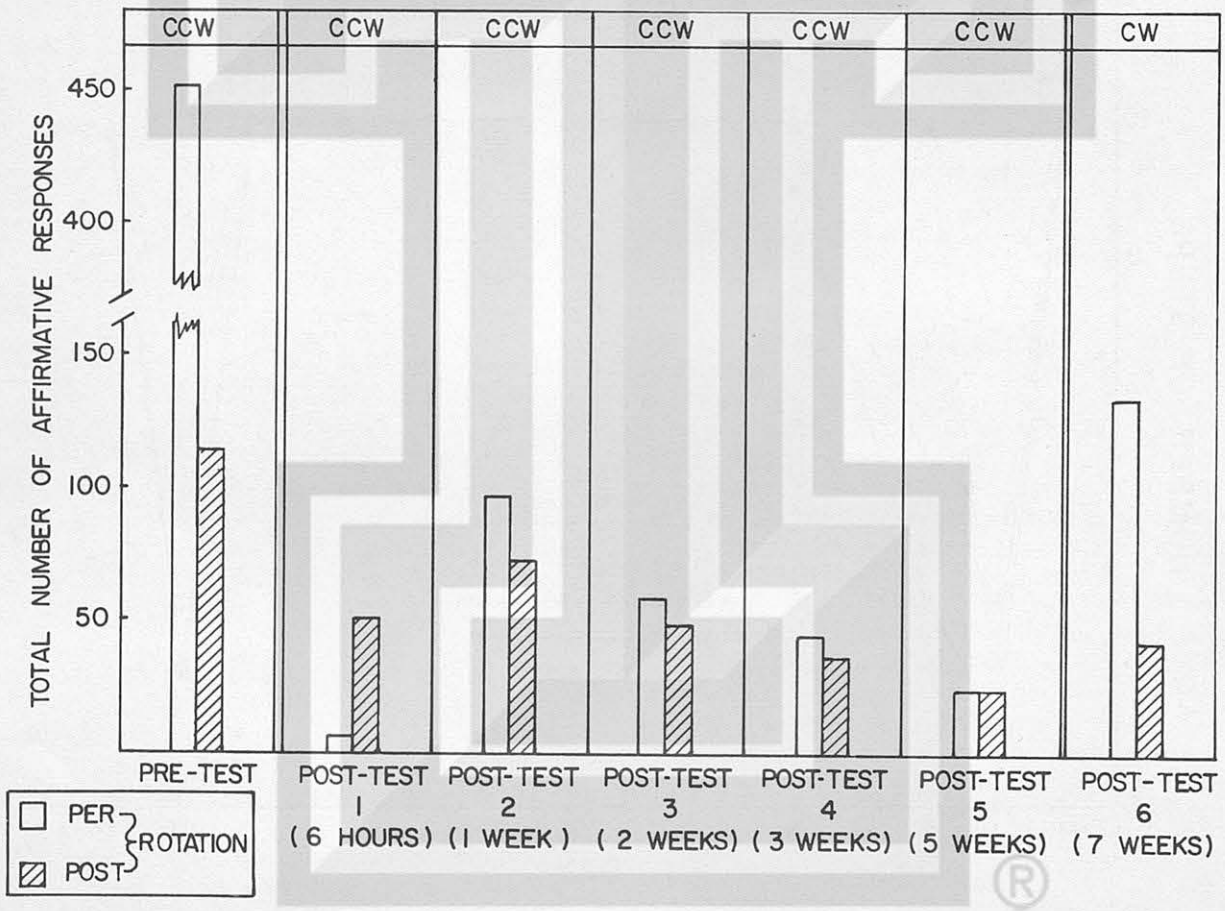


FIGURE 39. Pre- and Post-Tests Associated with a 3-Day Adaptation Schedule for Three Subjects on the SRR. (N=3)

level of artificial gravity required will, in all probability, more than suffice to ensure good postural stability. The qualifying word "probability" refers to the unlikely possibility that the radius of the spacecraft would be short and the angular velocity high.

Nonvestibular factors are of greater importance than vestibular factors in connection with postural stability while standing, walking, or handling equipment in a rotating environment. These problems are considered in great detail by Stone and coworkers [28] and summarized in nomograms along with other spacecraft design criteria.

The ataxia manifested in the rotating room resembles that experienced aboard ship, and it is possible to demonstrate the contributing role of the vestibular organs by comparing the responses of normal and of labyrinthine defective (L-D) subjects (Figs. 40 A, B [152]). With onset of rotation, both normal and L-D subjects experienced difficulty in walking, which is maximal initially, progressively decreasing over a period of days, followed by little further change. This may be shown by a test for postural disequilibrium designed to reveal small differences between normal and L-D subjects in a stationary environment. One significant difference is that the normal subject, on sudden movement of the head, is more disturbed in his postural equilibrium than the L-D subject. On cessation of rotation, both normal and L-D subjects manifest ataxia when walking. These sensations differ from those experienced upon disembarking after a sea voyage, in that the subjects report that they feel unstable on a stable platform, whereas after a voyage the platform seems to be unstable too. Again, the normal subject who quickly rotates his head experiences disequilibrium and perhaps dizziness but these are not experienced by the L-D subject.

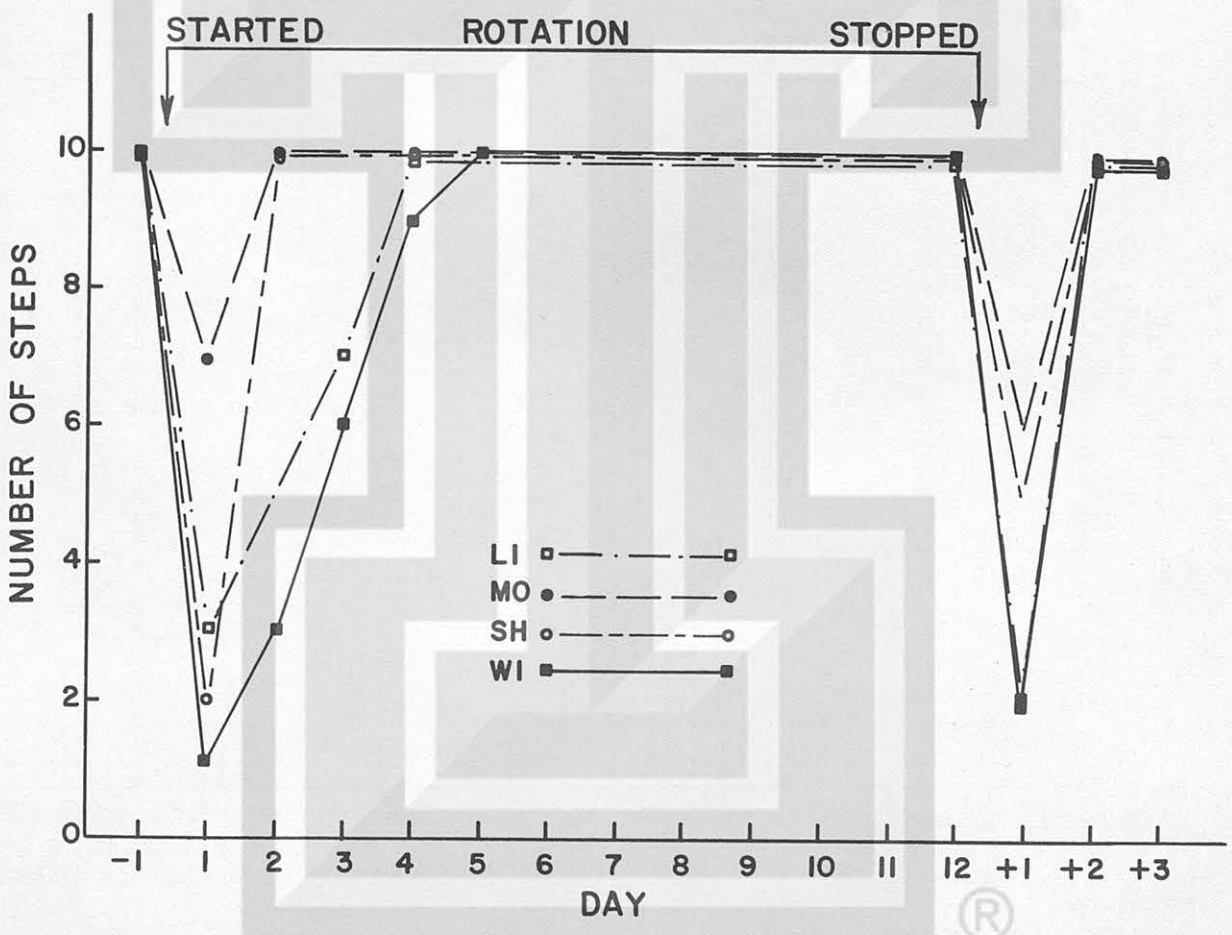


FIGURE 40-A. Heel-to-Toe Walking Scores for Four Normal Subjects.

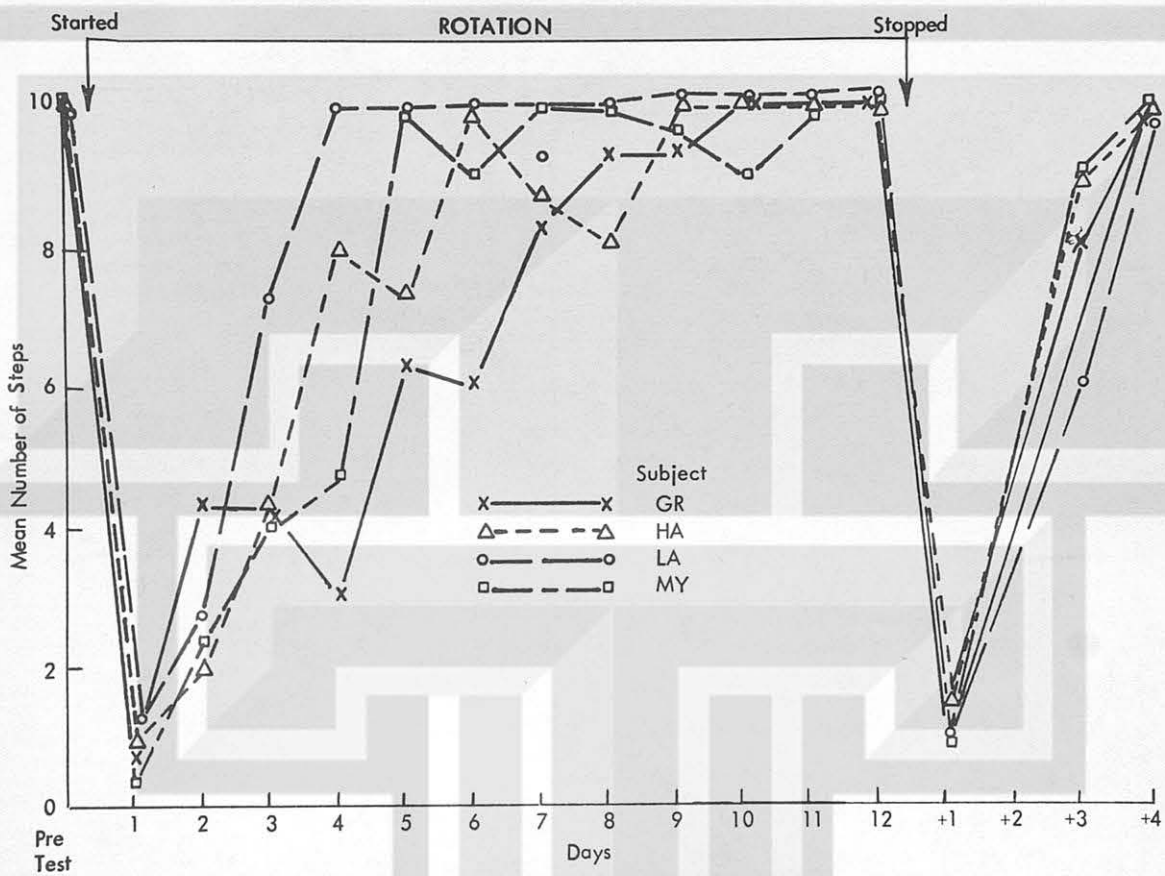


FIGURE 40-B. Individual Test Performance of Four L-D Subjects on a 3-Inch-Wide Rail Along the Time Axis of Rotation [152].

Drugs

The dial test has been used on the SRR also in the evaluation of antimotion sickness drugs (Fig. 41 [153]). Only those drugs with parasympatholytic or sympathomimetic action and certain antihistamines were notably effective under the stimulus conditions. Wood and Graybiel [154] demonstrated that a combination of promethazine 25 mg with d-amphetamine 10 mg had the same range of effectiveness as scopolamine 0.6 mg plus d-amphetamine 10 mg. The substitution of ephedrine 50 mg for the amphetamine, while slightly less effective, was the best combination for freedom from side effects. The drowsiness (sophite) syndrome, nausea, and vomiting require different therapy. Coffee or its alkaloids have long been used to increase alertness, and the amphetamines should be reserved for "contingencies." Once the nausea syndrome is well-established, which should be a rarity, drugs taken by mouth may either remain in the stomach or be regurgitated. The combination of preventing head motions and injection of an antimotion sickness remedy should suffice. The most effective measure would be the use of a soporific or antimotion sickness drug in an amount to ensure sleep.

PREVENTION OF VESTIBULAR SIDE EFFECTS AND GENERATION OF ARTIFICIAL GRAVITY

The rotating portion of the space base is assumed to have a radius of about 80 feet and maximal angular velocity to be 4 rpm. The problem posed by postural instability will not be discussed since nonvestibular factors are of chief importance here. Only worst-case situations will be considered: initial transition into weightlessness, subsequent (initial) transition to rotation at 4 rpm with one-third fractional g-loading, and sudden transitions between rotating and nonrotating portions of the space base.

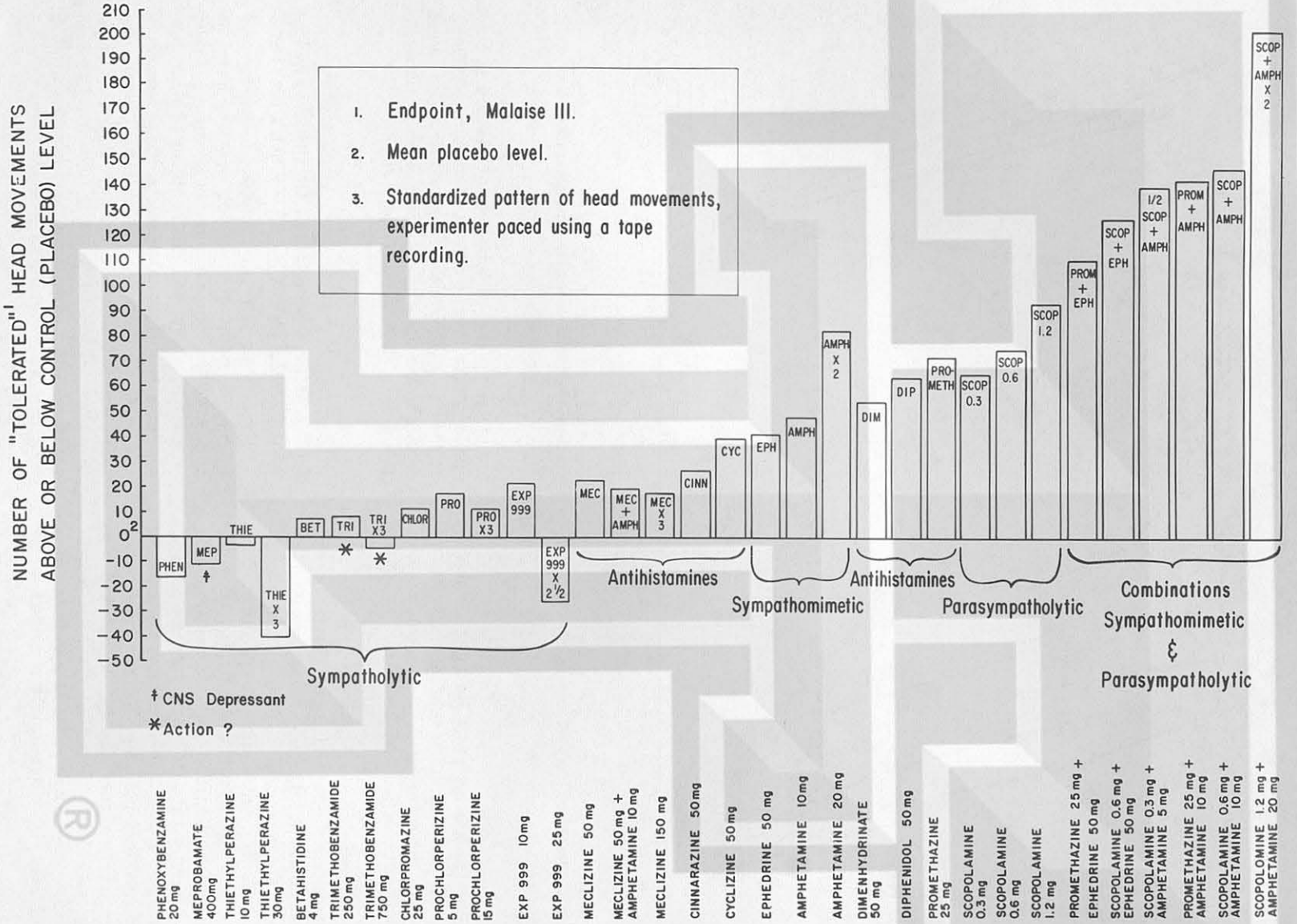


FIGURE 41. Effectiveness of Antimotion Sickness Drugs in Preventing SRR Sickness in 60 Subjects Exposed on 500 Occasions in a Rotating Environment, Using the Dial Test.[3] [153].

Transition into Weightlessness

Information presently available makes it possible, by means of selection procedures, to not only distinguish between astronauts and astroscientists who are or are not susceptible to vestibular side effects in weightlessness, but also to rank those who are according to degree of susceptibility. In other words, it should rarely (if ever) be a surprise that astronauts exhibit unexpected responses when making the initial transition into weightlessness, and seldom any surprise in the case of astroscientists.

Transition into the Rotating Environment

In the transition into the rotating environment, a novel experience, the principal unknown element is the effect of the fractional g-load. Until pertinent information is available (now under development), a conservative approach will help to avoid selecting those who are susceptible to motion sickness in weightlessness. With few exceptions (according to findings), persons relatively insusceptible to motion sickness in weightlessness are those relatively insusceptible in the SRR. Consequently, there should be no problem for persons with high adaptive capacity in the SRR and low susceptiblity to motion sickness in weightlessness in making a sudden transition to 4 rpm in a space base, if prelaunch adaptation has been carried out. This does not obviate the necessity for small rotating devices to permit incremental adaptation if needed.

Sudden Transitions between Rotation and Weightlessness

Novel stimulus conditions are again being dealt with in sudden transitions between rotation and weightlessness. And again, it would be helpful to know the shape of the curves depicting susceptibility to vestibular side effects as a function of subgravity levels. It is possible, according to evidence, to rank persons by their acquisition and retention of adaptation to 4 rpm in the SRR. It is further indicated that persons fully adapted can make the transition between stationary and rotating environments without motion sickness or reflex vestibular effects, except as they contribute to ataxia. It is not known to what extent adaptation effects acquired in the SRR would transfer to the space base condition. This again points to the necessity for providing incremental adaptation in case of need. Incremental adaptation is more difficult to program in weightlessness than in a rotating environment, unless there are means for substituting passive for active motions. Frequent transitions (measured in days) are necessary to preserve adaptation to both rotating and nonrotating environments under terrestrial conditions, which is a reasonable expectation under space base conditions.

Susceptibility to vestibular side effects can be decreased considerably by the use of drugs, often with little impairment of proficiency. Individual assessment is a prerequisite to best accomplish this end.

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Value of Exercise at One-Half Earth Gravity in Preventing the Deconditioning Effects of Simulated Weightlessness

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HOCHE, J., and A. GRAYBIEL. *The value of exercise at one-half Earth gravity in preventing the deconditioning effects of simulated weightlessness.* Aerospace Med. 45(4):386-392, 1974.

Twelve male subjects participated in two identical experimental series to determine the value of exercising 4 hr daily at one-half Earth gravity (simulated) to prevent loss of exercise capacity and orthostatic tolerance when exposed to 14 days of simulated weightlessness. In one series, four subjects exercised at half-gravity (HGE subjects) on treadmills mounted in a human centrifuge and four exercised on treadmills mounted on inclined planes; in the other series the subjects switched exercise devices. Four subjects served as no-exercise controls throughout both series. Orthostatic tolerance was measured in a lower body negative pressure device and exercise capacity was measured with the aid of a treadmill. Additional measurements included: plasma volume and red cell mass, urinary sodium and potassium, and peripheral renin activity. The findings revealed no significant differences between the responses elicited during exercise in the centrifuge or on the inclined plane, hence, use of the latter device will greatly increase cost effectiveness in any future experiments. A difference in LBNP tolerance between the two groups was not demonstrated when measurements were made before and at the end of the deconditioning period and after recovery. There was evidence, however, that the time course of 6:00 a.m. peripheral renin activity differed in the two groups. Exercise capacity diminished in both groups, but there was a twofold greater loss in the control compared with the HGE group. Control subjects manifested greater losses of plasma volume but smaller losses of weight than HGE subjects. No significant differences between the two groups were found in the patterns of urinary electrolytes or the loss in red cell mass. The results are discussed not only in terms of the present experiment but also in terms of their significance for long-range plans involving the use of artificial gravity as a countermeasure on space missions.

MANNED SPACE Exploration, in centering attention on adjusting to life in a weightless spacecraft, has inevitably called attention to the environment from which man came and must return. Man's adaptation on Earth is not a one-time transaction but a continual interaction with the gravitoinertial force environment. The difference between spacecraft and Earth is not merely 1.0 G but the G loads engendered by the acceleration of gravity and referred to as body weight when man is passive, or gravitoinertial force when active. There is general agreement that passive exposure to weightlessness (2,3,6,8,13) or simulated weightlessness (5,6,9,10, 11) quickly leads to deterioration at organizational levels, such as muscle and bone, and that eventually the noxious effects will reach cellular and subcellular levels. In order to maintain fitness in a weightless spacecraft, some of the means required to maintain fitness on Earth must be introduced and will be referred to as countermeasures. The real purpose of all countermeasures is not adaptation to weightlessness but *prevention* of adaptation; the object is preservation of adaptation to the Earth's environment.

At this time, the only countermeasure ensuring safety in prolonged space missions (and return to Earth) is artificial gravity (9,12,14). Two methods have been proposed, namely, exposure to high G loads for short periods in an on-board centrifuge or continual rotation of part of a space station, presumably at fractional G loads (2,14). However fractional-gravity is generated, its beneficial effects are specific and permanent, i.e., not subject to decay. The goal is to find out how much less than 1.0 G will suffice. The present experiment represented an initial step toward this long-range goal and had two immediate objectives. One was to determine the effectiveness of exercise at one-half Earth gravity in preventing adaptation to simulated weightlessness. The second object was to compare the effectiveness of a human centrifuge and a sloped wall in simulating this G load.

MATERIALS AND METHODS

Subjects: Twelve male subjects, 20 to 22 years of age, were selected from a group of volunteer college students based on the findings revealed in a comprehensive medical and psychological evaluation and personal interview.

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This study was supported by Contract T-5904B, Biomedical Research Division, National Aeronautics and Space Administration, Lyndon B. Johnson Space Center, Houston, Tx. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

Method: Exercise at 0.5 G_z was accomplished using specially designed treadmills mounted in a slow rotation room (SRR) or on an inclined plane. The apparatus in the SRR is shown in Fig. 1. Subjects were comfortably supported in the Earth-horizontal plane by a helmet, 22.5-cm (9-in) chest sling, a 27.5-cm (11-in) hip sling, and upper and lower leg supports, each on an adjustable vertical cable attached to the 3.6-m (12-ft) overhead. Each lay on his right side, along a radius, head inward, facing away from the direction of rotation. With the man's center of mass at a radius 5.9 m (19.5 ft), rotation at 8.7 ± 0.1 rpm generated a force approximately 15% less than 0.5 G_z at head level and 15% more at the feet.

The apparatus using an inclined plane is diagrammed in Fig. 2. Subjects were supported by fitted slings on a stationary rack tilted 30° with feet lower than head. The resultant component of the Earth's gravitational vector produced ± 0.5 G_z force (sin 30° = 0.5) down the long axis of their body (with no head-to-toe gradient) against which they exercised. Each 2 hr of exercise consisted of three 40-min periods of walking at 3.2, 4.8, and 6.4 km/hr (2, 3, and 4 mph), respectively, for 20, 10, and 5 min with a 5-min rest between each period. These were intended to be submaximal exercise periods and were performed twice daily. Oxygen consumption ranged from 15-20% of maximum at 3.2 km/hr (2 mph) to 25-30% of maximum at 6.4 km/hr (4 mph).

The procedure for measuring orthostatic tolerance using a lower body negative pressure (LBNP) device has been described elsewhere in detail (4). The lower half of the subject's body was placed supine in the LBNP chamber and the airtight seal completed by stretching a latex lower-abdominal-sleeve about the lips of the mold. After baseline data were recorded for 5 min, the pressure inside the chamber was lowered 70 mm Hg below atmospheric pressure over a period of 30 s. Blood pressure at 1-min intervals, electrocardiogram, and instantaneous heart rate were monitored by a physician at the subject's side and recorded on a UV oscillograph along with respiration and vectorcardiogram. The duration of exposure to the point of "presyncopal grayout" was used as the measure of orthostatic tolerance. At endpoint, the pressure in the chamber was returned to atmospheric level within 2 s and the recording continued for 5 min during recovery.

Exercise capacity was measured using a modification of the method of Balke (1) and a precordial electrocardiogram was recorded continuously, beginning 2 min before the run while the subject was seated. The subject began running at the constant speed of 9.14 km/hr (500 ft/min) with the treadmill level, a submaximal warmup workload. After 1 min the slope of the treadmill was increased to 4%, and each minute thereafter the slope was increased another 2% while the speed remained constant. After n minutes of running, a subject had completed a 2 n% grade and in that nth minute his work expenditure in vertical ascent was 10 nW ft-lb (13.56 nY joules) where W is his weight in pounds. An "exhaustion" endpoint was used with the subject signaling when he felt he could not possibly complete another minute at a 2% higher incline. For 5 min during recovery heart rate was measured (half-minute intervals) with the subject sitting. The number of minutes a subject was able to run was used as the measure of his exercise capacity.

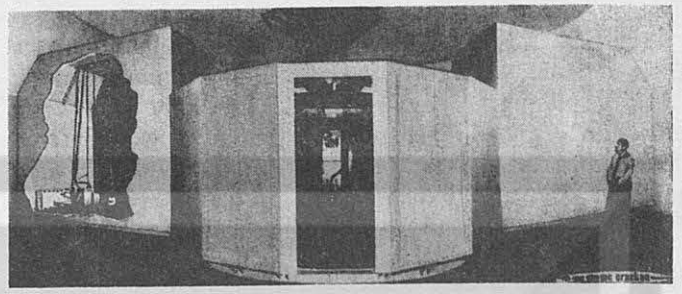

Fig. 1. Human centrifuge modified at extremities to permit two subjects (one shown) to exercise simultaneously on treadmills when exposed to fractional G levels.

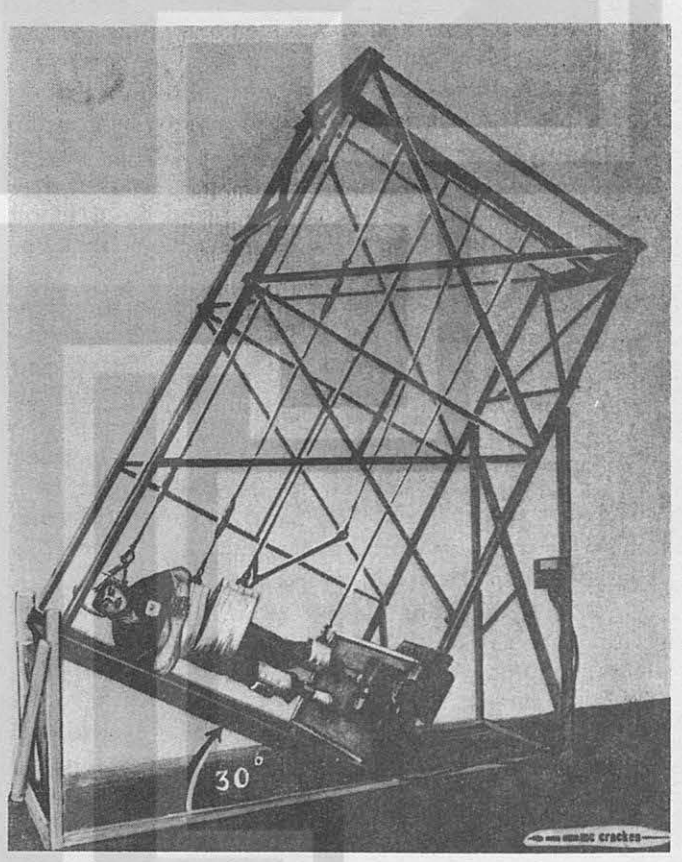

Fig. 2. Subject exercising on inclined plane simulating +0.5 G_z.

Weightlessness was simulated for periods of 2 weeks using head-out supine water immersion (8 hrs) and bedrest for the remainder of the day. Each subject had his own 3,409 l (750-gal) Fiberglas-lined water immersion tank which was filled daily with isotonic saline and maintained at 35 ± 0.5°C (95 ± 0.5°F) by thermoregulator. During the 14-day periods, all subjects were continually supine; they were transferred on stretchers and were required to use bedpans. Though allowed up on

one elbow to eat, they were never allowed to sit up or experience full Earth gravity along their longitudinal axis. The subjects were provided a regular hospital-selection diet containing at least 5 g of NaCl with no caloric restriction. Canned juices, water, and milk were offered frequently throughout the day. Although tobacco and alcohol were prohibited, snacks brought during visiting hours were not restricted. This was intended to benefit morale as well as to satisfy any craving for salt, water, or food. Daily body weight (a.m.), intake and output, vital signs and nursing notes were recorded by hospital corpsmen.

Daily 24-hr urine collections extended through the first 48 hr of recovery. In addition to routine urinalysis, the urine was examined for total volume, osmolality, sodium, potassium, and creatinine. In addition to routine CBC with differential count and sedimentation rate, serum sodium, potassium, chloride, creatinine, urea, total protein, albumin, and osmolality were measured before bedrest, bi-weekly during the deconditioning, and on the third day of recovery. At 6:00 a.m. on the first day of immersion and on the first day of recovery, plasma volume and red cell mass were determined from blood drawn before and 15 min after intravenous radioimmunoassay (RISA) injection.

Peripheral renin activity (PRA) response to orthostatic challenge was determined by RISA of 3-hr angiotensin 1 activity by the method of Haber (7) before and within 1 min of LBNP during baseline testing and on Days +1 and +3 after deconditioning. PRA was also determined before and immediately after the morning 2 hr of half-gravity exercise on the eighth and 14th day of the 2-week immersion periods. Peripheral renin activity was also measured at the same time in controls undergoing immersion for comparison.

General Plan: The subjects were arbitrarily divided into two sets, and tests were conducted on each set during alternate months of a 4-month period. Each set comprised two subjects who served as controls, two who exercised on the inclined plane, and two who exercised in the SRR. During the 2-week deconditioning period, all subjects spent 4 hr twice a day in the water. The control subjects spent the remainder of the day at strict bedrest. The other four subjects exercised for 2 hr twice daily (against +0.5 G_z) for a total of 2 G_z hours/day and spent the remainder of the time at bedrest. In the week before each deconditioning period, the subjects (who had become familiar with all procedures and devices) were tested on three separate days to determine their baseline orthostatic tolerance and exercise capacity. At least 4 hr intervened between LBNP and exercise tests.

After each of the 2 week deconditioning periods, the subjects were retested for orthostatic tolerance and exercise capacity on days 1, 3, 7, and 10. On the first day after deconditioning, each subject was returned to bedrest immediately following his LBNP testing and ate lunch at least 2 hr before his treadmill run in the afternoon. In an attempt to prevent acute orthostatic hypotension from interfering with treadmill performance, each subject arose from bed 1 hr before his exercise test and was allowed to walk (escorted) about the building and outside. For baseline tests and tests on all other recovery days, the subjects were not required to return to bed after the morning LBNP runs.

In order to compare the fractional gravity simulational capability of these two methods—the rotating room and inclined plane—each group of six subjects returned to repeat the entire sequence 5 weeks after the end of their first deconditioning period. During this second exposure the HGE pairs switched fractional gravity devices while the controls remained the same. This yielded data for eight controls and 16 HGE subjects.

RESULTS

Findings were analyzed by a split-plot factorial analysis of variance having one between-subjects' measure (control, centrifuge, inclined plane) and one within-subjects' measure (time). One HGE subject, during his second 2-week deconditioning period, withdrew from the program after 10 days and, therefore, a least-squares solution was computed. The subjects' second deconditioning period did not produce any results significantly different from the first, therefore, the data presented here combine both exposures. No significant differences were found between the effects of exercise in the centrifuge and on the inclined plane so these findings are combined into one exercise group ($n = 15$) for comparison with the control group ($n = 8$). When differences across time were found, a Tukey's HSD test for pairwise comparisons was used to identify which days varied significantly. The key parameters which showed significant changes across time are presented in Fig. 3 for comparison.

Orthostatic tolerance was markedly reduced in all subjects (Fig. 3) after 2 weeks of simulated weightlessness $F(4, 84) = 27.2761$ ($p<.01$). When measured on abandoning bed rest the morning of Day +1, LBNP tolerance had fallen in control and HGE groups, respectively, to 40 and 46% of baseline values. By Day +3, however, within 48 hours of returning to normal ambulatory activity, LBNP tolerance had returned to control values. HGE subjects were indistinguishable from controls in the loss and recovery of LBNP tolerance throughout the entire experiment.

Exercise capacity, on the other hand, remained higher in HGE than in control subjects (Fig. 3), but all subjects showed a statistically significant loss, $F(4, 80) = 12.730$ ($p<0.01$). The reduction was, on Day +1, 1.3 min in control subjects (baseline 7.4 min) and 0.6 min in HGE subjects (baseline 7.2 min). On Day +3, the loss of exercise capacity still persisted in the controls who remained 0.9 min below baseline value ($p<0.01$). HGE subjects, on the other hand, were back to within 0.3 min of their baseline performance by Day +3, which is not a statistically significant difference. On Days +7 and +10, exercise capacity had returned to baseline levels in control subjects and did not differ significantly from values in the HGE group.

Both HGE and control subjects (Fig. 3) manifested a significant loss of plasma volume over the 2-week deconditioning period, $F(1, 21) = 45.235$ ($p<0.01$). This loss was significantly greater ($p<0.01$) in control subjects, 710 cc or 17.0% of their plasma volume, as

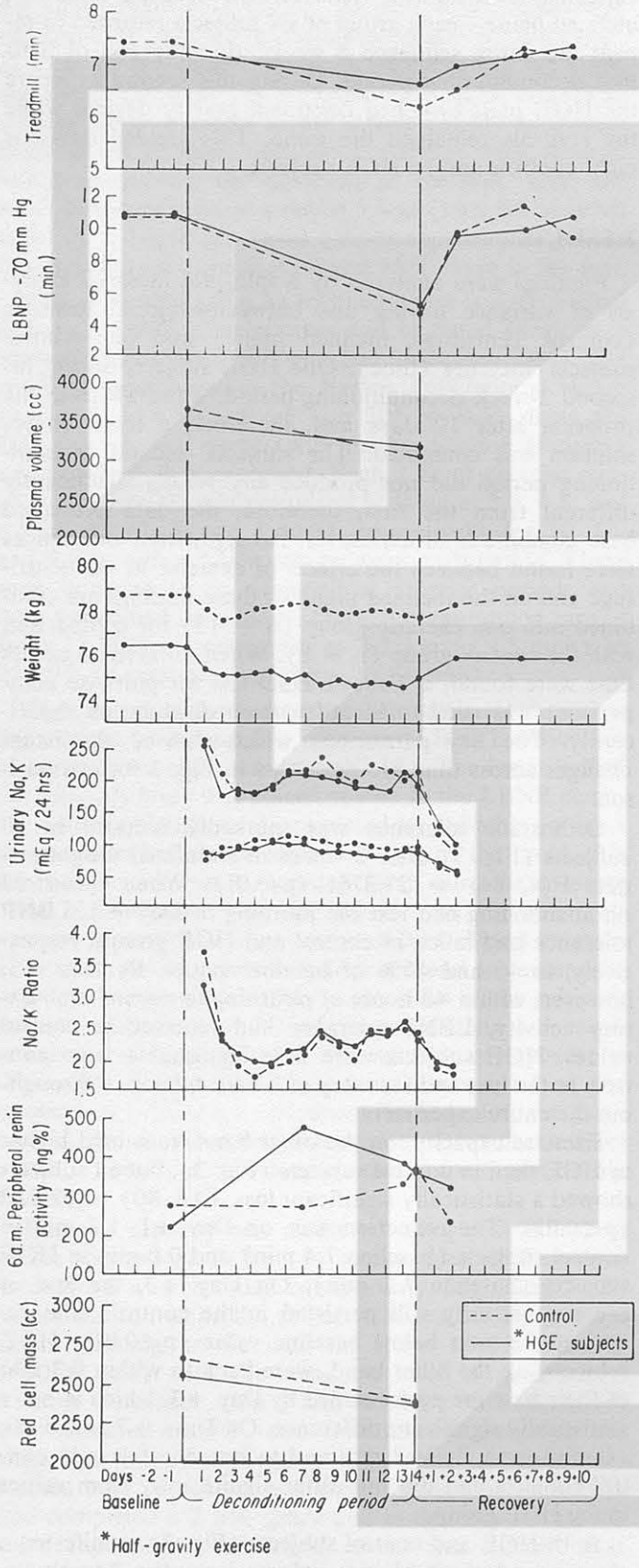

Fig. 3. A comparison of findings obtained in half-gravity exercise group (n = 15) and control group (n = 8). Measurements of key parameters are shown for periods before, during, and after deconditioning (head-out water immersion and bed rest).

compared with 287 cc or 8.4% in HGE subjects.

Both groups (Fig. 3) showed a significant, though smaller, loss of red cell mass than plasma volume, $F(1, 21) = 49.9676$ ($p<0.01$). Control subjects lost an average of 275 cc (10.4%) while HGE subjects lost 190 cc (7.4%).

Both groups (Fig. 3) lost a significant amount of body weight during the 2-weeks deconditioning, $F(4, 84) = 13.5163$ ($p<0.01$). The average weight loss was 1.05 kg (2.3 lbs) for control subjects and 1.41 kg (3.1 lbs) for HGE subjects. After returning to normal activity for 48 hrs, the control subjects were 0.45 kg (1.0 lbs) below baseline weight, and HGE subjects were 0.54 kg (1.2 lbs) below baseline ($p<0.05$). Both groups remained 0.45 kg (1.0 lb) below baseline weights on Days 7 and 10 of recovery.

The pattern of daily weight change during the 14 days of deconditioning differed between control and HGE subjects, $F(13,273) = 1.9818$ ($p<0.05$). Control subjects lost 1.08 kg (2.4 lbs) in the first 2 days of deconditioning after which they stabilized at approximately 1 kg below baseline. HGE subjects lost 1.18 kg (2.6 lbs) in the first 2 days but continued to show a weight decrease throughout deconditioning. From the sixth to the 14th day an additional 0.73 kg (1.6 lbs) were lost ($p<0.05$).

There were no significant differences in urinary sodium and potassium between control and HGE subjects (Fig. 3). During the 14 days of bedrest and water immersion, urinary sodium output was the greatest in the first 24 hrs, averaging 256 meq/24 hr; during the next 4 days, the urinary sodium output was significantly lower ($p < 0.01$), totaling, respectively, 188, 182, 177 and 190 meq/24 hr. Then, during the sixth, seventh and eighth day, the urinary sodium rose, respectively, to 211, 210 and 216 meq/24 hrs. Urinary sodium values then settled to the lower levels of 204, 191, 202, 195, 210 and 195 meq/24 hr during the last 6 days of deconditioning. When the subjects resumed activity, urinary sodium fell to the lowest levels of all ($p<0.01$), namely, 122 and 94 meq/24 hr, respectively, in the first 2 days.

During the first 2 days of deconditioning, urinary potassium was, respectively, 81.8 and 85.2 meq/24 hr. It rose the next 5 days, respectively, to 92.2, 96.7, 100.9, 101.9 and 101.4 meq/24 hr and then settled back towards the initial levels at 92.1, 91.3, 91.4, 85.2, 83.2, 88.8 and 87.4 meq/24 hr respectively, for the last 7 days of deconditioning. On return to normal activity, urinary potassium fell ($p<0.01$) to 65.5 and 51.9 meq/24 hr, respectively, for the first 2 days.

The ratio of urinary sodium to potassium was highest during the first 24 hrs of bedrest and water immersion (Fig. 3) for both groups, $F(15, 315) = 10.031$ ($p<0.01$). This ratio of 3.33 contrasts with the two periods when the ratios were lowest, namely, Days 4 and 5 of deconditioning (1.85 and 1.90) and the first 2 days of recovery (1.88 and 1.82). The urinary sodium to potassium ratio was lower on these 4 days than on Day 13 of deconditioning when this ratio reached 2.54 ($p< 0.05$).

Peripheral renin activity (6:00 a.m.) increased from a

baseline of 237 ng% to 366 ng% by the 14th day of deconditioning, and the next morning, before other testing, PRA was 361 ng%. After 2 days of normal activities, the 6:00 a.m. PRA (Fig. 3) had fallen back, respectively, to 287 ng%, $F(4, 84) = 6.035$, ($p<0.01$). Control and HGE subjects showed a significant difference in their 6:00 a.m. PRA only once, namely, at the beginning of the second week of deconditioning with values of 269 ng% (control subjects) and 473 ng% (HGE subjects), $F(4, 84) = 3.053$ ($p<0.05$).

Peripheral renin activity measured immediately after HGE subjects exercised 2 hr in the morning showed no statistically significant change from 6:00 a.m. values measuring 410 ng% and 458 ng%, respectively, after deconditioning periods of 1 and 2 weeks (Fig. 4). On the same occasion, PRA measured in control subjects (after 2 hr supine water immersion) were 224 ng% and 290 ng%; these values were not significantly different from 6:00 a.m. levels. Peripheral renin activity increased after exposure to LBNP, averaging 295 ng% before and 541 ng% after, $F(1, 20) = 55.80$, ($p<0.01$). In contrast, there was no significant difference in the magnitude of the renin response to LBNP (Fig. 5) either between groups of subjects or between the conditioned and deconditioned state $F(2, 40) = 2.7639$ (n. s.).

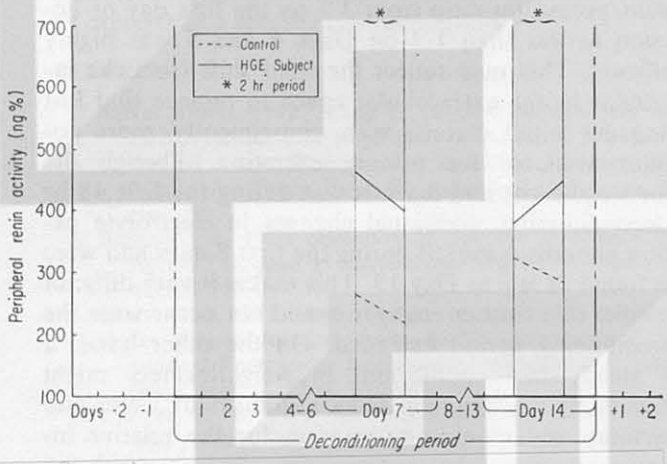

Fig. 4. PRA levels before and after a 2-hr half-gravity exercise and a 2-hr head-out water immersion (controls) on the 7th and 14th days of deconditioning.

DISCUSSION

All of the relevant experimental data support the conclusion that the effects of exercising at 0.5 G_z in a rotating room and on an inclined plane are indistinguishable. The greater cost-effectiveness of the inclined plane device compared with a rotating room is an important consideration in planning a program dealing with the effects of exposure to fractional gravity for whatever purpose.

At the end of the deconditioning period the decline in exercise capacity was greater in the control than in the HGE group, which was expected; what was not expected, however, were the identical declines in LBNP tolerance in the two groups. If LBNP tolerance had been measured at frequent intervals throughout the deconditioning period, curves depicting the time course of changes in LBNP tolerance in the two groups might have revealed differences.

At the beginning of the second week of deconditioning, 6:00 a.m. PRA was elevated only in the HGE group. Although 2 hr of half-gravity exercise were not immediately associated with a rise in PRA (an unexpected finding), the cumulative effect of such exercise twice daily, along with diuresis, fluid shifts, and blood pressure changes was, apparently, sufficient to elevate PRA, which was still at baseline levels in the control group. This elevation may have accounted for HGE subjects having a smaller loss of plasma volume than

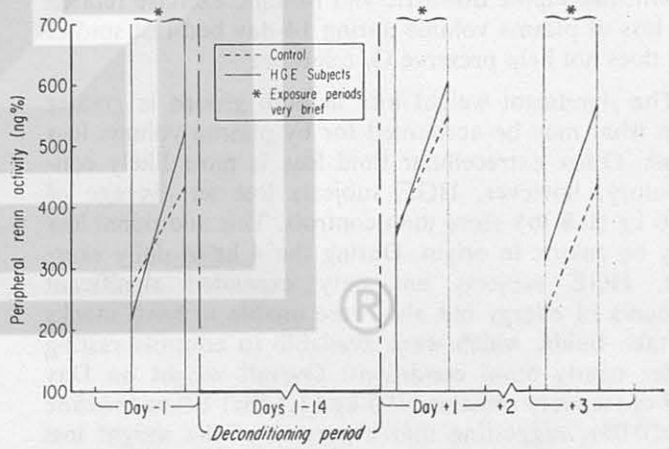

Fig. 5. PRA levels before and after exposure to −70 mm Hg LBNP prior to deconditioning and during recovery.

control subjects. Whereas diurnal variation would be expected to cause a decrease in PRA during the morning half-gravity exercise, a small increase in PRA (n. s.) was seen at this time after 2 weeks of deconditioning in the HGE subjects. One may speculate that this small increase in PRA signifies a lowered threshold sensitivity to orthostatic stress, perhaps as a result of diminished vascular tone.

It is worth noting that, although control subjects lacked the postural stimulus to increase PRA, perfusion at the juxtaglomerular level was ultimately affected by adaptation to simulated weightlessness. This is contrary to the notion that bedrest diuresis is no more than compensation for the increased circulating blood volume caused by the supine position. Although no significant differences were found in the percent increase in PRA response to LBNP among baseline, deconditioned, and recovery states, the subjects tolerated this orthostatic stress for less than 5 min when deconditioned and 10 to 11 min during baseline conditions and after recovery. Peripheral renin activity stands out as the key measurement indicating early adaptation to weightlessness and, at least at the renal level, a sign of circulatory deconditioning. The elevation of 6:00 a.m. PRA after 2 weeks of deconditioning was consistent with decreased plasma volume and accords with experience in Apollo spaceflights (3).

The loss of exercise capacity, which was still substantial on the third day of recovery in control subjects, emphasizes the deconditioning effect of simulated weightlessness. The small, though significant, 8.3% loss in treadmill endurance found in HGE subjects on Day + 1 is probably due to the relatively low level of exercise demanded of them. All subjects felt their previous normal daily activities were far more vigorous than these periods of walking at only 3.2, 4.8, and 6.4 km/hr (2, 3, and 4 mph). Further experience with these treadmills indicates that most subjects are more comfortable jogging at 8 and 9.6 km/hr (5 and 6 mph) than walking fast at 6.4 km/hr (4 mph). It would be simple to increase the work of the exercise task to maintain better the baseline exercise tolerance of active male subjects. Fractional-gravity exercise apparently did reduce the plasma volume loss of HGE subjects (8.5%) in comparison to control subjects (17.0%). Other investigators (6,11) have shown that supine isometric and isotonic exercise retards the loss of plasma volume during 14-day bed-rest studies but does not help preserve G_z tolerance.

The significant weight loss in both groups is greater than what may be accounted for by plasma volume loss alone. Other extracellular fluid loss is most likely contributory; however, HGE subjects lost an average of 0.36 kg (0.8 lb) more than controls. This additional loss may be caloric in origin. During the 4 hr of daily exercise, HGE subjects not only expended significant amounts of energy but also were unable to have snacks or take fluids, which were available to controls resting under nearly basal conditions. Overall weight on Day +3 of recovery remained 0.5 kg (1.1 lbs) below baseline ($p<0.05$), suggesting that a portion of the weight loss came from elsewhere than a fluid compartment where restoration is rapid. A 0.45 kg (1.0 lb) deficit, though not statistically significant, persisted in all groups through Days +7 and +10, and complaints of loose-fitting clothing were common among participants in the project.

The fact that the urinary sodium and potassium values did not differ between groups indicates that the half-gravity exposure was not sufficient to influence the electrolyte balance of the subjects or to prevent the hypodynamic effects of simulated weightlessness. Urinary sodium loss, which was greatest the first day of deconditioning, decreased and stabilized during the remaining 13 days with a transient rise on Days 6, 7, and 8 in both groups. The urinary potassium which was lowest on the first day of diuresis, rose gradually, peaked during Days 5, 6, and 7, and returned to intermediate levels for the remainder of the deconditioning. The fall in urinary sodium/potassium ratio from 3.3 on the first day of immersion to less than 1.9 on Days 4 and 5 was highly significant. This may reflect the fluid shift from the intracellular to the extracellular space to replace that lost during the initial diuresis with, consequently, more potassium available for urinary excretion. Though the major weight loss and diuresis was during the first 48 hr of deconditioning, additional changes in electrolyte excretion patterns occurred during the first 8 days and were even found as late as Day 13. This makes it very difficult to predict that further changes would not occur were the deconditioning period extended. On the other hand, a new steady-state equilibrium in weightlessness might ultimately be reached with reduced total body water and respiratory and renal compensation for the relative intracellular acidosis and extracellular alkalosis produced by the shift of potassium and hydrogen ions. The fall in urinary sodium and potassium during the first 48 hr of recovery demonstrates how quickly the kidneys can recoup these losses and readapt to Earth gravity.

The significant loss of red cell mass found in both groups over the 2-week time periods may require both decreased production and increased destruction for explanation. One may theorize that the hypodynamic state deprives the marrow of the normal stimulus provided by growth hormone. Likewise, alteration in the normal distribution of blood flow may result in accelerated red cell "aging," perhaps through more frequent exposure to the spleen and resultant faster removal from the circulation.

Lastly, it is necessary to comment briefly on the significance of our findings in terms of the generation of artificial gravity in space flight. In a space base, part of which rotates continually, the astronaut might spend 4 hr of the day in the weightless (nonrotating) part and the remaining 20 hr lying, sitting, standing, or walking, say, at 0.5 G. The beneficial effects of artificial gravity on the musculoskeletal system would be least during sleep, when the antigravity muscles would be relaxed and the direction of force at right angles to the long axis of the body. It is difficult to equate the musculoskeletal effects when seated, standing, or walking (for the remaining 12 hr) with 4 hr of exercise (simulated in our experiment) but similarities outweigh differences.

Our data raise the important question whether loss of orthostatic tolerance is a handicap at one-half Earth gravity. In any event, orthostatic tolerance is readily preserved using LBNP devices (4), hence, provides little

justification for generating artificial gravity. Our findings clearly indicate beneficial musculoskeletal effects at 0.5 G, but the period of exposure was too short and the intensity of exercise was too low to establish the point when exercise capacity remains constant. Our findings suggest it would be worthwhile to repeat the experiment at the same G load but make provisions not only for much longer exposure but also better simulation of the astronauts' space base activities while seated, standing, or exercising. These "activities" should be designed to reflect actual living and working conditions aloft and avoid exercises falling in the category of directed countermeasures. In other words, it is highly desirable to determine separately the beneficial effects of ordinary living and working aloft and attempts to use increased amounts of exercise as a specific countermeasure.

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Comparison of Five Levels of Motion Sickness Severity as the Basis for Grading Susceptibility

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MILLER, E. F. II, and A. GRAYBIEL. *Comparison of five levels of motion sickness severity as the basis for grading susceptibility. bility*. Aerospace Med. 45(6):602-609, 1974.

The motion sickness susceptibility of 275 healthy male subjects was measured quantitatively by a standardized laboratory procedure using a Stille rotational chair. The results, in terms of velocity of the chair and the number of active head movements, were combined into a single numerical score that represented the total stressor stimulus sustained in reaching, in turn, each of five specific criteria for diagnosing the severity of motion sickness; viz, frank sickness (FS), severe malaise (M III), moderate malaise (M IIA and M IIB), and mild malaise (M I). The stressor value (E factor) of a single head movement at each test rpm was adjusted to yield an equivalent susceptibility score (Coriolis [Cross-coupled angular acceleration] Sickness Susceptibility Index, or CSSI) independent of the endpoint selected. Close agreement among the CSSI scores obtained at each endpoint was found in intercorrelations, test-retest reliability coefficients, and frequency distributions, which reflected the orderliness and stability in the appearance, ramification, and intensification of the acute symptomatology evoked in progressing from MI to FS. The endpoint M IIA appeared, however, to yield the best balance between subject acceptability and test confidence and was used without exception to calibrate the motion sickness susceptibility of 250 additional subjects.

VOMITING or retching and nausea represent severe expressions of motion sickness well recognized by the layman and most favored as test endpoints by investigators interested in the measurement of susceptibility to this malady. Recent efforts at Pensacola have been directed toward finding less severe endpoints that are based upon milder diagnostic signs and symptoms, yet offer equivalent validity and reliability using standardized procedures in the diagnosis of acute motion sickness. Initial studies revealed that severe malaise (M III), one of a four-category test system for qualitatively defining the severity of acute motion sickness, met these requirements while avoiding, with rare exceptions, frank sickness with vomiting and its systemic complications; greater subject acceptability was a natural consequence (1,7,10,11). Investigations of the appropriateness of using still milder sickness levels for this purpose became dependent upon a more precise determination of possible test endpoints than provided for in the original four-part categorization of motion sickness severity, *viz*, the "other symptoms" category was not identified and a rather broad category existed between M III and the first general and unspecified symptom or sign, termed slight malaise (M I), which had no practical value as a test endpoint. These limitations were overcome by a) identifying and assigning point values to all qualifying symptoms according to their type and severity, and b) quantitatively defining, in terms of the total points accrued among the manifested symptoms, the original severity criteria levels of frank sickness (FS), M III, and M I as well as the two newly established categories of moderate malaise, M IIA and M IIB, as outlined in Table I (2,7).

The diagnostic value of the M III criterion was demonstrated in a previous study that evaluated a standardized laboratory procedure for grading susceptibility (7). This procedure was used in the present study to determine the diagnostic validity of less severe endpoints since a) it provided highly effective stressor conditions that typically evoked a gradual growth in the number and intensity of symptoms, and b) the results, in terms of rotational rate and number of head movements, could be reduced to a single numerical score that represented the total stressor stimulus sustained by the subject in reaching, in turn, each of the five specific endpoints (6,7). Thus, serial scores obtained on a subject reflected meaningful quantitative changes in response to the stressful acceleration, and differences in scores among a group not only furnished an accurate rank order of susceptibility, but also quantitative differences among them.

MATERIALS AND METHODS

Subjects: Group 1 included 250 men who were 193 aviators, aviation students, or flight crew personnel; 11 nonaviator officers; 41 enlisted men; and 5 civilians. These men ranged in age from 16 to 43 years; 232 of

This study was supported by Contract T-81633, Biomedical Research Office, NASA, Johnson Space Center, Houston, Tx, and Contract T-5904B, Office of Life Sciences, NASA, Washington, DC.

Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views and endorsement of the Navy Department.

TABLE I. DIAGNOSTIC CATEGORIZATION OF DIFFERENT LEVELS OF SEVERITY OF ACUTE MOTION SICKNESS.

Category	Pathognomonic 16 points	Major 8 points	Minor 4 points	Minimal 2 points	AQS* 1 point
Nausea syndrome	Nausea III,† retching or vomiting	Nausea II	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing/Subjective
Cold sweating		III	II	I	warmth $\geq$ II
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Persistent Headache $\geq$ II
Central nervous system					Persistent Dizziness Eyes closed $\geq$ II Eyes open III
	Levels of Severity Identified by Total Points Scored				
Frank Sickness (FS) $\geq$ 16 points	Severe Malaise (M III) 8-15 points	Moderate Malaise A (M IIA) 5-7 points		Moderate Malaise B (M IIB) 3-4 points	Slight Malaise (M I) 1-2 points

* AQS—Additional qualifying symptoms. † III—severe or marked, II—moderate, I—slight.

them fell within the range of 19 and 26 years. Thirty of these subjects were retested to determine test-retest reliability among the various malaise levels through M III. Twenty-five additional subjects, four aviators or aviation students and 21 enlisted men (Group 2), served in determining the relationship among the four specific malaise levels and frank motion sickness. Another sample of 250 men (Group 3) of similar background to Group 1 (155 pilot type, 2 nonaviator officers, 67 enlisted men, and 26 civilians) were stressed only to the M IIA endpoint.

In addition to the standard flight-qualifying medical examination, all subjects were given specific tests for function of the otoliths (4,5) (ocular counterrolling) and semicircular canals (3,8) (caloric threshold or oculogyral illusion threshold). Each subject manifested vestibular responses that were well within normal limits.

Procedure: The standardized procedure for generating set patterns of cross-coupled angular acceleration, described fully in another report (7), was followed. Cross-coupled angular acceleration was introduced at one of several constant velocities (1.0, 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 20.0, 25.0, and 30.0 rpm) by having the subject bend his neck and upper body as necessary to effect approximately 90° positive and negative movements of the head from the upright position within the frontal and sagittal planes according to the following pattern: front, upright, pause; right, upright, pause; back, upright, pause; left, upright, pause; front, upright, rest (Fig. 1). Each of the movements to a new position or the return to upright was executed smoothly over a 1-s period. The pauses between movements were of the same (1-s) duration with the final pause (rest) lasting for 20 s. The time schedule of these test procedures was achieved by having the subject follow tape-recorded instructions. The head movement sequences continued until the accumulated symptom point values totalled at least 8 for the severe malaise (M III) endpoint of Group 1;

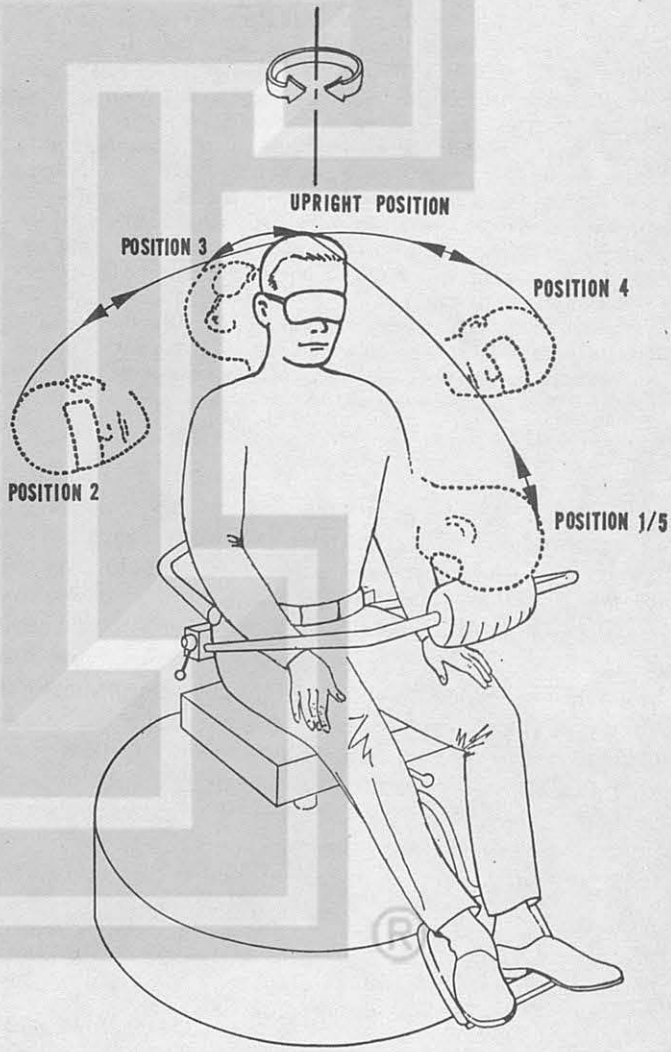

Fig. 1. Diagram of standardized procedure for making each sequence of head movements to and from tilt position 1 through 5 during chair rotation.

TABLE II. ROTARY CHAIR TEST (M IIA ENDPOINT) VELOCITIES MOST OFTEN ASSOCIATED WITH AVERAGE EXPERIENCE AND SYMPTOM LEVELS CODED FROM MOTION EXPERIENCE QUESTIONNAIRE.

		SYMPTOMS *S*										
	M IIA	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
EXPERIENCE *X*	0.5	7.5*	7.5	7.5	7.5	7.5	7.5	7.5	5.0	5.0	5.0	5.0
	1.0	10.0	10.0	10.0	7.5	7.5	7.5	7.5	5.0	5.0	5.0	5.0
	1.5	10.0	10.0	10.0	10.0	7.5	7.5	7.5	7.5	5.0	5.0	5.0
	2.0	12.5	12.5	10.0	10.0	7.5	7.5	7.5	7.5	5.0	5.0	5.0
	2.5	12.5	12.5	10.0	10.0	10.0	10.0	7.5	7.5	5.0	5.0	5.0
	3.0	15.0	15.0	12.5	12.5	10.0	10.0	7.5	7.5	7.5	5.0	5.0
	3.5	15.0	15.0	12.5	12.5	12.5	10.0	7.5	7.5	7.5	5.0	5.0
	4.0	20.0	20.0	15.0	15.0	12.5	12.5	10.0	10.0	7.5	5.0	5.0
	4.5	25.0	25.0	20.0	20.0	15.0	12.5	12.5	10.0	7.5	5.0	5.0
	5.0	30.0	30.0	25.0	20.0	20.0	15.0	12.5	10.0	7.5	5.0	5.0

* Rotary chair velocity (rpm)

16 for the frank sickness (FS) endpoint of Group 2; and 5 for the moderate malaise (M IIA) endpoint of Group 3 subjects.

Table II lists the best current estimate of the chair's rotational test rate (rpm) for the M IIA endpoint that we have determined empirically from the average level of experience (X) and intensity of symptoms (S) reported by subjects in the Motion Experience Questionnaire (7).

Comparable estimates for the M III endpoint have been reported previously (7).

The subject was informed of the method of executing the sequence of head movements and the expected symptoms. He was then secured in the rotary (Stille) chair and blindfolded. After the subject had demonstrated the head movement sequence while stationary, the chair was accelerated 5°/s² in the clockwise or counterclockwise direction, selected at random, until the desired constant velocity was reached; at no less than 60 s thereafter, the first head movement sequence was begun. Immediately upon reaching either the M III (Group 1), FS (Group 2), or M IIA (Group 3) level, the head movements were terminated, the subject retured to his upright position, and the chair was decelerated (5°/s²) to a stop.

During this procedure, the test was not terminated until the selected terminal endpoint or a limit of 204 (FS), 166 (M III), or 150 (M IIA) head movements was reached. However, as the test progressed and as each of the defined levels of motion sickness severity (Table I) appeared in advance of the selected terminal point, the cumulative number of head movements executed was duly registered. This method of identifying within one test session the successive appearance of up to five potential test endpoints (five motion sickness severity levels) avoided possible intertest subject differences.

In the comparison of the several specific malaise and frank sickness levels, it was of great advantage to employ the concept of an index score of susceptibility (7) (Coriolis or Cross-coupled angular acceleration Sickness Susceptibility Index, CSSI). This method of grading motion sickness susceptibility removes the need for separately citing the test velocity of the rotational chair and the number of head movements executed and, instead, allows an individual's susceptibility to be graded by a single numerical score. In a previous study, the index was found to depend upon the average stressor effect, termed the *E* factor, of a single head movement that was found to be directly related to the rotational velocity of the chair (6). An individual's susceptibility was, therefore, based upon this measure (CSSI) of the total stimulus sustained in reaching the selected endpoint

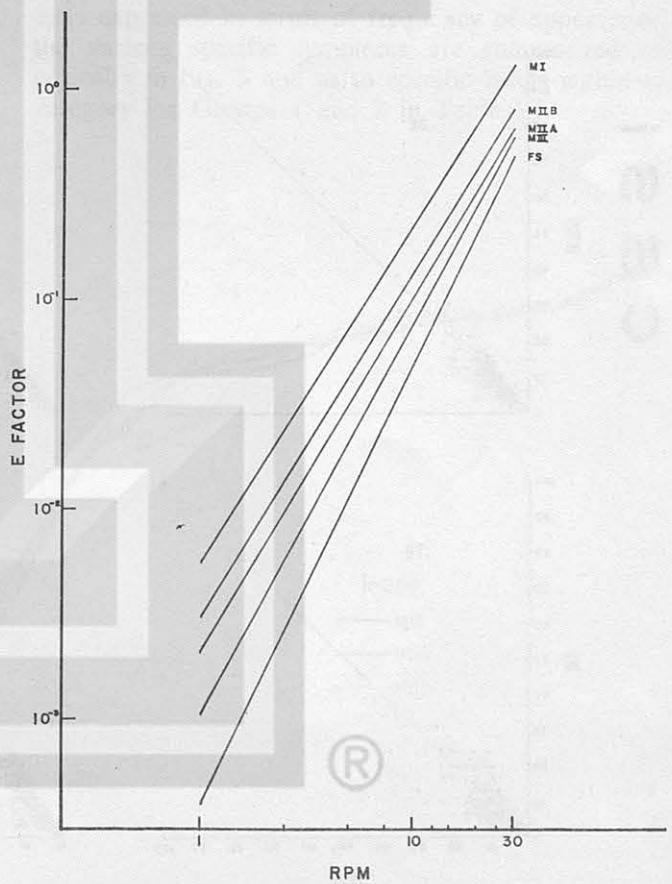

Fig. 2. *E* factor vs rpm for five levels of motion sickness severity used as basis for calculating individual Coriolis sickness susceptibility index (CSSI).

(M IIA or M III); i.e., susceptibility equals the product of the E factor specified for either the M IIA or M III endpoint at each of several test velocities times the number of standardized head movements (CSSI = $E \times N$). The absolute E factor was arbitrarily adjusted to yield, independent of the selected endpoint, a CSSI score of 0 to 100 points.

As the first step of this study to determine the relative value of the several malaise levels in grading susceptibility, new sets of E factors associated with each of the test velocities were determined for the moderate malaise, M IIB, and slight malaise, M I, categories as well as that of frank sickness, FS. These values were at first grossly estimated from those representing the M III and

TABLE III. TABLE OF E FACTORS ASSOCIATED WITH SPECIFIC ROTATIONAL TEST VELOCITIES AND THE FIVE LEVELS OF MOTION SICKNESS SEVERITY.

Velocity (rpm)	Levels of Motion Sickness Severity				
	M I	M IIB	M IIA	M III	FS
30.0	1.31	0.82	0.67	0.60	0.49
25.0	0.98	0.61	0.48	0.43	0.33
20.0	0.69	0.43	0.33	0.28	0.21
15.0	0.435	0.263	0.205	0.165	0.115
12.5	0.325	0.195	0.150	0.118	0.078
10.0	0.225	0.135	0.105	0.078	0.049
7.5	0.142	0.084	0.064	0.046	0.027
5.0	0.083	0.043	0.032	0.021	0.012
2.5	0.024	0.014	0.010	0.006	0.0036
1.0	0.005	0.003	0.002	0.001	0.0004

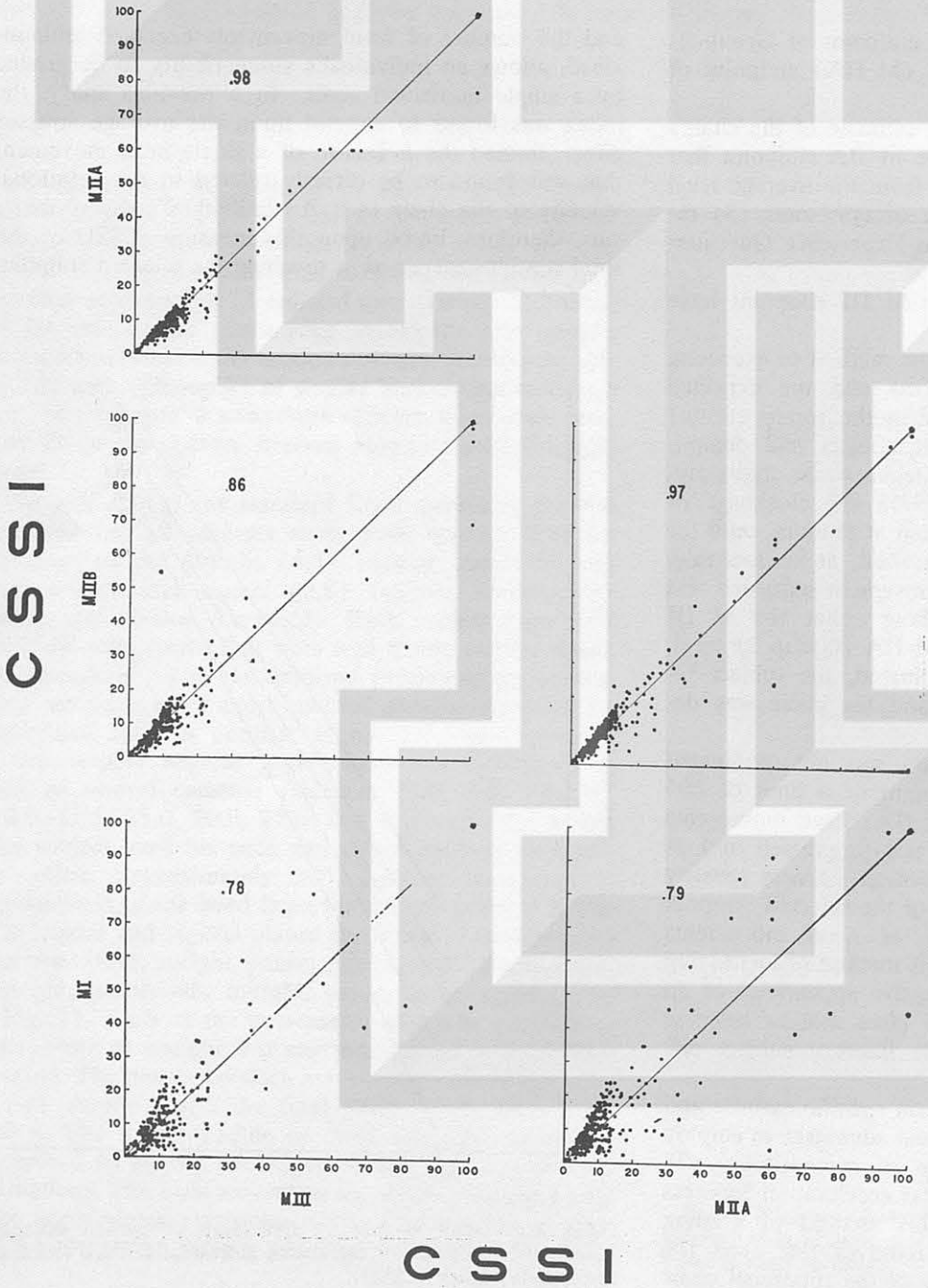

Fig. 3. Scattergrams showing relationships among individual CSSI scores (Group 1 subjects) derived from each of the four malaise levels.

M IIA endpoints (6), then adjusted empirically to yield the best fit to lines of regression in comparisons between all endpoints. The resultant E factors versus rpm data for the five endpoints are listed in Table III and portrayed as a family of straightline curves with slightly different slopes in Fig. 2.

By using the appropriate E value, the CSSI was calculated on an individual basis for each of the four malaise (M I, M IIB, M IIA, M III) and frank motion sickness (FS) criteria, and this served as the common measurement for determining intercorrelations, test-retest reliability, and frequency distributions of these criteria.

RESULTS

Correlations Among Indices of Motion Sickness Susceptibility: The relationships among the individual CSSI scores of the Group 1 subjects derived from each of the four malaise levels are indicated by the several scattergram plots and associated correlation coefficients presented in Fig. 3. Relatively high correlations were revealed among the CSSI scores calculated from data obtained at each of the malaise levels. With few individual exceptions the plotted scattergram positions of the various endpoint CSSI scores grouped about the regression lines. An almost perfect relationship, for example, was found ($\rho = 0.98$ and 0.97) between the M III versus M IIA, and M IIA versus M IIB endpoint scores. The group correlations decreased and the scattering of data points increased somewhat with M I comparisons. Surprisingly though, even these data based upon the mildest form of malaise (I), *viz,* the manifestation of a single specific sign or symptom that qualifies for the assignment of a single point value, correlated relatively well ($\rho = 0.78$ and 0.79) (Fig. 3) with those of severe (III) and of moderate malaise (IIA).

TABLE IV. CORRELATIONS AMONG CSSI SCORES OF 25 SUBJECTS (GROUP 2) DERIVED FROM DATA ACQUIRED AT EACH OF FOUR MALAISE ENDPOINTS AND FRANK SICKNESS.

	FS	M III	M IIA	M IIB	M I
FS		.993	.980	.936	.934
M III			.917	.870	.854
M IIA				.932	.917
M IIB					.966
M I					

Table IV lists similar correlations among the four malaise levels as well as frank motion sickness in the small group (Group 2). Of primary interest here is the finding that each of the malaise-criteria CSSI values correlated very highly with those representing the frank sickness level.

Reliability: Test-retest reliability results from 30 subjects are listed in Table V, where it is seen that high reliability coefficients were found among each of the malaise categories.

Frequency Distributions: The cumulative frequency distribution of the individual CSSI scores of the Group 1 subjects as determined for each of the four malaise levels approached coincidence (Fig. 4).

Symptomatology: The results from the Group 1 subjects expressed in terms of frequency of appearance of the various specific symptoms are summarized categorically in Fig. 5 and as to specific levels within each category for Groups 1 and 2 in Table VI.

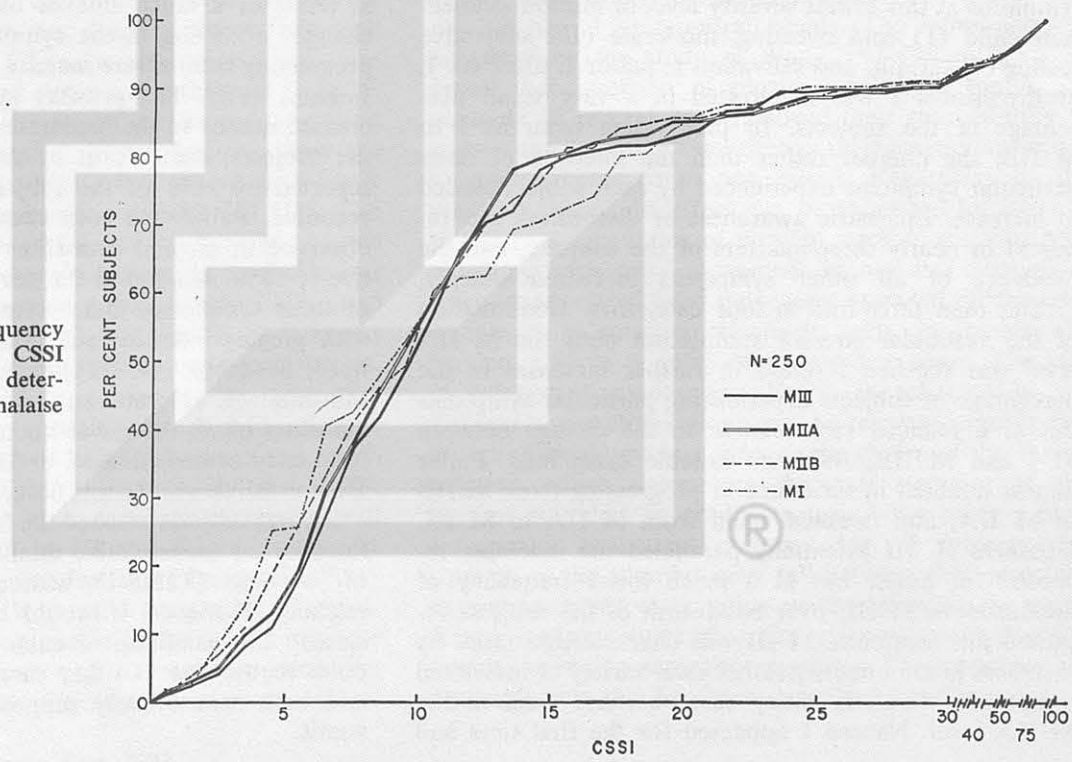

Fig. 4. Cumulative frequency distributions of individual CSSI scores (Group 1 subjects) determined for each of the four malaise levels.

TABLE V. TEST-RETEST RELIABILITY OF CSSI SCORES OF 30 GROUP 1 SUBJECTS BASED UPON M I, M IIA, M IIB, AND M III ENDPOINTS.

	M III	M IIA	M IIB	M I
M III	.87			
M IIA		.90		
M IIB			.86	
M I				.91

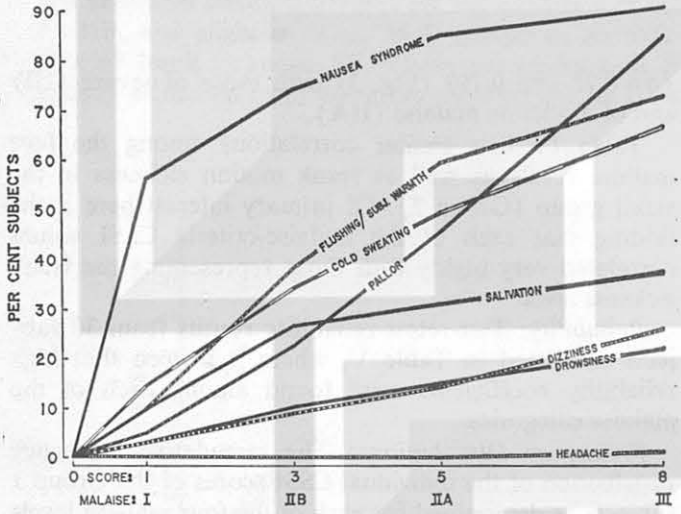

Fig. 5. Results from Group 1 subjects expressed in terms of frequency of appearance of various specific symptoms.

TABLE VI. FREQUENCY OF APPEARANCE OF SPECIFIC SYMPTOMS ASSOCIATED WITH THE FOUR MALAISE CRITERIA (GROUP 1 SUBJECTS) AND FRANK SICKNESS (GROUP 2 SUBJECTS).

SYMPTOMS	M I	M IIB	M IIA	M III	FS
Flushing/subjective warmth $\geq$ II	9.6*	38.0*	59.2*	72.4*	92.0†
Dizziness $\geq$ II	2.8	8.8	14.0	25.6	52.0
Headache $\geq$ II	—	—	—	1.2	8.0
Drowsiness I	2.8	9.6	13.6	14.4	12.0
Drowsiness II	—	0.4	1.2	7.2	12.0
Cold sweating I	14.4	32.0	43.6	43.2	28.0
Cold sweating II	—	2.0	5.6	21.6	36.0
Cold sweating III	—	—	—	1.6	16.0
Pallor I	4.8	21.6	41.2	48.4	16.0
Pallor II	—	0.8	4.0	36.0	68.0
Pallor III	—	—	—	—	16.0
Salivation I	9.6	24.8	28.4	30.4	32.0
Salivation II	—	1.6	2.4	6.8	24.0
Epigastric awareness/ Discomfort	56.0	74.0	84.8	58.8	12.0
Nausea I	—	—	—	31.6	36.0
Nausea II	—	—	—	—	48.0

* Percent subjects (Group 1, N = 250).
† Percent subjects (Group 2, N = 25).

The primary symptom characterizing M I was found to be epigastric awareness or discomfort, the mildest form of the nausea syndrome, that appeared in slightly over half of the subjects. Much less frequently seen symptoms at this lowest severity level of motion sickness were mild (I) cold sweating, moderate (II) subjective feeling of warmth, and salivation I; pallor I, dizziness I, or drowsiness I was manifested in a very small percentage of the subjects. In progressing from M I to M IIB, the number rather than the intensity of these particular symptoms experienced by each subject tended to increase. Epigastric awareness or discomfort was reported in nearly three-quarters of the subjects, and the incidence of all other symptoms increased sharply, greater than three-fold in four categories. Continuation of the vestibular stressor stimulation until the M IIA level was reached resulted in further increases in the percentage of subjects experiencing particular symptoms but at a reduced rate relative to the change between M I and M IIB, with two notable exceptions. Pallor almost doubled in incidence in progressing from M IIB to M IIA, and doubled again from M IIA to M III. Dizziness II, III essentially paralleled the increases recorded for pallor but at a much lower frequency of incidence; at M III, over one-fourth of the subjects reported this symptom. M III was characterized more by increases in the intensity rather than variety of individual symptoms, which in many cases became fixed at the M IIA level. Nausea I appeared for the first time and replaced epigastric awareness or discomfort in more than one-fourth of the test population, while over nine-tenths reported one of these forms of the nausea syndrome. Among the approximately two-thirds reporting cold sweating, the moderate level (II) increased almost four-fold, with a few manifesting the severest level (III). Headache II began to be reported by a small number of the subjects and drowsiness II increased six-fold. Increases in the subjective feeling of warmth and salivation were much less marked.

The results of testing Group 2 (Table VI) revealed, in terms of a much smaller number of subjects, those changes occurring in the symptomatic patterning when progressing from severe malaise (M III) to frank motion sickness (FS). The primary symptom change was increased nausea to the moderate level (II) in almost half the subjects; some form of the nausea syndrome was reported by 96% of the subjects. Nausea III was not recorded. Pallor and cold sweating at some level were observed in all and four-fifths of the subjects, respectively; 16% manifested the severest level (III) of each of these symptoms. Other symptoms of FS manifested with greater intensity and frequency than with M III were: headache (II, III); dizziness (II, III); increased salivation (I, II); and subjective warmth (II, III). On the other hand, there was no substantial increase in the frequency of drowsiness I or II; and neither drowsiness III nor salivation III was observed.

Several subjects reached the frank sickness level, as defined by an accumulative total of symptom point values of 16 points (Table I), without the act of vomiting or retching. However, it would have been impossible to classify the condition of each of these subjects at this point in the test as other than being less than "sick," and each was actively suppressing a strong desire to vomit.

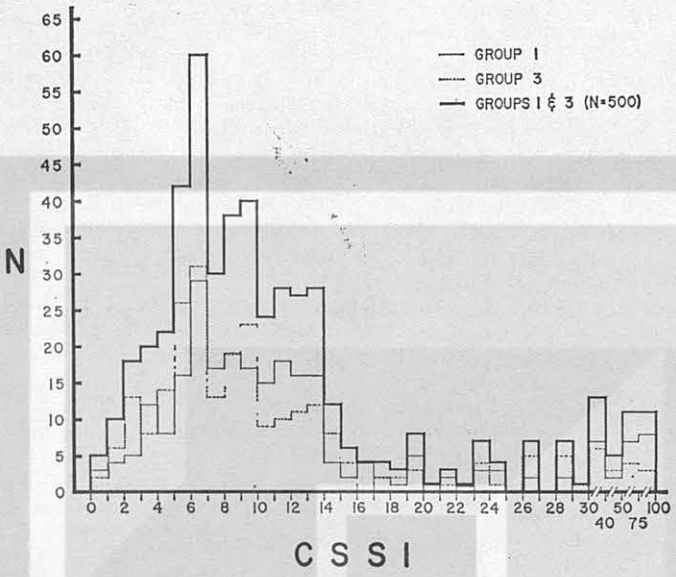

Fig. 6. Separate and combined frequency distributions of CSSI scores of Groups 1 and 3 subjects based upon M IIA endpoint.

Frequency Distributions of the CSSI Scores of Groups 1 and 3 Subjects Based Upon the M IIA Endpoint: The separate and combined frequency distributions of the CSSI scores of Groups 1 and 3 subjects are presented in Fig. 6. The distributions of the CSSI scores of these two groups were similar, each revealing wide ranges of susceptibility and marked right skewness.

DISCUSSION

The results make evident that the specific diagnostic symptoms set forth in Table I appear, ramify, and intensify in an orderly fashion. The regularity of this process beginning with the initial (point-rated) symptom of malaise I, usually stomach awareness or discomfort, was marked by the high correlations found among the rest of the malaise levels and frank sickness. The high test-retest reliability of all endpoints indicates the temporal stability of each of these measurements in terms of the grading technique as well as the individualistic symptomatological patterning. These findings show the potential value of using criteria less severe than frank motion sickness (FS) and severe malaise (M III). The choice of endpoints short of FS was thus widened to one of four malaise criteria that could provide a reliable and valid basis for grading motion sickness susceptibility and might better fit the subject or test condition. It is our present opinion that, in all but exceptional circumstances, however, M IIA, may be the lowest malaise level that is of practical value for assessing susceptibility since it appears to represent the best balance between test confidence and subject acceptability. Specifically, the M IIA criterion: a) yields data that correlate extremely well with those obtained with M III and FS endpoints: b) clearly avoids the subjective feeling of being "sick"; c) allows a rapid recovery from mild symptoms; d) in almost all cases is not objectionable to the subject in single or multiple measurements; and e) makes malingering difficult since it requires the manifestation of several symptoms that must correlate.

M I, in contrast, is described by a single subjective symptom and, therefore, may be highly dependent upon the subject's introspective ability, his honesty, or willingness to report symptoms. With a good observer in certain test situations, the M I criterion can be highly useful since it provides the first definite diagnosis of a provocative effect. However, M I may not indicate a true measure of susceptibility, at least in terms of the CSSI scale, since it does not assure that the test is being conducted at a stressor level higher than the subject's ability to compensate; not infrequently, M I symptoms will be manifested during the initial part of the test only to disappear as the test is continued. Thus, the M I criterion may falsely indicate that the subject has low susceptibility or even is unsusceptible. These "misses," or false measurements of susceptibility, are not present in the data of this study since each test was eventually carried beyond this malaise level. If the selected endpoint were not reached initially, the test was considered invalid and these particular subjects were retested at a higher stressor level (chair velocity) on a subsequent day for inclusion in this study. Manifestation of at least the M I criterion proved a considerable advantage since it provided information that often served to determine the chair velocity increase necessary to reach the desired endpoint in accordance with the CSSI test method.

The stressor conditions of the standardized test provoked principally those symptoms denoted in Table I. Without exception, symptoms other than those recognized in this table were rarely observed or reported and, when present, were not useful in the diagnosis. Although, among this limited variety of categories, there were distinct individual differences in symptom development and patterning, the order of release and intensification of symptoms was similar in the majority of subjects. These events seem dependent upon a summation process involving neural or humoral agents. The latter agent is suggested by the study of Wang and Chinn (9) who found that insertion of plastic barriers in the fourth ventricle of several dogs removed their susceptibility to nausea and vomiting even though their emetic thresholds to apomorphine were not raised. Regardless of the mediating agent, its effect can be expressed for illustrative purposes in terms of units of stressor stimulus provided by each head movement in our test procedure. Each standardized head movement executed during constant-velocity rotation effectively adds, in incremental fashion, a given quantity of provocative stress. The rate of release of autonomic effects, as reflected in the buildup in symptomatology, can be regulated simply and in a predictable manner through the choice of the chair's velocity, which determines the unit step-size of the stressor stimulus. In grading susceptibility using a physiologically equivalent endpoint for all subjects, the strength of the stimulus must fall between that necessary to override homeostatic adjustments preventing the manifestation of symptoms of motion sickness and that which avoids provoking explosive responses. The technique for accomplishing this has been described elsewhere (7).

SUMMARY

The motion sickness susceptibility of 275 healthy male subjects was measured quantitatively by a standardized laboratory procedure using a Stille rotational chair. The results, in terms of velocity of the chair and the number of active head movements, were combined into a single numerical score that represented the total stressor stimmulus sustained in reaching, in turn, each of five specific criteria for diagnosing the severity of motion sickness; *viz,* frank sickness (FS), severe malaise (M III), moderate malaise (M IIA and M IIB), and mild malaise (M I). The stressor value (*E* factor) of a single head movement at each test rpm was adjusted to yield an equivalent susceptibility score (Coriolis [Cross-coupled angular acceleration] Sickness Susceptibility Index, or CSSI) independent of the endpoint selected. Close agreement among the CSSI scores obtained at each endpoint was found in intercorrelations, test-retest reliability coefficients, and frequency distributions, which reflected the orderliness and stability in the appearance, ramification, and intensification of the acute symptomatology evoked in progressing from M I to FS. The endpoint M IIA appeared, however, to yield the best balance between subject acceptability and test confidence and was used without exception to calibrate the motion sickness susceptibility of 250 additional subjects.

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Human ocular counterrolling measured during eight hours of sustained body tilt

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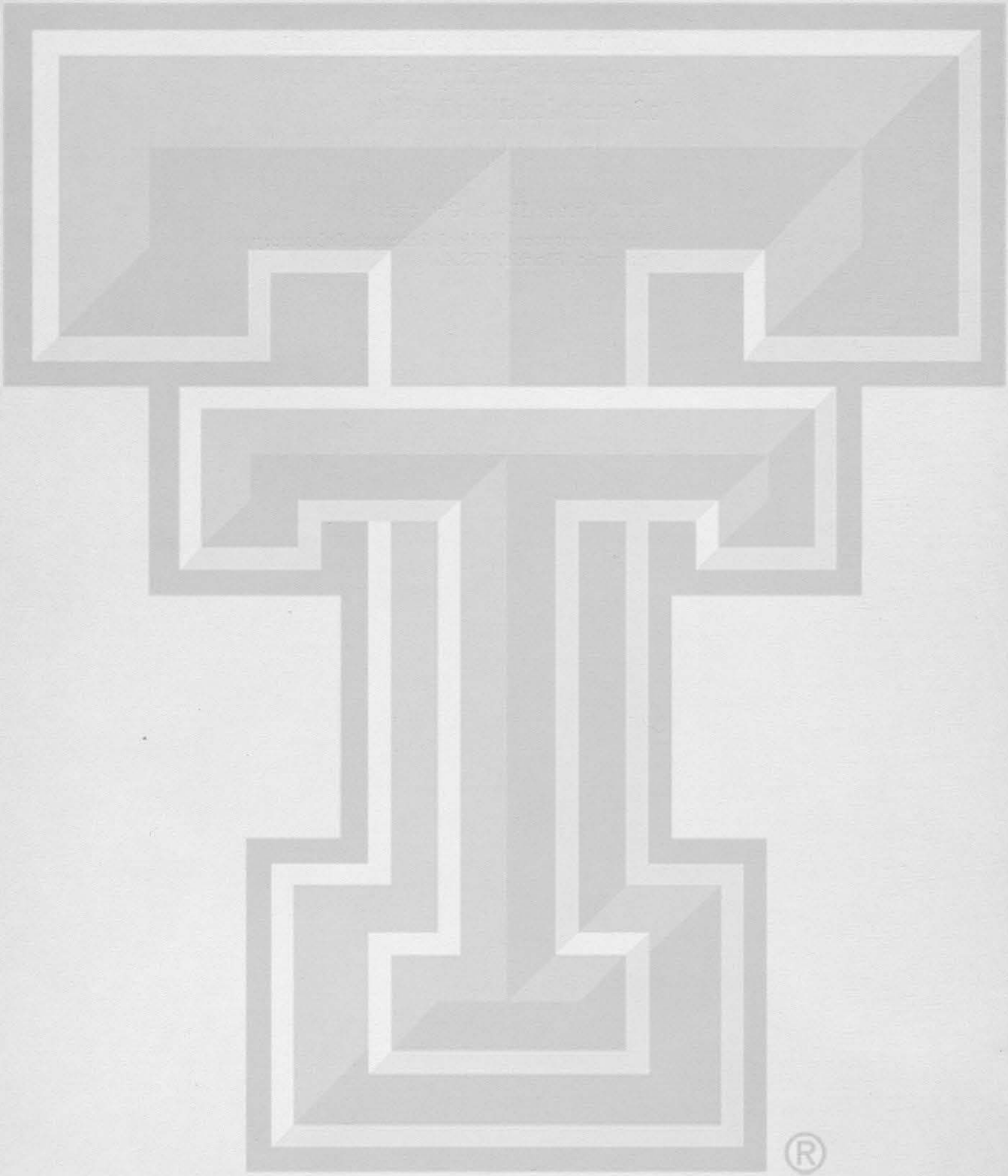
Estratto da MINERVA OTORINOLARINGOLOGICA

Vol. 24 - N. 4 - Pag. 247-252 (Ottobre-Dicembre 1974)



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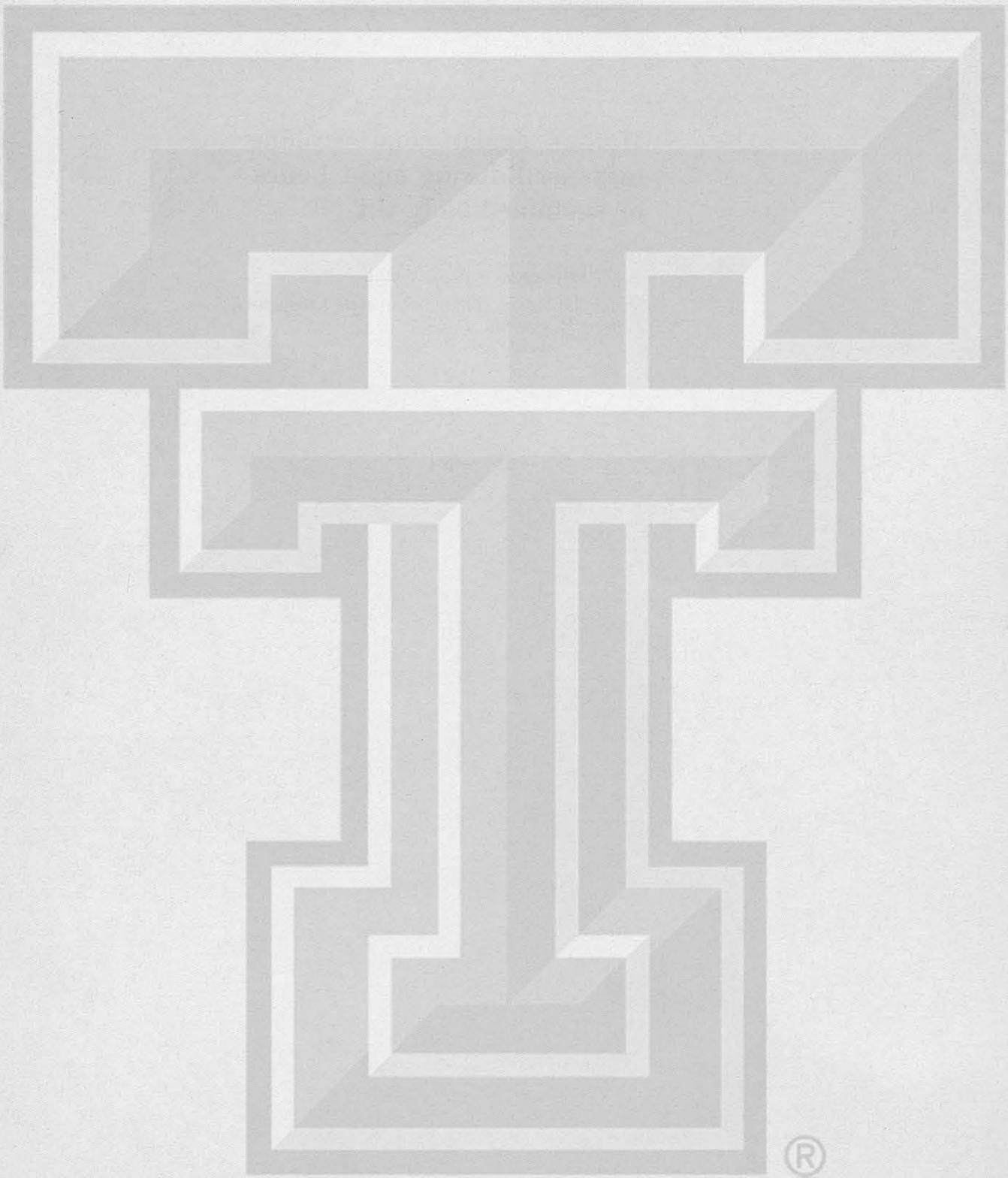


SUMMARY.—Adaptation of otolith organ activity was investigated by monitoring the ocular counterrolling response of four normal individuals and three persons with severe bilateral loss of labyrinthine function. Several ocular photographs were made every 30 minutes during a period of 8 hours in which the subject was held in a lateral tilt (60°) position. The recorded eye roll position varied to an expected small extent within each test session; this variation about a given mean roll position was similar among the test sessions for all subjects. The mean roll position, on the other hand, changed from session to session in substantial amounts, but these changes appeared to be random with respect to time and among subjects. Furthermore, the intersessional variation in the mean torsional eye position of the normal subjects was equivalent to that of the labyrinthine-defective subjects who displayed little or no counterrolling. These results provide evidence that the human counterrolling response is maintained by essentially nonadapting macular receptors.

KEY WORDS.—Human ocular counterrolling - Otolithic organ adaptation - Macular receptors.

Maintenance of equilibrium without a visual framework while the head (body) is held in a given position must rely upon nonvisual stimulus-response mechanisms that provide continuous valid information on the relative direction of gravity. It is well known that the cilio-otolith system as a specialized gravireceptor mechanism acts as a major influence in man's nonvisual perception of the upright, at least in those measurements made during a typically brief course of an experiment, and a physiological basis for this system's possible role in sustained static orientation has been indicated by the recordings of vestibular neural signals in animals. The frequency of these signals was found by several investigators to be significantly different in a tilted animal position compared to an upright reference level and showed little accommodation over periods up to several minutes' duration (Adrian, 1943; Björk and Kugelberg, 1953; Cramer, 1962; Fujita *et al.*, 1968; Lowenstein and Roberts, 1950). Man's ability to orient himself to a gravitoinertial frame of reference without empirical visual cues over much longer periods of time was well demonstrated by the relative constancy of the oculogravic illusion as observed by four experienced subjects throughout a 4-hour period of exposure to constant lateral centripetal acceleration (Clark and Graybiel, 1962). The cilio-otolith system under these conditions probably acted as the primary sensory mechanism, but nonotolithic systems, including touch, pressure, and kinesthesis,

This study was supported by Contract T-81633, Biomedical Research Office. NASA, Johnson Space Center, Houston, Texas and by Contract T-5904B, Office of Life Sciences, NASA, Washington, D.C.

Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views and endorsement of the Navy Department.

responding to the resultant acceleration vector could have played a part in these observations (Graybiel *et al.*, 1968). In order to monitor more directly the effect of sustained gravitational stimulation upon man's otolithic activity with relative freedom from nonotolithic gravireceptor influences, the ocular counterrolling reflex was selected as the test parameter for the present study (Miller, 1966). This choice, however, did not necessarily rule out all extraneous factors such as spontaneous changes in extraocular muscle tonus which would affect eye roll position during the 8-hour recording period. For this reason, bilateral labyrinthine-defective individuals who were apparently normal in all other respects were included in this study as our control subjects.

Procedure

Subjects

Four healthy Navy enlisted men, 19 or 20 years of age, served as the normal subjects, and tests revealed normal hearing, as well as normal nonacoustic labyrinthine function; their counterrolling response was in the high normal range (Counterrolling Index = 383 to 456) (McLeod and Meek, 1962; Miller, 1962; Miller, 1966). The control group comprised three deaf persons with severe loss of vestibular function as detailed in Table 1.

Method

The counterrolling test device, described elsewhere (Miller, 1966; Miller, 1970) and portrayed in Figure 1, was used for positioning the subject with respect to gravity. The subject was first stationed erect in the carrier portion of the device in a semistanding position, with his weight distributed between a saddle-type seat arrangement and an adjustable footrest platform. A locked headrest and biteboard assembly kept the subject's head precisely, yet comfortably in this position. The platform was raised or lowered by a hydraulic mechanism, and the subject was shifted sidewise until the center of the pupil of his right eye, during proper fixation of a ring target supplied for this purpose, fell on the optic axis of the camera system. Coincidence was determined when the pupillary image was concentric with specific circular markings on the camera's ground-glass viewing screen. In this position several straps and a tight-fitting vest constructed of velcro material secured the subject's body to the device. Foam-rubber padding was used in this particular study to cushion the right side and arm of the subject when held in the tilted position.

One or two drops of 1 per cent pilocarpine hydrochloride was instilled approximately 15 minutes prior to the initial testing and subsequently as required to reduce the overall size and physiological oscillations of the pupil, which aided the subsequent analysis of eye position based upon natural iris landmarks. The analytical procedure has been described elsewhere (Miller, 1962).

Thirty-six photographic recordings of the subject's right eye were made when he was upright; then the subject was slowly tilted 60 degrees in the rightward direction. Sixty seconds after reaching this tilt position, the first of 18 photographs was taken; an identical number was recorded every 30 minutes during the 8-hour period of sustained tilt. After 8 hours the subject was slowly returned to the upright, and his iris photographed 36 more times over a period of approximately 5 minutes. The average roll positions of his eye as recorded in the initial and terminal upright positions were averaged and used as the baseline (zero) position to which all other measurements were related. During the several minutes that separated the test sessions, the subject remained fixed in his tilted position, but his biteboard was removed for comfort.

TABLE 1.—*Clinical findings in three subjects with bilateral labyrinthine defects.*

Subject	Age	Deafness		Hearing		Caloric response*		Counterrolling index**
		Etiology	Age at onset	R	L	R	L	
HR	30	Meningitis	13	Nil	Nil	Negl.	Negl.	43
LR	24	Meningitis	6	>110 dB	>110 dB	Negl.	Negl.	51
MY	26	Meningitis	8	Nil	Nil	Negl.	Negl.	99

*Negligible or no observable nystagmus when tympanum irrigated with ice water.

**Calculated as one half the sum of the eye roll measured in minutes of arc at the 50° rightward and leftward tilt positions.

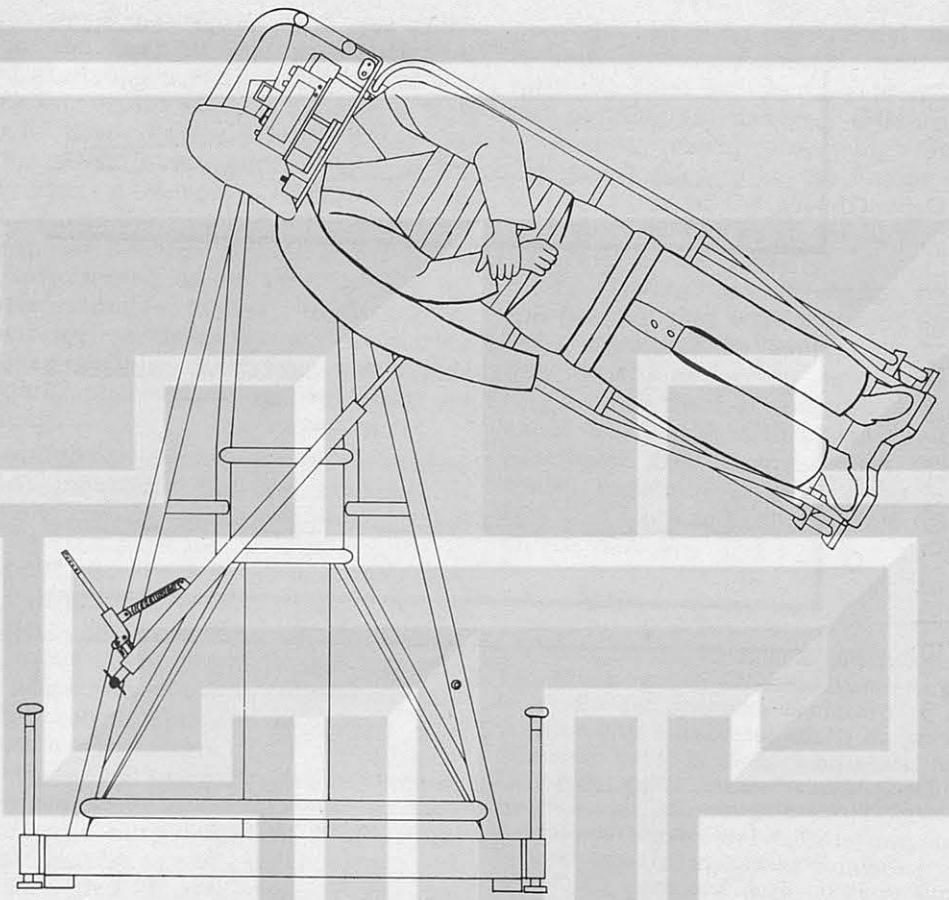


Fig. 1.—Diagram showing subject positioned in the counterrolling test device and tilted at 60 degrees from upright. Camera recording system shown on platform in front of subject's face.

Results

Figures 2 and 3 summarize the changes in ocular counterrolling of the normal and labyrinthine-defective (L-D) subjects as a function of time within and among the various test sessions, respectively. Figure 2 portrays the extremely small intrasessional torsional variations (average deviations) of the eyeball about the mean position measured for each session; the variability found for subjects of both groups throughout the 8-hour test period was relatively small, but somewhat greater deviations were recorded within the normal group. Figure 3 presents the mean ocular roll position of each subject as recorded during each of the several test sessions. As expected from the preliminary calibration tests, the L-D subjects clearly manifested less ocular counterrolling than the normals, but their individual data tended to complement those of the normal subjects in forming a continuum of response over a range from essentially none to greater than 10 degrees of arc. Within the 8-hour test period each normal and L-D subject manifested substantial intersessional changes (up to approximately ± 2 degrees) in mean eye roll position, but this appeared to be independent of the duration of sustained tilt. A measure of the randomness of the intersessional changes was provided by averaging individual data according to subject group. The resultant average curves of the normal and L-D subjects are relatively smooth and appear to follow essentially horizontal and therefore time-independent courses. The break in the curves of the normal group (Figure 3) marks the session in which the data of HO were lost for technical reasons.

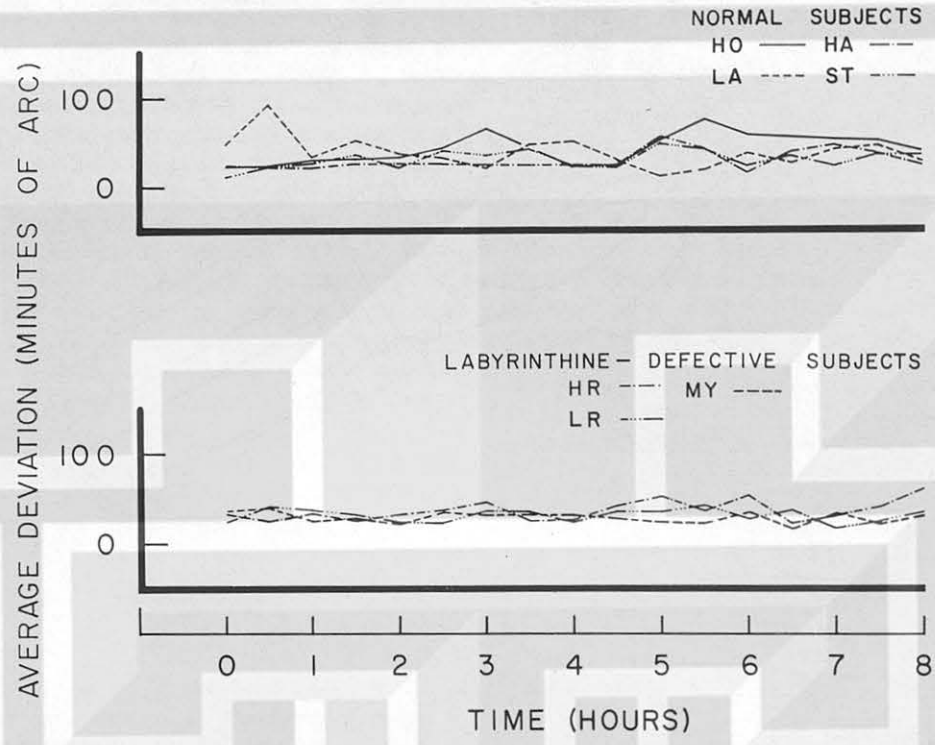
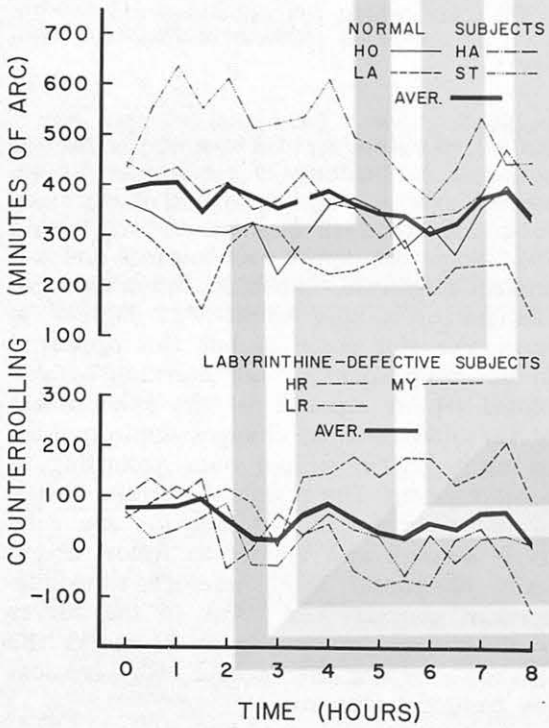


Fig. 2.—Ocular counterrolling intrasessional variability (average deviation of eigteen eye roll recordings per test session) in the normal and labyrinthine-defective subjects as a function of time held in a 60-degree body tilt position.



Discussion

Although constant error changes in the eye roll position were recorded for the normal and labyrinthine-defective subjects, the amount was relatively small and inconsistent throughout the 8-hour test period. On the basis of these data and the previously found evidence that this response closely reflects otolith activity (Miller, 1970; Miller and Graybiel, 1971; Miller *et al.*, 1966), it would appear that the macular source of tonic innervation to the extraocular muscles was effectively undiminished by time. These results can be explained either by the existence of nonadapting macular receptors in man or by some artifact in the test procedure. In the present experiment,

Fig. 3.—Average ocular counterrolling values of the normal and labyrinthine-defective subjects plotted individually and as groups as a function of time held in the 60-degree body tilt position. Each of the individual data points represents an average of eighteen eye roll recordings.

for example, the subject's head was stabilized by the simplest and most practical method available: a biteboard/headrest system. This restraint method assured a high degree of head rigidity (otolith organ stabilization), but it is conceivable that extremely fine movements might have occurred, particularly when the biteboard was removed between test sessions, which could have served as an everchanging accelerative stimulus to the otolith organs. The extreme precision in the measuring techniques, on the other hand, precluded any significant error being introduced by this factor.

The different sources of tonic innervation that influenced the measurements in this study can be differentiated to some extent by comparisons of the results of the normal and the L-D subjects who manifested little or no counterrolling. The latter subjects provided data on extraocular muscle tonus under the prolonged test conditions which was primarily dependent upon nonotolithic neurochemical processes. The intrasessional variations in eye roll position among these L-D subjects was extremely small, which tends to confirm the evidence that the basic tonic equilibrium of the extraocular muscles is more persistently maintained than that of other skeletal muscles (Björk and Kugelberg, 1953) and indicates that this activity can be independent of normal otolithic inputs. In fact, the slightly greater general intrasessional variability in the recordings of normal subjects would suggest that otolithic activity acts to decrease ocular stability.

Some support of this possibility is offered by the recordings of spontaneous irregular firing activity of the otolith organs in animals. It has been reported, for example, that the neuronal signal recorded from cells of the lateral vestibular nucleus in cats held in a specific tilt position was marked by a wide scatter of interspike interval values which they judged would require a probabilistic approach to identifying head position (Fujita *et al.*, 1968). These spontaneous variations in otolith signals with a given body position may also offer partial explanation for the perceptual phenomenon of rotary autokinesis (Miller and Graybiel, 1963). However, it is unknown whether the eyes fluctuate in their torsional position in simple accord with this perceptual illusion; more likely, the illusion is based upon the complex neural activity resulting from an interplay of nonotolithic and otolithic gravireceptor inputs that have undergone central processing. Gravireceptors are implicated by the finding that prolonged lifting of the g-load tends to reduce variability in the judgment of horizontality (Graybiel *et al.*, 1967).

The slower rates of change in the eye roll position that were recorded among sessions, separated by approximately 30 minutes, would appear to be nonotolithic in origin since the L-D subjects, and in particular subject HR with essentially complete functional loss of his otolith organs, revealed variations in mean ocular roll position that were indistinguishable from those of the normals.

Riassunto

L'adattamento funzionale dei recettori della membrana otolitica è stato valutato mediante lo studio del nistagmo oculare di 4 individui normali e di 3 individui affetti da grave deficit bilaterale della funzione labirintica. Numerose fotografie della posizione degli occhi furono eseguite ogni 30 minuti in un periodo di 8 ore durante il quale ogni soggetto era mantenuto in posizione di inclinazione laterale del capo di 60°. La posizione degli occhi presentava, in ciascun esame, una piccola modificazione, attorno ad un valore medio, facilmente prevedibile. Questa modificazione è stata riscontrata in tutti i soggetti. Invece la posizione degli occhi nello sguardo controlaterale variava notevolmente negli esami successivi, con variazioni del tutto casuali rispetto al tempo ed ai soggetti esaminati. Inoltre nei vari esami fu riscontrato che la posizione oculare media di deviazione controlaterale nei soggetti normali era equivalente a quella dei soggetti con lesione labirintica che praticamente non erano in grado di eseguire una deviazione controlaterale del bulbo oculare. Questi risultati dimostrano che la deviazione oculare controlaterale è legata al mancato adattamento dei recettori maculari.

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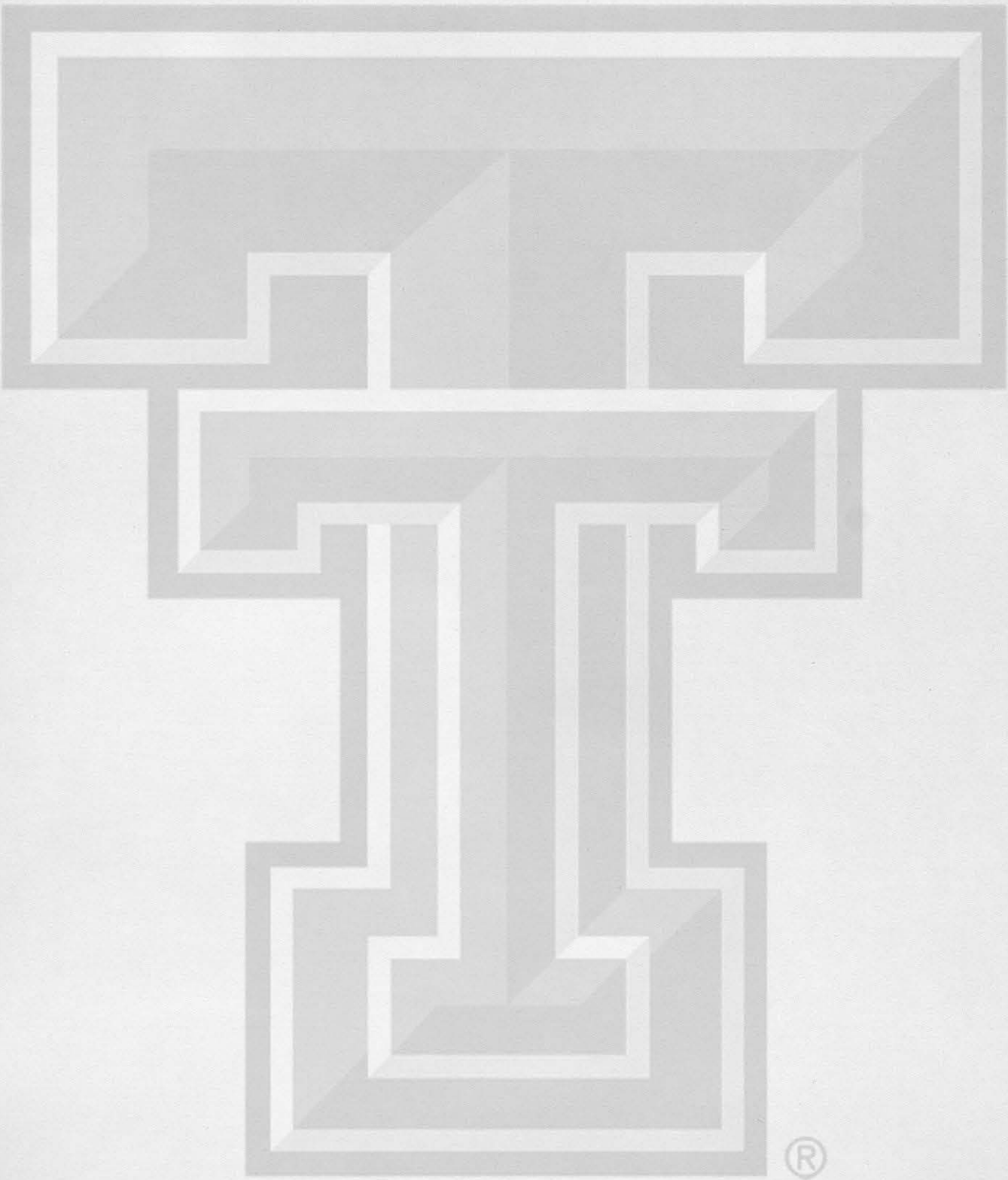

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VOLUME 46

NUMBER 9

SEPTEMBER 1975

AVIATION SPACE and ENVIRONMENTAL MEDICINE

(Formerly AEROSPACE MEDICINE)

Human Assay of Antimotion Sickness Drugs

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GRAYBIEL, A., C. D. WOOD, J. KNEPTON, J. P. HOCHE, and G. F. PERKINS. *Human assay of antimotion sickness drugs.* Aviat. Space Environ. Med. 46(9):1107-1118, 1975.

The present study was undertaken to improve previous testing procedures, involving the use of a slow rotation room, for assessing the efficacy of antimotion sickness drugs which had validity for groups of subjects but not for each individual in the group. Three major changes were introduced: first, the use of an incremental increase in the intensity of the stressful stimuli of constant intensity; second, a systematic distribution of placebos, rather than a random distribution, in using a modified Latin-square design; third, categorizing the responses as "inconsequential," "beneficial," and "detrimental"—the range of the "placebo responses" was doubled to define the inconsequential range and response above or below were, respectively, beneficial or detrimental. Only drugs known to have antimotion sickness effectiveness were tested and the cardinal findings can be briefly summarized: 1) The group responses were similar to the data previously reported; 2) Great individual differences in response to antimotion sickness drugs were revealed, implying that individual assessments must be made for maximal benefits; 3) The fixed-dose combination of promethazine hydrochloride and ephedrine sulfate (25 mg each) proved to be outstanding as this combination of homergic drugs clearly exhibited a supra-summation effect; and 4) A few tests were conducted using larger than usual doses and the results supported previous findings that, for a maximal beneficial effect in response to a single dose, individuals may vary both with regard to the choice of drug and the amount administered.

THE FACT that antimotion sickness drugs are effective in any motion environment implies that their effectiveness may be evaluated in any motion environment, but it must be kept in mind that persons may differ in their susceptibility to motion sickness under different stimulus conditions. We have exploited the advantages of a slow rotation room (SRR) in a laboratory setting for assessing antimotion sickness drugs (1). In a SRR, the stressor effect is trivial unless a person moves his head out of the plane of the room's rotation; hence, the experimenter can remain symptom-free while observing the subject, who is required to execute head movements in a standardized manner. Susceptibility to motion sickness was measured as a function of length of exposure using a stimulus of constant intensity, i.e., standardized head movements while rotating at a predetermined angular velocity. Subjects were given the drugs (usually *seven*) and placebos (three, regarded as drugs) according to a 10-unit Latin-square design using a double-blind technique. When the data from experiments on 60 subjects were summarized (2), ranking the drugs in terms of their antimotion sickness effectiveness tended

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to place them in classes according to their pharmacological activity, an observation that supported the validity of the procedure used. Moreover, there was a clear indication that beneficial effects were related to central parasympatholytic and symathomimetic actions.

Shortcomings in the method were also revealed, attributable in part to the necessity of having subjects serve as their own controls, in part to a low ceiling on the test (nonmotion sickness endpoint), and in part to the fact that the results, while valid for the group of subjects, varied in their validity for individuals within the group. This report describes three experiments directed at overcoming these handicaps and also provides new information on representative antimotion sickness drugs.

EXPERIMENT I

MATERIALS AND METHODS

Subjects: For participation as paid volunteers, 14 men, 21 to 28 years of age, were selected. All were college students and selected from among a larger number on the basis of a comprehensive medical evaluation and the absence of vestibular defects based on specific tests on canalicular, otolithic, and combined vestibular functions. Persons with exceptionally high or low susceptibility to motion sickness were not accepted.

The Stress Profile: Stressful types of accelerative stimuli were generated by the active rotation of the subject's head and body out of the plane of the room's rotation, which was always counterclockwise. The head movements were executed while the subject (tested individually) was seated in a specially designed chair (Fig. 1) that had adjustable pads front, back, left, and right, acting as "stops" limiting head movements in the four quadrants to 90°. Head movements "over" and "back" in the four cardinal directions were randomized and a taped recording set the cadence at one movement every 2 s (3). Forty head movements were executed at 1 r.p.m. and were repeated at 1 r.p.m. increments in angular velocity (standardized at 40 seconds) until either the ceiling on the test, 30 rpm, or the motion sickness endpoint (defined below) was reached. If the motion sickness endpoint was reached prior to the execution of 40 head movements, it presented a minor problem in scoring; sometimes it was convenient and more accurate to deal with the number of head movements rather than r.p.m., but usually the score was measured in 0.1 r.p.m.'s (four head movements) and added to the completed r.p.m. score.

Scoring the Severity of Motion Sickness: The observer, in collaboration with the subject, estimated the levels of severity of the symptoms after every set of 40 head movements; the 40-s intervals during change in r.p.m. were for this purpose. The levels of severity of motion sickness were given numerical scores according to the diagnostic criteria in Table I (4). In Experiment I, the motion sickness endpoint was either slight nausea or 12 points, whichever came first. Subjects rarely gave the

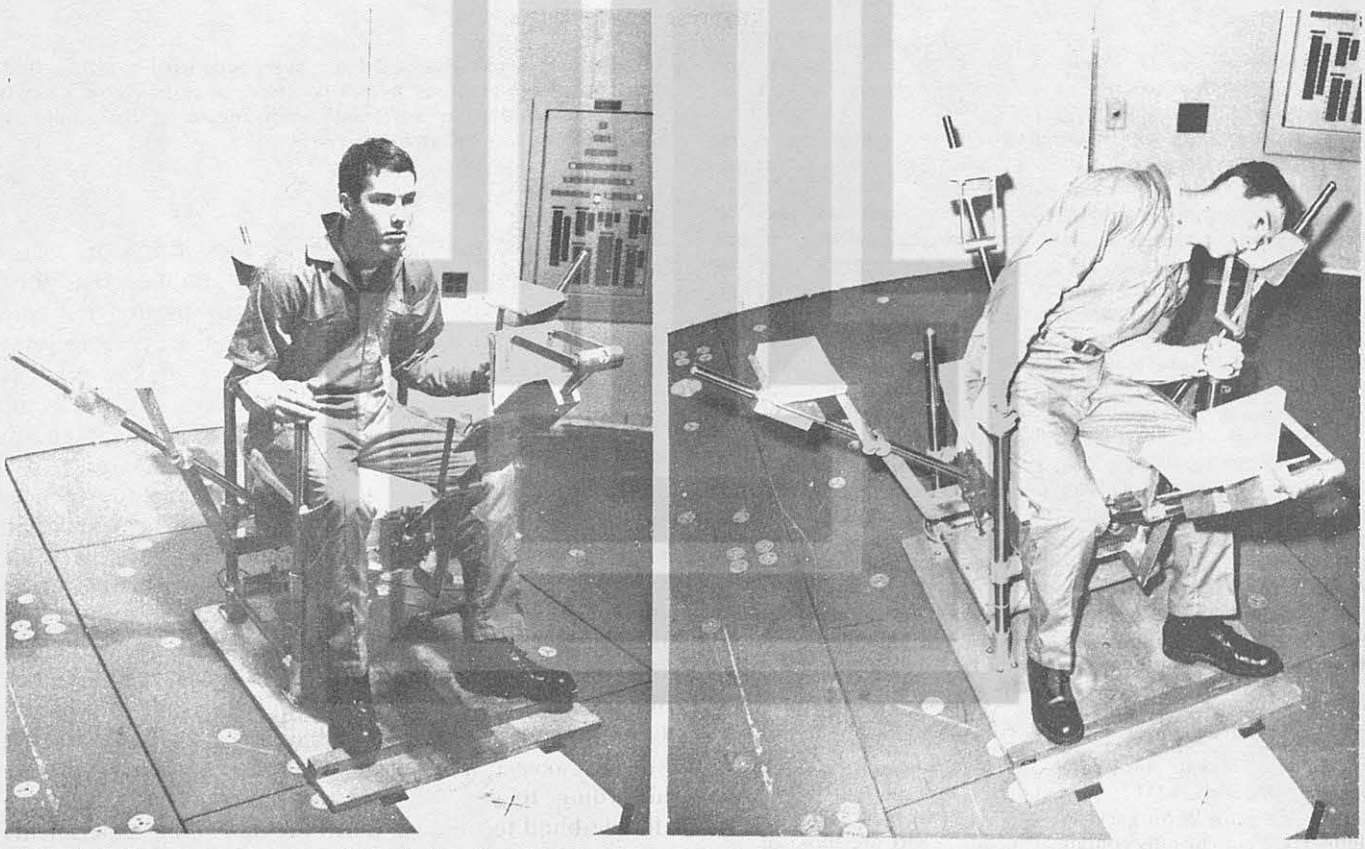

Fig. 1. Subject seated on a specially designed chair in a slow rotation room. The hand holds facilitate the execution of head movements and the adjustable stops ensure control over the arc of rotation.

TABLE I. DIAGNOSTIC CATEGORIZATION OF DIFFERENT LEVELS OF SEVERITY OF ACUTE MOTION SICKNESS.

Category	Pathognomonic 16 Points	Major 8 Points	Minor 4 Points	Minimal 2 Points	AQS* 1 Point
Nausea syndrome	Nausea III,† retching or vomiting	Nausea II	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing/Subjective warmth ≥II
Cold sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Headache (persistent) ≥II
Central nervous system					Dizziness (persistent)
					Eyes closed ≥II
					Eyes open III

Levels of Severity Identified by Total Points Scored				
Frank Sickness (FS) ≥ 16 points	Severe Malaise (M III) 8-15 points	Moderate Malaise A (M IIA) 5-7 points	Moderate Malaise B (M IIB) 3-4 points	Slight Malaise (M I) 1-2 points

* AQS = Additional qualifying symptoms
† III = severe or marked, II = moderate, I = slight

signal to stop a test before a motion sickness endpoint was reached; this only occurred at high r.p.m.

Drugs and Their Administration: The following drugs were chosen for evaluation, based mainly on previous findings (2,5) demonstrating their effecacy:

1) l-scopolamine hydrobromide (0.6 mg)
2) dimenhydrinate (50 mg)
3) d-amphetamine sulfate (10 mg)
4) l-scopolamine (0.3 mg) + d-amphetamine sulfate (5 mg)
5) l-scopolamine (0.6 mg) + d-amphetamine sulfate (10 mg)
6) dimenhydrinate (50 mg) + ephedrine sulfate (50 mg)
7) promethazine hydrochloride (25 mg) + ephedrine sulfate (50 mg)

Ten of the 14 subjects were fitted into a 10-unit Latin-square design that was typical, except that two extra placebos were added as tests No. 1 and No. 12. When these additions resulted in a series of three placebos, the opportunity was taken to substitute a drug for a placebo. The four "extra" subjects were treated as Subjects 1-4 in a second 10-unit Latin-square design.

Measuring the Effect of a Drug on Motion Sickness Susceptibility: Taking account of variations in placebo responses always posed a problem, and the following criteria were used in establishing a placebo baseline or "level": 1) when the variations were similar and small, i.e., ≤2 r.p.m., a mean value level baseline was used; 2) when there was a rise or fall in placebo scores but the variation was relatively small (≤3 r.p.m.) the placebo level was indicated by one or more best-fit sloped baselines. When the variations in placebo scores were greater than 3 r.p.m., the placebo level was estimated using the placebo score immediately preceding a particular test score, keeping in mind evidence of adaptation effects. First, the extremes of the placebo range were estimated and the mean placebo level or baseline identified. Next, the range for "inconsequential" motion sickness response was defined as lying within limits representing twice the values of the placebo range. To qualify as a "beneficial" effect, the difference between the placebo baseline score and the motion sickness endpoint score had to equal or exceed twice the difference in r.p.m. between the placebo baseline and the score indicating the upper limit of the inconsequential range. When the motion sickness endpoint score equaled or exceeded twice the difference between the placebo baseline and the lower limit of the inconsequential range the therapeutic effect was termed "detrimental."

Plan: There was an initial period of familiarization that included provocative tests in the SRR designed to determine susceptibility of motion sickness. Subjects reported at 0730 hours without breakfast and were given 4 oz of orange juice and a small package of crackers. Prior to each test, the subject was interviewed with the aid of a "pre-experiment questionnaire" to ensure that he was fit for the test that day. At 60 min prior to testing, the capsule containing the drug or placebo was given along with a tablespoon of applesauce if desired. At least 48 h elapsed between tests: this period varied from 2-14 d and was usually 2-5 d. Much of the adaptation acquired in a brief test decays in a period of 2 d; at worst, variations in the intervals between tests only adds to the difficulty in drawing a placebo level or baseline.

RESULTS AND DISCUSSION

One subject failed to complete the experiment, one required an operation unrelated to the study and was forced to withdraw, and another was dropped for lack of motivation. The findings on 11 subjects are presented in Table II. An estimate of the placebo level was impossible in two tests. In three more instances, the 30-r.p.m. ceiling on the test was reached before the motion sickness endpoint. In these and subsequent instances, the sign for "greater than," >, is used before the notation of "change" in r.p.m. and "percent change in r.p.m."

TABLE II. INDIVIDUAL RESPONSES TO SEVEN DIFFERENT ANTIMOTION SICKNESS DRUGS (EXPERIMENT I).

Subject	Drug 1. Scopolamine (0.6 mg)					Drug 2. Dimenhydrinate (50 mg)					Drug 3. Amphetamine (10 mg)					Drug 4. Scopolamine (0.3 mg) + Amphetamine (5 mg)				
	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance[2] of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of r.p.m. Change
	I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo			
	r.p.m.[1]	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%	
1	20.0	[3]				19.0	11.3	+7.7	+68	B	[5]					21.0	[3]			
2	22.0	12.2	+9.8	+80[7]	B	17.0	11.0	+6.0	+55	B	13.0	11.4	+ 1.6	+14	I	16.0	11.0	+5.0	+45	B
3	17.0	13.0	+4.0	+30	B	10.0	13.0	−3.0	−23	D	14.0	11.0	+ 3.0	+27	B	10.0	12.0	−2.0	−17	D
4	15.0	13.4	+1.6	+12	I	16.0	15.6	+0.4	+ 3	I	14.0	14.9	− 0.9	− 6	I	11.0	14.5	−3.5	−25	D
5	15.0	16.0	−1.0	− 6	I	16.0	18.6	−2.6	−14	I	30.0[6a]	19.5	>+10.5	>+54	B	21.0	13.2	+7.8	+59	B
6	27.0	22.7	+4.3	+19	B	25.0[4]	23.0				24.0[4]	20.0				21.0	22.4	−1.4	− 6	I
7	22.0	13.0	+9.0	+69	B	23.0	18.0	+5.0	+28	B	18.0	16.2	+ 1.8	+11	I	17.0	15.0	+2.0	+13	I
8	15.0	13.0	+2.0	+15	B	19.0	11.5	+7.5	+65	B	13.0	13.0	0	0	I	14.0	11.0	+3.0	+27	B
9	13.0	11.0	+2.0	+18	I	17.0	12.0	+5.0	+41	B	12.0	13.0	− 1.0	− 8	I	16.0	10.0	+6.0	+60	B
10	12.0	11.0	+1.0	+ 9	I	17.0	15.8	+1.2	+ 8	I	12.0	11.0	+ 1.0	+ 9	I	18.0	18.4	−0.4	− 2	I
11	11.0	11.0	0	0	I	8.0	11.0	−3.0	−27	D	13.0	11.0	+ 2.0	+18	B	11.0	11.0	0	0	I
	n = 10				B I D	n = 10				B I D	n = 9				B I D	n = 10				B I D
$\bar{X}$ =	16.9	13.6	+3.3	+24	50% 50% 0%	16.2	13.8	+2.4	+17	50% 30% 20%	15.4	13.4	>+ 2.0	>+15	33% 67% 0%	15.5	13.9	+1.6	+12	40% 40% 20%

Subject	Drug 5. Scopolamine (0.6 mg) + Amphetamine (10 mg)					Drug 6. Dimenhydrinate (50 mg) + Ephedrine (50 mg)					Drug 7. Promethazine (25 mg) + Ephedrine (50 mg)					B	I	D
1	12.0	11.3	+ 0.7	+ 6	I	15.0	11.3	+ 3.7	+33	B	17.0	11.3	+5.7	+50	B	3	1	0
2	13.0	10.0	+ 3.0	+30	B	12.0	13.0	− 1.0	− 8	I	15.0	10.7	+4.3	+40	B	5	2	0
3	13.0	13.0	0	0	I	13.0	10.0	+ 3.0	+30	B	20.0	13.0	+7.0	+54	B	4	1	2
4	16.0	14.7	+ 1.3	+ 9	I	15.0	15.3	− 0.3	− 2	I	19.0	12.0	+7.0	+58	B	1	5	1
5	30.0[6b]	17.2	>12.8	>+74	B	12.0	14.6	− 2.6	−18	I	11.0	12.0	−1.0	− 8	I	3	4	0
6	26.0	22.8	+ 3.2	+14	B	27.0	22.5	+ 4.5	+20	B	25.0[4]	22.2				3	1	0
7	16.0	14.0	+ 2.0	+14	I	23.5	18.2	+ 5.3	+31	B	21.0	16.5	+4.5	+27	B	4	3	0
8	18.0	13.0	+ 5.0	+39	B	13.0	12.0	+ 1.0	+ 8	I	15.0	13.0	+2.0	+15	B	5	2	0
9	17.0	13.3	+ 3.7	+28	B	18.0	13.7	+ 4.3	+31	B	19.0	14.0	+5.0	+36	B	5	2	0
10	21.0	13.4	+ 7.6	+57	B	30.0	20.0	+10.0	+50	B	30.0[6c]	21.0	>+9.0	>+43	B	3	4	0
11	9.0	11.0	− 2.0	−18	D	11.0	11.0	0	0	I	9.0	11.0	−2.0	−18	D	1	3	3
	n = 11				B I D	n = 11				B I D	n = 10				B I D	n = 71		
$\bar{X}$ =	17.3	14.0	>+ 3.4	>+24	55% 36% 9%	17.2	14.7	+ 2.5	+17	55% 45% 0%	17.6	13.5	>+4.1	>+30	80% 10% 10%	B 52%	I 39%	D 9%

1 r.p.m. = revolutions per minute
2 B = beneficial; I = inconsequential; D = detrimental. See text.
3 No placebo baseline could be reasonably determined.
4 Subject did not reach endpoint because he complained of dizziness.
5 Subject did not receive this drug.
6 r.p.m. ceiling. Motion sickness scores: 6a = 10 points, 6b = 6 points, 6c = 9 points
7 ___ = subject's best response. D = detrimental response

Note in Table II that the difference between the r.p.m.'s representing the drug and placebo scores is also expressed as a percent and that the efficacy of the drug is categorized as beneficial (B), inconsequential (I) or detrimental (D). For each subject, the drug demonstrating the highest efficacy is underlined and the bold Ds are used to indicate detrimental responses. The striking feature in Table II is the great intra- and interindividual differences in response to drugs generally regarded as effective in preventing motion sickness. Subject 11 manifested only one beneficial response (following the administration of 10 mg amphetamine), and he accounted for three of the six detrimental responses. Subject 4 also manifested only one beneficial response (with 25 mg promethazine and 50 mg ephedrine) and accounted for one detrimental response (with 0.3 mg scopolamine and 5 mg amphetamine). Subjects 2, 8, and 9 manifested five beneficial responses, the first two in response to administration of the same drugs. It is noteworthy that the single best therapeutic response elicited in the 11 subjects involved all seven drugs.

When the subjects are considered as a group, the number of beneficial responses ranged from 33% (10 mg amphetamine) to 80% (25 mg promethazine and 50 mg ephedrine) and the average for all treatments was 52%.

EXPERIMENT II

In this experiment some procedural changes were introduced and half of the treatments involved promethazine and ephedrine.

MATERIALS AND METHODS

The procedure described in Experiment I was used with the following changes:

Subjects: To serve as paid volunteer subjects, 11 male students, 21 to 24 years of age, were selected but two soon withdrew because our schedule did not fit theirs.

Motion Sickness Endpoint: A score of 11 points, which must include at least 2 points (stomach discomfort) in the nausea syndrome, was used.

Drugs and Administration: The following drugs were given:

1) l-scopolamine hydrobromide (0.6 mg)
2) dimenhydrinate (50 mg)
3) promethazine hydrochloride (25 mg)
4) d-amphetamine (10 mg)
5) ephedrine sulfate (50 mg)
6) l-scopolamine hydrobromide (0.6 mg) + d-amphetamine sulfate (10 mg)
7) dimenhydrinate (50 mg) + ephedrine sulfate (50 mg)
8) promethazine hydrochloride (25 mg) + ephedrine sulfate (50 mg)

Modified (4 unit) Latin-squares were designed with five placebos arbitrarily placed, one at the start and finish and one separating every pair of drugs.

Plan: The tests were conducted every other day in order to meet scheduling requirements. Subjects were requested to appear 2 h 15 min before the test and to refrain from drinking alcoholic beverages beginning the afternoon prior to testing. The drug or placebo was always administered 2 h before testing to ensure efficient time for absorption. Orange juice and crackers were available if desired when the drugs were administered in order to avoid complaints that a drug "upset" their stomach.

RESULTS AND DISCUSSION

One subject withdrew from the experiment after experiencing a "dizzy spell" during the fourth test at 24 r.p.m.

Table III shows that, on six of the drug assays, the 30 r.p.m. ceiling on the test was reached before elicitation of the motion sickness endpoints. This problem was handled in the manner described in Experiment I. Three aborts resulted from unexplained loss of power in the SRR; placebos had been administered in all of these instances and a satisfactory estimate of the placebo level could be made except in Subject 13.

The individual variations in response to treatments were less striking than in Experiment I. Beneficial responses ranged from 25% in Subject 19, who also accounted for the only detrimental response, to 100% in Subject 15; the average for all subjects was 65%.

For the eight subjects who completed the experiment, the beneficial responses ranged from 37% for 10 mg amphetamine to 87% for the combination of 25 mg promethazine and 50 mg ephedrine. Neither 10 mg amphetamine nor 50 mg ephedrine preparations, but all of the remaining six drugs, accounted for the "highest efficacy" ratings.

EXPERIMENT III

In this experiment, an effort was made 1) to reduce the number of tests in which the motion sickness endpoint was not reached by increasing the intensity of the stressor, 2) to improve the measurement of the placebo baselines by increasing the number of placebos, and 3) to test the efficacy of the drug combination promethazine-ephedrine when the amount of ephedrine was halved.

MATERIALS AND METHODS

Subjects: Paid volunteer subjects were 12 male students, 19 to 28 years of age. They comprised part of a pool of 20 subjects who were available for a 6-week experiment. The medical assessment used was the same as that in Experiments I and II. None was selected on the basis of susceptibility of motion sickness. All had participated in experiments, however, involving the execution of head movements in the SRR. All agreed to refrain from the use of drugs, including alcohol, during the experimental period.

The Stress Profile: The stress profile differed from those previously used in one important respect, namely, the cadence was set at 4s, i.e., each discrete head movement was executed in the usual manner followed by a delay together totaling 4 s. This cadence was chosen after experimental probes indicated that the 4 s cadence was more stressful than 1-, 2-, or 3-s cadences (findings to be published elsewhere).

The Endpoints: The motion sickness endpoint was set

TABLE III. INDIVIDUAL RESPONSES TO EIGHT DIFFERENT ANTIMOTION SICKNESS DRUGS (EXPERIMENT II).

Subject	Drug 1. Scopolamine (0.6 mg)					Drug 2. Dimenhydrinate (50 mg)					Drug 3. Promethazine (25 mg)					Drug 4. Amphetamine (10 mg)				
	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance[2] of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	Motion Sickness Endpoint		Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change
	I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo			
	r.p.m.[1]	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%	
12	13.0	9.0	+ 4.0	+44[5]	B	11.0	9.0	+ 2.0	+ 22	B	10.0	9.0	+1.0	+11	I	9.0	9.0	0	0	I
13	28.0	16.5	+11.5	+70	B	24.0	[4]				24.0	20.0	+4.0	+20	B	18.0	18.0	0	0	I
14	30.0[3a]	22.6	> + 7.4	> +33	B	30.0[3b]	22.0	> + 8.0	> + 36	B	22.0	19.0	+3.0	+16	I	23.0	17.0	+ 6.0	+35	B
15	24.0	14.4	+ 9.6	+67	B	28.0	13.0	+15.0	+116	B	24.0	15.0	+9.0	+60	B	21.0	16.0	+ 5.0	+31	B
16	16.0	14.3	+ 1.7	+12	B	15.0	14.3	+ 0.7	+ 5	I	15.0	14.3	+0.7	+ 5	I	17.0	14.3	+ 2.7	+19	B
17	9.0	10.0	− 1.0	−10	I	13.0	9.0	+ 4.0	+ 44	B	13.0	11.0	+2.0	+18	I	12.0	10.0	+ 2.0	+20	I
18	15.0	11.8	+ 3.2	+27	B	17.0	13.0	+ 4.0	+ 31	B	17.0	13.0	+4.0	+31	B	13.0	11.6	+ 1.4	+12	I
19	8.0	8.0	0	0	I	6.0	8.0	− 2.0	− 25	D	10.0	8.0	+2.0	+25	B	8.0	8.0	0	0	I
	n = 8				B I D	n = 7				B I D	n = 8				B I D	n = 8				B I D
$\bar{X}$ =	17.9	13.3	> + 4.6	> +35	75% 25% 0%	17.1	12.6	> + 4.5	> + 36	72% 14% 14%	16.9	13.7	+3.2	+23	50% 50% 0%	15.1	13.0	+ 2.1	+16	37% 63% 0%

Subject	Drug 5. Ephedrine (50 mg)					Drug 6. Scopolamine (0.6 mg) + Amphetamine (10 mg)					Drug 7. Dimenhydrinate (50 mg) + Ephedrine (50 mg)					Drug 8. Promethazine (25 mg) + Ephedrine (50 mg)					B	I	D
	I Drug	II Placebo	Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	I Drug	II Placebo	Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	I Drug	II Placebo	Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change	I Drug	II Placebo	Column I minus Column II	r.p.m. Change	Significance of r.p.m. Change			
	r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%		r.p.m.	r.p.m.	r.p.m.	%				
12	10.0	9.0	+ 1.0	+11	I	13.0	9.0	+ 4.0	+ 44	B	9.0	9.0	0	0	I	11.0	9.0	+ 2.0	+22	B	4	4	0
13	17.0	19.0	− 2.0	−10	I	30.0[3c]	16.0	>+14.0	> + 88	B	24.0	20.0	+4.0	+20	B	30.0[3e]	17.0	> +13.0	> +76	B	5	2	0
14	23.0	20.4	+ 2.6	+13	I	30.0[3d]	24.2	> + 5.8	> + 24	B	26.0	18.0	+8.0	+44	B	30.0[3f]	21.5	> + 8.5	> +40	B	6	2	0
15	21.0	16.4	+ 4.6	+28	B	24.0	13.5	+10.5	+ 78	B	23.0	16.0	+7.0	+44	B	21.0	14.0	+ 7.0	+50	B	8	0	0
16	19.0	14.3	+ 4.7	+33	B	22.0	14.3	+ 7.7	+ 54	B	22.0	14.3	+7.7	+54	B	18.0	14.3	+ 3.7	+26	B	6	2	0
17	12.0	9.0	+ 3.0	+33	B	15.0	8.0	+ 7.0	+ 88	B	15.0	9.4	+5.6	+60	B	15.0	9.9	+ 5.1	+52	B	5	3	0
18	15.0	12.5	+ 2.5	+20	B	11.0	11.2	− 0.2	− 2	I	11.0	11.0	0	0	I	15.0	12.0	+ 3.0	+25	B	5	3	0
19	8.0	8.0	0	0	I	7.0	8.0	− 1.0	− 13	I	12.0	8.0	+4.0	+50	B	9.0	8.0	+ 1.0	+13	I	2	5	1
	n = 8				B I D	n = 8				B I D	n = 8				B I D	n = 8				B I D	n = 63		
$\bar{X}$ =	15.6	13.6	+ 2.0	+15	50% 50% 0%	19.0	13.0	> + 6.0	> + 46	75% 25% 0%	17.7	13.2	+4.5	+34	75% 25% 0%	18.6	13.2	> + 5.4	> +41	87% 13% 0%	B 65%	I 33%	D 2%

[1] r.p.m. = revolutions per minute

[2] B = beneficial; I = inconsequential; D = detrimental. See text.

[3] r.p.m. ceiling. Motion sickness scores: 3a = 6 points; 3b = 7 points; 3c = 11 points; 3d = 3 points; 3e = 6 points; 3f = 5 points

[4] Placebo test inconclusive due to device control problem.

[5] ___ = subject's best response; **D** = detrimental response.

at 12 points or slight nausea, whichever came first. The r.p.m. ceiling on the test was reached after execution of 40 head movements at 30 r.p.m.

Drugs: The following drugs were used:

1) l-scopolamine hydrobromide (0.3 mg)
2) l-scopolamine hydrobromide (0.6 mg)
3) ephedrine sulfate (25 mg)
4) l-scopolamine hydrobromide (0.3 mg) + d-amphetamine sulfate (5 mg)
5) l-scopolamine hydrobromide (0.3 mg) + ephedrine sulfate (25 mg)
6) l-scopolamine hydrobromide (0.6 mg) + d-amphetamine sulfate (5 mg)
7) dimenhydrinate (50 mg) + ephedrine sulfate (25 mg)
8) promethazine hydrochloride (25 mg) + ephedrine sulfate (25 mg)

Plan: The 12 subjects were divided into Groups A, B, and C, and the drugs were administered in a modified 5-unit Latin-square design, with a placebo intervening between each pair of drugs and with two placebos before the first and two after the last drug administered in each series. The design for Group C was the same as for Group A. The groups were staggered so that beginning with the fifth day one group was tested every third day.

The subjects were assigned bunks in a ward adjacent to the SRR the evening before the test-day. The next morning, tests were conducted at 2-h intervals beginning at 0800 hours. Prior to administering the capsule 2 h before the test, the subject completed a "pre-experiment" questionnaire; 30 min before the test, the subject was queried in order to learn if side effects were being experienced. The subject was interviewed immediately after the test, with the aid of a questionnaire, and again before departure; usually 2 h after the test.

RESULTS AND DISCUSSION

The findings in Table IV show at a glance the number of tests involving drugs that either were not carried out or in which problems were encountered: 1) Subject 25 was injured falling off a horse, 2) Subject 29 was ill, and 3) two envelopes containing the correct drug were switched in one series. This experimenter-error, involving the combination 0.6 mg scopolamine and 5 mg amphetamine, and the single drug 25 mg ephedrine, resulted in Subjects 21 and 23 receiving two doses of one drug and none of the other.

But by far the most important difficulty involved Subjects 21 and 22 who quickly reached the ceiling on the test. In the first two baseline tests when placebos were given, the mean motion sickness endpoints were, respectively, 11 and 14 r.p.m. However, in the third and fourth tests, respectively, these subjects reached the test ceiling without scoring any motion sickness points implying that either they adapted with unusual rapidity to the motion environment or the drugs were highly efficacious. In the third test, when 0.3 mg scopolamine + 5 mg amphetamine was administered to Subject 21, the ceiling on the test was reached. Subject 22 reached the ceiling on the fourth test when 0.3 mg scopolamine was given. In view of these responses, a change in procedure was made in the hope of reducing the acquisition of adaptation effects, namely, arbitrarily stopping the test when the r.p.m. was 10 above the placebo level. This arbitrary halting of a test was quickly abandoned when the ceiling on the test was reached even when placebos were administered. Subjects 21 and 22 remained participants in the experiments, using the scoring procedure described in Experiment I, but in retrospect such subjects could be tested more advantageously with more stressful stimuli or with a longer period between tests to permit decay of adaptation effects.

The beneficial responses ranged from 25% to 87% of the treatments; Subject 23 (100% efficacy) is not included because he failed to receive 25 mg ephedrine, the least efficacious preparation. On one or more occasions, six of the eight drugs, except scopolamine (0.3 mg) and ephedrine (25 mg), provided the highest efficacy ranking. It is worth noting that, although the single drug ephedrine (25 mg) accounted for only one beneficial response when administered to 10 subjects, the combination promethazine and ephedrine (25 mg of each) was the most effective among the eight preparations tested.

After completion of the last test in the series, each subject was interviewed with the aid of the questionnaire completed in connection with the 15 tests. A table was prepared (not shown) based on replies to the question, "Was a drug or placebo administered?" About two-thirds of the replies were correct for placebos about one-half for drugs. There were individual variations; e.g., two subjects nearly always thought they had taken a drug and three thought they had always, or nearly always, taken a placebo.

Possible Interactions Between Antimotion Sickness Remedies and Other Psychoactive Drugs: After Experiment III was underway, we began to suspect that certain subjects were drug users. This conclusion was based partly on their appearance and behavior and partly on the experimental findings. These subjects were the opposite of active, alert, and interested subjects, thus differing from other members of the group, and the effectiveness of some antimotion sickness drugs was less than expected.

After completion of the 15 scheduled tests, interviews brought out the fact that some of the subjects had indeed used marijuana in the past and two admitted they had not completely discontinued its use during the test period. It probably should be said in passing that there was almost no difficulty eliciting this information; most of the users were of the opinion that marijuana was less harmful than alcohol. Some additional tests were carried out with these subjects using higher doses than in Experiment III, and the results are summarized in Table V.

In this series of tests there was little, if any, change in the placebo baselines when compared with the baselines in the "regular" series. In general, there was increased effectiveness with increased doses. None of the responses was detrimental and, among the drugs demonstrating beneficial effects, the scopolamine and amphetamine combinations were outstanding.

Subject A took scopolamine (1.2 mg) and amphe-

TABLE IV. INDIVIDUAL RESPONSES TO EIGHT DIFFERENT ANTIMOTION SICKNESS DRUGS (EXPERIMENT III).

Subject	Drug 1. Scopolamine (0.3 mg)					Drug 2. Scopolamine (0.6 mg)					Drug 3. Ephedrine (25 mg)					Drug 4. Scopolamine (0.3 mg) + Amphetamine (5 mg)					B	I
	Motion Sickness Endpoint I Drug r.p.m.[1]	Motion Sickness Endpoint II Placebo r.p.m.	Column I minus Column II r.p.m.	r.p.m. Change %	Significance[2] of r.p.m. Change	Motion Sickness Endpoint I Drug r.p.m.	Motion Sickness Endpoint II Placebo r.p.m.	Column I minus Column II r.p.m.	r.p.m. Change %	Significance of r.p.m. Change	Motion Sickness Endpoint I Drug r.p.m.	Motion Sickness Endpoint II Placebo r.p.m.	Column I minus Column II r.p.m.	r.p.m. Change %	Significance of r.p.m. Change	Motion Sickness Endpoint I Drug r.p.m.	Motion Sickness Endpoint II Placebo r.p.m.	Column I minus Column II r.p.m.	r.p.m. Change %	Significance of r.p.m. Change		
20	8.3	5.8	+2.5	+43	B	10.2	5.8	+ 4.4	+76[12]	B	5.2	5.8	− 0.6	−10	I	7.5	5.8	+ 1.7	+ 29	I		
21	28.0[3]	21.0[4a]	>+7.0	>+33	B	21.0[4b]	11.0	>+10.0	>+91	B	19.0	18.5	+ 0.5	+ 3	I	21.0[4c]	11.0	>+10.0	>+ 91	B		
22	24.0[4f]	17.2	>+6.8	>+39	B	30.0[4g]	20.0	>+10.0	>+50	B	30.0[4h]	25.2	>+ 4.8	>+19	I	28.7[7]	21.3	>+ 7.4	>+ 35	B		
23	10.8	6.3	+4.5	+71	B	8.3	6.3	+ 2.0	+32	B	[5]					10.0	6.3	+ 3.7	+ 59	B		
24	15.0	15.0	0	0	I	11.0	12.8	− 1.8	−14	I	16.0	13.1	+ 2.9	+22	I	11.0	13.7	− 2.7	− 20	I		
25	[10]					5.4	4.2	+ 1.2	+29	I	3.5	4.2	− 0.7	−17	I	5.3	4.2	+ 1.1	+ 26	I		
26	15.1	10.8	+4.3	+40	B	15.2	10.8	+ 4.4	+41	B	10.3	10.8	− 0.5	− 5	I	17.1	10.8	+ 6.3	+ 58	B		
27	19.0	13.0	+6.0	+46	B	24.0	15.0	+ 9.0	+60	B	15.0	14.0	+ 1.0	+ 7	I	18.0	11.0	+ 7.0	+ 64	B		
28	9.0	8.0	+1.0	+13	B	6.0	5.5	+ 0.5	+ 1	I	6.7	5.5	+ 1.2	+22	B	9.0	8.0	+ 1.0	+ 13	B		
29	7.9	7.4	+0.5	+ 1	I	6.3	6.3	0	0	I	[11]					11.2	5.1	+ 6.1	+120	B		
30	11.0	10.0	+1.0	+10	I	15.0	8.0	+ 7.0	+87	B	10.0	9.7	+ 0.3	+ 3	I	17.5	9.0	+ 8.5	+ 94	B		
31	5.7	5.6	+0.1	+ 2	I	7.6	5.6	+ 2.0	+36	B	5.1	5.6	− 0.5	− 9	I	6.7	5.6	+ 1.1	+ 20	I		
	n = 11				B I	n = 12				B I	n = 10				B I	n = 12				B I		
$\bar{X}$ =	14.0	10.9	>+3.1	>+28	64% 36%	13.3	9.3	>+ 4.0	>+43	67% 33%	12.1	11.2	>+ 0.9	>+ 8	10% 70%	13.8	9.3	>+ 4.5	>+ 48	67% 33%		

Subject	Drug 5. Scopolamine (0.3 mg) + Ephedrine (25 mg)					Drug 6. Scopolamine (0.6 mg) + Amphetamine (5 mg)					Drug 7. Dimenhydrinate (50 mg) + Ephedrine (25 mg)					Drug 8. Promethazine (25 mg) + Ephedrine (25 mg)					B	I
20	8.5	5.8	+2.7	+47	B	7.1	5.8	+ 1.3	+22	I	6.5	5.8	+ 0.7	+12	I	7.6	5.8	+ 1.8	+ 31	I	3	5
21	30.0[4d]	21.0	>+9.0	>+43	B	[5]					19.0[6]	17.0	+ 2.0	+12	I	30.0[4e]	16.8	>+13.2	>+ 79	B	5	2
22	22.0[8]	13.9	+8.1	+58	B	30.0[4i]	18.0	>+12.0	>+67	B	26.0[9]	15.7	>+10.3	>+66	B	30.0	22.0	+ 8.0	+ 36	B	7	1
23	9.9	6.3	+3.6	+57	B	9.6	6.3	+ 3.3	+52	B	12.0	6.3	+ 5.7	+91	B	8.3	6.3	+ 2.0	+ 32	B	7	0
24	16.0	13.0	+3.0	+23	I	19.0	15.0	+ 4.0	+27	B	14.0	13.0	+ 1.0	+ 8	I	16.0	11.0	+ 5.0	+ 46	B	2	6
25	[10]					7.1	4.2	+ 2.9	+69	B	4.3	4.2	+ 0.1	+ 2	I	7.0	4.2	+ 2.8	+ 67	B	2	4
26	15.0	10.8	+4.2	+39	B	14.4	10.8	+ 3.6	+33	B	11.2	10.8	+ 0.4	+ 4	I	13.0	10.8	+ 2.2	+ 20	B	6	2
27	20.0	13.0	+7.0	+54	B	19.0	14.5	+ 4.5	+31	B	18.0	15.0	+ 3.0	+20	B	25.0	14.5	+10.5	+ 72	B	7	1
28	8.0	8.0	0	0	I	5.0	5.5	− 0.5	− 1	I	6.0	5.5	+ 0.5	+ 1	I	7.0	5.5	+ 1.5	+ 27	B	4	4
29	9.1	7.4	+1.7	+23	B	9.1	6.7	+ 2.4	+36	B	7.6	6.7	+ 0.9	+13	B	11.1	6.7	+ 4.4	+ 66	B	5	2
30	30.0[4j]	12.0	+18.0	+150	B	17.0	9.0	+ 8.0	+89	B	12.0	8.0	+ 4.0	+50	B	15.0	10.0	+ 5.0	+ 50	B	6	2
31	8.0	5.6	+2.4	+43	B	6.6	5.6	+ 1.0	+18	I	6.1	5.6	+ 0.5	+ 9	I	9.5	5.6	+ 3.9	+ 70	B	3	5
	n = 11				B I	n = 11				B I	n = 12				B I	n = 12				B I	n = 91	
$\bar{X}$ =	16.0	10.6	>+5.4	>+51	82% 18%	13.1	9.2	>+ 3.9	>+42	73% 27%	11.9	9.5	>+ 2.4	>+25	42% 58%	15.0	10.0	>+ 5.0	>+ 50	92% 8%	63%	37%

[1] r.p.m. = revolutions per minute.
[2] B = beneficial; I = inconsequential. See text.
[3] Subject 21 did not reach endpoint because he complained of "arm and back fatigue." Motion sickness score: No points.
[4] r.p.m. ceiling. Motion sickness scores: 4a = 2 points; 4b = 2 points; 4c = 2 points; 4d = 11 points; 4e = 3 points; 4f = 8 points; 4g = no points; 4h = 11 points; 4i = 9 points; 4j = 8 points.
[5] Experimenter error. See text.
[6] Subject 21 did not reach endpoint because he was extremely drowsy and fell asleep. Motion sickness score: 8 points.
[7] Subject 22 did not reach endpoint due to equipment failure. Motion sickness score: 3 points.
[8] Subject 22 did not reach endpoint because he complained of dizziness. Motion sickness score: 10 points.
[9] Subject 22 did not reach endpoint because he had urgent need to urinate. Motion sickness score: no points.
[10] Subject 25 missed due to injury.
[11] Subject 29 no test due to illness.
[12] ___ = subject's best response.

tamine (10 mg) on three occasions with excellent results, although after the first dose he complained of side-effects. His response to promethazine (100 mg) + ephedrine (50 mg) was not beneficial, although when small doses (25 mg of each) were administered in Experiment III a beneficial response was obtained.

Subject B on successive tests received, respectively, 10 and 20 mg of amphetamine; after administration of 10 mg there were no side-effects and after 20 mg he reported feeling a little "drowsy" and "groggy." The response to the larger dose was beneficial. In the regular series his response to scopolamine (0.6 mg) and amphetamine (5 mg) was not beneficial, but he manifested an excellent response when the doses were doubled.

Subject C demonstrated excellent responses to increased doses of all five drugs administered, including the only outstanding response to dimenhydrinate (100 mg) and ephedrine (50 mg).

Subject D in the regular series often manifested satisfactory responses in terms of percent of change in r.p.m., but the highest r.p.m. reached was 7.1 after taking scopolamine (0.6 mg) + amphetamine (5 mg). When the doses were doubled on two occasions he reached 9.1 r.p.m. in one test and 10.3 r.p.m. in the other.

In summary, the possibility has been raised that antimotion sickness drugs do not have the same effect on persons who use marijuana and those who do not. If subsequent studies confirm this conclusion it would still not be a surprising finding but its practical significance is self-evident.

GENERAL DISCUSSION

In the three experiments when the drugs were administered in usual doses, 225 tests were conducted involving 31 subjects; the responses were substantially beneficial in 135 tests, detrimental in 7 and inconsequential in 83. By assuming that the percent change in r.p.m. had similar interpretive validity in all three experiments, it is possible to extract some additional information from the combined data.

In Table VI, the 15 drugs administered are ranked in terms of group responses to their overall beneficial effectiveness. The weighted responses take into account detrimental effects; one detrimental effect is made the equivalent of two inconsequential effects. Attention is directed to the roles played by promethazine (bold Ps) and ephedrine (bold Es). In doses of 25 mg, the efficacy of ephedrine ranked last and promethazine was in a tie for ninth place but, combined, the overall effectiveness was outstanding; among 12 subjects, 11 manifested a substantially beneficial effect and in the remaining subject, the 31% increase in r.p.m. was just short of meeting the criterion for "beneficial." This combination of two homergic drugs clearly manifests suprasummation effects. The combination promethazine (25 mg) and ephedrine (50 mg) also was highly beneficial. Ephedrine participated in the combinations with the topmost three rankings and they comprised the only drugs beneficial in more than 75% of the subjects tested. Promethazine has long been used not only in the prevention of motion sickness (5,6) but also for the prevention of nausea and vomiting in patients (7). In contrast, ephedrine has been used only under experimental conditions (1,8) except in a fixed dose combination of 25 mg promethazine and 50 mg ephedrine in Skylab IV (9). A combination of 25 mg each promethazine and ephedrine has been used for relief of respiratory allergies (10).

Beneficial effectiveness, however, does not necessarily mean maximum effectiveness, shown in the last two columns in Table VI. It is seen that there are some important changes in rankings, the combination scopolamine (0.6 mg) plus amphetamine (10 mg) and dimenhydrinate (50 mg) demonstrating higher rankings and scopolamine (0.3 mg) alone or in combination with ephedrine (25 mg), lower ranking.

Table VII shows the four subjects and four drugs involved in seven substantially detrimental (bold Ds) responses. In these same subjects are shown, in parentheses, the responses that were not detrimental. Subject 3, whose responses were the least efficacious among the 31 subjects tested, differed from the others in having four beneficial responses; this was only very slightly below the average for the entire group. It is interesting that among Subject 3's four best responses, promethazine (25 mg) plus ephedrine (50 mg) ranked best. Moreover, Subject 3 manifested his only inconsequential response when scopolamine (0.6 mg) plus amphetamine (10 mg) was administered, indicating that the detrimental response with half the dose represented a valid test. The responses of Subject 4 closely resembled those of Subject 3. Subject 11, with the worst record in the entire group of 31 subjects, manifested only one beneficial response which followed the administration of amphetamine (10 mg). The responses of Subject 19 resembled those of Subject 11; his two beneficial responses, not shown in the table, followed the administration of promethazine (25 mg) and the combination dimenhydrinate (50 mg) plus ephedrine (50 mg). The latter was Subject 19's best response by far and strongly contrasts with his response to dimenhydrinate (50 mg) alone.

The possibility must be raised that differences in procedure accounted for six of the seven detrimental responses appearing in Experiment I. The most likely source of an error is in taking proper account of great variations in placebo responses, but in each instance these variations were small, hence did not pose a problem. The most reasonable explanation is based on individual differences in response. Although one may not draw a generalization from tests on a few subjects the findings strongly indicate that, even for highly efficacious antimotion sickness drugs, subjects show curious but consistent patterns in responses to these drug.

A table was prepared (not shown) that summarized the findings when the drug effects were inconsequential (neither substantially beneficial nor detrimental) and ranked their effectiveness for comparison with the rankings when the effects were beneficial. These inconsequential effects ranged from a 31% increase to a 20% decrease in r.p.m. The smaller the percentage of tests in the "inconsequential" category the higher the

TABLE V. SOME CHANGES IN EFFECTIVENESS OF DRUGS GIVEN IN HIGHER THAN USUAL DOSES.

Drug	Subject A			Subject B			Subject C			Subject D		
	Pretest Side Effects	Change in r.p.m.[1] % Significance[2]		Pretest Side Effects	Change in r.p.m. % Significance		Pretest Side Effects	Change in r.p.m. % Significance		Pretest Side Effects	Change in r.p.m. % Significance	
1. scopolamine (1.2 mg)							Dry mouth, "light-headed"	+112	B			
2. amphetamine (10 mg)				No side effects	+ 2	I						
3. amphetamine (20 mg)				"drowsy"	+36	B						
4. scopolamine (1.2 mg) + amphetamine (10 mg)	dizziness, dry mouth, "feel high"	+75	B	"light-headed"	+88	B	"light-headed"	+117	B	No side effects	+131	B
5. dimenhydrinate (100 mg) + ephedrine (50 mg)	"feel high"	+27	B	No side effects	+ 7	I	"lightheaded"	+ 88	B	drowsy, stomach awareness	+ 24	I
6. promethazine (50 mg) + amphetamine (10 mg)				"light-headed"	+104	B						
7. promethazine (50 mg) + ephedrine (25 mg)										drowsiness	+ 84	B
8. promethazine (50 mg) + ephedrine (50 mg)							No side effects	+ 88	B	"feel . . . pill"	+ 74	B
9. promethazine (100 mg) + ephedrine (50 mg)	No side effects	−9	I				"lightheaded"	+ 58	B			
10. promethazine (100 mg) + ephedrine (100 mg)				"light-headed"	+96	B						
Change in placebo level from Experiment III		r.p.m. −0.4			r.p.m. −1.6			r.p.m. −0.1			r.p.m. 0	

	Percent change in r.p.m.			Percent change in r.p.m.			Percent change in r.p.m.			Percent change in r.p.m.		
	Range		Mean	Range		Mean	Range		Mean	Range		Mean
Table IV (usual doses)	−1	+27	+ 9	−9	+70	+24	−10	+76	+31	−17	+69	+29
Table V (higher than usual doses)	−9	+75	+30	+2	+104	+55	+58	+117	+93	+24	+131	+78

[1] r.p.m. = revolutions per minute

[2] B = beneficial; I = inconsequential; none were detrimental. See text. 78% beneficial; 22% inconsequential.

TABLE VI. DRUGS RANKED IN TERMS OF PERCENT BENEFICIAL RESPONSES TO USUAL DOSES OF ANTIMOTION SICKNESS DRUGS ADMINISTERED IN THREE EXPERIMENTS. WEIGHTED RESPONSES TAKE ACCOUNT OF DETRIMENTAL EFFECTS: ONE DETRIMENTAL EFFECT EQUALS TWO INCONSEQUENTIAL EFFECTS. DRUGS ALSO RANKED IN TERMS OF HIGHEST R.P.M. ACHIEVED IN A TEST AND GREATEST % INCREASE IN R.P.M.

		Overall Beneficial Effectiveness				Maximal Effectiveness	
Drug	Number of Subjects	Unweighted Response %	Unweighted Response Rank	Weighted Response %	Weighted Response Rank	Terminal r.p.m. Rank	% Increase Rank
P (25 mg) E (25 mg)	12	92	1	92	1	4	1
P (25 mg) E (50 mg)	18	83	2	79	3	1	4
S (0.3 mg) E (25 mg)	11	82	3	82	2	10	9
S (0.6 mg) A (5 mg)	11	73	4	73	4	6	5
S (0.3 mg)	11	64	5	64	5	10	12
S (0.6 mg)	30	63	6	63	6	7	6
S (0.6 mg) A (10 mg)	19	63	6	63	6	2	2
D (50 mg) E (50 mg)	19	63	6	63	6	3	7
D (50 mg)	17	59	7	50	7	5	3
S (0.3 mg) A (5 mg)	22	55	8	50	7	8	5
P (25 mg)	8	50	9	50	7	9	8
E (50 mg)	8	50	9	50	7	13	12
D (50 mg) E (25 mg)	12	42	10	42	8	11	10
A (10 mg)	17	35	11	35	9	12	11
E (25 mg)	10	10	12	10	10	13	12

A = d-amphetamine sulfate; D = dimenhydrinate; E = ephedrine sulfate; P = promethazine hydrochloride; S = l-scopolamine hydrobromide.

TABLE VII. SUBJECTS AND DRUGS INVOLVED IN SEVEN DETRIMENTAL RESPONSES AMONG 225 EVALUATIONS IN 31 SUBJECTS. IN THESE SAME SUBJECTS ARE SHOWN, IN PARENTHESES, THE RESPONSES THAT WERE NOT DETRIMENTAL

Subject No.	B	I	D*	Dimenhydrinate (50 mg)	Promethazine (25 mg) + Ephedrine (50 mg)	Scopolamine (0.3 mg) + Amphetamine (5mg)	Scopolamine (0.6 mg) + Amphetamine (10 mg)
3	4	1	2	D − 23%‡	(B; best of 4 + 54%)	D − 17%	(I 0%)
4	1	5	1	(I + 3%)	(only B response + 58%)	D − 25%	(I + 9%)
11	1	3	3	D − 27%	D − 18%	(I 0%)	D − 18%
19	2	5	1	D − 25%	(I + 13%)	Not adm.	(I − 13%)

*B = beneficial, I = inconsequential, D = detrimental, ‡ = % change from placebo level.

TABLE VIII. A COMPARISON OF GROUP RESPONSES USING THE OLD AND NEW PROCEDURES (SEE TEXT) WHEN THE SAME DRUGS WERE ADMINISTERED.

	Average Number Head Movements Increased Over Placebo Level	
Drugs (listed in order of Overall Beneficial Effectiveness)	Previous Studies Using Dial Test* 60 Subjects	Present Study Using Incremental Stress
P (25 mg) E (50 mg)	100 (3)	>192 (1)
S (0.3 mg)	60 (5)	>124 (6)
S (0.6 mg)	70 (4)	>160 (3)
S (0.6 mg) A (10 mg)	140 (1)	>188 (2)
D (50 mg)	50 (6)	>140 (4)
S (0.3 mg) A (5 mg)	135 (2)	>120 (7)
P (25 mg)	70 (4)	128 (5)
E (50 mg)	40 (8)	80 (9)
A (10 mg)	45 (7)	> 84 (8)

A = d-amphetamine sulfate; D = dimenhydrinate; E = ephedrine sulfate; P = promethazine hydrochloride; S = l-scopolamine hydrobromide.

Clin. Pharm. & Therapeutics 11:621-629, 1970.

rank in terms of efficacy, hence these rankings were roughly in the reverse order of the rankings summarizing the beneficial responses. Two striking exceptions involved an increase in efficacy when dimenhydrinate (50 mg) was administered and a decrease in efficacy when this drug was combined with ephedrine (50 mg).

Table VIII compares the group responses in this series of experiments with previous findings on 60 subjects using the "old" procedure (1). These comparisons are limited to nine drugs administered in the same doses and the responses are specified in terms of the mean change in the number of head movements. Every change contributed an increase in the number of head movements indicating that, in every instance, the net value was above rather than below the placebo level. When the rankings are compared, the differences are small except in the case of the combination scopolamine (0.3 mg) and amphetamine (5 mg), which ranks far lower in the new compared with the old series.

When the dose was doubled, the rankings were similar.

Finally, the difficulties and approximations inherent in testing the efficacy of antimotion sickness drugs are visible at nearly every step in the procedure, hence the data are more suited to clinical application than to elucidation of underlying mechanisms. Nevertheless, the first question that came to mind after carrying out the present series of experiments was whether the results were in accord with a theory underlying our previous drug studies (2): namely, that summation effects were observed with certain combinations of drugs, one with central sympathomimetic and the other with parasympatholytic actions. This generalization has some surface validity for group responses but does not explain the great differences in response to the same drug for individuals within the group. We share the opinion of other investigators (11-13) that the central actions of antimotion sickness remedies are largely unknown.

ACKNOWLEDGEMENT

We are much indebted to the military and civilian technical team whose efforts were essential for the proper execution of this study. We gratefully acknowledge the constructive criticism received from Drs. Jane Shaw, Kenneth Money, and James Lackner. The technical assistance of Mr. R. K. Upchurch, Mr. T. L. Trimble, and Mr. R. J. Garlock is also gratefully acknowledged. Mr. D. N. Turner of the Aerospace Psychology Department, NAMRL, kindly typed several of the tables in final format.

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Perception & Psychophysics
1975, Vol. 17 (3), 329-332

Thresholds for the perception of angular acceleration as indicated by the oculogyral illusion

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A motorized chair (with precise servo controls) accelerated the observer in a clockwise (CW) or counterclockwise (CCW) direction at rates that ranged in logarithmic progression from 0.02 to 6.00 deg/sec^2. The target, a narrow collimated line of light, was contained within a goggle device worn by the observer and therefore fixed in relative position to him. The illusion, appearing as rightward or leftward movement of the visual target in the direction of acceleration, was determined by a double staircase procedure among 300 normal and 4 labyrinthine-defective observers. None of the latter perceived the illusion. The majority of normal observers revealed no substantial directional difference (CW vs. CCW threshold). Threshold frequency distributions ranged in rate (deg/sec^2) from 0.020 to 0.950; the threshold of response in more than half the normal observers was less than 0.10, in over three-fourths was less than 0.20, in over 90% less than 0.30, and 100% less than 1.00.

The oculogyral illusion may be perceived by a person passively exposed to angular acceleration as apparent motion (in the direction of turn) of visual objects that are fixed relative to him (Graybiel & Hupp, 1946). The illusion has its genesis in the semicircular canals, and a knowledge of cupuloendolymph mechanisms, the role of adaptation effects, and the influence of secondary etiological factors are all essential for predicting its behavior under different stimulus conditions (Clark, 1967; Clark & Stewart, 1968; Doty, 1969; Graybiel et al., 1948). Studies have shown that its perception under ideal test conditions yields lower threshold values than other canal response indicators: the manifestation of nystagmus and the sensation and aftersensation of rotation (Clark, 1967; Clark & Stewart, 1969; Dockstader, 1971; Gray, Note 1; Van Dishoeck, Spoor, & Nijhoff, 1954). Indeed, the thresholds of the illusion are so low that their measurement is limited by the precision of the rotating device. A highly sophisticated servo-controlled device, the rotating litter chair (RLC), was developed expressly for determining with this indicator any changes in cupular thresholds of response that might occur during the prolonged weightless Skylab missions (Miller & Graybiel, 1973). The purpose of this report is to measure thresholds of perception of the illusion with this new device in a large sample of normal male observers and in four deaf persons with severe bilateral labyrinthine defects.

This study was supported by Contract T-81633, Biomedical Research Office, and Contract T-5904B, Office of Life Sciences, National Aeronautics and Space Administration, Johnson Space Center, Houston, Texas. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

METHOD

Subjects

Three hundred normal healthy men, ranging in age from 17 to 49 years, served as test observers; most (261) of these observers were less than 26 years of age. This group comprised 203 pilots or pilot trainees, 44 enlisted personnel, and 53 civilians. Each was accepted as a subject after demonstrating normal otolith and semicircular canal function, as indicated, respectively, by ocular counterrolling (Miller, 1962, 1970) and caloric response (McLeod & Meek, Note 2). In addition, four deaf individuals with severe bilateral labyrinthine defects, as defined in Table 1, served in determining nonlabyrinthine influences upon the perception of rotation.

Apparatus

Rotating litter chair. The RLC is a relatively lightweight (≈145 lb) motor-driven rotational chair device that is described elsewhere in detail (Miller & Graybiel, 1973). A servo-controlled dc brush-type motor is programmed to rotate automatically a seated observer at any one of 24 velocity vs. constant time (90 sec) profiles (Figure 1) within extremely narrow limits of precision. The 24 which ranged from ±0.0007 (Step 1) to ±0.0084 (Step 24) deg/sec extended trapezoidal-shaped profiles yielded in progressive logarithmic steps a range of constant accelerations from 0.02 deg/sec^2 (Step 1) to 3.00 deg/sec^2 (Step 23); two log units of acceleration separated Steps 23 and 24 (6.00 deg/sec^2). The man-supporting superstructure and motor of the RLC are directly coupled to eliminate gear slack and perceptible vibration and therefore meet the physiological requirement of eliminating small performance errors that are normally within the sensitivity range of the delicate vestibular organs.

Vestibular test goggle. The vestibular test goggle (VTG), described in detail elsewhere (Miller & Graybiel, 1972), is a self-contained device worn over the observer's eyes (Figure 2). The collimated line-of-light target, the only thing visible to the observer, is self-illuminated by a radioactive source (tritium gas, 100 mCi, AEC license No. 09-06979-03) contained in the goggle. Two knurled knobs permit the target to be rotated 360 deg about its center and moved vertically, from a straight-ahead position, ±20 deg about the center of rotation of the viewing right eye; the left eye is occluded by being covered with a portion of the goggle. The device is held on the face by its attachment to a biteboard assembly, which, in turn, is secured by an adjustable support connected to the RLC. The distance between the ocular and occlusal planes is adjusted so that

Table 1
Clinical Findings in Four Deaf Observers With Bilateral Labyrinthine Defects

Observers	Age	Deafness: Etiology	Deafness: Age of Onset	Hearing (dB): R	Hearing (dB): L	Caloric Response*: R	Caloric Response*: L	Date of Clinical Tests	Counter-rolling Index†
G.R.	48	Mastoiditis	12	Nil	160	Negligible	Negligible	1967	60
G.U.	22	Meningitis	4½	> 145	> 145	Negligible	Negligible	1967	89
M.Y.	26	Meningitis	8	None	None	None	None	1967	99
P.E.	33	Meningitis	12	None	None	Negligible	Negligible	1967	77

**Negligible or no observable nystagmus when tympanum irrigated with water at a temperature of 11 °C or less.*
†Calculated as one-half the sum of the eye roll measured in minutes of arc at the 50-deg rightward and leftward tilt positions.

the observer's visual axis in its primary position is essentially in the "horizontal" plane containing the optic axis of the target system. The target was found to be completely visible to all observers having a wide range of interpupillary distances; so no means of lateral adjustment was incorporated in the goggle.

Procedure

The oculogyral illusion was demonstrated at the time of the biteboard fitting by having the observer observe the apparent movement of the test-goggle target during gentle side-to-side movements.

The observer was then secured in a seated position within the RLC, and his biteboard and the VTG were affixed to the support mechanism of the chair. He engaged the biteboard with his teeth and donned the VTG by tilting his head forward 20 deg. The target viewed by his right eye was adjusted so that it appeared vertical and straight ahead. The purpose of the fixed head tilt was to place the "plane" of the lateral canals closer to the plane of rotation.

A sound source for signaling the normal observer was situated directly over his head, which eliminated it as a cue to the chair's rotational direction; the labyrinthine-defective observer was signaled by lightly tapping the top of his head. The rotational chair was located in a test cubicle, which permitted this area to be darkened and thereby removed any possible influence of any small openings between the goggle's padding and the face. During testing, auditory directional cues were effectively removed by having the normal observer wear earphones. All observers used hand-held, color-coded lights to signal, when requested, the direction of apparent movement of the target. After one of the 24 acceleration rates was selected on the basis of the predetermined test schedule and observer performance, the program start switch of the RLC was pressed. After 2 sec of constant positive acceleration, the observer was signaled to open his eyes, after 5 sec accumulative time, he was signaled again to judge whether the target appeared to move rightward or leftward, or to remain stationary. If the observer did not respond after 15 sec accumulative time, a third signal was given. If no response was received within 20 sec accumulative time, the end of the constant acceleration period and the beginning of the 25-sec constant velocity phase, it was assumed and recorded that no movement was perceived. The observer was instructed to close his eyes immediately after each response.

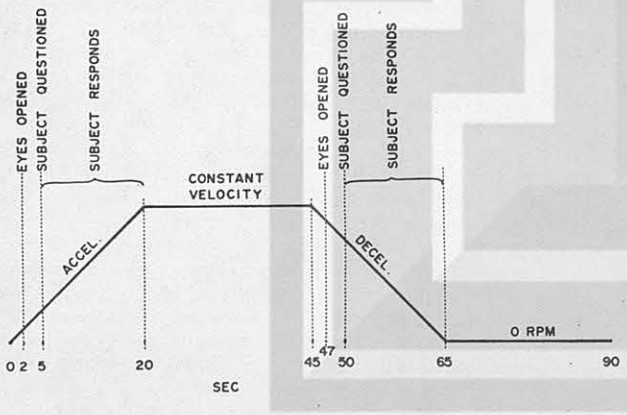

Figure 1. Diagram of a test-cycle profile indicating chair rotational mode and experimental activity as a function of time.

The down ramp of the profile required the observer, as in positive acceleration, to open his eyes at 2 sec and to respond between the 5th and 20th second after deceleration had begun. After reaching 0 rpm, the RLC remained stationary for at least 25 sec. In some cases, the next profile was not initiated for up to several minutes when: (1) the total test time exceeded 30 min, (2) when the observer requested additional rest time, or (3) for operational reasons, e.g., wiping the goggle lens to remove a moisture film that occasionally was found to accumulate. The direction of rotation among the profiles was varied at random according to a predetermined schedule.

In selecting an intertrial period between velocity ramps of at least 25 sec, an attempt was made to reduce the test time without introducing significant poststimulus response effects. Although the analysis of such effects was not part of this study, it was found in the development of the test method that these particular test conditions yielded on the average no essential differences between up-ramp and down-ramp responses of the same direction when the interval between profiles was several times that between ramps. This assumption is more acceptable for this study when it is considered that only relatively low levels of acceleration (<1.00 deg/sec^2) were employed for the normal subjects.

Our early experimental probes had indicated that a brief period of feedback training at an acceleration level well above response threshold was necessary to establish that the observer understood the task and could readily observe the illusory movement. The observer was also fully apprised that apparent movement of the target in this situation did not also require its apparent displacement, particularly at or near his response threshold level. During training conducted at Acceleration Step 12, or higher if necessary, the observer was informed of his results and coached until he could consistently identify the direction of the oculogyral illusion. During the actual test, the observer was not provided this feedback.

Mechanically, the stimulus to the cupuloendolymph system and therefore its response with clockwise (CW) acceleration is equivalent to those for counterclockwise (CCW) deceleration, as in the reverse sense are the pair of complementary directions of acceleration and deceleration. For convenience, each stimulus pair is henceforth identified only by its associated direction of acceleration.

A response threshold for each of the two directions of acceleration was defined as the lowest acceleration at which the observer could correctly identify the expected direction of apparent movement in three out of four or in four out of six trials. When a difference in perception of the illusion for the two directions of acceleration was manifested at any step, the threshold for the

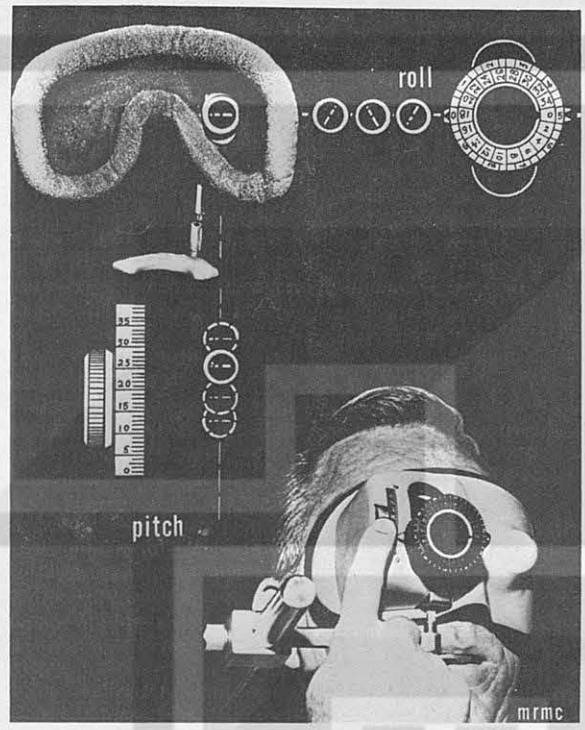

Figure 2. Diagram of the vestibular test goggle (VTG).

direction of better performance was pursued first. Testing generally followed a double-staircase method (Cornsweet, 1962). Initially, an attempt was made to bracket the threshold within six log steps. If, for example, at least one response associated with the first test profile (usually Step 12) was correct, testing proceeded to Step 6. If a response of like direction was correct at Step 6, further testing continued in the range of accelerations between Steps 1 and 6; if not, the test range fell between Steps 6 and 12. On the other hand, if both responses at the initial step were incorrect, the two staircases proceeded from, usually, Step 15 and the initial acceleration step. In all cases, testing followed the pattern of alternately lowering the higher step and raising the lower one of the indicated range. Securing the testing if it became apparent that the threshold was in a different range, the 6 or less log step bracket was shifted in the appropriate direction. Ascending-descending staircases permitted an ever decreasing range of testing until the threshold was captured between two steps of acceleration. This permitted a relatively rapid gross estimation of a threshold, with the greater portion of the test time spent in "fine tuning" of the threshold. Typically, repeated trials were alternately made at the final two steps until the threshold criteria were established. On occasion, the threshold fell between the two steps and in this case the threshold was assigned to the higher acceleration step. There were four subjects who exceeded the threshold criterion even at the lowest acceleration level (Step 1) provided by the device prior to assigning a threshold. Except in this instance, it was always established that the next lower step failed to meet the threshold criterion. If the thresholds for CW and CCW acceleration were different, testing continued in similar fashion using, if possible, the data already obtained until the higher threshold was determined. The test was completed in more than half the observers within 30 min, and in most within 40 min, although occasionally about 1 h was required. In no case was the observer tested longer than 30 min without one or more rest periods prior to completion of the test; each rest period of about 5 min was instituted with the observer remaining in the RLC but with his head removed from the goggle and biteboard support.

The oculogyral illusion threshold of each normal observer was measured by this procedure on two different occasions, separated by at least 24 h, in order to determine test-retest reliability.

RESULTS AND DISCUSSION

The large number of trials and long test periods often covering many days or weeks that are typical in measurements of a response threshold were avoided in this study without apparent undue compromise in sensitivity or reliability by using 24 logarithmic step levels of accelerative stimuli. On a linear basis, this schedule introduced ever-increasing increments of acceleration among the progressive test steps with the result, desirable from a practical point of view, that

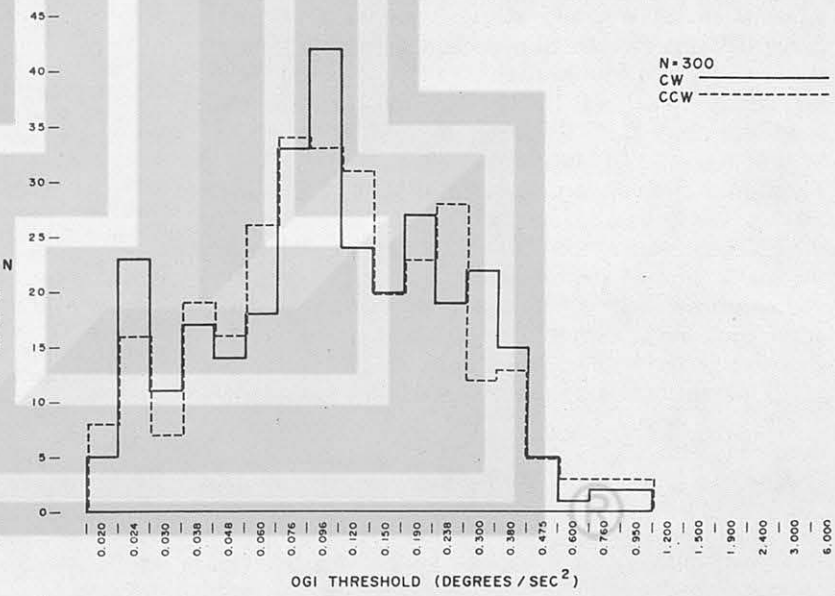

Figure 3. Frequency distribution of the oculogyral illusion threshold for clockwise (CW) and counterclockwise (CCW) directions of acceleration among 300 normal observers.

differentiability among individuals decreases as an indirect function of threshold level.

Directional difference, i.e., a difference in threshold for CW and CCW acceleration, was not manifested in 35%, was less than 0.1 deg/sec^2 in 84%, and less than 0.2 deg/sec^2 in 94% of the normal observers; the remaining observers revealed a difference that ranged from 0.2 to 0.7 deg/sec^2. Furthermore, a moderately high correlation ($p = .72$) was found to exist between data obtained with CW and CCW acceleration. A substantial directional (CW vs. CCW) difference in the oculogyral illusion (OGI) threshold response would therefore not be the expected result in a normal individual. A follow-up investigation of the small number of observers who demonstrated a relatively large directional difference was not conducted, but a study of unilaterally labyrinthectomized individuals gave some evidence that an acute unilateral vestibular disturbance may cause a difference (Miller et al., Note 3).

The individual thresholds for CW and CCW acceleration were averaged to obtain a single measure of test-retest reliability, which proved to be moderately high ($p = .70$). This level of reliability and the brief test period required make the method feasible as a clinical-type test of semicircular canal function. The large sample of normative data offers a substantial basis for comparing the OGI thresholds of response of individuals with possible vestibular disfunction.

Frequency distributions of the oculogyral illusion threshold values among all the normal observers for CW and CCW acceleration are presented in Figure 3. The distributions were similar for the two directions of angular acceleration and ranged in terms of rate (degrees per second per second) from 0.020 to 0.950, means of 0.146 (CW) and 0.152 (CCW), a median of 0.096 (CW, CCW), and modes of 0.096 (CW) and 0.076 (CCW). The distributions on a linear scale are skewed right. More than half the individual thresholds fell below 0.10 deg/sec^2; over three-fourths were less than 0.20 deg/sec^2; over 90% less than 0.30 deg/sec^2; and 100% less than 1.00 deg/sec^2. These findings compare well with those of Clark and Stewart (1968) who found that the OGI thresholds of their 32 observers ranged from 0.04 deg/sec^2 (close to the lower limit of their device) up to 0.28 deg/sec^2, and confirm their conclusion that normal healthy adult men have semicircular canals that are highly sensitive to accelerative stimulation.

All labyrinthine-defective observers failed repeatedly to perceive the oculogyral illusion at the highest acceleration step (6.00 deg/sec^2) offered by the RLC test device, giving further evidence that the basic underlying mechanism for this illusion is the copuloendolymph system.

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(Received for publication April 1, 1974;
revision received December 2, 1974.)

Technical Note

A Z-Axis Recumbent Rotating Device for Use in Parabolic Flight

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GRAYBIEL, A., and E. F. MILLER, II. *A Z-axis recumbent rotating device for use in parabolic flight.* Aviat. Space Environ. Med. 47(8):893, 1976.

A prototype apparatus for exposing persons to rotation about their Z-axis in parabolic flight is described. Although it resembles Earth-horizontal axis devices, added features are its strength and portability, and the fiber glass "couch" with adjustable elements providing support and restraint. Even under ground-based conditions, this device provides unique opportunities for investigations involving not only canalicular and macular mechanoreceptors, but also touch, pressure, and kinesthetic receptor systems.

THE SO-CALLED ZARR (Z-axis recumbent rotating) apparatus was specifically designed for use in parabolic flight, where a person is exposed to gravitoinertial forces that may exceed a typical range from zero G to 2 G. As we expected it would have limited use, the low-cost device was fabricated in our shop on a time-available basis.

Fig 1 shows its principal features. A cylindrical module 53.5 in long and 42 in in diameter (134 x 105 cm.) is supported by axles attached to A-frames, thereby allowing for rotation about the long axis. The A-frames in turn are mounted on a 4 x 8 ft (1.2 x 2.4 m) aluminum plate 3/4 in (1.9 cm) thick. This plate is supported by a fulcrum, and the entire device can be tilted about this fulcrum over a 20° range by means of four jacks. Rubber-tired wheels can be swung into place for transport purposes.

MATERIALS AND APPLICATIONS

A fiber glass body mold with features for fitting and restraining subjects is mounted inside the module and comprises the "couch." The Z-axis of the subject's head and trunk can be positioned in the axis of rotation of the module. The knees must be flexed to allow the feet to slip into a foot restraint (persons up to 5 ft 11 in tall can be accommodated).

A one-quarter horsepower constant speed (1800 rpm) electric motor, with gear reduction and clutch, provides the necessary torque through an open-loop control system, to achieve angular accelerations of 1 rpm/4 s to a maximum velocity of 60 rpm. The open-loop control necessitates careful balancing for every subject in every position. Deceleration is accomplished by electrical damping through the motor. A foot brake is available to achieve rapid decelerations when necessary.

Slip rings provide electrode couplings with recording and display devices. A marker signals every rpm on the recording when the subject is in the nose-up position. A satisfactory signal-to-noise ratio is achieved for ECG and EOG recordings when the device is properly grounded.

CONCLUSION

Preliminary testing indicates that the device will extend the present scope of our research dealing with mechanoreceptor systems, even under ground-based conditions. This applies not only to the labyrinthine organs, but also to touch, pressure, and kinesthetic receptor systems.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the roles played by John C. Taylor and Louis B. Lamolinara in fabricating the ZARR device.

Fig. 1. Z-axis recumbent rotating apparatus.

Opinion or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department. This research was supported by the National Aeronautics and Space Administration, Contract T-5904B.

*Deceased.

Sopite Syndrome: A Sometimes Sole Manifestation of Motion Sickness

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GRAYBIEL, A., and J. KNEPTON. *Sopite syndrome: A sometimes sole manifestation of motion sickness.* Aviat. Space Environ. Med. 47(8):873-882, 1976.

Drowsiness is one of the cardinal symptoms of motion sickness; therefore, a symptom-complex centering around "drowsiness" has been identified which, for convenience, has been termed the sopite syndrome. Generally, the symptoms characterizing this syndrome are interwoven with other symptoms but under two circumstances the sopite syndrome comprises the main or sole overt manifestation of motion sickness. One circumstance is that in which the intensity of the eliciting stimuli is closely matched to a person's susceptibility, and the sopite syndrome is evoked either before other symptoms of motion sickness appear or in their absence. The second circumstance occurs during prolonged exposure in a motion environment when adaptation results in the disappearance of motion sickness symptoms, except for responses characterizing the sopite syndrome. Typical symptoms of the syndrome are: 1) yawning, 2) drowsiness, 3) disinclination for work, either physical or mental, and 4) lack of participation in group activities. Phenomena derived from an analysis of the symptomatology of the sopite syndrome are qualitatively similar but may differ quantitatively from abstractions derived in other motion sickness responses. One example is the sometimes unique time course of the sopite syndrome. This implies that the immediate eliciting mechanisms not only differ from those involved in evoking other symptoms but, also, that they must represent first order responses. Diagnosis is difficult unless the syndrome under discussion is kept in mind. Prevention poses a greater problem than treatment.

IT IS GENERALLY acknowledged that drowsiness is one of the cardinal symptoms of motion sickness (10,12,14,21) and that mental depression may characterize chronic or prolonged motion sickness (1,11,17,-19). The purpose of this report is to present evidence indicating that these manifestations are only part of a symptom-complex that, for convenience, we have termed the sopite syndrome. The evidence has been gleaned in large part from systematic observations in connection with experiments conducted in slow rotation rooms, including many observations not published heretofore. The criterion used in identifying "evidence" was based on instances in which the sopite syndrome formed the main or sole clinical manifestation of motion sickness. These instances occurred either before other typical symptoms of motion sickness appeared or after their disappearance, implying that the time course of the sopite syndrome may differ somewhat from that of the general symptomatology of motion sickness. These relatively rare instances comprising *evidence* for the existence of the sopite syndrome must not be used to indicate its *incidence,* for this syndrome occurs much more frequently when other symptoms of motion sickness are present than when they are absent.

The material to be presented is primarily organized around four different motion environments; namely, rotating rooms, at sea, in the air, and in orbital flight. When the sopite syndrome occurs either before other typical symptoms of motion sickness appeared or after their disappearance, they are distinguished, respectively, by the terms "early sopite syndrome" and "late sopite syndrome." A further distinction is made between brief and prolonged exposures. Inasmuch as the main object is to prove the existence of a new symptom-complex, little attention will be given in this report to the far more common circumstance when the sopite symptoms are intertwined with other symptoms of motion sickness.

THE SOPITE SYNDROME DURING ROTATING ROOM EXPERIMENTS

In a room rotating at constant velocity, stressful ac-

This study was supported by the National Aeronautics and Space Administration, Contract T-5904B and the Bureau of Medicine and Surgery, project MR041.01.01-0120. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

celerations are not generated unless head and body movements are made out of the plane of the room's rotation (6). Stress-free head motions include turning the head rightward or leftward when seated, standing, or walking upright. A knowledgeable onboard experimenter or observer tries to avoid motion sickness by exploiting stress-free head motions and by restricting stressful motions, especially at the first indication that symptoms are imminent. An experienced subject can also avoid stressful head motions in these ways, but the unsophisticated subject is less aware of the cumulative effects of the eliciting stimuli and less skillful in avoiding them than the onboard experimenter/observer. The experimental design determines whether a subject makes head motions incidental to carrying out specified tasks, or executes experimenter-paced head movements in a standardized manner, or some combination of the two.

In an experiment, persons aboard a slow rotation room (SRR) are usually exposed either to a predetermined velocity (rpm, clockwise or counterclockwise) achieved in one step or to an incremental stepwise increase in angular velocity (5,15). Adaptation to rotation in one direction temporarily increases susceptibility to motion sickness when the direction of rotation is reversed, although this "direction-specific" phenomenon was poorly understood until recently (4,18).

Early Sopite Syndrome—Brief Exposures: In assessment tests, subjects are usually required to execute standardized head movements, paced by means of a taped recording, out of the plane of rotation until a motion sickness endpoint is reached. At least one onboard experimenter or experienced observer monitors every test and may monitor as many as three or four tests a day. The log books of experimenters and observers have been reviewed from the standpoint of their own susceptibility to the syndrome under discussion, and case reports presented are in decreasing order of their susceptibility and severity of symptoms.

Case 1: Experimenter 1, a physiologist now 50 years of age, has never been seriously ill. At the age of 26, tinnitis and vertigo were experienced as complications of a severe attack of "flu." Tinnitis has never disappeared, and on occasion Experimenter 1 has experienced vertigo, usually on lying down. He has a high-frequency hearing loss, which is thought to be the consequence of using a rifle. When he was 33 years of age, a diagnosis was made of rheumatic fever without cardiac involvement. During the period of experimental interest, repeated health and fitness evaluations were conducted with no significant abnormalities being revealed. These evaluations have included: 1) a comprehensive medical examination, 2) rigid qualification tests for participating in parabolic flight maneuvers, and 3) special assessment of canalicular, otolithic, and visual functions. Susceptibility to acute motion sickness was "average," and he willingly undertook assignments involving frequent exposures in a rotating room. Three periods deserve brief mention.

Rotation Period 1: During a 5-month period (28 Aug. to 27 Jan.) Experimenter 1 participated in 243 tests, an average of two or three tests each workday. These tests involved the use of an incremental adaptation schedule, usually 1-rpm steps to 6 rpm, rotating either counterclockwise or clockwise (infrequent). Although Experimenter 1 avoided typical symptoms of motion sickness, he often had to make a conscious effort to overcome feelings of lethargy, and he gradually became aware that some of the side effects he experienced were cumulative. The following quotations from his log book are typical.

18 Nov. . . . "Since 28 Aug. have noticed that after two series of clockwise rotations [more stressful for him than counterclockwise] . . . a decreased ability to concentrate and swift recall from memory, such as word selection, is slower than usual . . . I have more frequently . . . thought of occurrences in my past than I did before."

19 Nov. . . . "I am extremely tired in the evening after a day of rotating in the new slow rotation room . . . no desire to read [only] to sleep."

20 Nov. . . . "Clockwise rotation at 1300 hours put me into a stupor—drowsy and inattentive [state] but upon making the following counterclockwise rotation at 1420 hours I was more alert."

1 Dec. . . . "After two [tests] up to 6 rpm counterclockwise . . . I began to feel very drowsy . . . after two clockwise [tests] I became very drowsy [with] loss of ability to . . . concentrate."

In summary, Experimenter 1 experienced symptoms not only when exposed to the eliciting stimuli but also aftereffects, both near-term and prolonged.

During a typical workday, he felt mentally fatigued and daydreamed "a lot." Moreover, when not busy, he dwelt on "occurrences" in his past and began to link contemporary events with past activity. Not only was this behavior unusual but also long-forgotten events were vividly recalled. He also began to dream a lot at night, which was highly unusual. There was some tendency for these effects to accumulate, and they disappeared only gradually over a month's time after the 5-month period, with the exception that he continued to dream at night.

Rotation Period 2: This period began about 6 weeks after Period 1 ended and lasted 4 months, during which Experimenter 1 participated in 76 tests. The tests involved clockwise and counterclockwise rotation, using 1-rpm incremental changes, usually up to terminal velocities of 10 to 15 rpm. His symptoms were similar to those described for Rotation Period 1, although more severe on those occasions when high angular velocities were reached.

30 May . . . "This was a day of six counterclockwise rotations from 7 to 24 rpm. Some drowsiness, stomach awareness and discomfort, apathy [and] headache."

7 June . . . "After 6 h [exposure] entirely lethargic, loss of willpower. Unable to concentrate . . . on subject matter"; 4 h later, "still lethargic, drowsy, sleepy, difficult to carry on mental activity."

The stomach awareness and discomfort reported 30 May represented one of the three occasions when more than a trivial additional symptom of motion sickness was experienced. Experimenter 1 dreamed a lot at night and was not refreshed after more than the usual amount of sleep. Recovery was similar to that described for Period 1 and required about 4 weeks.

Rotation Period 3: During this period of a year, which began about 5 months after Period 2 ended, Experimenter 1 conducted 273 tests involving clockwise and counterclockwise rotations up to terminal velocities ranging from 4 to 30 rpm. The symptomatology was qualitatively similar to that manifested in the first two periods but somewhat more intense.

12 April . . . "Since 9 April I have been riding from 6-12 rpm maximum velocities each day [total of 9 runs in 4 d]. By 6 p.m. [6-7 h post-run] I am lethargic and apathetic with no desire to talk or think. I have to constantly be wary of myself committing errors."

19 April . . . "Prone to daydream a lot. More frequently lost attention to . . . carrying out my onboard duties . . . Mental concentration seemed more impaired than previous runs."

30 Aug. . . . "Lethargic on this morning's clockwise adaptation runs, one to 12 rpm and another to 24 rpm. Dreaming a lot at night during sleep."

Recovery was virtually complete in about 3 weeks. The one remaining effect was a tendency that was greater than usual to dream at night.

Comment: It would appear that the stressful stimulus conditions revealed a personality vulnerable to neurosis or psychoneurosis. At all times, Experimenter 1 was

in solid touch with reality, and at no time was there even a hint of fantasy. The test schedule was fortuitous in the sense that it was not designed to reveal a latent neurotic tendency. The fact that it did points to a line of direction to take if such a study is attempted. Experimenter 1's personality symptoms must fall into the category of a "complication" of the sopite syndrome. It is also fairly safe to assume that the prolonged aftereffects of a single day's exposures are complications.

Case 2: Observer 1, a technician 52 years of age, has participated in about 3000 brief exposures to a rotating environment over a period of 18 years. Although he is well adapted to rotation and does not experience acute motion sickness, he still, occasionally, daydreams, gets drowsy, and may even fall asleep. On these occasions, Observer 1 is of the opinion that stimulus conditions, such as high rpm, rotation clockwise (the unusual direction), and the need to move about (make head motions) are the main etiological factors and not his state of physical or mental fitness on those days.

Case 3: Observer 2 estimates that he has participated in some 1000 brief exposures in a SRR over a period of 10 years. Unless adapted, Observer 2 falls in the range of average susceptibility to motion sickness, and unless there is a reversal in direction of rotation, Observer 2 is virtually symptom-free. During a recent series of 30-rpm tests, however, he wrote ". . . associated with a feeling of complete fatigue was a mental attitude that I have expeienced before after long periods of rotation. A desire to be left alone, not having to converse with anyone; was very easy to fall asleep in almost any position." On another occasion, after a clockwise exposure he wrote . . . "I seemed overly tired that night . . . Again this week was exposed to CW rotation and (had) drowsiness during a 25-min lull in recording at 6 rpm . . . Again noted the drowsiness during a lull in recording at 10 rpm."

Case 4: Observer 3, a technician 57 years old, has participated in approximately 400 brief exposures in a period of about 5 years. He is well adapted to stimulus conditions. The fact that he sometimes felt "physically tired" at the end of a day's test possibly may be attributed to stimulus conditions.

Case 5: Experimenter 2 participated in about 500 tests as a member of the staff when 25 to 30 years of age. He was far less susceptible than average to motion sickness and never experienced symptoms characteristic of the syndrome under discussion.

Comment: Among the five experimenters and observer-technicians with much experience in conducting brief tests in the SRR, great differences in susceptibility to the early sopite syndrome were demonstrated, although the full spectrum was not revealed. The differences demonstrated were revealed at stimulus levels not eliciting other cardinal overt symptoms of motion sickness. Except in the case of Experimenter 1, who manifested complications, the chief symptoms were yawning, drowsiness, daydreaming, and falling asleep. The absence of symptoms implies low susceptibility to motion sickness, rapid adaptation, or a combination of the two.

Prolonged Exposures: In one experiment, four subjects were exposed to rotation for nearly 25 d (7). The main object was to prevent motion sickness at a terminal angular velocity of 10 rpm by means of nine stepwise increases: the first step was a 2-rpm increase from zero velocity and the remaining steps were 1-rpm increases. The final period at 10 rpm was approximately 8 d long. Four Navy enlisted men, 17 to 19 years of age, served as subjects. A comprehensive medical evaluation and an array of vestibular and clinical tests revealed no significant abnormalities. The subjects' schedule was designed to keep them busy during a workday of approximately 8 h.

The choice of a 2-d period of "natural activities" at each incremental step was based on the likelihood that this period would more than suffice for the execution of the requisite number of head movements (out of the plane of rotation) to achieve adaptation. Nonetheless, there were two reasons the opportunity was always present, at each step-increase, for intraindividual and interindividual differences in the acquisition of adaptation to be revealed. One was the fact the periods of rest, immobility, and sleep (when stressful head movements were minimal) were different from one day to the next. The second reason involved individual differences in readiness of acquiring adaptation to the motion environment. At the time the study was conducted, we were not properly aware of direction-specific adaptation effects; hence, sufficient attention was not given to periods or occasions when such effects might be elicited.

During adaptation in a slow rotation room simultaneous acquisition of direction-specific and nondirection-specific adaptation effects takes place (4,18). The direction-specific effects are acquired first, or at least predominate, during the early stages, thereby causing the subject to lose his adaptation to the stationary environment and to render him highly susceptible to motion sickness if the direction of rotation is reversed. If a subject is poised to experience direction-specific effects, they would appear under such circumstances as: 1) a result of sudden or rapid cessation of rotation even if a person is motionless, 2) during the execution of head movements after cessation of rotation, and 3) upon reversal of direction of rotation, especially if head movements were made out of the plane of rotation. In the experiment referred to here (7), a stationary environment was simulated by counterrotating the subject in an onboard rotating chair. It is equally important to emphasize that the absence of symptoms, when the subject is exposed to stimulus conditions designed to elicit direction-specific effects, indicates that the subject has acquired at least an "adequate" level of adaptation.

Special tests were conducted that required the subject to execute standardized head movements in different orientations relative to the axis of the room's rotation.

What follows is based on a careful review of the original experimental findings and the logbooks kept by the subjects and a Navy physician, Experimenter 3. On Day 1 at 1930 hours the SRR was accelerated up to 2 rpm in about 1 min. Experimenter 3's comments relative to the subjects have been extracted from his log book.

Day 1 (2 rpm): "All doing well."

Day 2 (2 rpm) a.m.: "Subjects today more tired. Got up slower, talked about noon siesta. Spent most the time lying down on deck and sitting. Food intake slightly down."

1400: "Most of the subjects feel quite well adapted. Subject D sacked out all today—slept much more than normal."

Day 3 (2 rpm): "Boys definitely tired this morning, especially Subjects A and D. Level of performance is somewhat but not definitely down."

1400: "Subject D still sacking out. Subjects mak-

ing small errors today. After work period everybody, including me, sacked out."

Day 4 (3 rpm): "Subjects less sleepy today."

Day 5 (3 rpm): "Subjects ate little for breakfast. Didn't like food."

Day 6 (4 rpm): "Hardest to get subjects up and working. Slow to get to breakfast, ate less. Subjects got to work 1½ h later than usual. Tempers slightly shorter."

Day 7 (4 rpm): 'Subjects eating fairly well. Went to work relatively easy this morning."

Day 8 (5 pm): "Subjects fine."

Day 9 (5 rpm): No comments regarding subjects.

Day 10 (6 rpm): "Subject D still sleeps more than the others. Some wrangling (among the subjects) but no real sweat. Mainly, Subjects D and B."

Day 11 (6 rpm): "Subject C is the 'work leader' of the group. Quiet but always [field days] starts others to work without being asked. Subject A goes next. Needs minimal if any pushing. Subject B is much less helpful, and Subject D is no help. Others do his work. Sacks most of time."

Day 12 (7 rpm): "Things went well till lunch. While eating noted room apparently moving CW [rotation was CCW], i.e., slowing down. [Oculogyral illusion.] Had emergency freeze [subjects motionless], 2 lying, 2 sitting . . . Down 30 min. Some friction, especially Subject D vs. Subject B."

Day 13 (7 rpm): "Somewhat more though still not great friction [among subjects]. Subject A entering into it to some degree."

Day 14 (8 rpm): "Two unscheduled stops last night, the first about 0830 hours due to mechanical failure, then about 0200 while the subjects were asleep the SRR was stopped slowly for repairs. This lasted 45 min and no one awoke."

Day 15 (8 rpm): No comments regarding subjects.

Day 16 (9 rpm): "Subjects today, much more sacking out, i.e., after work they lay down and slept rather than watched TV or played cards as normal. Subjects choose mainly carbohydrates but don't eat all of the food given them."

Day 17 (9 rpm): "Subjects much sleepier today but still do work. After work they sack out fast."

Day 18 (10 rpm): 'No one (of the subjects) has significant motion sickness so far."

Day 19 (10 rpm): "We have already proven that we can get a group gradually to 10 rpm without motion sickness symptoms. Feel strongly an isolation-type control experiment should be done sometime."

Day 20 (10 rpm): "Ran a dial-type test [subjects executed standardized head movements] to check adaptation with subjects 90° to the axis rotation. All three [Subject B did not run] made 10 min of movements without any symptoms."

Day 21 (10 rpm): "Have had Subjects A and D on the chair, preconditioning them to 0 rpm. Never any motion sickness symptoms but they are far more tired than on another day. Both agree it is a significant increase. Things going well."

Day 22 (10 rpm): "Second day of preconditioning of Subjects A and D, no problems."

Day 23 (10 rpm): "Subjects quite tired. Read or sack out at every opportunity, especially Subject D. Subjects still favor carbohydrates and sweets."

Day 24 (10 rpm): "Subject D very sluggish. Food intake yesterday low for the run."

Day 25 (10 rpm): Cessation of rotation at 0955 hours.
1415: "Everyone sacking out [after completion of tests]."

Day 26 (zero rpm): "Subjects very tired and lethargic."

Day 27 (zero rpm): Experimenter 3's last note: "Major characteristic is marked lethargy, fatigue and desire to be 'left alone.' Any stimulation causes many mumbled gripes, especially by Subject B. Three men sit about and sleep and one wants to be completely passive. The requests for mental arithmetic are particularly noxious to the subjects."

The subjects' logs added little to what was gleaned from the questionnaires they filled out every day. (Each morning, the subjects completed a form dealing with their state of health.) On three to five occasions during the day, they filled out a "motion sickness" questionnaire with a section for the experimenter's comments. Their logs differed greatly in kind and amount of information except on one point; namely, vestibular side-effects. All were surprised not to have experienced prolonged motion sickness and commented on the increasing postural disequilibrium with step-increases in angular velocity. For all subjects, their interest was aroused by events out of the ordinary, "poor chow," "square needle," letters and pictures from fans, and publicity.

A complete review of all of the findings provided the information in Table I. Subjects A and D were chosen to participate in most of the special tests; why they were chosen is unknown, but they were the "cut-ups." Only Subjects B and C experienced episodes of acute motion sickness, implying a slower rate of acquisition of adaptation effects than in the case of Subjects A and D. The fact that Subjects B and C experienced acute motion sickness indicates not only that they were actively adapting but also reinforces the notion that, prior to experiencing motion sickness, they were poised to experience the sopite syndrome.

Comment: As the result of prolonged exposure to mild eliciting stimuli, the sopite syndrome was evoked in the virtual absence of other overt symptoms of motion sickness. This syndrome clearly dominated the clinical picture, and this domination required the right combination of individual variability and stimulus profile. The onset was insidious, and the unsophisticated might attribute the yawning and drowsiness to boredom and relaxation. More distinctive symptoms, however, included a disinclination to be active physically or mentally, the subject's facies and posture often reflecting these feelings. An additional diagnostic clue that the symptoms were in response to eliciting stimuli was the fact that they were inappropriate at the time of day. When properly

TABLE I. REVIEW OF EXPERIMENTAL FINDINGS FROM FOUR NAVY ENLISTED MEN (17-19 YEARS OF AGE) EXPOSED TO ROTATION FOR NEARLY 25 DAYS (7).

	Number of Days Sopite Syndrome Manifested		Acute Motion Sickness Episodes			
Subjects	Regular Activities	Special Test Days	Regular Activities	Test Conditions	Unscheduled Stops	Superimposed on Sopite Syndrome
A	5	1				
B	5		1	1		
C	5	1	1 (?)		1	1
D	7	3				

alerted, some of the subjects were able to overcome their lethargy and carry out most designated tasks. After cessation of stimulation, the symptoms disappeared gradually. In all of these instances of the early sopite syndrome, it may be inferred that the initial symptoms, at least, represented first order responses. The very gradual onset suggests an underlying cumulation characteristic of hormonal release and buildup.

Late Sopite Syndrome

During prolonged exposure in a stressful motion environment and when symptoms of frank motion sickness are alleviated through adaptative mechanisms, complete restoration to health and high spirits may still require a period of days. The question arises whether we are dealing with the continuing effects of the eliciting mechanisms or spontaneous restoration by virtue of homeostatic processes, or both. Under experimental conditions there is an opportunity to resolve this problem in differential diagnosis but, insofar as we are aware, an experiment specifically designed to achieve this goal has not been carried out. However, in reviewing the findings in an experiment (9) when four subjects were exposed to 10 rpm in an SRR for 12 d, it appeared that eliciting stimuli were acting long after frank motion sickness had disappeared and that the residual symptoms fit into our notion of the late sopite syndrome.

The subjects were young, highly motivated officers, two Marine Corps and two Navy, with a history of low susceptibility to motion sickness. Their task was to carry out a variety of tests and to avoid becoming frankly sick if possible. Their indoctrination included demonstrations that the stressful stimuli were generated only when head movements were executed out of the plane of the room's rotation and that there was a latent period before symptoms of motion sickness appeared. Each subject was fitted with a modified orthopedic collar which when worn greatly minimized head tilt with reference to the thorax. In addition to clinical observations and performance measurements, biochemical determinations were designed to study water balance, acid-base balance, intestinal absorption, excretion of electrolytes, release of stress hormones, glucose metabolism, and changes in certain serum enzymes.

The subjects lived in the SRR for 4 d prior to rotation and 2 d after cessation of rotation. Acceleration to an angular velocity of 10 rpm was quickly achieved in a single step. With the sudden onset of rotation, all of the subjects immediately experienced difficulty in walking and in carrying out tasks involving bodily movements. The full impact was not felt at once, and there was much individual variation in onset and intensity of motion sickness symptoms.

Subject AI did not vomit but lost 2 pounds during Day 1 because of nausea and consequent food and fluid restriction. He slept at every opportunity during Days 1 and 2 and fell asleep during his "watch" at the end of Day 1. He regained his appetite on Day 3. Subject AI had his "first real desire" to work on Day 5. During the remainder of the run he continued to nap occasionally during leisure periods and complained in the morning of excessive drowsiness and fatigue, even after 8 or 9 h of sleep.

Subject BI experienced the first of his eight vomiting episodes within 35 min of Day 1 and the last during the evening of Day 2. He was able to carry out the performance tests but minimized all other activities. He exhibited a weight loss of 6 pounds by the end of Day 2 and regained this weight by Day 8. He discarded the head brace on Day 3, and that evening his appetite had improved. Thereafter, he did not restrict his head movements but continued to restrict body movements. Feelings of drowsiness and fatigue, although less prominent after Day 4, persisted throughout the run. Subject BI occupied his leisure time either with activities that required little mental effort or by resting or sleeping.

Subject CI on Day 1 wore a head brace but, nonetheless, experienced typical symptoms of motion sickness within the first hour and vomited once in the afternoon. He restricted head movements through Day 2 and regained his appetite by the evening of Day 3. A weight loss of 3 pounds was regained by Day 4. On Day 6 he was in "good spirits," but his first desire for exercise was satisfied with "a few push-ups." With the exception of Day 8, his log contained references to fatigue, such as "very tired at end of the day" (Day 11) and "very tired despite more sleep" on the morning of Day 12.

Subject DI experienced slight nausea on Day 1, but this was limited to the first 3 h. He found it "difficult to stay awake" on Day 2, was "tired and sleepy" on Day 3, and had a "good day" although "no desire to work" on Day 4. He complained of fatigue on Days 5 and 6. On Day 10 he wrote, "typical day, the tests are becoming tiresome and fatigue is a big problem." He was the only one of the four subjects to gain weight during the early prerotation period; he gained 2 pounds during Days 1 and 2 but lost 1 pound during Days 3 and 4.

Experimenter 2, who was onboard for this experiment and is always highly insusceptible to motion sickness, had more than 500 hours experience at different velocities in the SRR. During the present experiment he reported slight dizziness during the first hour which rapidly subsided. Thereafter, he was virtually symptom free.

Comment: In the original report (9), it was noted that, even after symptoms of nausea and anorexia disappeared and no further head restrictions were enforced, all of the subjects continued to experience drowsiness and fatigue and to restrict their physical activity, which in turn minimized their head movements. None of the subjects had fully adapted to the experimental conditions by the end of Day 12. The common complaint was "fatigue," and although they were carrying out all of their assignments, the employment of their free time was directed toward rest and relaxation rather than toward things which required mental alertness or physical work. Subject BI complained most and Subject DI least, but the differences between the subjects were not pronounced.

This clinical distinction between an early period typified by the "nausea syndrome" and a late period typified by the "fatigue syndrome" not only was strongly emphasized but also there were biochemical correlates. Thus, the increase in urinary corticoids in the late prerotation period alone was significant, and the question arose whether this increase was in response to increasing the head movements (eliciting stimuli) or an increase in exercise. A conclusion was not possible but the matter was put as follows: "With the disappearance of nausea this restriction on head movements was lifted, thus increasing the bizarre stimulus to the semicircular canals. This paved the way for the appearance of effects which either 1) necessitated a longer time-course of adaptation than did nausea, 2) required a stronger stimulus for

their exhibition, or 3) had different transfer-patterns in terms of levels of stimulation." Clearly, the way was shown in which further experimentation would be worthwhile.

THE SOPITE SYNDROME AS PART OF SYMPTOMATOLOGY OF MOTION SICKNESS

As indicated earlier, the signs and symptoms of the sopite syndrome are commonly intertwined with the constellation of symptoms and symptom-complexes comprising motion sickness. The situation is analogous to that of the nausea syndrome when it is sometimes convenient to designate a symptom-complex and at other times to mention particular symptoms comprising part of the syndrome. The following section is a brief discussion in which a distinction is made between acute episodes of motion sickness and prolonged or chronic signs and symptoms that have been observed in slow rotation rooms.

Acute Episodes of Motion Sickness in Rotating Experiments

Assessment for susceptibility to acute motion sickness has been made in the SRR using a variety of procedures to elicit symptoms and various criteria for diagnosing different levels of intensity of the responses. Yawning and drowsiness are common early symptoms, and falling asleep has been reported as a rare manifestation during the execution of standardized head movements.

One series of systematic observations (unpublished data) involved 98 students, 19 to 33 years of age. These tests were conducted in a lighted rotating room and the subjects, with eyes open, were required to execute 40 standardized head movements at 1 rpm and at 1-rpm increments in angular velocity until the motion sickness endpoint M III (8) was reached. Frank motion sickness, which may include vomiting (8), begins after this endpoint. The time allowed for execution of each discrete head movement was 2 s in 84 instances and 4 s in the remaining 14. The findings in 28 of the 98 subjects who experienced drowsiness are summarized in Table II, where a distinction is made between exposures of 30 min or less (N = 12, mean = 18.3 min for Group A) and exposures longer than 30 min (N = 16, mean = 35.8 min for Group B). A noteworthy difference between the two groups is the greater percentage of incidence in drowsiness, both during and after rotation, in the more-motion-sickness-susceptible subjects of Group A. Although the long perseverance of symptoms after brief exposures was confined to drowsiness in this series of tests, in other tests we have observed persistence of additional symptoms as well; e.g., dizziness, headache, and increased susceptibility to sweating.

In another series of assessment tests, 250 normal subjects with eyes covered executed head movements at a predetermined angular velocity, judged to be stressful, in a rotating chair for periods ranging from 1 to 4 min (13). The motion sickness endpoint was Malaise III. Among the five cardinal overt symptoms of motion sickness—nausea syndrome, sweating, pallor, salivation, and drowsiness—the incidence of drowsiness was lowest, 21.6%. The decay time for disappearance of drowsiness was not measured but, with few exceptions, overt symptoms of motion sickness disappeared in minutes rather than hours.

Sea Sickness

The vast literature dealing with sea sickness is replete

TABLE II. SUMMARY OF OBSERVATIONS IN 28 OF 98 MEN, 19-37 YEARS OF AGE, WHO PARTICIPATED IN A SERIES OF STANDARD HEAD MOVEMENTS AT 1-RPM INCREMENTS IN VELOCITY ON A SLOW ROTATION ROOM (SRR) UNTIL THE MOTION SICKNESS ENDPOINT M III WAS REACHED.

Group A - SRR Exposures 30 Min or Less			Group B - SRR Exposures Longer Than 30 Min		
Subject Identification	Intensity of Drowsiness*		Subject Identification	Intensity of Drowsiness*	
Number	Prerotation	Postration (period)	Number	Prerotation	Postration (period)
2	I	0	5	0	I (< ½ h)
22	I	0	8	I	III (< ½ h)
25	I	0	10	I	0
30	0	I (< ½ h)	13	0	III (< ½ h)
31	0	I (< ½ h)	16	0	I (< ½ h)
38	II	II (8 h)	19	0	II (1 h)
44	I	I (< ½ h)	29	I	0
51	I	0	33	I	0
63	I	0	35	I	0
64	I	I (2 h)	40	0	II (< ½ h)
65	I	I (< ½ h)	41	0	II (< ½ h)
77	I	III (8 h)	49	I	0
			50	0	I (1 h)
			88	I	0
			91	I	0
			92	I	0

N = 12	I	II	III	0	I	II	III	0	N = 16	I	II	III	0	I	II	III	0
Incidence:	75%	8%	0%	17%	42%	8%	8%	42%		56%	0%	0%	44%	19%	19%	12%	

*I = slight, II = moderate, III = extreme, 0 = not drowsy.

with descriptions emphasizing not only nausea and vomiting but also a syndrome characterized by "psychic depression." Byrne (1) stated: "The effects of seasickness on the nervous system have been frequently alluded to in previous chapters. The psychic depression is frequently so extreme, and cerebral function so completely perverted, that self-control becomes an impossibility. Many of the numerous cases of suicide that occur at sea have for their immediate cause this psychic depression. . . ." Quix (17) listed three categories, one of which is "psychic disorders: state of depression, manifesting itself through slow ideation, lack of inclination to work, aboulia, weakness, fatigue, feeling of uneasiness, apathy that can lead to melancholy." Hill (11), under the heading of Lethargy, stated: "Sleep has an important bearing, so far unexplained, upon the problems of sea-sickness. It often has a strikingly recuperative virtue, the generalized inhibition which accompanies it favouring in some way the restoration of autonomic balance. This effect is not limited to the period of sleep, but usually continues for some time afterwards. Drowsiness, apathy, and occasionally mental hebetude without actual somnolence, are signs of vagotonia." Schwab, a psychiatrist with experience in World War II, pointed out (19) that motion sickness "involves a large number of minor symptoms that build up before actual nausea and vomiting occur. The first symptom is rather a subjective one and is described as an uneasy feeling with a certain amount of lack of interest in the task being done, the book being read, or the person with whom one is talking. No visible signs are shown by the subject at this point and a great many travelers bothered by motion sickness may pass through this phase alone and never develop further symptoms or complaints because of the termination of their trip. Such passengers would not admit to being ill even though they were aware of this rather subtle change in their habits." It is evident that Schwab clearly distinguished a depressed state that he regarded as "prodromal to motion sickness," comparable to what we have discussed above under the *Early Sopite Syndrome*.

Under conditions in which vomiting occurs repeatedly over long periods without replacement of fluid and electrolytes—let alone the problem of nutrition—it is difficult to make the distinction between such complicating effects and first order responses of vestibular origin.

Weekend sailors who are not fully adapted, as are sailors who are at sea for prolonged periods, are the largest group with which we are acquainted who regularly experience the syndrome under discussion. In a typical case, the symptoms appear after a long latent period and persist for periods measured in hours, rather than minutes, after return. The lethargy and drowsiness induced is not unpleasant; indeed, it is referred to as a desirable relaxing experience. Many in this group experience the typical symptomatology of motion sickness in ocean races and rely on antimotion sickness remedies.

One of our well-regarded technicians, with much experience at sea as well as in the SRR, has described experience on destroyers which may be summarized as follows: After a long period at sea when most of the crew members he knew were thoroughly adapted to the range of stimulus conditions commonly experienced, they did not lose this adaptation after a brief period ashore. But after a week—say on duty in a harbor where there was little turbulence—on resuming their cruise some would become sick, others experience drowsiness (the sopite syndrome), and the rest would remain symptom-free, not having lost their adaptation.

Air Sickness

Over 30 years ago Wendt (22), in summarizing his studies on "motion sickness in aviation," wrote: "It is suggested that much motion sickness is of a severity so low that it escapes the attention of both the victim and his associates. This 'subclinical' phase may not progress beyond the early stages of mild emotional depression and loss of motivation. It is hypothesized that the loss of motivation due to this degree of motion sickness will deleteriously affect the subject's motor coordinations and mental efficiency. "We suggest (without satisfactory supporting evidence) that much motion sickness is of a severity so low that it comes to the attention neither of the victim nor of his associates, being characterized only by emotional depression and loss of interest in work. Such motion sickness might be called 'subclinical'."

Air sickness, an important operational problem prior to cabin pressurization and before the introduction of jet aircraft, has largely been prevented. Even in the absence of sufficient turbulence to cause overt motion sickness in persons with average susceptibility, however, the sopite syndrome has been recognized during prolonged flights. It is also worth noting that antimotion sickness remedies, ordinarily eliciting mild drowsiness, may, nonetheless, exhibit efficacious effects.

Space Flight

During the orbital part of Skylab (SL) missions, motion sickness was experienced by some of the astronauts under operational or field conditions. The well-known difficulty in diagnosing motion sickness, short of nausea and vomiting, under operational or "field" conditions held true in Skylab missions, even though the astronauts were experienced in diagnosing experimentally induced acute motion sickness.

Fig. 1 represents an attempt to show the time course and intensity of motion sickness symptoms in the nine Skylab astronauts and indicates when antimotion sickness drugs were taken. The workshop findings that deserve special emphasis here involve the scientist pilot (SPT) in Skylab II and the three astronauts in Skylab III who did not take antimotion sickness (AMS) drugs prior to becoming motion sick. The Skylab IV crew was programmed to take AMS drugs through mission day 3, and thereafter as required; hence, the comparative absence of symptoms does not necessarily imply that they were insusceptible to motion sickness.

Skylab II: During operational conditions of the first manned mission (SL II) the commander (CDR) and pilot (PLT) did not experience symptoms of motion sickness, but the SPT, in a debriefing, commented as

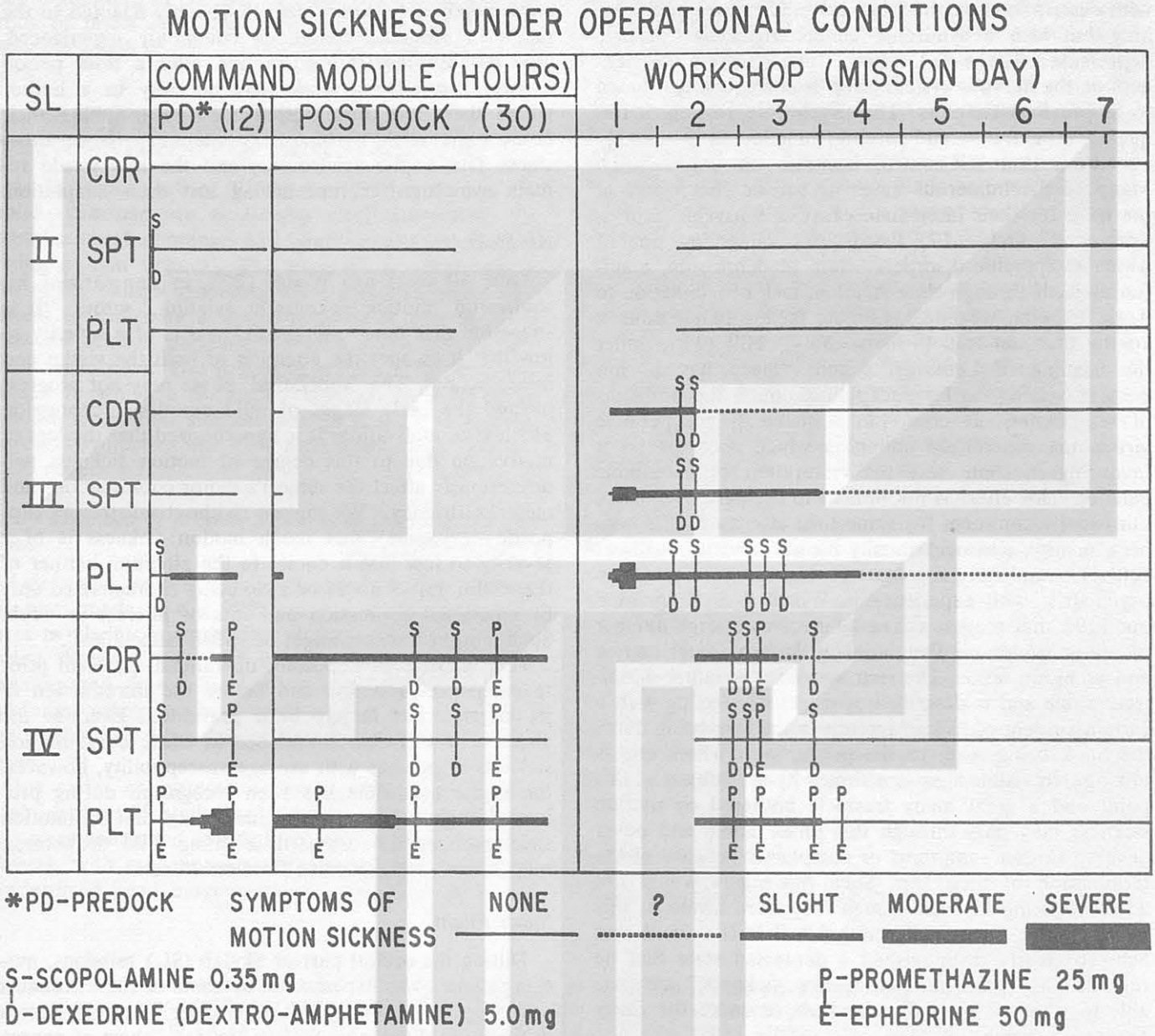

Fig. 1. Reported incidence of symptoms of motion sickness by astronauts during operations aboard Skylabs (SL) II, III, and IV. Antimotion sickness drug prevention and treatment with oral capsule is also shown. (CDR = commander, SPT = scientist pilot, PLT = pilot.)

follows: "I took the one 'scop/dex' (scopolamine 0.35 mg plus amphetamine 5 mg) right after insertion into orbit that I had preprogrammed myself to take, whether I needed it or not. . . . I felt that, although we had no overt symptoms of motion sickness or any other specific syndome related to transitioning to weightlessness, my appetite was a little bit less, neglecting Day 1 when it was completely normal and that it was a little less for somewhere like the first week. I don't know why this is. As I said, I had no particular symptoms. I felt fine during those first 7 d, but I thought I felt even better after that." In elaborating on this statement, the SPT reported that more mental effort was required to complete his tasks than on the first day; moreover, that his appetite was not so good. By the sixth or seventh day, the SPT had regained his bouyancy and his normal appetite.

In retrospect, the SPT agreed that the antimotion sickness drug may have accounted for his feeling very fit during the first day and that "motion sickness" might explain his mild symptoms, not reported during the operation, for the next 4 or 5 d.

In this connection, it is worth mentioning that Experimenter 3 (7) after making the transition to 4 rpm (Day 6) in the 25-d experiment recalled that he felt better on Day 1, when he took scopolamine and amphetamine, than on Day 2, when the drug was omitted. Experimenter 3 wrote in his log: "Observer 2 and 1 are less energetic than yesterday, wonder whether amphetamine cushioned the rotational fatigue." Another possibility was the antimotion sickness efficacy of the drug.

Although systematic observations have not been carried out, competent observers have noted that even antimotion sickness remedies with a depressant effect nonetheless seem to counter the early sopite syndrome.

Skylab III: The SL III astronauts were quite confident that they would not become sick in weightlessness and, hence, did not take AMS drugs as a preventive measure. Nevertheless, the PLT experienced mild symptoms of motion sickness within 1 h of insertion into orbit; these symptoms appeared in close relation to doffing his space suit. The scopolamine-d-amphetamine combination ameliorated his symptoms for a few hours. The PLT deliberately refrained from taking another antimotion sickness capsule while in the command module and, when his symptoms returned, he restricted his activities.

During the activation of the workshop, about 11 h into the flight, the CDR and SPT also reported the onset of motion sickness, and the SPT vomited. Shortly thereafter, the PLT also vomited. In Fig. 1 it is seen that the severity and duration of definite motion sickness symptoms were greatest in the case of the PLT and least in the CDR.

Skylab IV: In the light of the SL III findings, the SL IV crewmen had a choice of two AMS drugs when promethazine 25 mg plus ephedrine 50 mg was added. One or the other AMS drug combination was taken through mission Day 3 and thereafter as required.

Comment: In astronauts experiencing motion sickness, our interest centers on the periods, measured in days, between the disappearance of the typical symptoms of motion sickness and complete restoration of fitness and well-being. During these periods of mild asthenia, it is difficult to sort out the countervailing influences of active eliciting and passive restoring mechanisms.

GENERAL DISCUSSION

It is instructive to contrast the well-known nausea syndrome with the sopite syndrome. Typically, feeling sick (nausea) is preceded by a vague "stomach awareness," then "stomach discomfort," which symptoms may at first come and go. Nausea is more likely to remain and may be followed by vomiting with its second and higher order complications. In a motion environment, nausea or nausea and vomiting are virtually pathognomonic symptoms. Indeed, under operational conditions, a diagnosis of motion sickness based on symptoms other than nausea and vomiting may be questioned. There is nothing "normal" about nausea and vomiting; hence, differential diagnosis is not required.

In most instances, symptoms characterizing the sopite syndrome are also experienced under normal conditions; hence, differential diagnosis is a requirement. A diagnosis is usually based on the symptoms per se and on the fact that they are inappropriate under the circumstances. Under experimental conditions, a correct diagnosis is made far easier than under operational conditions. Even the experimenter or experienced observer has difficulty under operational conditions, and this points to a need for diagnostic tests that supplement clinical appraisal.

When one is dealing with acute experimental motion sickness under carefully controlled conditions, the diagnosis is often clear-cut. Dramatic instances are those when subjects have fallen asleep while executing head movements. The word "drowsiness" does not always precisely fit what the subject experiences. The subject sometimes loses his interest in the task (executing head movements) and, especially at high rpm, indicates his desire to stop, giving one or more of a variety of reasons such as fatigue, "back pain," and aching in the neck region. After adaptation, however, such a request from the same individual is rare. It is worth mentioning here that tests carried out under the influence of antimotion sickness drugs with mild narcoleptic effects may actually prevent the manifestations of the sopite syndrome.

If it is assumed that the sopite syndrome may be experienced in the virtual absence of other symptoms or after other symptoms have disappeared, then it follows that we are dealing with first order effects. In other words, this syndrome may have a time course that differs from all other overt symptoms of motion sickness. The sometimes-long exposure before symptoms appear and their relatively slow disappearance suggest that a neurohumoral factor is responsible.

Already there is proof that exposure to eliciting stimuli results in a release of ADH (20) and increased urinary excretion of adrenalin, noradrenalin, and 17-hydroxycorticosteroids (2). It is worth speculating whether the sleep factor described by Papenheimer and his associates (3,16) might be involved.

In one of our subjects, a latent vulnerability to psychosomatic disorder was demonstrated. The period required for its demonstration, however, renders the procedure followed unsuitable for investigative purposes. Our recent experience in compressing in time the acquisition of adaptation effects indicates that there is a possibility that this objective can be achieved in the elicitation of psychosomatic manifestations.

ACKNOWLEDGMENT

We are greatly indebted to the helpful suggestions of our colleagues and have profited from the constructive criticisms made by Dr. William E. Collins based on a review of the manuscript.

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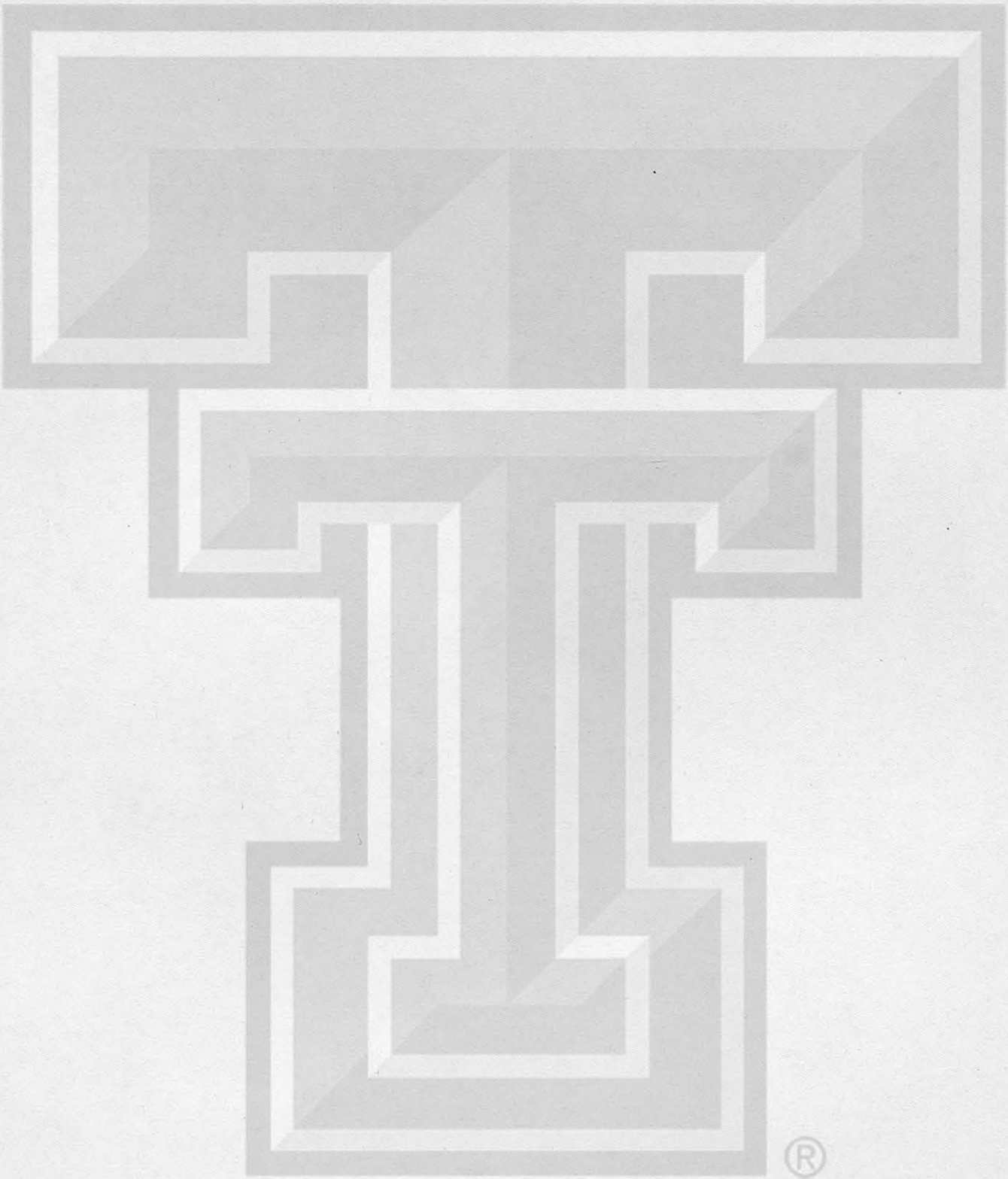

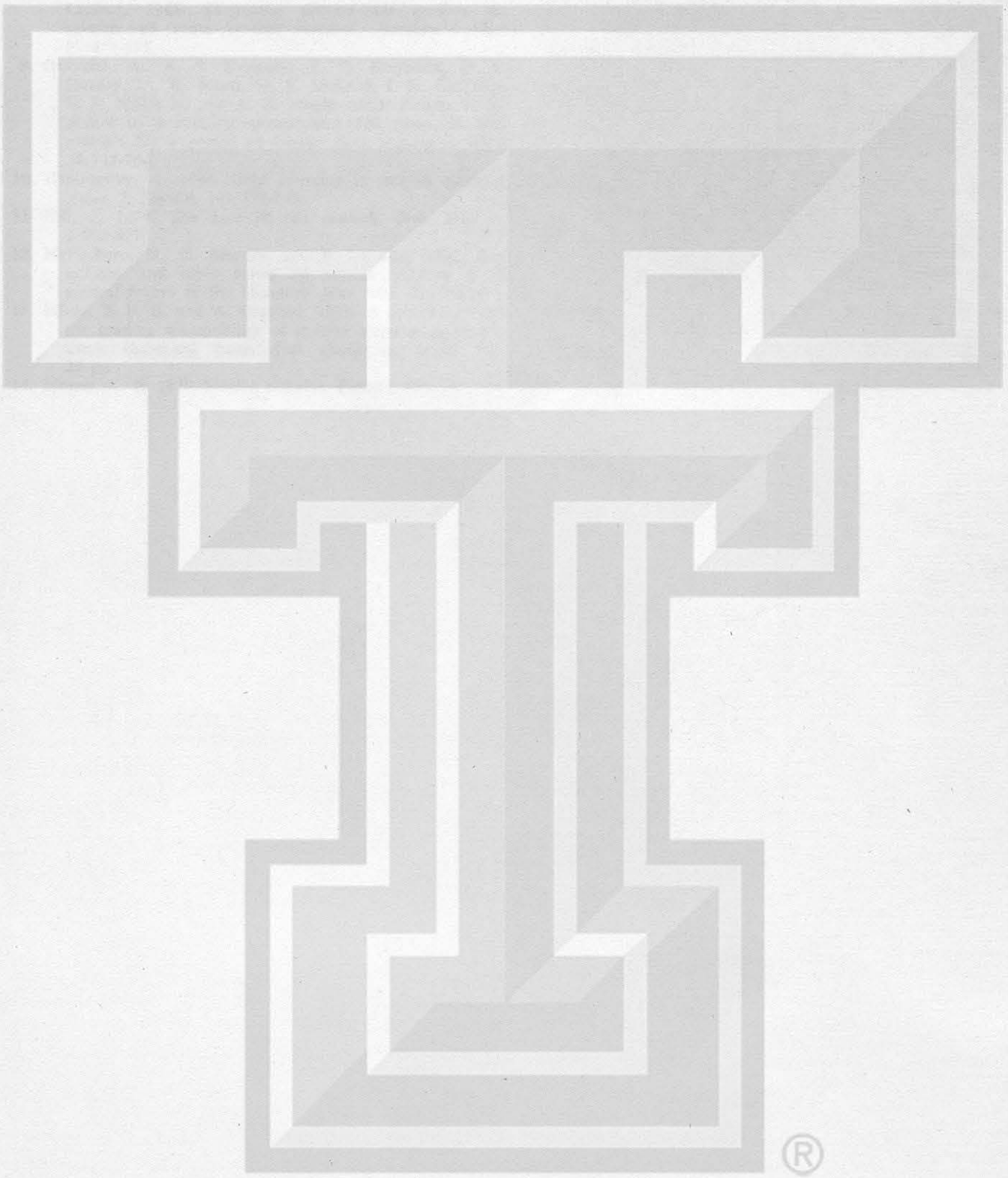

Airborne Testing of Three Antimotion Sickness Preparations

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JOHNSON, W. H., K. E. MONEY, and A. GRAYBIEL. *Airborne testing of three antimotion sickness preparations.* Aviat. Space Environ. Med. 47(11):1214-1216, 1976.

Thirteen human volunteers were exposed to weekly flights in which standardized, steep turns were used to produce motion sickness. A combination of promethazine hydrochloride (25 mg) plus ephedrine sulphate (25 mg) was found to be equally as effective as the combination of l-scopolamine hydrobromide (0.35 mg) plus d-amphetamine sulphate (5 mg). Droperidol (2.5 mg) was indistinguishable from the placebo. It was concluded that the treatment of choice for motion sickness is promethazine plus ephedrine.

AN IMPORTANT advance in antimotion sickness drug therapy is the recent discovery (1) that, in the slow rotation room (Pensacola, Fl), a combination of promethazine and ephedrin is equally as effective as the longer-used scopolamine plus amphetamine combination, which has been found repeatedly to be the best drug treatment for the prevention of motion sickness (2-4). If the generality became well established—that the new promethazine plus ephedrine combination is equally as effective as scopolamine plus amphetamine—probably this would become the treatment of choice for motion sickness, because this medication can be considered safer for repeated use and can be expected to be more effective for motions of long duration. An independent comparison of the two combinations, and in a different (inflight) environment, was therefore carried out. Tests of the effectiveness of droperidol, which is known (5,6) to suppress vertigo and nystagmus, were included in the study.

Supported by a grant from the National Aeronautics and Space Administration, Washington, DC. Report No. 76-X-41.

MATERIALS AND METHODS

The Subjects: 20 normal volunteer subjects were chosen on the basis of a selection questionnaire (7) and on the basis of vestibular, auditory, and general medical screening. These 20 were given a preliminary test flight to establish susceptibility to the motion sickness stimulus, and the 14 most susceptible were selected. One of these 14 withdrew before the end of the experiment, so that the procedures were completed with 13 subjects.

The Drugs: Four different preparations were placed in opaque capsules, with uniform packing by the Faculty of Pharmacy of the University of Toronto. The four preparations were:

1) l-scopolamine hydrobromide (0.35 mg) plus d-amphetamine sulphate (5 mg)
2) promethazine hydrochloride (25 mg) plus ephedrine sulphate (25 mg)
3) droperidol (2.5 mg)
4) lactose (placebo)

The capsules were placed in envelopes marked 1, 2, 3, or 4, and the code whereby these numbers related to the preparations was unknown to the experimenters and the subjects. Although the code was available in case of serious adverse drug reaction, it was kept sealed until after the experiment was finished and the statistical analysis of the results was completed (double-blind technique).

Plan: Each subject experienced four flights in addition to the selection flight, and these were spaced at least 6 d apart (usually seven). One of the four capsule preparations was used in each of the four flights. The subjects reported for the flights in the morning after only a small liquid breakfast and after refraining from consumption of alcohol or any other drugs during the preceeding 24 h. They filled in the pre-test questionnaire (7), which revealed their fitness for the flight and any deviations from preflight instructions, and then ingested the capsule from a designated numbered envelope at 1.5 h before aircraft boarding time; this was approxi-

TABLE I. ORDER OF CAPSULE ADMINISTRATION.

Subject Number	PREPARATION CODE NUMBER First Flight	Second Flight	Third Flight	Fourth Flight
1	1	2	3	4
2	1	4	2	3
3	1	3	4	2
4	2	1	4	3
5	3	1	2	4
6	4	1	3	2
7	2	3	1	4
8	4	2	1	3
9	3	4	1	2
10	2	4	3	1
11	3	2	4	1
12	4	3	2	1
.....				
13	3	2	4	1

mately 2 hours before motion stimulus time. Each participant was randomly assigned a number, and the subject's number decided the order sequence of drug administration (Table I). The sequences were chosen so that any possible order effects would be cancelled out.

The subjects flew in groups of four, and each subject always occupied the same seat in the aircraft and was observed by the same observer. Two observers, who had been previously habituated to the stimulus flew with the subjects. Each observer observed two subjects and recorded signs of sickness before takeoff, after landing, and at 2-min intervals during the provocative motion. The subjects also recorded their own symptomatology at these times, and the severity of sickness during each 2-min interval was rated numerically according to the diagnostic criteria of Graybiel *et al.* (1).

The motion was provided by a Canadian Forces 10 TAG de Havilland Otter aircraft (DHC 3, CSR123) of 400 Squadron, and all flights were flown by the same pilot (K.M.) with the exception of one flight by a pilot who had accompanied the preliminary flights. When the aircraft reached the designated training area, the motion stimulus pattern was imposed for 15 min for eight of the subjects and for 25 min for the four least susceptible subjects. The motion consisted of 30° banked turns from east to north to east, etc., at constant altitude, using maximum rate of roll into the turns. When the stimulus time was half over, the aircraft was turned around and the remaining turns were made from south to west to south, etc. In this aircraft, flying at 90 knots, the cycle from north to east and back to north required 30 s, so that the frequency of the stimulus was two complete cycles per minute, a frequency perhaps lower than ideal for production of motion sickness (8).

RESULTS AND DISCUSSION

Several flights were missed by some of the first 12 subjects, for a variety of reasons, and the make-up flights were used also to test the thirteenth subject. The scores of sickness severity after ingestion of each of the four preparations were analyzed statistically by the 2-min intervals using the Kruskal-Wallis four-sample rank test (9). Table II illustrates this analysis.

TABLE II. KRUSKAL-WALLIS VALUES FOR H FOR TEST INTERVALS (FOUR-SAMPLE RANK TEST).

Interval (min)	2	4	6	8	10	12	14
H	1.34	3.58	1.88	2.74	5.10	7.36	8.76

For four samples of randomly distributed ranks, H behaves approximately as a X^2 variable with three degrees of freedom. A significant H value indicates a tendency for at least one sample to differ from all samples taken together. Critical values for H are 6.25 at the 10% level of confidence, and 7.81 at the 5% level.

The four-sample rank tests did not reveal any significant difference among the four kinds of capsules until the 12-min intervals, although the relatively large increase in H between intervals 8 and 10 is possibly caused by the difference beginning to appear. Statistical treatment was given to only the durations common to all the tests (seven 2-min intervals for a total of 14 min), but in the four subjects who endured 25 min of the stimulus, the trends established in the first 14 min appeared to continue for the remaining 11 minutes. The scores of sickness severity were significantly lower after ingestion of the promethazine plus ephedrine combination and of the scopolamine plus amphetamine combination; the scores were higher after the placebo and after droperidol.

Two sample tests did not reveal any significant difference between the severity of sickness following droperidol and that following the placebo, nor any significant difference between the severity with scopolamine plus amphetamine and with promethazine plus ephedrine.

The scopolamine plus amphetamine combination was the most effective in preventing motion sickness for six subjects and tied for best in one more, subject No. 9; the promethazine plus ephedrine combination was most effective for four subjects and tied for best in subject No. 9; droperidol was most effective in two subjects; the placebo was the most effective in no subject.

Vomiting occurred in 10 of the 52 subject tests; five times after ingestion of droperidol, four times after ingestion of the placebo, once after ingestion of scopolamine plus amphetamine, and never after ingestion of promethazine plus ephedrine. The percentage of persons protected from vomiting by a drug, as described by Holling *et al.* (10) is not universally regarded as a valuable index (11,12), but it is not without usefulness for comparative purposes (13). If, for purposes of calculating the percentage of persons protected, droperidol be considered another placebo, then in the 26 placebo tests, vomiting occurred in 35%. In the 13 tests of promethazine plus ephedrine there was no vomiting (100% protection), and in the 13 tests of scopolamine plus amphetamine there was only the one instance of vomiting (77% protection).

It is clear that, in this experiment, the effectiveness of the scopolamine (0.35 mg) plus d-amphetamine (5 mg) combination is not distinguishable from the effectiveness of the promethazine (25 mg) plus ephedrine

(25 mg) combination, and that the finding of Graybiel *et al.* (1) is confirmed.

Vestibulo-gastric illness can be caused by a wide variety of stimuli, some of which (14,15) do not even involve bodily movement as the prime cause. There is also a wide variety of response-time relationships of different drugs (12,16) and a wide variety of doses that might be investigated. It is difficult, therefore, to have confidence in generalities concerning antimotion sickness drugs; it seems reasonable, nevertheless, to say that there is no present evidence that any preparation is better than the promethazine plus ephedrine combination, and it seems reasonable to consider this combination as the drug of choice for motion sickness.

Another matter of significance is the finding of the relative ineffectiveness of droperidol (2.5 mg) in the prevention of motion sickness in these airborne tests, even though this medication has proven to be markedly effective in the control of spontaneous nystagmus due to vestibular disease (6). Although disturbance of the vestibular end-organs may well constitute the primary activating stimulus involved in both motion sickness and many vestibular disorders (e.g. Menière's disease), the findings of this investigation may indicate involvement of different central pathways.

The excellent results found here with this new drug combination are particularly impressive because the motion stimulus was of short duration and because the interval between ingestion and the start of the stimulus was only 2 h. According to its antihistaminic action in skin, promethazine reaches its maximum blood concentration after 3 to 5 h following oral ingestion, and it retains activity for 48 h (12,16,17). It is reasonable, therefore, to think that if this new combination is equally as effective as scopolamine plus amphetamine under the conditions of this experiment, then under conditions of long-duration motion promethazine plus ephedrine should be superior to scopolamine plus amphetamine, a conclusion that might be drawn also from previous studies of these drugs used singly (12, 18).

ACKNOWLEDGMENTS

The authors gratefully acknowledge Ron Cardin, J. Laufer, Al Nicholas, and Doug Topliff for technical assistance, Dr. W. O'Hara for medical screening and supervision, Prof. G. Walker, Faculty of Pharmacy, University of Toronto for preparation of the capsules and the double-blind code, Bud Rodden for help with experimental design and statistical analysis, the 10th tactical air group and 2 RSU for supplying aircraft and crew, NASA (Grant No. NSG 7079) for financial support, and the experimental subjects for repeatedly enduring the unendurable; appreciation is also expressed to McNeil Laboratories (Canada) Ltd.

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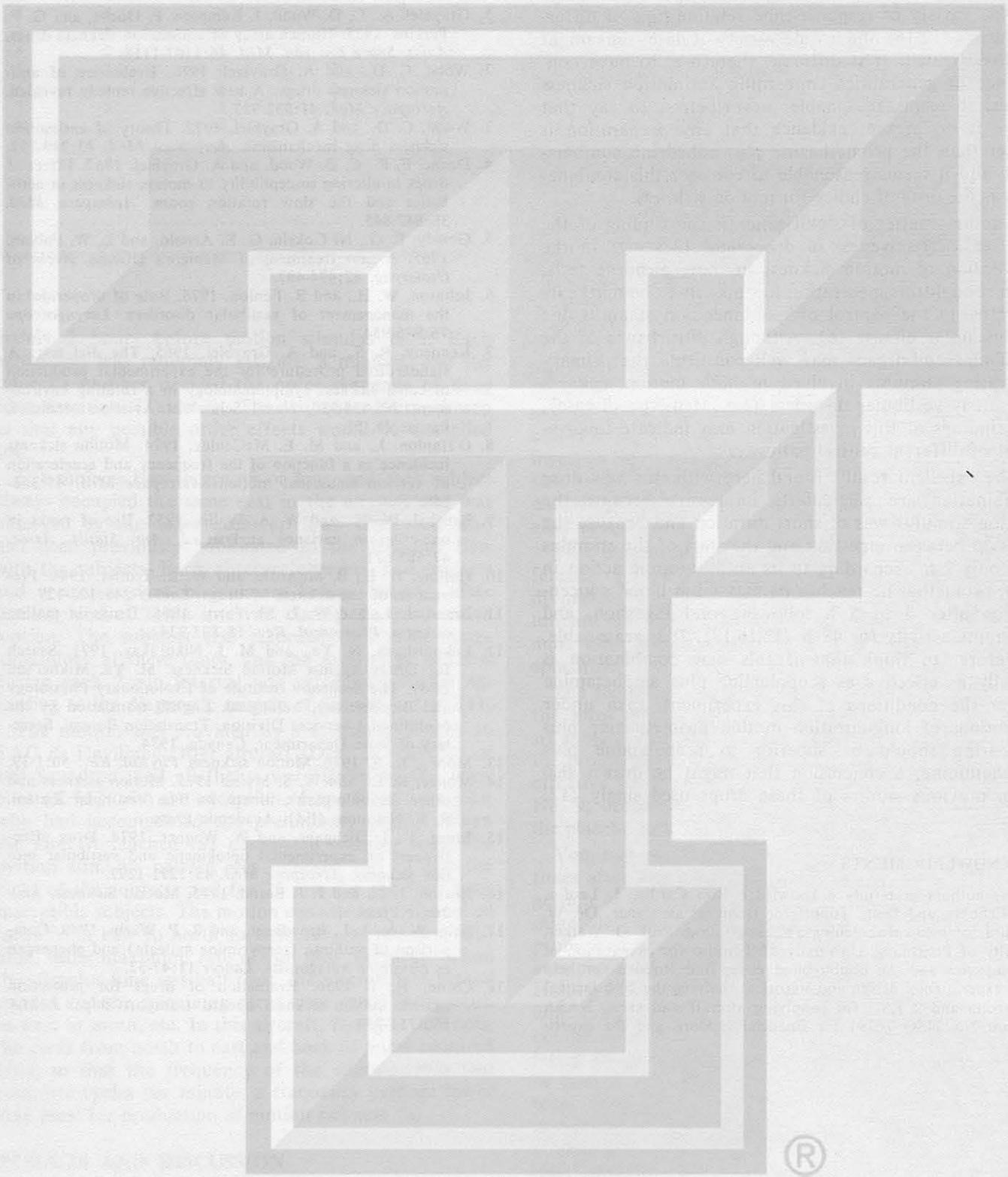

NASA ORDER NO. T-5904B
FINAL PROGRESS REPORT NO. 35

THE PREVENTION OF VESTIBULAR SIDE EFFECTS IN WEIGHTLESSNESS

Submitted to

Office of Life Sciences, Lyndon B. Johnson Space Center,
National Aeronautics and Space Administration, Houston, Texas

By

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Period Covered
1 January 1976 - 30 December 1976

The past four years, working under NASA Order No. T-5904B (which subsumed Contract NDPT-T-81633) marked the transition from Skylab to Spacelab. During this four-year period 18 reports were published (1-18), and some insight has been gained in explaining and dealing with side effects experienced by Skylab astronauts.

Skylab findings under operational conditions aloft were clear-cut in revealing performance decrement in five astronauts due to symptoms characteristic of motion sickness. The findings, under experimental conditions, on and after Mission Day 8 were equally clear-cut in revealing trivial, if any, symptoms of motion sickness, but curious side effects in the rotating litter chair (RLC) were elicited. Fortuitously, some recent investigations have provided an explanation for the so-called "vertigo" experienced in the RLC, but our explanation for the symptoms characteristic of motion sickness has not satisfied everyone.

It would be difficult to raise a more important question than whether free fall qualifies as a motion environment in the sense that head movements are essential to elicit symptoms of motion sickness. If this question is answered in the affirmative then it follows that executing head movements is essential in acquiring adaptation. Our studies are tackling this problem from two aspects. In the KC-135 susceptibility to motion sickness in the free-fall parts of the parabola are compared with head-fixed and head-moving while seated and while rotating at 30 rpm. The second aspect deals with the opinion expressed by some of the astronauts and investigators associated with the Skylab program that a headward shift of body fluids was the important factor eliciting motion sickness in orbit. Our approach is to compare susceptibility to motion sickness while rotating about the Z-axis at 30 rpm with head 10 degrees above and 10 degrees below the horizontal.

Assuming the problem of etiology is solved, we would still require, in brief Spacelab missions, the means of preventing performance decrements due to motion sickness in some persons. Antimotion sickness remedies provide the simplest and sometimes the only means. Recent studies have been directed both toward prevention and treatment. For prevention we are attempting to identify, on an individual basis, two long-term highly efficacious antimotion sickness drugs for every subject. For treatment of early or acute symptoms of motion sickness we are identifying highly efficacious remedies for intramuscular injection.

In addition to the tasks mentioned above, progress, in varying degrees, has been made in carrying out the following assessments:

1. Susceptibility to motion sickness in the KC-135 during free fall.
2. Rate of acquisition of adaptation effects in the laboratory.
3. Transfer of overadaptation acquired in the laboratory to free-fall parts of the parabola in the KC-135.
4. Rate of recovery from acute motion sickness.

It is convenient to summarize all of the work accomplished under the following three headings:

1. Attempts to determine if free-fall is a "true" motion environment.

1.1 In the KC-135 during free fall, differences in susceptibility to motion sickness are measured between head fixed and head moving while restrained in a seat and during rotation at 30 rpm. The first step has been to place subjects in one of three categories based on their responses during the first two flights. In our first group of 40 subjects, 18 were virtually symptom-free (Category I), 11 became frankly sick (Category III), and the remaining 11 fell in between Category I and Category III, i.e., Category II.

In Table I are summarized the findings in 14 of 18 members in Category I. The results are in terms of whether they manifested a change in category with head moving compared with head fixed. When restrained in the seat two of the 14 subjects demonstrated a substantial change. When rotating at 30 rpm four subjects demonstrated a substantial change; all four, on one or more tests, became frankly motion sick.

In Table II are summarized the findings in tests similar to those mentioned above on most of the 11 subjects in Category II. In seven subjects tested while seated, four became frankly sick when executing head movements on at least one occasion when the control test (in a particular series) showed no changes in category. When rotating at 30 rpm three of four subjects tested became frankly sick when executing the head movements.

To sum up, there is some evidence that supports the view that execution of head movements in the free-fall phases of parabolic flight evokes motion sickness. It is to be expected that the elicitation of symptoms would occur more readily in the RLC than while restrained in a seat. One additional finding may be significant, namely, the most stressful movement was to bend forward and return to the upright (FU); this movement might stimulate the receptors in the otolith organs when rotating at 30 rpm. In contrast, rapid swiveling movements (right-left) generating higher angular accelerations were notably less stressful.

1.2 It is difficult to refute investigators who maintain that motion sickness in zero gravity is due to such factors as headward shift of body fluids, changes in electrolytes and low blood pressure. The reason is that not only are secondary etiological factors always acting, but a secondary factor may even be the most important cause for appearance of symptoms.

The results of an experiment just published (16) exploited the fact that normal persons rotated about an Earth-horizontal axis vary in their susceptibility to motion sickness. The rationale was to use the head-horizontal position as a model for zero gravity. Twelve subjects after exposure for one hour with head horizontal, 10 degrees head-up and 10 degrees head-down, were then rotated for one hour at 30 rpm; there were no significant differences observed in susceptibility to motion sickness. One more experiment is planned using longer exposures (6 or 8 hours) prior to rotation.

2. Attempt to identify, on an individual basis, two long-term highly efficacious antimotion sickness drugs for every subject.

2.1 Assessments in a slow rotation room.

The efficacy of antimotion sickness drugs may be evaluated in any motion environment if it is kept in mind that persons may differ in their susceptibility to motion sickness in different motion environments. Scopolamine, for example, has been proven to be efficacious at sea, during vertical oscillation under laboratory conditions, in aircraft and in a rotating room. Recently we have demonstrated the efficacy of a combination of promethazine and ephedrine, and it has proved to be efficacious in aerobatic flight (17).

Assessments under operational conditions usually rely on large numbers of subjects presumed to be average and normal, using vomiting or nausea as the endpoint. Efficacy of the drug or drugs tested is usually given in terms of per cent of the group responding favorably.

Most of our bioassays for testing the influence of drugs on motion sickness have been carried out using a slow rotation room (SRR) in a laboratory setting. In the past, the procedure (described elsewhere in more detail (19)) involved: 1) the selection of subjects, which included not only a comprehensive medical evaluation but, also, selective assessment of canalicular and otolith function; 2) familiarization; 3) generation of stressful stimuli by the execution of standardized head movements during rotation at a predetermined angular velocity; 4) the use of a motion sickness endpoint (or the execution of a given number of head movements); and 5) administration of drugs and placebos using a latin square of order 10 and a double-blind technique. Shortcomings in the method included 1) the ceiling on the test was often reached before the motion sickness endpoint, 2) the placebo baseline was inadequate, and 3) the results did not apply to individuals within these groups.

A substantial effort was made (15, 20) to improve the procedure by 1) substitution of an incremental stress profile for a predetermined constant level of stress, 2) modification of a latin square of order 4 or 8 to provide a better placebo baseline, and 3) categorizing response as inconsequential, substantially beneficial (hereafter beneficial) and substantially

detrimental. It was found that 1) a large number of placebos were indeed needed to establish a baseline with which the response to a drug could be satisfactorily compared, and 2) a relatively long period between tests was required to minimize the retention of any adaptation effects. A strict double-blind procedure was followed except for the fact that a very high rpm score on one test would imply that a placebo would be administered on the next test. High scores may also be due to adaptation effects.

Some details of the present method are described with the aid of Figure 1, which represents actual findings in a recent experiment. The range of placebo endpoints is defined by drawing two horizontal lines and the mean placebo endpoint within this range indicated. Twice the range above and below the mean defines the limits which the response to administration of a drug is deemed "inconsequential." Above and below the inconsequential range are, respectively, the beneficial and detrimental ranges. Quite often the placebo range is influenced by adaptation effects in which event sloping baselines must be used. Rarely, a placebo baseline is virtually or actually flat, in which event an arbitrary inconsequential rpm range (usually 2 rpm) is defined. Also, rarely, the rpm ceiling on the test is reached when a placebo is administered. This phenomenon has vitiated the results in a few tests.

Thus far, the two best prospects for long-term use are scopolamine administered transdermally and a combination of promethazine and ephedrine, 12.5 mg each. In Table III the high efficacy of scopolamine is demonstrated when given orally, but, for long-term use, it must be administered transdermally. Preparations have been made for using a transdermal delivery system twice as potent as that shown at the top of Table III.

Table IV summarizes our findings with promethazine plus ephedrine. Note the much smaller doses used than in the last Skylab mission. We have yet to demonstrate long-term efficacy, and this is where the small doses should prove to be advantageous. If these two preparations (TTS-scopolamine and the combination of promethazine and ephedrine) meet our expectations, a satisfactory response in some 80-90 per cent of our subjects would be a conservative estimate.

2.2 It is convenient here to mention the use of antimotion sickness drugs administered by intramuscular injection. The KC-135 offers almost a unique opportunity to treat acute severe motion sickness. This stems from the fact that about one-quarter of our subjects are highly susceptible to motion sickness when seated with head fixed. Among our first 40 subjects the 11 in Category III all experienced nausea and vomiting not later than the 16th parabola. They tolerate treatment by injection of an antimotion sickness remedy in the KC-135 (an exciting experience), a measure they would object to in the laboratory.

Table V summarizes our experience in the KC-135. At first we were hesitant in resorting to injection, based partly on the dislike for "shots" expressed by the subjects. This dislike has changed, and a subject sometimes requests an injection. During our learning period we used promethazine, and Table V discloses that if the drug is administered during the parabola when frank sickness is experienced (or the antecedent parabola) the results are highly efficacious. We next tried dimenhydrinate in the recommended dosage with obviously less efficacious results. Lastly, we have used scopolamine in relatively large doses (eliciting prominent side effects) with excellent results.

3. Assessments that can be validated in orbital flight.

3.1 Susceptibility to motion sickness during free fall in the KC-135.

The difficulty here is that parabolic flight falls into the category of a complete motion environment, i.e., persons may become motion sick by the movements of the plane per se. As indicated above, only 18 of our first 40 subjects were symptom free or nearly symptom free. If thisholds true for a random group, only half could be properly tested in the free-fall part of the parabola by comparing head fixed and head moving stimulus conditions.

Two observations may be worth noting. Among our first 40 subjects the categorization based on the first two flights predicted susceptibility in subsequent flights except in four instances. In one instance a subject symptom free in the first two flights subsequently became frankly motion sick. In the remaining three subjects, one in Category III and two in Category II gradually adapted to the stimulus conditions.

At this time, only subjects in Category I would qualify for experiments involving validation in orbital flight.

3.2 Rate of acquisition of adaptation.

Some knowledgeable investigators hold the opinion that rapid adaptation in a motion environment is a more desirable characteristic than is low susceptibility. Most of our findings have been obtained incidentally. A few experimental trials have been conducted in an effort to compress in time the period required to assess this important phenomenon. The results suggest that tests on three consecutive days may be necessary.

Figure 2 illustrates extremely rapid acquisition and excellent retention of adaptation in a subject substantially less susceptible to motion sickness than the average (around 8 rpm) in the slow rotation room.

Figure 3 shows results in a subject even less susceptible than the subject mentioned above who also reached the ceiling on the test (executing 1080 head movements) following administration of the first drug. Yet there is no evidence of retention of whatever adaptation was acquired.

Figure 4 illustrates a subject with higher susceptibility than the average; hence, executed relatively few head movements but retained a substantial amount of the little adaptation that may have been acquired.

Our goal is to develop a quick assessment to reveal the rate of acquisition of adaptation effects. It is hypothesized that the rate of acquisition of adaptation is similar insofar as involvement of the vestibular system is concerned in all motion environments. This hypothesis will be tested.

3.3 Transfer of overadaptation acquired in the laboratory to the zero-gravity phase of parabolic flight.

Recently, the phenomenon of "overadaptation" has been proven in a rotating room, the full extent of which remains to be demonstrated. In the SRR execution of a single head movement through 90 degrees of arc using small increments in rpm up to 7 rpm will ensure virtual immunity to motion sickness up to 10 or 12 rpm not only counter-clockwise, in the practiced direction, but, also, clockwise. Moreover, it has been shown that this adaptation is retained for periods at least as long as a month. To expedite the acquisition of such high levels of adaptation a new device has been fabricated at the Applied Physics Laboratory at Johns Hopkins (Figure 5) and will soon be installed.

3.4 Rate of recovery from acute motion sickness.

Many incidental findings reveal great individual variation in the rate of recovery from acute motion sickness, and it is altogether likely that these variations are subject-related rather than related to the motion environment. In other words, subject-related recovery would hold true in different motion environments and especially if secondary etiological factors were similar, e.g., eyes open or eyes closed.

Systematic measurements have been made on a few subjects to aid in devising a brief assessment test. The stress profile required the execution of 80 head movements at 2 rpm and at each 2-rpm step increase in angular velocity until the motion sickness end-point (slight nausea) was reached. The subject, with head fixed, remained at the terminal velocity until symptom-free, then slowly returned to zero velocity. At the end of one hour the test was repeated. The same procedure was followed on three consecutive days. The findings suggest that the one-day test may suffice.

Exploratory Probes

1. Effect of high gravitoinertial force on susceptibility to motion sickness. Systematic measurements have not revealed that the execution of head and body movements at the center and periphery of a SRR significantly affects susceptibility. Before publishing the findings, tests will be repeated using the PHM device, thus ruling out possible secondary factors associated with "hard" and "easy" work.

2. The elicitation of nystagmus and the oculogyral illusion using a Sear's vibrator deserves continued exploitation for the reason that it is suitable for use in orbital flight.

3. We have a very-short-arm (VSA) centrifuge and Dr. Grand is putting it into operation. Dr. Matsunaga in Japan will cooperate with us in its use. Dr. Matsunaga is best known for his work on differentiating central and peripheral causes of abnormal nystagmograms.

Subjects and Devices

Subjects. Our pool of subjects, nearly all from the Liberty Bible College, is around 60, but some 20 will be leaving the Pensacola area after June. Routine assessments include 1) a careful, comprehensive medical evaluation with attention directed to such factors as maturity, mental stability, and possible presence of psychobiological defects; 2) qualification for flights in the KC-135; 3) administration of a motion sickness questionnaire; 4) assessments ensuring functional integrity of the visual, otolithic and canalicular systems; and 5) tests measuring susceptibility to motion sickness in different motion environments.

We have explored the possibility of using female subjects from the Bible College. This will not pose a problem if we satisfy the administrators that they will, in effect, be properly chaperoned. We still need to get together with the Dean and work out additional details centering around the menstrual period.

Devices other than the KC-135. We have two slow rotation rooms. A SRR is only a "partial motion environment" in that the subject (if near the center of rotation) is virtually symptom-free unless head movements or head and body movements are made out of the plane of the room's rotation. Zero gravity is also a partial motion environment if head (and body) movements are required for elicitation of side effects. Assuming zero gravity is a motion environment, it presents only one level of a stressor effect. Any head movement presumably makes it a "complete" motion environment until adaptation has been achieved.

One of our two rooms (the old SRR) is now "down" for the reason that the foundation has settled and the supporting structure nearly touches the deck. The room will be jacked up some three inches as soon as a contract with a Dallas firm is approved by local administrators.

Off-vertical rotating chair. This device, Figure 6, can be used in the upright or tilted mode. When tilted, during constant angular velocity, a rotating linear acceleration vector is generated that continually (and selectively) stimulates, in the labyrinth, the macular receptor systems. In provocative testing both the angle of tilt and the rpm are manipulated in different ways. Motion sickness endpoints can be expressed as a single score facilitating comparisons in susceptibility among subjects. This device is in constant use.

Z-axis recumbent rotator. A new apparatus termed the Z-axis recumbent rotator (ZARR) device, was especially built for use in the KC-135 (Figure 7). Two new features (rotation about the Earth-horizontal is not new) have greatly added to its usefulness,

namely, the provision to tilt the subject head down and the means to manipulate touch, pressure, and kinesthetic receptor systems. Early findings include elicitation of types of disorientation experienced by Skylab astronauts.

Cineglobe. This comprises the equipment and movies shown at the World's Fair when it was held near Shea Stadium. Motion sickness is elicited in many subjects who view the movies for periods varying from a few minutes up to an hour. Ataxiometry will be an added feature, using a Kistler device.

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KC-135 Category I: Findings in 14 of 18 Members of 1st Pool of 40 Subjects

	In Seat				Rotating 30 RPM					
	Head Fixed		Head Move		Head Fixed		Head Move*			
Subj.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	Eff. Drug** (M/S pts) Head Fixed	Head Move
1	2	No	8	No	2	No	4	2 = III	Not tried	
2	2	No					3‡	No	Not tried	
4	2	No	5	No			3	2 = II 1 = III	Not tried	
5	3	No	3	2 = II	3	III 3	2	III 1	2, 0	1, 8, 6
6	2	No	2	No	1	No	1	No		
7	2	No	6	No	1	No	1	No		
8	2	No	2	No	1	No	1	III		
9	5	No	4	No	1	II	1	III	Not tried	
12	2	No	4	No						
14	3	1 = II	3	1 = II	2	1 = III	1	III	Not tried	
15	2	No	1	No						
16	2	No	1	No						
17	2	No	6	No	1	No	1	No		
18	3	No	7	1 = II 2 = III						

*Zero-gravity parts of parabolas.

**P & E 25 mg each

‡On two occasions direction of RLC reversed.

Table I

KC-135 Category II: Findings in 8 of 11 Members of 1st Pool of 40 Subjects

	In Seat						Rotating 30 RPM			
	Head Fixed		Head Move.		Eff. Drugs		Head Fixed		Head Move.	
Subj.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	No Drugs	P & E	No. Tests	Δ Cat.	No. Tests	Δ Cat.
6	6	3 = II 3 = I	7	1 = III 1 = II 5 = I			1	I	2	1 = I 1 = III*
7	5	1 = II 4 = I	4	4 = I			1	I	1	III*
21	9	2 = II 7 = I	11	5 = II 6 = I			2	2 = I	3	1 = I 1 = II 1 = III*
26	3	1 = I 1 = II 1 = III	3	2 = I 1 = III*	FS 6,3	5,3,3				
28	4				7,13,0	1				
30	8	2 = II 6 = I	3	3 = III	2 = III	1 = III				
31	4	2 = I 2 = II	8	4 = I 3 = II 1 = III						
37	4	2 = II 2 = I	7	7 = I			1	1 = I	2	2 = I

*Front-up.

Table II

Responses to scopolamine administered 1) transdermally, 2) by mouth, and 3) in fixed-dose combination with amphetamine and ephedrine: Assessments in SRR.

Drug	Number of Subjects	Response % Beneficial	Response % Highly Efficacious
TTS (long-term use)	8	62.5	25
TTS x 2			
scopolamine p. o. (short-term use)			
S (0.3 mg)	8	50	25
(0.3 mg)	11	64	
S (0.6 mg)	8	67	62
(0.6 mg)	30	63	
S (0.3 mg) A (5 mg)	22	55	
S (0.3 mg) E (25 mg)	11	82	
S (0.6 mg)	30	63	
S (0.6 mg) A (5 mg)	22	55	
S (0.6 mg) A (10 mg)	19	63	

Transdermal Therapeutic System-scopolamine = TTS; l-scopolamine hydrobromide = S; d-amphetamine sulfate = A; ephedrine sulfate = E.

___ = recent series.

Table III

Response to Promethazine and Ephedrine Alone and in Fixed-Dose Combinations: Assessments in SRR

Drug	Number of Subjects	Response % Beneficial	Range % >B1
P (12.5 mg)	8	50	12.5
P (25 mg)	8	50	
P (12.5 mg) E (12.5 mg)	8	75	37.5
P (25 mg) E (12.5 mg)	8	87.5*	62.5
P (25 mg) E (25 mg)	12	92	
P (25 mg) E (50 mg)	18	83	
E (12.5 mg)	8	12.5	0
E (25 mg)	10	10	
E (50 mg)	8	50	

P = promethazine hydrochloride; E = ephedrine sulfate; ____ = recent series.

*Assuming Subject 12 had all B responses.

Responses to Three Antimotion Sickness Remedies Administered Intramuscularly During Sorties in the KC-135

		Promethazine 25 mg			Scopolamine 4.3 mg			Dimenhydrinate 50 mg		
Subj.	Trial	1st FS* prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS
19	1st	16**	21	38	12	12	0	12	13	24,29
	2nd	17	19	21,22				6	6	26
	3rd	23	25	0						
	4th	23	25	0						
	5th	26	26	0						
	6th				10	11	0			
33		11	13‡	14,15						
47	1st	30	30	30	12	12	0	24	25	29,32,40
	2nd				26	28	0			
8	1st	21	23	0						
	2nd	22	30	0						
10	1st	10	24	0	8	8	0			
	2nd	32	32	0						
	3rd	10	13	0						
16		15	19	22,23,38						
17	1st	0	11	13,17						
	2nd	9	10	0						
	3rd	0	10	13						

*FS = frank sickness; **16th parabola; ‡ promethazine 50 mg.

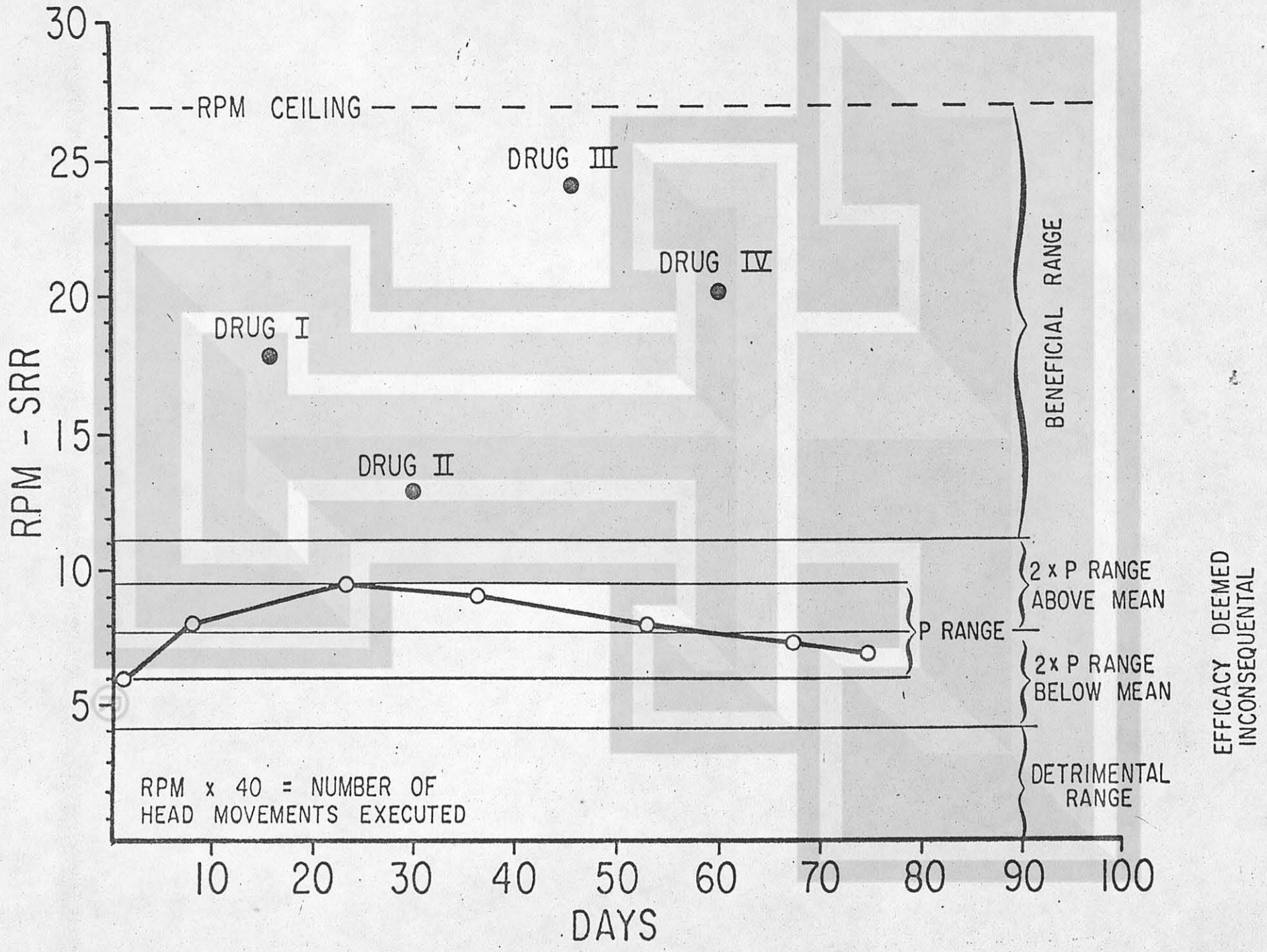
30
25
20
15
10
5
RPM - SRR
RPM CEILING
DRUG III
DRUG IV
DRUG I
DRUG II
BENEFICIAL RANGE
2 x P RANGE
ABOVE MEAN
P RANGE
2x P RANGE
BELOW MEAN
DETRIMENTAL
RANGE
EFFICACY DEEMED
INCONSEQUENTAL
RPM x 40 = NUMBER OF
HEAD MOVEMENTS EXECUTED
10
20
30
40
50
60
70
80
90
100
DAYS

Figure 1

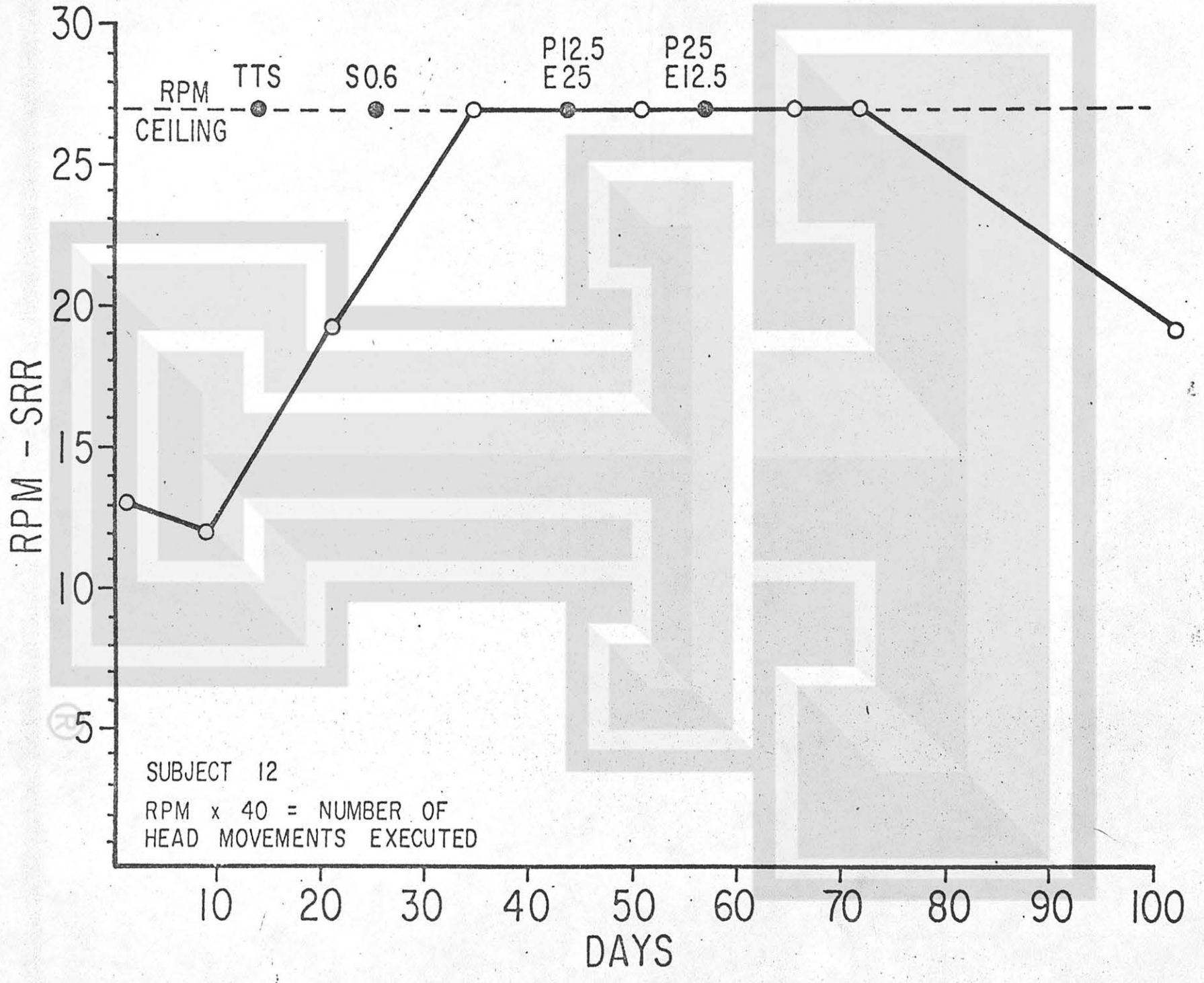
30
25
20
15
10
5
RPM - SRR
RPM CEILING
TTS
S0.6
P12.5 E25
P25 E12.5
SUBJECT 12
RPM x 40 = NUMBER OF HEAD MOVEMENTS EXECUTED
10
20
30
40
50
60
70
80
90
100
DAYS

Figure 2

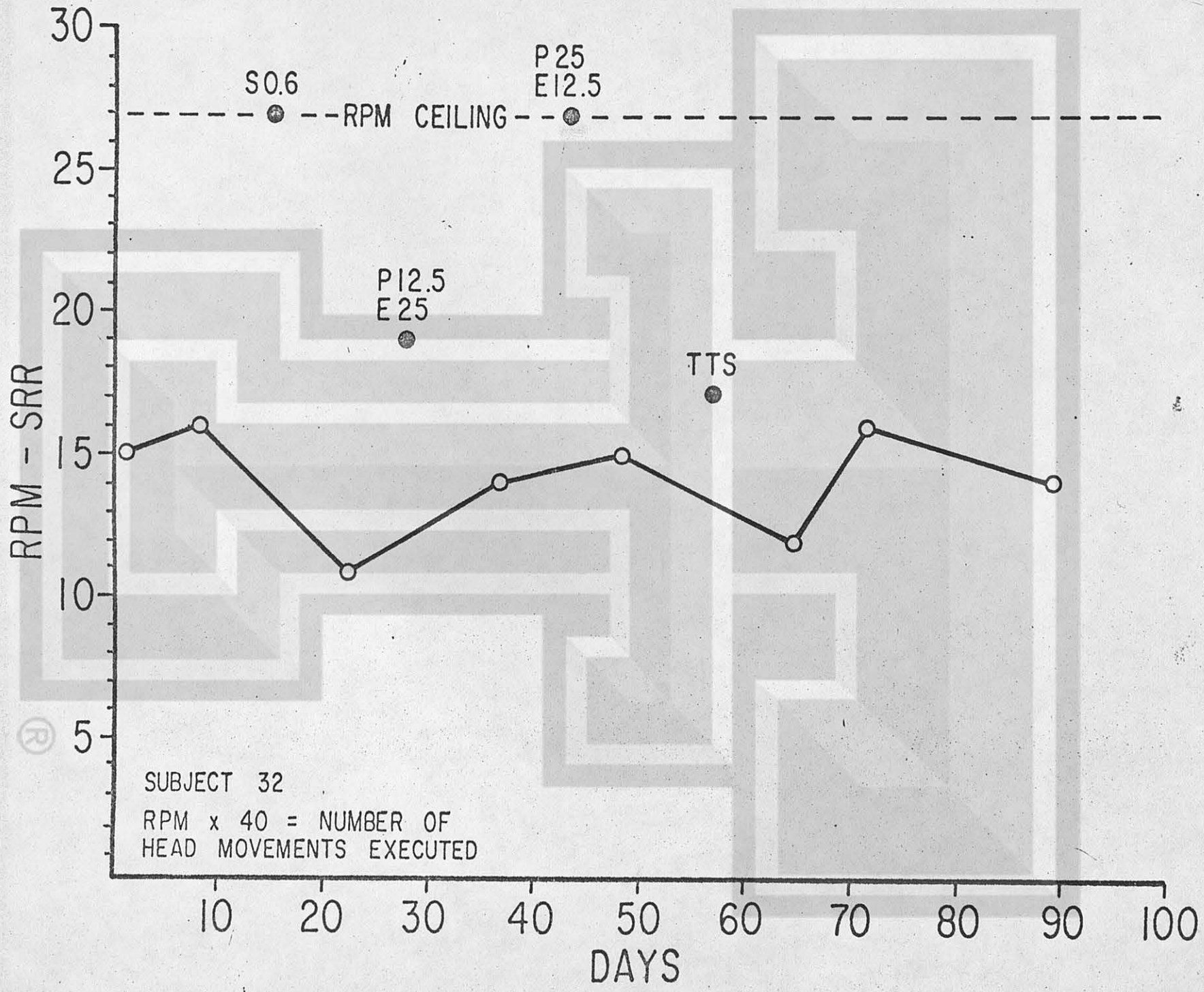
30
25
20
15
10
5
RPM - SRR
S0.6
P25
E12.5
RPM CEILING
P12.5
E25
TTS
SUBJECT 32
RPM x 40 = NUMBER OF
HEAD MOVEMENTS EXECUTED
10
20
30
40
50
60
70
80
90
100
DAYS

Figure 3

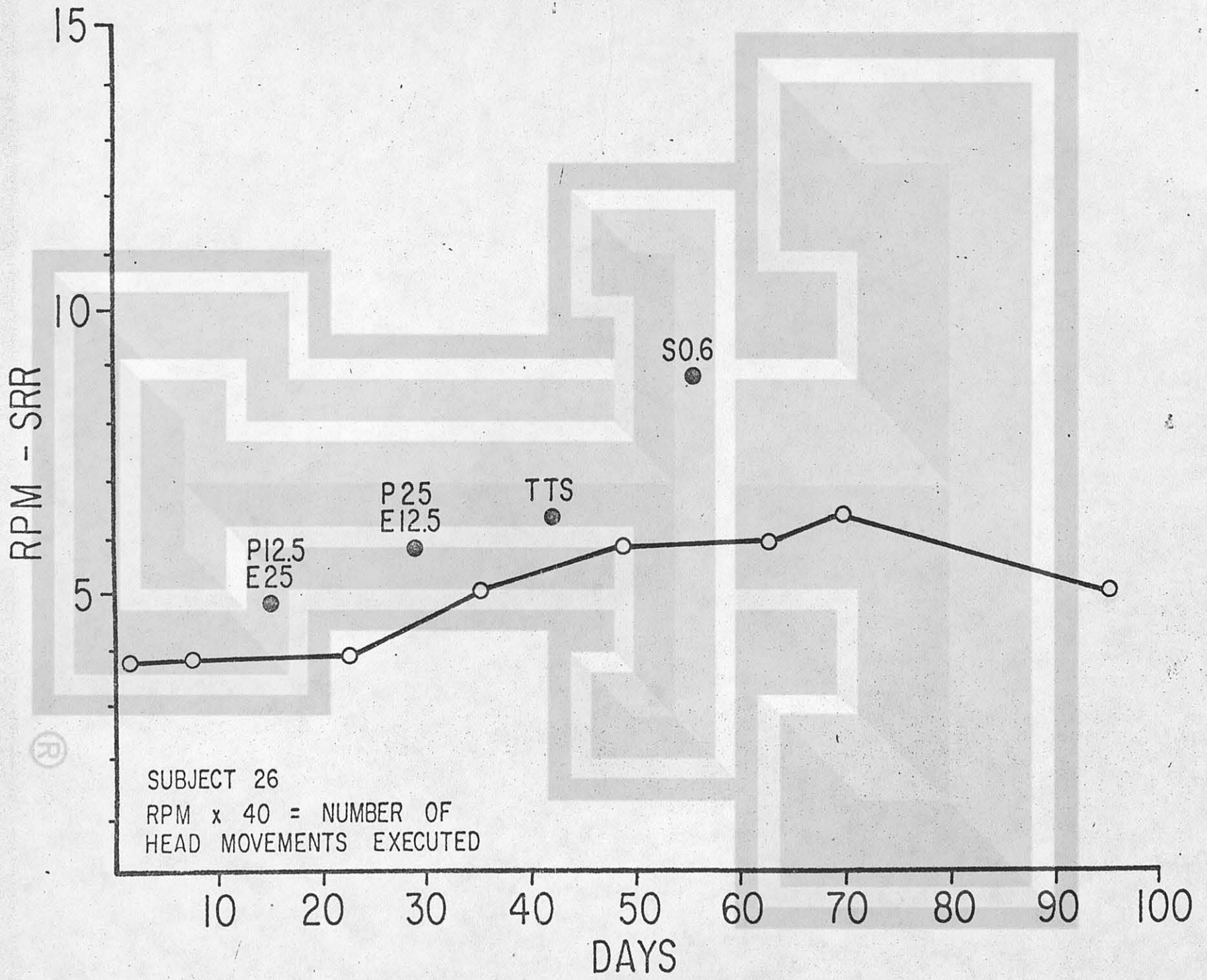
15
10
5
RPM - SRR
S0.6
P25
E12.5
TTS
P12.5
E25
SUBJECT 26
RPM x 40 = NUMBER OF
HEAD MOVEMENTS EXECUTED
10
20
30
40
50
60
70
80
90
100
DAYS

Figure 4

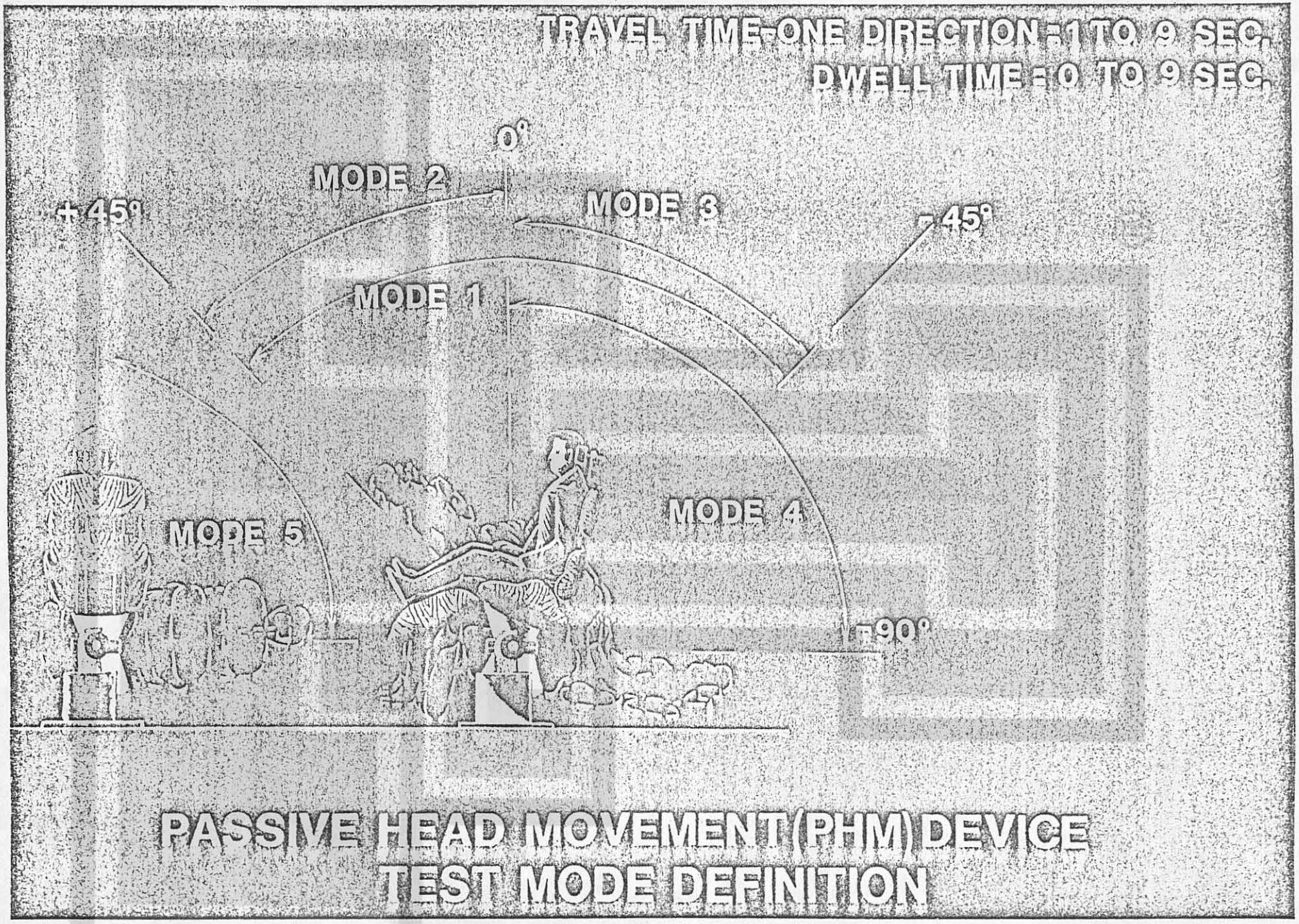
TRAVEL TIME-ONE DIRECTION = 1 TO 9 SEC.
DWELL TIME = 0 TO 9 SEC.
0°
MODE 2
MODE 3
+45°
-45°
MODE 1
MODE 5
MODE 4
-90°
PASSIVE HEAD MOVEMENT (PHM) DEVICE
TEST MODE DEFINITION

Figure 5

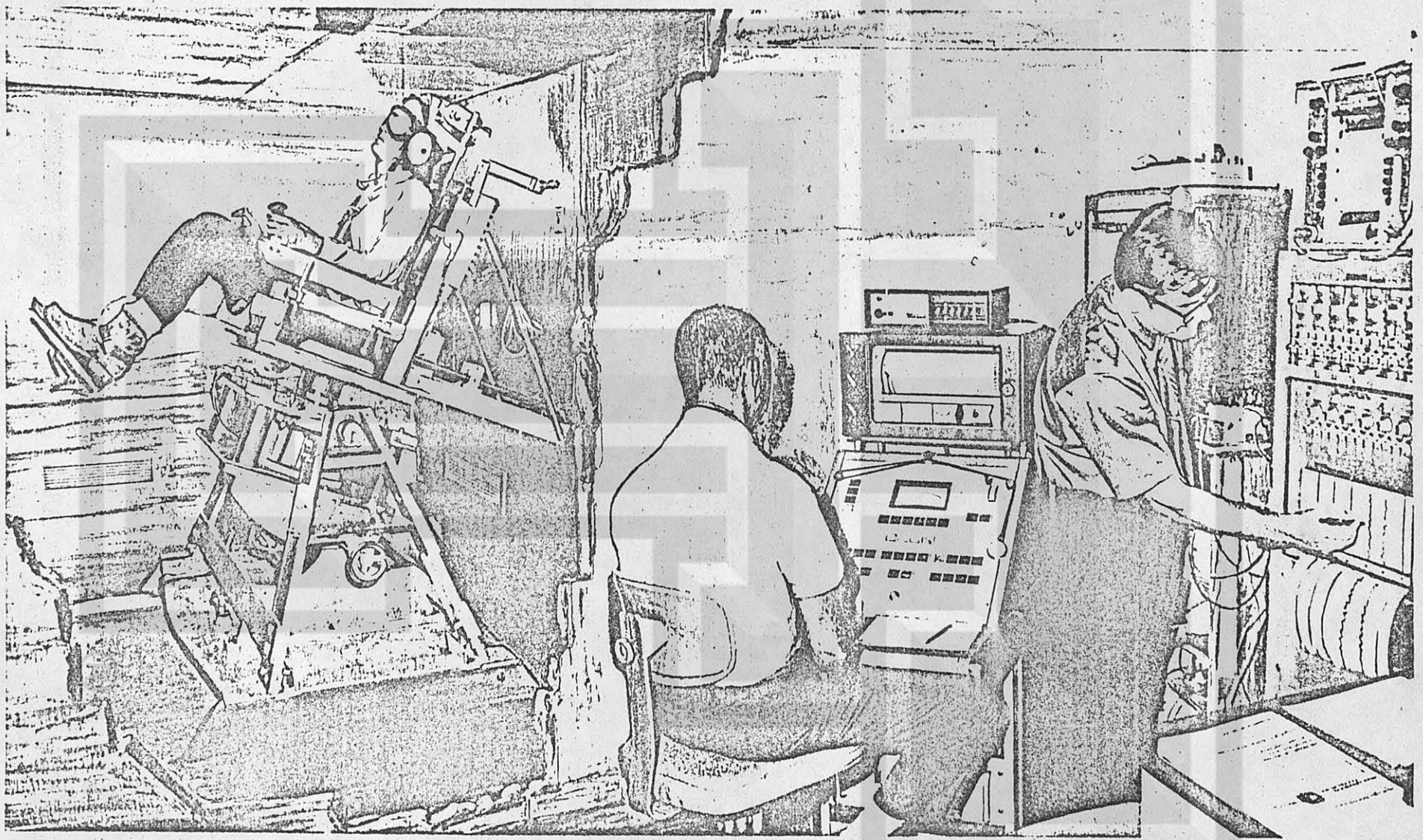

Figure 6

Financial Statement

1 January 1976 through 30 December 1976

Direct Salaries	$ 86,785
Acceleration (leave, benefits, etc.)	25,342
Overhead	105,258
Travel	18,923
Subjects	33,636
Supplies, Governmental	2,752
Supplies, Commercial	4,762
Printing	137
Equipment Maintenance Contract	61
Contractual Services, Government source	770
Equipment*	310
	$278,736

*Recorder, located in Bldg. 1811.

Reprint from:

COSPAR

LIFE SCIENCES AND SPACE RESEARCH XIV

Proceedings of the Open Meeting of the Working Group
on Space Biology
of the Eighteenth Plenary Meeting of COSPAR
Varna, Bulgaria — 29 May — 7 June 1975

and

Symposium on Gravitational Physiology
Varna, Bulgaria — 30 and 31 May 1975

Edited by
P. H. A. SNEATH

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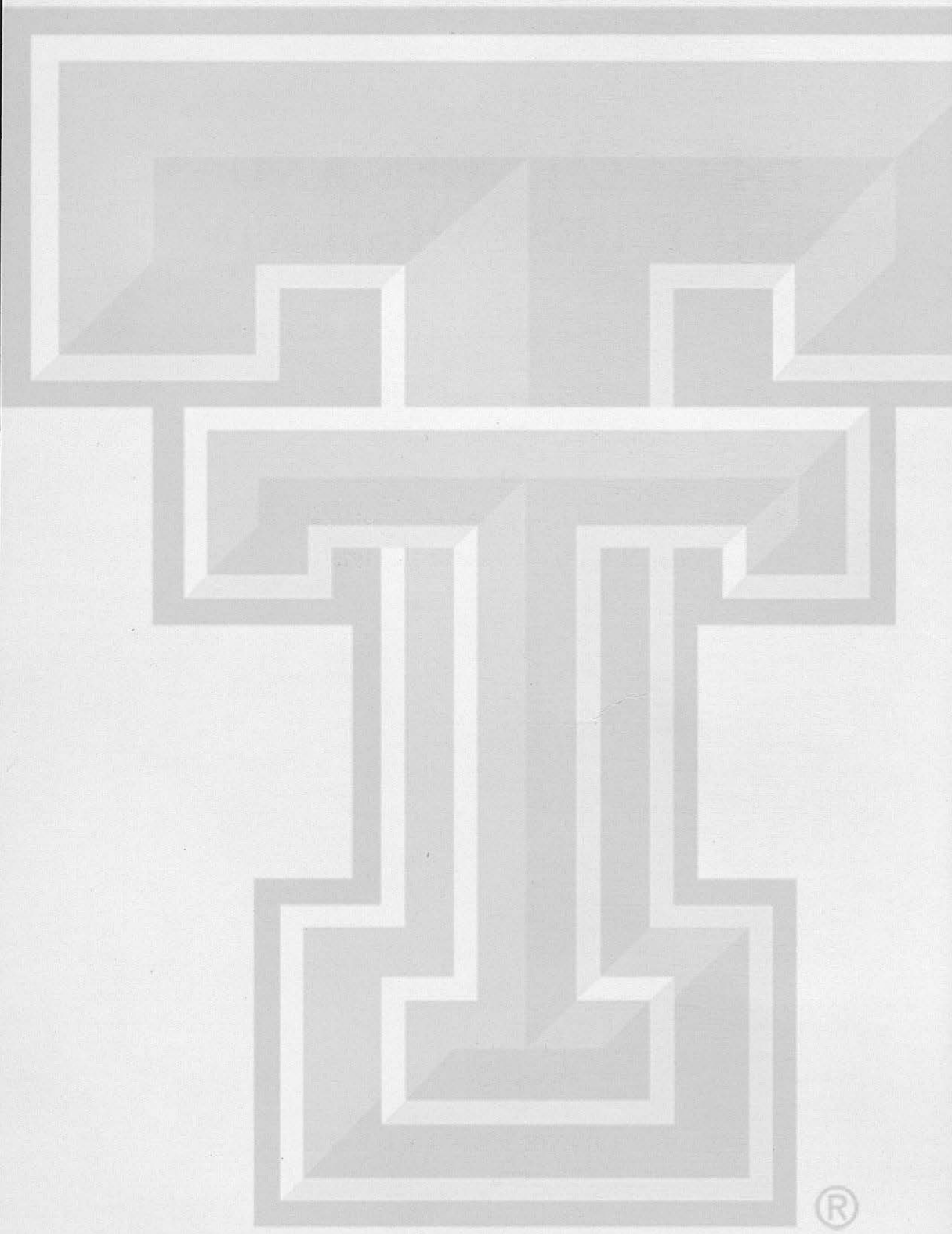
1976



Life Sciences and Space Research XIV — Akademie-Verlag, Berlin 1976

THE PREVENTION OF MOTION SICKNESS IN ORBITAL FLIGHT

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A question has arisen whether zero gravity qualifies as just another "motion environment" in which motion sickness may be elicited, or if one or more undetermined etiological factors are present which render such terms as "motion environment" and "motion sickness" inappropriate. The question is of more than academic interest for the reason that in the forthcoming Shuttle Program we have either one problem or two: one if we are concerned solely with prevention, but two if we must tackle the problem of covert etiological factors as well. This problem points up the need to define motion sickness if investigators, world-wide, hope to resolve the matter in the most economical manner.

Meanwhile, substantial reliance must be placed on the use of antimotion sickness drugs and some recent findings are presented based on tests carried out in a rotating room using a new procedure. Whereas previous findings in our laboratory dealt with group responses, the new findings are not only valid for a group, but also valid for each subject tested. It was demonstrated that the effects of a drug may be efficacious for a group yet may be detrimental for one or more individuals in that group.

1. Introduction

This report falls into three parts. The first is an attempt briefly to define motion sickness. The second raises the question whether zero gravity qualifies as a motion environment, or whether we are dealing simply with "symptoms characteristic of motion sickness". The third part summarizes some recent findings dealing with the effectiveness of representative antimotion sickness drugs.

2. Motion Sickness: A Brief Definition

2.1. Terminology

The term motion sickness, proposed by Irwin [1] in 1881, has slowly gained wide acceptance because it met the test of convenience by its etiologic and symptomatic connotations. Objections have been raised to the use of "motion sickness" in scientific discourse but it is satisfactory for our use here in treating motion sickness as a clinical syndrome that may be experienced in conveyances (motion environments) of different types. *Experimental motion sickness* broadens the use of the term, especially if we include responses elicited in conducting a wide variety

of laboratory tests which involve the vestibular system. The term *amotion motion sickness* identifies the category when the vestibular and organs are not stimulated such as may occur in simulators [2], when viewing movies projected on a hemispherical screen and during optokinetic stimulation [3]. In the clinic patients suffering from a variety of afflictions may experience *symptoms characteristic of motion sickness* either spontaneously or as a consequence of head and body movements. All of these distinctions are usually clear from the context.

2.2. Etiology

The side effects elicited as a result of a too rapid transition into certain stressful motion environments tend to fall into two categories [4]. One comprises the immediate reflex disturbances (IRD) such as nystagmus and postural and visual illusions. The other, i.e. motion sickness, is a delayed epiphenomenon comprising a constellation of symptoms and syndromes resulting from a failure in homeostatic mechanisms that permits irradiation of impulses or influences to sites outside the vestibular and visual systems where first-order responses have their origin. First-order responses, acting as stimuli, may elicit second and higher-order responses and so on, until the organism is generally involved. Although the vestibular system is essential for the elicitation of motion sickness (persons who have lost vestibular function are immune), an array of secondary etiological factors among which visual influences are prominent, are always involved even in healthy persons.

These secondary influences constitute an important yet poorly understood aspect of motion sickness and account for much of the lack of agreement (even among students of motion sickness) concerning its "cause". It may be assumed that any factor tending either to evoke or inhibit a response characteristic of motion sickness will affect susceptibility; "cold" sweating for example is elicited quickly in a warm environment but much later if the environment is cold [5]. Vision is ambivalent in this regard; sea sickness is more readily elicited below deck (or even with eyes closed) than while fixating on the horizon. The great importance of secondary influences is best demonstrated by circumstances in which they play a greater etiologic role than does stimulation of the vestibular end organs, i.e. psychological influences, notably conditioned responses. It is also important to distinguish between persons who are healthy and persons who are either in ill health or experiencing a concomitant functional disturbance that is not secondary or of a higher order of response or even a complication induced by such responses. For example, alterations such as changes in electrolyte balance and distribution of body fluids may precede the elicitation of motion sickness or be one of its consequences. The distinction is important from the standpoint of causation of symptoms.

2.3. Incidence

All normal persons are probably susceptible to motion sickness unless countermeasures are taken. All persons with bilateral labyrinthine defects [6] are probably immune. Persons with loss of vision remain susceptible including those who have never perceived light [7]. Variations in susceptibility are so great, however, that some persons do not experience motion sickness in conveyances.

2.4. Symptomatology and derived Phenomena

It is convenient to distinguish not only between acute brief episodes and chronic or prolonged manifestations of motion sickness but also between the responses *per se* and what might be termed derived phenomena.

Acute Motion Sickness. Symptoms of acute motion sickness useful in making a clinical diagnosis include pallor, sweating, salivation, drowsiness, and most important from a practical standpoint, the nausea syndrome. Release of the antidiuretic hormone [8] and urinary excretion of 17-hydroxycorticosteroids and catechol amines [9] are among the many biochemical responses that may be manifested within a short time. Acute motion sickness may be experienced under operational conditions and brief exposures are commonly used to test for susceptibility under laboratory conditions.

Derived Phenomena. From an analysis of the symptomatology in a typical instance of acute motion sickness the following characteristics emerge: (i) delay in appearance of symptoms, (ii) temporal summation, and either (iii) preservation of symptoms after cessation of stressful stimuli or (iv) acquisition of adaptation effects. From an analysis of the symptomatology obtained from repeated exposure of one person either to the same level of stress or to the same incremental increases in levels of stressful stimuli, variations in responses are predictable only within a certain range. From analysis of data on groups of persons, derived phenomena include individual differences in (i) susceptibility to motion sickness, (ii) rate of acquisition and decay of adaptation effects, (iii) transfer of adaptation from one motion environment to another, (iv) amount of performance decrement for comparable levels of severity of symptoms, and (v) responses to countermeasures.

Chronic Motion Sickness. A sharp distinction cannot be made between acute and chronic motion sickness which includes the recovery period or convalescence. A person severely ill for no longer than 1 to 2 hours may require "days" to recover. Moreover, it may become difficult or impossible to distinguish between the period of susceptibility (with some response being made to eliciting stimuli) and the recovery period unless there is a cessation of eliciting stimuli.

Symptoms. Symptoms of chronic motion sickness [10, 11] may or may not have an acute onset. With a gradual onset the symptoms do not appear, ramify and intensify in the order characteristic of acute motion sickness. One extreme is the so-called "avalanche phenomenon" and the other extreme is a syndrome characterized subjectively by apathy, drowsiness and fatigue, and objectively by sluggishness and performance decrement. It has been termed the sopite syndrome [12] and, under experimental conditions, it may be the only definite overt evidence of motion sickness. Although systematic observations are few, there is a clear indication that the time course for different symptoms may be different.

The recovery from motion sickness during continual exposure to the stressful accelerations is complicated. First, the sites of origin of symptoms must either be freed of eliciting influences or the intensity of restoring mechanisms must be greater than the eliciting influences. Thereafter restoration takes place continuously but not necessarily rapidly through homeostatic events and processes. Adaptation in the vestibular system is essential to prevent irradiation of vestibular activity beyond its confines. If a chemical etiological factor is also involved, considerable time may be required for its spontaneous disappearance. Thus, although

it appears that adaptation of symptoms of motion sickness directly involves their underlying systems, this is not the case.

Derived Phenomena. For self evident reasons, in chronic motion sickness, the identification of such important derivatives as temporal summation, perseveration of symptoms and acquisition of adaptation effects may be difficult to determine.

2.5. Diagnosis

The diagnosis of acute frank motion sickness is so easy that it is not a matter of professional concern, but two sorts of diagnostic problems do exist. One involves criteria to indicate levels of severity ranging from "frank sickness" to the point where motion sickness is no longer present. Unfortunately, there has not been a systematic attempt to categorize these manifestations as first, second or higher order effects, and agreement is lacking with regard to diagnostic criteria. The other problem involves chronic motion sickness when there is not a clear relation between adequate eliciting stimuli and responses. The sopite syndrome is readily mistaken for fatigue or boredom unless specifically kept in mind.

3. Etiology of Motion Sickness in Orbital Flight

There are important differences in the opinions expressed regarding the etiology of motion sickness in orbital flight. At one extreme, zero gravity is regarded as a typical motion environment. At the other extreme, motion sickness is likened to a "vestibular storm", i.e. symptoms appear spontaneously as in disease states. Between these extreme positions a combination of pathological and functional etiological factors are thought to play a role. These differences in opinion have practical as well as theoretical implications and will be discussed briefly in the light of findings obtained in orbital [13—15] and parabolic flight [16, 17].

3.1. Orbital Flight

Pre-Skylab Findings dealing with motion sickness aloft are summarized in Table 1. The US data clearly rule out the vestibular storm theory as the sole etiological factor. The USSR data suggest, but do not prove, that zero gravity should be

Table 1
Manned Space Flight Programs

United States			Russia		
Program	Number of space pilots	Incidence of motion sickness	Program	Number of space pilots	Incidence of motion sickness
Mercury	6	0	Vostok	6	1
Gemini	10	0	Voskhod	5	3
Apollo Command Module	25	9	Soyuz	13	0
Apollo Lunar Landing	12	0			

regarded as just another motion environment. This conclusion is inferred from the absence of motion sickness in Soyuz astronauts, suggesting that ground-based training was effective.

Skylab Findings. Fig. 1 shows [15] that under operational conditions motion sickness was experienced aloft by five of the nine astronauts. In the Command Module symptoms appeared after approximately 30 minutes in one astronaut and after several hours in two additional astronauts. Symptoms appeared in two astro-

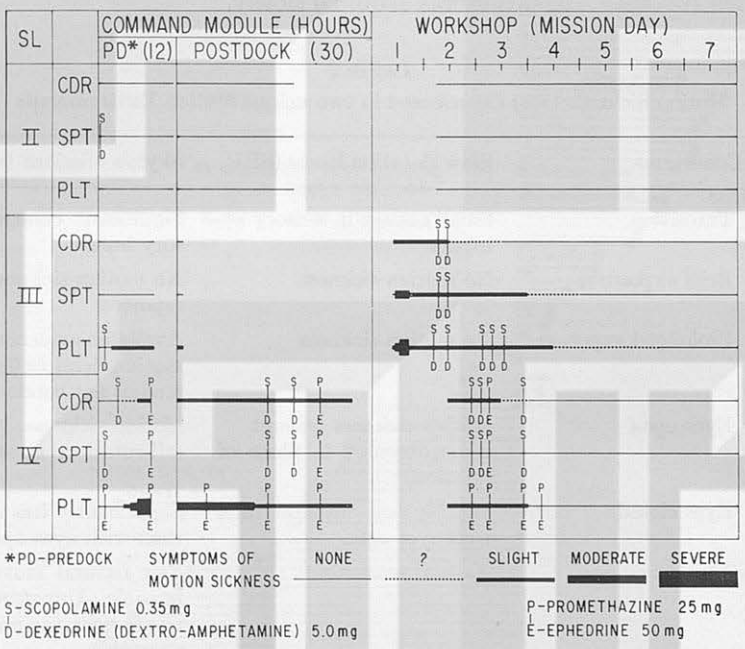

Fig. 1. Time course of motion sickness in five of nine astronauts during the orbital phase of Skylab Missions. The horizontal lines reflect two things. First, where the astronauts were based during the first week in orbit; the thickness and continuity of the lines indicate the onset and probable disappearance of symptoms of motion sickness. The vertical lines indicate when an antimotion sickness drug was taken and its composition.

nauts soon after their transition into the workshop where stimulus conditions were more stressful. In all five astronauts we are dealing with what might be termed chronic motion sickness.

Table 2 compares the findings in a slow rotation room (SRR) and in the orbital phase of Skylab missions. There is much resemblance between stimulus conditions in the two environments and, of course, substantial differences. Resemblances include the relation between activities that involve head movements or free floating activities and the elicitation of motion sickness. The second similarity involves the characteristic time course of the illness in both environments. Two differences deserve emphasis. First, the two vestibular organs are affected very differently during natural activities; the canals are stimulated normally while the constant stimulus to the otolith organs due to gravity is abolished. In the

SRR the canals are stimulated abnormally (except when turning in the plane of rotation) and the linear accelerations combine with the gravitational vector in stimulating the macular receptors in the otolith organs. The second difference concerns the potentialities aloft, at once limiting a person's natural movements and encouraging unnatural movements, that may result in unusual vestibular and visual sensory inputs, whereas, in the SRR, visual cues are familiar. In astronauts experiencing motion sickness it was demonstrated that (i) vestibular and visual inputs played important etiological roles, (ii) that symptoms were rarely severe, and (iii) that adaptation was acquired slowly.

Table 2

Motion Sickness (MS) experienced in two unique Motion Environments

Stimulus Conditions			Slow Rotation Room (SRR)	Skylab Missions (aloft)
Self-restraint	No head movements (HM)	Transition	Small change in sensory inputs	Significant change in sensory inputs
		Brief exposure	No motion sickness	No motion sickness reported
		Prolonged exposure	No motion sickness	Available evidence: no motion sickness (systematic studies not conducted)
	Head movements	Eyes open	Motion sickness (except when executed in plane of rotation)	Motion sickness (all rotations stressful)
		Eyes closed	Slightly less stressful than with eyes open	Significantly less stressful than with eyes open
General activities:			Natural movements	Few natural movements possible. Unnatural movements generate unusual stimuli
All stressful stimuli "on-off". Alternate "disturbance-recovery"			Duration of motion sickness: "days"	Much the same as in SRR (Self-diagnosis difficult)
SRR: Predetermined angular velocity Skylab: Command Module to workshop			Worst case situation	Worst case situation
Programmed adaptation			Highly successful	More difficult than in SRR but possible

Parabolic Flight. Findings in parabolic flight must be included here although their simulation of orbital flight is obviously imperfect. A systematic series of tests using a procedure similar to that used in the workshop revealed (Fig. 2) that a small majority of the subjects were less susceptible than they were on the ground and a large minority of the subjects were less susceptible aloft than in preflight [17]. Moreover it is well known that persons not experiencing symptoms while seated may experience motion sickness under free floating stimulus conditions.

In summary, there are good reasons to regard stimulus conditions in zero gravity as a motion environment with unique features in which persons not only adapt but retain their adaptation, in many instances, for prolonged periods. If there is a concomitant etiological factor such as that caused by the headward shift of body fluids this factor must be relatively unimportant. Systematic studies, however, will be required to establish the presence and significance of any such additional etiological factors.

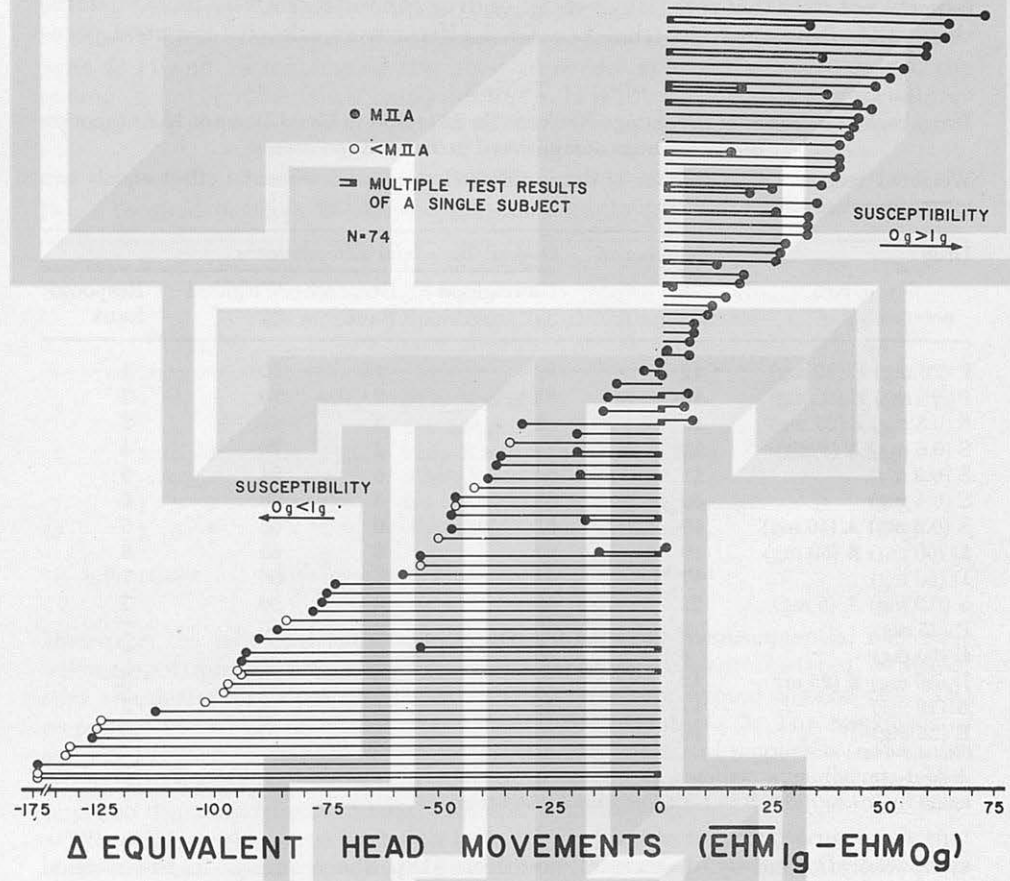

Fig. 2. Range of altered susceptibility among 74 subjects tested in zero g as generated by parabolic flight. Their susceptibility change is expressed as the difference between the number of equivalent head movements executed under zero- and earth-gravity conditions, reaching the endpoint of malaise IIA, or a limit of head movements imposed by the test conditions.

4. Antimotion Sickness Drugs

The efficacy of antimotion sickness drugs may be evaluated in any motion environment but it must be kept in mind that persons may differ in their susceptibility to motion sickness in different motion environments.

Most of our bioassays for testing the influence of drugs on motion sickness have been carried out using a slow rotation room (SRR) in a laboratory setting.

In the past, the procedure (described in more detail in [18]) involve (i) the selection of subjects, which included not only a comprehensive medical evaluation but also assessment of canalicular and otolith function, (ii) familiarization, (iii) generation of stressful stimuli by the execution of standardized head movements during rotation, (iv) the use of a motion sickness endpoint (or the execution of a given number of head movements), (v) administration of drugs and placebos using a 10-unit Latin-square design, and a double blind technique. The findings indicate not only that some single drugs or drug combinations were more effective than other drugs but also that beneficial effects were related to central para-

Table 3

Drugs ranked in Terms of Percentage Response (in 225 tests) to Usual Doses of 15 Antimotion Sickness Drugs administered in Three Experiments

Weighted response take account of detrimental effects; one detrimental effect equals two inconsequential effects.

Drug	Number of Subjects	Overall Beneficial Effectiveness			
		Unweighted %	Response Rank	Weighted %	Response Rank
P (25 mg) **E** (25 mg)	12	92	1	92	1
P (25 mg) **E** (50 mg)	18	83	2	79	3
S (0.3 mg) **E** (25 mg)	11	82	3	82	2
S (0.6 mg) A (5 mg)	11	73	4	73	4
S (0.3 mg)	11	64	5	64	5
S (0.6 mg)	30	63	6	63	6
S (0.6 mg) A (10 mg)	19	63	6	63	6
D (50 mg) **E** (50 mg)	19	63	6	63	6
D (50 mg)	17	59	7	50	7
S (0.3 mg) A (5 mg)	22	55	8	50	7
P (25 mg)	8	50	9	50	7
E (50 mg)	8	50	9	50	7
D (50 mg) **E** (25 mg)	12	42	10	42	8
A (10 mg)	17	35	11	35	9
E (25 mg)	10	10	12	10	10

A = d-amphetamine sulfate; D = dimenhydrinate; **E** = ephedrine sulfate; **P** = promethazine hydrochloride; S = *l*-scopolamine hydrobromide.

sympatholytic and sympathomimetic effects [19]. Shortcomings in the method were also revealed and it was evident that while the results had validity for groups of subjects, this did not apply to the individuals within these groups.

The changes in the procedure involved substitution of an incremental stress profile [20] for a predetermined constant level of stress, modification of the Latin-square design to provide a better placebo baseline, and distinguishing three categories of response: inconsequential, substantially beneficial (hereafter beneficial) and substantially detrimental.

Some of the findings in three experiments [21] are summarized in Table 3. The 15 drugs administered are ranked in terms of the percentage of doses (225 evaluations in 31 subjects) that were substantially beneficial. The weighted response takes into account detrimental effects; one detrimental effect is made the equivalent of two inconsequential effects. The efficacy of scopolamine alone or in

combination with amphetamine was an expected finding but results involving promethazine and ephedrine were somewhat surprising. The combination promethazine and ephedrine, 25 mg each, would have reached 100% effectiveness if one subject had executed a few more head movements. This resulted despite the fact that, administered as single doses, ephedrine was notably ineffective. In combination they may be regarded as homergic drugs manifesting suprasummation.

There were seven substantially detrimental responses (bold D's in Table 4) involving four subjects and four drugs. Only eight beneficial responses were elicited in these four subjects and subject 3 accounted for half of the total. Indeed, subjects 4, 11 and 19 manifested the worst responses among the entire group; the average number of beneficial responses was 4. It is interesting that among subject 3's four best responses, promethazine (25 mg) plus ephedrine (50 mg) ranked best.

Table 4

Drugs Involved in Seven Detrimental Responses among 225 Evaluations in 31 Subjects

Subject No.	B	I	D*	Dimenhydrinate (50 mg)	Promethazine (25 mg) Ephedrine (50 mg)	Scopolamine (0.3 mg) Amphetamine (5 mg)	Scopolamine (0.6 mg) Amphetamine (10 mg)
3	4	1	2	**D** — 23%	(B — best of 4 + 54%)	**D** — 17%	(I 0% change)
4	1	5	1	(I + 3%)	(only B response +58%)	**D** — 25%	(I + 9%)
11	1	3	3	**D** — 27%	**D** — 18%	(I 0% change)	**D** — 18%
19	2	5	1	**D** — 25%	(I + 13%)	Not adm.	(I — 13%)

*B = beneficial I = inconsequential D = detrimental

Moreover, the fact that subject 3 manifested his only inconsequential responses when scopolamine (0.6 mg) plus amphetamine (10 mg) was administered, indicated that the detrimental response with half the dose represented a valid test. The responses of subject 4 closely resembled those of subject 3. The responses of subject 19 resembled those of subject 11; his two beneficial responses (not shown in the table) followed the administration of promethazine (25 mg) and the combination dimenhydrinate (50 mg) plus ephedrine (50 mg).

The chief conclusion to be drawn from the findings in these experiments is that there are substantial individual differences in response to some of the best antimotion sickness remedies available, implying that careful assessment should be carried out on an individual basis.

5. Discussion

An attempt has been made to demonstrate the resemblance between motion sickness in a rotating environment and in a weightless spacecraft. In the rotating environment not only can motion sickness be prevented by an incremental introduction to the stressful stimuli but also this method of acquiring adaptation results with little or no penalty. In other words, the CNS patterning does not render a person susceptible to symptoms on return to a stationary environment; indeed the subject is rendered less susceptible to motion sickness in some but not

all conveyances provided there has not been too great a decay in the adaptation acquired in the rotating room.

On transition into orbital flight there is much evidence that symptoms of motion sickness may be elicited by activities that stimulate mechano-receptors in the vestibular organs and that visual inputs may also play an important etiological role. The vestibular inputs are unique for, even without moving, the constant stimulus due to gravity is absent thus ensuring an unusual input from the macular receptor system. After one week in orbit, when the motionsick Skylab astronauts had recovered, they were less susceptible to the stressful type of canalicular stimuli than pre-flight. If the findings using the same rotation test in parabolic flight are valid, then it would appear that some persons are more susceptible and some less susceptible to motion sickness in zero gravity than on the ground.

Yet the exposures are too brief to invoke substantial charges in endolymph and perilymph. Moreover, the fact that adaptation is acquired and retained in zero gravity suggests the involvement of CNS patterning rather than temporary changes in circulation or changes in electrolyte balance. Admittedly, none of these arguments completely rule out a concomitant unknown secondary etiological factor but it would seem to rule out a primary factor.

The prevention and treatment of motion sickness by means of drugs leaves much to be desired. Involved here is not only the selection of a drug used as a single dose on an individual basis but the assessment of drug therapy covering periods measured in days.

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We had just computed the 2nd study using a 6-hr rest period. No difference (Bed-rest)

Comparison of Susceptibility to Motion Sickness During Rotation at 30 rpm in the Earth-Horizontal, 10° Head-Up, and 10° Head-Down Positions

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GRAYBIEL, A., and J. R. LACKNER. *Comparison of susceptibility to motion sickness during rotation at 30 rpm in the Earth-horizontal, 10° head-up, and 10° head-down positions.* Aviat. Space Environ. Med. 48(1):7-11, 1977.

Normal persons rotated about an Earth-horizontal axis vary in their susceptibility to motion sickness. The purpose of this experiment was to measure intraindividual differences in susceptibility in 12 subjects when rotated 10° head up and 10° head down as well as in the horizontal position. Subjects assumed the test-position 60 min prior to rotation, thus providing an opportunity for translocation of body fluids. Physiological and psychophysical measurements were conducted throughout the experiment. There were no intraindividual differences in susceptibility to motion sickness in the three positions tested, although there were significant differences in vital capacity, demonstrating the expected fluid shifts. It was concluded that, in the sample of subjects tested, short-term effects of fluid shifts greater than those that would be manifested in zero gravity had no definite effect on motion sickness susceptibility.

SOME OF THE ASTRONAUTS and investigators associated with the Skylab program (1-4) have expressed the opinion that headward shift of body fluids was an eliciting factor causing motion sickness in orbit. The immediate purpose of the present experiment was to evaluate that possibility by comparing intraindividual differences in susceptibility to motion sickness during rotation with the head horizontal, 10° up, and 10° down. The rationale was to use the head-horizontal position as a model for zero gravity, since Patterson (5), in discussing the question of changes in the cerebral circulation on transition into zero gravity, had concluded that cerebral blood flow and blood pressure would probably be much the same as in the Earth-horizontal position under ground-based conditions.

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This study was supported by the National Aeronautics and Space Administration, Contract T-5904B.

Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

MATERIALS AND METHODS

Subjects: Twelve college students 19 to 23 years of age participated as paid volunteers. All 12 had passed the medical evaluation and indoctrinational test required for parabolic flights in the KC-135 aircraft. Otolithic, canalicular, and visual functions were normal, based on an array of functional tests. Assessments for susceptibility to motion sickness in different motion environments had been carried out, but the 12 subjects were selected for this study solely on the basis of availability.

Rotation Device: This device, especially designed for use in zero gravity, has been termed the Z-axis recumbent rotating (ZARR) device and has been described elsewhere (6). When he is secured in the ZARR, the subject's knees are flexed, the amount depending on his height. The base of the ZARR can be tilted about a horizontal axle, thereby permitting head-up and head-down positioning. With the aid of slip rings, electrical contact can be maintained with the subject, allowing a variety of physiological and psychophysical tests to be carried out during rotation.

Motion Sickness Ratings: The diagnostic criteria long used for measuring severity of acute motion sickness were used (7). A motion sickness rating of "12 points" in the rating system was chosen as the level for terminating the experimental run. This cut-off point was chosen because, although it involves the "nausea syndrome," it avoids frank illness including vomiting. All of the subjects were experienced in reporting the appropriate symptoms, e.g., dry mouth, sweaty palms, stomach awareness, etc., and were instructed to indicate to the experimenters whenever any of these symptoms appeared. In addition, every 15 min during the experimental run the subject was questioned on a checklist of symptoms and the experimenters also noted whether the subject exhibited pallor.

Experimental Design: Each of the 12 subjects participated in three experiments; namely, with head horizontal, 10° head-up, and 10° head-down. The conditions were presented in a counterbalanced design so that an equal number of subjects had each of the positions first, second, and third. Rotation was preceded by exposure for 1 h in the test position. The device was then accelerated ($2°/s^2$) to 30 rpm and maintained at this

velocity for 60 min or until the motion sickness endpoint had been reached.

Vital Capacity: Measurements (in cubic centimeters) of vital capacity were made with a spirometer ("Spirotel," Computer Instruments Corp.), which furnished an electrical signal that was displayed on a paper-chart recorder (Hewlett-Packard 7702B). Vital capacity was measured at four stages during each experimental session: a) prerotation with the subject seated in a chair; b) prerotation with the subject positioned in the ZARR, head facing up, after having been in position for 15 min; c) postrotation with the subject positioned head facing up in the ZARR; and d) postrotation with the subject seated after having been out of the ZARR and upright for 15 min.

Four measurements of vital capacity were taken in each of the stages a-d, and their average served as the vital capacity index for that measurement period. When the four trials within a stage varied by more than 250 cc, the measurements were repeated until consistency was obtained; only twice was this necessary.

Heart Rate: The subject's heart rate was also monitored during stages a-d by means of electrocardiographic recordings. During measurements of heart rate in the ZARR, the subject was on his back facing up.

Blood Pressure: The subject's blood pressure was monitored during the experiment at the same times that heart rate was measured. Blood pressure was measured with an electronic sphygmomanometer.

Nystagmograms: The position of the subject's eyes was monitored during the experimental procedures by means of conventional d. c. electrooculography. Eye position was displayed on a heat-writing Transacoustic polygraph.

RESULTS

Vital Capacity: Table I summarizes the measures of vital capacity for each subject in each of the experimental conditions. As can be seen from the table, every sub-

TABLE I. CHANGES IN VITAL CAPACITY (IN CC) ASSOCIATED WITH DIFFERENT BODY ORIENTATIONS BEFORE AND AFTER ROTATION.

			Prerotation				Postrotation				
Subject	Order	Seated	HU*	HH	HD	Diff	HU	HH	HD	Seated	Diff
1	2 (HH)	4200	3980			220	4010			4210	200
	1 (HU)	4340		4080		260		3990		4320	330
	3 (HD)	4240			3800	440			3800	4250	450
15	3	3920	3750			170	3730			3900	170
	1	3960		3580		380		3600		3920	320
	2	4040			3490	550			3540	3960	420
26	2	4440	4160			280	†			4325	—
	3	4480		4120		360		†		4460	—
	1	4540			4090	450			†	†	—
37	3	5600	5320			280	5360			5640	280
	2	5600		5150		450		5300		5620	320
	1	5650			5050	600			5050	5750	700
10	1	4550	4390			160	4410			4620	210
	3	4440		4160		280		4330		4720	390
	2	4620			4170	450			4130	4580	450
39	1	4140	3960			180	4000			4170	170
	2	4150		3890		260		4010		4230	220
	3	4130			3820	310			3750	4060	310
30	1	4020	3300			720	†			3820	—
	2	3900		3140		760		3180		3700	520
	3	3240			2260	980			2020	2780	760
21	3	4300	4025			275	4050			4700	650
	1	4520		3920		600		3650		4675	1025
	2	4810			4120	690			4100	4850	750
13	2	4500	4100			400	4100			4520	420
	3	4850		4350		500		4220		4800	580
	1	5000			4400	600			4420	5000	580
4	1	4950	4650			300	4500			4900	400
	2	4925		4500		425		4420		5000	580
	3	4980			4400	580			4340	4980	640
7	2	4900	4740			160	4500			5000	500
	3	5020		4600		420		4350		4800	450
	1	5020			4250	770			4020	5000	980
9	3	4820	4380			440	4600			5000	400
	1	4950		4280		670		4460		5000	540
	2	4900			4150	750			4080	4920	840

* HU = Head up 10°; HH = Head horizontal; HD = Head down 10°.
† Measurement could not be made because subject was motion sick.

ject exhibited a considerable decrement in vital capacity pre- and postrotation when tilted from the upright to one of the experimental positions. Moreover, every subject showed a progressively decreasing vital capacity from his 10° head-up to his head-horizontal to his 10° head-down conditions. Accordingly, these conditions reflect increasingly large headward displacements of body fluid.

Heart Rate and Blood Pressure: These measures are summarized in Tables II and III. There was a nonsignificant tendency for heart rate to be depressed and for blood pressure to be somewhat elevated when the subject was tested in the ZARR pre- and postrotation compared with seated upright.

Nystagmograms: Each subject exhibited nystagmoid eye movements of varying durations during rotation; the exact character of the nystagmus pattern depended upon the orientation of the subject's head with respect to the gravitational vertical; e.g., nose pointing up or pointing down. A report on these records is in preparation.

Motion Sickness Ratings: No systematic relationship between position of the head (10° head-up, head horizontal, 10° head-down) and incidence of motion sickness symptomatology was present.

The results for each subject's experimental trials are presented in Table IV. Three of the subjects were symptom-free throughout all experimental conditions. One subject was symptom-free in all conditions except for registering one point in the head-down condition. Of the remaining eight subjects, only one was worse in the head-down position compared to the head-up and head-horizontal positions. The other seven subjects were either less susceptible or equally susceptible in the head-down position.

TABLE II. HEART RATE (BPM) BEFORE AND AFTER ROTATION FOR DIFFERENT BODY ORIENTATIONS.

Subject	Order	Condition	Prerotation	Postrotation
1	2	Head up 10°	56	48
	1	Head horizontal	52	52
	3	Head down 10°	68	52
15	3	Head up 10°	56	52
	1	Head horizontal	52	51
	2	Head down 10°	72	68
26	2	Head up 10°	60	52
	3	Head horizontal	56	60
	1	Head down 10°	52	52
37	3	Head up 10°	52	48
	2	Head horizontal	56	52
	1	Head down 10°	60	48
10	1	Head up 10°	68	60
	3	Head horizontal	56	52
	2	Head down 10°	60	55
39	1	Head up 10°	64	54
	2	Head horizontal	68	70
	3	Head down 10°	66	64
30	1	Head up 10°	72	64
	2	Head horizontal	80	64
	3	Head down 10°	84	56
21	3	Head up 10°	64	64
	1	Head horizontal	64	68
	2	Head down 10°	76	76
13	2	Head up 10°	76	68
	3	Head horizontal	72	68
	1	Head down 10°	76	80
4	1	Head up 10°	68	68
	2	Head horizontal	64	64
	3	Head down 10°	64	60
7	2	Head up 10°	48	60
	3	Head horizontal	60	48
	1	Head down	48	60
9	3	Head up 10°	60	56
	1	Head horizontal	64	64
	2	Head down 10°	64	64

DISCUSSION

The diagnosis of motion sickness is easily made under experimental conditions when it is based on the close temporal relation between the motion-environment stressor and the appearance of typical symptoms. The diagnosis under operational or field conditions in zero gravity is difficult, not only because the motion environment is unique but also because symptoms of motion sickness are nonspecific; that is, one or more are manifested in many other physiological and pathological states. Skylab findings strongly indicate, if they do not prove (8), that zero gravity (prior to adaptation) contributes one part and head movements one part to a motion environment that is analogous to the motion environment in a rotating room where head movements are also essential for eliciting motion sickness.

The earliest recorded onset of motion sickness after transition into orbit happened in the third Skylab mission, when the pilot reported symptoms within minutes. This incident occurred in close relation to the pilot's activity in doffing his space suit; thereafter, his symptoms were favorably influenced by restricting activity and by taking an antimotion sickness drug. Skylab findings also demonstrate that conditions after transition into the workshop were more stressful than in the command module, thereby emphasizing the roles played by unusual body movements and visual inputs. In brief, high susceptibility to motion sickness was demonstrated within minutes after transition into orbit, persisted for days, but on or after Mission-day 8, all of the astronauts were preternaturally insusceptible (9).

If we accept the evidence that, in zero gravity, we are dealing with a motion environment to which some persons must adapt, then it is important to distinguish carefully between two categories of secondary etiological factors that may contribute to the elicitation of motion sickness in this environment—one directly or indirectly exerting its influence via the vestibular system, and one having an influence independent of the vestibular system but tending to elicit one or more symptoms indistinguishable from those of motion sickness.

The present experiment represents an attempt to determine whether a headward shift of body fluids constitutes a secondary etiological factor falling into either of the above categories. Under the stimulus conditions employed, no definite evidence for such a secondary role was obtained. However, since it may be difficult to detect the presence of secondary etiological factors unless their influence is substantial, it is necessary to take into account those factors in our experiment that were favorable

TABLE III. CHANGES IN BLOOD PRESSURE (mm Hg) ASSOCIATED WITH DIFFERENT BODY ORIENTATIONS BEFORE AND AFTER ROTATION.

			Prerotation			Postrotation		
Subject	Order	Seated	HU*	HH	HD	HU	HH	HD
1	2	90/70	110/68			138/66		
	1	104/66		112/74			128/84	
	3	122/62			142/74			144/74
15	3	138/66	128/74			136/74		
	1	188/70		120/100			140/72	
	2	140/78			132/70			†
26	2	140/52	130/66			†		
	3	118/58		122/68			†	
	1	130/60			116/82			†
37	3	120/74	122/72			130/70		
	2	140/68		118/62			124/84	
	1	136/76			140/78			132/84
10	1	98/74	118/64			122/70		
	3	116/68		118/76			122/84	
	2	124/68			128/70			124/86
39	1	132/70	106/68			118/82		
	2	124/72		118/68			114/68	
	3	132/70			98/60			110/80
30	1	118/70	98/74			112/78		
	2	112/66		114/64			114/84	
	3	118/64			112/70			110/76
21	3	118/50	108/63			116/70		
	1	112/62		108/70			128/78	
	2	114/58			116/68			114/62
13	2	118/66	122/68			116/88		
	3	122/64		112/68			136/84	
	1	116/74			112/72			132/84
4	1	128/72	128/66			130/70		
	2	128/74		120/70			110/68	
	3	128/64			118/70			118/80
7	2	138/70	114/74			114/92		
	3	130/70		128/66			126/76	
	1	132/74			116/74			150/76
9	3	124/60	108/60			118/76		
	1	130/58		120/62			127/68	
	2	128/60			122/62			116/76

* HU = Head up 10°; HH = Head horizontal; HD = Head down 10°.
† Measurement could not be made because subject was motion sick.

and those that were unfavorable for revealing differences in susceptibility. Favorable factors were: 1) measurement of the displacement of body fluid, 2) use of a quantifiable stressor, 3) a counterbalanced design for the three body positions, and 4) a carefully assessed group of 12 subjects. Unfavorable factors were: 1) the brief exposure in a given position, 2) the great individual variability in susceptibility to motion sickness, and 3) lack of measurements reflecting cerebral blood flow, cerebral blood pressure, and cerebrospinal fluid pressure.

In a relevant experiment, Kakurin *et al.* (10) studied the effects induced by "antiorthostatic hypokinesia" in eight subjects who were kept in bed for 5 d on two occasions. Using a cross-over design, four subjects were exposed to 0°-tilt and −8° head-down positions and the remaining four subjects to −4° and −12° head-down positions. They concluded that −8° head down is the most suitable model for zero gravity and that hemodynamic changes played the major role in causing a variety of disturbances. In all head-down positions most subjects experienced illusory sensations, and some subjects reported "mild dizziness and nausea upon abrupt head movements"; how long it took before these symptoms first appeared is not specified.

Few measurements have been made in human subjects that bear even indirectly upon the changes in cerebral circulation in weightlessness. Patterson's (5) measurements in one subject indicate that, in the upright position on Earth, the intracranial pressure "can become subatmospheric," whereas in recumbency it is "slightly positive . . . as would be expected in weightlessness." Although persons are accustomed to changes in position between recumbency and upright, exposures in these positions are usually measured in hours. Patterson (5) speculated that long-term exposure to subatmospheric intracranial pressure might have significant consequences and account for symptoms of motion sickness experienced by the astronauts.

It seems safe to conclude that under the conditions of the present experiment, the fluid shifts manifested were not a significant factor contributing to the elicitation of

TABLE IV. MOTION SICKNESS POINTS AS A FUNCTION OF ELAPSED ROTATION TIME FOR THE DIFFERENT EXPERIMENTAL POSITIONS.

Subject	Order	Condition	Elapsed Time of Rotation (Min) 1-10	11-20	21-30	31-40	41-50	51-60
1	2	Head up 10°	0	0	0	0	0	0
	1	Head horizontal	0	0	0	0	0	0
	3	Head down 10°	0	0	0	0	0	0
15	3	Head up 10°	1	1	1	1	1	1
	1	Head horizontal	0	1	4	6	N* abort 47 min	
	2	Head down 10°	0	4	5	5	7 N abort 52 min	
26	2	Head up 10°	FS* abort 7.5 min					
	3	Head horizontal	FS abort 3 min					
	1	Head down 10°	4	FS abort 14 min				
37	3	Head up 10°	0	0	0	0	0	1**
	2	Head horizontal	0	0	0	0	0	0***
	1	Head down 10°	0	0	0	0	0	0**
10	1	Head up 10°	0	0	0	0	0	0
	3	Head horizontal	0	0	0	0	0	0
	2	Head down 10°	0	0	0	0	0	0
39	1	Head up 10°	0	0	0	0	1	2†
	2	Head horizontal	0	0	0	0	0	0
	3	Head down 10°	0	0	0	0	1	1
30	1	Head up 10°	1	N abort 13 min				
	2	Head horizontal	3	N abort 15 min				
	3	Head down 10°	3	N abort 13 min				
21	3	Head up 10°	0	3	3	9	N abort 34 min	
	1	Head horizontal	4	11	N abort 20 min			
	2	Head down 10°	0	1	3	7	N abort 40 min	
13	2	Head up 10°	0	1	3	5	5	5†
	3	Head horizontal	0	0	2	2	N abort 42 min	
	1	Head down 10°	0	0	3	4	4	4†
4	1	Head up 10°	0	0	0	0	0	0
	2	Head horizontal	0	0	0	0	0	0
	3	Head down 10°	0	0	0	0	0	0
7	2	Head up 10°	0	0	0	0	0	0
	3	Head horizontal	0	0	0	0	0	0
	1	Head down 10°	0	0	0	0	1	1
9	3	Head up 10°	0	0	0	0	0	1***
	1	Head horizontal	1	1	1	2	4	4**
	2	Head down 10°	2	2	2	4	4	4**

* N = nausea; FS = frank sickness.
** Dizziness on deceleration.
*** Dizziness and epigastric awareness on deceleration.
† Epigastric awareness on deceleration.

motion sickness. An unqualified rejection of a possible etiological role of fluid shifts, however, is not justified. Further experimentation employing the ZARR device will include prerotation bedrest.

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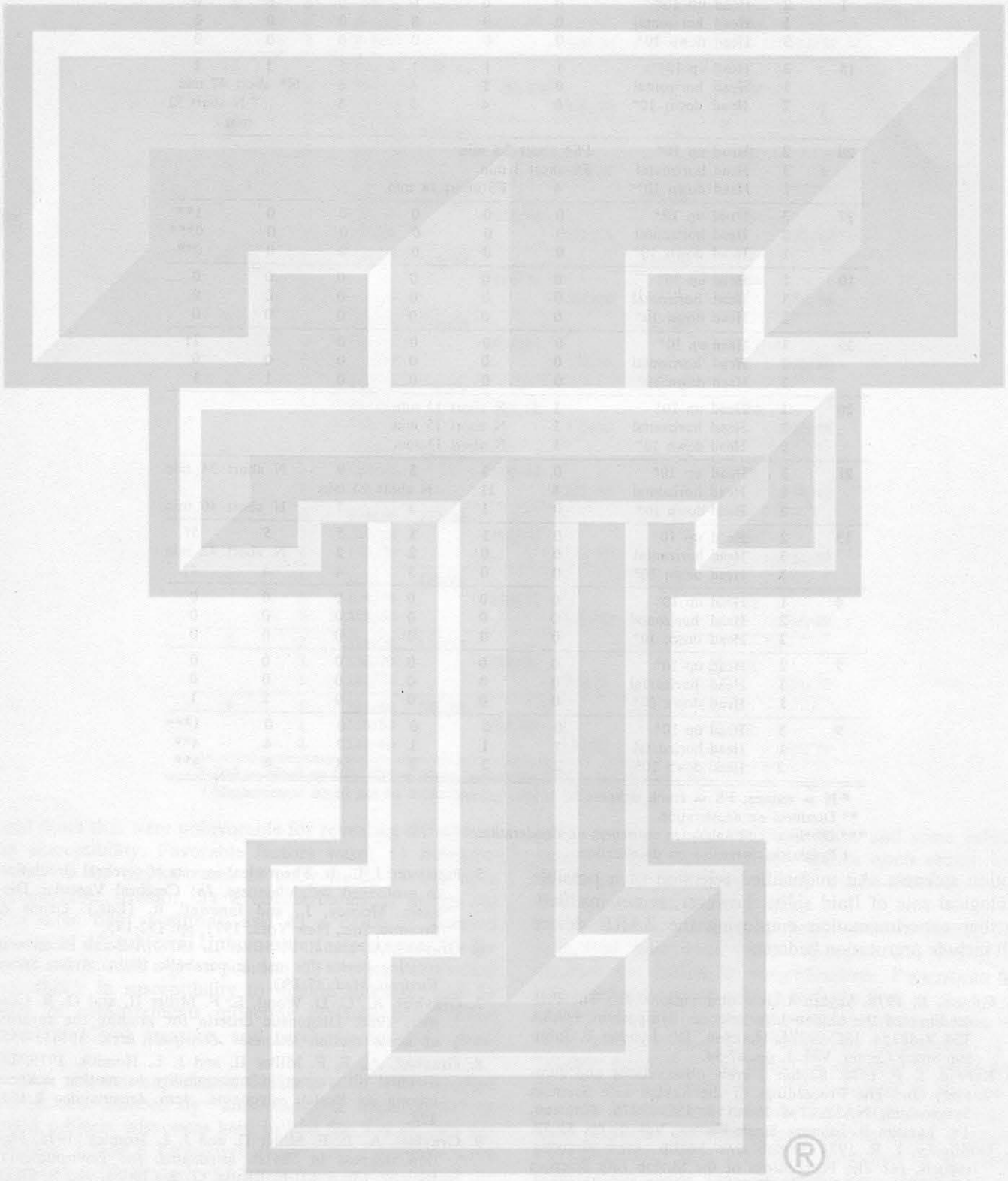

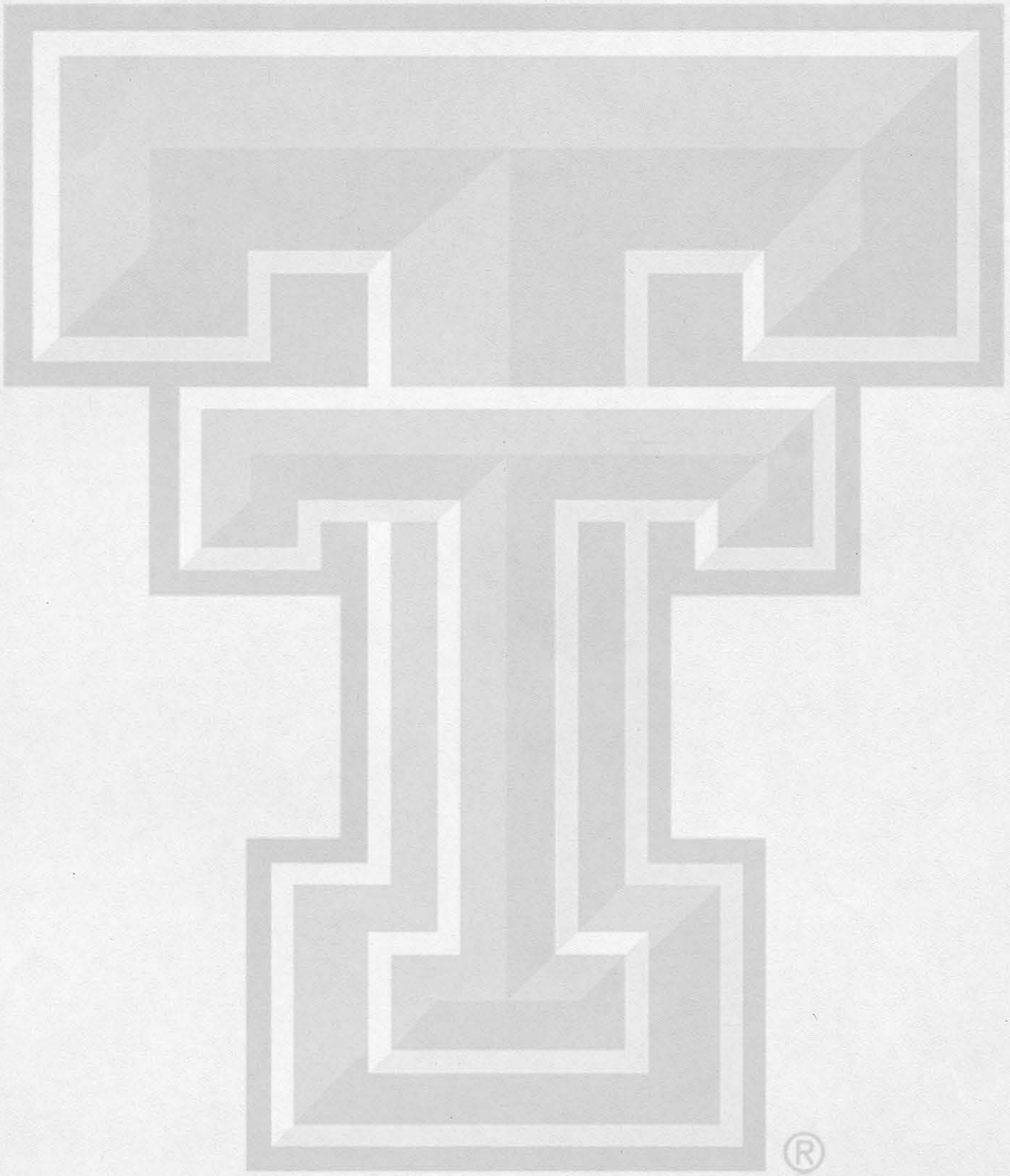

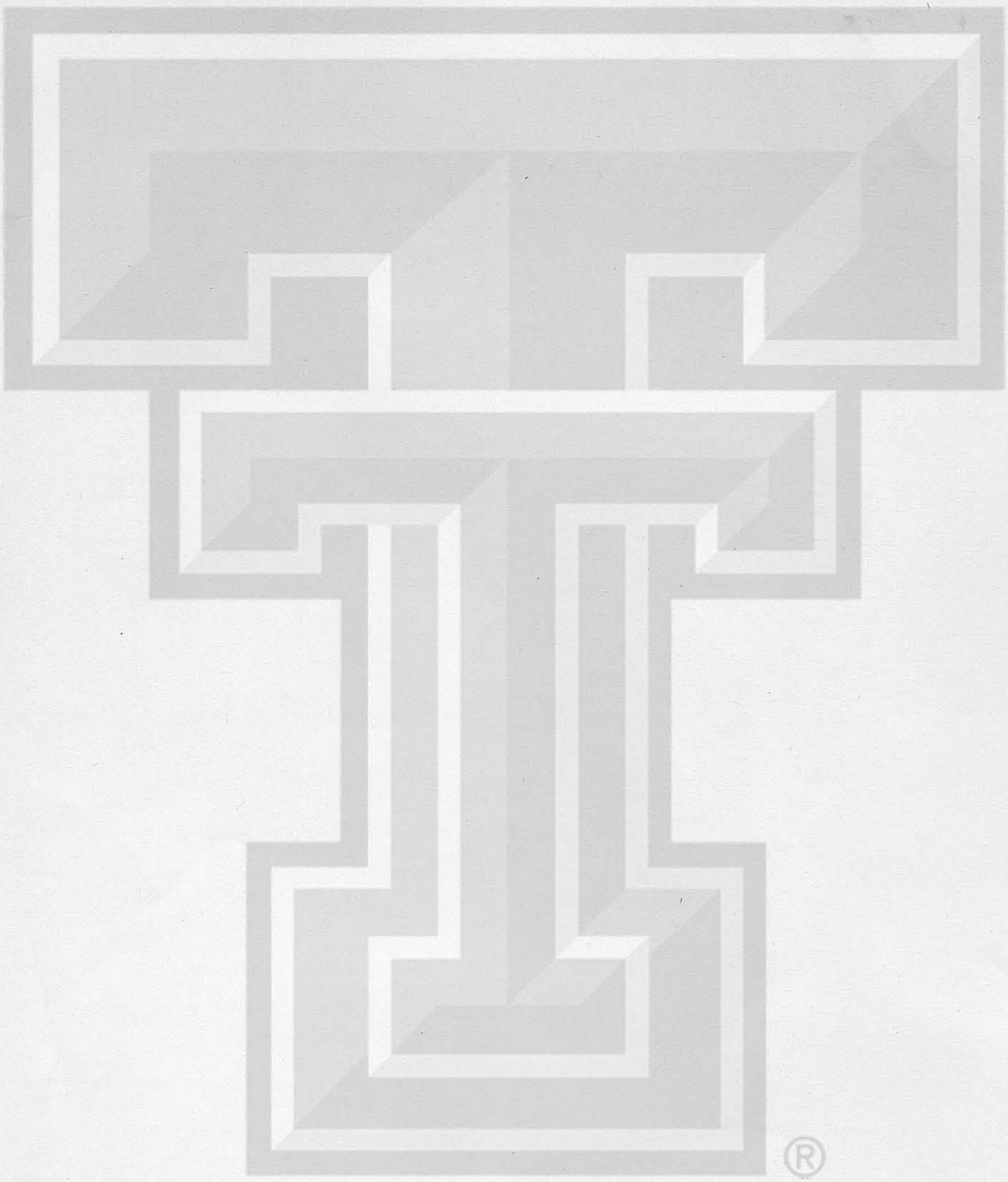

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

RESEARCH AND TECHNOLOGY OBJECTIVES AND PLANS

1. DATE PREPARED	2. AGENCY ACCESSION NO.	3. RELEVANCE CODE	4. CURRENT NUMBER/CODE
25 April 77			199-05

5. TITLE

SPACE MOTION SICKNESS

6. FORMER RTOP NO. *(If applicable)*

7. RELATED RTOP'S *(If applicable)*

8. CONSOLIDATION OF RTOP NUMBERS

9. SCIENTIFIC AND TECHNICAL AREAS (COSATI)

10. RESPONSIBLE NASA ORGANIZATION *(name and address)*

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11. STATUS OF THIS RTOP

FY _____

☐ NEW RTOP

☐ TERMINATING ACTIVITY

☐ RTOP COMPLETED THIS FISCAL YEAR

☐ CONTINUING RTOP: X NO CHANGE

_____ CHANGE IN SCOPE

11a. PROPRIETARY INFORMATION CONTAINED IN RTOP ☐ YES ☒ NO

12. BRIEF TECHNICAL SUMMARY *(Objectives and Approach)*

Abstract: Manned space flight to date has demonstrated that space motion sickness (0-g sickness) can be unpredictable and variable among individuals. A significant observation is that in individuals who do experience this problem, symptoms can persist through the third, fourth, or even fifth day of flight. Thus, on short duration Shuttle flights, a major portion of mission time could be spent with some crewmen who are not operating at maximum efficiency. The research program outlined by this RTOP is directed specifically toward resolving the problem of space motion sickness. An integrated program of basic and applied reserach on humans and animals will be conducted with four major objectives or end-products in view. These are: 1) a complete understanding of the causes of this syndrome in 0-g; 2) criteria for accurately identifying, prior to space flight, individuals susceptible to the problem; 3) satisfactory methods for the prevention of the problem and 4) effective methods for the treatment of symptoms when they occur.

Objectives: The overall objective of this research program is to produce the information required to solve the problem of space motion sickness and nuerosensory adaptation to the weightless environment.

Approach: A broad based program of interrelated studies will be undertaken to delineate the etiology of the space motion sickness syndrome and to develop effective measures for its prediction, prevention, and treatment. Specific attention will be directed toward

13. KEY WORDS Vestibular Function, Motion Sickness, Spatial Orientation, Performance, Drugs Neurophysiology, Electrophysiology, Audition, Vision, Equilibrium, Neuroanatomy.

INSTALLATION CONCURRENCE			HQ CONCURRENCE
DATE	DIVISION	DATE	DATE

INSTALLATION APPROVAL		HQ APPROVAL	
SIGNATURE AND TITLE	DATE	SIGNATURE AND TITLE	DATE

Approach (con't)

investigations of vestibular, proprioceptive, and visual function and their various interrelationships, both on a neurophysiological and behavioral basis. Studies involving other sensory systems and physiological functions will be included to the extent that they may provide information or methodological approaches critical to resolving various aspects of the space motion sickness problem. Included in this latter category will be studies of auditory, neuro-muscular, biochemical, and cortical as well as subcortical mechanisms. Also, orientation, sensorimotor coordination, postural control and locomotion will be investigated. In addition, studies will address the mechanisms which underlie changing levels of sleep, and arousal, attention, alertness, and motivation in the space flight environment. Detailed evaluations of sensory and physiological adaptation processes and various pharmaceutical agents will be key elements in many of the studies to be performed. Studies involving human subjects will utilize a variety of behavioral and advanced non-invasive bio-recording techniques. Additionally, a number of specific experiments will be performed with several small animal species utilizing invasive electrode recording techniques in order to obtain basic information on sensorineural activity. Anatomical and histological procedures will be included in the animal studies as needed. Throughout the course of implementing this program of research a wide variety of unique hardware devices will be employed which provide required controlled angular and linear accelerations or which simulate gravito-inertial alterations in the subject's perceived environment. Parabolic flight experiments will be included to the extent possible.

14. Justification: The nervous system demands particular attention in that it constitutes the controlling mechanisms for human performance and behavior. That the dynamic equilibrium of this and related mechanisms can be seriously disturbed has been dramatically demonstrated during previous space flight missions during which crewmen experienced symptoms of motion sickness. Such disturbances have affected crew health and performance and have impacted mission timelines and operational objectives. The nature of Shuttle missions demands that past difficulties be avoided, if at all possible. It is imperative that neurophysiological function, and all of its ramifications, not be impaired by exposure to any of the stresses which are experienced during the course of a manned mission. In view of specific problems which occurred during Skylab missions and their implications for the success of future Shuttle missions, primary attention will be given to the careful, investigation of those neurosensory and related physiological mechanisms believed to be associated with the 0-g motion sickness syndrome. With regard to space motion sickness, problems which have been identified and amplified by Skylab may be assigned to four major categories:

a. Available information is inadequate to explain the causes or underlying mechanisms of the space motion sickness syndrome.

b. Techniques for reliably identifying individuals who are susceptible to space motion sickness are lacking. In this regard, it is noteworthy that none of the preflight test data obtained on the Skylab astronauts correlated in any fashion with the actual occurrence of inflight symptoms.

c. Techniques for effectively preventing the occurrence of this syndrome in 0-g are lacking. For example, although very limited in scope, attempts to pre-habituate the Skylab crewmen by rotating chair and/or T-38 aerobatic exposures were not visibly useful. Also the use of anti-motion sickness drugs was less than satisfactory in preventing symptoms inflight.

14. Justification (con't)

d. Techniques for effectively treating inflight symptomatology are currently inadequate. In this regard, the use of anti-motion drugs by crewmen with symptoms had limited therapeutic value. Also, little definitive information is available concerning processes inherent in the purposeful acceleration of adaptation to weightlessness.

It must be clearly recognized that the overall problem of space motion sickness is extremely complex and in many ways bound to a very specific stimulus condition, i.e., weightless space flight. Thus research conducted prior to the institution of this RTOP may be only marginally applicable to the problem of space motion sickness and sensory adaptation to 0-g. New and unique approaches must be pursued if required solutions are to be developed.

15. Operating Plan:

a. Technical Objectives: The technical objectives or goals of the research program defined by this RTOP are derived primarily from the above stated problems. First, a broad-based program of ground based studies, with human and animals, will be undertaken which has as its goal the elucidation of mechanisms underlying the motion sickness syndrome in 0-g, the development of techniques for reliably predicting on an individual basis who is prone to this problem in 0-g and, finally, the development of effective countermeasures. Of necessity, work in each of these areas must proceed in parallel.

Secondly, human and animal experiments designed to acquire basic information and validate the results of the ground based studies will be defined for potential application to future flight programs.

Thirdly, advanced instrumentation and measurement techniques required to support the ground based research and flight experiments will be defined and developed as required.

b. Approach:

Ground-Based Research With Man - With regard to the goal of elucidating mechanisms underlying space motion sickness, a comprehensive and integrated program of studies will be designed to investigate a number of processes which are suspected of having direct or indirect etiological significance. Paramount among these will be studies which examine the theory of sensory confusion or sensory conflict as it may relate to the production of motion sickness in the novel space flight environment. Included will be investigations of canal-otolith sensory misintegration or conflict, visual-vestibular conflict and sensory conflict involving proprioceptive or kinesthetic mechanisms. Throughout the course of these studies, emphasis will be placed on motion sickness resulting from altered otolithic stimulation. Studies of sensory adaptation and transfer of adaptation from one motion environment to another will be performed as a means of investigating sensory conflict and motion sickness. Stimulus devices to be used in these studies will include centrifuges, rotating rooms and chairs, linear accelerators, horizontal axis rotators, parallel swings, balancing platforms (and rails), optokinetic nystagmus drums, cinerama, and other devices which permit canicular as well as otolithic stimulation. Response parameters will include, but not be limited to the measurement of susceptibility to motion sickness, nystagmus, ocular counterrolling, postural reflexes, electromyography, and various subjective reactions. New quantitative response measurement techniques must also be developed. A second approach to the elucidation of underlying mechanisms will be to investigate body fluid shifts and vestibular function.

15. Operating Plan
    b. Approach
    Ground-Based Research with Man (con't)

Studies with humans will include measurements of vestibular sensitivity or responsivity (e.g., via nystagmography) during exposure to head down tilt. A third approach will be to determine the possible relationship between biochemical factors and 0-g sickness. A fourth approach will be to investigate neurophysiological correlates of space motion sickness. Finally, studies will be performed to determine the role of idosyncratic psychophysiological or behavior responses to the 0-g environment as a causal factor. The aim of the approach would be to isolate, if possible, traits associated with motion sickness susceptibility.

With regard to the development of predictive techniques, or crew selection criteria, a major approach to be pursued, at least initially, will be to attempt to establish meaningful correlations between susceptibility to motion sickness and other measurable responses including: 1) post-rotary vestibular responses, 2) ocular counterrolling, 3) spinal reflexes and 4) possible biochemical factors. Also carefully designed and conducted experiments during parabolic flight will be required to validate tolerance to parabolic flight stresses as a predictor of susceptibility to motion sickness in 0-g.

With regard to the development of countermeasures, two major approaches will be pursued. One approach will be a series of experiments dealing with adaptation to motion environments, the ultimate goal being the development of vestibular training or habituation procedures. Specifically, the rate of acquisition and decay of adequate effects and the value of overadaptation and transfer effects will be investigated using slow rotation rooms and other stimulation devices. Individual variations typically observed in these adaptation parameters will be analyzed with a view toward predicting adaptation behavior in 0-g on the basis of behavior in other motion environments, including the weightless phase of parabolic flight.

A second major approach to developing countermeasures will be an exhaustive series of experiments to evaluate the efficacy and side-effects of anti-motion sickness drugs. Both single and repeated doses of all available drugs will be tested on large groups of calibrated subjects. Side-effects to be evaluated will include: performance, sensory function, and vital physiological function alterations (e.g., heart rate and blood pressure). All of these drugs studies will be performed with a view toward selecting drugs optimally suited to the individual. Finally, other novel approaches to developing countermeasures will be attempted. Included will be a study using biofeedback techniques to train human subjects to control one or more of their autonomic responses and, thereby, avoid the debilitating effects of motion sickness.

Ground-Based Research with Animals - Neurosphysiolgical, behavioral, anatomical, and histological studies of the vestibular, proprioceptive and visual systems of animals will be directed toward understanding mechanisms of motion sickness in man. Investigations with animals will offer distinct advantages. Large numbers of subjects can be tested and more importantly invasive procedures can be utilized. Thus, studies will be conducted in which the vestibular appartus of different species will be modified by various surgical, chemical, or mechanical methods and neural responses directly recorded with electrodes. Again considerable emphasis will be placed upon investigating the responses of normal and treated animals exposed to different sensory conflict situations. Parabolic flights will be conducted with several species to attempt to analyze transient

15. Operating Plan
    b. Approach
    Ground-Based Research with Animals (con't)

weightless phenomena and to further examine the validity of parabolic flight as a test bed for measureing otolith and other related neural activity during zero gravity. Cross habituation studies will be carried out including behavioral and neurophysiological studies at various stages during the habituation process. Finally, highly specific invasive techniques will be used to investigate discrete functions which cannot be studied in the intact human. Included will be studies to directly measure intralabyrinthine and intracranial fluid pressure under various conditions. Also included will be studies to determine the site of action of anti-motion sickness drugs and studies to determine if peripheral neural responses can be favorably altered with drugs. These ground-based animal studies will be designed not only to complement the human research, but also to answer fundamental questions concerning vestibular physiology and to define requirements for flight experiments with animals.

Flight Experiment with Man - Flight experiments with man should fall under two major categroies. The first major series of experiments should be designed to provide the final validation of techniques for the prediction, prevention, and treatment of space motion sickness. These experiments assume that it will be possible to assign crewmen and passengers to control and experimental groups. The latter would be selected on the basis of defined criteria and exposed to various pre-habituation procedures and drugs which evolved from the ground-based research program. These individuals would then be observed inflight and postflight to detect the presence (or absence) and degree of motion sickness symptomatology. The measurement techniques that should be employed, especially inflight techniques, should be simple and brief. This experimental series would undoubtedly shed some light on mechanisms underlying motion sickness in man, but would lack the precision and detail required to obtain data fundamental to a complete understanding of underlying mechanisms. Other experiments utilizing specialized hardware and sophisticated measurement procedures would be required.

Experiments in this second category should focus on the pre-, and in-, and postflight assessment of otolithic, canicular, proprioceptive, and neuro-muscular responses. These experiments should be designed in large part to determine the rate with which these sensory systems adapt to 0-g and re-adapt to 1-g. Particular attention should be given to the quantitative evaluation of those responses generated by or influenced by the otoliths. The variety of tests which could be performed pre- and postflight is fairly extensive, however, because many ground-based test devices and measurement procedures will not be appropriate for use in the weightless Spacelab, the types of tests that can be performed inflight will be more restricted. It will be necessary to develop new measurement hardware and procedures which would enable more detailed inflight analysis of otolith as well as canicular and proprioceptive reflexes. With regard to the fluid shift hypothesis, space flight testing should involve special cardiovascular and fluid balance experiments and other special measurements of alterations in cephalic blood supply. Also more detailed analysis of neurological and biochemical changes should be performed in a manner which allows careful comparison with the time course and type of motion sickness symptomatology.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY OBJECTIVES AND PLANS

DATE PREPARED	CURRENT NUMBER/CODE	PAGE ____ OF ____
25 April 77	199-05	

JUSTIFICATION, OBJECTIVES AND PLANS, REVIEW AND REPORTING *(Items 14, 15 and 16)*

15. Operating Plan
    b. Approach

Flight Experiments with Animals - In order to acquire neurophysiological data fundamental to understanding mechanisms of space motion sickness in man and sensory adaptation to O-g in general, a series of animal experiments should be developed for Spacelab. These experiments should be logically derived from the ground-based animal research program. Also an attempt should be made to develop many of the inflight animal experiments in parallel with the human flight experiments so that specific information unobtainable from humans can be acquired from animals via the use of invasive measurement techniques.

One basic approach to the development of a well defined series of flight experiments with animals would be to first identify a few species which have a well developed and easily measured motion sickness syndrome in 1-g. These species would then be observed and tested inflight without invasive techniques, to see which best represents man in terms of motion sickness and sensory adaptation difficulties in O-g. Having selected one or two such species further detailed experiments would be developed using invasive techniques. Included would be studies in which various portions of the vestibular system have been modified (e.g., by surgery) in an attempt to isolate the responsible sensory channels. In both treated and non-treated animals, classical neurophysiological techniques should be employed to record neural activity from various sites in the peripheral and central nervous system. Pending the outcome of certain of the ground-based studies with animals, other specific inflight experiments could be developed. For example, one or a series of studies could be required to unequivocally prove or disprove the role of fluid pressure changes in space motion sickness.

The above statements regarding flight experiments with man and animals are examples of the type of research that should follow ground based studies in order to bring the space motion sickness program to a logical and complete conclusion. The solicitation, review, approval, funding and development of such experiments will be handled by other methods outside the scope of this RTOP.

Hardware and New Technology Development - A vast array of unique and sophisticated hardware devices and measurement techniques are required to implement the research outlined by this RTOP. The ground-based devices required for exposing both man and animals to a wide range of controlled stimulus conditions which effect the vestibular, visual, proprioceptive, neuromuscular, and other related neurophysiological processes are largely available. A major shortcoming, however, with research technology for human vestibular physiology is the heavy reliance of subjective reporting from the subject. A concerted attempt must be made to develop new quantitative response measurement and analysis techniques.

A greater challenge will lie in the development of flight hardware systems and O-g compatible response measurement and analysis techniques for both man and animals. With regard to inflight experiments with man, devices which provide controlled angular (rotating or torsion swing chair) and linear (horizontal oscillator) accelerations should be available. Many of the same advanced response measurement techniques developed for ground-based studies should be adapted for inflight use.

15. Operating Plan
    b. Approach
    Hardware and New Technology (con't)

With regard to animals, a small centrifuge and linear acceleration device should be available on the Spacelab. Again advanced electrophysiological measurement, recording, and analysis techniques will be developed. A host of technological problems ranging from animal maintenance facilities to RF and vibration isolation of instrumented preparations must be dealt with in the context of research in the area of vestibular physiology.

Milestone Schedule:

16. Review and Reporting

    a. Progress Report

    Progress report are included with each of the T-41 task descriptions.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY OBJECTIVES AND PLANS

PAGE ____ OF ____

DATE PREPARED	TITLE	RTOP CODE NO.
5 May 77	Space Motion Sickness	199-05-01

17. RESOURCE REQUIREMENTS

Johnson Space Center

A. DIRECT MANPOWER *(Manyears)*

	FISCAL YEAR				
	PRIOR FY- 77	CURRENT FY- 78	FY- 79	FY- 80	FY- 81
DIRECT PROFESSIONAL	1.5	1.5	1.5	1.5	1.5
DIRECT SUPPORT					
TOTAL DIRECT MANPOWER	1.5	1.5	1.5	1.5	1.5
NRC Associate	.75				

B. FACILITIES

N/A

C. R&D FUNDS

	FISCAL YEAR				
	PRIOR FY- 77	CURRENT FY- 78	FY- 79	FY- 80	FY- 81
CONTRACTED R&D	540	645	635	635	635
IN-HOUSE DIRECT RESEARCH	50	50	50	50	50
IMS	0	304	305	305	305
TOTAL R&D FUNDS	590	999	990	990	990

CONTRACTS *($100K and above)*

	CONTRACT NO.	DATE	CONTRACTOR	AMOUNT	FY
IN-HOUSE R&D	T-9140E	1 Jan 77	NMARL, Pensacola	250	77

D. CONTRACTOR SUPPORT MANPOWER *(Manyears)*

	PRIOR FY- 77	CURRENT FY- 78	FY- 79	FY- 80	FY- 81
TOTAL MAN YEARS	0	8	8	8	8

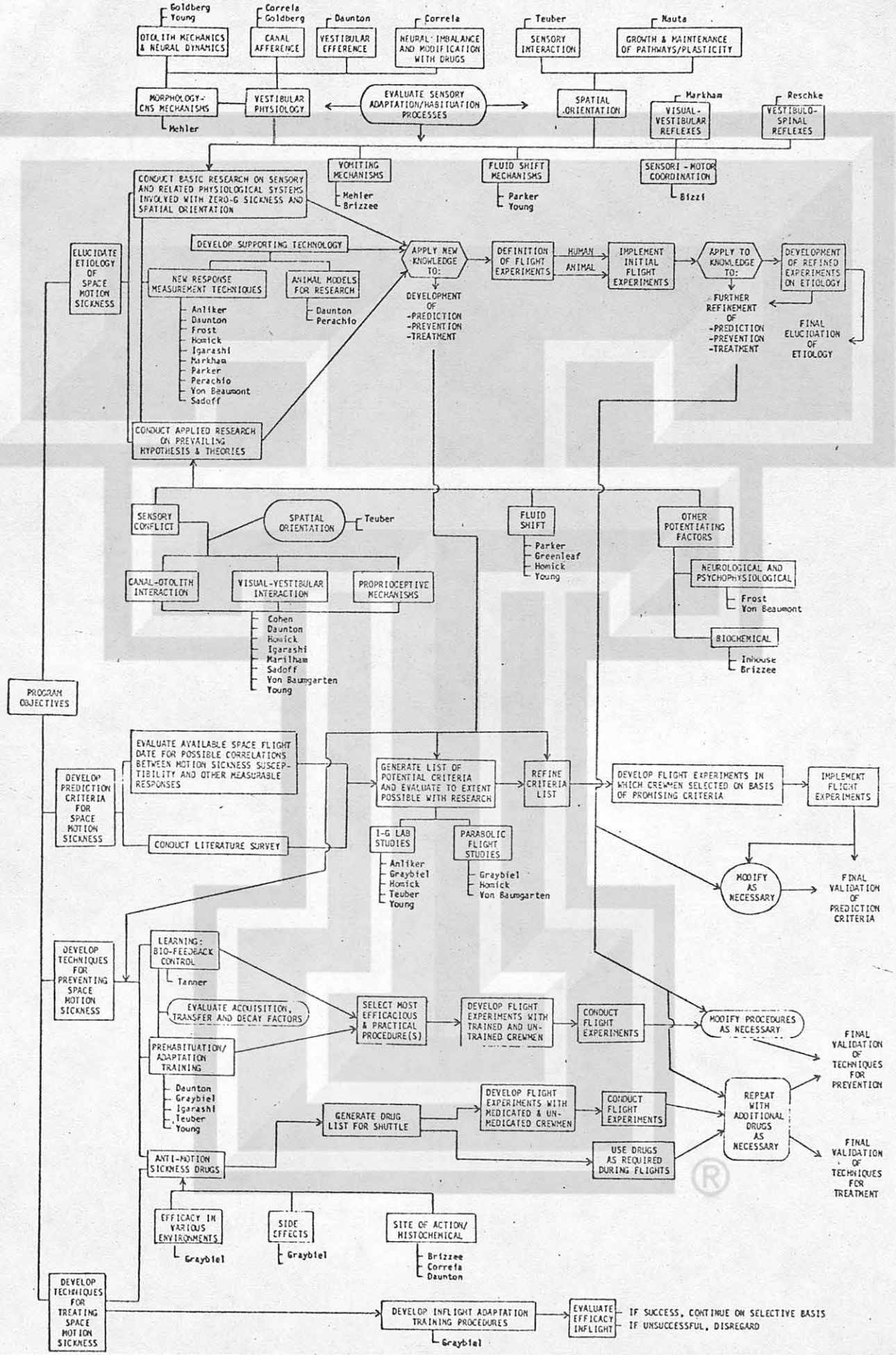
199-05 SPACE MOTION SICKNESS

T-43 PRIORITY LIST

JOHNSON SPACE CENTER

PRIORITY	CODE NO.	INVESTIGATOR/INSTITUTION
1	01-03	Homick/JSC
2	01-01	Graybiel/NAMRL
3	01-05	Igarashi/Baylor College of Medicine
4	01-04	Parker/Miami University (Ohio)
5	01-02	Frost/Methodist Hospital, Houston
6	01-07	Correia/UTMB, Galveston
7	01-10	Anderson/U. of Michigan
8	01-13	Homick/JSC (KC-135)
9	01-09	Kales/Pennsylvania State Univ.
10	01-14	Homick/JSC (New Start)
11	01-12	Bullock/U. of California, San Diego

SPACE MOTION SICKNESS RESEARCH PLAN



NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: The Prevention of Vestibular Side Effects in Weightlessness

3. NUMBER/CODE: a. PROPOSAL: | b. CURRENT: 199-05-01-01

4. PERFORMING ORGANIZATION:
Naval Aerospace Medical Research Laboratory
Pensacola, Florida 32512

5. CONTRACT/GRANT NO.: T-9140E

6. DATE: a. STARTING: 1 Jan 77 | b. ANNIVERSARY: 1 Jan 78

7. INVESTIGATOR'S NAME: A. Graybiel | TEL. NO.: (904)452-3255

8. NASA ALT. TECH MONITOR'S NAME: N/A | TEL. NO.:

9. INSTITUTION CATEGORY CODE: OT

FISCAL YEAR	STATUS a.	MANPOWER (MY) IN-HOUSE b.	MANPOWER (MY) S/C c.	FUNDING (In K) IMS d.	FUNDING (In K) R/D e.	FUNDING (In K) TOTAL f.
10. PRIOR	C		0	0	250	250
11. CURRENT	C		0	0	220	220
12. BUDGET	C		0	0	200	200

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The basic strategy is to develop and validate acceptable techniques for the prediction, prevention and treatment of vestibular side effects, notably motion sickness, caused by exposure to stressful gravito-inertial force environments including zero gravity.

b. Progress - Accomplishments during past year include: 1) Measurements of susceptibility to motion sickness in about 25 subjects during free-fall phase of parabolic flight (KC-135) with head fixed and head moving while seated and while rotating at 30 RPM. 2) Study using ZARR device in which headward shifts of body fluid did not alter motion sickness susceptibility. 3) Drug studies using SRR and KC-135 which indicated scopolamine administered transdermally and oral promethazine/ephedrine (12.5 mg. each) as best prospects for long term use. 4) Drug studies using KC-135 indicating high efficacy of promethazine injected I.M. in dealing with severe, acute motion sickness. 5) Studies to determine variables in the rate of acquisition of adaptation, transfer of overadaptation in the lab to the zero-g phase of parabolic flight and rate of recovery from acute motion sickness.

c. Planned Tasks - 1. Continued studies to identify in various test situations efficacious anti-motion sickness (AMS) drugs with emphasis on drug type, dose level and route of administration. 2. Continued investigation of rate of acquisition of adaptation using a new passive head movement (PHM) device and transfer of adaptation to other stressful environments. 3. Continued investigations of recovery from acute motion sickness. 4. Further experimentation employing ZARR device, including pre-bedrest (2 hours) to determine whether prolonged headward displacement of body fluids influences susceptibility. 5. Continued use of parabolic flight to evaluate motion sickness susceptibility and AMS drug efficacy, if KC-135 aircraft is available for use.

d. Bibliography - 1. Graybiel, A. and Miller, E. F. 1976. A Z-axis recumbant rotating device for use in parabolic flight. Aviat. Space Environ. Med. 47, 893.

2. Graybiel, A. and Knepton, J. 1976. Sopite syndrome: A sometines sole manifestation of motion sickness. Aviat. Space Environ. Med. 873-882.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

3. Graybiel, A., Knepton. J., and Shaw, J. 1976. Prevention of experimental motion sickness by scopolamine absorbed through the skin. Aviat. Space Environ. Med., 1096-1100.

4. Graybiel, A. and Lackner, J. R. 1977. Comparison of susceptibility to motion sickness during rotation at 30 RPM in the earth-horizontal, 10° head-up and 10° head-down positions. Aviat. Space Environ. Med. 7-11.

5. Graybiel, A. and Knepton, J. 1977. Evaluation of a new anti-nauseant drug for the prevention of motion sickness. In press.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Neurophysiological Correlates of Space Motion Sickness

3. NUMBER/CODE
- a. PROPOSAL:
- b. CURRENT: 199-05-01-02

4. PERFORMING ORGANIZATION
Methodist Hospital
Texas Medical Center
Houston, Texas 77025

5. CONTRACT/GRANT NO.: NAS9-13870

6. DATE
- a. STARTING: 15 Feb 74
- b. ANNIVERSARY: 1 Sep 77

7. INVESTIGATOR'S NAME: J. D. Frost, Jr. TEL. NO.: (713)790-3105

8. NASA ALT. TECH MONITOR'S NAME: N/A TEL. NO.:

9. INSTITUTION CATEGORY CODE: UM

FISCAL YEAR	STATUS a.	MANPOWER (MY) IN-HOUSE b.	MANPOWER (MY) S/C c.	FUNDING (In K) IMS d.	FUNDING (In K) R/D e.	FUNDING (In K) TOTAL f.
10. PRIOR	C		0	0	40	40
11. CURRENT	C		0	0	50	50
12. BUDGET	C		0	0	50	50

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - This effort will utilize computerized EEG and other neurological measurement techniques to assess possible mechanisms underlying space motion sickness, as well as vestibular and neuromuscular alterations induced by exposure to zero-g.

b. Progress - Final computer analysis of Skylab EEG data confirmed the presence of potentially significant alterations in cortical electrical activity in the crewmen tested. These findings could not be explained satisfactorily by metabolic or drug induced changes or psychological factors. It was concluded that weightlessness per se was responsible for at least part of this change. While vestibular influences on EEG could not be ruled out entirely, the investigator hypothesized that intracranial endema resulting from body fluid shifts may be the cause of the EEG alterations and in turn have a bearing on the expression of motion sickness symptomatology. Additionally, EEG data were obtained on 2 subjects during a 28 day bedrest study. Preliminary data analysis indicate moderate changes which were not like those observed during Skylab.

c. Planned Tasks - A benign intracranial hypertension model will be used. This model will permit analysis of EEG inpatients who present signs and symptoms of raised intracranial fluid pressure, but without evidence of intracranial pathology or ventricular dilation. EEG and other neurological data will be obtained from patients during the acute and recovery phases of this syndrome, as well as in persons expressing signs and symptoms of vestibular dysfunction. Also, using a triaxial vector accelerometry technique, measurements will be obtained in these individuals to quantify any neuro-muscular disturbances (ataxia) which may accompany intracranial pressure or vestibular alterations. Similar data will be obtained from normal persons exposed to vestibular stimulation.

d. Bibliography - Frost, J. D. Automated EEG System and EEG correlates of space motion sickness. Final report, Contract NAS9-13870, Feb., 1977.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Mechanisms Underlying Motion Sickness in Man

3. NUMBER/CODE
a. PROPOSAL:
b. CURRENT: 199-05-01-03

4. PERFORMING ORGANIZATION
Neurophysiology Laboratory
NASA - Johnson Space Center

5. CONTRACT/GRANT NO.: In-House

6. DATE
a. STARTING: 1 Oct 74
b. ANNIVERSARY: 1 Oct 77

7. INVESTIGATOR'S NAME | TEL. NO.: J.L. Homick & M.F.Reschke 483-5056

8. NASA ALT. TECH MONITOR'S NAME | TEL. NO.: N/A

9. INSTITUTION CATEGORY CODE: FC

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	c. S/C	FUNDING (In K) d. IMS	e. R/D	f. TOTAL
10. PRIOR	C	1.5	0	0	50	50
11. CURRENT	C	1.5	8	304	50	354
12. BUDGET	C	1.5	8	304	50	354

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The basic strategy is to investigate several neurosensory processes which have potential etiological significance for the space motion sickness syndrome. Related efforts are the identification and evaluation of factors which may have predictive value for this syndrome and the evaluation of selected countermeasures.

b. Progress - 1) Methods for the acquisition and computer analysis of vestibulospinal (H-reflex) responses were refined. Data were collected on human subjects in the laboratory and during parabolic flight. Flight data indicated a potentiation of the H-response during the 0-g phase of parabolas and an inhibition of the response during the hyper-g phase. These activities and finding provided the basis for a Spacelab I experiment proposal. 2) Techniques developed in the laboratory for recording from single otolith units in the 8th nerve in frogs were incorporated into an experiment for SMD test III, scheduled for May 1977. 3) Using a computer controlled rotating chair, new procedures were developed for the acquisition of per- and post-rotary sensation and nystagmus responses (cupulograms). Assessments of the value of this procedure for evaluating vestibular function are continuing. 4) Vestibular data were obtained on 6 subjects before and after a 28-day bedrest study. Results indicated bedrest is not a suitable analog of 0-g with regard to vestibular function.

c. Planned Tasks - With regard to etiology, single cell recording methods and non-invasive electrophysiological or psychophysical procedures will be used with small animals and man respectively to study sensory interaction processes. Also, the relationship between body fluid shifts and vestibular function in man will be examined. Efforts to identify etiological, as well as, predictive factors will focus on the correlation between motion sickness susceptibility and other measurable vestibular related responses including 1) post-rotary responses and 2) vestibulospinal reflexes. With regard to countermeasures, limited assessments of the acquisition and transfer of vestibular adaptation will be made. Unique experiments which address specific aspects of the above tasks will be done in parabolic flight.

d. Bibliography - 1. Reschke, M. F., Anderson, D. J., Moore, M. J. and Homick, J. L. Vestibular-spinal responses as a function of zero-g. Presented at Society for Neuroscience, Toronto, Canada, November, 1976.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

2. Homick, J. L., Reschke, M. F., Moore, M. J. and Anderson, D. J. The effects of 28-days supine bedrest on vestibular system function. In: Report of 28-Day Bedrest Simulation of Skylab. Methodist Hospital, Contract NAS9-14578, December 1976.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Intra-Labyrinthine Fluid Pressure Dynamics

3. NUMBER/CODE
a. PROPOSAL:
b. CURRENT: 199-05-01-04

4. PERFORMING ORGANIZATION
Department of Psychology
Miami University
Oxford, Ohio 45051

5. CONTRACT/GRANT NO.: NAS9-14538

6. DATE
a. STARTING: 15 Feb 75
b. ANNIVERSARY: 1 Apr 78

7. INVESTIGATOR'S NAME | TEL. NO.: D. E. Parker (513)529-3116

8. NASA ALT. TECH MONITOR'S NAME | TEL. NO.: N/A

9. INSTITUTION CATEGORY CODE

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	c. S/C	FUNDING (In K) d. IMS	e. R/D	f. TOTAL
10. PRIOR	C		0	0	24	24
11. CURRENT	C		0	0	25	25
12. BUDGET	C		0	0	25	25

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The essential strategy of this effort is to examine a possible mechanism of space motion sickness, specifically the relationship between labyrinthine fluid pressure and acute redistribution of body fluids. Additionally, vestibular (otolith) fatigue following sustained linear acceleration will be investigated in an attempt to better understand otolith response dynamics in 0-g.

b. Progress - A series of experiments with guinea pigs and monkeys demonstrated that CSF and perilymph fluid pressures change rapidly following simulated zero-g (torso elevation) and that there is no apparent divergence of pressures at these locations during stimulation. Similar measurements on guinea pigs during parabolic flight were inconclusive. The data to date do not support a fluid shift hypothesis of 0-g sickness, however, critical measurements of endolymph pressure have yet to be made. A separate series of experiments demonstrated a clear temporary threshold shift in linear motion detection following linear acceleration. This is a fundamental and previously unobserved response property of the otolith receptors.

c. Planned Tasks - 1) An attempt will be made to develop a reliable method for recording endolymph fluid pressure in guinea pigs. Endolymph, perilymph and CSF pressure will be measured in guinea pigs during simulated zero-g as well as parabolic flight. 2) Inner ear impedence measurements during head down tilt will be made in humans as a further means of examining the relationship between fluid shifts and labyrinthine function. 3) Three experiments related to otolith fatigue following sustained linear acceleration will be undertaken. The first will deal with effects of body orientation, and the second with the effects of long duration fatigue exposure. Finally, the possibility that sustained linear acceleration modifies oscillation detection thresholds will be investigated.

d. Bibliography - 1. Parker, D. E. Labyrinthine and cerebral spinal fluid pressure changes in guinea pigs and monkeys during simulated zero-g. Aviat. Space Environ. Med., in press.

2. Parker, D. E.,Littlefield, V. M., Gulledge, W. L. and Tublis. Vestibular fatigue following intense, oscillating linear acceleration. In preparation.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Semicircular Canal and Otolith Interaction Processes

3. NUMBER/CODE
a. PROPOSAL:
b. CURRENT: 199-05-01-05

4. PERFORMING ORGANIZATION
Department of Otorhinolaryngology
Baylor College of Medicine
Houston, Texas 77025

5. CONTRACT/GRANT NO.: NAS9-14546

6. DATE
a. STARTING: 1 May 75
b. ANNIVERSARY: 1 May 78

7. INVESTIGATOR'S NAME: M. Igarashi | TEL. NO.: (713)790-4678

8. NASA ALT. TECH MONITOR'S NAME: N/A | TEL. NO.:

9. INSTITUTION CATEGORY CODE: UM

FISCAL YEAR	STATUS a.	MANPOWER (MY) IN-HOUSE b.	FUNDING (In K) S/C c.	IMS d.	R/D e.	TOTAL f.
10. PRIOR	C		0	0	35	35
11. CURRENT	C		0	0	40	40
12. BUDGET	C		0	0	45	45

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The basic strategy of this program is to evaluate the role of vestibular and visual system sensory conflict or sensory misintegration as an etiological factor in space motion sickness. Additionally, efforts will be made to develop and evaluate non-pharmaceutical techniques which may be used to minimize or prevent this syndrome.

b. Progress - In one study designed to evaluate otolith-semicircular canal interactions in squirrel monkeys it was shown that the elimination of otolith end organ inputs (two stage utriculosacculectomy) resulted in reduction of horizontal rotary nystagmus even though the canal end organs were intact. In another study horizontal optokinetic nystagmus (OKN) and optokinetic afternystagmus (OKAN) were examined before and after utriculo-sacculectomy in 7 squirrel monkeys. It was found that slow ocular pursuit was not markedly changed by elimination of otolith inputs. A third study in this area which investigated cross-interaction between post-rotary nystagmus and OKAN revealed significant enhancement or inhibition of nystagmus depending upon stimulus directional matching. In a separate series of tests skin conductance during vestibular stress (caloric irrigation) was measured in squirrel monkeys as an index of motion sickness. Results were variable, but similar to those previously obtained with human subjects. In a final series of experiments it was demonstrated that pre-operative motor exercise enhanced the rate with which monkeys recovered from locomotor deficits following unilateral utricular nerve section.Also pilot studies were done to evaluate the H-reflex in squirrel monkeys.

c. Planned Tasks - 1) Analysis of vestibulo-visual conflict in the squirrel monkey model will continue using appropriate rotary and optokinetic stimulation apparatus. Normal specimens and those with unilateral or bilateral lesions will be tested and compared. Evaluations of OKN and OKAN in both the horizontal and vertical directions will be performed. 2) Studies will be performed investigate experimentally induced motion sickness in squirrel monkeys with unilateral labyrinth ablations. Physiological signs and symptoms of motion sickness will be monitored using quantitative methods previously developed under this effort. These same response parameters will also be evaluated in normal subjects exposed to stressful optokinetic or conflicting vestibulo-visual stimuli. 3) Studies will be continued to determine the effect of varying the duration of post-surgery exercise on the rate with which monkeys learn

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

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to compensate or improve locomotor performance following unilateral utricular nerve sections. Also, the effect of post-operative continuous constraint on locomotor compensation following partial or total labyrinthine ablation will be evaluated. The H-reflex will be investigated in normal squirrel monkeys and in those with labyrinthine or otolith end organ ablations in the laboratory and during parabolic flight.

d. Bibliography - 1. Igarashi, et al. Effect of otolith end organ ablation on pendular rotation nystagmus in squirrel monkeys. Arch. Oto - Rhino - Laryng., in press. 2. Igarashi, et al. Effect of otolith end organ abliation on horizontal optokinetic nystagmus and optokinetic afternystagmus in the squirrel monkey. ORL, in press. 3. Igarashi, et al. Optokinetic afternystagmus and postrotary nystagmus in suqirrel monkeys. Submitted to Acta. Otolaryng.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Spontaneous Vestibular Primary Afferent Discharge.

3. NUMBER/CODE: a. PROPOSAL: | b. CURRENT: 199-05-01-07

4. PERFORMING ORGANIZATION:
Department of Otolaryngology
University of Texas Medical Branch
Galveston, Texas

5. CONTRACT/GRANT NO.: NAS9-14641

6. DATE: a. STARTING: 1 May 75 | b. ANNIVERSARY: 1 May 78

7. INVESTIGATOR'S NAME: M. J. Correia | TEL. NO.: (713)765-2721

8. NASA ALT. TECH MONITOR'S NAME: N/A | TEL. NO.:

9. INSTITUTION CATEGORY CODE: UM

FISCAL YEAR	STATUS a.	MANPOWER (MY) IN-HOUSE b.	MANPOWER (MY) S/C c.	FUNDING (In K) IMS d.	FUNDING (In K) R/D e.	FUNDING (In K) TOTAL f.
10. PRIOR	C		0	0	30	30
11. CURRENT	C		0	0	30	30
12. BUDGET	C		0	0	35	35

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy: This effort will deal with a description of primary vestibular afferent neural input to the CNS (including what constitutes an imbalance in discharge patterns), and how this input may be modified by efferent control. The effort will also attempt to describe the biological generating mechanism for the afferent input both on a neural and morphological level.

b. Progress: Further examinations of the morphological and physiological characteristics of the vestibular primary afferent system of the pigeon were completed. The following illustrate significant progress for this effort. 1) Signal detection models of the spontaneous discharge from ampullarly primary afferents (APA's) indicated an improved way of determining cell thresholds. 2) Sinewave analysis of the APA system indicated several amplitude dependent and frequency dependent nonlinearities. 3) Morphologically, it was demonstrated that multiple type I hair cells within a single nerve chalice are more prevalent in the peripheral regions of the ampulla and type II appear to be more prevalent on the central region. Also, efferent innervation was demonstrated and a quantative estimate of myelinated afferent fibers in the crista-ampullaris of the pigeon was determined.

c. Planned Tasks: 1) Spontaneous and driven (rotation stimuli) neural activity from vestibular neurons in the pigeon will be recorded. Theoretical models based on biological processes will be tested against the empirical data to determine the most appropriate physiological basis for the mathematical process which best describes the neural responses. Efferent influences on afferent input to the CNS will then be studied by removing efferent control via surgery and recording afferent activity from the 8th nerve. 2) Biological generating mechanisms will be investigated by recording responses generated by normal physiological stimuli (angular acceleration) and by electrical stimulation and comparing these responses on Bode plots. Confirmation of models devised to describe the biological generating mechanism will be obtained through light and electron microscopy.

d. Bibliography: 1. Brassard, J. R. and Correia, M. J. Acomputer program for fitting multimodel probability density functions. Computer Prog. Biomed., in press.

2. Landolt, J. P. and Correia, M. J. Mechanisms for initiation of spontaneous discharges in peripheral anterior semicircular canal neurons in the pigeon. Submitted for publication.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR		
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

3. Correia, M. J. and Landolt, J. P. A point process model of the impulse-generating mechanism in anterior semi-circular canal crista. Submitted for publication.

4. Anderson, D. J. and Correia, M. J. The detection and analysis of point processes in biological signals. Proc. IEEE, in press.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Quantitative Evaluation of Anti-Motion Sickness Drug Side Effects

3. NUMBER/CODE: a. PROPOSAL: | b. CURRENT: 199-05-01-09

4. PERFORMING ORGANIZATION:
Department of Psychiatry & Pharmacology
Pennsylvania State University
Hershey Medical Center
Hershey, PA 17033

5. CONTRACT/GRANT NO.: New Start

6. DATE: a. STARTING: 1 Sep 77 | b. ANNIVERSARY: 1 Sep 78

7. INVESTIGATOR'S NAME | TEL. NO.: A. Kales & E. O.Bixler

8. NASA ALT. TECH MONITOR'S NAME | TEL. NO.: N/A

9. INSTITUTION CATEGORY CODE: UM

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	c. S/C	FUNDING (In K) d. IMS	e. R/D	f. TOTAL
10. PRIOR	N		0	0	60	60
11. CURRENT	C		0	0	50	50
12. BUDGET	C		0	0	60	60

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The strategy is to evaluate the effects of available anti-motion drugs on human performance, behavior and physiological function in order to ensure that the user's performance capabilities and well-being are not jeopardized. Attempts will be made to verify that the use of these drugs will not compromise the collection and interpretation of space flight experimental biomedical data.

b. Progress - This is a proposed new start; no progress to report.

c. Planned Tasks - A series of studies using human subjects will be conducted to evaluate potential detrimental side effects of single and repeated doses of selected anti-motion sickness drugs under consideration for use during the Shuttle Program. Parameters to be investigated will include: 1) simple and complex motor performance, 2) sensory function, particularly vestibular and visual function, 3) heart rate, blood pressure, respiration rate and other vital physiological functions that may be affected. If indicated, limited studies will be conducted to evaluate sleep quality and quantity under the influence of the drugs. In order to understand possible deleterious synergistic effects the combination of anti-motion sickness drugs with other commonly used medication will be evaluated. All of these studies will be performed with a view toward selecting a drug or drugs optimally suited to the individual. These studies will be closely coordinated with ongoing anti-motion sickness drug research at Pensacola and inhouse. Because the use of drugs as a countermeasure may be unavoidable (vestibular "training" may prove to be ineffective for a significant number of space travelers), it is essential that the side-effects of these drugs be carefully evaluated.

d. Bibliography - None.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Evaluations of Postural Mechanisms Under Dynamic Conditions

3. NUMBER/CODE
a. PROPOSAL:
b. CURRENT: 199-05-01-10

4. PERFORMING ORGANIZATION
Kresge Hearing Research Institute
University of Michigan
Ann Arbor, Michigan

5. CONTRACT/GRANT NO.: NAS9-15244

6. DATE
a. STARTING: 1 Feb 1977
b. ANNIVERSARY: 1 Feb 1978

7. INVESTIGATOR'S NAME | TEL. NO.: D. J. Anderson (313)764-5186

8. NASA ALT. TECH MONITOR'S NAME | TEL. NO.: N/A

9. INSTITUTION CATEGORY CODE: UN

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	MANPOWER (MY) c. S/C	FUNDING (In K) d. IMS	FUNDING (In K) e. R/D	FUNDING (In K) f. TOTAL
10. PRIOR	C		0	0	30	30
11. CURRENT	C		0	0	30	30
12. BUDGET	C		0	0	30	30

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The primary strategy is to develop improved, quantitative test methods for the assessment of postural mechanisms in individual human subjects under dynamic, as well as static test conditions.

b. Progress - This is a relatively new start, however, accomplishments during a previous and related 6-month effort include: 1) design and initial fabrication of a prototype moving platform system; 2) development of a digital scan camera system for subject postion monitoring and 3) development of computer programs for driving the platform and for data analysis.

c. Planned Tasks - Development of a system for testing the dynamics of postural mechanisms will continue. This system will consist of equipment necessary to generate and deliver stimuli, condition physiological signals and sample, analyze and display results. A series of test protocols will be developed which require the subject to balance on the moving platform and force him to execute postural corrections which will reveal an accurate picture of his ability to compensate under dynamic conditions. Motion stimuli will include pseudo-random periodic waveforms and impulsive waveforms. Testing will be with eyes open and closed. The final outcome of this effort will include a recommendation for a test configuration and protocols suitable for potential use pre- and postflight biomedical evaluations of future flight crewmen.

d. Bibliography - 1. Anderson, D. J., Homick, J. L., and Jones, K. W. Line scan cameras applied applied to posturography. (Abstract) Presented at San Diego Biomedical Symposium, San Diego, California, February 1977.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 20 April 77

2. TITLE: Mechanisms of Compensation for Vestibular Lesions and Integrative Functions in Control of Equilibrium

3. NUMBER/CODE
a. PROPOSAL:
b. CURRENT: 199-05-01-12

4. PERFORMING ORGANIZATION
Department of Neurosciences
University of California, San Diego
LaJolla, California 92093

5. CONTRACT/GRANT NO.: NSG-9048

6. DATE
a. STARTING: 1 Jan 77
b. ANNIVERSARY: 1 Jan 78

7. INVESTIGATOR'S NAME: T. H. Bullock
TEL. NO.: (714)452-3636

8. NASA ALT. TECH MONITOR'S NAME: N/A
TEL. NO.:

9. INSTITUTION CATEGORY CODE: UN

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	c. S/C	FUNDING (In K) d. IMS T.P.	R/D	TOTAL
10. PRIOR	N		0	0	0	0
11. CURRENT	C		0	0	60	60
12. BUDGET	C		0	0	50	50

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - Primary strategy is to conduct research appropriate to gaining a better understanding of the operation of the vestibular system in normal performance, and especially to understand and influence the processes by which the CNS overcomes disturbances resulting from lesions or malfunctions of the vestibular system.

b. Progress - This effort was initiated 1 Jan 1977. With the exception of a 6 week trip by the investigator to Brazil to obtain fish specimens for research, no progress has been reported.

c. Planned Tasks - A series of interrelated tasks will be initiated to: 1) Assess the relative importance of sensory systems, vestibular and other, in equilibrium and postural control mechanisms in different species of vertebrates; 2) Determine which CNS structures are involved in compensation and adjustment processes occurring after vestibular lesions; 3) Determine by which mechanisms the deafferented vestibular nuclear complex regains activity during compensation after unilateral labyrinthectomy; 4) Determine the influence of training, additional brain lesions and drugs on vestibular compensation mechanisms. Behavioral, electrophysiological and brain lesion studies will use fish, amphibians, guinea pigs and rabbits. Pharmacological studies will use mammals exclusively. Histological examinations will be done to confirm lesion sites.

d. Bibliography - Effort has not resulted in published reports to date.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 3 May 77

2. TITLE: KC-135 Zero-Gravity Research Program

3. NUMBER/CODE: a. PROPOSAL: | b. CURRENT: 199-05-01-13

4. PERFORMING ORGANIZATION:
Neurophysiology Laboratory
NASA - Johnson Space Center
Houston, TX 77058

5. CONTRACT/GRANT NO.: Inhouse

6. DATE: a. STARTING: 1 Oct 77 | b. ANNIVERSARY: 1 Oct 78

7. INVESTIGATOR'S NAME: J. L. Homick | TEL. NO.: (713)483-5056

8. NASA ALT. TECH MONITOR'S NAME: N/A | TEL. NO.:

9. INSTITUTION CATEGORY CODE: FC

FISCAL YEAR	STATUS a.	MANPOWER (MY) IN-HOUSE b.	MANPOWER (MY) S/C c.	FUNDING (In K) IMS d.	FUNDING (In K) R/D e.	FUNDING (In K) TOTAL f.
10. PRIOR	-					
11. CURRENT	N		0	0	100	100
12. BUDGET	C		0	0	100	100

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The strategy of this effort is to fund utilization of the NASA KC-135 zero-gravity aircraft for the purpose of conducting specialized vestibular related research on humans and animals as defined by tasks 199-05-01-01, 199-05-01-04 and 199-05-01-05.

b. Progress - Accomplishments by Graybiel on the KC-135 during the prior year include: 1) Measurements of susceptibility to motion sickness in about 25 subjects during the 0-g phase of flight with head fixed or moving while stationary or rotating. 2) Evaluations of the efficacy of several anti-motion sickness drugs including promethazine administered I.M. to treat severe, acute motion sickness; 3) Evaluations of transfer of laboratory acquired vestibular adaptation to the parabolic flight environment; (ref. task 199-05-01-01). Accomplishments by Parker include a brief series of flights during which CSF and perilymph fluid pressure were directly measured in guinea pigs; results were inconclusive.(ref. task 199-05-01-04). Accomplishments by the JSC inhouse laboratory include an extensive series of flights during which H-reflex data were obtained on humans. Results indicated a potentiation and an inhibition of the H-response during the 0-g and hyper-g phases of the parabolas, respectively (ref. task 199-05-01-03).

c. Planned Tasks: A series of studies will be directed by Graybiel to: 1) Further evaluate the efficiacy of selected anti-motion sickness drugs, with particular emphasis on dose level and route of administration; 2) Evaluate transfer of laboratory acquired adaptation to parabolic flight and 3) Evaluate methods which might predict susceptibility to motion sickness caused by exposure to parabolic flight. Parker will attempt to measure endolymph, as well as, perilymph and CSF pressure in guinea pigs in order to better establish support for or against the fluid shift hypothesis of motion sickness. The JSC inhouse laboratory will continue to investigate vestibulo-spinal reflex (H-reflex) stimulus-response parameters in order to establish the H-reflex as a valuable approach to assessing otolith function. Included will be a series of H-reflex studies using normal squirrel monkeys and those with selective vestibular lesions. The squirrel monkey studies will be supported by Igarashi (ref. task 199-05-01-05.).

d. Bibliography - See each of the tasks referenced above.

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
RESEARCH AND TECHNOLOGY RESUME

1. DATE PREPARED: 3 May 77

2. TITLE: Astronaut Motion Sickness Suceptibility Test Program

3. NUMBER/CODE: a. PROPOSAL: | b. CURRENT: 199-05-01-14

4. PERFORMING ORGANIZATION:
Neurophysiology Laboratory
NASA - Johnson Space Center
Houston, Texas 77058

5. CONTRACT/GRANT NO.: Inhouse

6. DATE: a. STARTING: 1 Oct 77 | b. ANNIVERSARY: 1 Oct 78

7. INVESTIGATOR'S NAME: J. L. Homick | TEL. NO.: (713)483-5056

8. NASA ALT. TECH MONITOR'S NAME | TEL. NO.: N/A

9. INSTITUTION CATEGORY CODE: FC

FISCAL YEAR	STATUS a.	MANPOWER (MY) b. IN-HOUSE	MANPOWER (MY) c. S/C	FUNDING (In K) d. IMS	FUNDING (In K) e. R/D	FUNDING (In K) f. TOTAL
10. PRIOR	--					
11. CURRENT	N		0	0	40	40
12. BUDGET	C		0	0	40	40

13. DESCRIPTION *(a. Brief statement on strategy of investigation; b. Progress and accomplishments of prior year; c. What will be accomplished this year, as well as how and why; and d. Summary bibliography)*

a. Strategy - The strategy of this task is to devise and administer a select battery of vestibular tests to a population of astronauts who have flown in space, as well as non-astronauts, with the purpose being to identify specific ground based tests which significantly correlate with the actual incidence of space motion sickness.

b. Progress - This is a proposed new start. However, research work currently being done by investigators at JSC, ARC, Pensacola and elsewhere to develop predictive tests of susceptibility to zero-g sickness is directly applicable to this effort.

c. Planned Tasks - Initially, this effort will focus on the definition, development and evaluation of a battery of quantitative tests to assess various aspects of vestibular system function. Emphasis will be placed on provocative test methods including motion sickness experimentally induced by coriolis and optokinetic stimulation, off-vertical and horizontal rotation, linear and vertical oscillation, cineglobe motion exposure and other methods which introduce visual-vestibular conflict. If feasible, other incidental data (biochemical, metabolic and cardiovascular) will be compared with suceptibility to motion sickness induced by the above methods. Sufficient data will be collected on a non-astronaut population to refine data collection and analysis methods. From these initial studies an attempt will be made to isolate a small group of tests which would be administered to astronauts with previous space flight experience. Appropriate analysis will be done to compare ground based test results with each individual's history of space motion sickness in an effort to identify reliable predictive tests or selection criteria for future flight personnel. An attempt will be made to develop and consolidate required facilities for the above test program at JSC, however, resources limitations may dictate that unique test facilities at other NASA supported laboratories be occasionally utilized, especially during the definition phase of this program.

d. Bibliography - None

	TYPED NAME AND SIGNATURE	DATE
TECHNICAL MONITOR	J. L. Homick	
APPROVING OFFICIAL		

NASA FORM T43 DEC 74 REPLACES NASA FORM T8 WHICH IS OBSOLETE.

Somatosensory Motion After-Effect Following Earth-Horizontal Rotation About the Z-Axis: A New Illusion

JAMES R. LACKNER and ASHTON GRAYBIEL

Brandeis University, Waltham, Massachusetts 02154 and Naval Aerospace Medical Research Laboratory, Pensacola, Florida 32512

LACKNER, J. R., and A. GRAYBIEL. *Somatosensory motion after-effect following earth-horizontal rotation about the Z-axis: A new illusion.* Aviat. Space Environ. Med. 48(6):501-502, 1977.

During rotation about the Z-axis while recumbent one is exposed to a changing pattern of pressure cues over the body surface. If the body is only loosely padded in the experimental apparatus, then apparent motion of part of the body surface may be experienced sometime after rotation has been terminated. This somatosensory motion aftereffect of opposite sign is temporarily abolished if one looks at the affected body area, but is again re-experienced when the gaze is shifted elsewhere. The similarity of this motion aftereffect to those contingent on vestibular and visual stimulation is discussed.

FOR MANY YEARS, Von Békésy (1) explored the common functional characteristics of the visual, auditory, and somatosensory systems. From his work it became apparent that sensory inhibition was a basic property of nervous system organization and underlay, in part, the dependence of the perception of movement on intensity and temporal parameters of stimulation of neurally contiguous receptor populations. Many models have been developed using the principle of reciprocal inhibition to explain the negative after-effects and motion after-effects that appear following prolonged visual, auditory, and vestibular stimulations (5). The great generality of this principle is demonstrated by the fact that reciprocal inhibition has also been used to explain aspects of motor coordination ranging from the reflex organization of the spinal cord (8) to central pattern generating mechanisms underlying autochthonous movements (10).

The observations to be depicted demonstrate the existence of motion after-effects of opposite sign following somatosensory stimulation. Such after-effects have not previously been described and their existence further extends the list of common functional properties of the various sensory systems. Unlike motion after-effects contingent on the termination of visual or vestibular stimulation, which appear immediately, the somatosensory after-effects to be described only emerged 4-8 h after the inducing stimulation had been terminated. In this context, it should be noted that after-effects from prolonged tactile stimulation sometimes last for hours after removal of the stimulus, e.g. the long lasting "ring" after-effect from wearing a hat with a band that is tight on the head.

In the present situation, subjects had been exposed to clockwise rotation around their long body axis while that axis was horizontal or at an angle of 10° with the horizontal. The goal of the experiment had been to evaluate the effects of varying degrees of headward shift of movable body fluids on susceptibility to motion sickness; for this reason the subject's body axis had been placed in varying orientations (7). The experimental apparatus has been described elsewhere (4); one of its integral parts is a fiberglass body mold which is cushioned with removable foam-rubber pads. These are adjusted individually for each subject to prevent him from flopping about as he is rotated in barbecue-spit fashion.

When the foam rubber pads are not positioned properly nor in sufficient thickness, the subject is exposed to strong asymmetric pressure on his torso as he is rotated. For three of the subjects, including one of the authors, during one of the experimental runs the back was properly padded but the chest area had too little padding. The distribution of padding was such as to cause asymmetric tactile stimulation during rotation but not sufficient to cause frank discomfort. All three subjects underwent clockwise rotation at 30 rpm for 1 h while horizontal. Under this circumstance, the pattern of pressure cues on the body changed in a counter-clockwise direction. No subject preceived correctly the rotation of his body but experienced himself as moving in a counter-clockwise orbit about a central axis while always facing in the same direction (7).

Immediately after the experiment, none of the subjects experienced illusory motion of his body or any part of it. However, from 4 to 8 h later each of the three subjects—when not looking at his chest—experienced il-

This study was supported by the National Aeronautics and Space Administration, Contracts T-5904B, T-590413. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

lusory clockwise movement of his chest area in relation to the rest of his body. The experience was one of clockwise movement without displacement and was confined to the chest surface. When the subject looked at his chest, the apparent motion ceased; when he looked away it again would begin. The velocity of apparent movement was approximately half the velocity of the moving pressure stimulus during body rotation. For two of the three subjects the apparent motion continued—when they were not looking at their chests—for about 15 min for one and 30 min for the other. In experimental runs in which these subjects were fully padded in the chest as well as the back regions, none of them later experienced tactile after-effects.

The present observations are of fourfold significance: a) they demonstrate the existence of somatosensory motion after-effects contingent on prolonged asymmetric pressure stimulation of the body surface, b) they indicate that somatosensory motion after-effects involve a dissociation of sensed movement and sensed displacement, a dissociation characteristic also of visual and vestibular motion after-effects (cf. the oculogyral and audiogyral illusions first described by Graybiel and Hupp (3) and Clark and Graybiel (2), respectively), c) they show that sight of the relevant area will override somatosensory motion after-effects, as it is well known from other studies that visual cues can dominate proprioceptive cues about limb position and body orientation (6), and d) they verify that a remapping is possible for the apparent positions of different parts of the body in relation to others. Years ago, Stratton (9), in describing the apparent orientation of his body after he had exposed himself to prolonged optical inversion and reversal of his visual field, reported that that part of his body which he had been able to see through the lens system felt inverted and reversed in relation to the rest of his body. The present observations are consistent with the dissociation described by Stratton. In fact, a comparable dissociation of apparent orientation was experienced by some of our subjects during exposure to rotation about their horizontal, long-body axis: they felt their head and trunk to be vertical and rotating counterclockwise and their lower half to be horizontal and rotating counterclockwise.

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Clinical Medicine

Evaluation of a New Antinauseant Drug for the Prevention of Motion Sickness

ASHTON GRAYBIEL and JAMES KNEPTON

Naval Aerospace Medical Research Laboratory, Naval Air Station, Pensacola, Florida 32508

GRAYBIEL, A., and J. KNEPTON. *Evaluation of a new antinauseant drug for prevention of motion sickness.* Aviat. Space Environ. Med. 48(9):867-871, 1977.

The antimotion sickness efficacy of a new drug, AHR 5645B, administered orally in 20, 50, and 100 mg doses, was compared with that of l-scopolamine 0.3 mg and of a placebo. Also evaluated were four "old" drugs, new only in the sense that the dosage or drug combinations had not been tested previously. Promethazine 12.5 mg and ephedrine 12.5 mg were given alone and combined; the fourth drug was a fixed-dose of meclizine 50 mg plus ephedrine 25 mg. Eight college students aged 18 to 26 years participated as paid volunteers. Each subject was tested individually in a slow rotation room where the stressful stimuli were generated by requiring the subject to execute standardized head movements at 1-r.p.m. increments until either the motion-sickness endpoint or the ceiling on the test (30 r.p.m.) was reached. Efficacy of the eight drugs was assessed in terms of placebo effects and categorized as beneficial, inconsequential, or detrimental. The effects of scopolamine were beneficial in 50% of the subjects, a little below expectation (62.5%). All of the responses to the AHR 5645B drugs were inconsequential except for one beneficial effect (100 mg) and two detrimental responses, one each with doses of 20 mg and 50 mg. Among the other drugs tested, only one of the responses was detrimental. Beneficial responses were 62.5% for promethazine 12.5 plus ephedrine 12.5 mg, 50% for promethazine 12.5 mg, 37.5% for ephedrine 12.5 mg, and 25% for meclizine 50 mg plus ephedrine 25 mg.

THE NEW DRUG, AHR 5645B,* was offered to us for assessment of its efficacy in reducing susceptibility to motion sickness. This preparation is a pyrolidine derivative unrelated to known drugs, and reports indicate that its effects are comparable to actions following the administration of the phenothiazine and nonphenothiazine drugs in both patients and animal models.

For two reasons, of which the second is by far the more important, we readily accepted the proffered opportunity: first, the likelihood that it would prove to be efficacious, at least for some subjects, and, second, its demonstrated suitability for long-term use. Scopolamine 0.3 mg was used as a control. The opportunity was taken to extend our bioassay of the combination promethazine plus ephedrine and a new combination, meclizine 50 mg plus ephedrine 25 mg.

In all of our studies dealing with the efficacy of antimotion sickness drugs, stressful accelerations have been generated by requiring the subject to execute standardized head and body movements out of the plane of rotation in a slow rotation room (SRR). In early studies (1) we used a predetermined stimulus of constant intensity (constant angular velocity), and susceptibility to motion sickness was measured as the number of head movements executed either before the motion-sickness endpoint was reached or a total of 300 executed. This ceiling on the test (300 head movements) was often reached before the motion-sickness endpoint, a shortcoming. This handicap was largely overcome in subsequent studies by requiring the subject to execute head movements at 1 r.p.m., and step increases of 1 r.p.m., until the motion-sickness endpoint or the r.p.m.-ceiling (27 or 30 r.p.m.) was reached (2). A second handicap was the use of a latin square design of order 10 that yielded results valid for large groups but not individuals in a group, a present-day requirement. This problem has been met by using a modified latin square arrangement

This study was supported by the National Aeronautics and Space Administration, Contract T-5904B and the Naval Medical Research and Development Command, Project MF51.524.005-7015. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

*The drugs were provided by the A. H. Robins Co., Richmond, Va.

whereby the number of placebos is increased and by using one or more reference drugs that served as controls (3).

The problems posed by adaptation are met fairly well by increasing the interval between tests, but this tends to aggravate a second problem, namely, variation in motion-sickness susceptibility within individuals. In most subjects, substantial variations are uncommon or explicable, but in some subjects we have not uncovered the cause or causes for these variations.

MATERIALS AND METHODS

Subjects: The eight male subjects, 18 to 26 years of age, used in this experiment were selected from a subject pool solely on the basis of availability. All of the subjects in the pool were physically and mentally qualified for parabolic flights, and assessments revealed normal canalicular, otolith, and visual functions. None was selected on the basis of susceptibility to motion sickness, however much this factor influenced their willingness to serve as a subject.

Procedure—The stress profile: The procedure, described elsewhere in detail (2), required the subject to execute 40 head movements (4 s between commands) out of the plane of the room's rotation at 1 r.p.m. and 1-r.p.m. increments in angular velocity until either the ceiling on the test, 30 r.p.m., or the motion-sickness endpoint was reached.

Assessing susceptibility to acute motion sickness: The observer, in collaboration with the subject, estimated the levels of severity of the symptoms after every set of 40 head movements. The levels of severity of motion sickness were given numerical scores according to diagnostic criteria (4) found to be satisfactory when acute experimental motion sickness was evoked. The motion-sickness endpoint was slight nausea or a score of 12 points including stomach awareness, whichever came first.

Drugs and their administration: The following drugs were evaluated:

1. 1-scopolamine hydrobromide (0.3 mg)
2. AHR 5645B (20 mg)
3. AHR 5645B (50 mg)
4. AHR 5645B (100 mg)
5. meclizine (50 mg) + ephedrine sulfate (25 mg)
6. promethazine hydrochloride (12.5 mg)
7. ephedrine sulfate (12.5 mg)
8. promethazine hydrochloride (12.5 mg) + ephedrine sulfate (12.5 mg)
9. placebo (lactose)

Nineteen preparations in identical opaque capsules (eight drugs and 11 placebos) were individually sealed in small envelopes and numbered. The numbers on the envelopes reflected an arrangement based on a latin square design of order 8. The administration of placebos was generous but arbitrary. Two placebos were given before the first and after the last drug was taken. In addition, seven placebos separated contiguous drugs in the latin square arrangement.

The 19 preparations for each subject were placed in a large envelope and kept under lock and key. The two capsules to be administered on test day were given to the inside observer who ensured that the subject swallowed the capsules, along with a little bland food.

Plan: The subjects were carefully instructed regarding all aspects of the experiment. As part of the overall assessment prior to becoming a member of the experimental group, a test in the SRR was carried out that met the need for "familiarization." The tests in the series were carried out at approximately weekly intervals. The shortest interval was 3 d and the two longest ones were 19 d (Subject 4 had a respiratory infection) and 29 d (Subject 6 sprained his ankle); the average was 6.8 d. On test days, subjects reported 2.5 h prior to rotation. The routine, involving an inside observer and an experimenter, comprised the following duties:

Observer: 1) Administered a pre-experimental questionnaire regarding the subjects' state of health and general fitness; 2) Obtained physiological measurements of pulse rate, blood pressure, oral temperature, and postural equilibrium, using a heel-to-toe Romberg test; 3) Conducted psychophysical evaluations using Wechsler's digital symbol substitution test (5), Graham and Kendall's Memory-for-Designs test (6), and the Clyde Mood Scale (7); 4) Two hours before rotation, ensured that the subject swallowed the two capsules; 5) Shortly before rotatoin, repeated the physiological measurements; 6) Following rotation, repeated the physiological measurements.

Experimenter: 1) Thirty minutes before rotation—90 min after capsules taken—queried subject with regard to

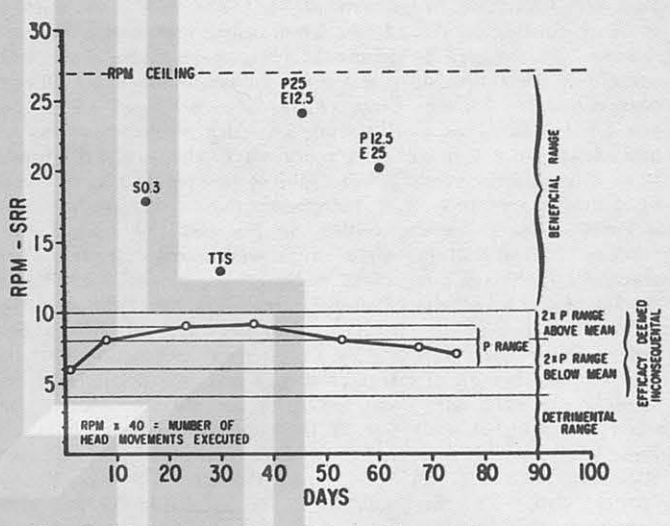

Fig. 1. Method for determining efficacy of responses to four antimotion sickness drugs—scopolamine, promethazine plus ephedrine and a transdermal therapeutic system (TTS) delivering scopolamine directly into the blood—based on actual experiment conducted in a slow rotation room. The ordinate measures the motion sickness endpoints in r.p.m. unless the r.p.m.-ceiling on the test was reached first. The abscissa indicates the periods measured in days between tests. By connecting the open circles (when placebo was administered) the placebo range (P) is defined, and the line between the extremes represents the mean placebo level or baseline. Twice the range above or below the mean placebo range defines, respectively, entry into the beneficial and detrimental ranges. Between these ranges efficacy is deemed "inconsequential." The beneficial range may be subdivided into multiples of 2 × P above the mean.

side effects of the medication; 2) Following rotation queried subject regarding symptoms experienced.

Scoring: The method of scoring the efficacy of the drugs administered is described with the aid of findings in an actual experiment (Fig. 1). In the plot, the ordinate indicates the motion-sickness endpoint in terms of r.p.m. of the slow rotation room; the r.p.m. multiplied by 40 yields the number of head movements executed. If the range of placebo scores is no greater than that shown in the figure, a mean value serves as the departure line in scoring the responses in three ranges. Twice the placebo range above the mean defines the entry into the beneficial range, and the same procedure below the mean is used in defining the detrimental range. Every score between these ranges defined the inconsequential response. In two circumstances the above procedure is unsatisfactory, namely, when the placebo range is very small or great; e.g., greater than 2.5-3.0 r.p.m. In the first instance, 1.5 to 2 r.p.m. above or below the mean may serve, respectively, for entry into the beneficial and detrimental zones. The most common cause of a great range is the acquisition of adaptation effects. In this event, sloping baselines are used, and it may be necessary to divide the baseline into as many as three (rarely more) parts.

RESULTS

Table I summarizes the findings. It is noteworthy that the responses in the beneficial category to scopolamine 0.3 mg (50%) were a little below expectation (62.5%) based on previous studies using much the same procedure (3). This implies that the subjects' responses to the drugs, as a group, might be below the average. This implication finds support in the greater-than-average individual variation in beneficial responses; four subjects accounted for 15 of the 19 beneficial responses, and nearly half of these responses were highly beneficial.

It is immediately apparent that, under the experimental conditions, AHR 5645B, regardless of dose was inefficacious. The one beneficial response was just at the border of the inconsequential range. A table was prepared (not shown), indicating whether the responses to the preparations were within, above, or below the placebo range. When doses of 20 mg were given, seven of the eight responses were within the placebo range; one was far below (detrimental). When 50 mg does were given, five responses were within the placebo range and three were below. With the administration of 100 mg doses, five responses were within the placebo range, two were below, and one just entered the beneficial range. In other words, 17 of the 24 responses were not distinguishable from placebo and thus the drugs served as drug-placebos.

The combination, meclizine plus ephedrine was highly beneficial in two instances and detrimental in one. It is important to note that, in the case of Subject 5, it was the only drug registering a beneficial response. In Subject 3, who manifested four beneficial responses, the efficacy of meclizine plus ephedrine was not excelled by any other drug and equalled only by scopolamine.

The fixed-dose combination, promethazine and ephedrine 12.5 mg each, had not been evaluated previously, and the beneficial responses (62.5%) were above expectations. This is based both on a comparison with responses to scopolamine in this experiment and with comparisons in previous experiments. When these drugs were given singly in the same dose, the greater efficacy of promethazine was demonstrated.

Highly beneficial effects were scored in eight assessments involving three subjects and four drugs. Subjects 3, 7, and 5 accounted, respectively, for four, three, and one high score. Each of the following drugs accounted for two highly efficacious responses: scopolamine, promethazine, promethazine plus ephedrine, and meclizine plus ephedrine.

Evidence of side effects due to administration of the drugs was sought by the use of tests and interviews. Graham and Kendall's memory-for-designs and Wechsler's digital symbol substitution test revealed no definite evidence that the scores were influenced after taking a drug. Oral temperature, pulse rate, blood pressure, and ataxia scores indicated no definite effect as the result of taking a drug.

Table II summarizes the symptoms ("side effects") reported by the eight subjects 90 min after taking a drug on eight occasions and a placebo on 11 occasions. At the

TABLE I. INDIVIDUAL RESPONSES* TO EIGHT ANTIMOTION SICKNESS DRUGS ASSESSED IN A SLOW ROTATION ROOM.

S	S 0.3 mg	E 12.5 mg	P 12.5 mg	P 12.5 mg + E 12.5 mg	M 50 mg + E 25 mg	AHR 20 mg	AHR 50 mg	AHR 100 mg	% B Responses: All drugs	% B Responses: All but AHR drugs
1	B	B	I	B	I	I	I	B	50	60
2	I	I	B	I	I	I	I	I	12.5	20
3	>B	I	>B	>B	>B	I	D	I	50	80
4	I	I	I	I	D	D	I	I	0	0
5	I	I	I	I	>B	I	I	I	12.5	20
6	I	B	B	B	I	I	I	I	37.5	60
7	>B	B	>B	>B	I	I	I	I	50	80
8	B	I	I	B	I	I	I	I	25	40
%B	50	37.5	50	62.5	25	0	0	12.5		

*B = Beneficial: >B highly beneficial.
I = Inconsequential
D = Detrimental

TABLE II. SYMPTOMS (SIDE EFFECTS) REPORTED BY EIGHT SUBJECTS 90 MIN AFTER TAKING TWO CAPSULES (CONTAINING DRUG OR PLACEBO) ON 19 OCCASIONS.

BID* Score				Incidence of side effects				Number of side effects				%
				8 Drugs		11 Placebos		8 Drugs		11 Placebos		Identified
S	B	I	D	No.	%	No.	%	No.	%	No.	%	Correctly
1	4	4	0	1	13	1	9	2	25	2	18	52
2	1	7	0	4	50	2	18	6	75	2	18	68
3	4	3	1	0	0	0	0	0	0	0	0	50
4	0	6	2	2	25	1	9	2	25	2	18	58
5	1	7	0	4	50	7	64	7	87.5	11	100	43
6	3	5	0	0	0	2	18	0	0	2	18	44
7	4	4	0	3	37	6	55	6	75	10	91	41
8	2	6	0	1	13	2	18	1	13	2	18	51

*Beneficial, Inconsequential, and Detrimental responses after taking a drug.

Rank order of side effects experienced in more than two instances.

	Drug	Placebo
0. No symptoms	49	67
1. Drowsy	3	11
2. Unsettled stomach	6	4
3. Sedated feeling	3	3
4. Headache	3	3
5. Stomach awareness	4	2
6. Blurred vision	3	2
7. Dry mouth	1	4

left is the beneficial, inconsequential, detrimental (BID) score and below is the rank order of side effects experienced in more than two instances. Also included in Table II is the percentage at which each subject correctly identified the capsule as containing a drug or placebo.

Subjects 2, 5, and 7 accounted for nearly 90% of the side effects when drugs were administered, and over 77% when placebos were taken.

Subject 2 was correct in his identification on 13 of the 19 occasions (68%), but this was not reflected in his single beneficial-response score. Indeed, this beneficial response involved promethazine 12.5 mg, prior to which he reported zero symptoms.

Subject 5 was correct in his identification nearly half of the time but reported no side effects after taking meclizine plus ephedrine when he registered his single beneficial response.

Subject 7 experienced side effects on six occasions when taking placebos and five of the six most commonly experienced symptoms were involved. He registered four beneficial responses, and experienced symptoms when promethazine and ephedrine were administered alone or in combination, but not after taking scopolamine.

Subject 4, who did not register a single beneficial response, had the second highest correct identification score.

In sum, the findings dealing with side effects reveal no proof of performance decrement in the tests administered and the subjective evidence (side effects) is equivocal because symptoms were experienced after taking drug or placebo. The findings are definite, however, in providing an unexpected control in that symptoms experienced before rotation were not helpful in distinguishing drug from placebo.

DISCUSSION

Two methodological problems were encountered; namely, inability to draw a highly satisfactory placebo baseline in the case of Subjects 2, 4, 6, and 7, and the rather low efficacy (50%) of scopolamine 0.3 mg, the reference drug. Fortunately, these problems were easily met, except in the case of Subject 4, by virtue of the high efficacy of promethazine and ephedrine alone or in combination (80%) and the fact that the responses to AHR preparations were nearly always in the placebo range.

Fig. 2 is a plot showing the responses of Subject 4. For over 2 months, the placebo baseline was highly satisfactory, ranging between 9.5 and 11.5 r.p.m. and implying that he was substantially less susceptible to motion sickness than the average normal member of our subject pool. When interviewed after completion of the experiment, he stated that he disliked the food furnished as a snack (after taking the capsules), and the odor in the SRR sometimes made him sick. Unfortunately, these complaints were not made during the experiment. Not shown in Table II are the symptoms he experienced after taking the capsules. He experienced stomach awareness 90 min after taking AHR (20 mg) when a low r.p.m. endpoint was registered and after AHR (100 mg) when the response was well within the placebo range. On a third occasion, after taking the second placebo, his motion sickness endpoint was the highest score prior to experimental Day 80. Subject 4 is a delicately tempered, highly cooperative person who, after review of all the assessments and tests carried out, reveals a strong tendency toward inconsistency.

The control of accelerative stimuli posed no problems.

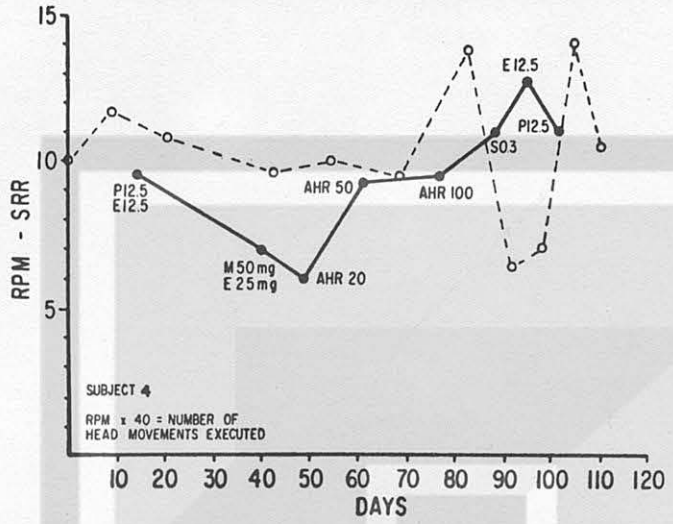

Fig. 2. A plot of Subject 4's responses to administration of the 8 drugs and 11 placebos. For more than 2 months there was little variation in the placebo baseline, and the level (mean 10.3 r.p.m.) indicates that Subject 4 was less susceptible than the average subject (around 8 r.p.m.). Thereafter, there is great variability in the placebo scores exceeding, by far, any other inexplicable variations in placebo scores we have observed.

None of the subjects reached 30 r.p.m., the ceiling on the test.

CONCLUSIONS

1. The responses after giving scopolamine 0.3 mg, the standard for reference, were below expectations (50%), implying that the responses for the group might be less efficacious than anticipated.

2. The new drug, AHR 5645B, used in doses of 20, 50, and 100 mg was not efficacious in preventing experimental motion sickness.

3. The new combination meclizine 50 mg and ephedrine 25 mg, although eliciting a beneficial response in only two subjects, was not surpassed in efficacy in these instances by any other drug given. Moreover, it was the only beneficial response elicited in one subject, hence deserves further study.

4. The heretofore untried combination of promethazine and ephedrine 12.5 mg each was outstanding in this series.

5. The findings in this experiment point to the difficulty in identifying a highly efficacious antimotion sickness drug for everyone.

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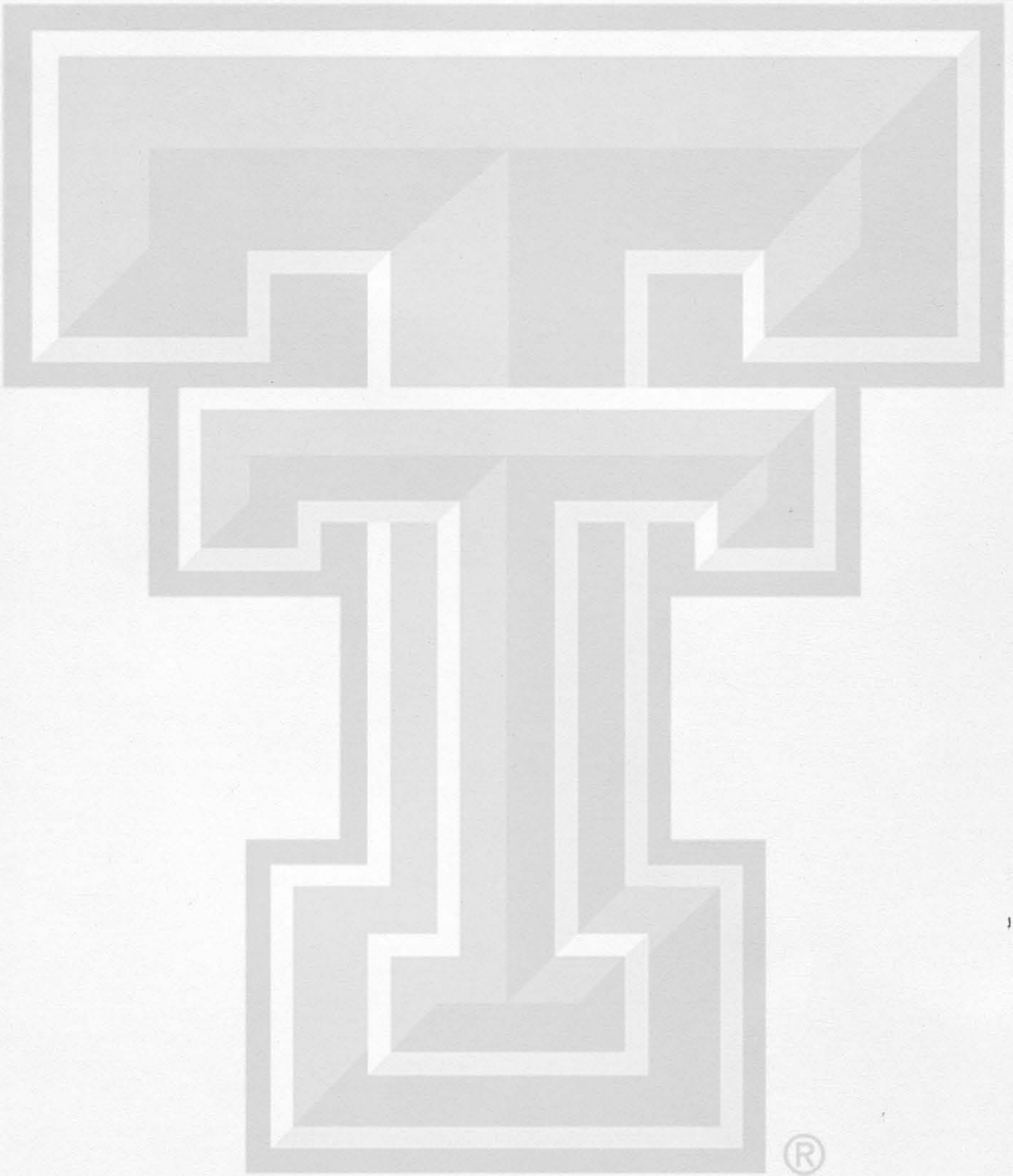

Femoral Development in Chronically Centrifuged Rats

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SMITH S. D. *Femoral development in chronically centrifuged rats.* Aviat. Space Environ. Med. 48(9):828-835, 1977.

Groups of 30-d-old male and female rats were centrifuged at 2.00 G (RE, Rotation Experimental), 1.05 G (RC, Rotation Control) or exposed to the noise and wind of the centrifuge at 1.00 G (EC, Earth Control) for periods of 1, 2, 4, 8, and 16 weeks. Measurements of their femurs indicated that exposure to centrifugation a) decreased femoral length in RE animals, b) increased femoral length in RC animals, c) reduced femoral diameter in RE and RC animals, d) increased L/D ratios in RC animals, e) decreased L/D ratios in RE animals, f) increased femur length/body weight in RE animals, g) decreased cortical thickness (CT) in RE animals, h) increased relative CT in RE animals, and decreased it in RC animals, i) accelerated ossification in RC femoral heads, j) thinned and distorted RE epiphyseal plates, and k) thickened condylar cartilage in RE females. The effects tended to be strongly sexually dimorphic, with females more severely affected by the stress than males.

IN A PREVIOUS PAPER (1) we demonstrated that hypergravity produced by chronic centrifugation markedly alters the length and proportions of developing rat femurs. In addition, some marked effects of rotation alone were noted, including lengthening, thinning, and advanced ossification compared to earth control siblings. These earlier data were obtained from rats kept on the centrifuge for three generations, and are thus open to the criticism that the changed rats may have been selected for by the altered environment, rather than having been directly affected by the gravitational status.

The present study was undertaken with naive developing rats in an attempt to demonstrate that rotation and hypergravity do in fact produce pronounced, and in some respects opposite, effects upon femoral development. It will be shown that there may indeed have been some selection going on in the previous experiments, but that selective pressures alone cannot account for the results.

MATERIALS AND METHODS

There were 75 male and 75 female Sprague-Dawley rats obtained for these experiments. Arrangements were made to have them delivered at 23 d of postnatal age. They were immediately divided into groups of five, placed in standard 48.26 × 26.67 × 20.32 cm plastic cages, and kept for 1 week to assure that they were healthy. When they were 30 d old, the cages were divided into three principal groups; 10 earth control (EC), 10 rotational control (RC), and 10 rotation experimental (RE) cages. RE and RC cages were placed on the centrifuge as in Fig. 1, while EC cages were placed on the floor beneath the arms of the centrifuge. The centrifuge has an effective radius at the cage floor, and at a speed of 28 rpm, of 1.9812 m (6.5 ft). This arrangement resulted in RE animals being exposed to 2.00 G, RC animals to 1.05 G, and EC animals to 1.00 G, plus the noise and windblast that the RE and RC animals experienced. After the cages were emplaced and the centrifuge started, the only stops were for cage maintenance and water (<1% of total elapsed time), and to remove groups for sampling (< 1% of total elapsed time). The light/dark cycle was 10/14 h.

One cage of males and one of females, each containing five animals, were removed at 9:00 a.m. after 1, 2, 4, 8, and 16 weeks of continuous exposure. Individual animals were removed from the cages, weighed, nembutalized, and sacrificed. After tissue sampling by other investigators, the femurs were removed by disarticulation at knee and pelvis, cleaned of adherent muscle, fixed in 10% neutral buffered formalin at 4°C, and placed in a 4°C cold box for 7 d. At the end of this period, they were removed, and gross measurements of length (tip of greater trochanter to trans-condylar plane) and diameter (major diameter at the narrowest point of the shaft) were made with vernier calipers. The femurs were then returned to the fixative and prepared for histological examination. Longitudinal sections of the right femur were cut at 6 μm in the frontal plane. Transverse sections of the left femur were cut at 6 μm from the region measured for diameter. The sections were stained with Hematoxy-

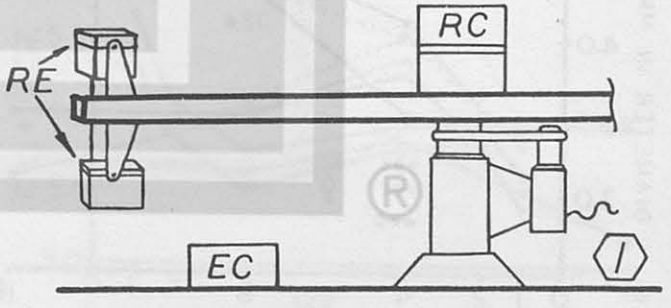


Fig. 1. Illustration of cage placement on the centrifuge. RE = Rotation Experimental (2.00 G), RC = Rotation Control (1.05 G), and EC = Earth Control (1.00 G)

lin and Eosin, mounted in permount, and examined with a Zeiss photomicroscope. Measurements of the thickness of the cortex were made with an ocular micrometer at the abasperal border of the transverse sections.

Ocular micrometer measurements of the thickness of the distal epiphyseal plate and condylar cartilage were also made on the 4, 8, and 16 week longitudinal sections.

The measurement data and the ratios derived from them were subjected to statistical analysis using Student's t-test corrected for finite series. The formula used is shown in Eq. 1.

$$t = \frac{\overline{X}_1 - \overline{X}^2}{\sigma \sqrt{1/N_1 + 1/N_2}} \qquad \text{(Eq. 1)}$$

where: $\overline{X}_1$, $\overline{X}_2$ = mean values, N_1 and N_2 = degrees of freedom of the means, and

$$\sigma = \sqrt{\frac{N_1(S_1)^2 + N_2(S_2)^2}{N_1 + N_2 - 2}} \qquad \text{(Eq. 2)}$$

where: S_1, S_2 = standard deviations of the means.

RESULTS

Length (L): Fig. 2 presents the results of the length measurements in graphic form (key to symbols given in Fig. 2). In both males and females, RE animals differed from RC and EC animals at the $p<0.005$ level of significance beginning at 1 week. The difference became even greater with time up to 4 weeks, then stabilized. RE and RC animals tended to differ less, but at 16 weeks p-values were $p<0.05$ for females and $p<0.005$ for males. Sexual dimorphism is apparent in the response when EC and RC curves are compared. EC males had shorter bones than their RC counterparts, whereas the reverse was true for females. The curves also demonstrate that growth tends to slow in females after 60 d, but continues in males until at least 90 d.

Log_{10}/log_{10} plots of the length vs. time curves emphasize this point. Prior to 4 weeks, the slope for females is 1.67. After 4 weeks, it drops to 0.67. For males, the slope is 2.0 prior to 8 weeks, then drops to 1.3 for RE

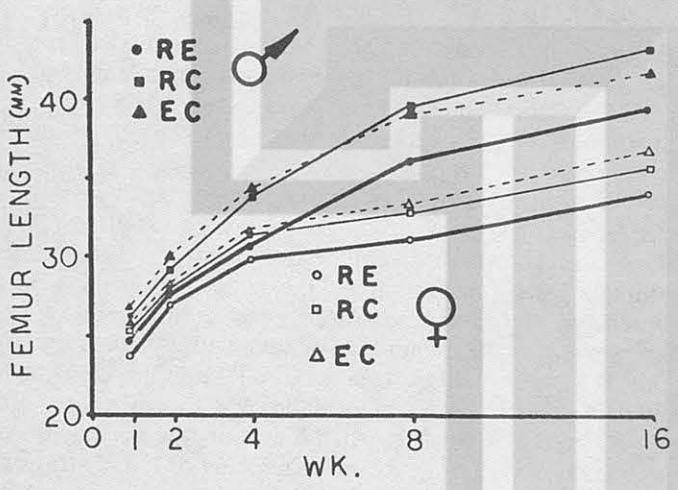
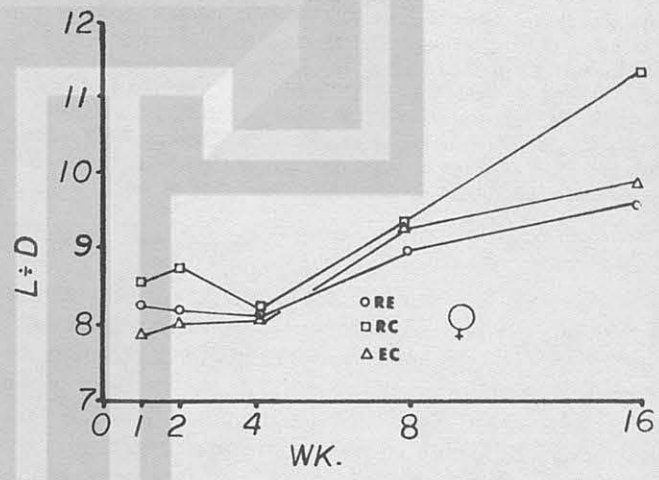


Fig. 2. Femur length vs. time of exposure in weeks.



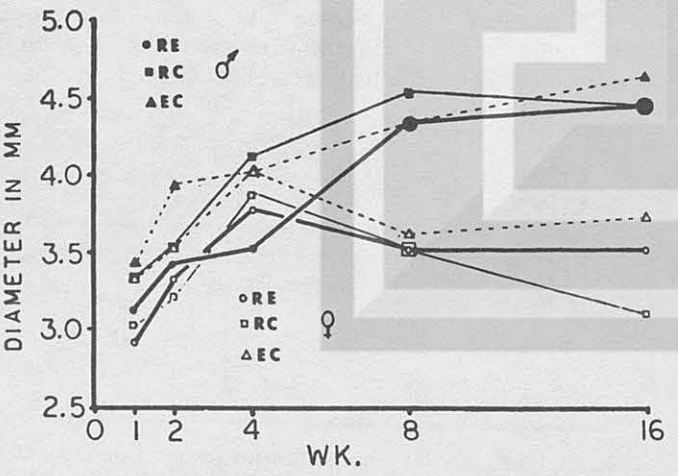


Fig. 3. Femoral diameter (major diameter at narrowest point of shaft) vs. time of exposure in weeks.

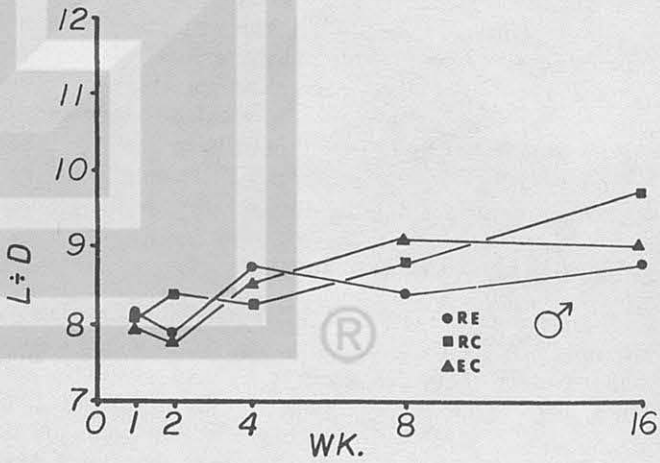


Fig. 4. Femoral length in millimeters divided by diameter in millimeters vs. time of exposure in weeks. a. = females, b. = males

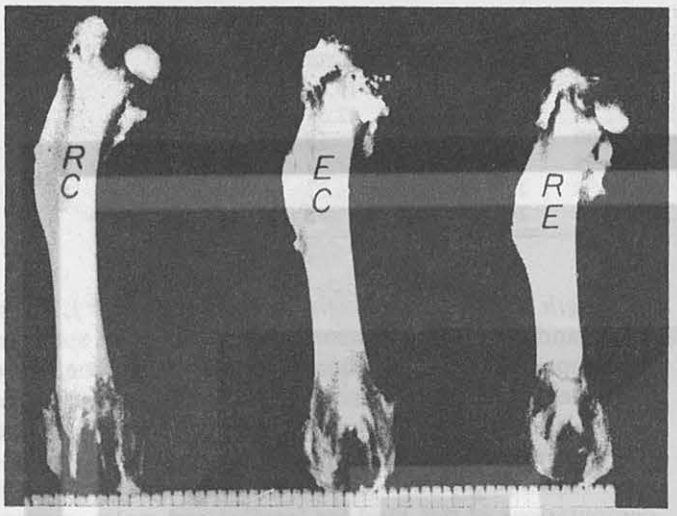


Fig. 5. Photographs of 16-week female femurs, illustrating the effects of centrifugation. RC = Rotation Control, EC = Earth Control, RE = Rotation Experimental. Scale markings: 1 Div. = 1 mm.

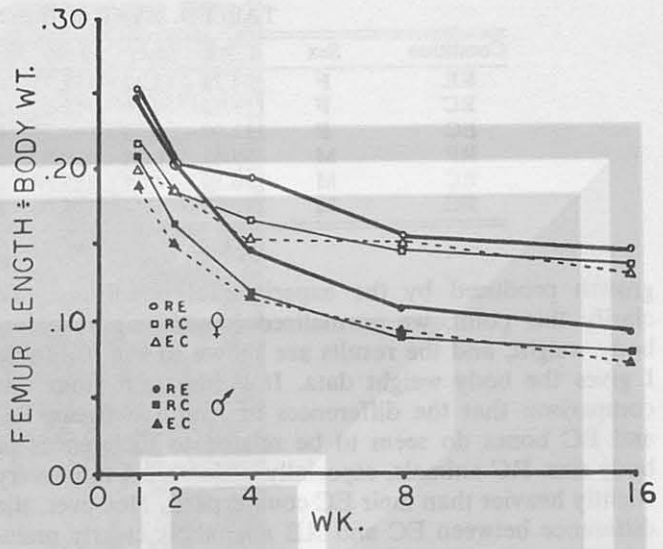


Fig. 6. Femur length in millimeters divided by body weight (in grams) vs. time of exposure in weeks.

and RC animals, and to 0.67 for earth controls. This is possibly of importance to the response, since the EC and RC curves cross between 4 and 8 weeks in males.

In any case, it is clear that not only increased G forces, but also rotation itself can markedly influence bone growth.

Diameter (D): Sexual dimorphism is even more pronounced when one examines the curves in Fig. 3, illustrating changes in bone diameter with time. Males showed a continuous increase in diameter, except for a brief leveling off in the growth rate for RE and EC animals between 2 and 4 weeks. Females, on the other hand, responded differently. Initially, their bones increased in diameter at about the same rate as males. However, after 4 weeks there was an absolute drop in diameter, coinciding with the time at which growth in length seemed to slow (Fig. 2).

In both males and females, diameter of RC and RE bones was less than that of EC counterparts ($p<0.005$) at 16 weeks. The differences between RE and RC values were significant for females ($p<0.005$), but not for males ($p>0.10$) at 16 weeks. At 4 and 8 weeks, however, RE and RC values were very different in males ($p<0.005$ and 0.05), but not in females ($p>0.05$ and $p>0.10$).

Aspect Ratio (L/D): The curves illustrating the L/D ratio (Fig. 4) confirm our earlier results. At 16 weeks, RE bones are significantly shorter ($p<0.05$) for diameter than are EC counterparts, and RC bones are very significantly longer ($p<0.005$). Fig. 5 is a photograph of three femurs from 16-week males. The differences are readily apparent to the eye. The RC femur is decidedly more gracile than the EC one, while the RE bone is just as evidently more robust. The effect is the same in both males and females, though more pronounced in females.

Length to Body Weight Ratio (L/BW): One may suggest that the differences observed in femur length (or diameter) may simply reflect general alterations in

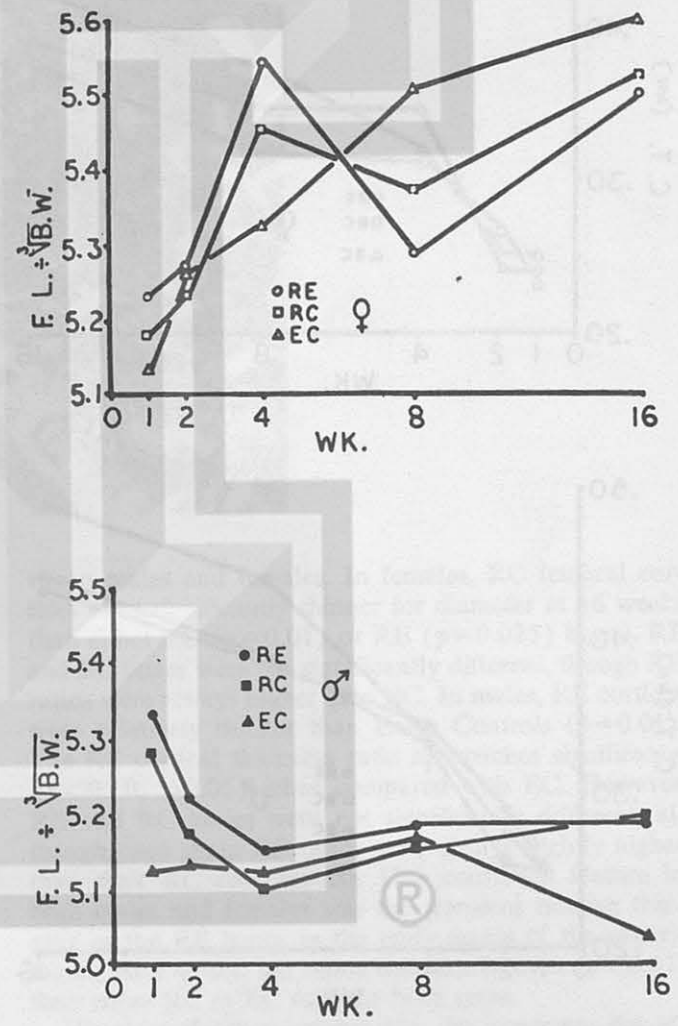


Fig. 7. Femur length in millimeters divided by $\sqrt[3]{}$body weight in grams vs. time of exposure in weeks. a. = females, b. = males

TABLE I. AVERAGE BODY WEIGHTS AT SACRIFICE.

Condition	Sex	1 wk	±	2 wk	±	4 wk	±	8 wk	±	16 wk	±
RE	F	94.25	15.37	132.75	8.23	152.75	14.41	199.00	19.00	230.40	4.39
RC	F	117.75	10.25	152.00	14.19	191.25	11.67	225.50	42.51	262.13	9.91
EC	F	132.00	6.40	152.75	13.64	208.00	10.17	222.00	5.35	271.63	22.85
RE	M	99.63	10.04	130.75	5.67	209.75	10.87	331.00	14.40	427.75	35.82
RC	M	126.50	14.32	178.50	14.40	286.50	27.02	442.25	16.83	557.50	24.58
EC	M	140.63	6.77	198.00	14.23	293.00	24.09	428.00	17.93	555.67	73.52

growth produced by the experimental conditions. To clarify this point, we normalized femur length against body weight, and the results are shown in Fig. 6. Table I gives the body weight data. It is apparent from this comparison that the differences in length between RC and EC bones do seem to be related to differences in body size. RC animals, especially males, tend to be very slightly heavier than their EC counterparts. However, the difference between EC and RE animals is clearly maintained ($p>0.005$) when the L/BW ratio is calculated. RE bones are longer for a given body weight than those of RC or EC animals. No sexual differences are evident in these data.

Length to $\sqrt[3]{\text{Body Weight}}$ Ratio ($L/\sqrt[3]{BW}$): Amtmann and Oyama (2), reasoning that it may be spurious to compare a linear function to a volumetric one, have suggested that the cube root of body weight may be a more valid figure to compare with bone length, since it represents a "linearization" of a volumetric determination. Accordingly Fig. 7a and 7b graphically represent computations of this kind for females and males, respectively. Interestingly, RE and RC animals now resemble each other closely in both male and female groups, while EC animals are significantly different ($p<0.005$) after 16 weeks. An examination of the curves reveals that, once again, there is sexual dimorphism in the responses.

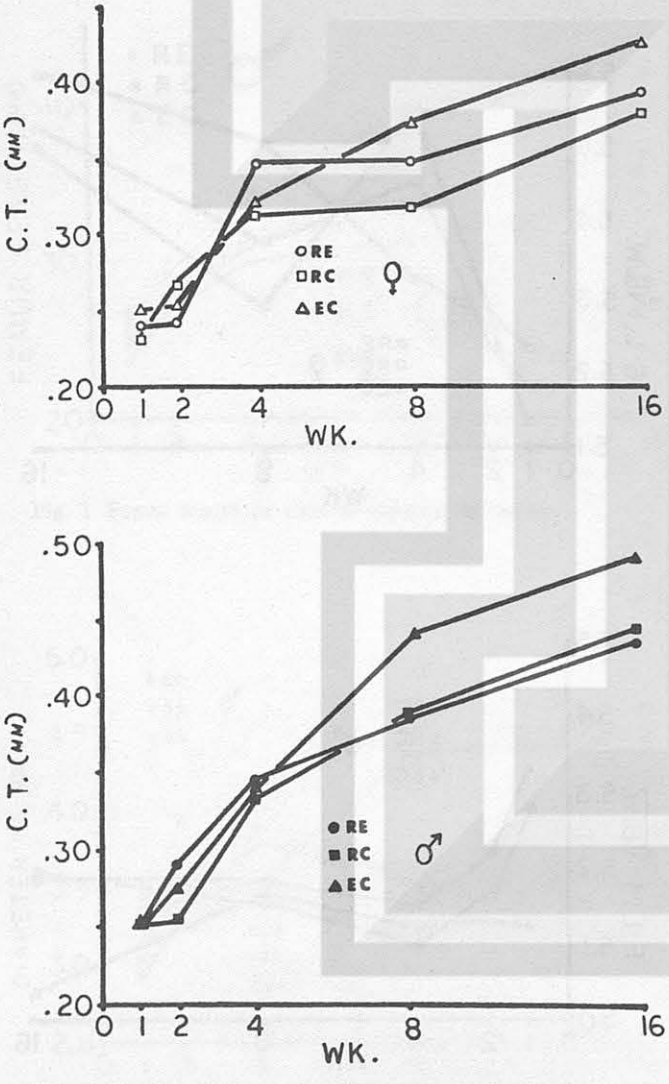


Fig. 8. Cortical thickness in millimeters at the abasperal border of the narrowest point of the femoral shaft vs. time of exposure in weeks. a. = females, b. = males

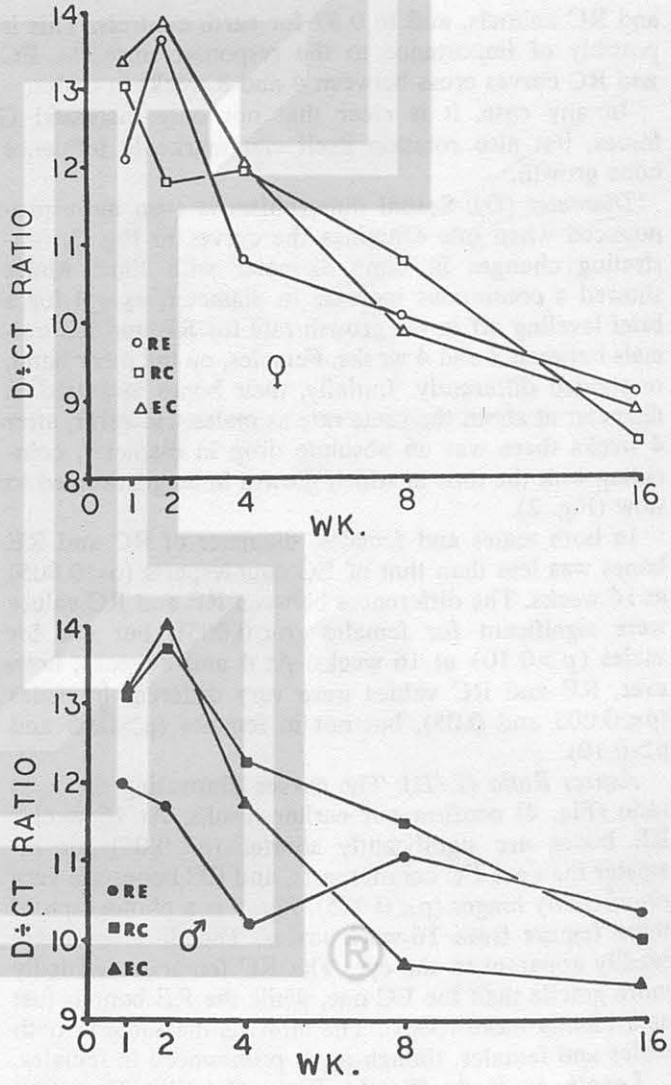


Fig. 9. Diameter in millimeters divided by cortical thickness in millimeters vs. time of exposure in weeks. a. = females, b. = males

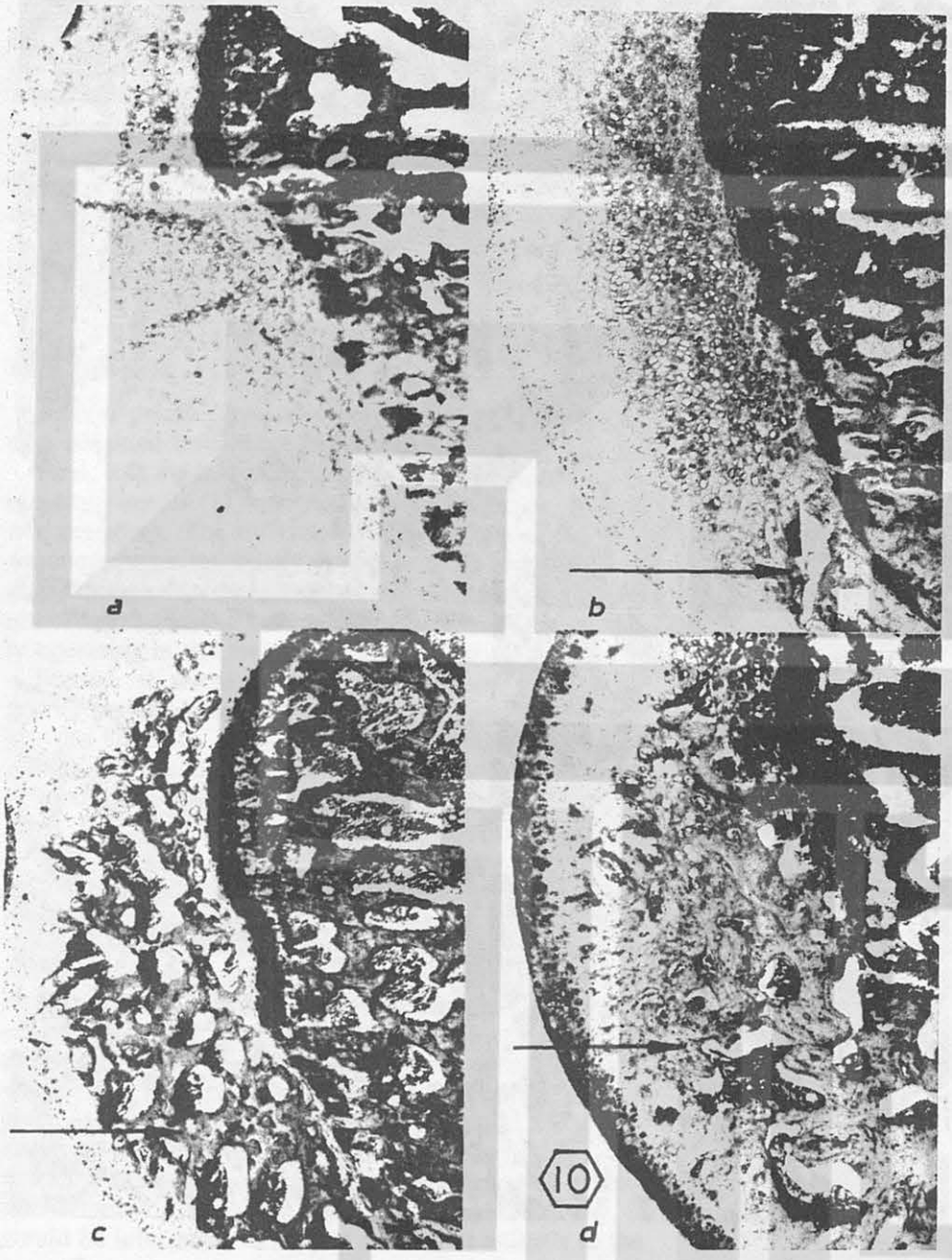


Fig. 10. Photomicrographs of 16-week femoral heads. 77X. a. = EC male, b. = RE male, c. = RC male, d. = RC female. The arrows indicate secondary ossification centers.

Female EC bones are longer in relation to $^3\sqrt{BW}$ than are RC and RE femurs, while male EC bones are shorter. Once again, these relationships seem to be established after rapid growth slows at about 60 d in females and 90 d in males.

Cortical Thickness (C.T.): Fig. 8a and 8b demonstrate the results of these measurements. Prior to 4 weeks, there were no differences between groups in either males or females. After 4 weeks, however, Earth Control animals continued to add to the cortex, while RE and RC animals seemed to slow the process. Thus, at 16 weeks EC animals had thicker cortices than either their RE or RC counterparts ($p<0.005$). The differences in thickness between RE and RC cortices were not significant at 16 weeks in either sex.

Diameter/Cortical Thickness (D÷C.T.) Ratio: This final ratio demonstrates in Fig. 9a and 9b that once again, there were considerable differences in response between males and females. In females, RC femoral cortices were significantly thinner for diameter at 16 weeks than either EC ($p=0.01$) or RE ($p=0.025$) bones. RE and EC bones were not significantly different, though RE ratios were always higher than EC. In males, RE cortices were relatively thicker than Earth Controls ($p=0.01$). The RC cortical thickness ratio approaches significance ($p<0.10$, >0.05) when compared with EC. However, RE and RC bones were not significantly different, although once again RE ratios were always slightly higher than their RC counterparts. One consistent feature in both males and females was the transient relative thinning of the RE bones in the early stages of the experiments. At 4 weeks, RE ratios were much lower ($p<0.01$) than either RC or EC ratios in both sexes.

Histological Observations: Fig. 10 illustrates the effects of these experiments on ossification of the femoral head after 16 weeks. In general, though not in every case,

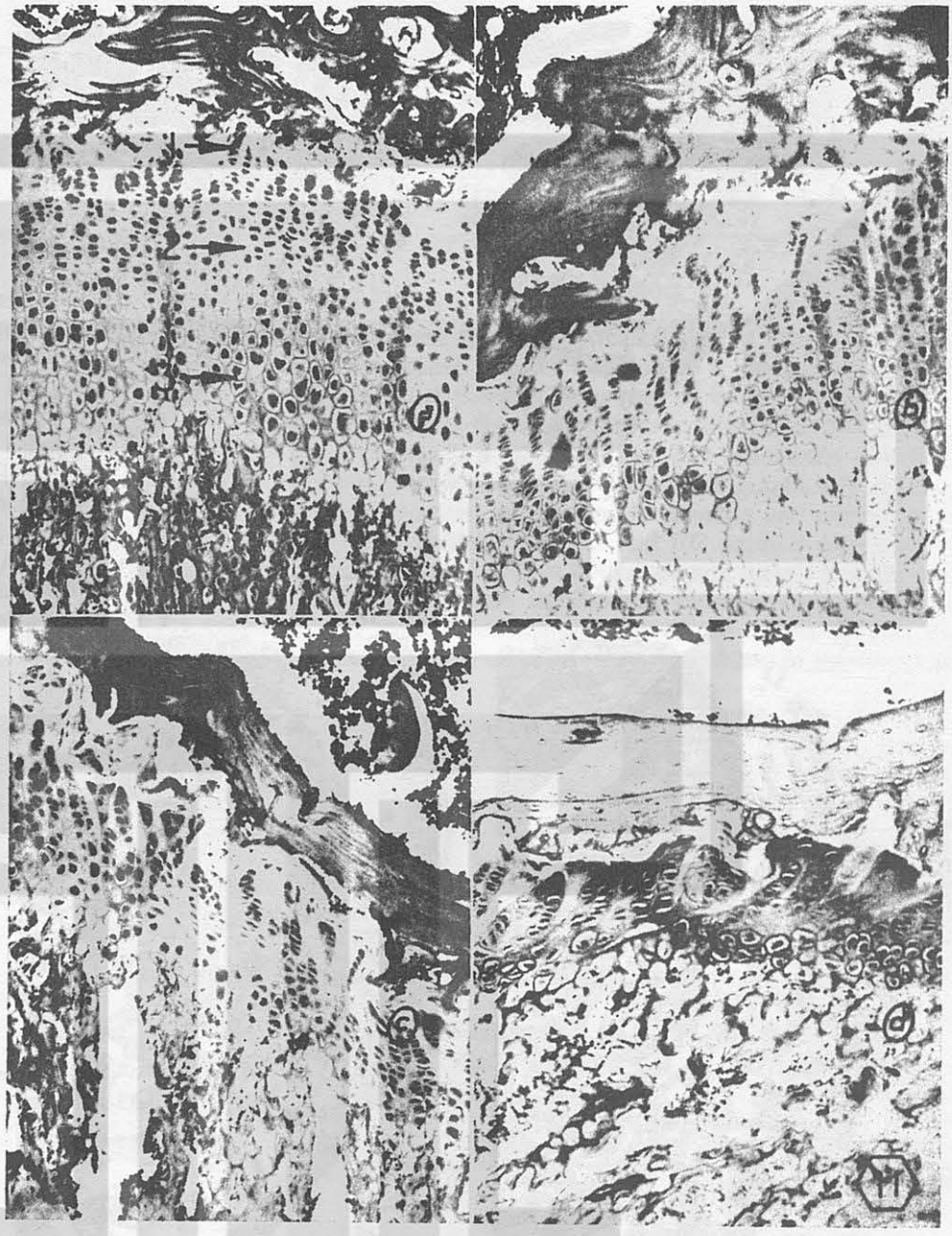


Fig. 11. Photomicrographs of 16-week epiphyseal plates. 223X, a. = EC female, b. = RC female, c. = RE female, d. = RE male. Arrows: 1 = zone of proliferation, 2 = zone of hypertrophy, 3 = zone of cellular dissolution.

RE femoral heads tended to be slightly more advanced than EC heads in both males and females (Fig. 10a and b). Fig. 10c illustrates a typical RC male femoral head and demonstrates, by the considerably larger secondary ossification center, that RC animals uniformly showed ossification which was much more advanced than in RE or EC animals. Fig. 10d is an extreme example, taken from an RC female at 16 weeks. The epiphyseal plate has been partially obliterated, a state never approached in RE or EC animals. In general, the effect was much more pronounced in females than males, though it occurred in both sexes.

If one turns to an examination of the distal epiphyseal plate (Fig. 11), a different pattern appears. EC animals of both sexes at 16 weeks showed essentially normal plates (11a). So did RC animals (11b), though the plate was slightly thinner ($p \sim 0.10$) than the Earth Control, and had shorter cell columns. Striking alterations were apparent in the RE plates (11c and d), which were thinner than either RC or EC plates in both males ($p < 0.005$) and females $p < 0.05$), though the difference was much more pronounced in males. In some animals (11c), the zones of hypertrophy and cellular dissolution were shortened, while the zone of proliferation seemed relatively normal. In others (11d) the disruption was much more marked, with the zone of proliferation nearly obliterated, accompanied by distorted and shortened cell columns. The stronger disruptions occurred often in males and very seldom in females.

When the cartilage covering the femoral condyles was examined, a rather surprising effect appeared. Fig. 12 illustrates this. At 16 weeks, RE condylar cartilages in females (12c) were much thicker ($p < 0.005$) than those of either Rotation (12a) or Earth (12b) Controls. In addition, the condensation normally apparent at the surface facing the joint cavity was less pronounced than in

the RC or EC animals. This result was a very consistent one, being evident from 4 weeks on. RC cartilages were always thinner than EC ones ($p<0.05$).

In males, a contrasting pattern was evident. RE cartilages were thinner than EC ($p<0.025$), but thicker than RC ($p<0.05$). RC cartilages were much thinner than EC counterparts ($p<0.005$). Thus, we see once more a pattern of common effects (RC always thinnest) and sexually dimorphic ones (RE cartilages thickened in females, thinned in males).

DISCUSSION

Several points seem obviously to be indicated by the data obtained from these experiments.

First, it is evident that the data gathered in our previous experiments (1) were not entirely the result of selective pressures. The differences noted in the present experiments were essentially similar to those in the previous ones, though the magnitude of the differences was less, indicating that some selective pressures were undoubtedly operating in the multi-generation experiments.

Second, it seems obvious that rotation and hypergravity may, to some degree, produce opposite effects on growing animals. Rotation tends to produce enhanced growth and gracility of form, whereas hypergravity tends to retard growth in length, while producing more robust form. In addition, both rotation and hypergravity seem to affect "aging" in opposite directions, as reflected by ossification—rotation by advancing the formation of secondary ossification centers, hypergravity by depressing the function of the epiphyseal plates. These opposing effects may, to some degree, explain the rather bewildering reports by various laboratories, some showing growth enhancement and some retardation in their centrifugation experiments (see Smith (3) for a recent review). It may well be true that the result one eventually obtains from a given experiment depends upon the particular mix of rotation vs. hypergravity used by the investigator. Such disparity of results argues rather strongly for some review of the literature with this end in mind. Alternatively, it would be interesting to subject a series of animals to the same G stress on centrifuges of varying radii, thus altering the rotational component. One might expect a spectrum of results allowing the establishment of some set of standards which seems to be lacking at present.

Third, there are rather considerable differences between the responses of males and females to the same stress. A number of possibilities come to mind to explain the differences seen here. Since males and females obviously grow at different rates, and since the females slow their growth considerably sooner than males, one might expect those differences dependent upon general alteration of growth to be more strongly manifested in males than females, since males would have been rapidly growing longer. Such does not seem to be true. Reductions in bone length and body weight seem to be proportionally similar for both males and females.

In contrast, those differences dependent upon the remodeling seen as maturity approaches might be expected to be more strongly influenced in the earlier-developing females. Alteration of bone diameter L/D ratio, cortical

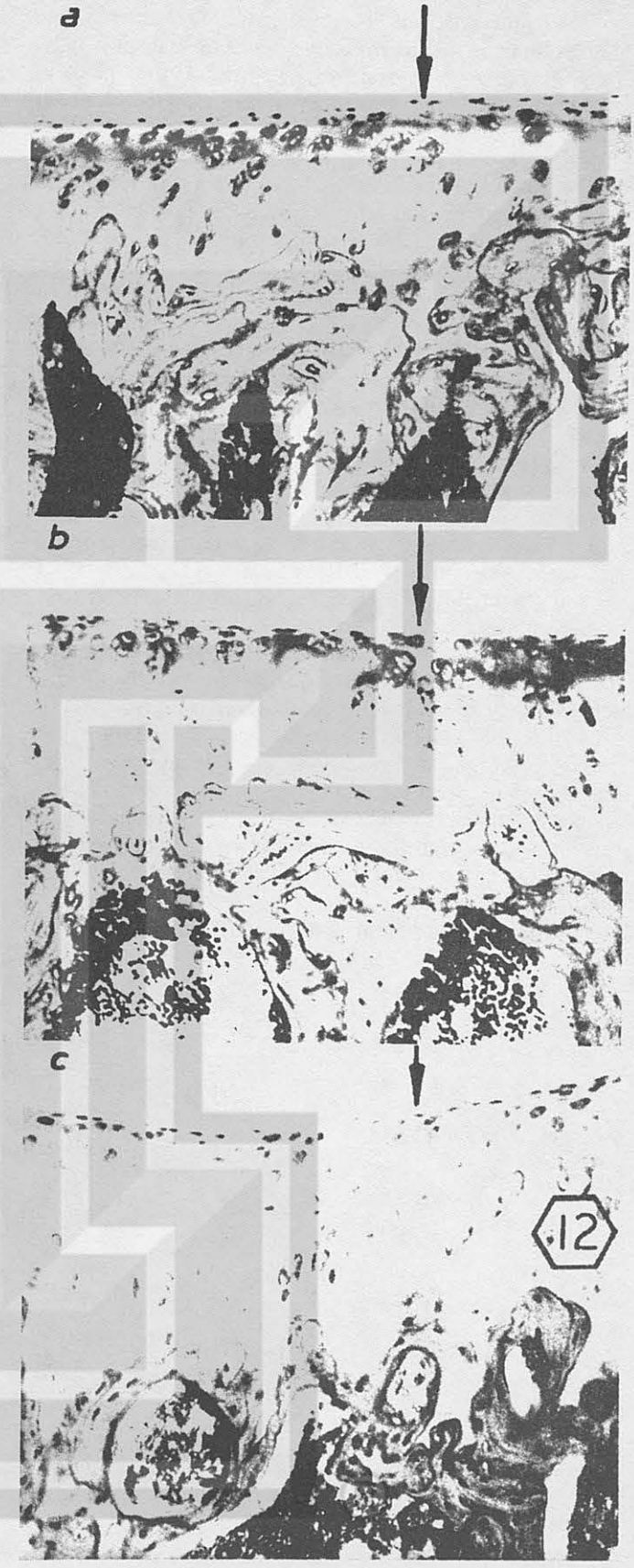


Fig. 12. Photomicrographs of condylar cartilage of 16-week females. 293X. a. RC, b. EC, c. RE. Note condensation at surfaces (arrows) of RC and EC cartilages, and relative lack of condensation at surface of RE cartilage.

thickness, and D/C.T. ratio fall reasonably into this category and are, indeed, more strongly influenced in females than males at the same age and exposure time. Thus, it may be reasonable to surmise that females have been subjected to the stress for an effectively longer period than males, though the absolute time is identical. Experiments subjecting males and females to hypergravity for the same proportional periods of development would seem to be in order to resolve this possibility.

Alternatively, one can invoke strong physiological and hormonal differences between males and females to obtain the disparity of effect. Estrogen has been shown by Negulesco (4) to potentiate bone growth inhibition in centrifuged chicks. If the hormone acts by simply arresting changes in cartilage, it may explain the generally more healthy appearance of the epiphyseal plate and thicker condylar cartilage of RE females compared to males. However, it does not help to explain the poorer preservation of the epiphysis of the femoral head in RE females.

The advanced ossification of RE females compared to RE males may also well be a matter of generally advanced maturity. Oyama and Zeitman (5) reported depressed plasma calcium levels in rats chronically centrifuged at 4.7 G for 1 year. In contrast, Sannes and Hayes (6) reported no significant reduction at 2 G for 60 d in gerbils. They did report hyperactive parathyroid glands, indicating that calcium metabolism is affected by hypergravity combined with rotation, though they reported no differences between the stimulation in males and females.

In sum, there is at present no certain explanation for the disparities of response between males and females. Time and further investigation will be required to settle the questions raised.

Fourth, it is apparent that the influences of hypergravity and rotation upon young and growing musculoskeletal systems may be qualitatively and quantitatively different from those on adult animals. Comparison of our data with those of Amtmann, Oyama, and Fisher (7), and Amtmann and Oyama (3) indicates that the effects on younger animals are much more marked, quantitatively. These authors present no histological observations to allow an assessment of qualitative differences.

ACKNOWLEDGMENT

This study was carried out under contract No. NSG 2187 from the National Aeronautics and Space Administration.

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ORAL CHOLINE ADMINISTRATION TO PATIENTS WITH TARDIVE DYSKINESIA

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Abstract We gave pharmacologic doses of choline to patients with tardive dyskinesia in an attempt to suppress involuntary facial movements. Choline is the physiologic precursor of acetylcholine, and its administration elevates brain acetylcholine levels in laboratory animals and, possibly, in human beings. Hence, we thought that its use could benefit patients with diseases like tardive dyskinesia, which is believed to result from deficient central cholinergic tone. Twenty patients with stable buccal-lingual-masticatory movements took oral doses of choline for two weeks according to a double-blind crossover protocol. Plasma choline levels rose from 12.4±1.0 to 33.5±2.5 nmol per milliliter (mean ± S.E.M.; $P<0.001$) during this period. Choreic movements decreased in nine patients, worsened in one and were unchanged in 10. Thus, oral doses of choline can be useful in neurologic diseases in which an increase in acetylcholine release is desired. (N Engl J Med 297:524-527, 1977)

TARDIVE dyskinesia is a choreic movement disorder characterized by involuntary twitches in the tongue, lips, jaw and extremities.[1] It typically occurs in susceptible persons after chronic ingestion of neuroleptic drugs and may involve an imbalance in the postulated reciprocal relation between dopaminergic and cholinergic neurons in the basal ganglions.[2-4] Thus, drugs that either block catecholamine synthesis (alpha-methyl-p-tyrosine),[3,5] deplete the brain of monoamines (reserpine, tetrabenazine)[6] or antagonize dopamine's actions on synaptic receptors (phenothiazines, haloperidol)[7] often suppress tardive dyskinesia, whereas drugs that indirectly stimulate dopamine receptors (amphetamine, levodopa) often exacerbate the abnormal movements.[3,8] Drugs assumed to increase the amount of acetylcholine within brain synapses (physostigmine, deanol) also tend to suppress the chorea of tardive dyskinesia, whereas anticholinergics (scopolamine) make it worse.[3,9]

Cohen and Wurtman showed that choline administered by injection[10] or dietary supplementation[11] increases blood and brain choline and brain acetylcholine levels in rats. These increases are present within the terminals of cholinergic neurons[12] and are associated with postsynaptic effects compatible with enhanced release of the transmitter.[13,14] In human beings, oral doses of choline caused both a dose-related rise in blood choline levels and a significant increase in the choline concentration of cerebrospinal fluid.[15] These observations suggest that choline administration might be useful in treating patients with diseases that, like tardive dyskinesia, presumably arise from deficient central cholinergic tone. Early reports have tended to support this inference.[16,17] We have examined the possible utility of choline therapy in a double-blind crossover study of 20 patients with tardive dyskinesia.

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Supported in part by grants from ADAMHA (MH-28783), the National Aeronautics and Space Administration (NGR-22-009-627) and the John A. Hartford Foundation (Dr. Growdon is the John R. Whittier Fellow of the Committee to Combat Huntington's Disease, and Ms. Hirsch is the recipient of a predoctoral traineeship [MH 05479-01] from the U.S. Public Health Service).

MATERIALS AND METHODS

We selected 20 subjects at random from a large group of inpatients with stable chronic buccal-lingual-masticatory dyskinesia at Medfield State Hospital, Medfield, Massachusetts. Each patient had received phenothiazines or haloperidol in the past, and 13 were still taking such drugs when the study began (Table 1). Anticholinergic medications (benztropine or trihexyphenidyl) were discontinued during the study, but the doses of all other medications, including neuroleptics, were unchanged.

Each patient and his or her family gave informed consent for participation in the study according to the provisions of a protocol (on choline administration to patients with tardive dyskinesia) that had been approved by both the Medfield State Hospital Committee for Research on Human Subjects and the Committee on the Use of Humans as Experimental Subjects at the Massachusetts Institute of Technology.

We evaluated the severity of the chorea by counting the number of eye blinks, tongue protrusions, slow tongue movements inside the mouth, jaw closures, or lip movements visible during a 30-second interval. Each patient sat in a quiet private room with the ward nurse and two investigators, one of whom (J.H.G.) was present during all examinations. The investigators counted the movements independently on two separate days before the study began and made subsequent counts every three days thereafter. We tabulated the mean counts during the control periods, the second week of choline and the second week of placebo ingestion and scored the percentage change as follows: −25 to +25 per cent, no change (i.e., falling within the anticipated day-to-day variation); 25 to 50 per cent, moderately changed; and >50 per cent, greatly changed. We took movies of the facial movements before the drug trial and again during the final weeks of choline and placebo administration.

Choline chloride (150 mg per kilogram per day during the first week and 200 mg per kilogram per day during the second week) was mixed in a sweet commercial beverage (Kool-Aid) and dispensed in three daily divided doses. The placebo, sucrose octa acetate, was also dissolved in Kool-Aid (10 mg per liter) and administered in the same manner and volume as the choline. Both solutions tasted bitter, but the placebo did not impart the "fishy" odor sometimes noted in patients who chronically ingest choline.[18,19]

Half the patients received choline, and the other half placebo, for two weeks; these schedules were reversed after a 10-day interval during which neither choline nor placebo was dispensed. The patients, nursing staff and examiners were all unaware of whether a particular dose of Kool-Aid did or did not contain choline.

Blood samples for choline measurements were collected from every patient before the drug trial began and on three subsequent occasions: during the second week of therapy, on the ninth day of the drug-free interval and during the second week of the crossover period (the final two weeks of therapy). All blood samples were collected before breakfast. During the treatment periods, they were obtained one hour after the subjects ingested the Kool-Aid. Serum

Table 1. Clinical Characteristics of 20 Patients with Tardive Dyskinesia.

Case No.	Age	Sex	Primary Diagnosis	Severity of Tardive Dyskinesia	Current Medication	Dosage
	yr					*mg/day*
1	36	F	Schizophrenia	Moderate	Thiothixene	100
2	55	F	Schizophrenia	Moderate	Chlorpromazine Trifluoperazine	300 40
3	38	F	Schizophrenia	Moderate	Haloperidol Phenytoin Phenobarbital	15 300 100
4	75	F	Senile dementia	Severe	Thioridazine	75
5	63	M	Schizophrenia	Severe	Phenytoin	300
6	85	F	Senile dementia	Severe	Diazepam Phenytoin	8 300
7	79	F	Schizophrenia	Moderate	None	
8	66	F	Mental retardation with psychosis	Severe	Phenytoin	300
9	73	F	Schizophrenia	Severe	None	
10	48	F	Schizophrenia	Severe	Haloperidol Phenobarbital	5 120
11	72	F	Schizophrenia	Moderate	Chlorprothizene	150
12	80	F	Schizophrenia	Severe	Thioridazine Diphenhydramine	50 100
13	63	F	Schizophrenia	Mild	Thioridazine	300
14	52	F	Schizophrenia	Mild	Chlorpromazine Phenytoin Phenobarbital	100 300 100
15	62	F	Schizophrenia	Moderate	None	
16	37	M	Schizophrenia	Mild	Fluphenazine	25
17	76	M	Senile dementia	Severe	Diphenhydramine	50
18	32	M	Mental retardation with psychosis	Moderate	Haloperidol Phenytoin	40 300
19	37	F	Mental retardation with psychosis	Severe	Phenytoin Phenobarbital	300 160
20	66	M	Schizophrenia	Mild	Thioridazine	400

samples were separated, frozen and assayed for choline content by a radioenzymatic method.[20]

Results

Before treatment, plasma choline levels ranged between 8.6 and 20.5 nmol per milliliter (12.4±1.0, mean ± S.E.M.). During the second week of choline ingestion (200 mg per kilogram per day), plasma choline levels in blood obtained one hour after a choline dose increased in all patients and ranged between 18.2 and 60.1 nmol per milliliter (33.5±2.5, mean ± S.E.M., a 170 per cent increase; $P<0.001$ by Student's t-test). Plasma choline levels measured during placebo administration and at the end of the 10-day "washout" period did not differ significantly from control levels.

Buccal-lingual-masticatory movements lessened in nine patients during the period of choline administration; five patients improved greatly, and four improved moderately (Table 2). Case 1 had rapid, tremulous tongue movements, which virtually ceased during choline therapy. Cases 2 and 3 had slower, rolling tongue movements within the mouth; these movements, too, were greatly suppressed during choline treatment, but not during placebo administration.

Tongue movements also decreased markedly, but not completely, in two patients with more severe dyskinesia. Case 4 protruded her tongue ("serpent's tongue") 20 times per 30 seconds during the initial observation period. In the final week of choline thera-

Table 2. Clinical Effect of Choline Administration on the Buccal-Lingual-Masticatory Movements in 20 Patients with Tardive Dyskinesia.

Classification	No. of Patients	Mean No. of Movements/30 Sec		% Change*
		Before Choline	During Choline	Range
Greatly improved	5	12.6	4.2	+74 – +84
Moderately improved	4	21.2	11.7	+41 – +55
Unchanged	10	13.4	13.6	+18 – −21
Worsened	1	4.5	27.5	−511

*+ indicates improvement, & − worsening of the chorea.

py, the rate decreased to five times per 30 seconds, although the tongue continued to roll inside her mouth. (Placebo ingestion had no effect on the rate of tongue protrusions.) Two weeks after she stopped taking choline, her tongue protrusions returned to their pretreatment rate of 20 per 30 seconds. Within a week of the beginning of a second course of choline treatment (200 mg per kilogram per day), the rate of tongue protrusions again decreased to six times per 30 seconds.

Case 5 protruded his tongue 20 to 30 times per 30 seconds during initial observations but did not protrude it at all during the second week of choline ingestion. It continued to move inside his mouth, but the movement frequency decreased by 49 per cent.

Buccal-lingual-masticatory movements decreased moderately (25 to 50 per cent) in another four subjects. Cases 6 and 7 had fewer jaw movements during choline ingestion, but their tongue motions did not change. The number of jaw movements also diminished during choline therapy in Case 8, although the frequency of her eye blinks did not change. Tongue and lip movements decreased during choline ingestion in Case 9, but jaw movements were unaffected.

The frequency of tongue movements increased markedly in Case 20 (from four to 27 times per 30 seconds) during the period of choline ingestion, but returned to control counts when the choline was discontinued. Neither choline nor placebo altered buccal-lingual-masticatory movements in the remaining 10 patients.

Another patient with severe akathisia was included in the study; she did not exhibit facial chorea, however, and is not listed in the tables. She was unable to sit still and moved her feet 30 times every 30 seconds. These movements were not altered during placebo ingestion but nearly ceased during choline administration.

No serious side effects were encountered in any subject during the course of the study. Cases 2 and 3 were more withdrawn than usual and possibly depressed during choline treatment. Three patients (Cases 4, 7 and 15) experienced symptoms of mild cholinergic toxicity, including lacrimation, blurred vision, anorexia and diarrhea, while taking 200 mg of choline per kilogram per day. All the effects were dose related and subsided when the dosage was reduced.

Discussion

The 20 patients who participated in our study all exhibited "permanent" buccal-lingual-masticatory characteristic of tardive dyskinesia,[1,21] and all had taken neuroleptics in the past (although these drugs had been discontinued in seven patients before the study began). Most subjects were elderly women who had taken neuroleptics for many years; the drugs and doses listed in Table 1 are minimal estimates and do not include medications received before admission to Medfield State Hospital. Since the onset of tardive dyskinesia was documented only in Case 13, it is possible that some patients in the series had senile chorea, or the mannerisms of mentally retarded or psychotic patients, and not true drug-induced tardive dyskinesia. The variety of their responses to choline (nine better, one worse and 10 unchanged) suggests that the patient sample was indeed heterogeneous, at least in the involvement of cholinergic mechanisms. This confusion about causes will remain a problem until an accurate diagnostic test for tardive dyskinesia is found.

Most attempts to treat tardive dyskinesia are based on the theory that neuroleptic drugs, by blocking intrasynaptic dopamine receptors, cause a reflex overactivity of dopaminergic neurons, which may be due to increased dopamine turnover[22] or to "denervation" supersensitivity.[23] Either action would excessively suppress striatal cholinergic neurons (which receive inhibitory impulses from the dopaminergic nigrostriatal pathway[24]) at times of day when the blockade of dopamine receptors was incomplete. Although no therapy is completely satisfactory, numerous efforts to treat stable tardive dyskinesia have employed drugs thought to decrease the amount of dopamine released into central synapses; such approaches were the subject of a recent review.[25] Other therapeutic strategies designed to increase cholinergic tone at the next synapse distal to that employing dopamine have had only limited success. The choline precursor deanol apparently does produce some benefit in a few specific cases[26-28] but not in most others,[29,30] and its efficacy has not been established in a double-blind study. Intravenously administered physostigmine, a centrally active anticholinergic drug, reportedly decreased buccal-lingual-masticatory movements in some patients with tardive dyskinesia[17,31]; its route of administration, however, precludes its use in chronic therapy.

The demonstration that exogenous choline elevates brain choline and acetylcholine levels in rats[10,11] suggests that choline administration might also increase brain acetylcholine levels in human beings, and thus provide a practical way to restore deficient cholinergic tone. Shortly after the results of animal studies were published, Davis et al. described a patient in whom the administration of choline (16 g per day) decreased the choreiform movements of tardive dyskinesia.[16] The therapeutic utility of choline presumably arises from the ability of orally administered choline to elevate plasma choline levels significantly in human beings,[15,32] a finding confirmed in the present study.

Buccal-lingual-masticatory movements decreased in nine patients during the period of choline consumption but were unaffected by the placebo. The occurrence of cholinergic side effects in three of our subjects provides additional indirect evidence that exogenous choline enhances neuronal acetylcholine syn-

thesis and release in human beings as it does in rats[13] and probably accounts for the suppression of chorea in the nine patients who improved during choline therapy. The buccal-lingual-masticatory movements of these patients were not sufficiently different from those displayed by the group as a whole to permit identification of particular movements that might be especially responsive to choline treatment. The mean blood choline levels, both before and during treatment, in the patients who responded to choline did not differ significantly from the mean of the group as a whole — in nine responders, 13.1±1.4 nmol per milliliter before and 31.5±2.5 during treatment, and in the entire group, 12.4±1.0 nmol per milliliter before and 33.5±2.5 during treatment — nor did their age (63.3 years vs. 59.8 years), sex (predominantly women), primary diagnosis (predominantly schizophrenia), or concurrent neuroleptic medication (Table 1). Intravenous physostigmine was not administered in the current study, but a choreic patient's response to this drug might help to predict his or her ability to benefit from choline, as another study showed.[17]

Oral doses of lecithin, the major source of dietary choline, may be an alternate way to treat patients with tardive dyskinesia. We observe that lecithin administration, like that of free choline, elevates blood choline levels in human subjects[33]; however, its ability to suppress buccal-lingual-masticatory movements in patients with tardive dyskinesia remains to be tested.

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JOHNSON SPACE CENTER

FY 77 Medical Sciences Program Review

1. Title: The Prevention of Vestibular Side Effects in Weightlessness

RTOP/Task No.: 199-05-01-01

P.I.: Ashton Graybiel M.D., Naval Aerospace Medical Research Laboratory, Pensacola, Florida

Contract/Grant No.: T-9140 E (Continuation of T-5904B Started 1 Jan 73)

Funding:

Start/Renewal Date: S/ 1 Jan 77 R/ 1 Jan 78

2. Objectives:

The basic objective is to develop and validate acceptable techniques for the prediction, prevention and treatment of vestibular side effects, notably motion sickness, caused by exposure to stressful gravito-inertial force environments including zero gravity.

3. Technical Description:

Studies will be conducted in several related areas. These include:

1. Continued studies to identify in various test situations efficacious anti-motion sickness (AMS) drugs with emphasis on drug type, dose level and route of administration.
2. Continued investigation of rate of acquisition of adaptation using a new passive head movement (PHM) device and transfer of adaptation to other stressful environments.
3. Continued investigations of recovery from acute motion sickness.
4. Further experimentation employing ZARR device, including pre-bedrest (2 hours) to determine whether prolonged headward displacement of body fluids influences susceptiblity.
5. Continued use of parabolic flight to evaluate motion sickness susceptibility and AMS drug efficacy, if KC-135 aircraft is available for use.

4. Progress Report:

Accomplishments during past year include: 1) Measurements of susceptibility to motion sickness in about 25 subjects during free-fall phase of parabolic flight (KC-135) with head fixed and head moving while seated and while

seated and while rotating at 30 RPM. 2) Study using Zarr device in which headward shifts of body fluid did not alter motion sickness susceptibility. 3) Drug studies using SRR and KC-135 which indicated scopolomine administered transdermally and oral promethazine/ephedrine (12.5 mg each) as best prospects for long term use. 4) Drug studies using KC-135 indicating high efficacy of promethazine injected I.M. in dealing with severe, acute motion sickness. 5) Studies to determine variables in the rate of acquisition of adaptation, transfer of overadaptation in the lab to the zero-g phase of parabolic flight and rate of recovery from acute motion sickness.

5. Nature of Contacts with P.I.:

Correspondence, telephone and occasional (1-2 per year) meetings at JSC or Pensacola.

6. List of Publications:

1. Graybiel, A. and Miller, E. F., 1976. A Z-axis recumbant rotating device for use in parabolic flight. Aviat. Space Environ. Med. 47, 893

2. Graybiel, A. and Knepton, J., 1976. Sopite syndrome: A sometimes sole manifestation of motion sickness. Aviat. Space Environ. Med. 873-882

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4. Graybiel, A. and Lackner, J. R., 1977. Comparison of susceptibility to motion sickness during rotation at 30 RPM in the earth-horizontal 10^{o} head-up and 10^{o} head-down positions. Aviat. Space Environ. Med. 7-11.

5. Graybiel, A. and Knepton, J., 1977. Evaluation of a new anti-nauseant drug for the prevention of motion sickness. In press.

7. Assessment:

The results of this research program will be of value to NASA in the selection and training of crews for future space flight, as well as in the development of effective anti-motion sickness drugs. Also, further insight will be gained regarding adaptive processes in the vestibular and related physiological systems. These latter findings will be of extreme value in better understanding the space motion sickness problem that has plagued previous missions and which must be resolved, if at all possible, prior to Space Shuttle flights.

8. Recommendations and Future Plans:

a. This effort has not been reviewed by AIBS; a review is scheduled for July 1977.

b. Probable that this effort will continue in some fashion beyond FY 77.

c. See paragraph 3 above.

d. N/A

e. Pursue basic plan outlined in paragraph 3 above.

f. Conduct research in most areas defined in paragraph 3 above with probable emphasis on AMS drugs, ZARR and PHM.

9. Fiscal Data:

a.

Amount	Award Date	Code
$250 K	1 Jan 75	970-51-11-15
$250 K	1 Jan 76	199-05-01-01
$250 K	1 Jan 77	199-05-01-01

b. $250 K estimated requirement for FY 78 for 12 months period beginning 1 Jan 78.

c. Run-out cost unknown

10. Milestones:

N/A

11. Appendices:

See Attached

AGARD

ADVISORY GROUP FOR AEROSPACE RESEARCH & DEVELOPMENT

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on
Recent Advances in Space Medicine

NORTH ATLANTIC TREATY ORGANIZATION

SUCCESSFUL TRANSFER OF ADAPTATION ACQUIRED IN A SLOW ROTATION ROOM TO MOTION ENVIRONMENTS IN NAVY FLIGHT TRAINING

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Pensacola, Florida, U. S. A.

SUMMARY

Two flight students, grounded for the reason they were highly susceptible to motion sickness, completed their training after gradually adapting to 10 rpm, achieved by executing head movements during small stepwise increases in angular velocity. Subject 1 executed a total of about 77,000 head movements within a period of five months and Subject 2 executed about 108,000 head movements within a period of 42 days. The transfer of the adaptation acquired in the laboratory to most motion environments aloft was good; the notable exception involved weightless maneuvers in the case of Subject 1. Both were on flight status when contacted recently. The opportunity was taken to assess the current motion sickness susceptibility in Subject 1 in the fall of 1975. He reached our (mild) motion sickness endpoint, in the rotating room, at 17 rpm; the average endpoint is 7-8 rpm. Some practical and theoretical implications are discussed.

INTRODUCTION

If a person riding in a slowly rotating room makes a head movement outside the plane of the platform's rotation, cross coupled accelerations are generated which stimulate the vestibular apparatus in an unusual way. In the stationary state, head movements are associated with a pattern of accelerations that produce vestibular sensations consistent with the visual and propioceptive sensations associated with these head movements through past experience. By adding rotation, the vestibular sensations associated with the same head movements now include those sensations produced by the cross coupled accelerations. This produces a situation where the vestibular sensations are no longer consistent with the past visual and proprioceptive sensations. The subject's reactions to this unusual state can be grouped into two classes (1). The first class consists of reflexive reactions such as nystagmus, tumbling or turning sensations, and certain visual illusions. The first class seems to be a direct response to vestibular stimulation. A second class of responses less directly related to the vestibular stimulation constitutes the signs and symptoms of motion sickness. Inasmuch as these signs and symptoms have their immediate origins in non-vestibular systems, one must postulate a facultative linkage between vestibular and non-vestibular systems as an important element in the causation of this form of motion sickness (1). The signs and symptoms arising from this unusual vestibular stimulation have been well studied and a sensitive grading method is available (2).

It has been shown that subjects who perform sufficient head movements at one rpm increments can asymptomatically reach high angular velocities which would otherwise be intolerable (3). By having the subject execute a schedule of head movements at each increment in angular velocity, one has a simple method of providing adaptation to rotation. This scheme is called an incremental adaptation schedule. If the stress level of the incremental adaptation schedule is excessively high, the incidence of motion sickness will force the termination of the adaptation. Although the relationship between adaptation and motion sickness is not well understood, it is possible, using sufficiently small increments in rpm to achieve adaptation without overt symptoms of motion sickness.

Subsequent experience with incremental adaptation (4) has shown that this acquired adaptation has two components. The first to occur is a direction specific adaptation which decays in hours after the cessation of rotation. This direction specific adaptation provides increased tolerance to rotation only in the direction employed in the incremental adaptation schedule. It is also associated with a reduced tolerance to head movements at zero velocity and an even lower tolerance to head movements performed with rotation in the opposite direction. The rather rapid decay of the direction specific adaptation reveals a second component of adaptation which is not direction specific and decays slowly over days. This second component of adaptation is not associated with symptoms at zero velocity and does afford increased tolerance to head movements performed with rotation in the opposite direction. This second component of acquired adaptation is of practical interest since it decays slowly and is not stimulus specific.

A method of acquiring adaptation to unusual vestibular stimuli which is both persistent and not stimulus specific could be put to immediate practical use. Not infrequently, student aviators are dropped from flight training because of repeated episodes of severe air sickness. It is reasonable to assume that in their situation the stimulus level is so high that the prompt emergence of air sickness does not permit the occurrence of any significant adaptation. A similar situation may be created in the laboratory by repeatedly exposing the subject to a high angular velocity without the benefit of incremental adaptation. To test the practical usefulness of this phenomenon, it was decided to determine whether laboratory conducted incremental adaptation could be beneficial to student aviators with a history of severe air sickness.

MATERIALS AND METHODS

Subjects for this experiment were two flight students who were dropped from flight training due to repeated episodes of severe air sickness. Both students had a life long history of motion sickness. Other than the unusual history of motion sickness, medical examination revealed two young, healthy adult males, both highly motivated to remain in the flight program. By history and on the basis of their previous performance in the flight program, these two students demonstrated an incidence of air sickness far above average and one would expect a high susceptibility to motion sickness. This suspicion was confirmed in both studens where comprehensive vestibular testing revealed normal function with the exception of a very high susceptibility to motion sickness.

The rotating device used in this experiment is the Slow Rotation Room I (SRR) at the Naval Aerospace Reseach Laboratory in Pensacola, Florida. The experiment is conducted inside a windowless, air conditioned, circular room which is ten feet in diameter and seven feet high. This room is attached to a large, high mass centrifuge that is capable of very smooth rotation at angular velocities from one to thirty

revolutions per minute (rpm) (5).

By means of controlled vestibular stimulation each subject is well adapted to each increment of angular velocity. The rotation is provided by the SRR rotating at constant angular velocities. The vestibular stimulation consists of paced head movements. In this procedure the subject sits upright and upon command from a tape recorder he makes head movements to the left, right, forward and backwards. As shown in Figure 1, the angular displacement of the head movement is controlled by the placement of pads in each direction of the head movement at an angle of 45 degrees from the vertical. The subject moves his head in the desired direction until he lightly touches the appropriate pad. The commands from the tape recorder specify a given direction every four seconds with the command to return to the upright following the initial command by two seconds. With this arrangement, a discrete head movement is made every two seconds and at the end of 480 such head movements (16 minutes) the subject is given a three to five minute rest period during which he sits quietly with his head in the upright position. The incremental adaptation schedule will be designed on a daily basis by the authors with the objective of keeping the stress level as high as possible yet avoiding significant motion sickness. Measurements of the tumbling ("giant hand") illusion will be made at each new increment of angular velocity to estimate the intensity of the vestibular stimulation. The severity of motion sickness will be measured continually using a previously described grading system (2), which is summarized in Table 1. At the end of each daily rotation, head movements will be immediately conducted at zero velocity to assess the level of acquired direction specific adaptation. It has been proposed that the acquired adaptation which is not direction specific is continually overtaking yet always lagging behind the acquisition of direction specific adaptation (4). If a subject performs sufficient head movements at a given angular velocity, he can then continue his head movements at zero velocity without any incidence of motion sickness. This occurs, presumably, because he has continued his adaptation to the rotating environment for a period of time long enough to permit the decay of the more transient direction specific adaptation to occur, even as he is rotating. If the stress level is properly adjusted, the subject will display minimal illusions at each new increment in angular velocity and will transiently develop no more than one or two motion sickness points throughout rotation. At the conclusion of rotations the subject should remain essentially asymptomatic during the head movements at zero velocity. If the stress level is excessive the illusions will be more prominent, the motion sickness more severe, and the postrun head movements will elicit frank motion sickness. Each subject began at one rpm and worked his way to ten rpm as quickly as possible.

RESULTS

The first attempt at adaptation was conducted with Subject 1, whose motion sickness susceptibility was somewhat lower than that of Subject 2. These results are displayed in Table 2. This first experiment was conducted over a seven day period and involved rotation on six days. Rotation was always in the counterclockwise (CCW) direction.

On the first day Subject 1 reached 5 rpm and experienced no motion sickness throughout the day. The subject executed a total of 7200 discrete head movements. This corresponds to exactly 4.0 hours making head movements and was accomplished in 6.18 hours of rotation. Illusions were not prominent at each new increment in angular velocity. Due to a technical oversight, no postrun head movements were performed on this first day.

On the second day the subject reached 6 rpm and developed no more than 1 motion sickness point while rotating. He performed a total of 5760 head movements (3.2 hours) in 6.85 hours of rotation. Illusions were clearly present at first reaching 5 and 6 rpm. After stopping the subject developed 5 motion sickness points in 115 head movements.

On the third day the subject reached 8 rpm and displayed no more than 2 motion sickness points but remained at 1 point throughout most of the day. He performed 6240 head movements (3.47 hours) in 7.30 hours of rotation. Illusions were present but not prominent. During the postrun head movements the subject developed 6 motion sickness points in 90 head movements.

On the fourth day the subject did not exceed 8 rpm. He developed a maximum of 3 motion sickness points and displayed 2 points for much of the day. He performed 4320 head movements (2.4 hours) in 7.0 hours of rotation. Illusions were present but not prominent at 6-8 rpm. Upon stopping the subject developed 4 motion sickness points in 120 head movements.

On the fifth day the subject reached 10 rpm. He displayed a maximum of 2 motion sickness points at any time during rotation and was asymptomatic at 10 rpm. The subject executed a total of 6720 head movements (3.73 hours) in 8,05 hours of rotation. Illusions were detectable but not prominent. Upon stopping the subject developed only 2 motion sickness points in 120 head movements.

On the sixth day the subject spent most his time at 10 rpm. He displayed a maximum of 2 motion sickness points and was asymptomatic by the end of the day. The subject executed 3360 head movements (1.87 hours) in 4.57 hours of rotation. Illusions were present but not prominent. Upon the cessation of rotation the subject developed 3 motion sickness points in 120 head movements.

On the seventh and eighth days the subject was flown in an aircraft especially prepared for studying air sickness. The subject displayed normal susceptibility which was intrepreted as a significant improvement in his condition. Of the various maneuvers employed, the subject was most sensitive to "porpoising" which involved a few seconds of weightlessness. Several days later he participated in studies involving zero g parabolas of 30-45 seconds duration. Here he displayed such high air sickness susceptibility as to indicate that the incremental adaptation had afforded little protection for this particular type of maneuver.

Following the first incremental adaptation, periodic measurements of motion sickness susceptibility were made to estimate the rate of decay of the acquired adaptation. All of these tests were performed in the CCW direction, the same as that of the first incremental adaptation. At 12 days after the completion of the first study, there was minimal decay in the acquired adaptation. At 33 days there was significant decay and at 58 days the subject has returned to his previous baseline susceptibility.

Dissatisfaction with the incidence of motion sickness in the first incremental adaptation led to the decision to attempt a second, similar experiment. The objective was to examine the effects of lowering the stress level of the incremental adaptation schedule so as to reduce the incidence of illusions and motion sickness while rotating. This in turn would hopefully reduce the incidence of motion sickness caused by the postrun head movements. In this design the daily head movements always started at 1 rpm. This second CCW incremental adaptation was started 80 days after the completion of the first.

On the first day Subject 1 reached 3 rpm and was essentially asymptomatic throughout the day. He performed 3840 head movements (2.13 hours) in 3.50 hours of rotation. Illusions were not noted. Upon the

cessation of rotation, the subject developed only 1 motion sickness point in 240 head movements.

On the second day the subject reached 4 rpm and briefly displayed 2 motion sickness points upon initially reaching 4 rpm. He performed 3240 head movements (1.8 hours) in 3.2 hours of rotation. Illusions were not detected. Upon stopping the subject remained asymptomatic through 240 head movements.

On the third day the subject reached 5 rpm and briefly displayed a single motion sickness point at 1 rpm. He performed 2760 head movements (1.53 hours) in 2.4 hours of rotation. Illusions were not reported. After stopping the subject remained asymptomatic during 240 head movements.

On the fourth day the subject reached 6 rpm. He remained essentially asymptomatic but transiently developed 2 motion sickness points after a momentary power failure. The subject executed 2760 head movements (1.53 hours) in 2.4 hours of rotation. Illusions were not reported. Upon stopping the subject developed a single motion sickness point in 240 head movements.

On the fifth day the subject reached 8 rpm. He was intermittently symptomatic, displaying one or two points for much of the day. The subject executed 4920 head movements (2.73 hours) in 3.95 hours of rotation. Illusions were not noted. Upon halting the subject developed 2 motion sickness points in 240 head movements.

On the sixth day the subject did not exceed 8 rpm and remained asymptomatic throughout rotation. He performed 2760 head movements (1.53 hours) in 2.5 hours of rotation. Illusions were not noted. Upon stopping the subject developed 3 motion sickness points in 240 head movements.

On the seventh day the subject reached 9 rpm and intermittently scored 2 motion sickness points on two occasions during the day. He performed 3240 head movements (1.8 hours) in 2.85 hours of rotation. Illusions were not noted. Upon the cessation of rotation the subject displayed 2 motion sickness points in 240 head movements.

On the eighth day the subject reached 10 rpm and he briefly displayed 2 motion sickness points upon initially 10 rpm. He performed 5760 head movements (3.2 hours) in 4.3 hours of rotation. Illusions were absent. Upon stopping the subject remained asymptomatic in 240 head movements.

Although the second incremental adaptation employed slightly fewer head movements than the first, the successful adaptation to 10 rpm was accomplished with less motion sickness and a much lower incidence of illusions. Provocative tests to assess motion sickness susceptibility (6) were conducted at 7 and 8 days after the completion of the second incremental adaptation. When compared to the earlier baselines before both adaptation experiments, there was a substantial reduction in motion sickness susceptibility. When this test was conducted in the direction opposite to that of both incremental adaptations, i.e. clockwise, there was no evidence of transfer of adaptation to the opposite direction. This result was surprising since some transfer was expected. To examine this possibility in more detail, it was decided to conduct a clockwise (CW) incremental adaptation.

Subject 1 started a CW incremental adaptation 14 days after the conclusion of the second CCW adaptation experiment. The technique was to be the same as the second CCW experiment and the goal would be 10 rpm CW.

On the first day the subject reached a surprising 6 rpm and displayed a maximum of 2 motion sickness points during the day. He performed 5760 head movements (3.2 hours) in 4.75 hours of rotation. Illusions were reported upon first reaching 5 rpm. Upon stopping the subject developed 2 motion sickness points in 240 head movements.

On the second day the subject reached 10 rpm. At one point he briefly developed 3 motion sickness points but was back to 1 point within an hour. He performed 5160 head movements (2.87 hours) in 4.45 hours of rotation. Illusions were not present. Upon stopping the subject developed 1 motion sickness point in 240 head movements. The subject's rapid progress to 10 rpm CW was most likely due to transferred adaptation from the second CCW experiment.

At this point the subject was returned to flight training but due to a recurrance of a chronic sinusitis, he did not immediately return to flying status. Because of some difficulty in controlling this chronic sinusitis, Subject 1 was temporarily suspended from flying. However the problem finally subsided and the subject finished flight training with little difficulty. He is presently in an operational flying billet and periodic follow-up has indicated no abnormal incidence of motion sickness. In the fall of 1975 Subject 1 briefly returned to Pensacola and it was possible to again measure his motion sickness susceptibility. At this time he displayed a typical (mild) endpoint at 17 rpm which is well above the average of 7-8 rpm.

The incremental adaptation of Subject 2 consists of a single, lengthy adaptation to 10 rpm CCW. Some difficulty was anticipated in that Subject 2 was found to be one of the most motion sickness susceptible individuals ever tested at the Naval Aerospace Medical Research Laboratory. The plan was essentially the same as employed with Subject 1. The results of this experiment are displayed in Table 3.

On the first day Subject 2 reached 4 rpm in 0.25 rpm increments. He was symptomatic almost the entire day, averaging about 3 motion sickness points and once reaching 8 points. He executed 9120 head movements (5.07 hours) in 9.5 hours of rotation. Illusions were always present and prominent above 3.25 rpm. Upon halting the subject developed 12 motion sickness points in 240 head movements. Although the stress level was intentionally designed to be low, it was still excessive for this highly susceptible subject.

On the second day the subject did not exceed 2.5 rpm. The subject was symptomatic much of the time and averaged 2 motion sickness points. He performed 7680 head movements (4.27 hours) in 8.7 hours of rotation. Illusions were prominent above 1.75 rpm. Upon halting the subject developed 6 motion sickness points in 240 head movements. Again the stress level was excessive.

On the third day the subject did not exceed 1.75 rpm. Throughout the day he did not develop more than 1 motion sickness point. He performed 4320 head movements (2.4 hours) in 3.25 hours of rotation. Illusions were less prominent than on the previous two days. Due to technical difficulties, postrun head movements were not conducted on this day.

In view of the unusually slow progress toward 10 rpm, it was decided to attempt the incremental adaptation with the use of an effective antimotion sickness drug, d-amphetamine sulfate (7,8).

On the fourth day the subject did not exceed 2 rpm. This run employed 10 mg d-amphetamine sulfate p.o. and the subject was asymptomatic throughout the day. He performed 5760 head movements (3.2 hours) in 5.4 hours of rotation. Illusions were present but not prominent. Upon stopping the subject remained asymptomatic in 240 head movements.

Using this technique the subject gradually worked his way to 7 rpm, reaching it on the sixteenth day. The subject generally averaged one or two motion sickness points however the trend was toward greater motion sickness at higher angular velocities. He performed approximately 4000-5000 head movements per day.

Illusions remained present and were occasionally prominent. Postrun head movements were associated with gradually increasing motion sickness scores, reaching 8 points on the sixteenth day. At this point the drug was combined with the technique of starting all daily head movements at 1 rpm.

From the seventeenth through the twenty-fourth day the subject gradually worked his way to 10 rpm. D-amphetamine sulfate and the technique of starting all daily head movements at 1 rpm were continued. The subject was continually symptomatic and averaged about 2 motion sickness points during each day. He performed about 3000 head movements per day. Illusions were almost always present but rarely prominent. The postrun head movements produced from 6-10 motion sickness points.

On the twenty-fifth day the subject again reached 10 rpm and no drug was employed for this run. The subject displayed only 1-2 motion sickness points throughout the day. He performed 1920 head movements (1.07 hours) in 2.4 hours of rotation. Illusions were present but not prominent at 10 rpm. Upon stopping the subject developed 7 motion sickness points in 180 head movements.

Subject 2 subsequently returned to flight training which he completed with no unusual difficulty with air sickness. He is presently in an operational flying billet and periodic follow-up has not revealed any abnormal incidence of air sickness.

DISCUSSION

On the basis of the results of this experimental probe and the reports of other investigators (10), it is altogether likely that the incremental adaptation to 10 rpm was beneficial to the two flight students. Firm conclusions are difficult to achieve with such a limited number of subjects. However, both subjects have long felt that the adaptation experiments were of considerable aid in completing their flight training. It is clear that established laboratory tests demonstrate that these two subjects were able to reduce their motion sickness susceptibility while associated with the Laboratory. The relationship between the reduced motion sickness susceptibility upon leaving the Laboratory and the subsequent success in flight training requires more careful examination.

If, for example, the same tests that were used to measure motion sickness susceptibility before and after adaptation could be continued through flight training, then one might gain some insight into the relationship between incremental adaptation and improved flight training performance. To obtain a better comparison, students with comparably high susceptibility might be paired, one receiving incremental adaptation and the other continuing in the flight program. It would also be useful to periodically measure the motion sickness susceptibility of normal students as they progress through training. It is probable that the motion sickness susceptibility of student aviators as a group decreases as they progress through training. This effect must be considered before estimating any improvement attributed to vestibular adaptation.

There are several aspects of the data which deserve additional comment. In the case of Subject 1, there was good transfer of laboratory acquired adaptation to flight maneuvers with the exception of those involving weightlessness. A possible explanation may lie in the fact that weightlessness exerts a major effect upon the otolith apparatus whereas the vestibular stimuli employed in the laboratory primarily condition the semicircular canals. Since one would not expect a conditioning process involving the canals to necessarily transfer to the otolith apparatus, it is then understandable that the incremental adaptation to 10 rpm afforded little protection against weightlessness.

After the second CCW incremental adaptation of Subject 1, a motion sickness susceptibility test failed to reveal any significant adaptation to the opposite direction. This was surprising in view of earlier work (9) which predicted substantial transfer. When a subsequent CW incremental adaptation was conducted, the rapidity of the subject's progress clearly implied considerable transfer from the previous adaptation in the opposite direction.The only explanation presently available is that this test was conducted prematurely, before the complete decay of the direction specific component of adaptation.

In the case of Subject 2, the facilitation of adaptation through the use of drugs represents an interesting possibility that requires further investigation. Whether d-amphetamine sulfate promotes adaptability by suppressing motion sickness cannot presently be proven. With Subject 2, the decision to employ a drug was largely based on the desire to continue the incremental adaptation. The initial response to the drug was significant but due to the subject's complaints of nervousness, the dosage was gradually lowered. What effect increased dosage would have had on the increased motion sickness symptomatology above 6 rpm is not known.

The practical value of incremental adaptation is that it provides a method of reducing air sickness susceptibility which, although time consuming, can be accomplished safely, simply, and inexpensively with a minimal investment in equipment. This method does not involve the elicitation of motion sickness. Although the data presented here were collected on a slowly rotating room, there is no reason why the technique could not be arranged to utilize a simple rotating chair.

From a theoretical viewpoint, incremental adaptation represents a flexible experimental technique for gaining insight into the process of vestibular adaptation. By regulating the direction of rotation, the angular velocity, and the number of head movements, the investigator can reliably generate a variety of vestibular stress levels that range from the subthreshold to those which are frankly provocative of motion sickness. The relationship between motion sickness and adaptation is not well understood. It has been reported that adaptation can occur without incurring significant motion sickness (3) and this has again been shown in these results. However very little is known about the circumstances promoting optimal adaptation. From existing data it seems probable that motion sickness is not a necessary element of adaptation. This still allows the possibility that motion sickness actually retards adaptation which would seem to explain the behavior of some student aviators. If this should be true then the present method of making decisions on the presence of early or mild motion sickness symptomatology may not prove to be very efficient. In the present design the presence or absence of the tumbling illusion was noted with the initial head movements at each new increment of angular velocity. Although this information can be generally related to the adaptation process it is not presently clear how it alone might be used to establish an incremental adaptation schedule.

In summary, two well motivated flight students with a life long history of motion sickness were referred to the Laboratory due to persistent air sickness of such severity as to jeopardize their continued participation in the flight program. By executing numerous paced head movements on a rotating room of gradually increasing velocity, both students substantially reduced their motion sickness susceptibility to the laboratory rotating environment. After developing an essentially asymptomatic tolerance to 10 rpm through the technique of incremental adaptation, they returned to the flight program. Both students com-

pleted flight training and are presently in operational flying billets where they have experienced no unusual incidence of motion sickness. In these two cases it was possible to employ a recently described adaptation to vestibular stimuli which permits the effective transfer of reduced motion sickness susceptibility from the laboratory rotating environment to an operational flight situation.

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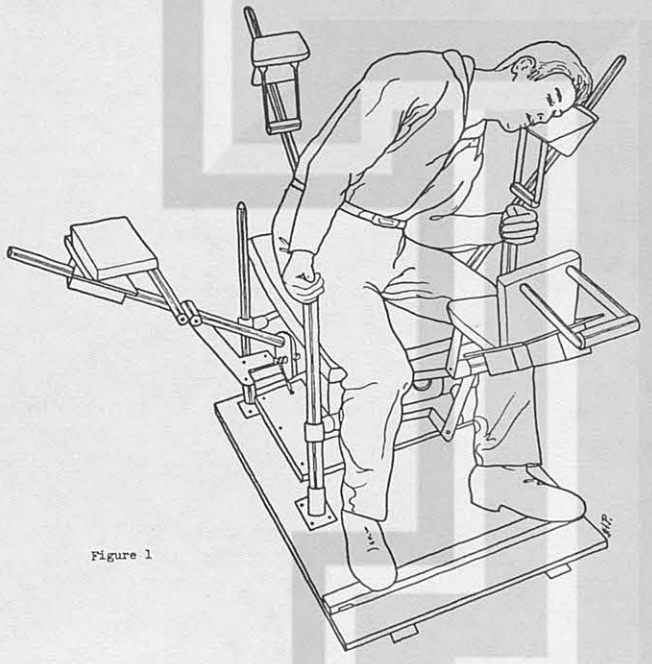

Figure 1

Scoring Severity of Acute Motion Sickness

Category	16 points	8 points	4 points	2 points	1 point
Nausea syndrome	Vomiting or retching	Nausea*II, III	Nausea I	Epigastric discomfort	Epigastric awareness
Skin color		Pallor III	Pallor II	Pallor I	Flushing
Cold sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Headache
Central nervous system					Dizziness:
					Eyes closed ≥ II
					Eyes open III

*III = severe or marked, II = moderate, I = slight.

Table 1

INCREMENTAL ADAPTATION — Subject 1

Date	Run Day	Angular Velocity (rpm) 0	1	2	3	4	5	6	7	8	9	10	Daily Total	Average MS Score	Postrun RM	Postrun MS Score
8 Jan '71	1 (CCW)	0.96*	0.96	1.92	1.92	1.44							7.20	0		
9	2					1.92	3.84						5.76	1	0.12	5
10	3					0.48	0.96	3.84	0.96				6.24	1	0.09	6
11	4						0.48	0.96	2.88				4.32	2	0.12	4
13	5						0.48	0.48	0.48	3.84	1.44		6.72	1	0.12	2
14	6									0.96	2.40	3.36	1	0.12	3	
		0.96	0.96	1.92	1.92	3.84	5.76	5.28	4.32	4.80	3.84				0.97	
													Grand Total: 34.17			
6 May '71	1 (CCW)	0.96	0.96	1.92									3.84	0	0.24	1
7	2	0.12	0.12	0.12	2.88								3.24	1	0.24	0
10	3	0.12	0.12	0.12	0.48	1.92							2.76	0	0.24	0
11	4	0.12	0.12	0.12	0.12	0.48	1.80						2.76	1	0.24	1
12	5	0.12	0.12	0.12	0.12	0.12	0.48	1.92	1.92				4.92	2	0.24	2
13	6	0.12	0.12	0.12	0.12	0.12	0.12	0.12	1.92				2.76	0	0.24	3
14	7	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.48	1.92			3.24	1	0.24	2
17	8	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.96	3.84		5.76	0	0.24	0
		1.80	1.80	2.76	3.96	2.88	2.64	2.28	4.44	2.88	3.84				1.92	
													Grand Total: 31.20			
1 June '71	1 (CW)	0.96	0.96	0.96	0.96	0.96	0.96						5.76	1	0.24	2
2	2	0.12	0.12	0.12	0.24	0.24	0.48	0.96	0.96	0.96	0.96	0.96	5.16	1	0.24	1
		1.08	1.08	1.08	1.20	1.20	1.44	0.96	0.96	0.96	0.96	0.96			0.48	
													Grand Total: 11.40			

* 1.00 = 1000 individual head movements, spaced at two second intervals

Table 2

INCREMENTAL ADAPTATION — Subject 2

Date	Run Day	Angular Velocity (rpm) 0	1	2	3	4	5	6	7	8	9	10	Daily Total	Average MS Score	Postrun RM	Postrun MS Score
31 Mar '71	1 (CCW)	1.92*	1.44	1.92	3.84								9.12	3	0.24	12
1 Apr	2	1.92	3.84	1.92									7.68	2	0.24	6
2	3	1.92	2.40										4.32	1		
5	4a	1.92	3.84										5.76	0	0.24	0
6	5a		2.88	0.96									3.84	0	0.24	0
7	6a		1.92	1.92									3.84	0	0.24	0
12	7b		0.96	2.88									3.84	0	0.24	2
13	8b			2.88	0.96								3.84	0	0.24	1
14	9b			0.96	2.88								3.84	0	0.24	1
15	10b				2.88	0.96							3.84	2	0.24	8
16	11b				1.92	1.92							3.84	0	0.24	1
19	12b				0.96	3.84							4.80	0	0.24	1
20	13b					1.92	2.88						4.80	1	0.24	5
21	14b						2.88	1.92					4.80	1	0.24	2
22	15c						0.48	0.48					0.96	4		
27	16b			0.48			0.48	2.88					3.84	2	0.24	7
28	17b	0.12	0.12	0.12	0.12	0.12	0.12	1.68	2.88				5.28	2	0.24	8
29	18b	0.12	0.12	0.12	0.12	0.12	0.24	0.48	1.20	0.96			3.48	2	0.24	7
3 May	19b	0.12	0.12	0.12	0.12	0.24	0.24	0.72	0.48	1.44			3.60	4	0.24	6
4	20b	0.12	0.12	0.12	0.24	0.24	0.24	0.24	0.48	2.16			3.84	3	0.18	10
5	21c	0.12	0.12	0.12	0.12	0.24	0.24	0.24	0.48	1.20			2.58	2	0.08	6
6	22c	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.36	0.96		2.28	2	0.21	6
7	23b	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.36	1.20		2.52	3	0.20	7
10	24c		0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.24	2.40		3.48	2	0.15	9
11	25	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.24	0.72		1.92	1	0.18	7
		8.64	18.84	14.52	14.52	10.56	7.80	9.12	8.00	6.96	5.28				3.00	
													Grand Total: 107.24			

* 1.00 = 1000 individual head movements, spaced at two second intervals
a 10 mg d-amphetamine sulfate, orally
b 5 " " " "
c 2.5" " " "

Table 3

This research was conducted under the sponsorship of the Bureau of Medicine and Surgery MR 041.01.01-0120 and the Office of Life Sciences, NASA, Johnson Space Center, Houston, Texas. Opinions and conclusions contained in this report are those of the authors and do not necessarily reflect the views of endorsement of the Navy Department.

DISCUSSION

K.E.Klein: Obviously, in the Skylab program, selection and training with respect to space sickness was not very effective. Would you please comment on the possible reasons for this, and on the improvement to be made in the Spacelab program, as your lack of transfer in one of your subjects of your adaptation effect to weightlessness seems rather discouraging.

W.J.Oosterveld: We have to keep in mind two things:

(1) The US astronauts were not subjected to any vestibular adaptation program. On a voluntary basis, they did a little flying in small airplanes, which cannot compete with a well designed adaptation program. This can explain the fact that more than 50% of the Skylab astronauts became motion sick.

(2) A well designed adaptation program gives a protection to air sickness and seasickness. There is a transfer of adaptation from one force environment to another. There is no reason why this transfer will not concern space sickness too. The coverage cannot be expected to be full, however, it will at least give a diminishing of chances to suffer from this.

The results with the second subject were not discouraging. They have proved that there was a strong transfer of adaptation from the incremental adaptation schedule to the force environment in an airplane with the exclusion of direct effect of weightlessness. This means that besides an adaptation as described, the candidate astronaut needs training in parabolic flight too.

G.Perdriel: Que pensez-vous de l'intérêt de l'électronystagmographie (E.N.G.) et de la cupulométrie (seuil de sensation) pour apprécier l'aptitude d'un candidat au vol spatial?

W.J.Oosterveld: I think that neither electronystagmography, nor cupulometry would be of interest for selecting candidates for space flight.

M.P.Lansberg: The very nice experiments of Dr Oosterveld have, I feel, once again shown that motion sickness is an extremely elusive condition. His motion sick pilot adapted well but for the situation of weightlessness. Astronauts who were notoriously unsusceptible to motion sickness became space sick, and it has yet to be proved that an adaptation procedure for susceptibles that gave no protection for the weightlessness situation could prevent non-susceptible aspirant astronauts from becoming space sick.

Concerning the question by General Perdriel, I would like to say that cupulometry, for all the good it has done to labyrinthology, has nonetheless no function in motion sickness physiology and pathology. Neither its sensation nor its nystagmus response bears any correlation for motion sickness susceptibility.

K.E.Klein: There has been an imbalance in astronauts after returning to earth (after splash down). Could you comment on the possibility that this is more an effect of muscular dysfunction than an effect of vestibular dysfunction?

W.J.Oosterveld: This imbalance is based more on muscular dysfunction than on vestibular effects. The vestibular system will rapidly adapt to the force environment on returning to earth and this is not the case with the musculature, which needs more time.

EVALUATION OF A NEW ANTINAUSEANT DRUG FOR THE PREVENTION OF MOTION SICKNESS

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This study was supported by the National Aeronautics and Space Administration, Contract T-5904B and the Bureau of Medicine and Surgery, Project MR 041.01.01-0120. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

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ABSTRACT

GRAYBIEL, A., and J. KNEPTON. Evaluation of a new antinauseant drug for the prevention of motion sickness. Aviat. Space Environ. Med.

The antimotion sickness efficacy of a new drug, AHR 5654B*, administered orally in 20, 50, and 100 mg doses, was compared with that of l-scopolamine 0.3 mg and placebo. Also included were four "old" drugs; new only in the sense that dosage or drug combinations had not been tested previously. Promethazine 12.5 mg and ephedrine 12.5 mg were given alone and combined; the fourth drug was a fixed-dose of meclizine 50 mg and ephedrine 25 mg. Eight college students aged 18 to 26 years participated as paid volunteers. Each subject was tested individually in a slow rotation room where the stressful stimuli were generated by requiring the subject to execute standardized head movements at 1 rpm increments until either the motion-sickness endpoint or the ceiling on the test (30 rpm) was reached. Efficacy of the eight drugs was assessed in terms of placebo effects and categorized as beneficial, inconsequential, or detrimental. The effects of scopolamine were beneficial in 50 per cent of the subjects, a little below expectation (62.5 per cent). All of the responses to the AHR 5654B drugs were inconsequential except for one beneficial effect (100 mg) and two detrimental responses, one each with doses of 20 mg and 50 mg. Among the remaining drugs none of the responses was detrimental; beneficial responses were 62.5 per cent for promethazine 12.5 plus ephedrine 12.5 mg, 50 per cent for promethazine 12.5 mg, 37.5 per cent for ephedrine 12.5 mg, and 25 per cent for meclizine 50 mg plus ephedrine 25 mg.

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*The drug was provided by the A. H. Robins Company, Richmond, Virginia.

INTRODUCTION

The new drug AHR 5645B was offered to us for assessment of its efficacy in reducing susceptibility to motion sickness. This preparation is a pyrolidine derivative unrelated to known drugs, and reports ( ) indicate that its effects are comparable to actions following the administration of the phenothiazine and nonphenothiazine drugs in both patients ( ) and animal models ( ). Scopolamine 0.3 was used as a control. The opportunity was taken to extend our bioassay of the combination promethazine plus ephedrine and a new combination, meclizine 50 mg plus ephedrine 25 mg.

In all of our studies dealing with the efficacy of antimotion sickness drugs stressful accelerations were generated by requiring the subject to execute standardized head and body movements out of the plane of rotation in a slow rotation room (SRR). In early studies the results were not valid for individuals in a group, a present-day requirement. Gradually a procedure is evolving that seems to have validity for the individual as well as for the group. A major improvement in methodology was devising a means of measuring the level of stressful stimuli as a single value. A second need that had to be met was satisfactory controls. Here we ran into two problems. The problem posed by acquiring adaptation was met fairly well by increasing the interval between tests. The second problem was unexplained variation in motion sickness susceptibility within individuals. In most subjects substantial variations are uncommon or explicable, but in some subjects we have not uncovered the cause or causes for these variations.

SUBJECTS AND PROCEDURE

Subjects

The eight male subjects 18 to 26 years of age used in this experiment were selected from a subject-pool solely on the basis of availability. All of the subjects in the pool were physically and mentally qualified for parabolic flights and assessments revealed normal canalicular, otolith and visual functions. None was selected on the basis of susceptibility to motion sickness however much this factor influenced their willingness to serve as a subject.

Procedure

The stress profile. The procedure, described elsewhere in detail ( ), involved the generation of stressful stimuli in a slow rotation room (SRR) by requiring the subject to execute head movements out of the plane of the room's rotation. Forty head movements were executed at 1 rpm and were repeated at 1 rpm increments in angular velocity until either the ceiling on the test, 30 rpm, or the motion-sickness endpoint was reached.

Assessing susceptibility to acute motion sickness. The observer, in collaboration with the subject, estimated the levels of severity of the symptoms after every set of 40 head movements. The levels of severity of motion sickness were given numerical scores according to diagnostic criteria ( ) found to be satisfactory when acute experimental motion sickness was evoked. The motion-sickness endpoint was slight nausea or a score of 12 points, whichever came first.

Drugs and their administration. The following drugs were evaluated:

1. L-scopolamine hydrobromide (0.3 mg)
2. AHR 5654B (20 mg)
3. AHR 5654B (50 mg)
4. AHR 5654B (100 mg)
5. Meclizine (50 mg) + ephedrine sulfate (25 mg)
6. Promethazine hydrochloride (12.5 mg)
7. Ephedrine sulfate (12.5 mg)
8. Promethazine hydrochloride (12.5 mg) + ephedrine sulfate (12.5 mg)
9. Placebo (lactose)

Nineteen preparations in identical opaque capsules (eight drugs and 11 placebos) were individually sealed in small envelopes and numbered. The numbers on envelopes containing a drug reflected an arrangement based on a latin square design of order 8. The administration of placebos was generous but arbitrary. Two placebos were given before the first and after the last drug was taken. In addition, seven placebos separated contiguous drugs in the latin square arrangement.

The 19 preparations for each subject were placed in a large envelope and kept under lock and key. The two capsules to be administered on test day were given to the inside observer who ensured that the subject swallowed the capsules, along with a little bland food.

Plan. The subjects were carefully instructed regarding all aspects of the experiment. As part of the overall assessment prior to becoming a member of the experimental group,

a test in the SRR was carried out that met the need for "familiarization." The tests in the series were carried out at approximately weekly intervals. The shortest period was three days and the two longest periods were 19 days (Subject 7 had the flu) and 29 days (Subject 41 sprained his ankle); the average was 6.8 days. On test days, subjects reported 2 hours and 30 minutes prior to rotation. The routine involving inside observer and experimenter comprised the following duties:

Observer:

1. Administered a pre-experimental questionnaire regarding the subjects' state of health and general fitness.

2. Obtained physiological measurements: 1) pulse rate, 2) blood pressure, 3) oral temperature, and 4) postural equilibrium using a heel-to-toe Romberg test.

3. Conducted psychophysical evaluations: 1) Wechsler's digital symbol substitution test (DSST), 2) Graham and Kendall's Memory-for-Designs (MFD) test, and 3) the Clyde Mood Scale.

4. Two hours before rotation ensured subject swallowed two capsules.

5. Shortly before rotation repeated physiological measurements.

6. Following rotation repeated physiological measurements.

Experimenter:

1. Thirty minutes before rotation (90 minutes after capsules taken) queried subject with regard to side effects of the medication.

2. Following rotation queried subject regarding the symptoms experienced.

The method of scoring the efficacy of the drugs administered is described with the aid of findings in an actual experiment (Figure 1). In the plot the ordinate indicates the motion-sickness endpoint in terms of rpm of the slow rotation room; the rpm multiplied by 40 yields the number of head movements executed. If the range of placebo scores is no greater than that shown in the Figure a mean value serves as the departure line in scoring the responses in three ranges. Twice the placebo range above the mean defines the entry into the beneficial range and the same procedure is used in defining the detrimental range. Every score between these ranges defined the inconsequential response. In two circumstances the above procedure is unsatisfactory, namely, when the placebo range is very small or great, e.g., greater than 2.5-3.0 rpm. In the first instance 1.5 to 2 rpm above or below the mean may serve, respectively, for entry into the beneficial and detrimental zones. The most common cause of a great range is the acquisition of adaptation effects. In this event sloping baselines are used and it may be necessary to divide the baseline into as many as three (rarely more) parts.

RESULTS

Table I summarizes the findings. It is noteworthy that the beneficial responses (50%) to scopolamine 0.3 mg were a little below expectation (62.5%) based on previous studies using the same procedure ( ). This implies that the subjects' responses to the drugs, as a group, might be below the average. This implication finds support in the greater than average individual variation in beneficial responses; four subjects accounted for 15 of the 18 beneficial responses and nearly half were highly beneficial.

It is immediately apparent that under the experimental conditions AHR 5654B, regardless of dose, was inefficacious. The one beneficial response was just at the border of the inconsequential range. A table was prepared (not shown) indicating whether the responses to the preparations were within, above, or below the placebo range. When doses of 20 mg were given, seven of the eight responses were within the placebo range; one was far below (detrimental). When 50 mg doses were given, five responses were within the placebo range and three were below. With the administration of 100 mg doses, five responses were within the placebo range, two were below and one just entered the beneficial range. In other words, 17 of the 24 responses were not distinguishable from placebos.

The combination meclizine plus ephedrine was highly beneficial in two instances and detrimental in one. It is important to note that in the case of Subject 5 it was the only drug registering a beneficial response. In Subject 4, who manifested four beneficial responses, the efficacy of meclizine plus ephedrine was not excelled by any other drug and only equalled following the administration of scopolamine.

The fixed-dose combination, promethazine and ephedrine 12.5 mg each, had not been evaluated previously and the beneficial responses (62.5%) were above expectations. This is based both on a comparison with responses to scopolamine in this experiment and with comparisons in previous experiments. When these drugs were given singly in the same dose the greater role of promethazine is demonstrated.

Two subjects accounted for seven of the eight highly beneficial effects, involving all drugs except ephedrine and the AHR preparations. Subject 3 demonstrated highly beneficial effects when the remaining four drugs were administered. Subject 5 manifested inconsequential

responses to all drugs except the combination meclizine and ephedrine which was highly beneficial. In the case of Subject 7, three of his four beneficial responses were highly beneficial.

Evidence of side effects due to administration of the drugs was sought by the use of tests and interviews. Graham and Kendall's memory-for-designs and Wechsler's digital symbol substitution test were administered and the findings revealed no definite evidence that the scores were influenced after taking a drug. Oral temperature, pulse rate, blood pressure and ataxia scores indicated no definite effect as the result of taking a drug.

Table II indicates the frequency with which subjects believed they felt a drug effect 90 minutes after taking drug or placebo. This belief was based on the symptoms listed, in order of frequency, at the bottom of Table II.

Three subjects (2, 5, 7) accounted for nearly 90% of the side effects when drugs were administered and over 77% when placebos were taken. Subject 2 was correct in his identification, 69%, but this was not reflected in his single beneficial-response score. Indeed, this beneficial response involved promethazine 12.5 mg prior to which he reported zero symptoms.

Subject 5 scored a single beneficial response after taking meclizine plus ephedrine which did not give rise to any symptoms.

Subject 7 scored four beneficial responses and experienced symptoms when promethazine and ephedrine were administered alone or in combination but not after taking scopolamine. It is noteworthy that he experienced symptoms on six occasions when taking placebos; five of the six most commonly experienced symptoms were involved after taking either drug or placebo.

Subject 4, who did not register a single beneficial response, had the second highest correct identification score.

In sum, the findings dealing with side effects reveal no objective proof of performance decrement and the subjective evidence is equivocal for similar symptoms were experienced after taking drug or placebo. The findings are definite, however, in providing an unexpected control, in that symptoms experienced before rotation were not helpful in distinguishing drug from placebo.

DISCUSSION

Two methodological problems were encountered, namely, inability to draw a highly satisfactory placebo baseline in the case of four subjects and the rather low efficacy (50%) of scopolamine 0.3 mg, the reference drugs. Fortunately, these problems were easily met except in the case of Subject 4 by virtue of the high efficacy of promethazine and ephedrine alone or in combination (80%) and the fact that the response to AHR preparations were nearly always in the placebo range.

In Figure 2 is a plot showing the responses in the case of Subject 4. When interviewed after completion of the entire experiment he stated that he disliked the food furnished as a snack after taking the capsules and the odor in the slow rotation room sometimes made him sick. Unfortunately, these complaints were not made during the experiment. A glance at the Table showing the symptoms he experienced 90 minutes after taking the capsules indicates that he experienced stomach awareness after taking AHR (20 mg) when a low rpm endpoint was registered and after AHR (100 mg) when the response was well within the placebo range. On a third occasion, after taking the second placebo, his motion sickness endpoint was the highest score prior to experimental day 80. Subject 4 is a delicately

and tests

tempered, highly cooperative person who, after review of all assessments carried out, reveals a strong tendency toward inconsistency.

The control of accelerative stimuli posed no problems. None of the subjects reached 30 rpm, the ceiling on the test.

SUMMARY AND CONCLUSIONS

1. The responses after giving scopolamine 0.3 mg, the standard for reference, were below expectations (50%) implying that the responses for the group might be less efficacious than anticipated.

2. The new drug AHR 5654B used in doses of 20, 50 and 100 mg was not efficacious in preventing experimental motion sickness.

3. The new combination meclizine 50 mg and ephedrine 25 mg, although eliciting a beneficial response in only two subjects, was not surpassed in these instances by any other drug given. Moreover, it was the only beneficial response elicited in one subject, hence deserves further study.

4. The heretofore untried combination of promethazine and ephedrine 12.5 mg each was outstanding in this series.

5. The findings in this experiment point to the difficulty of identifying a highly efficacious antimotion sickness drug for everyone.

Table I

Individual Responses* to Eight Antimotion Sickness Drugs Assessed in a Slow Rotation Room

S	S 0.3 mg	E 12.5 mg	P 12.5 mg	P 12.5 mg + E 12.5 mg	M 50 mg + E 25 mg	AHR 20 mg	AHR 50 mg	AHR 100 mg	% B Responses: All drugs	% B Responses: All but AHR drugs
1	B	B	I	B	I	I	I	B	50	80
2	I	I	B	I	I	I	I	I	12.5	20
3	B_2	I	$>B_2$	$>B_2$	$>B_2$	I	D	I	50	80
4	I	I	I	I	D	D	I	I	0	0
5	I	I	I	I	B_2	I	I	I	12.5	20
6	I	B	B	B	I	I	I	I	37.5	60
7	$>B_2$	B	$>B_2$	$>B_2$	I	I	I	I	50	80
8	B	I	I	B	I	I	I	I	25	40
	% B 50	37.5	50	62.5	25	0	0	12.5		

*B = Beneficial

I = Inconsequential

D = Detrimental

Table II

Symptoms Reported by Eight Subjects 90 Minutes After Taking 2 Capsules (Containing Drug or Placebo) on 19 Occasions

S	BID Score B	I	D	Incidence of "side effects" 8 Drugs No.	%	11 Placebos No.	%	Number of side effects 8 Drugs No.	%	11 Placebos No.	%	Drugs involved in 3 subjects with high incidence side effects. AHR 20 mg	AHR 50 mg	AHR 100 mg	P 25 E 25	P 25	E 25	S .03
1	4	4	0	1	13	1	9	2		2								
2	1	7	0	4	50	2	18	6	75	2	18	0	+	0	+	0	+	+
3	4	3	1	0	0	0	0	0		0								
4	0	6	2	2	25	1	9	2		2								
5	1	7	0	4	50	7	64	7	87.5	11	100	+	+	+	+	0	0	0
6	3	5	0	0	0	2	18	0	0	2	18							
7	4	4	0	3	37	6	55	6	75	10	91	0	0	0	+	+	+	0
8	2	6	0	1	13	2	18	1	13	2	18							

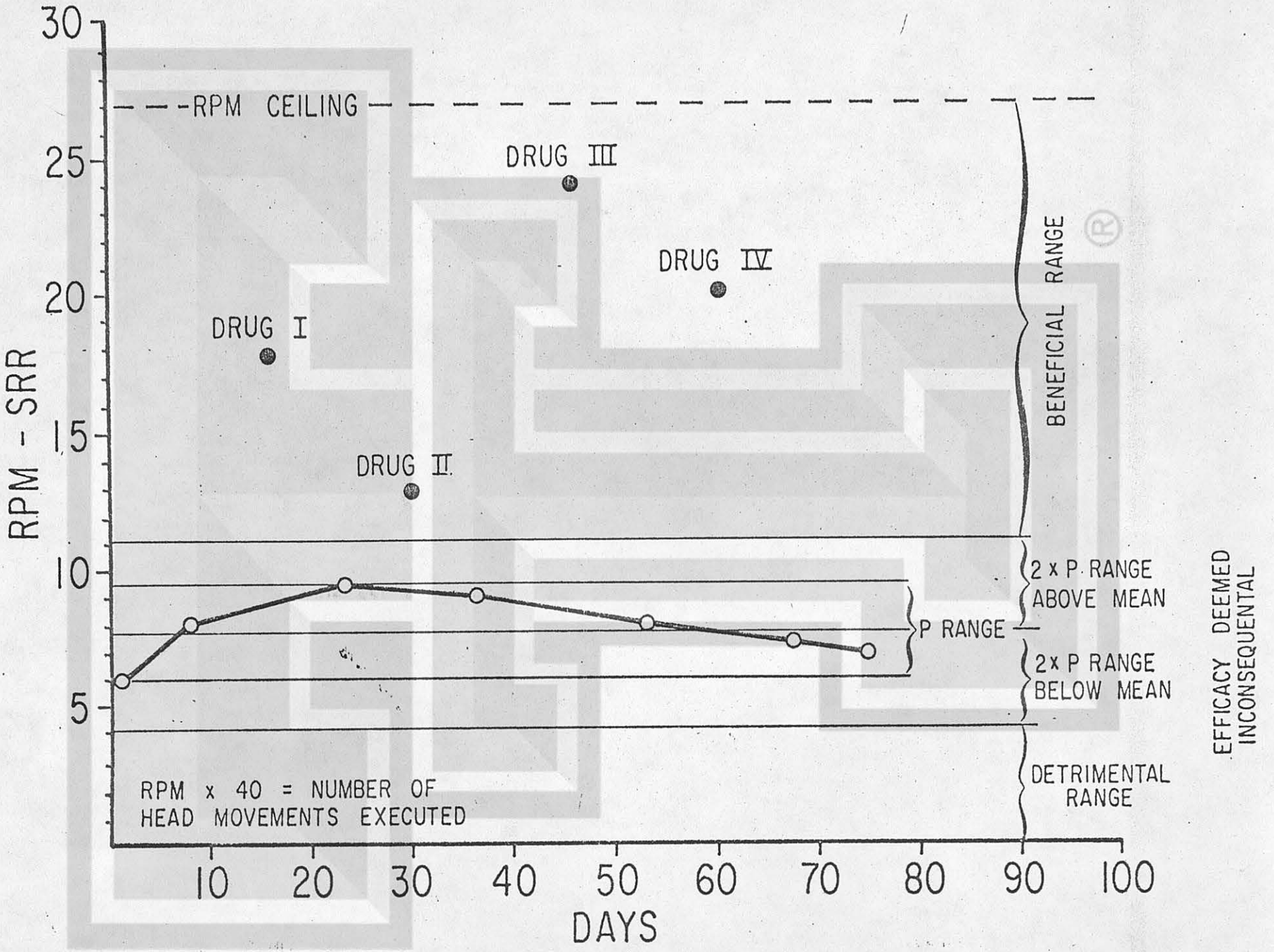
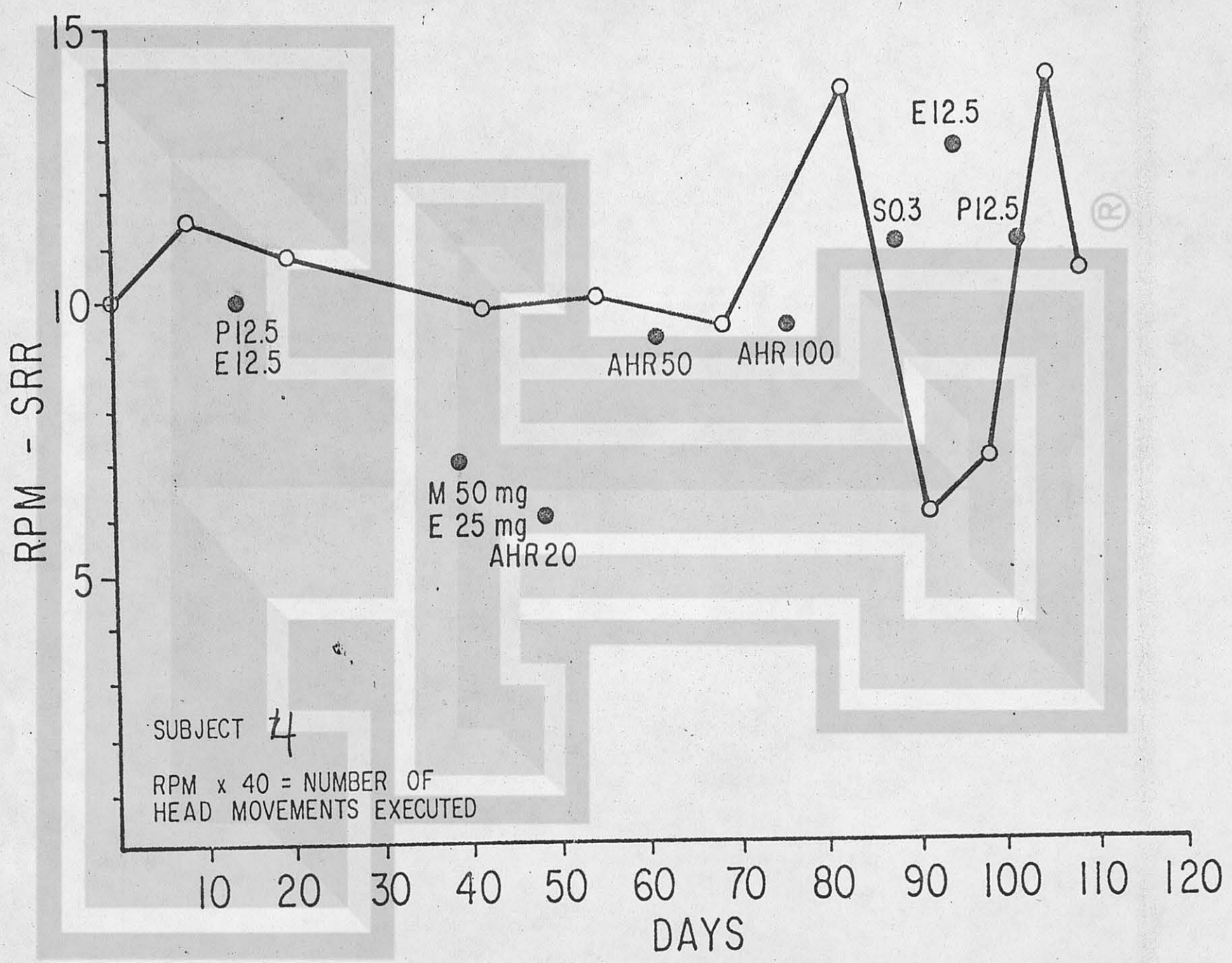

30
25
20
15
10
5
RPM - SRR
RPM CEILING
DRUG III
DRUG IV
DRUG I
DRUG II
BENEFICIAL RANGE
2 x P RANGE ABOVE MEAN
P RANGE
2 x P RANGE BELOW MEAN
DETRIMENTAL RANGE
EFFICACY DEEMED INCONSEQUENTAL
RPM x 40 = NUMBER OF HEAD MOVEMENTS EXECUTED
10 20 30 40 50 60 70 80 90 100
DAYS

Fig 1


15
10
5
RPM - SRR
P12.5
E12.5
M 50 mg
E 25 mg
AHR 20
AHR 50
AHR 100
S0.3
E12.5
P12.5
SUBJECT 4
RPM x 40 = NUMBER OF
HEAD MOVEMENTS EXECUTED
10 20 30 40 50 60 70 80 90 100 110 120
DAYS

Chapter 61

Motion sickness in skylab astronauts

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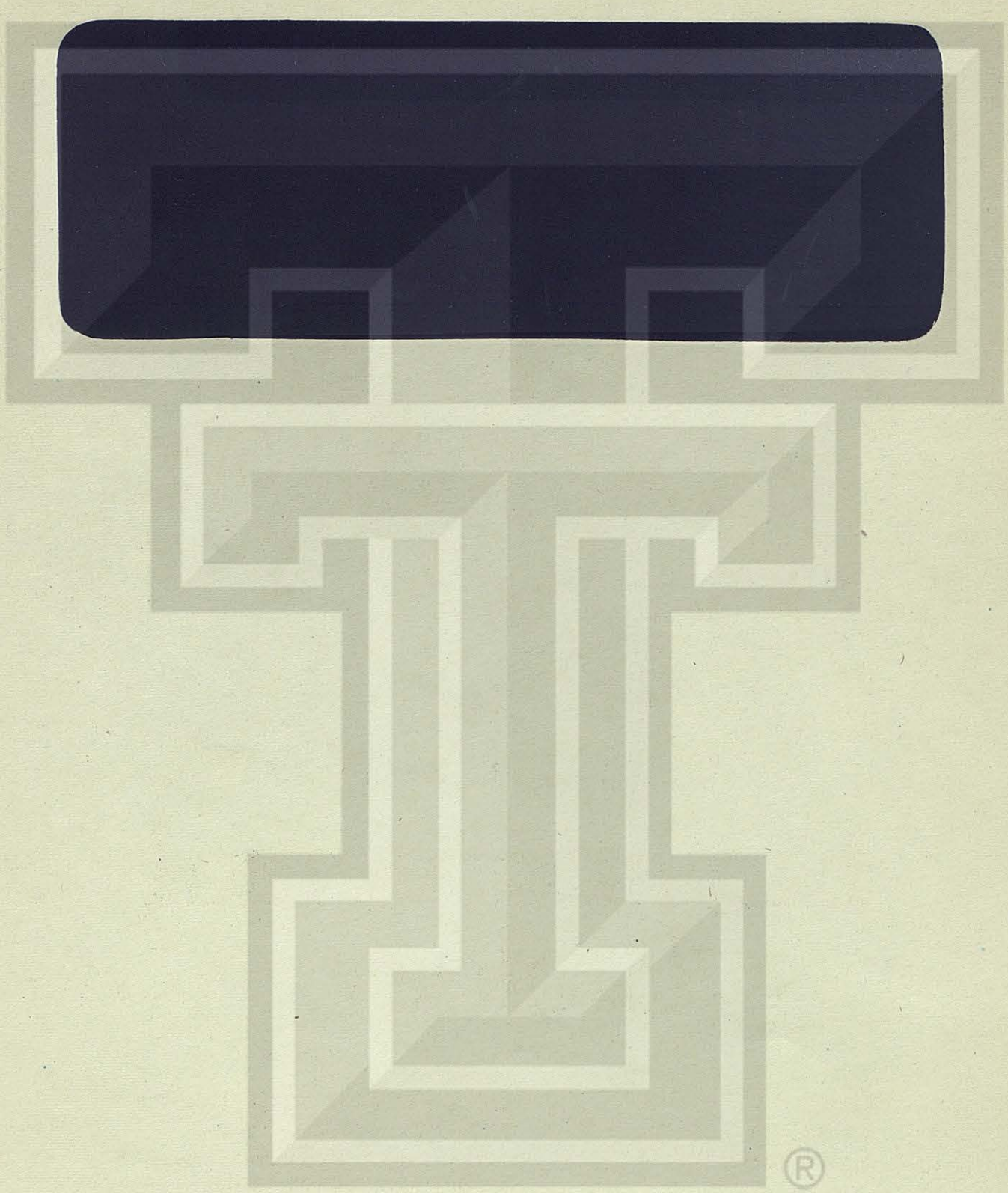
Reprinted From:

Selected Topics in

Environmental Biology

Edited by
B. BHATIA
G.S. CHHINA
BALDEV SINGH

Published by
INTERPRINT PUBLICATIONS
(Div. of Calendar Makers Corp.,)
Mehta House, 16A, Naraina, Phase II,
NEW DELHI–110028, INDIA



Chapter 61

Motion sickness in skylab astronauts

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In Skylab missions susceptibility to motion sickness was investigated under experimental conditions. Some crew members experienced motion sickness under operational conditions. The major findings in the first two missions dealing with motion sickness have been described (4). This report summarizes the findings obtained in all three missions.

METHODS

Astronauts. Table 61–1 summarizes findings in the 9 Skylab astronauts dealing with their susceptibility to motion sickness in different motion environments and their responses during tests of vestibular function. The SL II CDR had participated in the Gemini V mission and, along with the SL III CDR, took part in the Apollo 12 mission which included landing on the moon; symptoms of motion sickness were not experienced. Functional tests of the vestibular organs revealed no definite abnormality. A test (6) for grading susceptibility to motion sickness and yielding a single numerical score [Coriolis Sickness Susceptibility Index (CSSI)] was carried out. It was demonstrated prior to Skylab missions, however, that the scores obtained in this test do not predict susceptibility to motion sickness in the weightless phase of parabolic flight (7). Systematic studies of susceptibility to motion sickness in parabolic flight were not conducted on Skylab astronauts.

Stimulus conditions. Under operational conditions the astronauts made major transitions from land to orbital flight, to sea, and back to land. While aloft, transitions were made between the command module and the workshop and, during extravehicular activity, between the spacecraft and the outer environment. During re-entry there were variations in G-loading that terminated at splashdown, followed by transitions from the command module to the recovery aircraft carrier, and finally from the carrier to land.

Under *experimental conditions* [on and after mission day (MD) 8 aloft and on the ground] a stressful motion environment was generated by requiring the astronauts, with eyes covered, to execute head movements while in a rotating litter chair (RLC) (Fig. 61–1). The RLC could be revolved clockwise or counterclockwise at constant velocities up to 30 rpm. Each discrete head (and body) movement ("over" and "back") through an arc of 90 deg in each of the 4 cardinal directions (front, right, back, left, front) required one sec, and this was followed by a "hold" for one sec in the upright position. Head movements in the two orthogonal planes were made in sets of 5 (the forward movement was executed twice), and after each set the astronaut kept his head in the upright position for 20 sec.

Motion sickness endpoint. The diagnostic criteria for motion sickness used in the Skylab experiments are described in detail elsewhere (5). In brief, the severity of motion sickness symptoms was given a numerical score; 16 points and above comprised the range of "frank motion sickness." Under experimental conditions the diagnosis of acute motion sickness was aided by the close temporal relation between exposure to stressful stimuli and elicitation of responses. In

Table 61–1. HISTORY OF MOTION SICKNESS AND VESTIBULOMETRIC FINDINGS IN THE NINE ASTRONAUTS

SL	ASTRONAUT	AGE	HISTORY OF MOTION SICKNESS								CANAL FUNCTION		OTOLITH FUNCTION	CORIOLIS SICKNESS SUSCEPTIBILITY INDEX
			AIRCRAFT		OG MANEUVERS (NOT KC135)		SPACE FLIGHT		SEA MOD. TO HEAVY		CANAL THRESHOLDS OF RESPONSE	MODIFIED FITZGERALD-HALLPIKE PREPONDERANCE	OCULAR COUNTER-ROLLING	
			EXPERIENCE	SYMPTOMS	EXPERIENCE	SYMPTOMS*	EXPERIENCE	SYMPTOMS	EXPERIENCE	SYMPTOMS				
II	CDR	42	>2000 Hr	–	>100 TIMES	4	GEMINI V APOLLO XII	–	1-5 TIMES	SLIGHT	WITHIN NORMAL LIMITS	INSIGNIFICANT	158 LOW NORMAL	10.2
	SPT	40	>1000 Hr	–**	25-50 TIMES	4	NONE	NA†	1-5 TIMES	SLIGHT	WITHIN NORMAL LIMITS	INSIGNIFICANT	300 NORMAL	8.2
	PLT	40	>2000 Hr	–	>100 TIMES	2	NONE	NA	>100 TIMES	–	WITHIN NORMAL LIMITS	SIGNIFICANT (RETEST INDICATED)	374 NORMAL	19.8
III	CDR	40	>1000 Hr	–**	>100 TIMES	16‡	APOLLO XII	–	10-50 TIMES	SLIGHT	WITHIN NORMAL LIMITS	SIGNIFICANT (RETEST INDICATED)	365 NORMAL	23.1
	SPT	41	>1000 Hr	–	>100 TIMES	4	NONE	NA	>100 TIMES	MOD	WITHIN NORMAL LIMITS	INSIGNIFICANT	158 LOW NORMAL	26.4
	PLT	36	>2000 Hr	–	>100 TIMES	4	NONE	NA	5-10 TIMES	SLIGHT	WITHIN NORMAL LIMITS	INSIGNIFICANT	332 NORMAL	19.2
IV	CDR	40	>1000 Hr	–**	10-25 TIMES	16	NONE	NA	10-50 TIMES	SLIGHT	WITHIN NORMAL LIMITS	INSIGNIFICANT	494 NORMAL	7.5
	SPT	36	>1000 Hr	–**	>100 TIMES	8	NONE	NA	1-5 TIMES	SLIGHT	WITHIN NORMAL LIMITS	INSIGNIFICANT	261 NORMAL	8.9
	PLT	43	>1000 Hr	–**	>100 TIMES	8	NONE	NA	0	NA	WITHIN NORMAL LIMITS	INSIGNIFICANT	254 NORMAL	52.8

*MAXIMUM MALAISE LEVEL
**MILD SYMPTOMS ON RARE OCCASIONS
† NOT APPLICABLE
‡ EMESIS

all Skylab experiments the motion sickness endpoint, moderate malaise (MIIA) having a point score of 5 to 7, was of very mild intensity; the avoidance of more severe symptoms was an operational requirement. In the absence of a motion sickness endpoint the ceiling on the test was reached after 150 head movements were executed.

Drugs. The astronauts in SL II and SL III carried with them antimotion sickness (AMS) capsules containing I-scopolamine 0.35mg + d-amphetamine 5.0 mg; in addition to this drug the SL IV crew took along the drug combination promethazine hydrochloride 25 mg + ephedrine sulfate 50 mg, drugs which had proven to be effective under experimental (10) and operational conditions. This drug combination acts by raising the stimulus thresholds for eliciting motion sickness responses and is effective in any motion environment. Indeed, preflight bioassay tests were carried out on all 6 astronauts, and endpoints were not reached even at maximal angular velocities.

RESULTS AND DISCUSSION

It is convenient to present the findings dealing with motion sickness first under "operational conditions" and then under "experimental conditions."

Operational conditions. Attention will be centered on motion sickness during the orbital phase of the mission and will be discussed with the aid of Fig. 61–2. The horizontal lines reflect 2 things. First, the periods during which the astronauts were based in the command module and in the workshop during the first wk in orbit. Second, the thickness and continuity of the lines indicate the onset and probable disappearance of symptoms of motion sickness. The vertical lines indicate when an AMS drug was taken and its composition. The administration

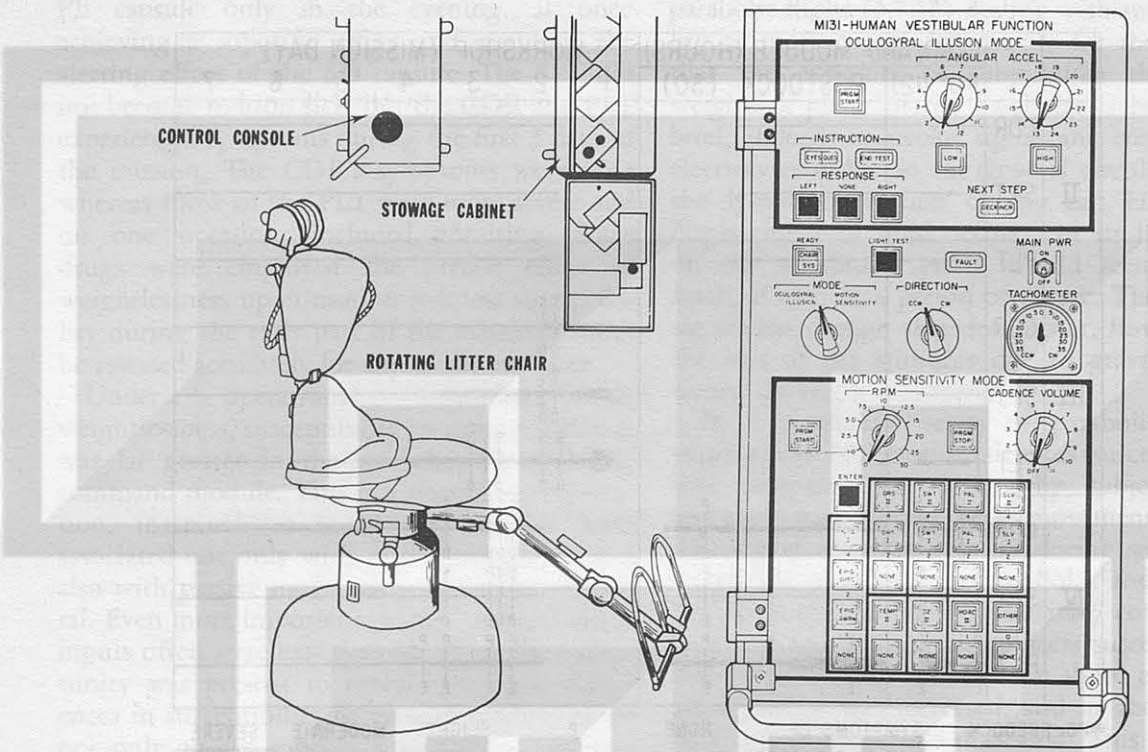

FIG. 61–1. The rotating litter chair (RLC), motion sickness test mode and console.

of drugs increases the difficulty of diagnosing motion sickness, hence, accuracy in diagnosis is greater in the absence of drug effects.

In Fig. 61–2 it is seen that none of the SL II crewmen was motion sick aloft. The CDR who had not experienced motion sickness during the Gemini V and Apollo XII missions was, in all likelihood, the least susceptible to motion sickness among the 9 Skylab astronauts. He never took an AMS drug and was symptom-free under all conditions. The SPT had arranged long before liftoff to take an AMS capsule after insertion into orbit. It is noteworthy that both the CDR and SPT reported that while engaged in spinning rapidly about their long axes or "running" around the inside of the workshop, they experienced immediate reflex vestibular side effects, mainly "false sensations" of rotation. Based on past experience, both astronauts expected that motion sickness would follow the reflex effects and were surprised by their immunity. The SL II PLT did not take an AMS drug aloft. He was not motion sick, although he was aware of illusory phenomena.

The fact that all of the SL II crewmen were symptom-free indicates that either there was never a need to adapt or that adaptation was achieved asymptomatically by means of an unprogrammed adaptation schedule. The need to adapt in the case of the CDR may not have been present, viewed in the light of his past experiences in space flight. It is certainly possible that the SPT and the PLT needed to adapt, especially to stimulus conditions in the workshop. Assuming that they needed to adapt to conditions in the workshop then the adaptation effects acquired under the less stressful circumstances when based in the command module must have transferred to the more stressful conditions in the workshop. There is the further implication that the period required to acquire adaptation in the command module was briefer than the period during which symptoms were present in all astronauts who became motion sick aloft.

The SL III astronauts were quite confident before their mission that they would not become motion sick in weightlessness and did not take AMS drugs as a preventive measure. The PLT, however, experienced mild symptoms of motion sickness within an hour after insertion into orbit. During launch he wore a space

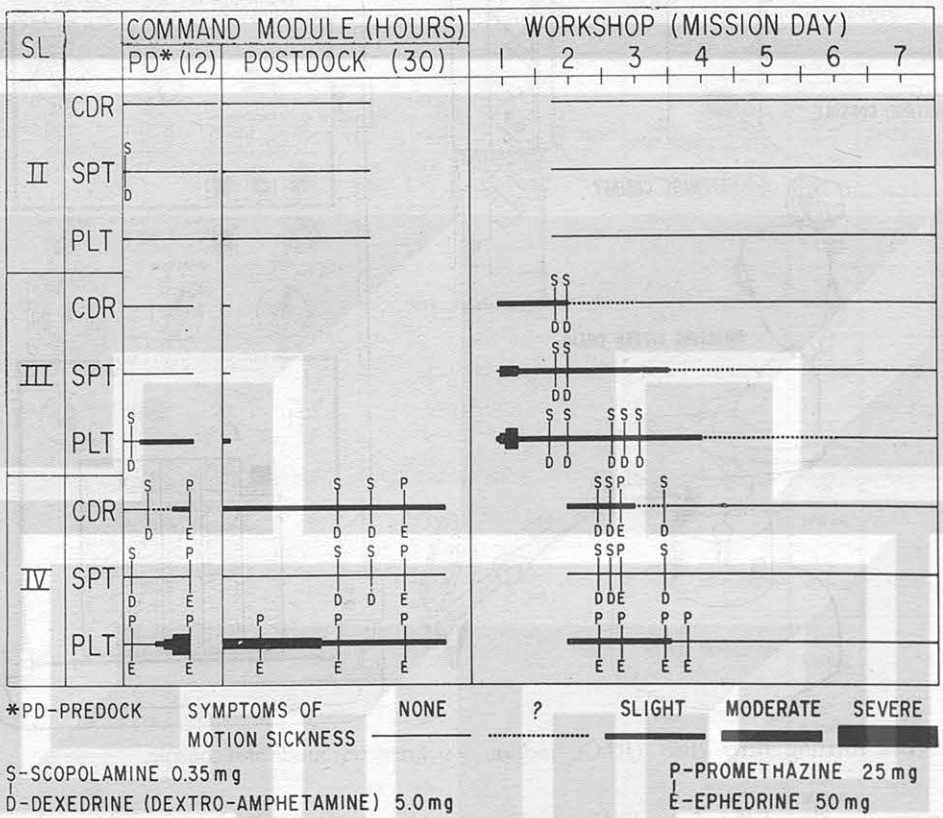

FIG. 61–2. Motion sickness under operational conditions.

suit and helmet (as did the other crewmen). He was not aware of any illusory phenomena on transition into zero gravity. Shortly after transition he removed his helmet and soon thereafter his space suit. It was in close relation to taking off the suit that the first symptoms of motion sickness were experienced. He took an AMS capsule that relieved his symptoms for a few hours. Later, symptoms returned and he restricted his activities; he deliberately avoided, however, taking another AMS capsule while based in the command module. The clear relation between the SL III PLT's activities and symptoms and the relief following administration of the AMS capsule support the diagnosis of motion sickness, the earliest diagnosis of this functional disorder among space crewmen on record. Subsequently, after transition into the workshop, symptoms included nausea and vomiting and treatment included restriction of activity and the use of AMS drugs. Symptoms persisted for 4 or 5 days. On MD 7 he had "fully recovered." In brief, the SL III PLT demonstrated high susceptibility to motion sickness after transition into orbit and adaptation was not achieved earlier than MD 4.

The SL III CDR and SPT were symptom-free while based in the command module but during the activation of the workshop, about 11 h into the flight, both experienced the onset of motion sickness. It is self-evident that stimulus conditions must have been more stressful in the workshop than in the command module. Moreover, it is a reasonable inference that whatever adaptation was acquired in the command module was inadequate to ensure immunity in the workshop. On MD 4 regular working hours were resumed, although recovery was incomplete.

The SL IV crew, as a result of the incidence of motion sickness among the SL III crew, made preparations to take AMS drugs throughout the early days of the mission. They were given a choice between 2 preparations, namely, scopolamine 0.35 mg + dexedrine 5.0 mg (SD) or promethazine 25 mg + ephedrine 50 mg (PE). In Fig. 61–2 it is seen that the PLT chose the PE capsule while the CDR and SPT took the

PE capsule only in the evening, at once achieving a soporific effect and avoiding the alerting effect of the SD capsule. The SPT did not become motion sick, but the CDR and PLT experienced symptoms during the first 3 days of the mission. The CDR's symptoms were mild whereas those of the PLT were more severe and on one occasion included vomiting. Since drugs were employed the precise effect of weightlessness upon motion sickness susceptibility during the early part of the mission cannot be assessed accurately for any of the crewmen.

Under operational conditions in weightlessness, susceptibility to motion sickness was far greater in the workshop than in the command module. This is a reasonable expectation, inasmuch as accelerative stimuli were associated not only with active movements but also with passive movements that were unnatural. Even more important, highly unusual visual inputs often were experienced. Thus, the opportunity was present to reveal individual differences in susceptibility to motion sickness based not only on the motion environment but also on unusual interacting vestibular and visual stimuli.

General agreement is lacking whether zero gravity should be regarded as simply another stressful motion environment with its own distinctive or unique features or if, on transition into weightlessness, a person experiences pathophysiological alterations that have a direct or indirect influence, especially on the vestibular system. Alterations such as cardiovascular adjustments, redistribution of body fluids and changes in electrolyte balance that might affect susceptibility to motion sickness, either via the vestibular system or more indirectly, are at various stages along their time course immediately after transition into zero gravity (9,11,13). Among the possibilities just mentioned, headward shift of fluid is the only etiological factor that could be effective within a matter of minutes, and then its role would be limited to that of a predisposing factor. Only if symptoms of motion sickness are elicited while the head remains fixed would it be possible clearly to distinguish between a so-called "vestibular storm" (similar to labyrinthitis caused by disease or injury) or the effects of an eliciting stimuli associated with activity.

It is relevant to mention here the findings in parabolic flight (2,7,12) dealing with susceptibility to motion sickness, mainly for the reason that the exposure of subjects to the near-weightless phase of the parabolas is brief, too brief, indeed, to evoke significant changes in electrolytes either in the general circulation or the lymph circulation of the ear. Headward displacement of fluid occurs, but its influence on the vestibular system would seem to be small, if any, in a period of 25 sec. The highly significant change that does occur, however, is the loss of the stimulus due to gravity mentioned above.

In a systematic series of parabolic flight experiments (7) motion sickness susceptibility was compared in 74 healthy subject who executed standardized head movements while rotating at constant velocity during sequential weightless phases of the parabolas and during periodic exposures under laboratory conditions. In about one-fifth of the subjects susceptibility was approximately the same; in about one-third susceptibility was increased, and in about one-half susceptibility was decreased. This decrease in susceptibility was substantial and in 15 of the 35 subjects motion sickness endpoints were not reached.

Prior to Skylab missions American astronauts did not report motion sickness in orbit (1) until the Apollo missions; the incidence was 36% (9 among 25). Among 24 cosmonauts 4 experienced motion sickness aloft, an incidence of about 17% (13).

All these findings strongly suggest that some persons, at least, do not need to adapt to weightlessness per se and that some persons do need to adapt.

Motion sickness susceptibility under experimental conditions. The findings in the SL II mission (Fig. 61–3) demonstrate that the SPT and PLT (the CDR did not participate) were less susceptible to motion sickness when they executed head movements during rotation aloft than when they did so on the ground. Preflight, on 3 widely separated occasions, the M II A endpoint was consistently elicited after 30 to 60 head movements while those astronauts were being rotated at 12.5 rpm (SPT) or 15 rpm (PLT). When rotation tests were carried out in the workshop, both of these astronauts were virtually symptom-free at the end of every test. Postflight there was no significant change in the

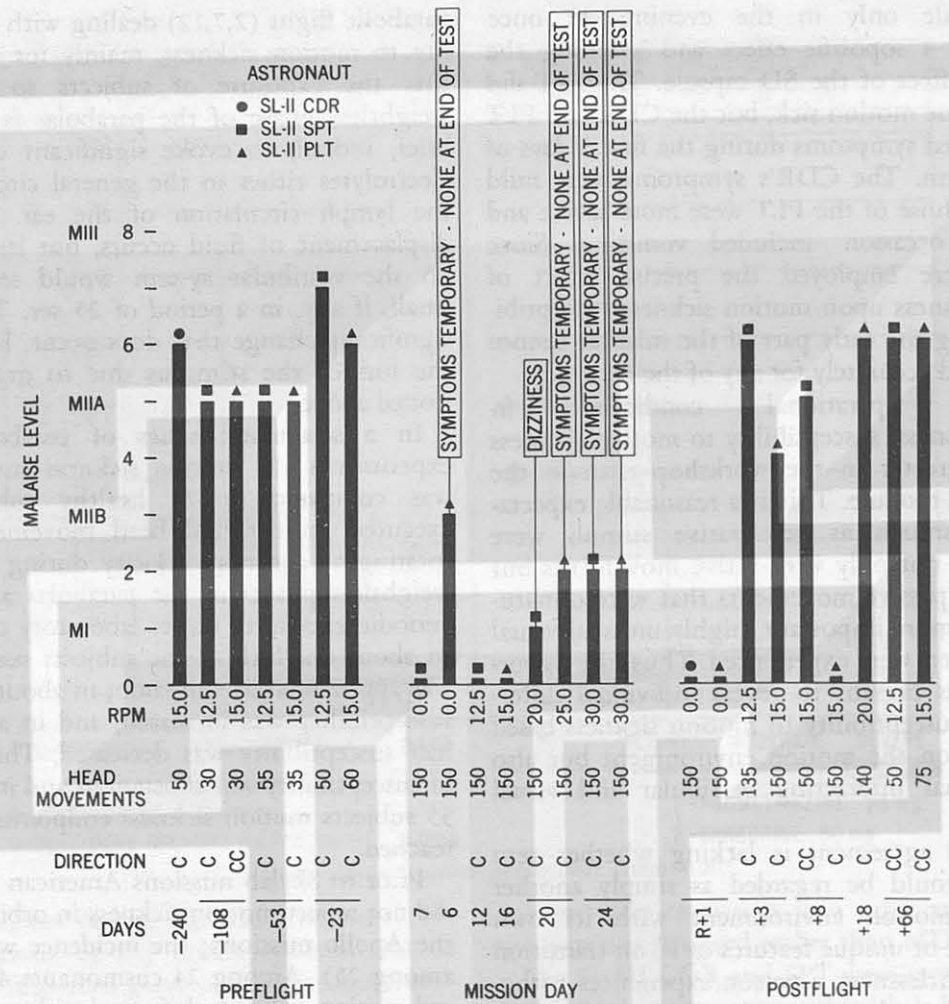

FIG. 61–3. Motion sickness symptomatology on SL II astronauts quantitatively expressed in terms of malaise level, as evoked by the test parameters (rotational velocity, number of head movements, and direction of rotation) used before, during, and after the SL II mission.

susceptibility of the SPT to motion sickness compared with preflight, and for the PLT, no significant change on recovery day +3 (R+3). The decrease in susceptibility manifested by the PLT on R+8 appears to be merely a temporary change in his susceptibility, since his preflight scores were again approximated at R+18 and R+66. These clear-cut findings indicate that under the experimental conditions the SL II crewmen were less susceptible to motion sickness in the workshop than on the ground.

The findings in the SL III mission are summarized in Fig. 61–4. It can be seen that all 3 of the astronauts were virtually immune to experimental motion sickness aloft and that their susceptibility was lower, at least temporarily, postflight than preflight. The rotation ceiling, 30 rpm, was tested earlier in the SL III crewmen than in the SL II crewmen. In the case of the SPT and PLT susceptibility to motion sickness was, probably, slightly lower during the first wk postflight than it was 10–12 days preflight.

The findings in the SL IV crewmen are summarized in Fig. 61–5. Preflight, the ceiling on the test was closely approached in the case of the CDR and PLT and nearly reached in the case of the SPT. In the workshop the ceiling of the test was quickly reached without eliciting any symptoms of motion sickness. In view of this immunity a change in the procedure was instituted. A bidirectional test procedure was used on MD 73 and 75; at the end of a regular

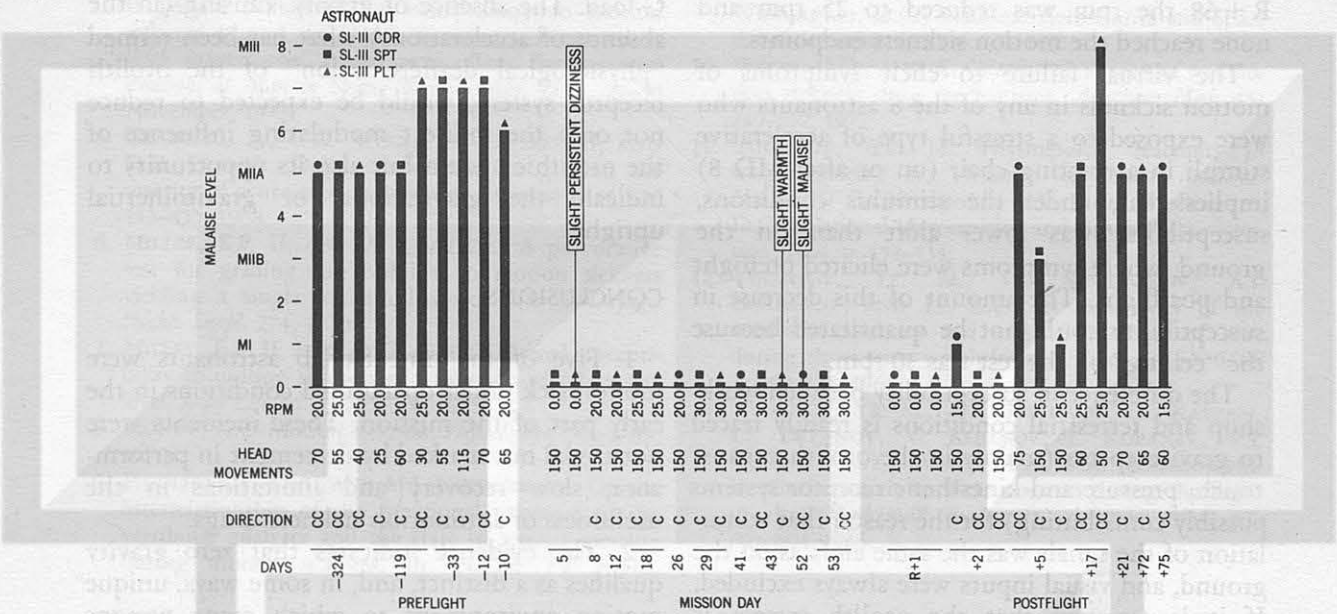

FIG. 61–4. Motion sickness symptomatology on SL III astronauts quantitatively expressed in terms of malaise level, as evoked by the test parameters (rotational velocity, number of head movements, and direction of rotation) used before, during, and after the SL III mission.

test the astronauts were immediately exposed to rotation in the opposite direction. The absence of symptoms after reversing the direction of turn indicated that the astronauts not only were immune but also that adaptation effects had not been acquired (3). Test conducted postflight on R+1, R+2, and R+5 revealed either very mild symptoms or immunity; the motion sickness endpoint was not reached. On R+17 the PLT reached the motion sickness endpoint. On R+31 both the PLT and SPT reached endpoints and the CDR scored 3 points. On

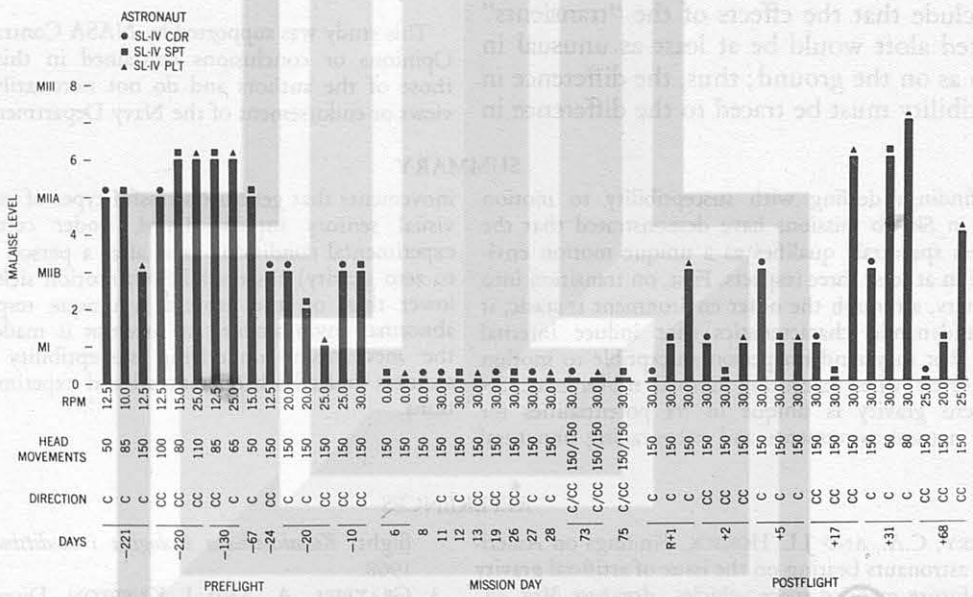

FIG. 61–5. Motion sickness symptomatology on SL IV astronauts quantitatively expressed in terms of malaise level, as evoked by the test parameters (rotational velocity, number of head movements, and direction of rotation) used before, during, and after the SL IV mission.

R + 68 the rpm was reduced to 25 rpm and none reached the motion sickness endpoints.

The virtual failure to elicit symptoms of motion sickness in any of the 8 astronauts who were exposed to a stressful type of accelerative stimuli in a rotating chair (on or after MD 8) implies that, under the stimulus conditions, susceptibility was lower aloft than on the ground, where symptoms were elicited preflight and postflight. The amount of this decrease in susceptibility could not be quantitated because the "ceiling" on the test was 30 rpm.

The difference in susceptibility between workshop and terrestrial conditions is readily traced to gravireceptors (mainly in the otolith organs; touch, pressure and kinesthetic receptor systems possibly contributing) for the reason that stimulation of the canals was the same aloft as on the ground, and visual inputs were always excluded. If it is assumed that the otolith system is responsible, then the absence of stimulation to the otolithic receptors due to gravity must have a greater influence than the influences of the transient centrifugal linear and Coriolis accelerations generated when head and trunk movements were executed in the RLC. These transient accelerative forces at 30 rpm are substantial, and their repetitive pattern is a characteristic that tends to elicit motion sickness through summation or cumulation (8). It is reasonable to conclude that the effects of the "transients" generated aloft would be at least as unusual in pattern as on the ground; thus, the difference in susceptibility must be traced to the difference in G-load. The absence of gravity, causing (in the absence of accelerations) what has been termed "physiological deafferentation" of the otolith receptor system, would be expected to reduce not only the indirect modulating influence of the otolithic system but also its opportunity to indicate the gravitational or gravitoinertial upright.

CONCLUSIONS

1. Five of the nine Skylab astronauts were motion sick under operational conditions in the early part of the mission. These incidents were not trivial but marked by decrement in performance, slow recovery and limitations in the usefulness of antimotion sickness drugs.
2. The evidence indicates that zero gravity qualifies as a distinct, and, in some ways, unique motion environment to which many persons must adapt.
3. In an experiment designed to compare susceptibility to motion sickness aloft (on or after mission day 8) with susceptibility preflight and postflight all of the 8 astronauts tested (with eyes covered) were symptom-free at the end of the tests conducted aloft. The decrease in susceptibility is explained on the basis of the zero gravity state but prior adaptation to weightlessness is a precondition.

This study was supported by NASA Contract T–81633. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

SUMMARY

The findings dealing with susceptibility to motion sickness in Skylab missions have demonstrated that the weightless spacecraft qualifies as a unique motion environment in at least three respects. First, on transition into zero gravity, although the outer environment is static, it has quasidynamic characteristics that induce internal changes that may render a person susceptible to motion sickness even when executing normal movements. Second, zero gravity is unique in its potentialities for limiting natural movements and encouraging unnatural movements that generate stressful types of vestibular and visual sensory inputs. Third, under certain specific experimental conditions (and after a person has adapted to zero gravity) susceptibility to motion sickness aloft is lower than on the ground, a unique response in an abnormal environment. An attempt is made to explain the mechanisms underlying susceptibility to motion sickness under both operational and experimental conditions.

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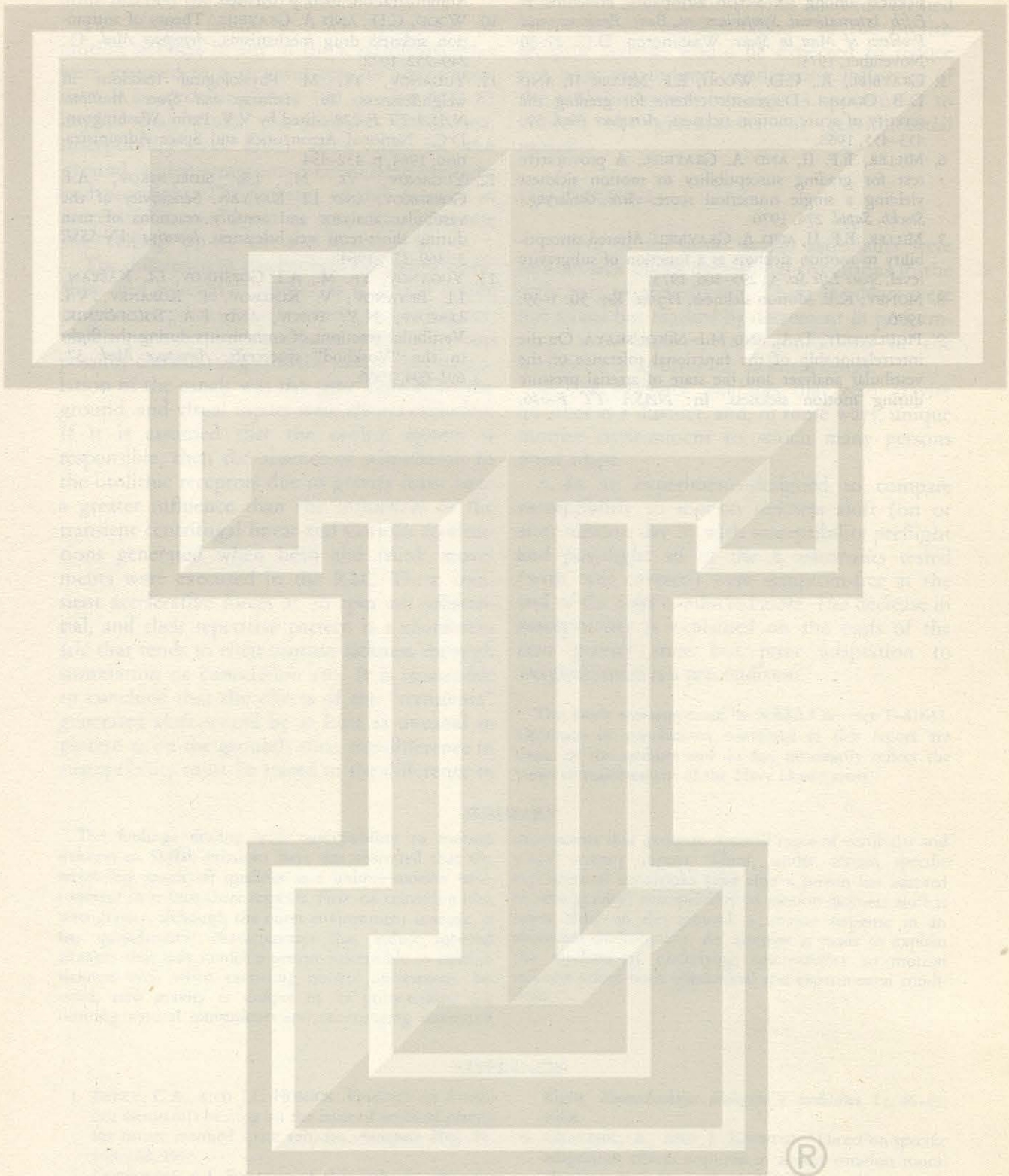

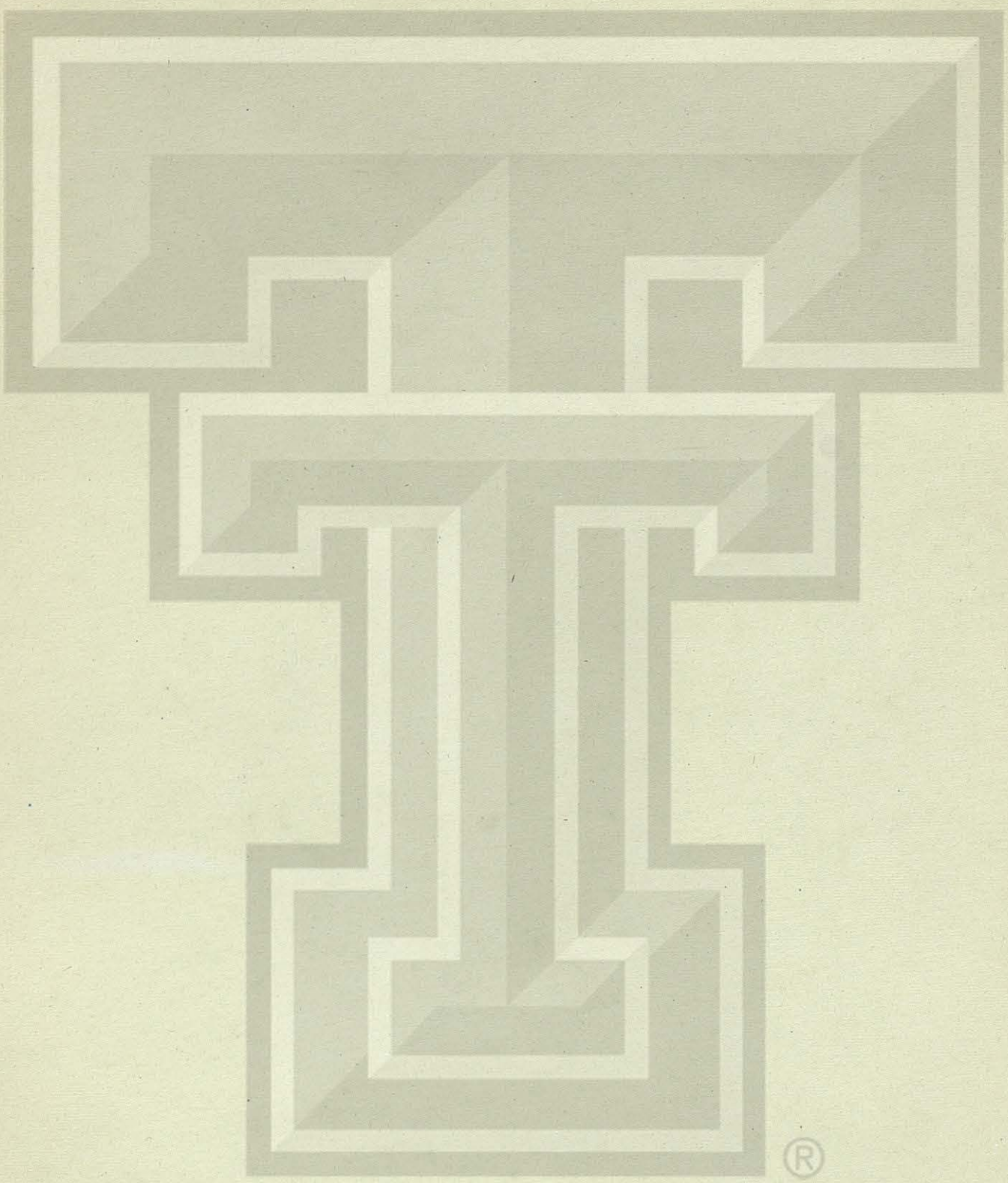

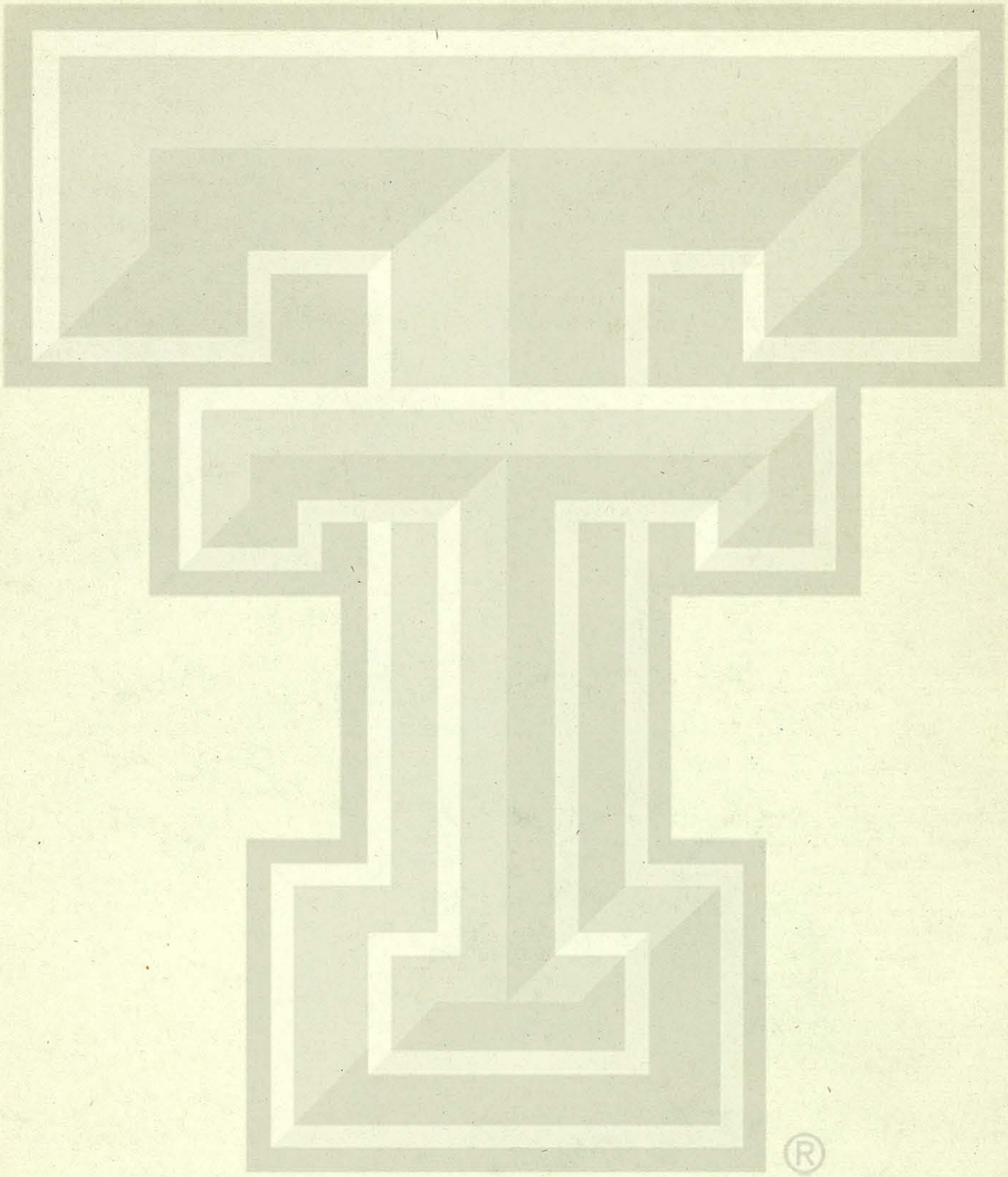

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Parameters for assessing vibration-induced cardiovascular responses in awake dogs

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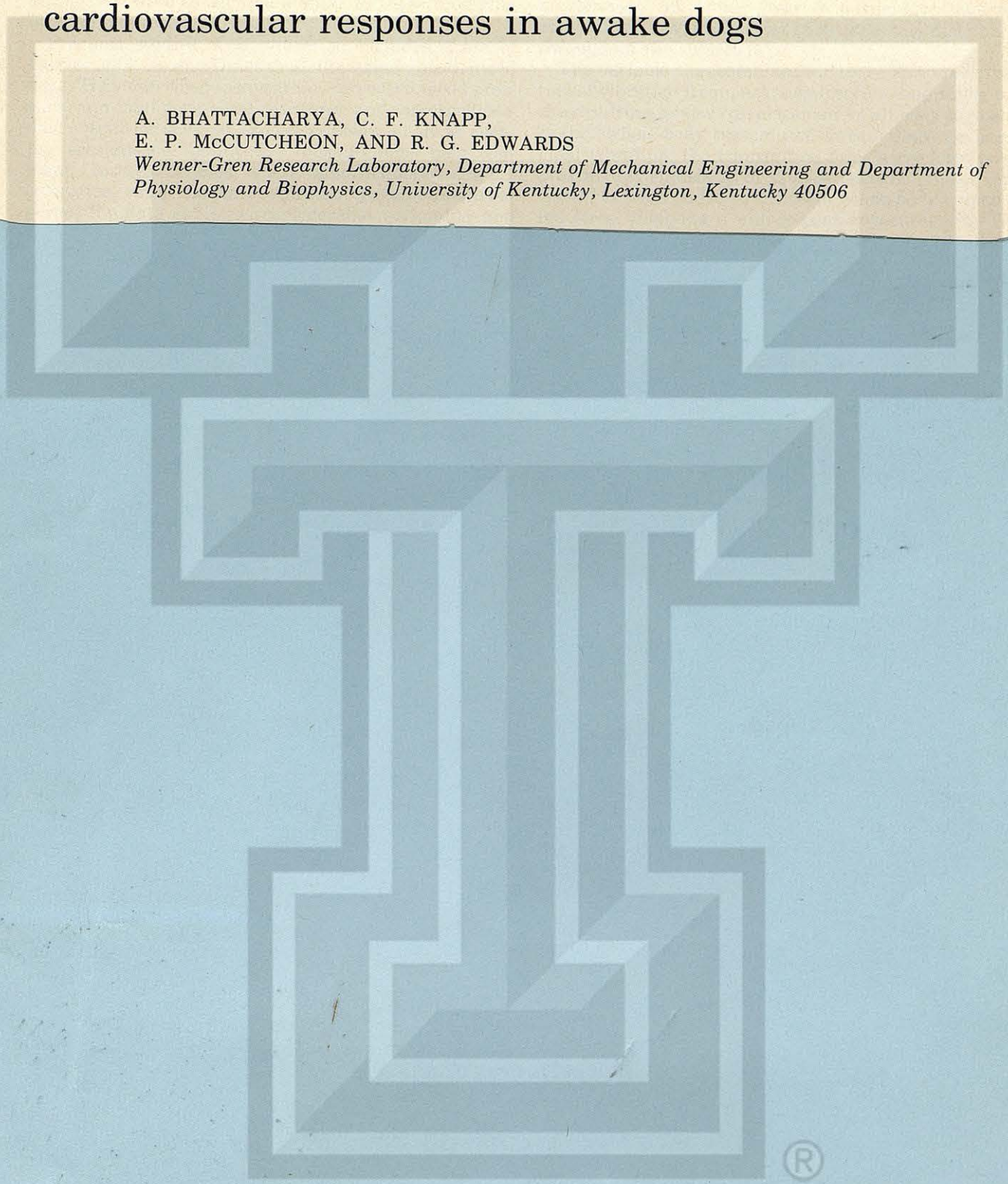

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BHATTACHARYA, A., C. F. KNAPP, E. P. McCUTCHEON, AND R. G. EDWARDS. *Parameters for assessing vibration-induced cardiovascular responses in awake dogs*. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 42(5): 682–689, 1977. – The vibration parameters for assessing the response of the cardiovascular system to whole-body vibration were studied. Six awake, chronically instrumented canines were restrained with their spines vertical, and exposed to G_z sinusoidal vibration of 2–12 Hz for a constant peak acceleration amplitude of ±1.0 G. Vibration exposures of 30 s with intervening recovery periods of 2 min were employed. The following variables were measured: mean heart rate (MHR), stroke volume (SV), mean aortic flow (MAF), mean aortic pressure (MAP), the peak net force transmitted to the canine/body weight (PNF/BW), and the vibration platform frequency (f_i), displacement, and acceleration. The percentage change from control (no vibration) of MAF varied linearly with PNF/BW for all cases. MAF also varied linearly with the log MHR/f_i for the number of dogs which primarily changed MHR during the vibration exposures. The response of MAP was minimal in all cases, indicating a decrease in total peripheral resistance with increasing PNF.

circulation; blood flow; blood pressure; heart rate; awake chronically instrumented canines; force transmission; biomechanics; acceleration physiology

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THE PHYSIOLOGICAL RESPONSES of subjects exposed to whole-body vibration can be classified into two major types. One category includes physiological changes produced directly by the applied, time-varying acceleration as a function of the biomechanical properties of the body. This category includes the reactions of the musculoskeletal, large body organ, and the fluid-vessel systems as determined by their mass, elastic, and damping characteristics. The second category includes the changes produced by compensatory or adaptive adjustments to the biomechanical stresses resulting from the vibration exposure. In this category are included the various neural, hormonal-metabolic, and hematologic feedback adjustments.

The cardiovascular system is of particular interest in understanding the physiological effects of vibration because this system is extremely susceptible to the inertial forces resulting from acceleration. The fluid columns contained in the long, large, elastic vessels are especially affected by vibration. The tendency of the heart to move with relative freedom about the axis of its attachment to the aorta and the ballistic components of its contraction pattern also make it susceptible to vibration stress. Such perturbation in the hydraulic circuits of the cardiovascular system initiate multiple feedback mechanisms which tend to minimize the disturbances.

Studies (2, 3, 6, 8) to quantify the response of the cardiovascular system to whole-body vibration have often yielded inconsistent and confusing results. Part of this problem was due to the limited description of the vibration function forcing the physiological system. The purpose of this study was to define the vibration parameters, or combination of parameters that show the best correlation with the cardiovascular responses to vibration stress. Standardization of the vibration parameters is essential for meaningful comparison between studies. It is also necessary for effective evaluation of those aspects of whole-body vibration which may produce a health hazard as opposed to those aspects which have potential therapeutic and diagnostic implications, e.g., an exercise substitute for assessing cardiovascular risk factors.

BACKGROUND

Early studies of the integrated cardiovascular response of dogs to vibration were conducted by Hood and Higgins (6). Anesthetized dogs were restrained supine in a form-fitting metal frame and vibrated in the G_x axis (anteroposterior) at selected frequency and acceleration levels. They found no correlation between the cardiovascular response and the frequency or duration of the vibration exposure, but cardiac output and other representative variables increased with increasing acceleration amplitude. The increased cardiac output was obtained mainly through increased heart rate.

Similar results for dogs and humans were reported by Clark et al. (2). They measured the cardiovascular responses of anesthetized dogs restrained horizontally and humans restrained vertically. Both were exposed to brief periods of vibration through the G_x axis of the body. Exposure durations of 90 s at 1 and 2 G acceleration levels for selected frequencies produced initial transient decreases in arterial blood pressure, with increased heart rate and constant stroke volume. As an explanation of the initial drop in average arterial pressure, they suggested that displacement of the dog's thor-

acoabdominal organs, due to resonance, stimulated mechanoreceptors in the hollow viscera and mesentery which caused a decrease in peripheral resistance. The alterations were considered similar to those occurring with mild exercise.

Previous studies of G_z vibration included those of Hoover et al. (8) and Dines et al. (3), using anesthetized dogs. They described tachycardia, decreased blood pressure, and total peripheral resistance and increased cardiac output for selected exposures below 10 Hz at varying acceleration amplitudes (displacement held constant). In these studies, where table frequency and acceleration were the only vibration parameters measured, the data exhibited considerable variability and poorly defined trends.

Edwards et al. (4) used chronically instrumented, anesthetized canines restrained vertically and exposed to G_z vibration. Phasic flows in the aorta and the carotid and femoral arteries were measured. They reported that the magnitudes of the changes, in extrema, for both pressure and flow were proportional to acceleration amplitude for any given frequency, with maximal effects occurring in the range of 3–9 Hz. They also reported that maximal peak net transmitted force corresponded to the same 3–9 Hz range. Thus, the greatest effects in phasic pressure and flow wave forms generally occurred when force transmission was highest. However, no effort was made to analyze the influence of the transmitted force in producing changes in the mean values of the cardiovascular variables, e.g., cardiac output.

In general, the vibration parameters measured by previous investigators (2, 6, 7) have not adequately defined the forcing function to the cardiovascular system. Thus, considerable confusion exists when results from different studies are compared. To help clarify this confusion, discussions of the vibration forcing function to the physiological system may be in order.

Vibration is characterized by its frequency, displacement, velocity, acceleration, and wave form. While values of these parameters may be used to describe the vibration applied by the moving platform to the subject, the same values may not necessarily describe the response of the subject as a whole or its individual parts. Consider, for example, a subject exposed to whole-body vibration of 4 Hz at 1 G_z (x_0 = 1.55 cm, where x_0 is the zero-to-peak platform displacement). A massless accelerometer on the heart may measure 2.5 G_z. Similarly, an accelerometer on the head might measure 2 G_z (x_0 = 3.10 cm), with a phase shift and wave form not only different from that of the platform but also from that measured on the heart. The responses of these two body segments are determined by the mass, elastic, and damping characteristics of the musculoskeletal frame through which the force from the platform is transmitted, the attachment of the segment in question to the frame, and the segment itself. In each application of the vibration stress, a force is transmitted through the points of contact between the subject and vibration platform; propagating through the musculoskeletal system, being modified as it progresses; and producing a forced disturbance to the internal organ and vascular system, which in turn elicits neural and hormonal feedback mechanisms. Thus, it is important to realize that the transmitted force is not a constant for a fixed platform acceleration amplitude over a particular frequency range (body resonance), nor is it uniformly distributed throughout the subject (11).

The variable that combines the three mechanical factors of vibration frequency, acceleration amplitude, and the resulting relative displacement of all body segments is the "whole-body transmitted force." Since for sinusoidal vibration, the transmitted force wave form is approximately sinusoidal or at least periodic (4), the term "peak" is often added to the term whole-body transmitted force, implying a null-to-peak measurement. This variable reflects the net integrated effects of the forces applied to the various segments of the physiological system and could serve as one of the best indices of vibration stress for correlation with the response of the cardiovascular system. Based on this reasoning, the study described below places primary emphasis on the relationship of peak net transmitted force to selected cardiovascular responses. Attention is also given to the time relationship between the vibration and cardiac cycles as another index of the response of the cardiovascular system to vibration.

METHODS

The response of the cardiovascular system to vibration stress, as measured by mean aortic pressure and flow, was studied in six chronically instrumented, unanesthetized canines (weight: 151.0–202.0 N). Use of the chronically implanted preparation was emphasized since it allowed comparison of repeated, awake tests on the same animal. Another very important advantage of the preparation is the greatly enhanced transducer stability, especially important for the vibration environment.

Instrumentation. A variety of methods have been developed to measure blood pressures and flows after recovery from surgical implantation procedures. The instrumentation characteristics and surgical techniques used in this study will be summarized briefly; detailed descriptions can be found in (16).

An electromagnetic flowmeter system (Biotronex BL-610 meter used with Biotronex or Zepeda transducer) was utilized for continuous measurement of ascending aortic flow (approximates cardiac output). Aortic flow was calibrated by comparison to repeated indocyanine green dye-dilution determinations of cardiac output (Waters densitometer) through implanted catheters. Aortic arch pressure was measured either chronically using a Konigsberg P-21 aspirin-type pressure gauge implanted through the subclavian artery, or acutely, using a manometer-tipped Millar PC-350 gauge inserted under local anesthesia through a femoral artery.

Surgical technique. The principles of laboratory care as outlined by the National Society for Medical Research were rigorously observed. Preoperative management included thorough clinical evaluation, with chest X ray and hematologic data obtained routinely.

The surgical procedures were performed aseptically in the experimental surgery facilities of the University of Kentucky Medical Center. Thoracic implantations were made through an incision in the left fourth intercostal space. After dissection from its attachments, the base of the ascending aorta was reinforced with nylon curtain material to promote fibrotic tissue growth. This growth provided support to the vessel wall as well as effective cushioning between the vessel and the transducer. The aortic pressure gauge was located snugly against the intimal surface of the vessel wall. Tolerance to this placement was greatly enhanced by a thin layer of silicone rubber poured over the backing of the transducer case prior to sterilization. Wires were exteriorized into a specially designed subcutaneous nylon velour pouch (15). It allowed access to the leads whenever desired without the need for local anesthesia or dissection. The thoracic incision was closed in layers and the animal allowed to recover.

Postoperative management included antibiotic coverage and particularly careful attention to nutritional, hematologic, and urinary factors in addition to overall clinical evaluation. Studies were not done unless and until these factors were stable at values indicating a satisfactory state of health. The duration of postoperative recovery routinely exceeded 2 wk; usually 3 wk or more elapsed before studies were instituted.

Effects of vibration on transducer stability. The vibratory input, as used here, is associated with severe movement of the various internal body organs and blood vessels. Hence cardiovascular transducers used to measure blood flow and blood pressure in a vibration environment should be sturdy and light weight, and securely attached to the blood vessel, to avoid artifacts due to relative movement of the transducer with respect to the walls of the vessel. To avoid such artifacts, chronic implants were used and transducer stability checked. To check the stability in the vibration environment, the responses of the chronically implanted animals, initially tested awake and then killed, were compared for the same vibration input. Results from one such test are shown in Fig. 1. It is evident that the effects of the vibration-induced, relative movement of the transducer with respect to the vessel wall are negligible.

Vibration exciter. The vibration exciter used for this study was designed and constructed by Sharp (18) and is located in the Wenner-Gren Research Laboratory, University of Kentucky. This system is driven hydraulically in a sinusoidal mode and can develop maximal displacement of 25 cm peak to peak, frequencies to 80 Hz, peak velocity of approximately 200 cm/s, peak acceleration at zero-added load to 12 G, and maximal force of 9,900 N if required. The usual wave form for these studies was sinusoidal, but a wide variety of other wave forms was available.

A custom-designed restraint chair in conjunction with load cells located immediately under the seat provided a signal proportional to the total transmitted force of the animal and chair. An adjacent accelerometer produced an output proportional to that component of the total force due only to the inert mass of the animal chair. Electrical subtraction of the accelerometer signal from that of the load cells yielded the "live load" force transmission, i.e., only the force transmitted to the animal.

General experimental protocol. The unanesthetized dogs were placed in the restraint chair which was initially horizontal. Noninvasive sensors (ECG, rectal temperature) were attached, and the implanted transducer leads were connected. The restraint chair was rotated to the vertical position and placed on the vibration exciter. Dogs were exposed to sinusoidal vibration (G_z) of 2-12 Hz for a constant acceleration amplitude of ±1.0 G for 30 s with intervening rest periods of 2 min. A schematic of the experimental arrangement is shown in Fig. 2.

Cardiovascular measurements were: mean heart rate (MHR, in beats/min or Hz); ascending mean aortic flow (MAF, equivalent to cardiac output less coronary flow, in l/min); and mean aortic pressure (MAP, in Torr). Total peripheral resistance (TPR = MAP/MAF, in (Torr · min/ml), and left ventricular stroke work (SW = SV × MAP, in Nm) were derived variables. Pertinent biomechanical variables, in addition to duration and table frequency (f_t, H_z), included vibration table displacement, acceleration, and peak net force transmitted at the interface of the dog and the vibration table (PNF, in N). Data were recorded on strip-chart and analog tape recorders (Beckman, Hewlett-Packard), and processed manually and automatically by computer (Raytheon 704, IBM 1800 and 360).

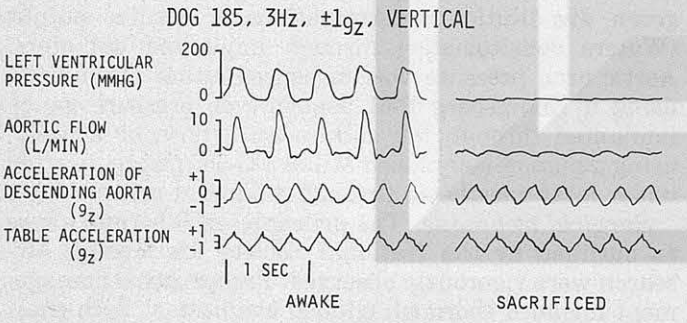

FIG. 1. Response of chronically implanted instrumentation to sinusoidal vibration (animal awake and killed).

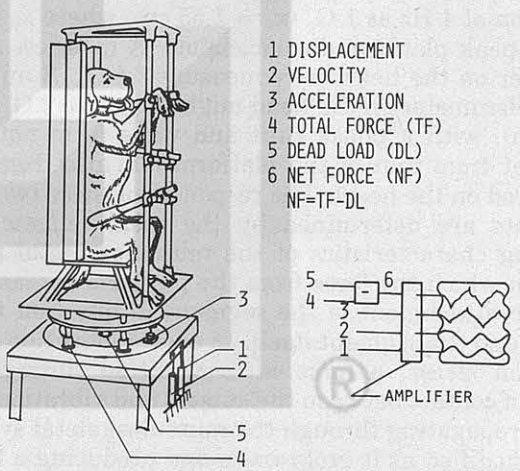

FIG. 2. Schematic of experimental arrangement for vibration along spinal axis of the animal (G_z).

RESULTS

In this study, meaningful vibration parameters or combinations of parameters were sought which could be used as indices for assessing the response of the cardiovascular system to vibration stress. MAF was chosen as the primary physiological variable of interest in this study. A dimensional analysis of the variables defining the present problem was employed to obtain dimensionless parameters for representing the experimental data. Dimensional analysis is an accepted tool (5, 13) producing generalized parameters which are independent of physical dimensions and, oftentimes, independent of the special experimental conditions. The degree of interdependence of physiological subsystems tends to limit the effectiveness of the analysis technique. However, as will be shown later the application of dimensional analysis provided better understanding of the phenomena involved, and improved the correlation coefficients of the functional relationships.

For a constant acceleration amplitude, changes in mean aortic flow due to mechanical vibration (MAF_v) can be expected to be a function of mean stroke volume (SV), mean heart rate (MHR), forcing function (PNF), body weight (BW), vibration frequency (f_t), and the subject's whole-body resonant frequency (f_r). Mathematically

$$MAF_v = MAF_v\ (SV, MHR, PNF, BW, f_t, f_r) \quad (1)$$

By applying the Buckingham pi-theorem, four independent dimensionless groups (in 3 fundamental dimensions; length, time, and mass) were found from the seven variables defining the present problem. The dimensionless groups were

$$\pi = \frac{MAF_v}{SV \times MHR}; \quad F = \frac{PNF}{BW} \times 100; \quad f_T = \frac{f_t}{MHR}; \quad \text{and} \quad f_R = \frac{f_t}{f_r}$$

Thus, the changes in MAF under vibration can be characterized by the following functional equation

$$\pi = \pi\ (F, f_T, f_R) \quad (2)$$

Selected dimensionless parameters given in *Eq. 2* can be redefined for a more meaningful representation of the data. The percent change in MAF can be defined as

$$Q = \frac{MAF_v - MAF_c}{MAF_c} \times 100 = \left[\frac{MAF_v}{SV_c \times MHR_c} - 1\right] \times 100 = (\pi - 1) \times 100$$

where MAF_c = previbration or control mean aortic flow; SV_c = previbration or control mean stroke volume; and MHR_c = previbration or control mean heart rate. Therefore, the percentage change from control of MAF is characterized by the functional equation: Q (F, f_T, f_R), where dimensionless force, F, highlights the role of PNF; dimensionless frequency, f_T, suggests the importance of the time relationship between the vibration and cardiac cycles, and the dimensionless frequency, f_R, elucidates the significance of nonlinear effects associated with vibration frequencies near the whole-body resonant frequency. In general F includes the effects of whole-body resonance since PNF becomes the greatest at the whole-body resonant frequency (f_r ranged between 2 and 5 Hz). However, for these values of PNF, the cardiovascular responses seem to exhibit the most variability, implying the uniqueness and nonlinear influence of that particular frequency. Thus, the term f_R is included for completeness. The exact nature of the functional relationship between the above parameters can only be determined from the experimental data.

A response of the cardiovascular system as measured in percent change from control (no vibration) of MAF (Q) is plotted versus vibration frequency (f_t) for one animal in Fig. 3. The whole-body peak net force (PNF) for the same animal versus vibration frequency is also plotted in Fig. 3. It is obvious from the graph that the functional relationship of percent change in MAF vs. f_t, and PNF vs. f_t are similar. Therefore, when percent change in MAF (Q) is plotted against PNF/BW × 100, (F), a linear relationship results (r = correlation coefficient = 0.75; Fig. 4). Normalization of MAF and PNF significantly improved the correlation between the two variables. For example, the correlation coefficient for the relationship between absolute values of MAF and PNF for all categories was 0.39. However, when both variables were normalized the value of r improved to 0.70. Similar improvements in r with nondimensionalization were found for almost all of the tests results.

A composite plot of percent change in MAF vs. PNF/BW from the data of 10 experiments on 6 animals is shown in Fig. 5. The regression equation for the relationship between percent change in MAF and PNF/BW is 0.476 (PNF/BW) × 100 + 0 with a standard error of estimate of ± 26.71% MAF and an r of 0.7. While the scatter in the composite plot of Fig. 5 is relatively large, the individual animals showed a better correlation (r = 0.75; Fig. 4). Mean aortic blood pressure during all the experiments showed a relatively small change with respect to PNF/BW.

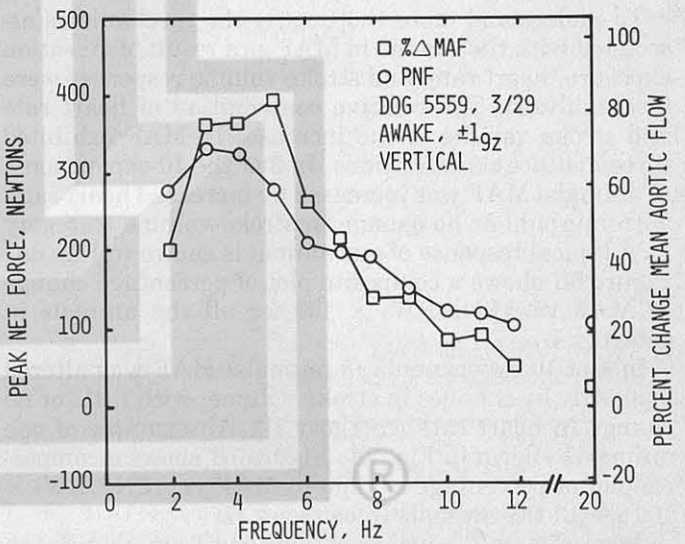

FIG. 3. Peak net force and percentage change in mean aortic flow versus vibration frequency (1 animal).

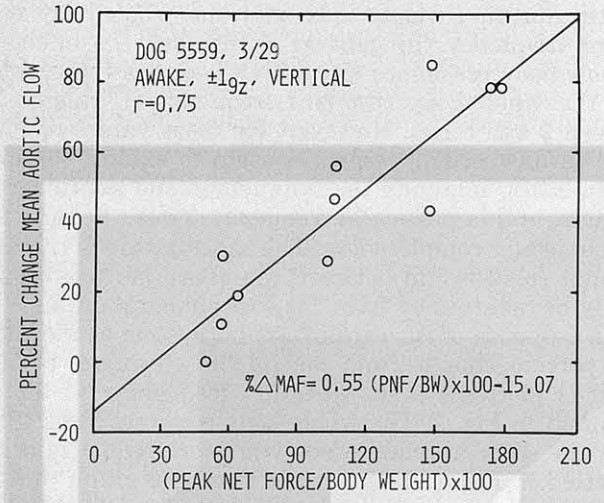

FIG. 4. Percentage change in mean aortic flow versus (peak net force/body weight) × 100 (1 animal)

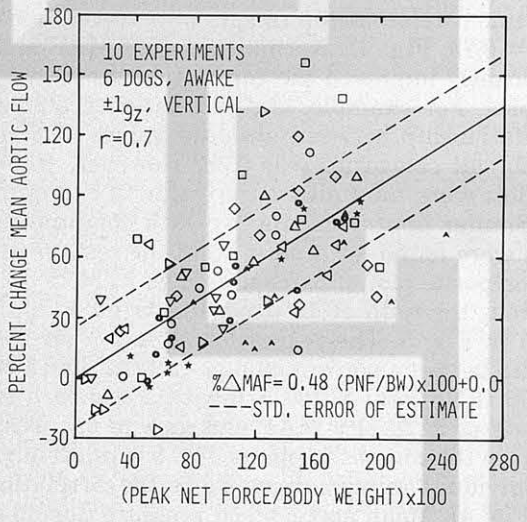

FIG. 5. Percentage change in mean aortic flow versus (peak net force/body weight) × 100 (6 animals, 10 experiments).

To understand more thoroughly the mechanisms associated with the change in MAF as a result of vibration exposure, heart rate, and stroke volume responses were also analyzed. The relative contribution of heart rate and stroke volume to the increases in MAF exhibited three distinct classifications. In 3 of the 10 experiments (2 animals) MAF was increased by increased heart rate, with minimal or no change in stroke volume (category I). A typical response of one animal is shown in Fig. 6*A*. Figure 6*B* shows a composite plot of percentage change in MAF vs. (PNF/BW) × 100 for all the animals in category I.

In 4 of 10 experiments (3 animals) MAF was altered primarily by changes in stroke volume, with little or no change in heart rate (category II). An example of one animal is shown in Fig. 7*A*. Figure 7*B* shows a composite plot of percentage change in MAF vs. (PNF/BW) × 100 for all the animals in category II.

Approximately equal contributions from changes in heart rate and stroke volume were present in 3 of the 10 experiments (3 animals). In this category both variables correlated poorly with PNF/BW (category III). An example is shown in Fig. 8*A*. Figure 8*B* shows a composite plot of percentage change in MAF vs. (PNF/BW) × 100 for category III. Like category I, MAP remained relatively unaltered in the other two categories. Since MAP was generally unchanged, and since MAF increased, total peripheral resistance decreased.

The increase in MAF for the category I and II animals also appeared to be a function of the heart rate level at the initiation of the vibration exposure. In those animals with initial heart rates under 150 beats/min (MHR_c) altered heart rate was the major response (cate-

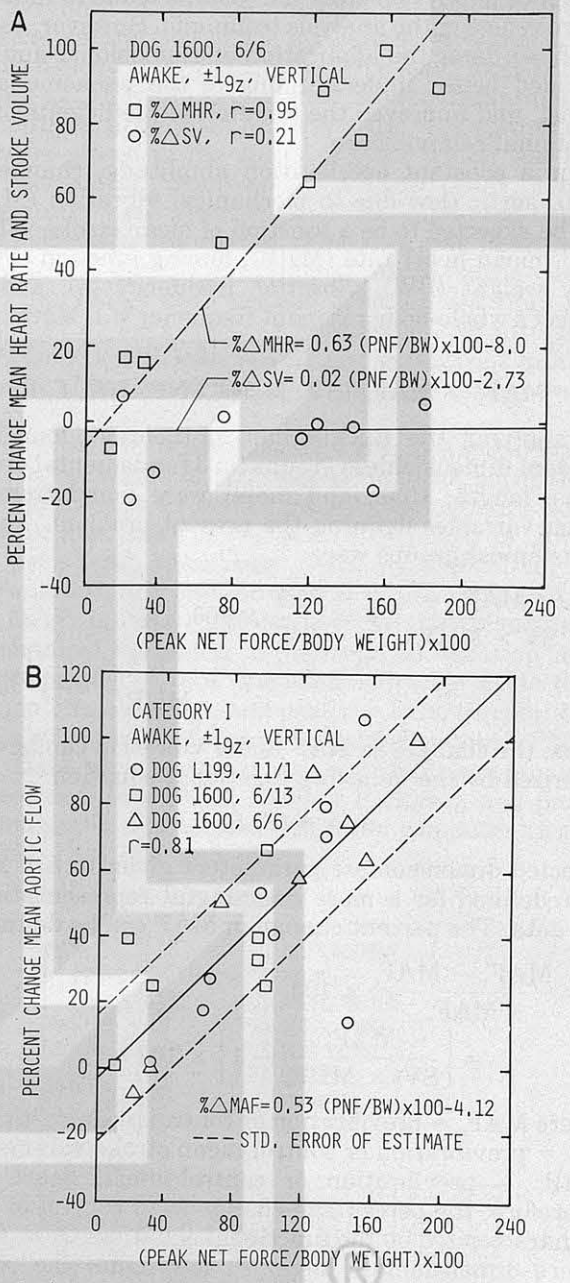

FIG. 6. *A*: percentage change in heart rate and stroke volume versus (peak net force/body weight) × 100 (1 animal). *B*: percentage change in mean aortic flow versus (peak net force/body weight) × 100 (category I).

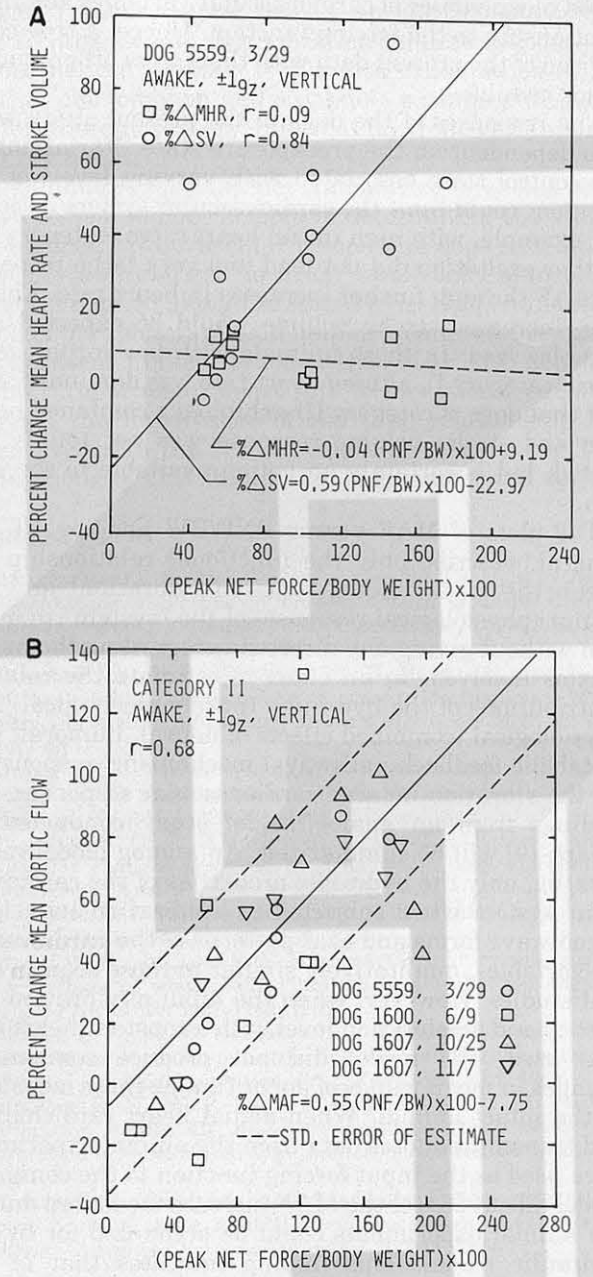

FIG. 7. *A*: percentage change in mean heart rate and stroke volume versus (peak net force/body weight) × 100 (1 animal). *B*: percentage change in mean aortic flow versus (peak net force/body weight) × 100 (category II).

gory I); for those animals with initial heart rates above 150 beats/min, altered stroke volume was dominant (category II). Initial heart rates were not the significant factor for those animals changing both heart rate and stroke volume (category III). In this category initial heart rates ranged from 78 to 204 beats/min.

The dimensional analysis presented in the beginning of this section showed that MAF could also be influenced by the time relationship between the cardiac and vibration cycles (f_T). The data of category I, in which animals consistently change HR, were analyzed with this observation in mind and Q was found to increase linearly with the log $1/f_T$. The plotted data are shown in Fig. 9.

DISCUSSION

The changes in MAF resulting from vibration exposure were found to be linearly related to PNF/BW and to the log of $1/f_T$ for individual animals. Such a functional dependency was consistent with the results of the dimensional analysis of the variables defining the problem.

The significance of the PNF measurement is that, in general, it combines the effects of vibration frequency, acceleration amplitude, and the deformation and relative movement of body organs. These observations suggest that MAF responses could be reasonably predicted by maintaining a constant PNF for any combination of frequency and G level. For example, in a preliminary study the present authors (unpublished data) one dog was subjected to a constant force, i.e., constant PNF at

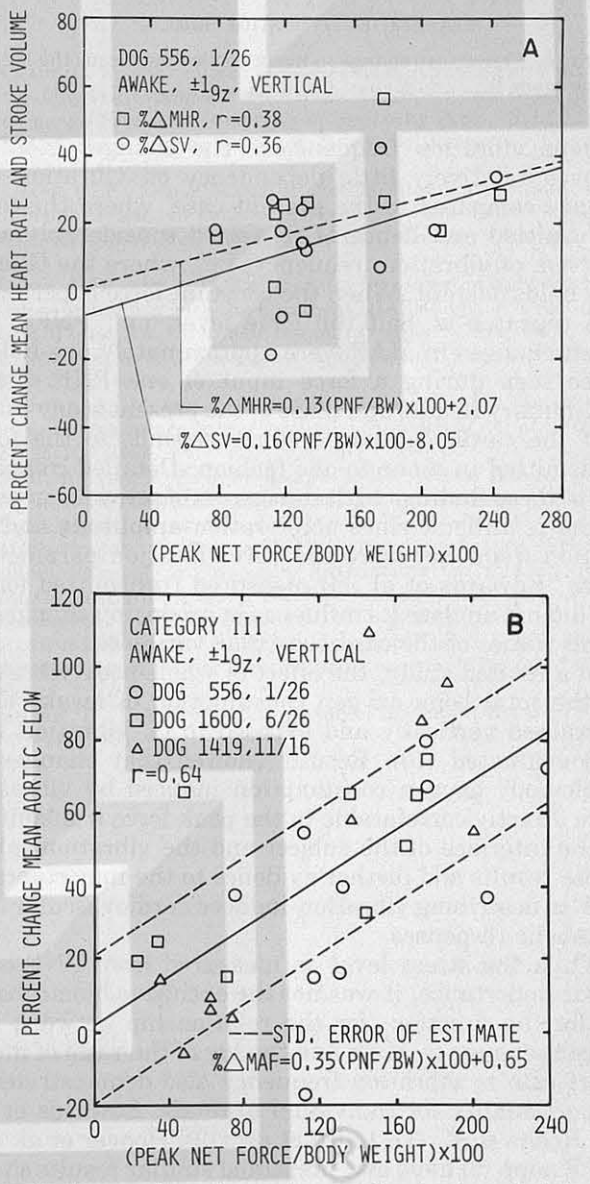

FIG. 8. *A*: percentage change in mean heart rate and stroke volume versus (peak net force/body weight) × 100 (1 animal). *B*: percentage change in mean aortic flow versus (peak net force/body weight) × 100 (category III).

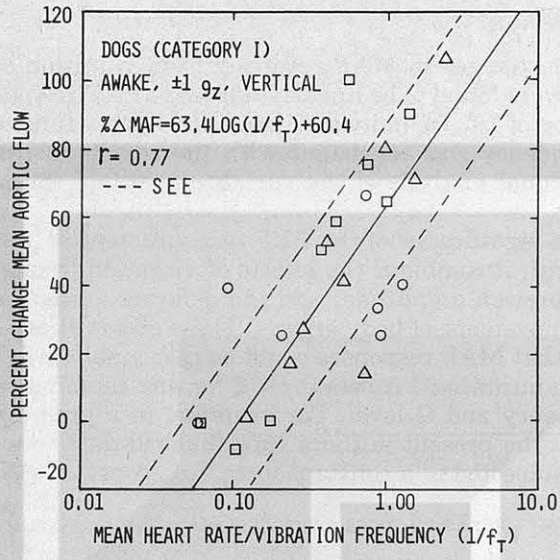

FIG. 9. Percentage change in mean aortic flow versus the log of $1/f_T$ (category I).

various vibration frequencies. The changes in MAF showed relatively little dependency on vibration frequency compared to the present case, where the force transmitted and hence MAF varied considerably as a function of vibration frequency, i.e., where the G level was held constant. When the constant force experiment was repeated at half the force level, i.e., PNF/2 the mean changes in MAF were approximately one-half of those seen during a force input of one PNF. These preliminary results and those of the present study imply that the cardiovascular system responds to the force transmitted in a one-to-one fashion. Detailed comparison of these findings with the results of previous investigators is difficult since acceleration amplitude and vibration frequency were the only vibration parameters given. Edwards et al. (4) measured transmitted force, but did not analyze its influence in producing changes in mean values of the cardiovascular variables.

In a related study, the effect of whole-body vibration on the total body oxygen consumption of awake dogs restrained vertically and exposed to G_z vibration was also evaluated (10). Results showed that changes in whole-body oxygen consumption induced by vibration were directly correlatable to the peak force transmitted at the interface of the subject and the vibration table. These results add further evidence to the importance of PNF in describing vibration-induced cardiovascular and metabolic responses.

While the stress level as measured from PNF is of major importance, it was not the exclusive biomechanical forcing function, for the relationship between the percent change in MAF and the log of the ratio of mean heart rate to vibration frequency also demonstrated a proportionality for individual animals. Edwards et al. (4), Hooks et al. (7), Laird et al. (12), Hoover et al. (8), and Knapp (9) have also presented similar results showing the presence of beat patterns and emphasizing the importance of the phase relationship between the heart and vibration cycles related to changes in pressures and flows. However, none of the previous investigators measured mean values of cardiovascular variables and their relationship to the forcing function. Hence, a true comparison of the present data with those from other studies is not possible.

The responses of the dogs in the present study were also dependent on the preexposure state. Variations in the control state associated with varying levels of excitement could limit the cardiovascular system options. For example, with high initial heart rates (category II), further excitation did not lead to a very large response in MAF through further increases in heart rate. Therefore, increased stroke volume would be expected and was observed. In those animals with low initial heart rates (category I), altered heart rate was dominant. The fact that dogs of category III exhibited a combined heart rate and stroke volume response was not totally expected, but is certainly an option available to the system.

The plots of MAF versus PNF/BW and log $1/f_T$, in general, describe only the functional relationship between the input forcing function (vibration) and the output (physiological response) of the "system" in question without giving any direct clue regarding the mechanisms involved. In an effort to estimate the relative contributions of the hydraulic (purely mechanical) and physiological (combined effects of neural, humoral, and metabolic feedback pathways) mechanisms responsible for the vibration-induced cardiovascular responses, the findings from an analog model study conducted by Knapp (9) will be summarized. An analog model incorporating only the hydraulic properties of the cardiovascular system when subjected to a vibration input-produced wave forms and beat patterns of the cardiovascular variables, qualitatively similar to those seen in animal studies. However, when the input of vibration frequency and acceleration level with a constant heart rate was used, the model did not produce comparable changes in mean values of aortic flow as those measured in the intact animal. When actual heart rate changes and transmitted force data from the animal experiment were used as the input forcing function to the computer model, about 25% of the MAF increase measured during the animal experiments could be accounted for by the hydraulic model. This finding indicates that of the changes in mean aortic flow measured in animals (0.5–3 G) approximately 25% or less was due to the reaction of the fluid-vessel (hydraulic) system, with the remaining approximately 75% due to neural and metabolic influence.

The importance of neural pathways excited by whole-limb vibration was also indicated by the work of Liedtke and Schmid (14). Peripheral vasodilation in the vibrated intact limb of anesthetized dogs was much greater than in the same limb following denervation. Neural mediation appears to be a far more important determinant of vibration response than direct hydraulic, metabolic and humoral effects. The power of this regulation is apparent in the stage of preparation for exercise, a predominantly neural process most closely simulated by hypothalamic stimulation (17). However, evidence of sustained cardiovascular responses to the vibration exposure presented by Bhattacharya (1) implies that the

induced response is not merely an alerting phenomenon. In other words, the vibration-induced response of unanesthetized animals is due to a combination of an alerting phenomenon and a possible sustained modulation of afferent sensory information from various mechanoreceptors.

In summary, the peak net transmitted force has been shown to be a major variable in determining the vibration-induced cardiovascular response of dogs restrained vertically and exposed to brief, whole-body sinusoidal vibration applied along the spinal axis. Such standardization of parameters should help in meaningful comparison between studies. The fact that MAF also depends on the ratio of mean heart rate to vibration frequency suggests the importance of the time relationship between events in the cardiac and vibration cycles. The implications of this finding could be important for future studies where the time relationship between vibration and cardiac cycles could be synchronized for maintaining a desired cardiovascular response. Such capabilities of heart synchronous vibration could open up avenues toward therapeutic applications of vibration.

The authors greatly acknowledge the expert surgical skill of Dr. Ward Griffen and Cecil Woolfolk, Dept. of Surgery, UK Medical Center and the indispensable technical assistance of J. Evans, F. Wibel, R. Stanifer, S. Beaver, T. Geoffroy, M. Jones, and T. Phillips of the Wenner-Gren Research Laboratory.

This research was supported by the Air Force Office of Scientific Research (AFOSR) Contract F44260-74-C-0012.

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Received for publication 29 December 1975.

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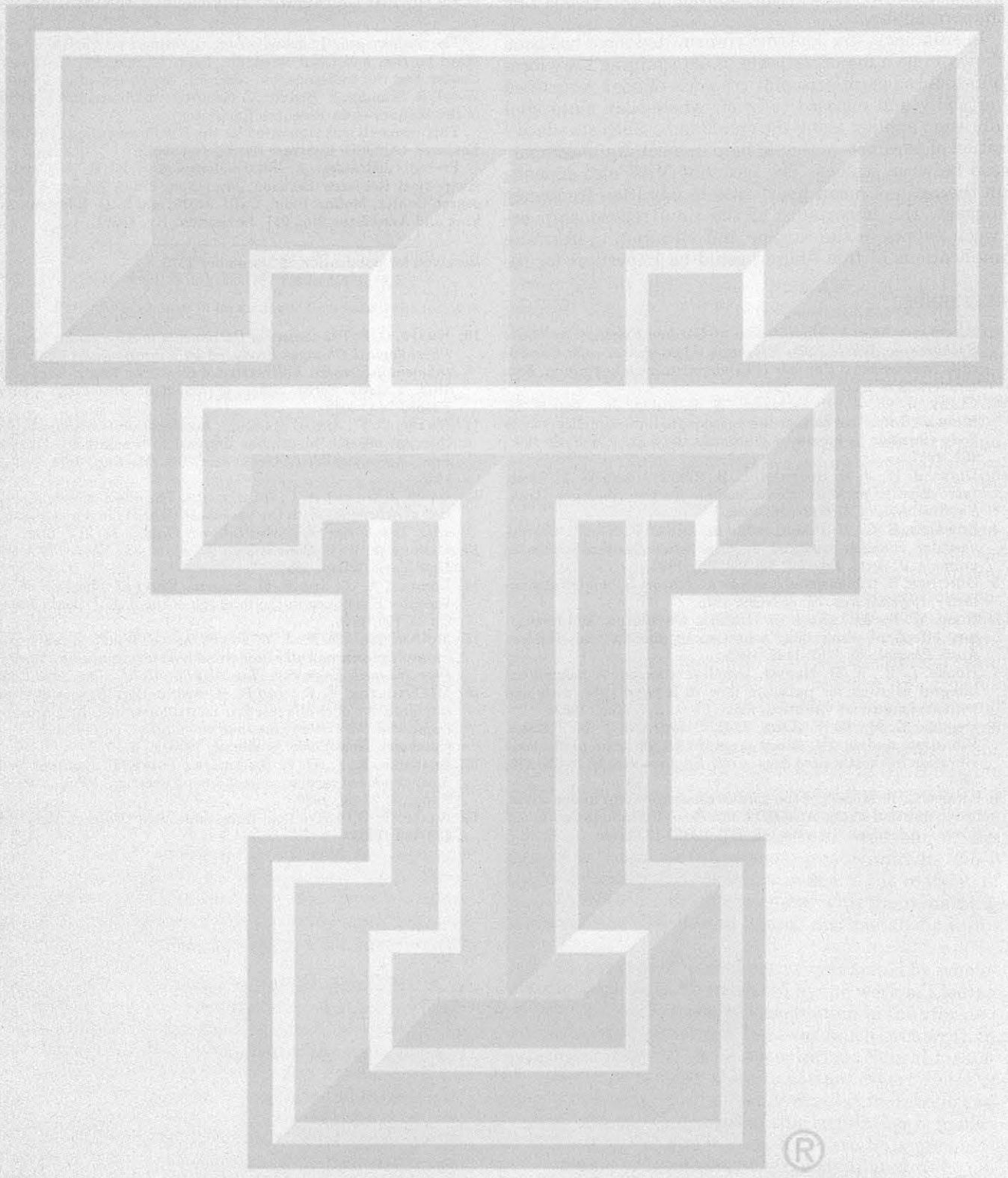

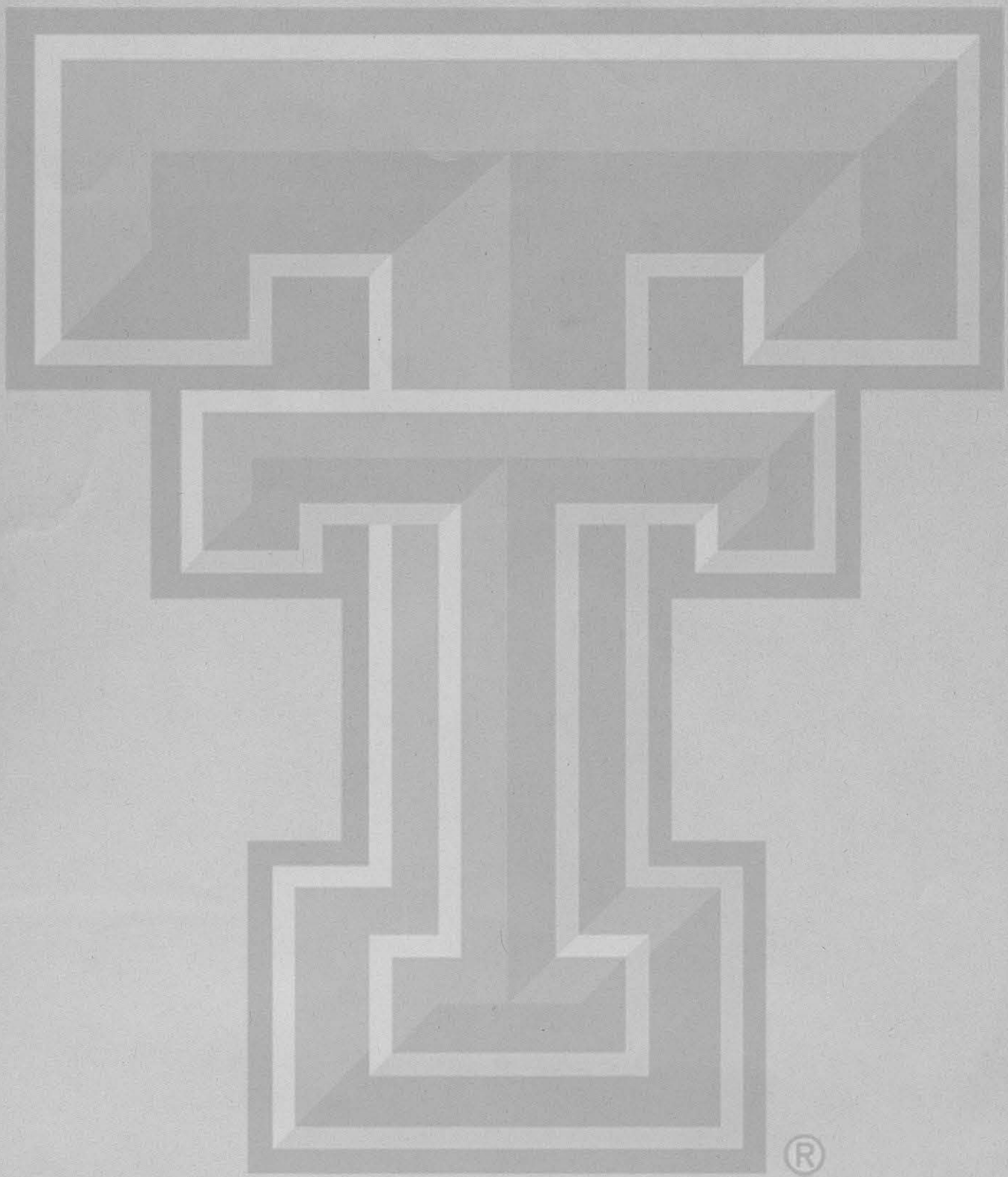

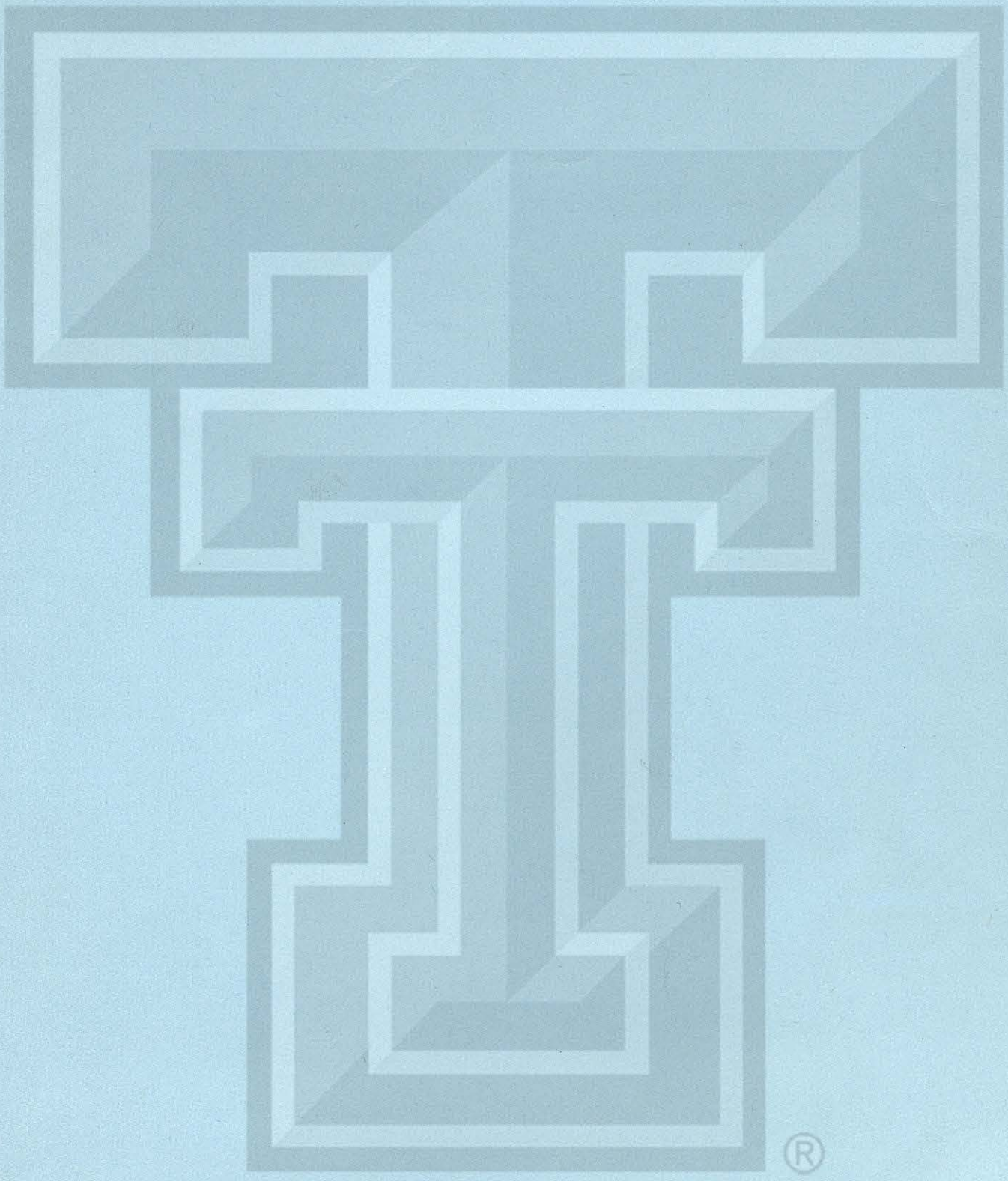

Prevention of Experimental Motion Sickness by Scopolamine Absorbed Through the Skin

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GRAYBIEL, A., J. KNEPTON, and J. SHAW. *Prevention of experimental motion sickness by scopolamine absorbed through the skin.* Aviat. Environ. Med. 47(10):1096-1100, 1976.

A double-blind placebo-controlled study compared the efficacy of the antimotion sickness drug scopolamine when administered by oral or transdermal routes. A secondary purpose was to extend our bioassay involving fixed-dose combinations of the homergic drugs promethazine and ephedrine. After receiving 12 apparently identical drug-placebo treatments, eight normal male students were exposed in a slow rotation room to stressful accelerations generated by their execution of 40 head movements out of the plane of the room's rotation at 1 rpm and at 1-rpm increments until either symptoms were experienced (just short of frank motion sickness) or the 27-rpm ceiling on the test was reached. Efficacy of a drug was defined in terms of the placebo-range and categorized as beneficial, inconsequential, or detrimental. The rank order of drugs with beneficial effects was: 1) promethazine 25 mg plus ephedrine 12.5 mg (86%); 2) scopolamine by mouth (75%); 3) scopolamine transdermally (63%); and 4) promethazine 12.5 mg plus ephedrine 25 mg (29%). The only detrimental effect was with scopolamine given orally. It is concluded that the advantages of the transdermal scopolamine, which include minimal side effects and prolonged effectiveness, deserve full exploitation.

IN A RECENT report (1), a method was described for measuring the efficacy of antimotion sickness drugs on an individual basis, and the findings revealed far greater individual variations in drug effects than hitherto suspected. Indeed, for some persons a satisfactory remedy was not identified while for others the responses to all drugs tested were beneficial. The chief purpose of the present report is to compare the results of administering scopolamine orally and by a device that permits absorption, transdermally, directly into the circulation. An additional purpose is served by continuing our studies dealing with the efficacy of the two homergic antimotion sickness drugs, promethazine plus ephedrine.

From the Naval Aerospace Medical Research Laboratory. This study was supported by the Bureau of Medicine & Surgery, Project MF51.524.005-7015 and the National Aeronautics and Space Administration, Contract T-5904B. Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

MATERIALS AND METHODS

Subjects: Eight college students, 19-24 years of age, participated as paid volunteers. They were chosen from our group of some 40 subjects on the basis of availability. The entire subject pool was selected on the ground that they could qualify for tests in parabolic flight; none was rejected for reasons of susceptibility to motion sickness. In addition to a medical evaluation, assessments included a test for: a) otolith function—ocular counter-rolling—(2); b) canal function—modified Fitzgerald-Hallpike procedure—(3); and c) postural equilibrium (4).

Stress Profile: The procedure, described elsewhere in detail (5), involved the generation of stressful stimuli by requiring the subject to execute head movements out of the plane of rotation of a slow rotation room (SRR). Forty head movements were executed at 1 rpm and were repeated at 1-rpm increments in angular velocity until either the ceiling on the test, 27 rpm, or the motion sickness endpoint—first appearance of slight nausea or a score of 12 points—was reached. All rotations were in the counterclockwise direction.

Scoring: The observer, in collaboration with the subject, estimated the levels of severity of the symptoms after every set of 40 head movements. The levels of severity of motion sickness were given numerical scores according to diagnostic criteria (6) found to be satisfactory when acute motion sickness was evoked.

Drugs and Administration: The following drugs were evaluated:

1. Transdermal therapeutic system—scopolamine (TTS-scopolamine).
2. *l*-scopolamine hydrobromide (0.6 mg).

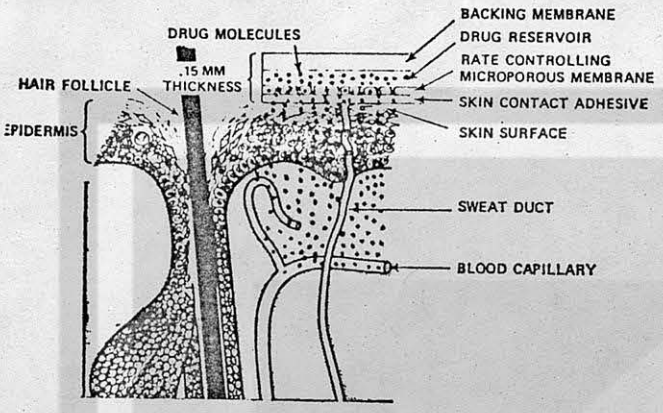

Fig. 1. Schematic diagram of a transdermal therapeutic system (not to scale).

3. promethazine hydrochloride (12.5 mg) + ephedrine sulphate (25 mg).
4. promethazine hydrochloride (25 mg) + ephedrine sulfate (12.5 mg).

The TTS-scopolamine and the transdermal device (TD)-placebo are identical in appearance; the disc applied to the skin is 0.15 mm thick and 11 mm in diameter. The TTS-scopolamine (Fig. 1) is designed to release the drug at a predetermined rate for about 72 h.

The subjects were fitted into two modified 4-unit Latin-square designs, and placebos were alternated with drugs except at the beginning and end of the experiment, when two placebos were administered consecutively.

Efficacy: Drug efficacy was deemed beneficial, inconsequential, or detrimental in terms of the response as compared with the placebo responses. The first step was to determine the range of placebo scores in terms of the extremes in revolutions per minute when placebo endpoints were reached. Usually a mean placebo baseline could be defined within this range, and the inconsequential range was defined as twice the value above or below this line. Values above and below the inconsequential range, respectively, were deemed beneficial or detrimental. Quite often the placebo range was influenced by adaptation effects; hence, sloping baselines were used.

Under two circumstances the above procedure was unsatisfactory. Rarely, a placebo baseline was virtually or actually flat (i.e., a range of zero) in which event an arbitrary inconsequential range (±20%) was defined. Also, rarely, the revolutions-per-minute ceiling on the test was reached when a placebo was administered; this phenomenon vitiated the results in two tests involving one subject in this series.

Plan: Each subject was tested at the same time of day and on the same day of each week for 11 successive weeks; 15 tests out of a total of 88 were not exactly 7 d apart (range 4 to 11: mean 7). Each subject received an identical treatment regimen. The afternoon before each test, the subject completed a preexperimentation questionnaire to establish his suitability for participating in the test; pulse rate, blood pressure, and oral temperature were measured. At that time, a TTS-scopolamine or a TD-placebo was applied to the skin behind the subject's ear.

The following day, the subject reported approximately 2.5 h prior to the scheduled time for the test. He again completed an identical questionnaire; pulse rate, blood pressure, and temperature were taken; and a "sharpened" Romberg (ataxia) test (4) was administered. Then he was asked whether he considered he had received any medication from his skin patch applied

TABLE I. COMPARISON OF INDIVIDUAL RESPONSES TO SCOPOLAMINE ADMINISTERED TRANSDERMALLY AND ORALLY.

Subj.	TTS-Scopolamine rpm Placebo	TTS-Scopolamine rpm Drug	TTS-Scopolamine Change in rpm	TTS-Scopolamine % Change rpm	TTS-Scopolamine Significance Change in rpm*	TTS-Scopolamine Urinary Excretion Scopolamine μg/h	Oral Scopolamine rpm Placebo	Oral Scopolamine rpm Drug	Oral Scopolamine Change in rpm	Oral Scopolamine % Change rpm	Oral Scopolamine Significance Change in rpm*	Oral Scopolamine Urinary Excretion Scopolamine μg/h
1	12.7	12.7	0	0	I	0.643	12.7	26.0	+13.3	+105	B	5.145
8	9.6	12.6	+ 3.0	+ 31	B	0.636	9.6	11.2	+ 1.6	+ 17	I	4.011
9	16.0	23.0	+ 7.0	+ 44	B	0.153	17.0	>27.0	>+10.0	>+ 59	B	1.325
12	12.0	>27.0	>+15.0	>+125	B	0.292	18.9	>27.0	>+ 8.1	>+ 43	B	3.223
26	5.0	6.3	+ 1.3	+ 26	I	0.159	5.8	8.8	+ 3.0	+ 52	B	
30	7.8	13.0	+ 5.2	+ 67	B	0.646	7.8	17.7	+ 9.9	+126	B	8.271
32	14.1	17.0	+ 2.9	+ 21	I	0.277	14.1	>27.0	>+12.9	>+ 91	B	0.853
34	14.0	17.0	+ 3.0	+ 21	B	0.320	12.0	9.0	− 3.0	− 25	D	2.825
		n = 8			B: 63%	n = 8		n = 8			B: 75%	n = 7
		x = >+4.7			I: 37%	$\bar{x}$ = 0.385 μg/h		x = >+7.0			I: 13%	x = 3.665 μg/h
					D: 0%	s = 0.220 μg/h					D: 12%	s = 2.510 μg/h
						s_x = 0.078 μg/h						s_x = 0.949 μg/h

*B = beneficial; I = inconsequential; D = detrimental.

the previous day. Two hours before the planned susceptibility test the subject, after a light snack, swallowed two capsules containing medication or placebo. Thirty minutes prior to testing (1.5 h after oral medication) each subject was questioned as to whether he considered he had received any medication in his oral capsules. Heart rate, blood pressure, and temperature were then monitored again, the subject voided, and the urine was discarded.

On completion of the susceptibility test in the SRR, the subject was again questioned regarding side effects, and the physiological measurements and the Romberg test were repeated. The subject voided and all of the urine sample was frozen. The TTS was then removed and the site inspected. The urine samples were sent to the Alza laboratory where the scopolamine excretion was reported as μg/h.

RESULTS AND DISCUSSION

Table I summarizes the findings, comparing not only the efficacy of TTS-scopolamine with a dose of 0.6 mg taken orally, but also the urinary excretion rates in micrograms per hour.

Only Subject 12 reached the 27-rpm ceiling on the test when the drug was given transdermally, and it is noteworthy that his urinary excretion rate was below the average for the entire group. Subjects 9 and 32 reached the rpm ceiling in the test and Subject 1 was only 1 rpm short when scopolamine was administered orally. With TTS-scopolamine, the increase in rpm over the placebo level was zero in Subject 1 (who had one of the highest excretion rates), 7.0 rpm in Subject 9 (who registered the lowest urinary excretion rate among the entire group), and 2.9 rpm in Subject 32 (an inconsequential response). Two inferences may be drawn; namely, the dose of TTS-scopolamine was too small for maximal benefits, and the urinary excretion rates were not a reliable guide.

Among the remaining four subjects, three registered beneficial effects when the drug was administered transdermally but only two when given by mouth. Subjects 26 and 30 registered much higher rpm endpoints with oral administration, implying the TTS dose was inadequate for maximal benefit. Subject 26 had one of the lowest urinary excretion rates (0.159 μg/h) and Subject 30 the highest (0.646 μg/h) when the drug was administered transdermally. Subject 34 manifested the only detrimental effect which followed oral administration but scored a 3-rpm increase with the TTS preparation.

With regard to side effects following administration of TTS-scopolamine, one subject reported "dry mouth" and one other "insomnia," compared with six complaints by two subjects when the TD-placebo was applied. When scopolamine was given orally, there were 22 complaints made by seven subjects. With placebo medications five subjects made 27 complaints (see later section on Side Effects).

The results with TTS-scopolamine are highly encouraging for three reasons. First, the delivery system "works," and if the quantity administered had been doubled the responses in nearly all of the subjects tested might well have been beneficial. Second, the steady-state administration over a prolonged period is frequently desirable. Third, the side effects are far less than with the oral preparation. One potential disadvantage is the 4 to 6 h required for the steady-state administration to be achieved.

In the past, a usual dose of scopolamine by mouth for children was 0.3 mg (7) and for adults 0.6 mg (8-13) or 1.2 mg (8,14-15). But it has been demonstrated (1,10,15) that 0.3 mg has equally beneficial effects in adults except in a few instances. Studies by Brand and Whittingham (16), who used intramuscular scopolamine, have indicated that the amount of a drug administered can be reduced, so that the peripheral side effects are minimized, yet a high degree of protection against motion sickness can be maintained. This finding raises the possibility that the central antimotion sickness effects of scopolamine may be manifested in association with systemic blood levels lower than those required to elicit the peripheral parasympatholytic effects accompanying conventional dosage forms of the drug.

Continuing Study on Efficacy of Two Homergic Drugs

TABLE II. A COMPARISON OF TWO FIXED-DOSE ORAL COMBINATIONS OF PROMETHAZINE AND EPHEDRINE

	Promethazine (12.5) + Ephedrine (25 mg)					Promethazine (25 mg) + Ephedrine (12.5 mg)				
	rpm		Change	% Change	Significance of Change	rpm		Change	% Change	Significance of Change
Subj.	Placebo	Drug	in rpm	rpm	in rpm*	Placebo	Drug	in rpm	rpm	in rpm*
1	12.6	11.5	− 1.1	− 9	I	12.6	22.0	+ 9.4	+ 75	B
8	9.6	10.4	+ 0.8	+ 8	I	9.6	13.4	+ 3.8	+ 40	B
9	23.0	23.0	0	0	I	15.0	22.0	+ 7.0	+ 47	B
12	>27.0	>27.0	—	—	—	>27.0	>27.0	—	—	—
26	3.9	4.8	+ 0.9	+ 23	I	3.8	5.8	+ 2.0	+ 53	B
30	7.8	20.0	+12.1	+156	B	7.8	23.4	+15.6	+200	B
32	14.1	19.0	+ 4.9	+ 35	B	14.1	>27.0	>+12.9	>+ 91	B
34	17.0	16.0	− 1.0	− 6	I	−13.0	12.0	− 1.0	− 8	I
			n = 7		B: 29%			n = 7		B: 86%
			x = +2.4		I: 71%			x = >+7.1		I: 14%
					D: 0%					D: 0%

—Comparison of two fixed-dose combinations of promethazine and ephedrine: Table II compares the responses when, instead of a fixed-dose of promethazine plus ephedrine (25 mg each), the amount of promethazine was halved in one test and that of ephedrine halved in the other. Unfortunately, Subject 12 reached the 27-rpm ceiling on the test with a placebo prior to testing for efficacy of the promethazine plus ephedrine combinations. This reduced the sample to seven, with consequent effect on the percentage of beneficial responses to promethazine plus ephedrine.

When the amount of promethazine was halved (Table II, left), responses of two of the seven subjects were beneficial and none was detrimental; when the amount of ephedrine was halved, the responses of six subjects were beneficial and one was inconsequential. The beneficial responses in Subject 30 were unexpectedly large—an increase of +12.1 rpm when the amount of promethazine was halved and 15.6 rpm when ephedrine was halved; the latter was the largest percentage gain recorded in the entire study.

Additional Findings Involving All Tests—Physiological measurements: As a result of wearing the TTS-scopolamine for 14 to 20 h there was a significant decrease in heart rate (Table III). Similarly, 90 min after oral administration of scopolamine there was a significant decrease in heart rate. Neither dose combination of promethazine plus ephedrine produced a change in heart rate. There was no significant change in blood pressure, pulse pressure, or oral temperature as a result of administering any of the medications.

Side Effects: Side effects reported by the subjects are listed in Table IV. The most noted effect was that of drowsiness, but the main documentation of this effect followed placebo medication. After oral scopolamine, many adverse effects were reported, including impaired coordination and impaired concentration. The only reported side effects with application of the TTS-scopola-

TABLE III. SUMMARY OF HEART RATE MEASUREMENTS

	TTS-scopolamine		Scopolamine (oral)		Promethazine (12.5 mg) + Ephedrine (25 mg)		Promethazine (25 mg) + Ephedrine (12.5 mg)	
Subject	Control Day*	Test Day†	Control Day*	Test Day‡	Control Day*	Test Day‡	Control Day*	Test Day‡
	Heart Rate (beats/min)							
1	72	58	50	48	46	50	52	58
8	74	52	60	42	56	62	58	60
9	60	56	70	56	80	90	68	70
12	82	68	80	60	76	68	88	82
26	54	46	52	56	52	58	66	62
30	62	62	64	54	60	68	84	66
32	76	54	60	50	64	62	78	70
34	64	56	72	68	72	94	70	80
t§	4.1		5.2		−1.85		0.64	
p	0.01-0.001		<0.001		n.s.		n.s.	

*Control measurements obtained at same time of day during evaluation of previous week's placebo medications.

†Heart rate monitored prior to administration of capsules; 14-20 h after skin applications.

‡Heart rates monitored 90 min. after administration of capsules; 30 min before test run.

§Paired t-test analysis.

TABLE IV. REPORTED SIDE EFFECTS FOLLOWING MEDICATION.

	Number of Observations Recorded Throughout the First Eleven Runs of the Study*					
	Placebo Medications		Active Medications			
Effect Reported	Transdermal† Device-Placebo	Oral‡ Capsule	TTS Scopolamine†	Scopolamine (0.6 mg)‡	Promethazine‡ (12.5 mg) + Ephedrine (25 mg)	Promethazine‡ (25 mg) + Ephedrine (12.5 mg)
Drowsiness		8		2	1	3
Dry mouth		2	1	2		
Dizziness		1		3		
Headache	2	2				
Lightheaded		4		4		
Stomach awareness	1	3		1	1	
Blurred vision		1		2		
Eye disorder				1		
Coordination impaired	1	2		3		
Concentration impaired	1	2		3		1
Reactions slow	1	1		1		
Increased temperature		1				
Insomnia			1			
Total comments	6	27	2	22	2	4
Number of subjects making comments	2	5	2	7	2	3
Number of questioning periods	80	64	8	8	8	8

*Each of the eight subjects was questioned twice during each of the 11 medication schedules.
†Subjects were questioned 15 min before oral medication.

mine were one instance each of dry mouth and insomnia. Four subjects reported drowsiness following administration of promethazine and ephedrine; in one instance when promethazine was halved and in three when ephedrine was halved.

Comment: The great inter- and intraindividual variations in responses with respect to the chosen drug and with the amount administered highlight the findings. With scopolamine, urinary excretion rates often correlated poorly with efficacy, indicating that other factors must be explored if these variations are to be explained. For practical reasons attention might center on subjects in whom excellent or highly satisfactory responses were not obtained. Expanding the scope of drugs administered and searching for defects in the experimental design are two lines of direction that can be explored fairly quickly.

CONCLUSIONS AND RECOMMENDATIONS

1. TTS-scopolamine has a place in the prevention of motion sickness if the dosage is doubled over that tested in the present study. The advantages are: a) the small amount required, with consequently small likelihood of troublesome side effects; b) the prolonged steady-state level of activity; and c) the ease of administration. Sometimes it may be used as an adjunct in treatment, but the 4 to 6 h required to reach full efficacy has a self-evident limitation. The possibility of increasing the efficacy of TTS-scopolamine by oral administration of another homergic drug should be investigated.

2. Scopolamine (0.6 mg) administered orally is highly efficacious in most, but not all, subjects. It is not suitable for long-term use.

3. Promethazine (25 mg) plus ephedrine (12.5 mg) may prove to be the ideal combination for general use of these two homergic drugs. This combination is suitable for long-term use.

4. The most striking phenomena were the great inter- and intraindividual variations that involved a) drug efficacy, both absolute and dose-related, and b) side effects.

5. Trying to account for these individual variations is a worthwhile scientific objective.

ACKNOWLEDGMENTS

We greatly appreciate the exceptional cooperation of the military and civilian support team that insured proper conduct of this study. The technical assistance of R. K. Upchurch, T. L. Trimble, and R. J. Garlock is gratefully acknowledged.

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KC-135 Category I: Findings in 14 of 18 Members of 1st Pool of 40 Subjects

	In Seat				Rotating 30 RPM					
	Head Fixed		Head Move		Head Fixed		Head Move*			
Subj.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	No. Tests	Δ Cat.	Eff. Drug** (M/S pts) Head Fixed	Head Move
1	2	No	8	No	2	No	4	2 = III +	Not tried	
2	2	No					3±	No −	Not tried	
4	2	No	5	No			3	2 = II +	Not tried	
								1 = III		
5	3	No	3	2 = II	3	III	2	III +	2, 0	1, 8, 6
						3		1		
6	2	No	2	No	1	No	1	No −		
7	2	No	6	No	1	No	1	No −		
8	2	No	2	No	1	No	1	III +		
9	5	No	4	No	1	II	1	III +	Not tried	
12	2	No	4	No						
14	3	1 = II	3	1 = II	2	1 = III	1	III +	Not tried	
15	2	No	1	No						
16	2	No	1	No						
17	2	No	6	No	1	No	1	No −		
18	3	No	7	1 = II						
				2 = III						

*Zero-gravity parts of parabolas.

**P & E 25 mg each

±On two occasions direction of RLC reversed.

Responses of 16 Subjects to Administration of Antimotion Sickness Drugs in Two Experiments Carried out in a Slow Rotation Room

Experiment I

Response of 8 Subjects to Transdermal Therapeutic System-Scopolamine, Scopolamine 0.6, Promethazine 25 + Ephedrine 12.5, and Promethazine 12.5 + Ephedrine 25.

	Beneficial Rank			
Subj.	>B2	B2	B	<B
1	2			2
8	1		1	2
9	4			
12	4			
26			1	3
30	3		1	
32	2	1		1
34-1st			1	3
34-2nd	1		1	2

Experiment II

Response of 8 Subjects to AHR 20, AHR 50, AHR 100, Scopolamine 0.3, Meclizine 50 + Ephedrine 25, Promethazine 12.5 + Ephedrine 12.5, Promethazine 12.5, and Ephedrine 12.5.

	Beneficial Rank			
Subj.	>B2	B2	B	<B
3			1	7
7				8
41			2	6
43			1	7
44	3		1	4
45		2	1	5
46			1	7
57			2	6

Susceptibility to Motion Sickness in 40 Subjects with Head Fixed
In First Two Flights in KC-135

S	Motion Sickness Points Test 1 Test 2	S	Motion Sickness Points Test 1 Test 2	S	Motion Sickness Points Test 1 Test 2
1	0 + 0	9	0 + 1	17	FS
2	FS	10	FS	18	0 + 0
3	FS	11	0 + 1	19	FS
4	FS	12	0 + 0	20	5 + 0
5	0 + 0	13	6 + 0	21	10 + 4
6	5 + 5	14	0 + 0	22	FS
7	0 + 13	15	1 + 4	23	FS
8	0 + 2	16	FS	24	4 + 2
25	0 + 9	33	FS		
26	9 + 0	34	0 + 0		
27	5 + 15	35	0 + 0		
28	7 + 13	36	0 + 0		
29	8 + 3	37	5 + 6		
30	10 + 3	38	FS		
31	10 - 0	39	1 + 1		
32	3 + 0	40	1 + 1		

Responses to Administration of Drugs Prior to Parabolic Flight in 13 Highly Susceptible Subjects

		P 25 + E 25 Sit		P 50 + E 50 Sit		S 0.6 + A 5.0 Sit		S 1.2 + A 10 Sit	
Cat.	S	Head Fixed M/S Score Pts	Head Move.* M/S Score Pts	Head Fixed M/S Score Pts	Head Move. M/S Score Pts	Head Fixed M/S Score Pts	Head Move. M/S Score Pts	Head Fixed M/S Score Pts	Head Move. M/S Score Pts
III	2	FS				2		0, 3	0
III	3	6,11,6,4,1,5	Abort 11 par.						
III	4	FS,FS, 3, 10, 3, FS	FS, FS, FS	FS				3, 2	4
III	19	0,6,0,3,FS,0		3, 5, 6					2
III	16	5, 2							5
III	17	0, 0, 1, 4							
III	22	3,7,8,6,4,4,6		6		3,1			
III	33	5,FS, 8, 6, 9							
II	26	3, 3	5						
II	28	1							
II	30		Abort						
I	8	0, 0, FS	0, 0, 3						
I	11	0, 2	1, 8, 6						

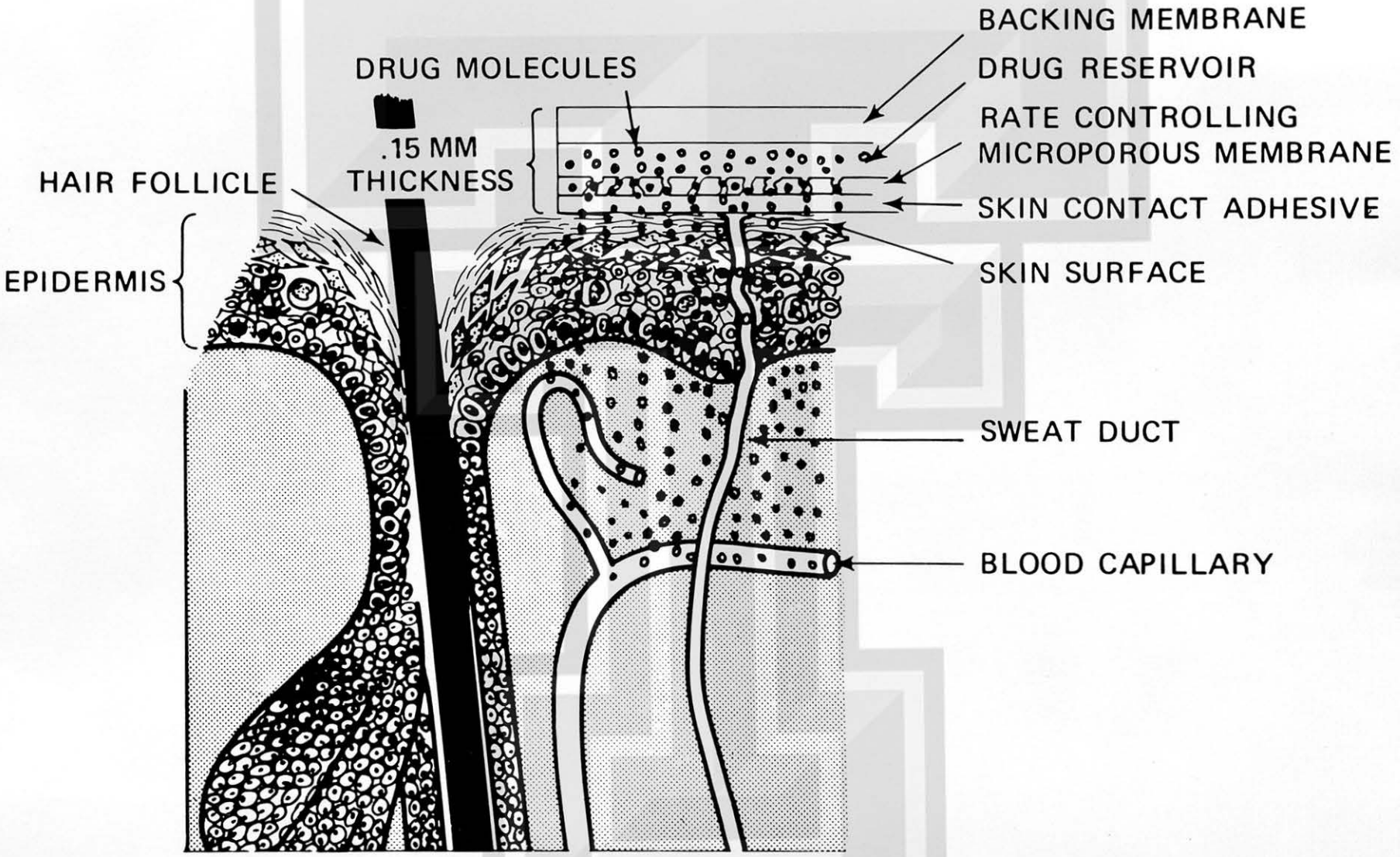
*Zero-gravity part of parabola.

Promethazine 25 mg + ephedrine 25 mg.
Promethazine 50 mg + ephedrine 50 mg.
Scopolamine 0.6 mg + amphetamine 5.0 mg.
Scopolamine 1.2 mg + amphetamine 10 mg.

Responses to Three Antimotion Sickness Remedies Administered Intramuscularly During Sorties in the KC-135

		Promethazine 25 mg			Scopolamine 4.3 mg			Dimenhydrinate 50 mg		
Subj.	Trial	1st FS* prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS
19	1st	16**	21	38	12	12	0	12	13	24,29
	2nd	17	19	21,22				6	6	26
	3rd	23	25	0						
	4th	23	25	0						
	5th	26	26	0						
	6th				10	11	0			
33		11	13‡	14,15						
47	1st	30	30	30	12	12	0	24	25	29,32,40
	2nd				26	28	0			
8	1st	21	23	0						
	2nd	22	30	0						
10	1st	10	24	0	8	8	0			
	2nd	32	32	0						
	3rd	10	13	0						
16		15	19	22,23,38						
17	1st	0	11	13,17						
	2nd	9	10	0						
	3rd	0	10	13						

*FS = frank sickness; **16th parabola; ‡ promethazine 50 mg.


BACKING MEMBRANE
DRUG RESERVOIR
RATE CONTROLLING MICROPOROUS MEMBRANE
SKIN CONTACT ADHESIVE
SKIN SURFACE
DRUG MOLECULES
.15 MM THICKNESS
HAIR FOLLICLE
EPIDERMIS
SWEAT DUCT
BLOOD CAPILLARY

Responses to scopolamine administered 1) transdermally, 2) by mouth, and 3) in fixed-dose combination with amphetamine and ephedrine: Assessments in SRR.

Drug	Number of Subjects	Response % Beneficial	% Highly Efficacious
TTS (long-term use)	8	62.5	25
TTS x 2			
scopolamine p. o. (short-term use)			
S (0.3 mg)	8	50	25
(0.3 mg)	11	64	
S (0.6 mg)	8	67	62
(0.6 mg)	30	63	
S (0.3 mg) A (5 mg)	22	55	
S (0.3 mg) E (25 mg)	11	82	
S (0.6 mg)	30	63	
S (0.6 mg) A (5 mg)	22	55	
S (0.6 mg) A (10 mg)	19	63	

Transdermal Therapeutic System-scopolamine = TTS; l-scopolamine hydrobromide = S; d-amphetamine sulfate = A; ephedrine sulfate = E.

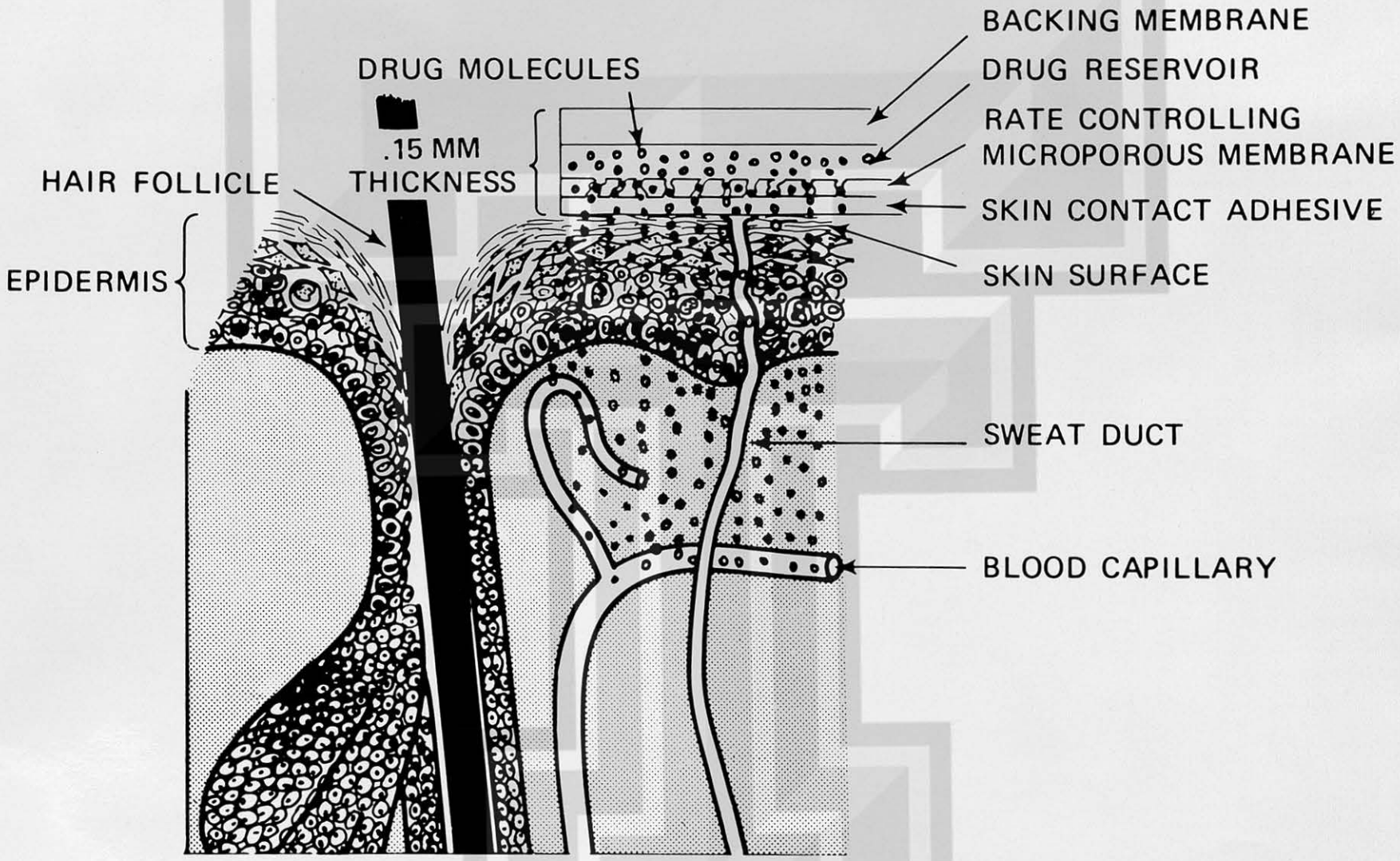
___ = recent series.

Response to Promethazine and Ephedrine Alone and in Fixed-Dose Combinations: Assessments in SRR

Drug	Number of Subjects	% Beneficial	Response Range	% >B1
P (12.5 mg)	8	50		12.5
P (25 mg)	8	50		
P (12.5 mg) E (12.5 mg)	8	75		37.5
P (25 mg) E (12.5 mg)	8	87.5*		62.5
P (25 mg) E (25 mg)	12	92		
P (25 mg) E (50 mg)	18	83		
E (12.5 mg)	8	12.5		0
E (25 mg)	10	10		
E (50 mg)	8	50		

P = promethazine hydrochloride; E = ephedrine sulfate; ____ = recent series.

*Assuming Subject 12 had all B responses.


BACKING MEMBRANE
DRUG RESERVOIR
DRUG MOLECULES
RATE CONTROLLING
MICROPOROUS MEMBRANE
.15 MM
THICKNESS
HAIR FOLLICLE
SKIN CONTACT ADHESIVE
EPIDERMIS
SKIN SURFACE
SWEAT DUCT
BLOOD CAPILLARY

Responses to Three Antimotion Sickness Remedies Administered Intramuscularly During Sorties in the KC-135

		Promethazine 25 mg			Scopolamine 4.3 mg			Dimenhydrinate 50 mg		
Subj.	Trial	1st FS* prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS	1st FS prior to injection	Inj.	Subsequent FS
19	1st	16**	21	38	12	12	0	12	13	24,29
	2nd	17	19	21,22				6	6	26
	3rd	23	25	0						
	4th	23	25	0						
	5th	26	26	0						
	6th				10	11	0			
33		11	13‡	14,15						
47	1st	30	30	30	12	12	0	24	25	29,32,40
	2nd				26	28	0			
8	1st	21	23	0						
	2nd	22	30	0						
10	1st	10	24	0	8	8	0			
	2nd	32	32	0						
	3rd	10	13	0						
16		15	19	22,23,38						
17	1st	0	11	13,17						
	2nd	9	10	0						
	3rd	0	10	13						

*FS = frank sickness; **16th parabola; ‡ promethazine 50 mg.

Table V

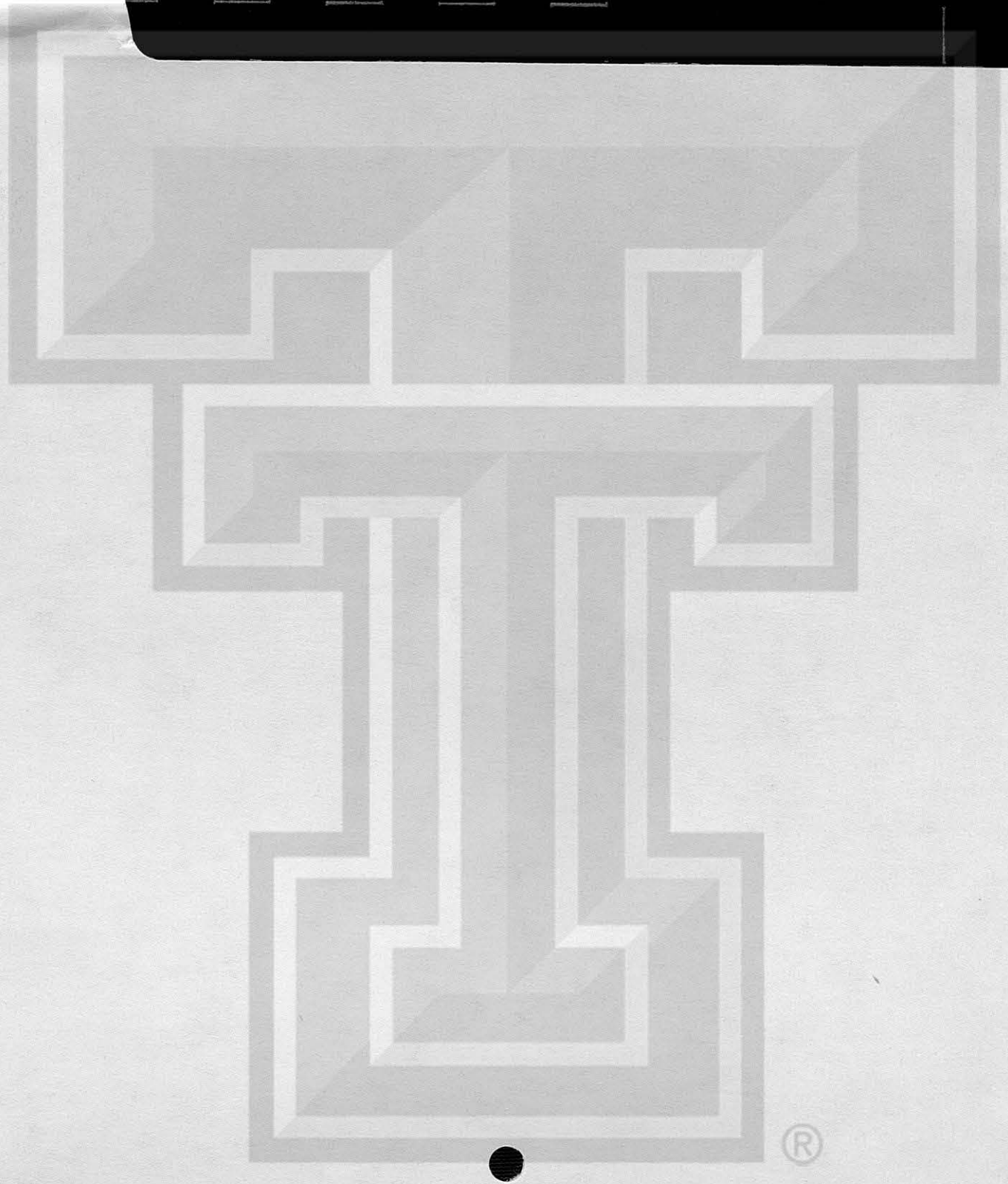
SPACE MOTION SICKNESS

- Review and Current Status -

December, 1976

SPACE MOTION SICKNESS

- INDEX -



SPACE MOTION SICKNESS

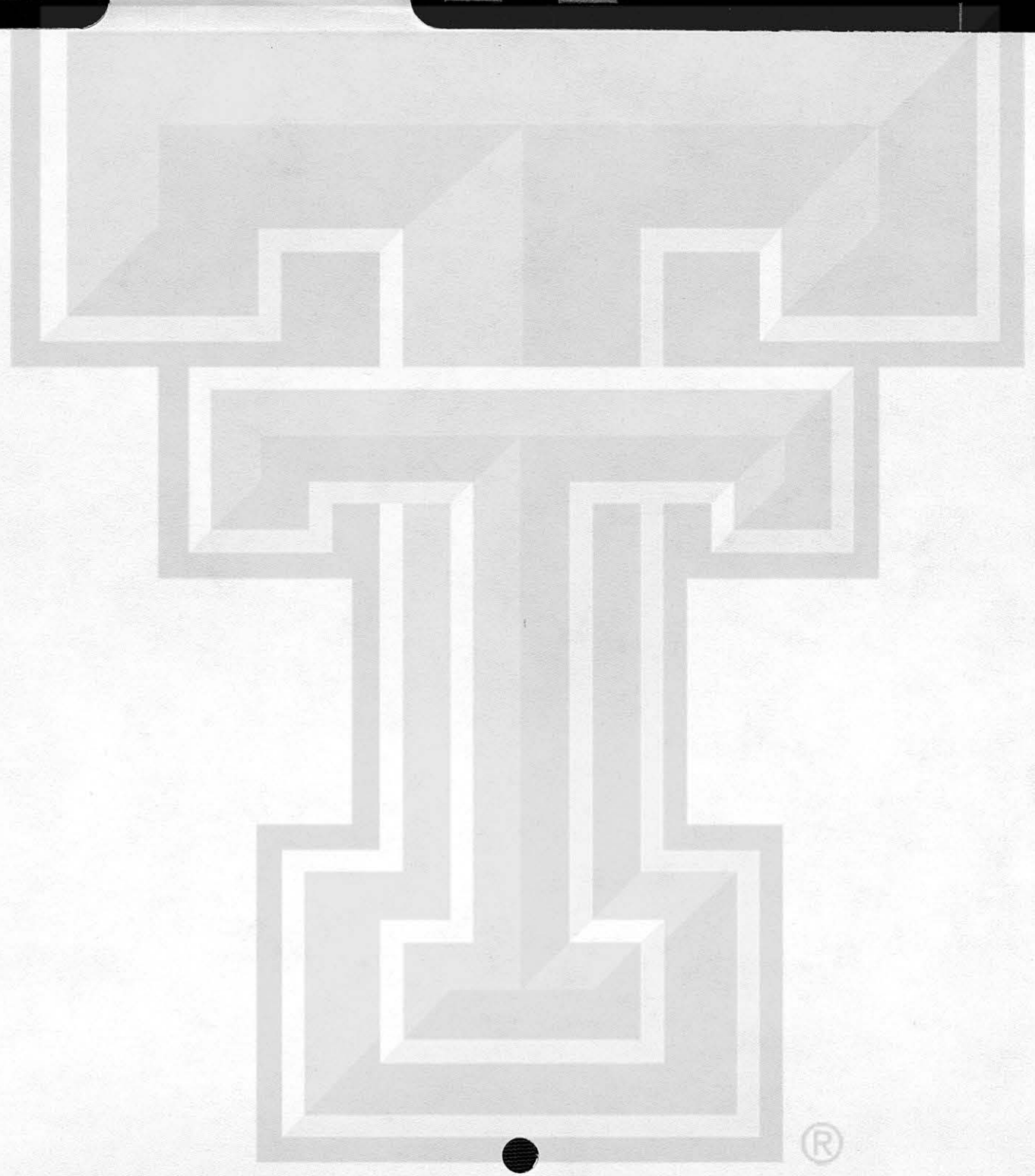
- BASIC SYMPTOMATOLOGY NOT UNLIKE SICKNESS RESULTING FROM EXPOSURE TO UNUSUAL MOTION ON SHIPS, CARS AND AIRCRAFT

- SYMPTOMS IN INCREASING ORDER OF SEVERITY

  - DECREASED MENTAL ALERTNESS/LETHARGY
  - VOLUNTARY RESTRICTION OF PHYSICAL ACTIVITY
  - DIZZINESS/VAGUE DISORIENTATION
  - HEADACHE
  - DECREASED APPETITE
  - STOMACH AWARENESS
  - COLD SWEATING/SUBJECTIVE WARMTH
  - PALLOR
  - NAUSEA
  - VOMITING

- INDIVIDUALS VARY GREATLY IN SUSCEPTIBILITY

- SPECIFIC CAUSES NOT WELL UNDERSTOOD; HOWEVER, MOST EVIDENCE POINTS TO SYNDROME AS HAVING ITS ORIGIN IN THE VESTIBULAR SYSTEM



MERCURY AND GEMINI PROGRAMS

- CONCERNS EXPRESSED PRIOR TO MERCURY PROGRAM ABOUT POSSIBLE DEBILITATING EFFECTS OF EXPOSURE TO WEIGHTLESSNESS
- SUBJECTIVE REPORTING BY CREWMEN INDICATED NO MOTION SICKNESS DURING ANY OF 6 MERCURY OR 10 GEMINI FLIGHTS
- ANTI-MOTION SICKNESS DRUG MAREZINE AVAILABLE TO CREWMEN BUT NOT USED
- VESTIBULAR EXPERIMENT M-9 (OCULAR COUNTERROLLING AND SPATIAL ORIENTATION) ON GEMINI V AND GEMINI VII CREWMEN PRODUCED NEGATIVE RESULTS

APOLLO PROGRAM

- 11 CREWMEN REPORTED MOTION SICKNESS TYPE SYMPTOMS; SEVERITY RANGED FROM MILD TO SEVERE (3 EXPERIENCED FRANK VOMITING)
- SYMPTOMS TYPICALLY MANIFESTED WITHIN HOURS AFTER ORBITAL INSERTION, WERE AGGRAVATED BY HEAD MOVEMENTS AND GRADUALLY DISSIPATED WITHIN 2-3 DAYS
- PREFLIGHT AEROBATICS INSTITUTED BY ASTRONAUTS FOLLOWING APOLLO 9
- ANTI-MOTION SICKNESS DRUGS MAREZINE AND SCOPOLAMINE-DEXETRINE USED SPARINGLY AND WITH UNCERTAIN SUCCESS
- CAUSE OF RELATIVELY HIGH INCIDENCE (ABOUT 33%) OF MOTION SICKNESS APPARENTLY DUE TO INCREASED MOBILITY IN COMMAND MODULE AND LUNAR MODULE
- NOVICE CREWMEN HAD SLIGHTLY GREATER TENDENCY TO DEVELOP SYMPTOMS THAN VETERAN ASTRONAUTS
- APOLLO MARKED FIRST U.S. FLIGHT EXPERIENCE WITH SPACE MOTION SICKNESS; IT WAS THE FIRST U.S. SPACECRAFT PERMITTING FREE MOVEMENT OF THE CREW WITHIN IT.

Vestibular-Related Symptoms Experienced by Apollo Astronauts

Mission	Astronaut	Motion Sickness History			Illusions/Motion Sickness Symptoms in Space Flight			
		In Land, Air and Sea Vehicles	In Zero-G Parabola	In S/C Egress or Egress Training	Tumbling Illusions	Stomach Awareness	Nausea	Vomiting
7	A	X						
	B	X	X	X				
	C	X		X	X			
8	D	X				X	X	X
	E	X	X	X		X	X	
	F	X	X			X		
9	G							
	H			X	X	X		
	I	X	X	X		X	X	X
10	J	X						
	K	X						
	L	X				X		
11	M	X	X	X				
	N	X	X	X				
	O	X	X					
12	P	X						
	Q							
	R			X				
13	S(E)	X	X	X				
	T					X	X	X
	U					X		
14	V	X						
	W	X						
	X							
15	Y(H)			X				
	Z		X		X	X		
	AA							
16	BB(X)	X						
	CC	X	X					
	DD	X	X					
17	EE(L)	X	X			X		
	FF	X	X			X		
	GG	X	X					

SKYLAB PROGRAM

- 5 OF 9 CREWMEN EXPERIENCED SYMPTOMS
- OPERATIONAL EFFICIENCY OF SEVERELY AFFECTED CREWMEN IMPAIRED DURING FIRST DAYS OF FLIGHT
- COMPLETE RECOVERY REQUIRED 3-5 DAYS
- ANTI-MOTION SICKNESS (AMS) DRUGS USED OF QUESTIONABLE THERAPEUTIC VALUE
- VALUE OF T-38 AEROBATICS BY SL-4 CREW UNCERTAIN BECAUSE OF PROPHYLACTIC USE OF AMS MEDICATION AND OTHER FACTORS
- UNEXPECTEDLY M131 EXPERIMENT REVEALED VIRTUAL IMMUNITY TO MOTION SICKNESS AFTER ADAPTATION TO WEIGHTLESSNESS HAD OCCURRED
- MOTION SICKNESS (SEA SICKNESS) EXPERIENCED BY SL-2 SPT AND PLT FOLLOWING SPLASHDOWN; SL-3 AND SL-4 CREWS MEDICATED PRIOR TO DE-ORBIT TO PREVENT SYMPTOMS

APOLLO-SOYUZ TEST PROJECT (ASTP)

- PREFLIGHT TESTING INDICATED CREW MODERATELY TO HIGHLY RESISTENT TO MOTION SICKNESS IN 1-G
- NO INFLIGHT OR POSTFLIGHT VESTIBULAR FUNCTION TESTING PERFORMED
- NO VESTIBULAR DISTURBANCES REPORTED DURING FLIGHT OR POSTFLIGHT
- SCOPOLAMINE-DEXEDRINE USED PROPHYLACTICALLY BY COMMAND MODULE PILOT EARLY DURING FIRST DAY OF FLIGHT
- BOTH COSMONAUTS EXPERIENCED SPACE MOTION SICKNESS

INCIDENCE OF SPACE MOTION SICKNESS IN US AND USSR

MANNED SPACE FLIGHT PROGRAMS

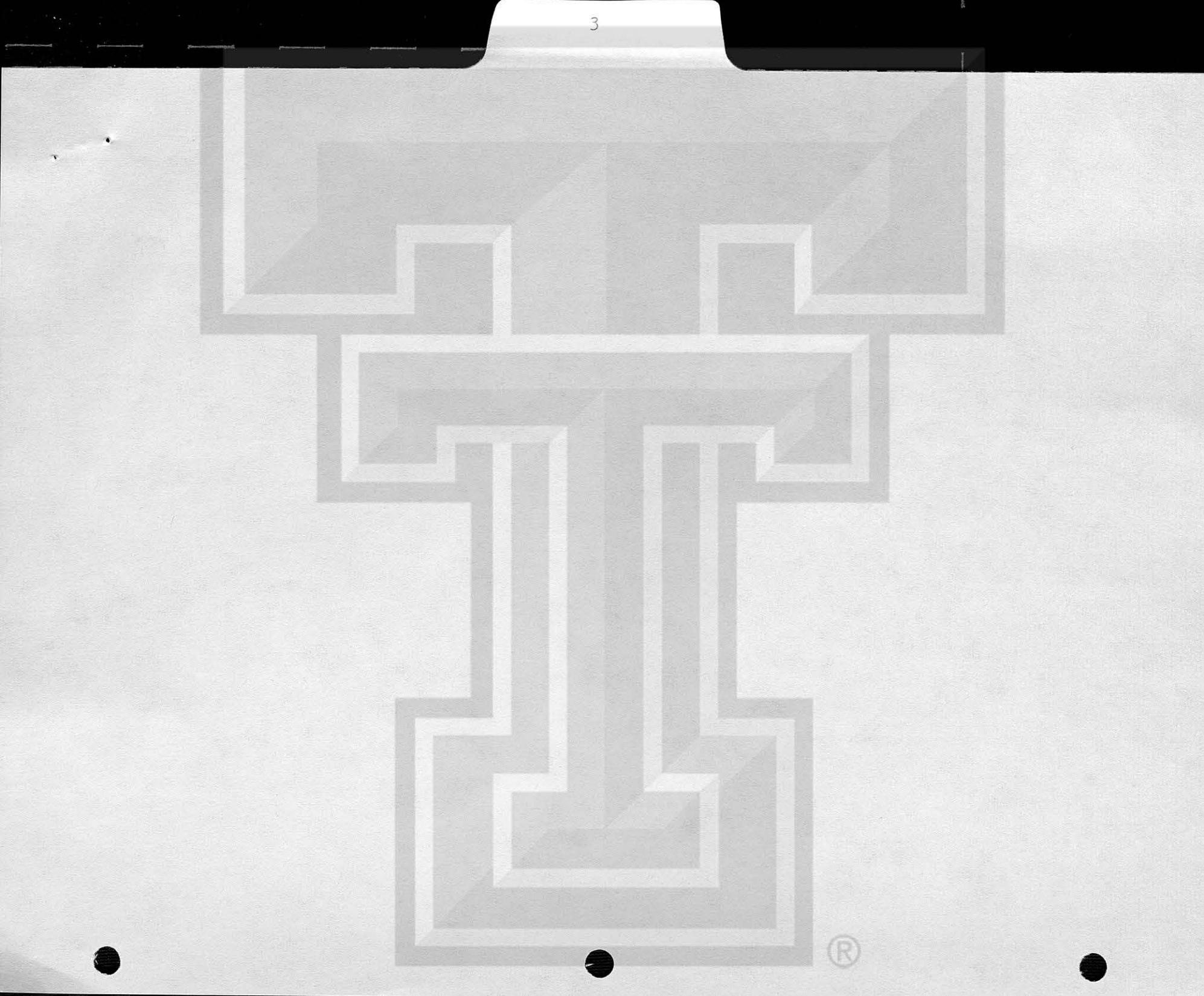
USA			USSR		
PROGRAM	NUMBER OF CREWMEN	INCIDENCE OF MOTION SICKNESS	PROGRAM	NUMBER OF CREWMEN	INCIDENCE OF MOTION SICKNESS
MECURY	6	0	VOSTOK	7	1 – Vom
GEMINI	20*	0	VOSKHOD	5	3 – Vom
APOLLO	33*	11**	SOYUZ	36#	19## – 9 Vom
SKYLAB	9	5	ASTP	2	2 – 1 Vom
ASTP	3	0			
TOTALS		16 ASTRONAUTS (Frank Vomiting in 6)			25 COSMONAUTS (Frank Vomiting in 15)

* INCLUDES 4 CREWMEN WHO FLEW TWICE DURING PROGRAM

** INCLUDES 1 CREWMAN WHO EXPERIENCED SYMPTOMS ON BOTH OF TWO FLIGHTS

\# INCLUDES 6 CREWMEN WHO FLEW TWICE DURING PROGRAM

9 WITH MAJOR SYMPTOMS; 10 ADDITIONAL WITH MINOR SYMPTOMS



SIGNIFICANCE OF SPACE MOTION SICKNESS FOR SHUTTLE

- FREQUENCY AND SEVERITY OF SYMPTOMS PRESENT POTENTIAL THREAT TO WELL-BEING AND OPERATIONAL EFFICIENCY OF SHUTTLE CREWMEN AND PASSENGERS

- FACTORS AMPLIFYING CONCERN

  - LARGE NUMBER OF HIGH WORKLOAD/SHORT DURATION FLIGHTS

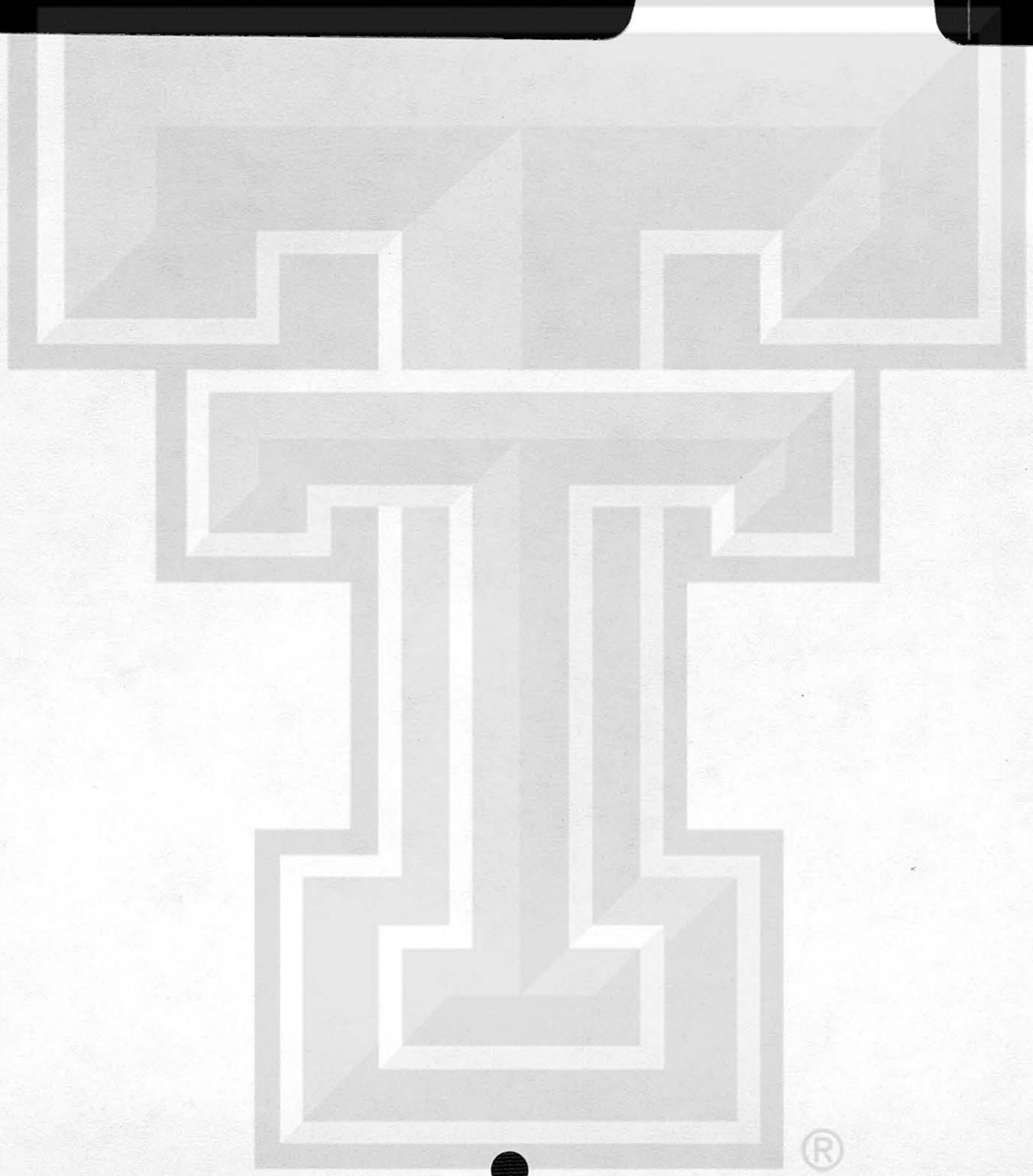
  - INTRODUCTION OF NOVICE CREWMEMBERS INEXPERIENCED WITH UNUSUAL GRAVITATIONAL-INERTIAL FORCE ENVIRONMENTS

  - VEHICLE CONFIGURATION PERMITS EXTENSIVE MOVEMENT BY CREWMEN

  - KNOWLEDGE OF ETIOLOGY AND METHODS FOR RELIABLE PREDICTION, PREVENTION AND TREATMENT OF SYNDROME CURRENTLY NOT OPTIMAL

TENTATIVE OPERATIONAL PLANNING FOR SHUTTLE
OFT PASSENGERS RE SPACE MOTION SICKNESS PROBLEM

- CONDUCT PREFLIGHT PERSONAL INTERVIEW
  - OBTAIN MOTION SICKNESS HISTORY
  - CONVEY RELEVANT STATE-OF-THE-ART KNOWLEDGE ABOUT SPACE MOTION SICKNESS
- PERFORM MINIMUM LABORATORY TESTS
  - EVALUATE INTEGRITY OF VESTIBULAR SYSTEM FUNCTION
  - DETERMINE MOTION SICKNESS SUSCEPTIBILITY THRESHOLD AND ACQUAINT INDIVIDUAL WITH RECOGNITION OF SYMPTOMS
  - IDENTIFY MOST EFFICACIOUS ANTI-MOTION SICKNESS (AMS) DRUG AND DOSE LEVEL
- EXPOSE INDIVIDUAL TO ZERO-G PARABOLIC FLIGHT (OPTIONAL)
  - PERMIT FAMILIARIZATION WITH UNUSUAL INERTIAL FORCE ENVIRONMENT AND ZERO G
  - FURTHER EVALUATE AMS DRUG EFFICACY/DOSAGE
- ENCOURAGE PROPHYLACTIC USE OF OPTIMUM AMS DRUG PRE-LAUNCH AND EARLY INFLIGHT



CURRENT POSITION

- NO SOUND BASIS FOR PREDICTION
  - PHYSIOLOGICAL MECHANISMS IN ZERO G NOT UNDERSTOOD
  - POOR CORRELATION BETWEEN MOTION SICKNESS IN DIFFERENT ENVIRONMENTS
- NO PROVEN METHOD FOR PREVENTION
  - MARKED INDIVIDUAL VARIATION IN DRUG RESPONSE
  - BIOFEEDBACK TECHNIQUES LOOK PROMISING
- HIGH LEVEL OF CONFIDENCE THAT WE CAN WORK AROUND THE PROBLEM

INVESTIGATIVE APPROACH

KEY FACTORS -

- o DEVELOPMENT OF SOLUTIONS FOR PROBLEMS IDENTIFIED WILL REQUIRE A BROAD BASED PROGRAM OF INTERDISCIPLINARY STUDIES USING HUMAN AND ANIMAL SUBJECTS

- o FUNDAMENTAL AND APPLIED ASPECTS OF THE MAJOR PROBLEM AREAS MUST BE INVESTIGATED IN PARALLEL

- o FINAL VALIDATION OF TECHNIQUES FOR PREDICTING, PREVENTING AND TREATING THIS SYNDROME WILL NOT BE POSSIBLE UNTIL SEVERAL SHUTTLE FLIGHT EXPERIMENTS HAVE BEEN CONDUCTED

SPACE MOTION SICKNESS RESEARCH PROGRAM

- PROBLEMS AND TASKS -

A. Etiology and Mechanisms of Space Motion Sickness

1 - Evaluation of Fluid Shift Theory of Etiology; Conflict Theory; Others

2 - Anatomical and Microelectrical Studies; Neurological Biochemistry

3 - Functional Studies; Behavioral Factors

4 - Mathematical Modeling

B. Determination of Individual Predisposition (Selection)

C. Development of Training Techniques to Diminish Susceptibility

D. Improved Countermeasures

1 - Improvement of Anti-Motion-Sickness Drugs

2 - Identification of Modifying Factors for Use in Prevention (Example: Biofeedback)

3 - Other Preventive/Therapeutic Techniques (Examples: In-Flight Adaptation Procedures, Fluid Shift Control)

E. Bioinstrumentation and Methodology Development

F. Preparation of Flight Experiments

GROUND BASED RESEARCH WITH MAN

- MAJOR EMPHASIS ON SENSORY CONFLICT AND MOTION SICKNESS INVOLVING OTOLITHS
- INCLUDED ARE INVESTIGATIONS OF
  - CANAL-OTOLITH INTERACTION
  - VISUAL-VESTIBULAR INTERACTION
  - VESTIBULO-SPINAL REFLEXES
  - PROPRIOCEPTIVE MECHANISMS
  - SENSORY HABITUATION
- STUDIES UTILIZE VARIETY OF STIMULUS GENERATION (INCLUDING PARABOLIC FLIGHT) AND RESPONSE MEASUREMENT TECHNIQUES
- ROLE OF FLUID SHIFT REQUIRES FURTHER ANALYSIS
- RESEARCH INVOLVING NEUROLOGICAL, PSYCHOPHYSIOLOGICAL AND BIOCHEMICAL FACTORS CURRENTLY LIMITED IN SCOPE
- DEVELOPMENT OF IMPROVED RESPONSE MEASUREMENT TECHNIQUES MUST EVOLVE FROM THESE PROGRAMS

HUMAN RESEARCH IN SPACE

- EMPHASIS ON PRE-, IN- AND POSTFLIGHT TESTS OF OTOLITH FUNCTION
- RELATED PRE-, IN- AND POSTFLIGHT EVALUATIONS OF
  - SEMICIRCULAR CANAL FUNCTION
  - NEUROMUSCULAR AND PROPRIOCEPTIVE FUNCTION
  - MOTION PERCEPTION AND SPATIAL ORIENTATION
- SPECIAL TESTS TO EVALUATE FLUID SHIFT AND OTHER SECONDARY POTENTIATING FACTORS
- MAJORITY OF EXPERIMENTS MUST BE CONDUCTED IN DEDICATED SPACELABS - WILL REQUIRE SOPHISTICATED HARDWARE AND EXTENSIVE CREW PARTICIPATION

GROUND BASED RESEARCH WITH ANIMALS

- NEUROPHYSIOLOGICAL, BEHAVIORAL, ANATOMICAL AND HISTOLOGICAL STUDIES OF VESTIBULAR, PROPRIOCEPTIVE AND VISUAL SYSTEMS
- ADVANTAGES OF USING ANIMALS
  - INVASIVE PROCEDURES
  - LARGE N
- EMPHASIS ON RESPONSES MEASURED IN SENSORY CONFLICT SITUATIONS
- PARABOLIC FLIGHT STUDIES TO EVALUATE RESPONSES TO HYPER AND HYPOGRAVIC STIMULI
- EVALUATION OF SPECIFIC PHENOMENA VIA INVASIVE TECHNIQUES
  - FLUID SHIFT MECHANISMS
  - ALTERATION OF NEURAL IMBALANCE WITH DRUGS
- STUDIES DESIGNED TO COMPLIMENT HUMAN RESEARCH AND DEFINE REQUIREMENTS FOR ANIMAL FLIGHT EXPERIMENTS
- WORK IS UNDERWAY IN ABOVE AREAS

ANIMAL RESEARCH IN SPACE

- ANIMAL EXPERIMENTS SHOULD COMPLIMENT HUMAN INFLIGHT EXPERIMENTS WERE POSSIBLE
- IDENTIFY SPECIES WITH EASILY MEASURED MOTION SICKNESS RESPONSE
- ELECTROPHYSIOLOGICAL TECHNIQUES TO MEASURE DISCHARGE OF CRITICAL COMPONENTS OF CENTRAL AND PERIPHERAL NERVOUS SYSTEM
  - PRIMARY AFFERENTS
  - VESTIBULAR EFFERENCE
  - VESTIBULAR NUCLEI
  - RETICULAR SYSTEM
  - SPINAL CORD MOTONEURONS
- RESOLVE FLUID SHIFT QUESTION
- SOPHISTICATED CORE REQUIRED, INCLUDING LINEAR ACCELERATOR AND CENTRIFUGE

PREDICTION (SELECTION CRITERIA)

- TOTAL APPROACH TO RESOLUTION OF THIS PROBLEM CANNOT BE DEFINED AT PRESENT
- SEVERAL POTENTIALLY FRUITFUL LINES OF INVESTIGATION CAN BE IDENTIFIED
  - STUDIES UTILIZING CENTRIFUGES AND SLOW ROTATING ROOMS
  - STUDIES UTILIZING LINEAR ACCELERATION TECHNIQUES
  - AIRCRAFT PARABOLIC FLIGHT (ZERO-G) STUDIES
  - DETERMINATION OF RATE OF ACQUISITION OF ADAPTATION
  - DETERMINATION OF CORRELATIONS BETWEEN MOTION SICKNESS SUSCEPTIBILITY AND OTHER MEASURABLE VESTIBULAR AND NON-VESTIBULAR RESPONSES
  - ATTENTION TO AGE AND SEX FACTORS

VALIDATION OF SELECTION CRITERIA AND COUNTERMEASURES

- GROUND BASED STUDIES WILL NOT PRODUCE IRREVOCABLE RESULTS
- FINAL VALIDATION WILL NOT BE POSSIBLE UNTIL A NUMBER OF SHUTTLE MISSIONS HAVE OCCURRED
- ESSENTIAL THAT CREWMEMBERS BE ASSIGNED TO EXPERIMENTAL AND CONTROL GROUPS
- LARGE SAMPLE SIZES REQUIRED FOR VALID STATISTICAL ANALYSIS AND INTERPRETATION
- OPERATIONAL PROBLEMS WITH THIS APPROACH MUST BE CONSIDERED
- EVALUATIONS SHOULD NOT REQUIRE SPECIAL INFLIGHT HARDWARE, CREW INFLIGHT INVOLVEMENT SHOULD BE MINIMAL

PREVENTION

- TWO BASIC APPROACHES UNDER INVESTIGATION
  - PREHABITUATION
    - FUNDAMENTAL QUESTIONS REGARDING APPROPRIATENESS OF VARIOUS TECHNIQUES MUST BE ANSWERED
    - TIME AND SOPHISTICATED FACILITIES REQUIRED MAY BE LIMITING FACTORS
  - ANTI-MOTION SICKNESS DRUGS
    - EFFICACY AS WELL AS SIDE EFFECTS MUST BE EVALUATED
    - SITE OF DRUG ACTION SHOULD BE BETTER UNDERSTOOD

TREATMENT

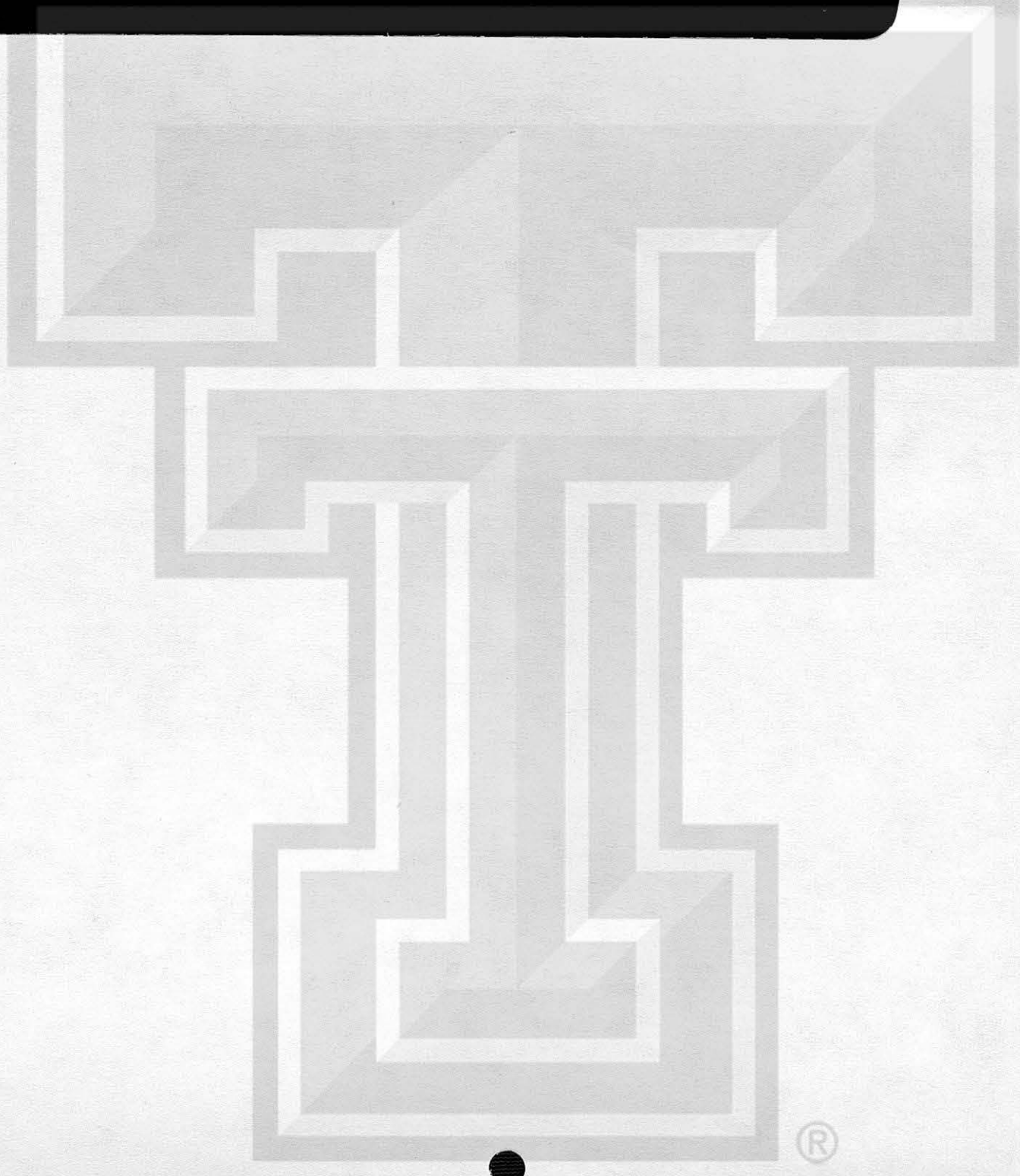
- ANTI-MOTION SICKNESS DRUGS PRIMARY REMEDY USED IN PAST
- LIMITED ATTEMPTS WITH SPECIAL INFLIGHT HABITUATION PROCEDURES NOT SUCCESSFUL
- EFFORTS IN PROGRESS FOCUSING ON
  - IMPROVED DRUG THERAPY
  - OPERATIONALLY ACCEPTABLE INFLIGHT HABITUATION PROCEDURES, POSSIBLY AIDED WITH DRUGS
  - MINIMIZATION OF MOVEMENT THROUGH IMPROVED PROCEDURAL CHECK LISTS, WORK LOAD REQUIREMENTS AND TASK GEOMETRY

SPACE MOTION SICKNESS

CURRENT SR&T PROGRAM (FY77)
BY PROBLEM AND TASK

RESEARCH PROBLEM AREA	TASKS FROM THIS RTOP PRIMARY OBJECTIVE OF TASKS:	A MAJOR OBJECTI OF TASKS:
A. Etiology and Mechanisms of Space Motion Sickness		
1. Evaluation of Fluid Shift Theory of Etiology	1-03 Homick 1-04 Parker	
2. Anatomical and Micro-electrical Studies	1-07 Correia 2-05 Perachio 2-07 Ebbesson 2-08 Goldberg 2-10 Daunton 2-11 Bizzi 2-12 Nauta 2-13 Markham	2-21 Brizze
3. Functional Studies	1-03 Homick 1-04 Parker 1-05 Igarashi 2-04 Teuber 2-05 Perachio 2-10 Daunton 2-11 Bizzi 2-12 Nauta 2-13 Markham 2-25 Sadoff	1-02 Frost 2-16 Young
4. Mathematical Modeling	1-06 Cohen 1-07 Correia 2-11 Bizzi	
B. Determination of Individual Predisposition (Selection)	1-01 Graybiel 2-16 Young	1-03 Homick
C. Development of Training Techniques to Diminish Susceptibility		1-01 Graybiel 2-16 Young

RESEARCH PROBLEM AREA	TASKS FROM THIS RTOP: PRIMARY OBJECTIVE OF TASKS:	A MAJOR OBJECTI OF TASKS:
D. Improved Countesmeasures		
1. Drugs	1-09 TBD 2-21 Brizze	1-01 Graybiel 1-03 Homick 1-07 Correia
2. Identification (and Prevention) of Modifying Factors	2-18 San Jose	1-03 Homick
3. Other	2-18 San Jose	1-05 Igarashi
E. Bioinstrumentation and Methodology Department	1-02 Frost 2-05 Perachio	1-03 Homick 1-04 Parker
F. Preparation of Flight Experiments		1-05 Igarashi 2-05 Perachio



SPACE MOTION SICKNESS

PROGRAM MILESTONES

Late Spring, 1977	AO for Dedicated Life Sciences Spacelabs
July, 1977	AIBS Vestibular Research Program Review
July, 1977	Completion of Ground Based Animal Investigations of Fluid Shift Hypothesis (Parker)
October, 1977	US/USSR Discussion of Space Motion Sickness (One of the Subjects to be Discussed)
March, 1978	Completion of Ground Based Human Investigations of Fluid Shift Hypothesis (Homick, Parker, and Greenleaf)
July, 1978	Completion of Preliminary Ground Based Evaluations of Predictive Tests of SMS Susceptibility; Establish Tentative Test Battery
October, 1978	Completion of Preliminary Ground Based Evaluations of Preconditioning (Training) Techniques to Minimize In-Flight SMS; Establish Tentative Training Plan
January, 1979	Completion of Ground Based Evaluations of New Drugs for Control of SMS
Fall, 1980	Conduct Selected Human Vestibular Flight Experiments on SL-1 (Young, Homick)
Fall, 1982	Complete Preliminary In-Flight Validation of Training, Predictive Tests and Countermeasures