

Space Motion Sickness

Symposium Proceedings

November 15 - 17, 1978



National Aeronautics and
Space Administration

Lyndon B. Johnson Space Center
Houston, Texas

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Space Administration



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Reply to Attn of: September 19, 1979

Dear Colleague:

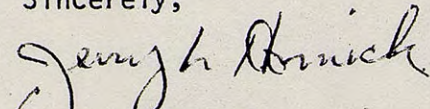
Enclosed is a copy of the proceedings of the Vestibular/Space Motion Sickness Symposium which was held at the Johnson Space Center last November. Note that I chose to use a slightly modified name for the meeting on the document cover.

It had been my intent to have the document completed and distributed no later than May of this year. However, a number of unforeseen events resulted in delays. Despite its somewhat late distribution, I hope that the document can be useful to you in your work. I am confident that it will be a valuable source of information for those of us at NASA.

At the present time I am pursuing the feasibility of releasing the report as a formal NASA publication. However, if you have not already done so, you should feel free to publish in other media the material you submitted for the symposium proceedings. Publication by NASA would not preclude publication of your paper in a scientific journal since our documents have a limited circulation. I will notify you when our publication plans are finalized.

I want to take this opportunity to personally thank you again for your participation in the symposium and for your written contribution to the proceedings.

Sincerely,


Jerry L. Homick

THE PROCEEDINGS OF A

**SPACE MOTION SICKNESS
SYMPOSIUM**

NOVEMBER 15 - 17, 1978

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Final Report

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Preface

Of the various human physiological disturbances resulting from exposure to weightless space flight, space (motion) sickness has been and continues to be one of the most significant and perplexing. Space sickness is significant in that the well-being and operational efficiency of affected crewmembers may be adversely compromised during the critical early days of a mission. On the basis of past manned space flight experience (both in the U.S. and U.S.S.R.) and an analysis of Space Shuttle operational requirements, it is not unreasonable to anticipate that without appropriate interventions as many as 40% of Shuttle crewmembers could experience some degree of space sickness. The issue of space sickness is perplexing in that despite the vast amount of ground based motion sickness research that has occurred during the past 30 years, we are unable to fully explain the mechanisms of this malady in weightlessness, nor do we have reliable methods for its prediction, prevention and treatment.

The issues surrounding space sickness should not be unsolvable. Properly conceived and implemented ground based and flight experiments should lead to solutions. Indeed, the National Aeronautics and Space Administration is currently sponsoring a broad based program of fundamental and applied research which is specifically directed toward the space sickness problem. This program has yielded a considerable amount of new information, however, it is obvious that much remains to be learned.

As we approach the first manned Space Shuttle flights increased emphasis must necessarily be placed on the operational issues of prediction, prevention and treatment. It was with this fact in mind that the Vestibular/Space Motion Sickness Symposium was convened in November 1978 at the Johnson Space Center. The primary objectives of the symposium were to review research currently being performed by NASA's vestibular research "team" and to formulate recommendations for future research and development with particular emphasis on the practical issues of prediction, prevention and treatment of space sickness. An additional objective was to discuss factors related to the etiology of space sickness where it was evident that such information was critical to the assessment of predictive techniques and countermeasures. The symposium was attended by approximately 40 people. This number included a majority of those vestibular investigators who currently hold NASA research grants or contracts, a group of six invited consultants and a variety of management personnel and vestibular investigators from the Johnson Space Center, Ames Research Center and NASA Headquarters.

The activities of the 2 1/2 day symposium were organized into two general categories. During the first day and part of the second day, invited papers were presented by 16 of the symposium participants. Brief question and answer periods followed each paper. The remainder of the symposium was devoted to four special workshop discussion sessions. The titles of these workshops were: "Vestibular/Motion Sickness Mechanisms", "Prediction of Susceptibility", "Training Countermeasures" and "Drug Countermeasures". The moderators or discussion leaders for each of these workshops were pre-selected from among the consultants and non-NASA investigators at the symposium. Because the workshops were arranged in a serial order, all of the symposium attendees were afforded the opportunity to participate in all of the workshops. Although a

number of discussion topics for each workshop were pre-defined by the NASA editor, the discussion leaders and other symposium participants were encouraged to introduce and discuss other relevant topics within the context of each workshop. Brief summaries of each workshop appear in this report. These summaries are based upon (a) transcripts derived from tape recordings of the sessions and (b) written reports submitted by the discussion leaders following the conclusion of the symposium. Unedited versions of the discussion leaders' reports appear as appendices in this document.

Regardless of the criteria one may choose to use, the Vestibular/Space Motion Sickness Symposium must be considered a successful meeting. The quality of the papers presented was excellent. The workshop discussions were lively, enlightening and informative. The overall enthusiasm of the meeting participants was reflected in a number of ways not the least of which was the fact that most discussions ran beyond their scheduled time resulting in the cancellation of several lower priority agenda items. One must conclude that the primary objectives of the symposium were met. However, in a realistic sense, it must be clearly recognized that this symposium did not solve the space sickness problem. It merely served to move us a few more steps in the right direction. Additional meetings of this type should be held at regular intervals in the future to exchange new data and concepts, update the results of this symposium and in general continue a scientific dialogue on the issues of space motion sickness and neurosensory adaptation to weightless space flight.

As a final note, sincere appreciation is extended to all of those individuals who helped to make this symposium a success. Special appreciation is offered to Dr. Sherman Vinograd for his inspiration and guidance in laying the foundation for the symposium. Special gratitude is tendered to Dr. Ronald Hoffman who assisted with the overall organization and implementation of the symposium and who later helped edit the workshop transcripts and prepare the summary report. Gratitude is also extended to the workshop discussion leaders who unselfishly devoted their time to preparing for, conducting and summarizing the various workshop sessions. Finally, a special note of thanks is offered to Benjy Ashley who typed this report.

Jerry L. Homick

Editor

SEP 7 1979

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INVITED PAPERS

Editors note: The individuals who presented invited papers were given the option of submitting an abstract of their paper or a short manuscript. No standardized editorial style was imposed a priori on these written submissions. These liberal instructions to the authors account for the fact that the papers contained in this summary report vary in length and format. In re-typing the submissions minor style changes were introduced by the editor, however, the technical content of each paper was unaltered. Two papers had not been submitted to the editor prior to the publication of this summary report.

EVALUATION OF VESTIBULAR FUNCTION USING SINUSODIAL OSCILLATION
PRODUCED DURING THE DAMPED TORSION SWING TEST

M. J. Correia, D. J. Ireland*, L. A. Singer, A. R. Eden,
C. M. Griffiths, and R. B. Price

Department of Otolaryngology
The University of Texas Medical Branch
Galveston, Texas 77550 USA

*Department of Otolaryngology
University of Manitoba School of Medicine
Winnipeg, Manitoba, Canada

Introduction

The Damped Torsion Swing Test (DTST) has been used for some time, primarily by French neuro-otologists (see, e.g., Greiner *et al.*, 1969), to detect dysfunction in both the peripheral nervous system (PNS) pathways and central nervous system (CNS) pathways associated with the vestibulo-ocular system. The DTST complements routine vestibular clinic tests such as the bilateral-bithermal caloric test in that the DTST has the following desirable features: (1) The DTST consists of gentle rotation. The test is not disturbing even to the vertiginous patient or child. (2) The DTST elicits a response from the patient to a rotational stimulus. In a small percentage of individuals referred to the vestibular clinic it is difficult to obtain a response to the Hallpike bilateral-bithermal caloric test. The DTST provides corroborative information as to whether a patient received an adequate caloric stimulus, or whether he has a unilateral or bilateral labyrinthine weakness. (3) The DTST utilizes controlled angular acceleration input to both labyrinths simultaneously and therefore tests the vestibulo-ocular response to synergistic input from both labyrinths; a stimulus condition the patient actually encounters in his daily endeavors. (4) The DTST produces results which, if properly interpreted, can indicate the presence of a latent or spontaneous nystagmus or a "centrally compensated" lesion in one of the labyrinths or its innervation. Moreover, the DTST has been shown to be effective in the determination of a "labyrinthine threshold" as well as "Labyrinthine hypo- and hyper-excitability" (Breiner *et al.*, 1969). (5) The DTST uses a relatively simple and inexpensive device to provide controlled vestibular stimulation.

The DTST provides information as to the integrity and excitability of the horizontal vestibulo-ocular reflex and associated neural systems. There is reason to believe that these two conditions may be correlated with motion sickness susceptibility and should be considered in crew selection for future space flights.

The DTST, by international convention, consists of two rotational sequences (Run 1 and Run 2) separated by a rest period. Each run

incorporates 15 sinusoidal oscillations which have an angular frequency of 0.05Hz and peak angular accelerations which decay exponentially from 18°/s to zero. Frequency of horizontal nystagmus (number of nystagmic beats) and quality of nystagmus waveform are the most frequently used response measures for the DTST (Greiner et al., 1969). Routinely, DTST results (see Fig. 1) are reported as plots of number of nystagmic beats per half cycle as a function of the logarithm (base e or base 10) of peak angular acceleration. Two plots are presented; one for Run 1 and a second for Run 2. Two curves are displayed in each of these plots. Number of beats/half cycle for left beating nystagmus (conventionally symbolized by X's) and number of beats/half cycle for right beating nystagmus (conventionally symbolized by O's) are plotted against ln angular acceleration.

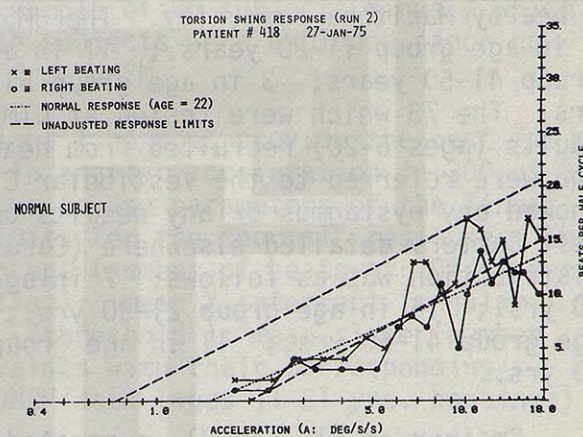
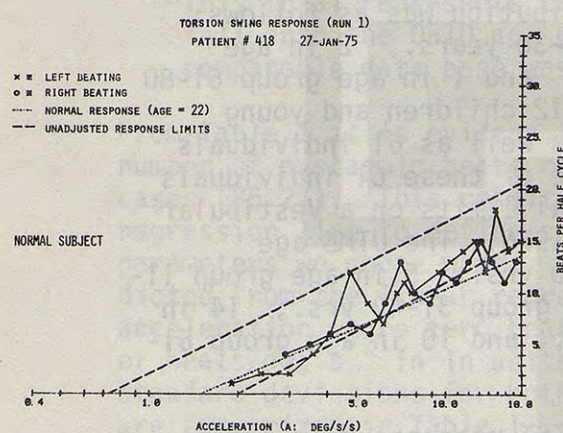


Figure 1. Displays of the response to Run 1 (left graph) and Run 2 (right graph) to the Damped Torsion Swing Test. Number of beats/half cycle are plotted against angular acceleration on a ln scale. Values based on the left beating portion of the nystagmic response are denoted by X's; those based on the right beating portion of the nystagmic response are denoted by O's. Normal limits denoted by the dashed lines are after the work of Greiner et al. (1969). The dot-dash line represents a reference line which changes as a function of the patient's age. The equation for this line is based on the work of Van de Calseyde et al. (1974).

Greiner et al. (1969), presented one set of confidence limits for the "normal" response to the DTST. These confidence limits are shown as dashed

lines in Fig. 1. Van de Calseyde *et al.* (1974), presented normative data for the DTST from 150 individuals in four different age groups (5-10 years, 1-25 years, 25-50 years, and 50 years and older) and showed that the responses from the different age groups are different. Based on these data, we developed an equation (R. B. Price, unpublished observations) to predict the normal response for different ages to the DTST. An example of the plot of this equation is shown as a dot-dash line in Fig. 1. Recently, we have completed a more rigorous analysis of the results of the DTST for 94 "normal" subjects of different ages from two vestibular clinics. These data have enabled us to establish normal confidence limits for DTST for each decade of age from 0 to 80 years.

Method and Results

The responses from 95 individuals to the DTST were chosen for analysis. Seventy-three of these individuals were tested at The University of Texas Medical Branch (UTMB), Galveston, Texas, USA, and 22 were tested at the University of Manitoba School of Medicine (UMSM), Manitoba, Canada. The 22 individuals from the UMSM group were mostly young adults recruited from a nearby Manitoba community. The UMSM age distribution was as follows: 5 in age group 11-20 years.; 11 in age group 21-30 years.; 2 in age group 41-50 years.; 3 in age group 51-60 years.; and 1 in age group 61-80 yrs. The 73 which were tested at UTMB included 12 children and young adults (ages 6-20) recruited from nearby areas as well as 61 individuals who were referred to the Vestibular Clinic. None of these 61 individuals showed any nystagmus or any results outside normal limits on a Vestibular Test Battery detailed elsewhere (Caruso *et al.*, 1976). The UTMB age distribution was as follows: 7 in age group 0-10 yrs.; 5 in age group 11-20 yrs.; 15 in age group 21-30 yrs.; 11 in age group 31-40 yrs.; 14 in age group 41-50 yrs.; 11 in age group 51-60 yrs.; and 10 in age group 61-80 yrs.

Greiner *et al.* (1969), suggested that the DTST response from normal individuals produces an exponential relationship between number of nystagmic beats and angular acceleration. We evaluated this suggestion for our data by performing a logarithmic (base e) transform on angular acceleration and then regressing number of nystagmic beats on $\ln$ angular acceleration with first- through fourth- order polynomials. Age groups 11-20 yrs., 21-30 yrs., 31-40 yrs., 41-50 yrs., 51-60 yrs., and 61-80 yrs. were compared and the results are presented in Table I.

TABLE I
NUMBER OF TIMES A POLYNOMIAL OF ORDER 2-4 PROVIDED A STATISTICALLY
SIGNIFICANT ($P < 0.01$) REDUCTION IN REGRESSION SUM OF SQUARES AS
COMPARED TO A FIRST-ORDER POLYNOMIAL

Data Base	Subjects	Data Sets	Total	Improvement (%)
UTMB	66	4*	264	42/264 (15.9)
UMSM	22	4	88	10/88 (11.4)
Total	88*	4*	352	52/352 (14.8)

*For each subject there were 4 data sets: Run 1-fast phase left;
Run 1-fast phase right; Run 2-fast phase left; Run 2-fast phase right.

**This total represents the complete sample of 95 subjects minus 7 which
fell into the 0-10 age group. These subjects were excluded since no
comparable data base was available from UMSM.

From Table I it is evident that a straight line does provide the best fit of
number of nystagmic beats regressed on $\ln$ angular acceleration in 300 of 352
cases (85.2%). This result encouraged us to use parameters of the linear
regression line to define confidence limits for the "normal" response. The
parameters we chose were: mean Y intercept (number of beats at $18^\circ/\text{s}^2$ pre-
dicted from the linear regression equation); mean X intercept (angular
acceleration where zero beats occurred - "threshold"); mean slope (number
of beats/deg. s^{-2} in $\ln$ units). These values with their corresponding
standard deviations for both UTMB and UMSM data (ages 11-81 yrs. combines)
are summarized in Table II.

TABLE II
COMPARISON OF MEAN PARAMETERS FOR UTMB (N = 66) AND UMSM (N = 22)

Run 1 (mean $\pm$ SD)	UTMB	UMSM	t val.*
Y intercept (# beats at $18^\circ/\text{s}^2$)	16.75 $\pm$ 3.65	13.88 $\pm$ 4.15	1.32
X intercept (ang. accel. $^\circ/\text{s}^2$)	2.24 $\pm$ 1.02	2.07 $\pm$ 0.84	0.31
Slope [# beats/deg. s^{-2} ($\ln$ units)]	8.09 $\pm$ 2.80	6.35 $\pm$ 2.19	1.14
Slope [# beats/deg. s^{-2} (Log units)]	18.61 $\pm$ 6.44	14.61 $\pm$ 5.04	
Run 2 (mean $\pm$ SD)			
Y intercept (# beats at $18^\circ/\text{s}^2$)	16.28 $\pm$ 2.84	13.45 $\pm$ 4.28	1.52
X intercept (ang. accel. $^\circ/\text{s}^2$)	2.41 $\pm$ 1.57	1.91 $\pm$ 0.92	0.60
Slope [# beats/deg. s^{-2} ($\ln$ units)]	8.19 $\pm$ 3.54	5.89 $\pm$ 2.25	1.22
Slope [# beats/deg. s^{-2} (Log units)]	18.84 $\pm$ 8.14	13.55 $\pm$ 5.18	

*Two tailed t-test, d.F. = 86.

As can be seen from the last column in Table II, two tailed t-test comparisons of the data from UTMB and UMSM failed to reveal statistically significant differences ($P < 0.05$) for any of the three parameters: mean X intercept, mean Y intercept, and mean slope. Therefore, the data for these parameters were pooled. However, when we performed two tailed t-test comparisons on the pooled data for each age group, significant differences were found for each of the three parameters (Appendices A1, A2 and A3). Therefore, we were not able to obtain mean values for X intercept, Y intercept, and slope for all ages combined. Mean values (standard deviation) of pooled UTMB-UMSM data for different age ranges are presented below in Table III.

Since separate plots are generally reported for Run 1 and Run 2 of the DTST, values for mean slope, mean Y intercept (number of beats at $18^\circ/\text{s}^2$) and mean X intercept (acceleration value for zero beats) are presented for Run 1 and Run 2. These mean values (plus or minus one standard deviation) form the confidence limits for plots in which we report DTST results for patients seen in the Vestibular Clinics at UTMB and UMSM.

TABLE III
MEAN (SD) NORMATIVE DATA FOR POOLED UTMB-UMSM RESPONSES
FOR DIFFERENT AGE GROUPS

Age range	N	Max. beats (at $\alpha = 18^\circ/\text{s}^2$)	Thresh. accel. (intercept for zero beats)	Slope [beats/deg. s^{-2} (Ln units)]
0-10 (Run 1)	7	12.07 (2.30)	1.92 (0.58)	5.33 (1.47)
0-10 (Run 2)	7	12.01 (2.69)	2.20 (1.12)	5.85 (2.70)
11-20 (Run 1)	10	15.88 (2.55)	1.71 (0.80)	6.70 (2.19)
11-20 (Run 2)	10	15.91 (2.54)	1.88 (1.04)	7.10 (2.34)
21-30 (Run 1)	26	15.18 (4.44)	2.24 (1.04)	7.21 (3.02)
21-30 (Run 2)	26	14.46 (4.19)	1.90 (0.94)	6.30 (2.40)
31-40 (Run 1)	11	16.25 (4.56)	1.69 (0.93)	7.05 (3.64)
31-40 (Run 2)	11	15.25 (2.64)	1.96 (0.89)	6.83 (2.03)
41-50 (Run 1)	16	16.06 (3.54)	2.41 (1.04)	8.01 (2.58)
41-50 (Run 2)	16	18.88 (3.00)	2.53 (1.22)	7.98 (2.50)
51-60 (Run 1)	14	16.68 (4.18)	2.18 (-.74)	7.92 (2.32)
51-60 (Run 2)	14	16.12 (4.05)	1.77 (0.85)	7.07 (2.76)
61-80 (Run 1)	11	17.46 (2.95)	2.89 (0.79)	9.50 (1.79)
61-80 (Run 2)	11	17.53 (2.32)	2.92 (1.21)	9.60 (2.59)

Discussion

Greiner et al. (1969), presented one set of confidence limits for all ages for the DTST when number of nystagmic beats/half cycle is plotted against $\ln$ angular acceleration. Van de Calseyde et al. (1974), showed that a family of curves resulted from the plot of number of nystagmic beats/half cycle against angular acceleration for different age groups. Furthermore, the family of curves demonstrated the following trends: (1) peak number of beats/half cycle at $18^\circ/\text{s}^2$ decreases with decreasing age and, (2) a linear approximation of the curvilinear function relating beats/half cycle and angular acceleration has a slope which appears different for different age groups. The slope appears to decrease with decreasing age. The present communication extends the results of Van de Calseyde et al. (1974), since we demonstrate statistically that: (1) in 300 of 352 cases (85.2%) a straight line best describes the relation between number of nystagmic beats/half cycle and $\ln$ angular acceleration when compared with higher-order polynomial fits (orders 2-4); (2) the parameters of the best fit straight line such as mean slope and mean Y intercept (number of beats/half cycle at $18^\circ/\text{s}^2$ change in a systematic (but not generally statistically significant) way as a function of age.

Table III presents results which confirm the trends described above for the data of Van de Calseyde et al. (1974), that is, mean Y intercept decreases with decreasing age and mean slope increases with increasing age. However, two tailed t-test comparisons among all age groups (presented in Appendices A1, A2 and A3) indicate that significant differences ($P < 0.01$) exist only between the mean slope of the linear regression line for the 61-80 yr. age group when compared to the 0-10 yr. and 21-30 yr. age groups. Moreover, the 61-80 yr. age group has a statistically significantly different ($P < 0.01$) "threshold" (mean X intercept) than the 11-20 yr. and 31-40 yr. age groups. Finally, it appears that the mean Y intercept is not statistically significantly different among age groups; the 0-10 yr. age group being an exception. The mean Y intercept for this age group is statistically different from the 11-20 yr., 31-40 yr., 41-50 yr., and 61-80 age groups.

Conclusions

The following conclusions regarding the DTST seem warranted from the results presented above: (1) number of nystagmic beats (either fast phase left or fast phase right) per half cycle is exponentially related to angular acceleration over the range $18^\circ/\text{s}^2$ to zero. (2) While three parameters (mean slope, mean X intercept, and mean Y intercept) associated with the linear regression line relating number of beats/half cycle and $\ln$ angular acceleration differ in a systematic fashion for different age groups, only the extreme age groups (0-10 yrs. and 61-80 yrs.) are statistically significantly different from the remaining ages grouped in decades. (3) Care must be exercised in the interpretation of an "abrupt relapse trace" (Van de Calseyde, 1974) produced by elderly people (61-80 yrs.). This trace, taken as a sign of vertebrobasilar insufficiency, is characterized by a large Y intercept and a steep slope. It has been shown, herein, that "normal" individuals in this age category have mean values for these parameters which are statistically significantly different ($P < 0.01$) from other

age groups. (4) Care must be taken in the interpretation of hypo- and hyper- excitability for different age groups since it has been shown herein that both the mean Y intercept and mean slope differ significantly for the 0-10 yr. age group as compared to the 61-80 yr. age group. (5) Because systematic trends do exist for mean Y intercept and mean slope in the DTST, resolution is affected by pooling age groups into categories greater than each decade, since pooled data will have wider confidence limits than those presented in Table III.

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APPENDIX A1

Two tail t-test values between mean slopes for decade age groups of best fitting linear regression of number of horizontal nystagmic beats on ln angular acceleration.

Age Groups	11-20	21-30	31-40	41-50	51-60	61-80	
0-10	1.437	1.583	1.221	2.5516	2.6779	5.1424***	Run 1
	1.018	.4294	1.6793	1.8369	.9614	2.9471**	Run 2
	15	31	19	21	19	16	D.F.
11-20	----	.4853	.2426	1.331	1.299	3.221**	Run 1
	----	.9017	1.4076	.8942	.0279	2.312	Run 2
	----	34	22	24	22	19	D.F.
21-30		----	.200	.879	.7648	2.335	Run 1
		----	2.7197	2.168	.9184	3.7359***	Run 2
		----	38	40	38	35	D.F.
31-40			----	.91851	.83129	2.1879	Run 1
			----	1.2075	1.622	.2093	Run 2
			----	28	26	23	D.F.
41-50				----	.0998	1.6563	Run 1
				----	.9476	1.6307	Run 2
				----	28	25	D.F.
51-60					----	1.862	Run 1
					----	2.3365	Run 2
					----	23	D.F.
61-80						----	Run 1
						----	Run 2
						----	D.F.

** P<0.01
*** P<0.001

APPENDIX A2

Two tail t-test values between mean Y intercepts for decade age groups of best fitting linear regression of number of horizontal nystagmic beats on ln angular acceleration.

Age Groups	11-20	21-30	31-40	41-50	51-60	61-80	
0-10	3.1516**	1.7754	1.4071	2.7221	2.6979	4.0918***	Run 1
	3.0425	1.4586	3.1206**	2.9298**	2.4157	4.631***	Run 2
	15	31	19	21	19	16	D.F.
11-20	----	.4672	.31367	.1393	.5362	1.3065	Run 1
	----	1.0193	.18193	.0262	.1444	1.5278	Run 2
	----	34	22	24	22	19	D.F.
21-30		----	.0552	.6713	1.0395	1.5573	Run 1
		----	1.0267	1.1798	1.2087	2.2748	Run 2
		----	38	40	38	35	D.F.
31-40			----	.4607	.7438	1.1499	Run 1
			----	.1571	.3141	1.849	Run 2
			----	28	26	23	D.F.
41-50				----	.44	1.077	Run 1
				----	.186	1.5328	Run 2
				----	28	25	D.F.
51-60					----	.5238	Run 1
					----	1.027	Run 2
					----	23	D.F.
61-80						----	Run 1
						----	Run 2
						----	D.F.

** P<0.01
*** P<0.001

APPENDIX A3

Two tail t-test values between mean X intercepts for decade age groups of best fitting linear regression of number of horizontal nystagmic beats on ln angular acceleration.

Age Groups	11-20	21-30	31-40	41-50	51-60	61-80	
0-10	.59	.7762	.4912	1.16014	.8099	2.7923	Run 1
	.605	.7208	.7457	.61077	.9844	1.538	Run 2
	15	31	19	21	19	16	D.F.
11-20	----	1.4502	.0549	1.8143	1.4836	3.398**	Run 1
	----	.0555	1.246	1.395	.2849	2.102	Run 2
	----	34	22	24	22	19	D.F.
21-30	----	----	1.5327	.5144	.1909	1.853	Run 1
	----	----	1.8978	1.8815	.4308	2.768	Run 2
	----	----	38	40	38	35	D.F.
31-40	----	----	----	1.876	1.4167	3.302**	Run 1
	----	----	----	.6221	1.6346	.0806	Run 2
	----	----	----	28	26	23	D.F.
41-50	----	----	----	----	.6883	1.292	Run 1
	----	----	----	----	1.9512	.8188	Run 2
	----	----	----	----	28	25	D.F.
51-60	----	----	----	----	----	2.3121	Run 1
	----	----	----	----	----	2.7922	Run 2
	----	----	----	----	----	23	D.F.
61-80	----	----	----	----	----	----	Run 1
	----	----	----	----	----	----	Run 2
	----	----	----	----	----	----	----D.F.

**

P<0.01

P<0.001

VISUAL-VESTIBULAR CONVERGENCE ON BRAINSTEM UNITS
AND THEIR CONFLICT APPEARING IN EYE NYSTAGMUS

T. Kubo and M. Igarashi

Department of Otolaryngology
and Communicative Sciences
Baylor College of Medicine
Houston, Texas 77030

Convergence of visual and vestibular inputs on brainstem unit was examined using the extracellular recording technique. The contents of two previous reports (4) (5) are summarized in this paper.

Experimental animals were albino rabbits, anesthetized with urethane, immobilized with gallamine triethiodide and maintained with artificial respiration. The animal was rotated sinusoidally in yaw plane in the dark to examine vestibular input. The rotation in the light with earth-fixed screen vertically striped was applied to a limited number of neurons to test visual and vestibular convergence. Electric stimulations of the optic disc, optic chiasm and superior colliculus were used for all neurons recorded to examine visual input. By stimulating the optic disc and optic chiasm, field potential with negative polarity could be recorded in pontine reticular formation (PRF). The peak latency was about 6.3 msec to optic disc stimulation and about 5.6 msec to optic chiasm stimulation. From the region where the field potential appeared unit responses could also be recorded. A total of 163 PRF units, including 86 neurons (cell bodies) and 77 axons, responded to single or to double shock stimulation of the optic chiasm. Latencies ranged from 3.0 to 17.8 msec. Of 86 PRF neurons, 22 (25.6%) showed positive response to vestibular stimulation, too. 75 neurons sensitive to vestibular stimulation were also identified in PRF. These results indicate the important role of PRF in visual-vestibular interaction.

Figure 1 shows discharge rate of type-II neuron recorded from left medial vestibular nucleus of a cerebellectomized rabbit. Straight lines under discharge curve in A indicate the presence of illumination, and thus the unit is exposed to visual stimulus simultaneously. 22 brainstem units of cerebellectomized subjects, which responded to rotational stimulation in the dark, were tested for visual and vestibular convergence in such a way. Of these, 5 vestibular nucleus (VN) neurons and 2 peri-VIth nucleus neurons were found to have visual and vestibular convergent inputs. Although all VN neurons recorded (71 units) including the unit in Fig. 1 did not respond to single or double shock stimulation applied on the optic chiasm, more than half of VN neurons (38/71) showed modulation of the discharge (i.e., inhibition or facilitation) when the optic chiasm and superior colliculus were repetitively stimulated at 50 - 70 Hz with 0.05 msec square pulses. Fig. 1B shows responses of the unit shown in A during repetitive stimulation of the optic chiasm (OX) ipsi- and contra-lateral superior colliculus (SC) stimulations. Effect of weak intensity stimulation of the optic chiasm is shown in a, and

that of strong intensity stimulus is in b. Facilitation of the discharge is produced by ipsi- and contra-lateral superior colliculus stimulations (c and d, respectively).

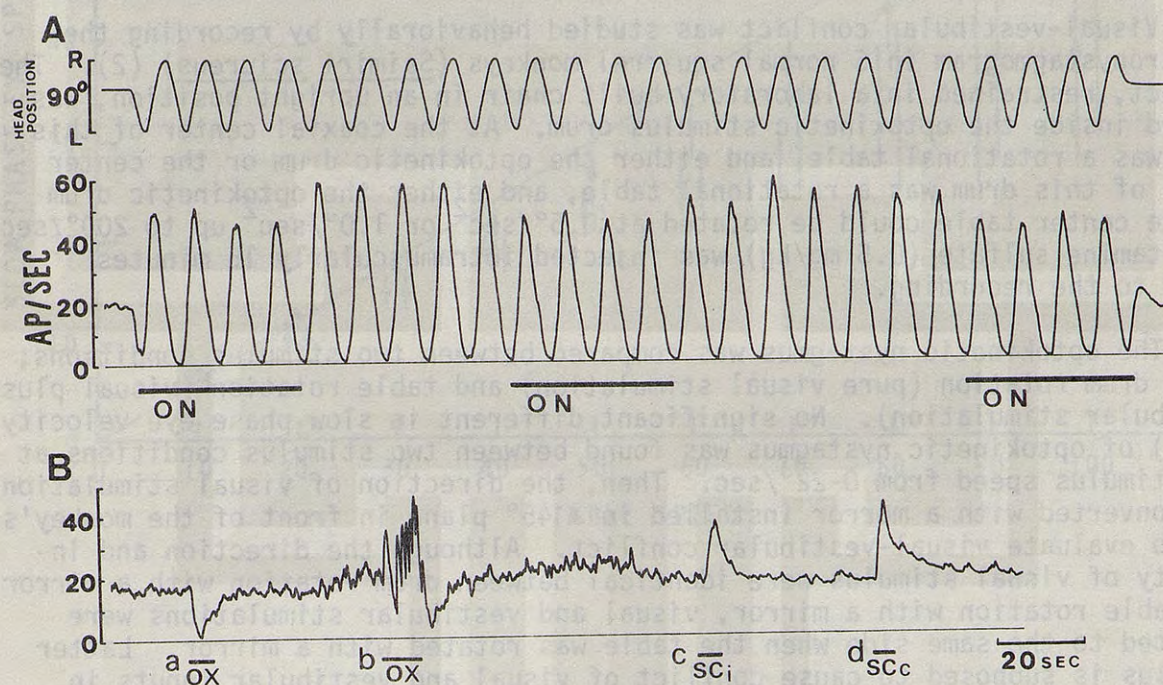


Figure 1. Discharge rate of type-II neuron recorded from left medial vestibular nucleus of a cerebellectomized rabbit.

Existence of visual input onto VN neurons has been well established by several authors using various kinds of animal species; goldfish, guinea pigs, rabbits, cats and rhesus monkeys. Visual pathway to VN has not yet been determined; however, since the ablation of the vestibulo-cerebellum caused loss of visual influence on vestibulo-ocular reflex, the part from the pretectum to the cerebellar cortex via the inferior olive (6) has been regarded as a responsible linkage for mediating visual signal to VN. The present experiment demonstrated that visual input onto VN neurons still existed after the cerebellectomy. The result agrees with a recent report using cats, which have shown positive effects of optokinetic stimulus on VN neurons of cerebellectomized subjects (3). Thus, the cerebellum is not essential to transmit visual impulse onto VN neurons; however, the vestibulo-cerebellum probably plays a role in performing adaptive gain control utilizing the visual signal (1).

Superior colliculus stimulation could not induce more prominent responses of VN neurons than the optic chiasm stimulation did. Therefore, the superior colliculus does not seem to be involved in the brainstem visual path to VN. Since brainstem reticular neurons receive more direct visual input than VN neurons, this structure may play an important role in transmitting visual signal. Although the pathway is still obscure, it is demonstrated in this experiment that visual-vestibular linkage in the brainstem has a polysynaptic feature.

Visual-vestibular conflict was studied behaviorally by recording the electronystagmogram in 6 normal squirrel monkeys (*Saimiri sciureus*) (2). The subject, restrained in a laboratory built chair in an upright position, was placed inside the optokinetic stimulus drum. At the coaxial center of this drum was a rotational table, and either the optokinetic drum or the center table of this drum was a rotational table, and either the optokinetic drum or the center table could be rotated at $0.5^\circ/\text{sec}^2$ or $1.0^\circ/\text{sec}^2$ up to $200^\circ/\text{sec}$. Amphetamine sulfate (0.5 mg/kg) was injected intramuscularly 15 minutes prior to the recording.

The optokinetic nystagmus was compared between two stimulus conditions; i.e., drum rotation (pure visual stimulation) and table rotation (visual plus vestibular stimulation). No significant difference in slow phase eye velocity (SPEV) of optokinetic nystagmus was found between two stimulus conditions at the stimulus speed from $0-22^\circ/\text{sec}$. Then, the direction of visual stimulation was converted with a mirror installed in a 45° plane in front of the monkey's eye to evaluate visual-vestibular conflict. Although the direction and intensity of visual stimulus were identical between drum rotation with a mirror and table rotation with a mirror, visual and vestibular stimulations were directed to the same side when the table was rotated with a mirror. Latter stimulus is supposed to cause conflict of visual and vestibular inputs in central nervous system. Figure 2 shows mean values and S.D. of SPEV obtained by different kinds of stimulation using a mirror. Closed circles represent SPEV induced by the drum rotation at $1^\circ/\text{sec}^2$. Open and closed triangles show SPEV during table rotation at $1.0^\circ/\text{sec}^2$ and $0.5^\circ/\text{sec}^2$, respectively. SPEV during the table rotation was significantly lower than that induced by the drum rotation at stimulus speed of $60-90^\circ/\text{sec}$. However, the difference was not significant when the table was rotated at different angular accelerations (0.5 and $1.0^\circ/\text{sec}^2$). Therefore, the largest factor influencing visual-vestibular conflict situation is the stimulus 'direction', the stimulus magnitude has secondary meaning. Under this situation, a large inter-individual difference was found.

We have previously reported that when the direction of visual and vestibular stimuli conflicted during pendular rotation, the phase lag of optokinetic nystagmus occurred (7). Average phase lag was about 90° and large inter-individual difference was observed. Under limited training, which was performed twice a week for 5 weeks, no improvement in the phase lag was admitted.

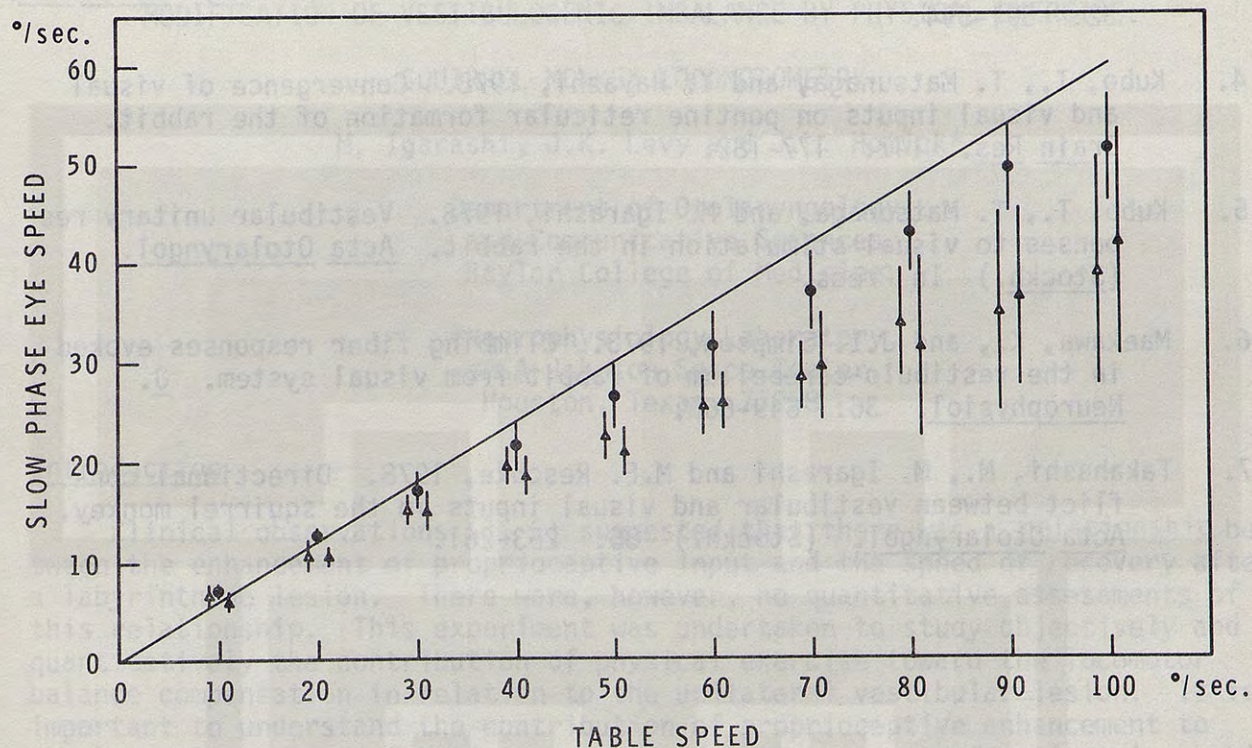


Figure 2. Mean values and S.D. of slow phase eye velocity obtained by different kinds of stimulation using a mirror.

As the experimentally created situation of visual-vestibular conflict does not frequently exist in the natural living environment, this caused significant decrease of SPEV in normal squirrel monkeys. It is considered that discoordination occurs in visual-vestibular integrative centers, presumably in the vestibular nuclei and the pontine reticular formation as revealed by our neurophysiological experiment, and possibly in the vestibular cerebellum. Such conflict of visual and vestibular inputs is considered to be one of the important triggering factors in the development of space motion sickness.

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MODIFICATION OF VESTIBULOGENIC IMBALANCE BY PHYSICAL EXERCISE:

SQUIRREL MONKEY LOCOMOTOMETRY

M. Igarashi, J.K. Levy and J.L. Homick*

Department of Otolaryngology
and Communicative Sciences
Baylor College of Medicine

*Neurophysiology Laboratory
NASA-Johnson Space Center
Houston, Texas 77058

Introduction

Clinical observations (1, 2) suggested that there was a relationship between the enhancement of proprioceptive input and the speed of recovery after a labyrinthine lesion. There were, however, no quantitative assessments of this relationship. This experiment was undertaken to study objectively and quantitatively the contribution of physical exercise toward the locomotor balance compensation in relation to the unilateral vestibular lesion. It is important to understand the contribution of proprioceptive enhancement to the locomotor balance function, not only for the purpose of patients' rehabilitation, but also for the control of space-motion-sickness.

A previous experiment on the locomotor dysequilibrium after unilateral labyrinthectomy in squirrel monkeys (4) could not detect a statistically significant difference in post-operative time to reattain the pre-operative performance level between the exercise and non-exercise groups. However, the exercised animals did better on rail test performance up to the third or fourth week, at which time the control group reached the same level.

The contents of the previous report in relation to the unilateral utricular neurotomy and exercise (5), are summarized in this paper. The effect of physical exercise (two kinds) on locomotor performance compensation was evaluated using the squirrel monkey platform runway test (3), which measures laterality and frequency of footstep deviation. This test does not demand the increased physical conditioning that the rail test required, and allows the animal to trot as it shuttles between two end boxes.

Method

Subjects were 21 adult squirrel monkeys (*Saimiri sciureus*). The monkeys' locomotor performance was evaluated by the squirrel monkey platform runway test (3). Subjects were trained to a pre-operative criterion level (7) and then were assigned to one of three groups; rotating cage exercise, railtraversing exercise and no exercise. Subjects received their respective treatments for 3 weeks prior to the unilateral utricular neurotomy. For the rotating cage exercise group, the animals were placed in the rotating cage (4) run at 12 rpm speed, five days per week. Exercise was given in a fashion of 10 minutes

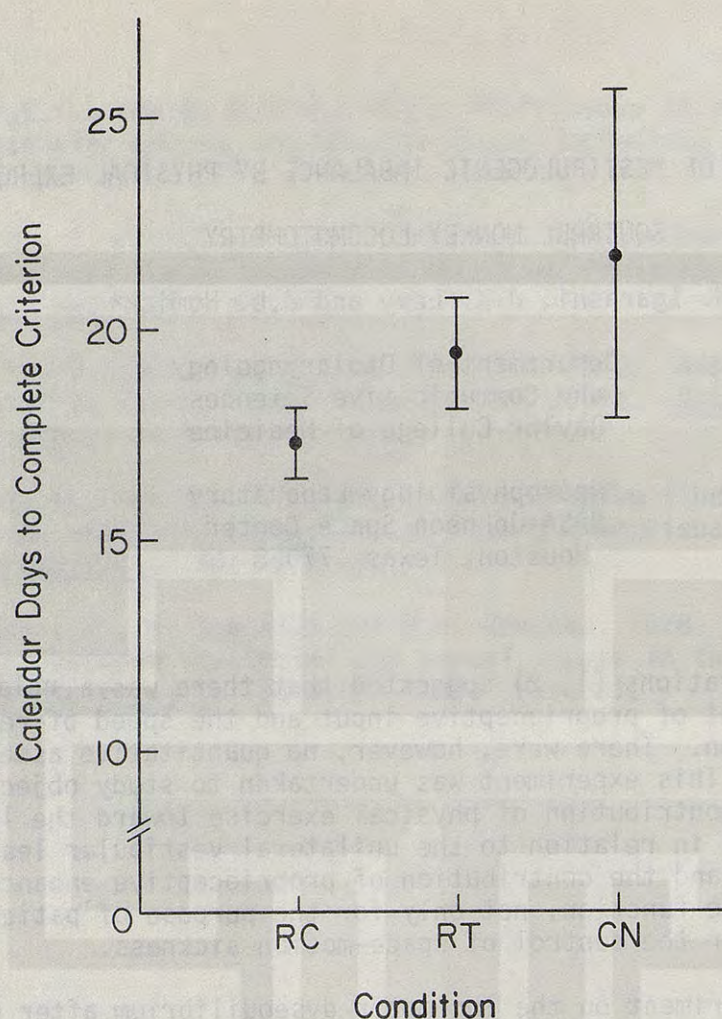


Figure 1. Mean post-operative calendar days to reattainment of pre-operative criterion level for each of the three exercise conditions.

than that in the control group. The greater variability in the control group and small sample size probably contributed to the lack of significance between the groups. These results lead us to further intensify the exercise application. In contrast, lack of proprioceptive input due to inactivity delays compensation to vestibulogenic dysfunction. An increase was observed in duration of spinal reflex asymmetry in the vestibular lesioned baboon which had been restrained with a lower limb case (6).

In the ongoing research to study the contribution of exercise to functional compensation, the effect of lengthening the daily exercise time in animals with unilateral labyrinthectomies is being evaluated. The daily exercist time has been increased by 150%; a total of 2 hours and 30 minutes. With only a few animals in each group to date, exercise reduced, on the average, the time to locomotor balance regainment in the unilateral labyrinthectomy animals as well. The results to date suggest that physical exercise could have some effect on locomotor balance compensation, but the type, daily amount, and number of days applied pre-operatively must be quite substantial. Furthermore, other equilibrium inputs involved with compensation, such as vision, should play an important part.

exercise, 5 minutes rest for a total exercise time of 1 hour. In the rail-traversing exercise group, the animals were assigned to shuttle 60 times per day on the squirrel monkey rail which was rotated at 200 RPM. The animal was required to make an impulsive locomotor performance followed by 20 sec. period of rest. The control group did not receive any physical exercise. At the end of the three week period, all subjects underwent unilateral utricular neurectomy. Post operative exercise and locomotor measurements began one day after the surgery and animals were placed in the exercise situation previously assigned. Exercise and platform runway test continued 5 days per week, until the animals had regained their pre-operative performance level at the established criterion. The animals were sacrificed by intracardiac fixative perfusion under deep anesthesia for confirmation of lesion placement by histological means.

Results

The mean post-operative calendar days to reattainment of pre-operative criterion level is shown in the ordinate of Figure 1. The forms of exercise (abscissa) were: rotating cage (RC), rail-traversing (RT) and no-exercise control (CN). Values with associated standard errors of the mean were 17.3 days for the rotating drum exercise group, 19.4 days for the rail-traversing exercise group, and 23.3 days for the non-exercise control group. However, due to the great variation in scores of the control group, analysis of variance of the days to compensation shows that the three groups' samples did not differ significantly ($p = .25$). And an individual comparison of the drum exercise vs. control groups also yielded non-significant yet borderline probability ($p = .10$). On the other hand, an analysis of first days to pre-operative performance level reacquisition yielded a significant difference in an individual comparison between rotating cage exercise and control groups ($p = .05$). Thus, while all groups did not differ significantly to the completion of functional compensation, the monkeys in the rotating cage exercise group seemed to reach the best performance level earlier than the non-exercise animals.

Figure 1. Mean post-operative calendar days to reattainment of pre-operative criterion level for each of the three exercise conditions.

A small increase in the platform running time was noted post-operatively; however, was evenly distributed across the three groups. When a correlation was done across all subjects between running time and the number of days to reach pre-operative performance level, a low value was determined ($r=0.22$).

Upon histological examination, the percentage of utricular nerve cut averaged 90% across all animals. All other end organs were found to be intact. One subject which belonged to the control group manifested a diffuse labyrinthine reaction and was excluded from the data analysis.

Discussion

The present experimental results suggested that, in the unilaterally utricular nerve cut animal; exercise might help in the compensation of locomotor imbalance, though the significance tests did not totally reflect this. In analysis of compensation times across the three groups, the variability of days to compensation in the rotating cage exercise group was much smaller

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VESTIBULAR FUNCTION IN OTOCONIA-DEFICIENT MICE

David J. Lim, M.D.

Otoligical Research Laboratories, Department of Otolaryngology
Ohio State University College of Medicine
Columbus, Ohio

Introduction

The basic mechanism(s) involved in space motion sickness are not clearly understood. It is commonly believed that conflicting sensory input received by the proprioceptive, visual, and vestibular systems is the underlying cause of these autonomic responses. It is well established that vestibular organs are required to produce motion sickness. Although their relative role is not clear, both gravity receptors and semicircular canals appear to be involved in causing motion sickness for both linear and angular acceleration (singularly or in combination). With the advent of space flight, astronauts and cosmonauts are exposed to prolonged zero-G, and many of them have experienced space motion sickness.

The purpose of this report is to review normal morphology, morphogenesis and maintenance of otoconia and to study behavioral or physiologic parameters of mutant mice that either entirely lack otoconia (pallid) or possess varying quantities of abnormal otoconia and correlate these data with the morphological information. These animal models will provide very useful information as to the functions of the saccule and utricle, as well as the canal sensory system function in the absence of gravity receptor input--a situation somewhat similar to the space environment. In order to shed some light on the effects of prolonged zero-G exposure on the brain stem, some preliminary information on the vestibular nuclei is included.

Morphology of the Otoconial Membrane

The whole membrane is called the statoconial membrane (synonymous with otolith membrane in bony fish), which is composed of the otoconial layer, gelatinous layer, and subcupular meshwork, as shown in Fig. 1. Some otoconia are partly embedded in the gelatinous layer, and the rest are loosely held together by the gelatinous matrix. The gelatinous layer, when fixed with osmic acid, is formed of amorphous and fibrillar material. The gelatinous layer, particularly near the striolar zone, is perforated. The gelatinous membrane is formed of two distinct parts: the upper layer, on which otoconia are placed, and the honeycomb layer. Each chamber of the honeycomb houses the top portion of a tall ciliary bundle of sensory cells. The basal end of the honeycomb layer is attached to the supporting cells of the sensory epithelium by the gelatinous meshwork (Fig. 1) and is called the subcupular meshwork by Dohman.

The composition, shape, and size of the otoconia vary considerably among species. For example, according to the x-ray diffraction investigation of Carlström & Engström, the otoconia consists of calcium carbonate crystallized in the form of calcite in mammals, birds, and sharks, of

calcium carbonate in the form of aragonite in amphibia, and of calcium phosphate in the lamprey. The otoconia of the salamander contain carbonate hydroxyapatite as well as aragonite.

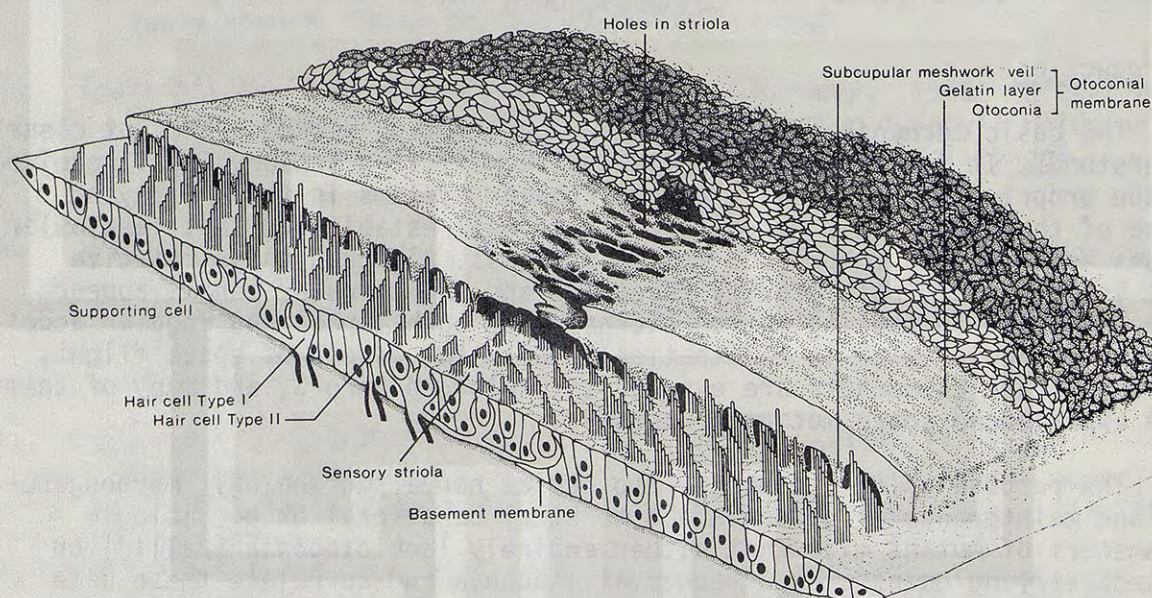


Figure 1. Schematic diagram of the mammalian/utricle shows three layers of the otoconial membrane. Illustration by Nancy Sally.

Recent electron microscopic study has demonstrated that the otoconia in mammals are formed with a dense organic nucleus and body, which also incorporate organic materials. The fish otolith is formed by alternating calcium-rich and gelatin-rich layers representing fast- and slow-growing zones. The ground substances of the crystals (after decalcification) are essentially similar, if not identical, to the ground substance of the gelatinous layer of the statoconial membrane, and histochemical study has shown that it is PAS-positive, indicating it is made up of glycoprotein and mucopolysaccharide. The histochemical staining properties of these structures are similar to those of the cupula.

According to Iurato and de Petris, the density of otoconia that are composed of a calcite is 2.71, while the density of those composed of aragonite is 2.93. Therefore, the otoconia increase the specific weight (gravity) of the statoconial membrane, which has the density of 1.9-2.2. This value is higher than that of the cupula and twice as high as that of endolymph (1.02-1.04), as measured by Trincker.

Besides providing the specific weight and mass necessary for making gravity receptors sensitive to gravitational force, calcium salts of the otoconia may take part in the process of calcification of bone and also may act in the storage of calcium in certain species. In amphibia a large number of crystals resembling otoconia are contained in the paravertebral calcareous sac at the level of the intervertebral foramina. The calcium content of the amphibian statoconia undergoes variations depending on differences in experimental conditions. Whether the same phenomenon occurs in mammals is unknown.

Morphogenesis of Otoconia

Little is known of the mechanism of the formation of otoconia or of the factors regulating their growth and final dimensions. As for the endogenous statoconia, there are three schools of thought: 1) the otoconia are formed in situ in the statoconial membrane in mammals; 2) the statoconia are secreted by the supporting cells of the gravity receptor organs in the statocyst of Aplysia; and 3) the otoconia are formed in the endolymphatic sac and transported to the gravity receptor organs in the chick and the shark.

Veenhof, using autoradiography, cytochemistry, and electron microscopy, studies the formation of otoconia in the mouse. He reported that the otoconia start to form between 13 days of gestation and a few days after birth, and the maximum activity of crystal formation appears to be between the 15th and 16th days of gestation. The transient increase in PAS staining and transient decrease in intensity of staining of the statoconial membrane (gelatinous) during the critical period of otoconial formation occurred during gestation days 13 through 15. Since PAS stains neutral sugars and toluidine blue and Alcian blue stain acid protein polysaccharide, the above results indicate that there are transient changes in composition of carbohydrates and related substances which may be critical for initiation of crystal formation. These chemical changes are coupled with the presence of alkaline phosphatase activity up to the 13th day of gestation, after which they begin to fade rapidly. This finding indicates that perhaps there are biochemical events taking place that make the gelatinous membrane favorable for crystallization during the critical period of otoconial formation. These biochemical changes in reverse in non-otoconia-forming structures of a similar nature in the inner ear (the tectorial membrane and cupula) may explain the deterring factor against otoconia formation in these structures, as discussed by Veenhof. His observations also indicate that there is no saturation of calcium in the tissue, although he could not determine whether a high concentration of calcium in the endolymph occurs before or during the crystallization period.

The "critical nucleation" concept of the initiation of crystal formation has been postulated. According to this concept pre-existing heterogeneous nucleation initiates the growth of crystals. The nucleation center described by a few investigators, who optically observed a nucleus in the crystal, later proved to be an organic nucleus and may serve as a nucleation point to form an otoconium. The absence of obvious nuclei in some otoconia can be explained by the possibility that only "Homogeneous nucleation" is responsible for otoconia formation. This process will take

place in the presence of ionized calcium and carbonate ions present in the endolymph. The carbonate ions are easily produced from CO_2 by the catalytic activity of the enzyme carbonic anhydrase, which is abundantly present in the inner ear.

Maintenance and Fate of Otoconia

A negligible amount of radioisotope-labeled calcium (^{45}Ca) was incorporated into the otoconia of young rats, mice, and gerbils. In contrast to this, the fetal mouse has shown a high uptake of radioisotope calcium by the otoconia during the gestation period (between day 13 and birth). This finding strongly suggests that the calcium turnover in the adult is very slow and negligible under normal conditions. However, it has been reported that when the otoconia are removed by high centrifugation from the gravity receptors they grow back. This finding has never been repeated or confirmed by recent experiments.

Two mechanisms for the disappearance of otoconia can be considered: destruction in situ or dissolution when they are displaced from the statoconial membrane. Ross et al reported otoconia partly destroyed by surface pitting or, in advanced cases, excavation, presumably due to loss of calcium in situ. This mechanism is thought to be involved in the loss of otoconia in aged individuals. It is also conceivable that the loss of otoconia can be secondary to the loss of the glue-like gelatinous material that helps to hold the crystals together.

Besides the thinning of the statoconial membrane by either loss of crystals due to fusion (aggregation) can occur, or total loss of otoconia can be caused by dislodgement of the entire statoconial membrane.

During the course of scanning electron microscopic study of the gravity receptors, the author accidentally observed numerous otoconia attached exclusively to the dark cell area of the utricle, which was evidence of decalcification as shown by the collapse of these otoconia (Fig. 2). This observation prompted the speculation that the dark cells may indeed be involved in the decalcification process of the otoconia that are dislodged from the statoconial membrane. On this basis the author has suggested that the utricular dark cells perhaps are also involved in calcium homeostasis in addition to their known function of ionic environment maintenance in the endolymph in the pars superior. Because of the former function, these cells assume a protective role in checking dislodged crystals. However, this concept cannot be applied to the saccule, as the saccular wall is not known to contain dark cells.

The role of the endolymphatic sac in the resorption of otoconia is virtually unknown at this point, and well-designed studies to test the function of the endolymphatic sac, stria vascularis, and dark cells are needed.

Possible Causes of Otoconial Degeneration (or Loss)

The clinical symptoms of subtle loss of otoconia are not well known. Even the massive loss often expected to accompany the degeneration of sensory cells is extremely difficult to diagnose. Schuknecht first described a

clinical symptom complex, cupulolithiasis, which he attributed to cupular deposits in the posterior ampulla. He summarized the possible etiologic factors for this disorder, characterized by brief spells of paroxysmal vertigo in association with head movements. He postulated that the calcareous deposits are dislodged otoconia or end products of degenerated otoconia. In addition to the above-mentioned conditions which may cause otoconial dislodgement or degeneration (or loss), there are several other conditions which can cause otoconial loss (See below).

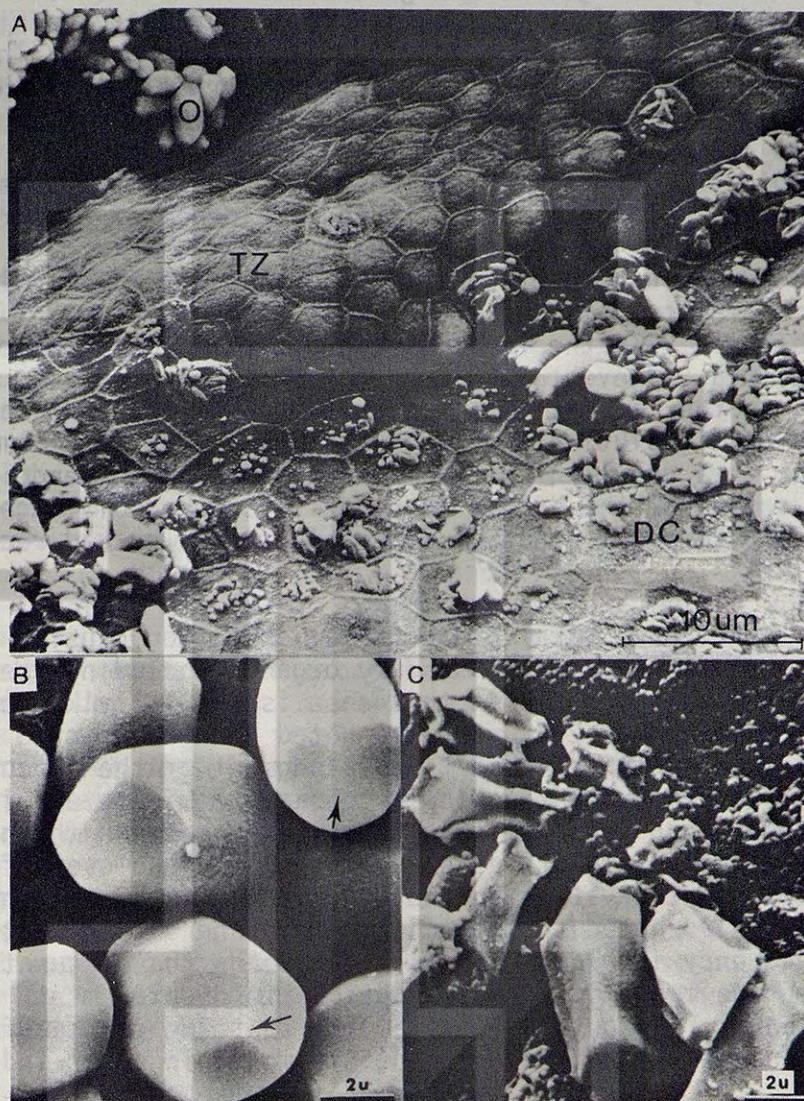


Figure 2(A) SEM photograph of a guinea pig utricle shows normal otoconia (L) in the macula region and collapsed otoconia that are attached to the dark cells (DC). Cells of the transitional zone (TZ) are free of otoconia. (B) Close-up view of normal otoconia. Arrows point to the pointed tips. (C) Otoconia that are attached to the dark cells are collapsed, due to decalcification, indicating the presence of a large amount of organic substance.

1. Aging. Johnsson and Johnsson and Hawkins reported cases of severe loss of otoconia, mainly from the saccule, in temporal bones of humans of advanced (over 60 years). Ross et al described the pitting or serration of otoconia surfaces and interpreted this to be the result of a loss of calcium in the process of degeneration. They also showed that degenerative changes, or otoconial destruction, are more pronounced in the saccule than in the utricle and correlate with the advancing of age. Unlike the residual saccular otoconia, most of the remaining utricular otoconia had no visible evidence of degeneration even though there might be loss. Ross et al also found evidence of degeneration in a four-year old child. They also described the immature form of otoconia, which has a multi-faceted appearance. They maintain that the individual otoconial crystal undergoes morphological changes during life (immature, mature, and aged).

2. Ototoxic Drugs. It has been reported that a considerable reduction in the number of otoconia and increased incidence of malformed otoconia are found in ototoxicity by streptomycin, ethacrynic acid, and neomycin. While most of the drug-induced otoconial changes appear to be related to severe loss of otoconia, malformation of otoconia, (formation of giant plate-like otoconia) is also observed. In the former, Harada and Sugimoto suggested that dislodging of otoconia and eventual dissolution by the vestibular dark cells are involved. In the latter, it is postulated that the abnormal (giant) otoconia are formed by dissolution and reaggregation by fusion of smaller otoconia, which occur as a result of biochemical changes in the endolymph due to pharmacological action of the drugs. Vyslonzil observed dislodged otoconia in the undecalcified temporal bones of a human patient who had received a toxic dose of neomycin.

3. Infection. Viral or bacterial infection causing labyrinthitis involves total destruction of sensory organs, including the gravity receptors. The fate of otoconia in this case is not fully known. A high incidence of otitis media (26%) was also noted among suspected cupulolithiasis patients. It is inferred that the dislodgment of the otoconial membrane as a result of labyrinthine reaction secondary to middle ear infection is a possible underlying cause of this correlation between the high incidence of otitis media and supulolithiasis. Wright et al however, found a higher incidence of giant crystals in the saccules of those patients who had otitis media. They also noted that otoconial membrane dislodgment occurred with greater frequency in older infants, suggesting that maturation of the otoconial membrane makes it more susceptible to displacement. If this is true, then one cannot rule out the possibility that the chance of otoconial membrane displacement is enhanced by otitis media in older individuals.

4. Sensory Degeneration. The loss and dislodgment of the statoconial membrane as a result of cochleo-saccular degeneration has been reported by Johnsson and Hawkins and recently by Gussen. In this type of degeneration otoconial loss is confined mainly to the saccule.

Johnsson et al described a human case of congenital deafness in which a large number of crystals were found in the apical coil of the cochlear duct. X-ray powder diffraction studies showed that the crystals consisted of apatite. Furthermore, in Dalmation dogs they found minute crystals attached to the atrophied stria vascularis. X-ray diffraction study proved that some

crystals apparently represented calcium phosphase.

5. Mechanical Trauma. Severe G force from linear or angular acceleration or head trauma can cause displacement or loss of otoconia. It can either be partial loss of some otoconia or total dislodgment of the statoconial membrane if the G force or trauma is extreme. The fact of the dislodged otoconia is not known. Among positional vertigo patients, 47% had longitudinal fracture of the temporal bone, and 21% had histories of head injury. Schuknecht has suggested that labyrinthine concussion may cause dislodgment of otoconia and result in cupulolithiasis.

The question of possible regeneration of lost otoconia remains unresolved. Some authors report reappearance of otoconia, presumably by neogenesis after removal of otoconia, in frogs, rabbits, and guinea pigs, and in carp. On the other hand, James failed to observe any evidence of new generation of otoconia following their removal in rabbits.

6. Vascular Insufficiency. Experimentally induced disruption of the anterior vestibular artery and nerve caused degeneration of the macula utriculi, which included changes in the statoconial membrane. It is most likely that the loss of otoconia represents a part of total degenerative changes of the macula.

7. Hydrops or Membrane Rupture. In three human specimens Johnsson and Hawkins observed otoconia made up of apatite rather than calcite, two cases had hydrops, and one had a collapsed saccular wall. One of these specimens was from a patient with congenital deafness and hydrops. In addition to abnormal otoconia, which were present in both the utricle and saccule, this ear had a calcification of all three cupulae, which consisted of apatite. Whether the abnormal crystals were altered otoconia or malformed otoconia preformed by some genetic disorder or prior pathology could not be determined. Inner ear hydrops was also reported in fetal pallid mice. The pallid is a mutant which exhibits otoconial deficiency or malformation. Whether there is a causal relationship between the transient hydrops and otoconial deficiency is not known, and they may be unrelated events.

Although the integrity of the otoconia when endolymph is mixed with perilymph is not known, saccular otoconial degeneration was observed in cats when the saccular wall was punctured experimentally. It is also possible that otoconia degeneration in cases of hydrops is secondary to the intermixture of perilymph with endolymph.

Congenital Otoconial Malformation and Dysgenesis

There are two groups of congenital otoconial pathology, one due to environmental factors during the critical period of gestation (during which the otoconia are formed), and the other due to genetic factors.

1. Environmental Factors

a. Trace Metals. It has been reported that deficiency of manganese or zinc in the diet of a pregnant mouse (thereby limiting the trace metals

available to the fetus during the critical period of otoconia formation) affects the formation of otoconia. It was found that the postural defects, particularly head tilting in guinea pigs, sheep, and many other laboratory animals, are associated with anomalous development of otoconia or deficiency of otoconia due to trace metal deficiency in the diet. Although the exact mechanism by which these trace metals are involved in the formation of otoconia is highly speculative, it has been postulated that manganese is essential for the normal biosynthesis of sulfated mucopolysaccharide, which is an essential ingredient for the statoconial membrane, and that zinc is essential for the enzyme carbonic anhydrase activity, which provides carbonic acid and mobilizes calcium ions.

b. Drugs. Chelating agents, such as tetracycline and sulfanamide, and carbonic anhydrase inhibitors, such as dichlorophenamide, taken during the gestation period are known to cause otoconial dysgenesis. The exact mechanism by which otoconial dysgenesis is caused by these drugs is not known; however, it is postulated that chelating agents may interfere with trace metals, which may act as co-factors for enzymes, and carbonic anhydrase inhibitors may interfere with carbonic anhydrase during the critical period of crystal formation.

c. Viral Infection. Viral infections, such as rubella, during the gestation period are known to cause cochleo-saccular dysgenesis when they occur during the time of the formation of the pars inferior. The exact pathology involving otoconia dysgenesis or degeneration of formed otoconia secondary to infection is not known.

d. Weightlessness. Vinnilov et al reported absence and/or poor development of the otolith in a fish (Branchyodanio rario) when it was hatched in a weightless environment for 5-6 days. However, the sensory epithelium was well differentiated. When similar experiments were carried out for 16 days with a toad (Xenopus laevis) at the tail bud state, abnormality of otoconia (glittering otoconia aggregated to form otolith) in the utricle and saccule and deficient otoconia in the lagena were observed, although the sensory epithelium was well differentiated. The authors ascribed these otoconial anomalies and otolith deficiencies to general abnormalities of calcium exchange.

2. Genetic Factors.

a. Cochleo-Saccular Cysgenesis. Lack of otoconia in the saccule in association with dysgenesis of the cochlea and saccular maculae has been reported. A Schiebe-type congenital anomaly (cochleo-saccular dysgenesis) in humans, dogs (Dalmatian), mice (Shaker), mink (Hedlund), and cats (albino) is known to be due to genetic factors. The absence of otoconia in some of these cases could be due to a failure of development (agenesis), but most likely is due to degenerative changes (or dysgenesis) involving the entire sensory organ that cause total dislodgment of the statoconial membrane.

b. Pallid Agenesis. The genetically mutant pallid mouse, which reveals head cocking and inability to swim, is noted to have an otoconial deficiency. In general, it is believed that this is the only consistent

pathology involving the inner ear.

Severe deprivation of manganese or zinc in the diets of normal pregnant mice causes large numbers of the offspring to show ataxic and tilted-head behavior and otoconial deficiency, mimicking the mutant pallid mice. Inversely, the head-tilting behavior and otoconial deficiency in the pallid mouse can be prevented by supplementing the diet of the pregnant mouse with manganese or zinc, indicating that there is a causal relationship between the availability of trace metals and the deficiency of otoconia.

It is interesting to note that the enzymes involved in mucopolysaccharide synthesis in cartilage also require manganese. Veenhof suggested that the PAS-positive substances (mucopolysaccharide) initiate crystallization in the macula covering membranes. The manganese-deficient and pallid mice, which lack otoconia, fail to incorporate labeled sulfate, suggesting that there might be subtle biochemical differences in the gelatinous layer of the statoconial membrane in those animals which fail to develop otoconia. Evidently, manganese is required only during the critical period of otoconial formation, as the effective period for manganese supplementation of the diet ends on gestation day 15 in mice (the early part of the critical period). In contrast to manganese deficiency, zinc deficiency affects statoconial formation as late as gestation day 16. Treatment with dichlorophenamide produces statoconial deficiency, and this effect may be mediated as late as gestation day 18. In the latter cases it was assumed that the statoconial deficiency is due to interference with carbonic anhydrase activity, and zinc is the co-factor for carbonic anhydrase, and dichlorophenamide inhibits carbonic anhydrase activity.

Recently, Wright et al reported a case of possible human pallid in a six-week old victim of sudden infant death syndrome. By surface microdissection technique, the gravity receptors were examined by light and scanning electron microscopy, and they found a total deficiency of otoconia in both utricle and saccular organs on both sides. However, the gelatinous statoconial membrane, neuroepithelium and innervation were morphologically normal and strikingly resembled the gravity receptors of the pallid mouse,

c. Genetic Malformation. The tilted-head mouse was discovered by Larsen and is known to have an otoconial deformity as well as deficiency. The pathology mainly involves total deficiency or the formation of a giant crystal, which under the microscope resembles flower petals or a butterfly (Fig. 3). Abnormal crystals, when decalcified, show irregular distribution of organic substance in a large crystal and lamellation of the subunits of the crystal. It is not clear whether the crystals are deformed from the start or are a reaggregation of smaller crystals. Electron micrographs suggest that in some cases they may be formed by fusion. Some abnormal crystals resembling those of the tilted-head mouse were also observed in streptomycin-treated guinea pigs and in presumably normal humans. Giant crystals with lamellar bodies are also found in pallid mice that develop some otoconia.

Unlike the pallid mouse, the tilted-head is quite resistant to treatment by manganese supplementation of its diet, suggesting that the biochemical mechanism involved in this genetic expression is different from that of the pallid. Another mutant mouse exhibits congenital otoconial defects and progressive loss of otoconia during the premature aging which are related to zinc

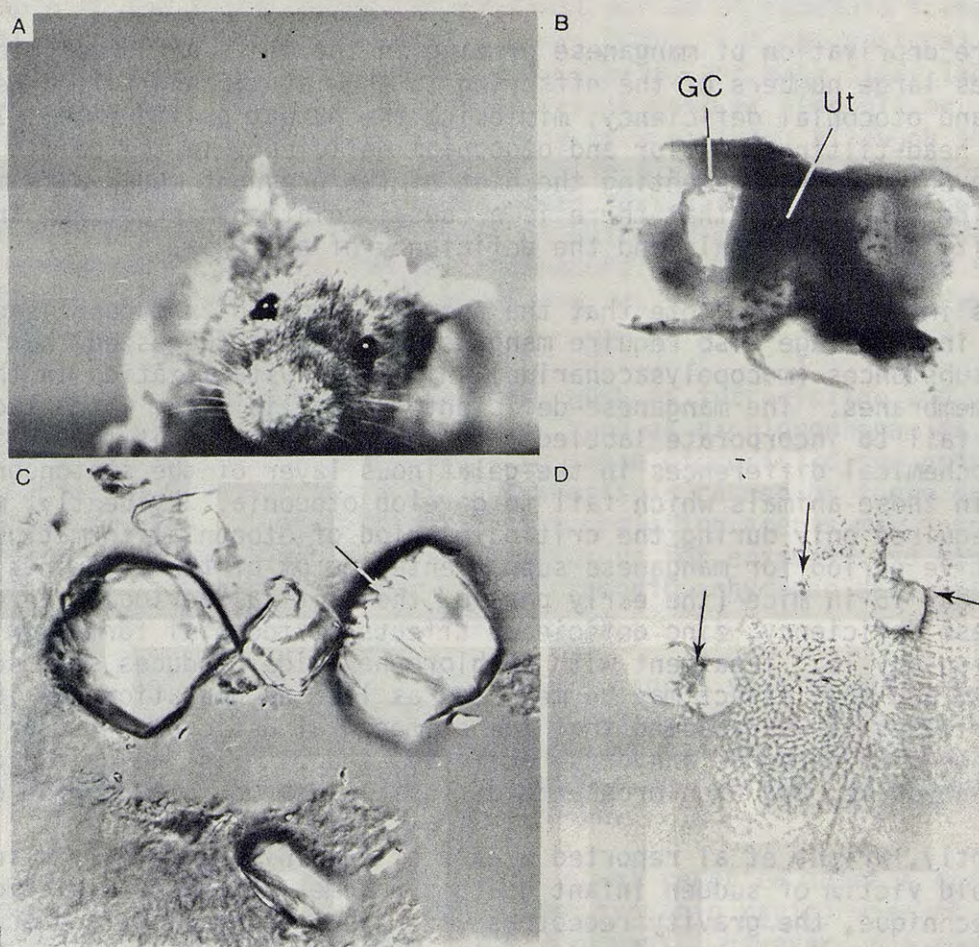


Figure 3. (A) Tilted-head mouse. (B) Surface preparation of utricle (UT) of tilted-head mouse, showing a giant crystal (GC). 50X. (C) Flower petal shaped giant crystals from tilted-head mouse. Arrow indicates lamellation. 200X. (D) Bow tie or butterfly shaped malformed giant otoconia with central narrowing (arrows). From a tilted-head mouse. 125X.

and/or manganese deficiency. These mutant mice produce zinc-deficient milk which is lethal to all sucklings.

The animals with otoconial anomaly reveal varying degrees of swimming difficulty. Some are totally disoriented (underwater circlers); some are vertical swimmers, maintaining a vertical position and keeping their mouths and noses above the water line; some are normal and maintain a horizontal body position without any difficulty. (Fig. 4). When the total area of sensory cells covered by crystals in the saccule is determined by light microscopic and scanning electron microscopic observation, the area covered or number of crystals present correlates well with the animal's swimming behavior in that the animals totally lacking otoconia in all gravity

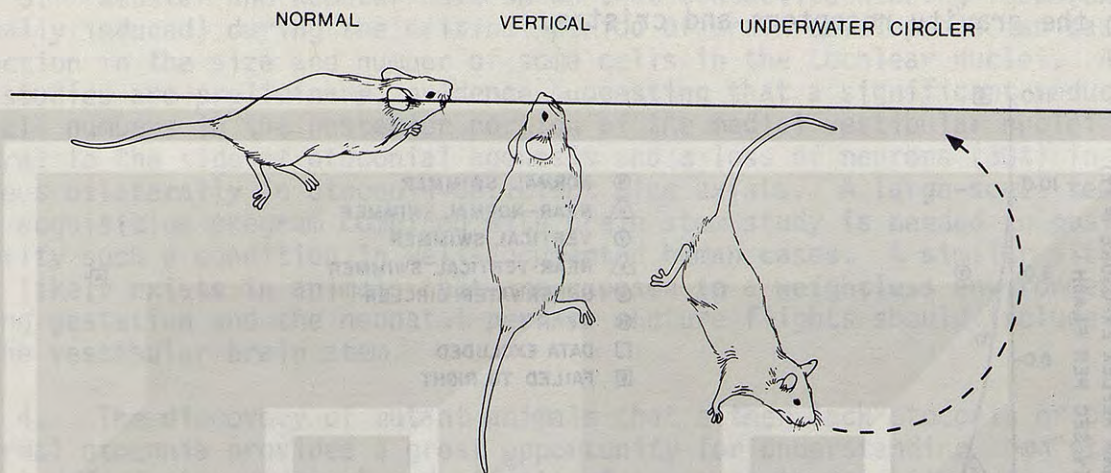


Figure 4. Swimming behavior is classified as: A--normal swimmer, B--vertical swimmer, C--underwater circler.

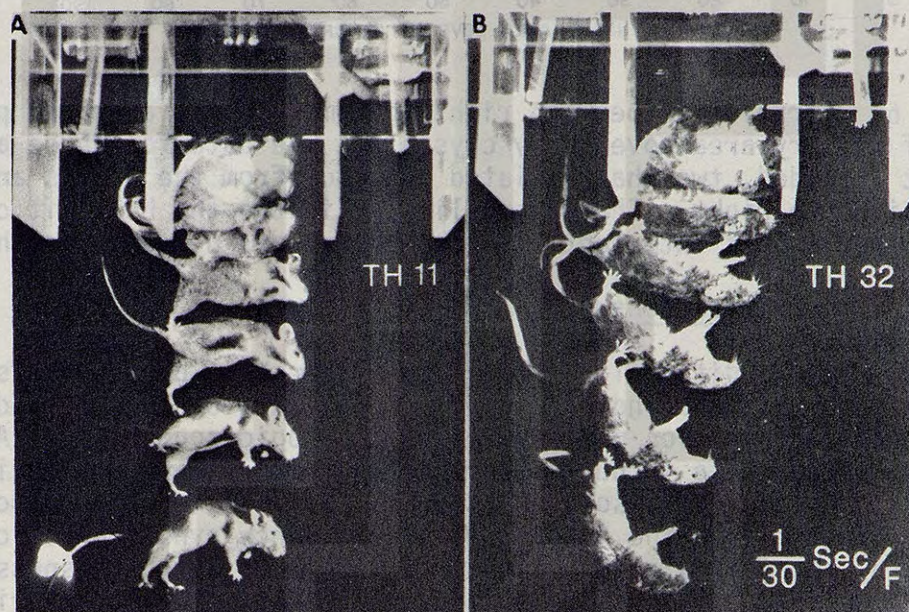


Figure 5. (A) This tilted-head animal righted at the 7th exposure (6.30 sec.), which is considered slower than normal, and is shown to have some otoconia in all gravity receptors. Timed strobe photograph. (B) This tilted-animal failed to right and is shown to have no otoconia in all gravity receptors.

receptors invariably had underwater circling behavior and those with some crystals had vertical swimming behavior. When 30% or more of the gravity sensory area in the saccule was covered by otoconia the animal exhibited normal swimming

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that failed to flight. The dotted line indicates the best fit curve extrapolate to its intercept even though we have no data for this area

Conclusion and Recommendations

to see if prolonged exposure to weightlessness alters the otocollin.

effort should be directed to the early identification of a gravity receptor

dysfunction.

3. Webster and Webster have shown that conductive hearing loss (experimentally induced) during the critical period of brain development can cause reduction in the size and number of some cells in the cochlear nuclei. Although the studies are preliminary, evidence suggesting that a significant reduction of cell numbers in the posterior portion of the medial vestibular nuclei ipsilateral to the side of otoconial agenesis and a loss of neurons (30%) in the "Y" nucleus bilaterally in otoconia-deficient mice exists. A large-scale temporal bone acquisition program combined with brain stem study is needed to positively identify such a condition in well-documented human cases. A similar situation most likely exists in animals that are exposed to a weightless environment during gestation and the neonatal period. Future flights should include study on the vestibular brain stem.

4. The discovery of mutant animals that either lack otoconia or possess abnormal otoconia provides a great opportunity for understanding the "statoconial deficiency syndrome" and effects of exposure to weightlessness. Furthermore, discovery that certain trace metals are involved in the morphogenesis and malformation of otoconia opens a new avenue for investigating the possible role of enzyme dysfunction in these mutant genes. The prospect that genetic disorders involving inner ear tissue can be manipulated and corrected by trace elements is an exciting one, as we may be able to understand the exact biochemical disruptions caused by malfunctioning genes in the formation of otoconia.

VESTIBULO-SPINAL REFLEXES DURING CHANGING LINEAR ACCELERATION

Millard F. Reschke
NASA/Johnson Space Center
Houston, Texas

Introduction

Data and observations from previous manned space flight suggest that significant alterations occur in vestibular, neuromuscular and related sensory system functions upon exposure to weightlessness. Of particular interest has been the observation of changes related to otolith input and vestibulo-spinal responses observed postflight.

Studies of postural equilibrium following some late flights and the Skylab missions (1) have indicated that prolonged exposure to weightlessness can modify those mechanisms responsible for postural stability. Using a modified version of a quantitative ataxia test developed by Graybiel and Fregley (2) all crewmen, and particularly those from the Skylab flights, demonstrated a considerable decrease in their ability to maintain balance when their eyes were closed. Improvement was slow, requiring from 7-10 days postflight before baseline levels were obtained. Results from the eyes open portion of the test were equal to, or better than preflight values. These results are in agreement with the Soyuz 9 (3), 19, 21 and 22 missions, and the Salyut 5 (4) postflight postural stability findings reported from the Soviet Union.

While these results do not directly implicate the otolith system, they do suggest that the otoliths may be responsible for the changes observed. To investigate this possibility we have studied vestibulo-spinal reflexes as a function of otolith stimulation.

In this investigation our laboratory has employed soleus/spinal H-reflex testing procedures as defined by Hugon (5) in conjunction with a linear acceleration of approximately 1.8g through 0-g to assess changes in postural muscles as a function of variable gravity on the otoliths. It is our intention, with this technique, to investigate vestibular induced changes in the vestibulo-spinal system responsible for equilibrium as a function of slow changes in linear inertial force through 0-g.

Methods

For the purposes of this investigation soleus/spinal H-reflex testing procedures were used in conjunction with the accelerative stimulus of NASA's KC-135 parabolic flight airplane. However, before any of the 25 subjects, both male and female, were flown, they were exposed to a battery of ground-based vestibular tests to insure normal adequate vestibular responses. These tests included an audiogram, cupulogram, tests for postural ataxia and measurements of motion sickness susceptibility.

The H-reflex technique involves elicitation of a monosynaptic reflex recorded from the soleus muscle by stimulation of large group I afferent fibers in the tibial nerve. Stimulating electrodes were placed on the subject's right leg with the cathode in the popliteal fossa, and the anode secured over the patella. A 1 msec square wave was delivered from a Grass shock generator through a constant current stimulus isolation unit. Current strength was a maximum of 10 ma. Physiological constraints required that shock pulses be presented only once every 3 sec. A bi-polar electrode configuration was used to obtain the H-reflex from the soleus muscle. All recording was differential with the anterior electrode active.

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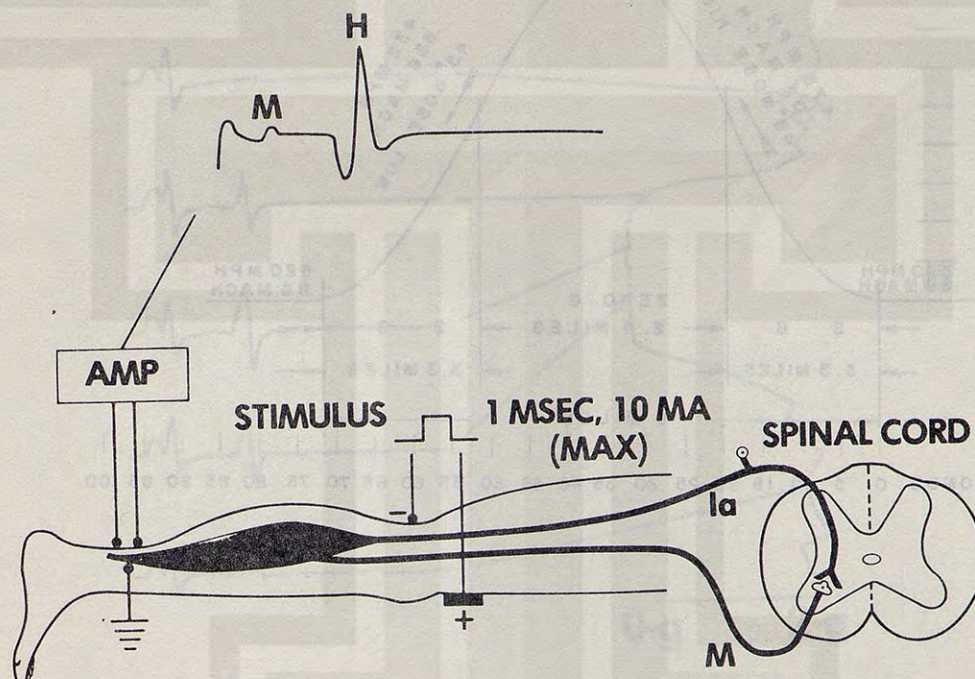


Figure 1. Schematic representation of H-reflex technique used to obtain the data for this investigation. The anode was a plate electrode secured to the leg with elastic straps, and the Cathode was a standard Beckman silver electrode. Recording was via a high impedance electrode probe with Beckman silver/silver chloride electrodes.

Vestibular stimulation was provided by a specially modified KC-135 jet aircraft which was flown over a parabolic arc to produce periods of 0-g which lasted as long as 25 sec. Each maneuver was initiated and terminated with a

pull up of 1.8 to 2g. All maneuvers were flown in roller coaster fashion with each flight comprised of approximately 40 parabolas. Subjects were placed in a supine position, and restrained in a litter so that all accelerations were through the X-axis of the body.

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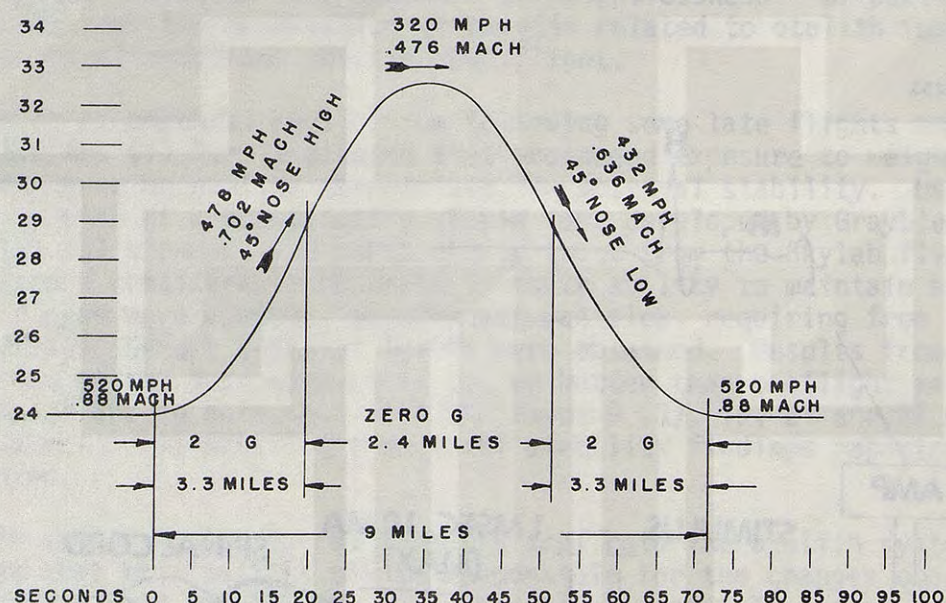


Figure 2. Linear acceleration for stimulation of the otoliths was obtained by flying a jet aircraft through a parabolic arc. Accelerations varied between 2g to 0g. The diagram illustrates the distance traveled, approximate altitude, speed and angle of attack through which the aircraft must fly to achieve the linear accelerations required for this investigation.

Prior to take-off, and periodically during level flight, baselines of 15 to 30 responses were collected against which the test data could be compared. Stimulus shock levels were adjusted such that the monosynaptic H-wave was approximately 50% of its maximum value and the orthodromic M-wave minimal but detectible. No attempt was made to synchronize the stimulus to the airplane's

trajectory, but occurred at random with respect to the acceleration.

Following each flight the data, which were recorded on an analog tape, were digitized with an LSI-11 microcomputer. Analysis of the H-reflex (on a PDP 11/40 minicomputer) elicited during the parabolic maneuvers was begun at the 1-g crossover just before the airplane entered 0-g, and included the period 20 sec before and 40 sec following this time. This 60 sec period was divided into 1 sec or 0.125 sec epics. Any response falling into one of these epics was averaged with other responses in those time frames. In this fashion 40 parabolas and associated responses could be represented as one averaged maneuver. All H-reflex data were normalized with respect to the baseline data.

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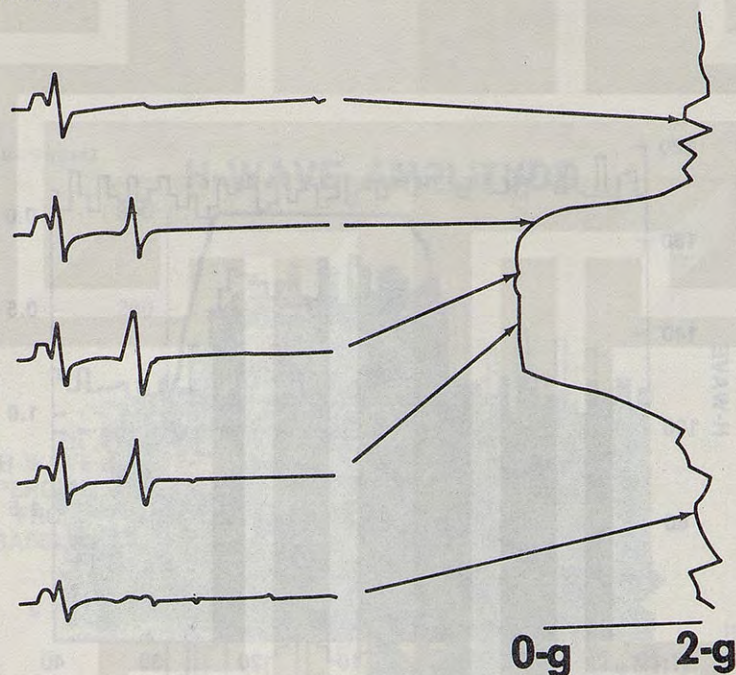


Figure 3. Illustration of analog data demonstrating modulation of the excitability in the spinal cord motor-neuron pool. Typical rate of data collection was one response every three seconds. Approximately every other response, or one-half the typical number of responses is depicted in this figure. Increased g loads resulted in a reduction of the excitability of the motor-neuron pool while 0g produced a larger recorded responses.

Results

The general results indicate that a linear acceleration of 1.8 to 0-g can

modulate the amplitude of the H-reflex. Weightlessness induces a potentiation of the H-reflex, which lasts throughout the period of 0-g, and hyper-g may in some cases produce an inhibition of this response. Figure 3 illustrates the modulation of the H-reflex. Selected responses are shown here referenced to the acceleration of the airplane (subject). Note that during the periods of hyper-g that the H-reflex is considerably attenuated, and that during the 0-g period the response is very large. In this case the potentiation of the H-reflex over baseline values was approximately 400%. All changes in the H-reflex were restricted to variations of amplitude. No difference was observed in latency measurements for either the M or H-waves.

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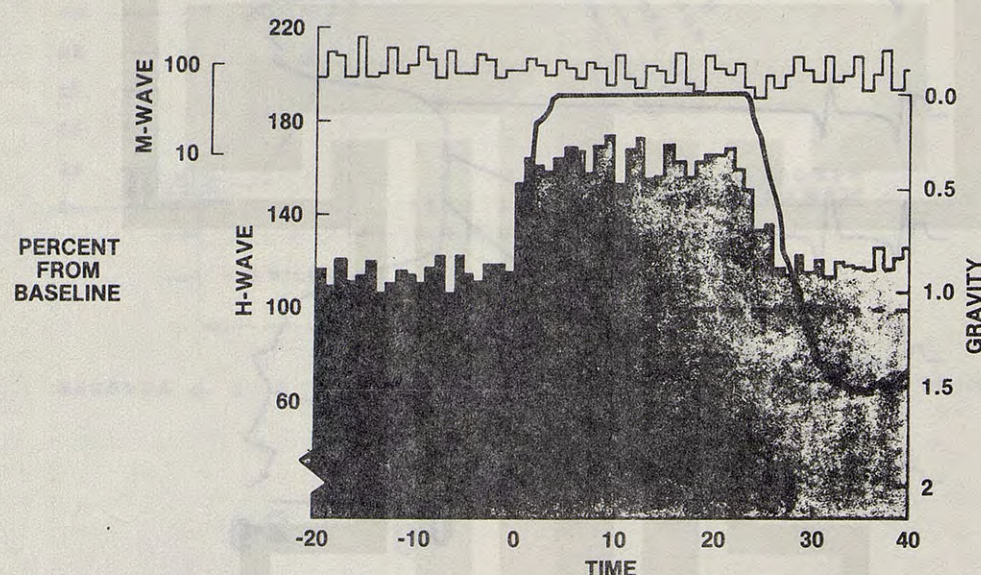


Figure 4. The data shown in this figure represents an average of 25 people and approximately 750 parabolas. The solid line is the average acceleration. H-wave activity is represented by the dark bar histogram, and the M-wave amplitude change is presented in the light bar histogram. All M and H-wave amplitude changes are calculated as the mean deviation from baseline values. One-hundred per cent represents this baseline value.

When the data from all 25 subjects were averaged together a potentiation of the H-reflex of 80% over baseline values for the weightless portion of the flight was found (Figure 4). The Standard Error of the Mean (SEM) for these averaged responses was no more than - 13%. M-wave values showed no change during any part of the acceleration profile indicating that the H-reflex potentiation may reflect a true loop gain change in the soleus/spinal motor-neuron pool produced by descending otolith input.

Adaptation of the weightless potentiated H-reflex was found to occur when eight of the 25 subjects were flown on a second flight (Figure 5). Data from the eight subjects' first flight showed an H-reflex potentiation during 0-g of 120% over baseline values while that for the second flight was reduced to 30% over baseline. The SEM for these data were respectively - 10%. A t test for related data computed for these two flights indicated a significant difference ($p = < .001$).

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H-WAVE AMPLITUDE

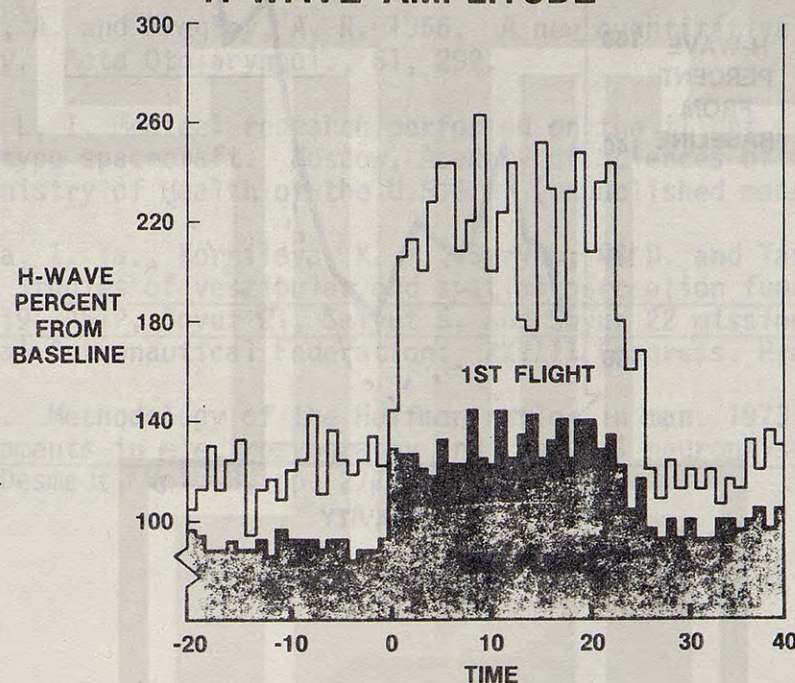


Figure 5. This figure represents data from 8 subjects which were flown on two separate flights. The light bar histogram and the dark bar histogram represent, respectively the average data from these subjects on the first and second flights. Amplitude modulation was recorded as H-wave percent change from baseline values.

When modulation of the H-reflex was plotted against acceleration to determine threshold, the results indicated that H-reflex responses for the 25 subjects

above baseline are not triggered until an acceleration of approximately 0.5g is attained. Figure 6 indicates this relationship. The dashed line in this figure represents the same 8, first flight subjects depicted in Figure 5. The dash-dot line represents the same 8 subjects on their second flight. Note that at the reduced g levels small changes in acceleration produce large amplitude changes in the H-reflex.

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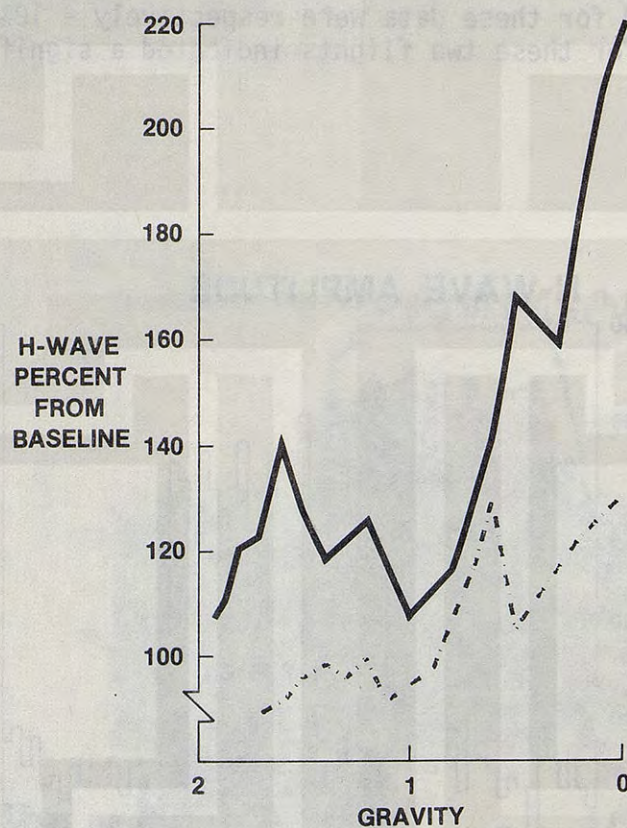


Figure 6. The data in this figure was computed from the histogram presented in Figure 5. The solid line is H-wave amplitude variation over baseline as a function of acceleration for the first flight of the eight subjects. The dashed line represents data from the second flight.

Discussion

The results indicate that vestibular stimulation (specifically otolith) can modulate the H-reflex. That loop gain changes in the spinal motoneuron pool are effected in this manner does now, however, imply that motion sickness susceptibility is directly related to the overall general response that all have recorded. We are currently working on this aspect, and have had some encouragement. Individual patterns indicate that some correlation may be possible. For example, individuals with high motion sickness susceptibility show a large potentiation of the H-reflex in 0-g with a tendency toward inhibition of the response during periods of hyper-g. Those individuals with very low susceptibility may show no potentiation of the H-reflex but the response is inhibited during hyper-g. Adaptation of the changes recorded during several flights appears to parallel the time course noted for adaptation of the Motion Sickness Syndrome.

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SELF-MOTION PERCEPTION DURING LINEAR OSCILLATION:
CHANGES WITH HEAD ORIENTATION AND FOLLOWING FATIGUE

Donald E. Parker

Department of Psychology
Miami University
Oxford, Ohio 45056

Modification of self-motion perception during linear oscillation on a parallel swing was investigated employing two types of independent variables: (i) orientation of the head with respect to the applied linear acceleration vector and (ii) sustained, "intense" linear oscillation (fatigue-inducing stimulation). The purpose of these investigations was to examine ways in which the information received by a central spatial orientation perceptual system (1) might be altered.

Experiment I examined changes in 144 subjects' direct magnitude estimation performance as a function of head orientation. The subjects were tightly restrained in a parallel swing and were placed in varying orientations with respect to gravity (see Fig. 1). Visual cues were eliminated during data collection. The subjects estimated magnitudes of perceived motion during oscillation at each of eight peak-to-peak levels, ranging from 15 to 120 cm. Performance was summarized employing Stevens' power law ($R = k S^n$, where R is perceived self-motion magnitude, k is a constant, S is amplitude of linear oscillation, and n is an exponent). The results of Experiment I indicated that the exponents, n , were greatest when the head was oriented 45 deg off-vertical (Fig. 2). Calculated across head orientations, exponent variability was highly correlated with exponent magnitude (Fig. 3).

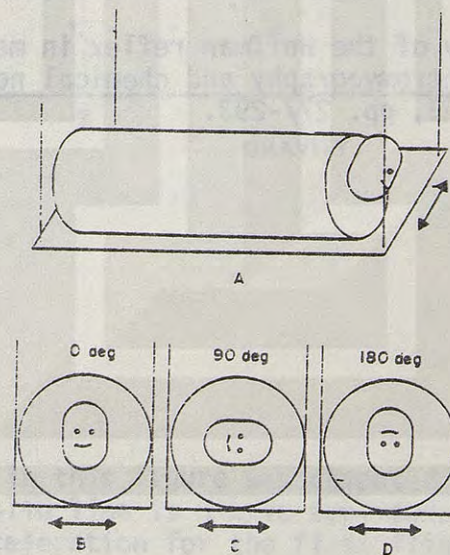


Figure 1. Parallel swing and subject illustrating three of the eight head orientations used in Experiment I.

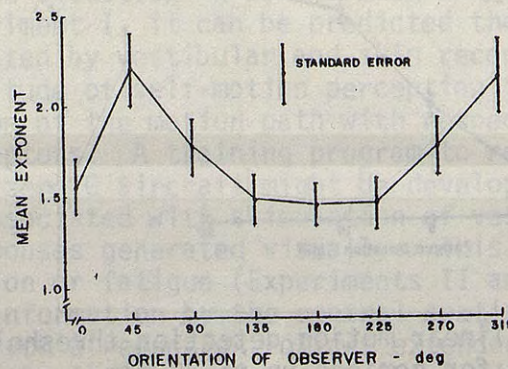


Figure 2. Means of magnitude estimation function exponents (across subjects as a function of orientation of applied oscillation with respect to subject's head. Maximum exponent values were obtained during oscillation in the 45- and 315- deg orientations.

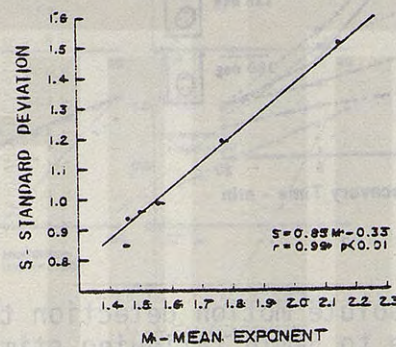


Figure 3. Scatter plot of mean exponent values and the standard deviations of these values. Each point represents statistics calculated for a particular head orientation across subjects.

Experiment II (2) demonstrated that thresholds for detecting linear motion increased following exposure of human subjects to sustained linear oscillation (fatigue-inducing stimulus) at 0.25 Hz and approximately 0.5 G peak-to-peak for durations up to 30 min (Fig. 4). Recovery to pre-exposure levels took place over a period of 10 to 15 min following the sustained oscillation termination. Differences in threshold shift magnitudes following sustained oscillation in various orientations support the interpretation that the observed threshold shifts resulted from fatigue of the utricular otolith receptors (Fig. 5).

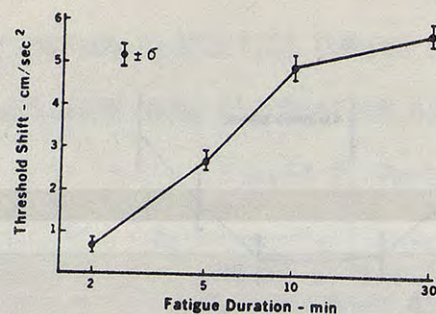


Figure 4. Shifts in linear motion detection thresholds following sustained oscillation for periods up to 30 min.

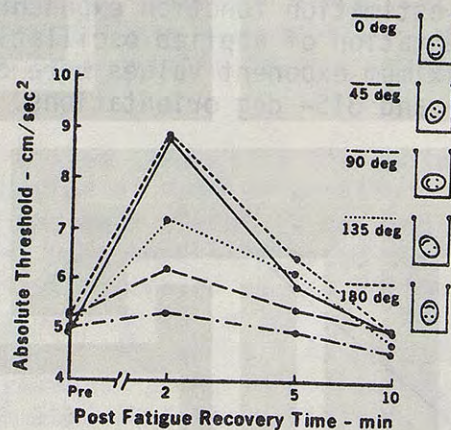


Figure 5. Increases in absolute motion detection thresholds and recovery following exposure to 5-min fatiguing stimulus in various orientations. Thresholds were determined in the 0-deg orientation; fatiguing stimulus exposure was in the 0-, 45-, 90-, 135-, and 180-deg orientations.

In Experiment III, self-motion magnitude estimation performance was observed before and after exposure to the fatigue-inducing stimulation, following the procedures employed in Experiment I. Magnitude estimation function exponents were increased following exposure to the sustained oscillation (Fig. 6). Similar changes have been reported for other sensory modalities following fatigue and masking (4).

All three experiments illustrate ways in which information received by a central spatial orientation perceptual system can be modified. Following the conflict theory, which was summarized by Reason and Brand (3), these modifications may be a contributing factor to development of disorientation and motion sickness.

For example, consider the situation in zero G when an astronaut moves along a linear path. From Experiment I, it can be predicted that the magnitude of self-motion perception generated by vestibular and skin receptors may or may not correlate with the magnitude of self-motion perception generated visually, depending upon the orientation of the motion path with respect to the astronaut's vestibular and skin receptors. A training program to reduce these potential conflicts employing the zero G aircraft might be developed. Further, reduced self-motion responses associated with stimulation of vestibular and skin receptors might conflict with responses generated visually. This reduction, which might be associated with adaptation or fatigue (Experiments II and III), could result in receipt of conflicting information by the central spatial orientation perceptual system. The view that such a reduction follows extended zero G exposure is supported by the observation that the Skylab astronauts exhibited a wide "dead band" for linear motion detection during the early post-flight period.

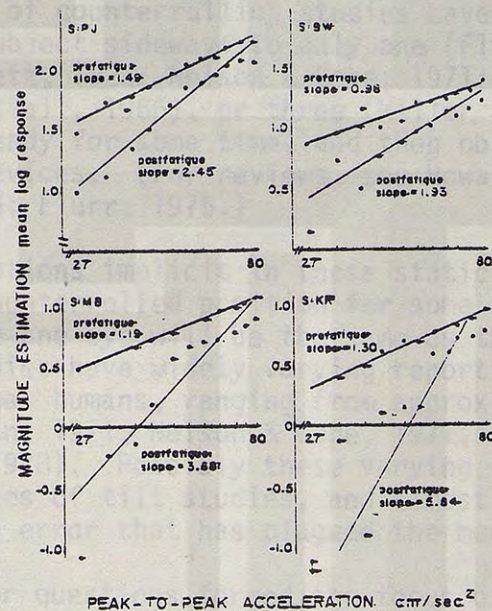


Figure 6. Mean magnitude estimations evoked by different levels of linear acceleration. The slope of the magnitude estimation function was greater after fatigue.

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ASYMMETRIES IN BINOCULAR COUNTERROLLING

IN HUMAN DURING DYNAMIC ROTATION

C. H. Markham and S. G. Diamond

Reed Neurological Research Center
UCLA School of Medicine
Los Angeles, California 90024

Introduction

When the head is tilted to one side, the eyes will roll in a direction opposite to the head tilt. This reflex action is called counterrolling and is considered to be governed by the otolithic receptors. A long but rather sparse history of counterrolling studies have for the most part consisted of tilting a subject sideways to only one (Fluur, 1975; Linwong & Herman, 1971; Kompanejetz, 1928; Nelson & Cope, 1971; Kanzaki, 1975), two (Walton, 1948; Miller et al., 1966), or three (Miller & Graybiel, 1963; 1965) positions, holding him steady for some time, and then observing one eye with a variety of measuring devices. (For reviews, see Howard & Evans, 1963; Howard & Templeton, 1966; Flurr, 1975.)

The assumptions implicit in these static methods is that the eye remains fixed in its counterrolled position for some time, and that the counterrolling observed in the one eye will be the same as the counterrolling in the unobserved eye. Past studies have widely varying reports of the total amount of counterrolling in normal humans, ranging from approximately 12° (Miller, 1962; Linwong & Herman, 1971; Nelson & Cope, 1971, Kanzaki & Ouichi, 1978) to 48° (Kompanejetz, 1928). Possibly these varying results may be due to the different degrees of tilt studies, and almost certainly some of it is due to the artifactual error that has plagued the measurement of this phenomenon.

Three major questions formed the focus of our study: 1) what is the range of counterrolling in normal humans under dynamic rather than static conditions; 2) do both eyes counterroll equally and conjugately; and 3) is there an equal amount of counterrolling when subjects are tilted to the right and to the left.

METHODS

Subjects were securely strapped into a large motor-driven tilting chair which had a line engraved on the back through the center of the rotation. This line was precisely horizontal when the chair was in the upright or zero position. A camera was firmly mounted on the frame of the chair such that a fine line etched on the view finder exactly overlay the line etched on the chair when the experimenter looked into it. The camera was also fitted with a film transport device that eliminated any vertical movement when the film was advanced. (For additional detail, see Diamond et al., 1979).

The subject's head, firmly positioned with a bite bar, was adjusted so that the horizontal line on the view finder passed through the centers of the

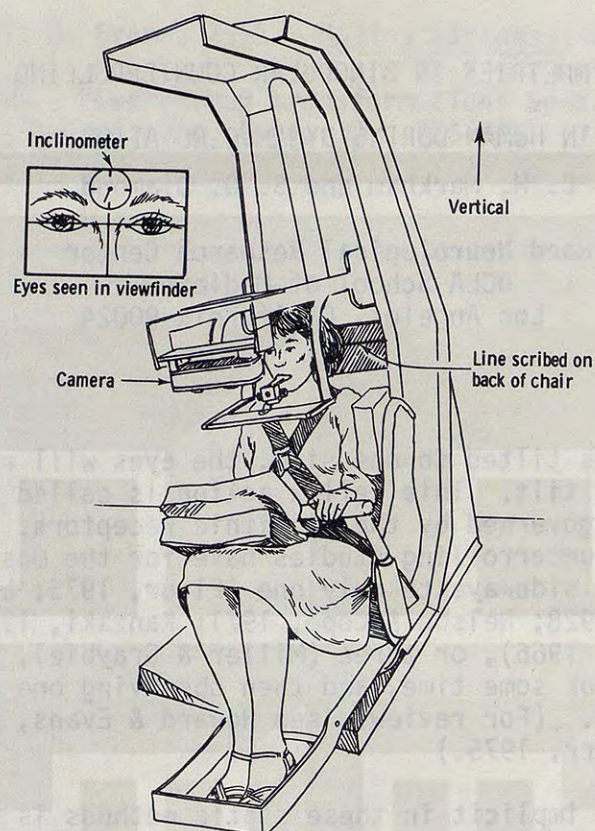


Figure 1. Illustration of motor-driven tilting apparatus.

two pupils. This precise horizontal alignment of the two pupils when the subject was in the upright position was the baseline from which were measured the torsional changes occurring during tilt.

After several photographs were taken at the baseline position, the subject was rotated about his naso-occipital axis through 360° at a constant velocity of $3^\circ/\text{sec}$. Photographs were taken at each 10° of rotation, and included the whole upper part of the face as well as an inclinometer which indicated the degree of tilt in each frame.

Seven subjects were rotated through a total of 27 trials. Subjects were five males and two females, aged 18 to 66 years. Rotations began either right ear down or left ear down, in random order. Most subjects had four trials, each trial being separated by a rest period of at least two minutes.

Counterrolling was measured with a two-projector system in a variation of Miller's (1962) technique. One projector, shown on the left in Figure 2 contained a slide of the eyes in the zero or baseline position. The other projector contained the film strip of the subject's eyes during rotation. This second

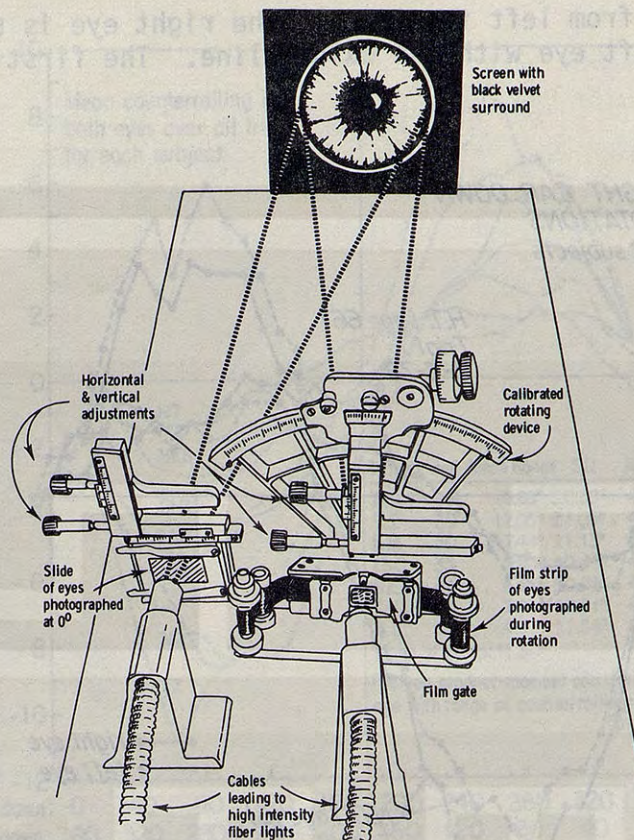


Figure 2. Illustration of two-projector system used for counterrolling measurements.

projector was built with a film gate from a professional motion picture camera which allowed the film to pass through with virtually no vertical or diagonal movement which might confound rotational measurement. This projector was also fitted with a calibrated rotating device, modified from a sextant, which allowed the projected image to be rotated. A projection screen was covered in black velvet except for a circle in its center, slightly larger than the size of the projected iris.

Measurements were done in the following way. The image of one eye in the first projector was projected on the screen. The image from the second projector was aligned and then rotated until it was exactly superimposed on the image from the first projector. The extent to which the second image had to be rotated from its baseline value to achieve this superimposition was the measure of counterrolling at a given position. Right and left eyes were always measured independently.

RESULTS

Figure 3 shows trials on two subjects, each beginning right ear down.

(This figure is read from left to right.) The right eye is shown with the solid line and the left eye with the dashed line. The first half of rotation

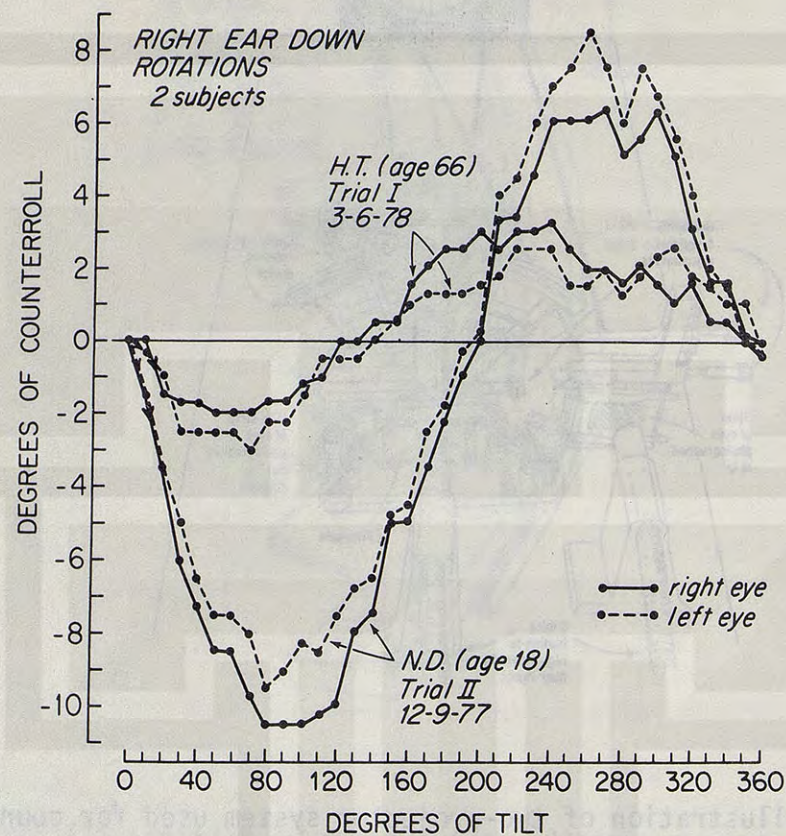


Figure 3. Right and left eye counterroll data from two subjects. The first half of rotation was with the right ear down.

in these trials is the right ear down segment, and after 180° the left ear is down. N.D. shows a range of about 17.5° of counterrolling from one extreme to the other, while H.T. has a range of about 5.5°. Note that the two eyes do not always move conjugately: H.T. at 300-320° has his two eyes moving in opposite directions, and N.D. at 90-110° and 260-280° shows the right eye holding steady while the left eye is changing. These kinds of disconjugate movements were seen in all seven subjects. Note also that at 260° N.D. has 6° of counterroll in her right eye and 8.5° in her left, a difference of 2.5°. Differences of 2° between the two eyes in a given position were not uncommon in other subjects.

The mean counterrolling of each subject in both eyes over all trials in both directions of rotation is shown in Figure 4. The group mean was 11.30°, but large individual differences may be seen, from a low of 4° to a high of about 17.5°. The table in the lower right quadrant of the figure

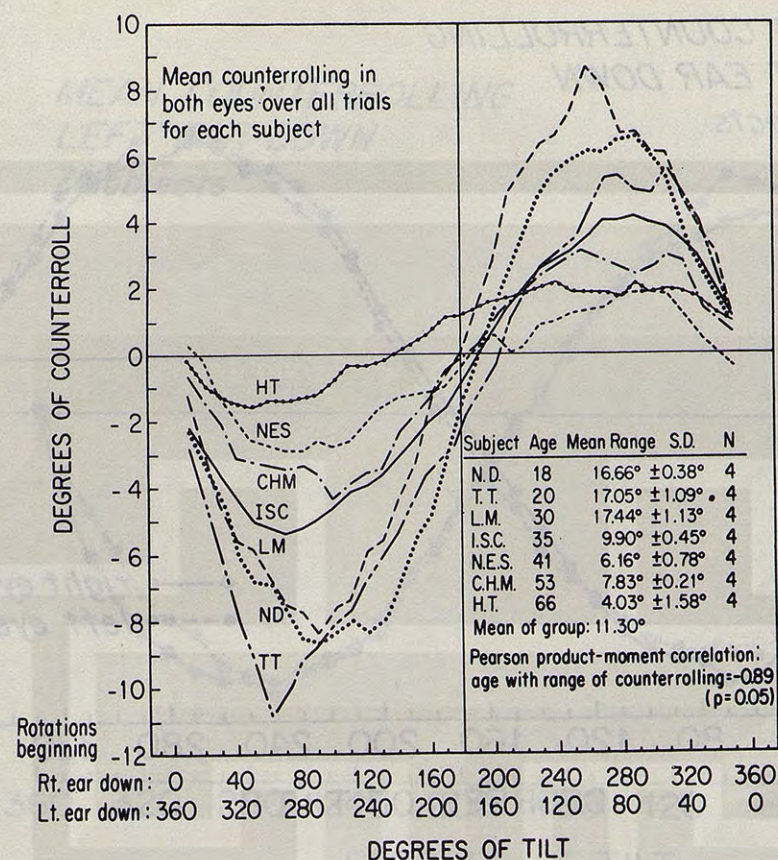


Figure 4. Mean counterrolling in both eyes over all trials for each of seven subjects. The table in the lower right quadrant of the figure shows the mean range of counterrolling in these subjects ranked by age.

shows the mean range of counterrolling in these subjects ranked by age. In these seven persons, the younger subjects clearly counterrolled more than did the older ones. A Pearson product-moment correlation coefficient of -0.89 was significant at the 0.05 level, suggesting that the amount of counterrolling declines with age.

Figure 5 shows the mean counterrolling of all seven subjects in 13 rotations beginning right ear down. (This figure is read from left to right.) In the first half, or right ear down portion of the rotation, maximum counterrolling is about 6°. In the second half, or left ear down position, the maximum is about 4°. In other words, there is considerably more counterrolling when the subjects are in a right ear down position than when in a left ear down position. In addition, in the right ear down position the right eye (shown with solid line) is counterrolled more than the left eye (dashed line); and in the left ear down position the left eye is counterrolled more than the right.

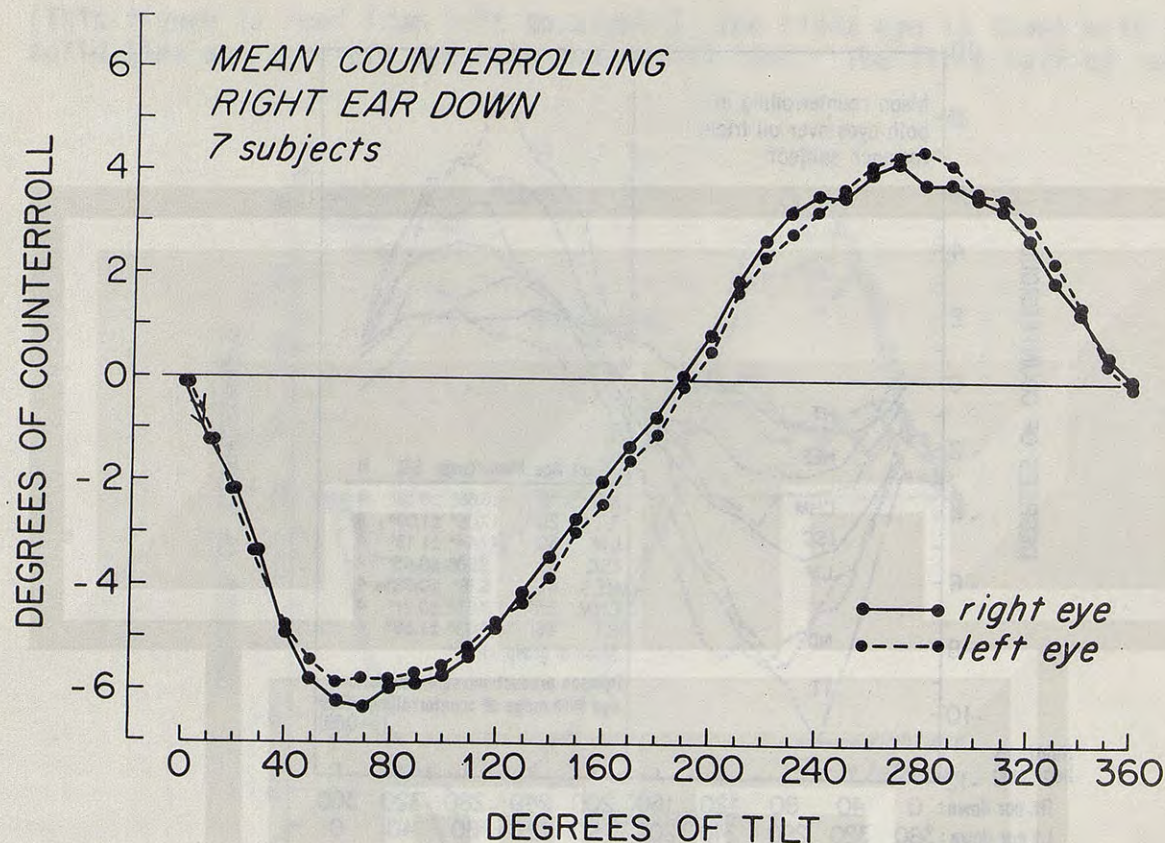


Figure 5. Mean right eye and left eye counterrolling data for all seven subjects in 13 rotations beginning right ear down.

Figure 6 shows the mean counterrolling of the seven subjects in 14 rotations beginning left ear down. (This figure is read from right to left.) The first half of rotation is left ear down, and maximum counterrolling is approximately 4.5°. In the second half, or right ear down portion, maximum is approximately 5.5°. Once again, more counterrolling is seen when subjects are positioned right ear down, even though the right ear down position is reached in the second half of rotation in these trials. Also, the left eye is again counterrolled more than the right during the left ear down portion; and the right eye is counterrolled more than the left during the right ear down position. This asymmetry in favor of greater counterrolling in the downward eye is significant at the level of $p < 0.001$ (binominal test).

In summary, our results indicate that, first: the mean range of counterrolling in normal humans under dynamic rotation is about 10°, which is approximately the same as most studies have reported.

Secondly, both eyes do not counterroll equally or necessarily conjugately,

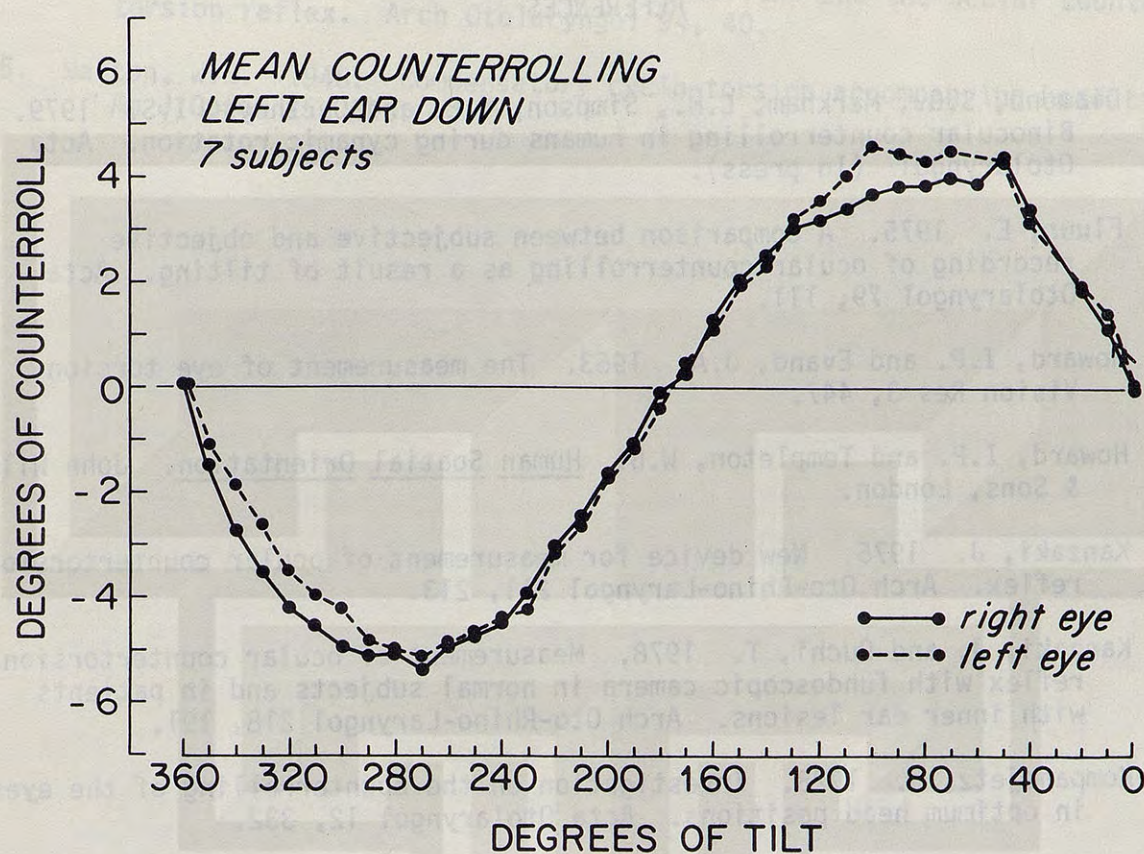


Figure 6. Mean right eye and left counterrolling data for all seven subjects in 14 rotations beginning left ear down.

with the downward eye consistently counterrolling more than the upward eye. A similar asymmetry was found in an earlier study (Markham et al., 1977) in which the lens of the downward eye was observed to accommodate in response to tilt while the upward eye showed either an anti-accommodative or no change. The asymmetry in ocular accommodation was attributed to asymmetrical influences from the left and right otolith receptors to the intra-ocular muscles of the two eyes. The asymmetry in ocular counterrolling may be due to similar imbalanced drive to the extra-ocular muscles.

Thirdly, a distinctly greater amount of counterroll is seen when subjects are tilted to the right than to the left, regardless of the order of tilting. Possibly these functional asymmetries may be secondary to structural asymmetries in the utricles.

Lastly, the finding in this group of seven subjects that the older the individual, the smaller the range of his counterrolling might suggest such factors as decreased elasticity of otolith membrane, or loss of receptor cells, otoconia or neurons with age.

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THE ETIOLOGY OF SPACE MOTION SICKNESS

Ashton Graybiel

Naval Aerospace Medical Research Laboratory
Naval Air Station
Pensacola, Florida 32508

In a motion environment if head movements are essential for the elicitation of symptoms they are, also, necessary to effect a cure. Under direction, a cure can be effected in a fraction of the time compared with no guidance. We postulate that free fall should be categorized as a partial, preternaturally weak motion environment in which some but not all persons are susceptible.

Motion Sickness Paraphrased

It is not proposed to give here a full description of motion sickness, rather will be given those aspects that have relevance to free fall.

Irwin in 1881 (1) suggested the term motion sickness to provide a general designation for similar syndromes experienced in different conveyances on water and land. Time has endorsed Irwin's term because it met the test of convenience by its etiologic and symptomatic connotations. Since Irwin's day, more types of conveyances have appeared, and we have learned the important contribution man makes to many motion environments by moving his head (2). We have also learned the important role of secondary etiological factors and the fact that motion of the visual environment alone may elicit symptoms.

Figure 1 illustrates motion environments (M.E.) in the laboratory and in conveyances. A slow rotation room is an obligatory incomplete M.E.; head movements out of the plane of the room's rotation are essential to render it complete. The off-vertical rotating device is an obligatory complete M.E.

Fig. 1 MOTION SICKNESS PARAPHRASED
Motion Implies Motion Environments (M. E.)

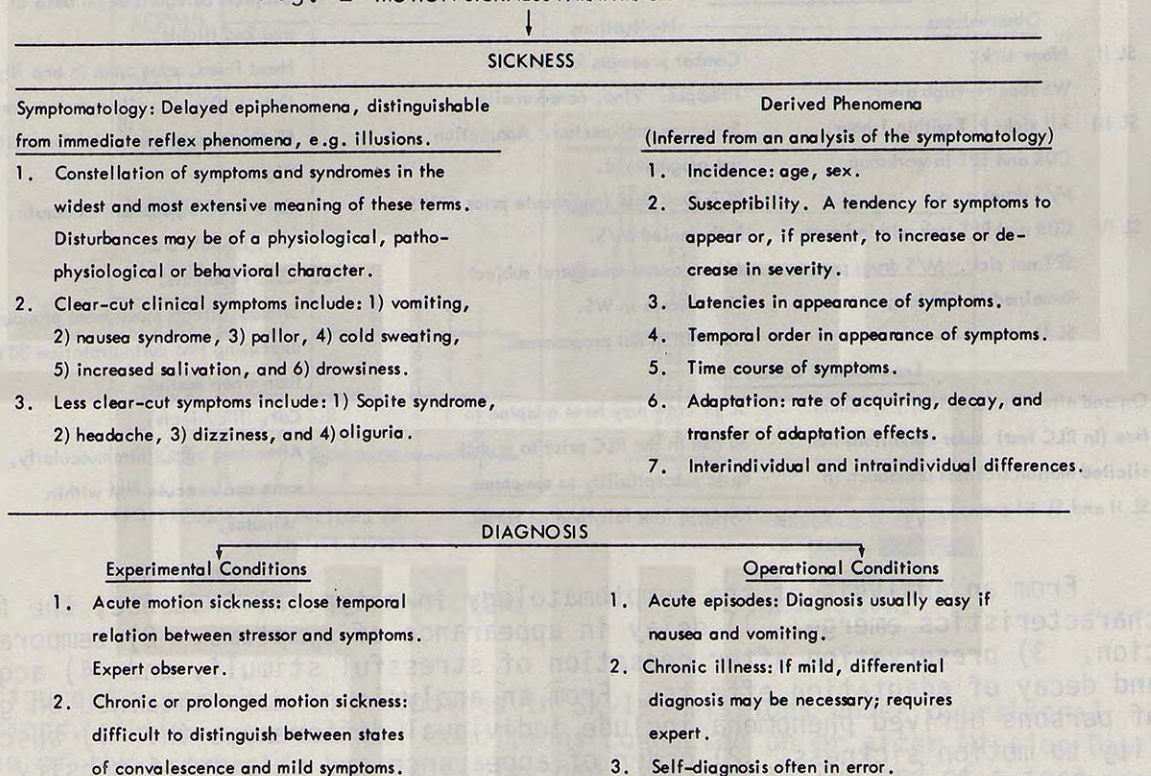
Laboratory		Conveyances	
Slow Rotation Room (SRR)	Off-Vertical Rotation (OVR)	Ships - Boats	Aircraft
Incomplete M. E.: Head movements (HM) out of the plane of rotation essential to generate stressor effects. Chief stressor: Cross-coupled angular accelerations. Eyes open increases slightly the stressor effect.	Complete M. E. Typical test: Head and body restrained and upright; eyes closed. Slow acceleration to constant rpm (15-25) then slow tilt to 15-25°. Pleasant experience until symptoms appear. "Instant" nausea if eyes opened or HM.	Potentially complete M. E. Turbulence variable. HM increase stressor effect. Eyes open may increase or decrease stressor effect.	Potentially complete M. E. HM increase stressor effect. Great difference in stressor effects between civilian and military flying. In latter, stressor effects may be coupled with danger.

Motion solely of the visual field:

Stressful environments include 1) movies (cineglobe), 2) motion simulators, and 3) certain carnival devices.

and notably pleasant until symptoms appear. Ships and aircraft are potentially complete M.E.'s, and head movements increase the stressor effects.

Fig. 2 MOTION SICKNESS PARAPHRASED



In Figure 2 a distinction is made between the symptomatology and inferences derived from an analysis of the symptoms. Typically, motion sickness is a delayed epiphenomenon, superimposed on any responses in the reflex category, due to vestibular influences that cross a temporary or facultative linkage to reach non-vestibular sites where first order symptoms have their immediate origin. First order responses may, in turn, elicit second and higher order responses (complications) until the organism is generally involved. The cardinal symptoms useful in making a clinical diagnosis include cold sweating, pallor, drowsiness, increased salivation, and the nausea syndrome. Release of anti-diuretic hormone and urinary excretion of 17-hydroxy corticosteroids and catechol amines are among the many biochemical changes that may be manifested. The nausea and vomiting syndromes are well known but not in some of their important aspects.

Fig. 3 MOTION SICKNESS IN FREE FALL

Skylab		Parabolic Flight
Operational Conditions		
Observations	Implications	
SL II None sick. WS repairs: High alert.	Combat preempts facultative linkages. ?Inc. noradrenalin.	1. Subjects categorized on basis of 1st and 2nd flights. Head fixed, eyes open in one flight. Cat. I 40% virtually symptom free. FF phases serve as model for orbital flight.
SL III All sick: PLT within 1 hour. CDR and SPT in workshop. M/S drugs p. o.	Symptoms unexpected. Adaptation not programmed. PLT: One dose inadequate prior to WS.	Cat. II 30% symptoms moderate. Cat. III 30% sick.
SL IV CDR and PLT sick within hours. SPT not sick. M/S drugs p. o. Remained in CM longer than SL II crew.	Both denied M/S. All regretted no control subject. None worse in WS. Adaptation not programmed.	2. Cat. I subjects. Stressor effects much more pronounced executing HM during rotation 30 rpm than when seated.
Experimental Conditions		
On and after Day 8 virtually symptom free (in RLC test) under conditions that elicited motion sickness prelaunch in SL II and SL III crews.	SL IV crew may have adapted to 30 rpm in the RLC prior to launch. Basic susceptibility to symptoms lower in free fall than on Earth.	3. Cat. III subjects. After drug adm. intramuscularly, some can execute HM within "minutes."

From an analysis of the symptomatology in a typical instance, the following characteristics emerge: 1) delay in appearance of symptoms, 2) temporal summation, 3) preservation after cessation of stressful stimuli, and 4) acquisition and decay of adaptation effects. From an analysis of data obtained on groups of persons derived phenomena include individual differences in: 1) susceptibility to motion sickness, 2) order of appearance and relative intensity of responses, 3) acquisition and decay of adaptation effects, 4) amount of performance decrement for comparable levels of stress, and 5) the manifestation of conditioned responses.

Diagnosis, in the absence of nausea and vomiting, is difficult under operational conditions. In the laboratory, acute motion sickness is readily diagnosed but becomes increasingly difficult both with increasing delay between exposure to the stressor and elicitation of symptoms and with increasing departure from typical symptomatology.

Figure 3 summarizes key findings in Skylab missions and in parabolic flight. In parabolic flight the evidence is convincing that some subjects insusceptible when restrained in the rotating litter chair (RLC) with head fixed, experienced motion sickness when head movements were executed during the free-fall phases of the parabolas. A similar test comparing the effects of restraint in a seat with head fixed and executing head movements during free-fall phases of the parabola was rarely decisive.

Fig. 4 MOTION SICKNESS UNDER OPERATIONAL CONDITIONS

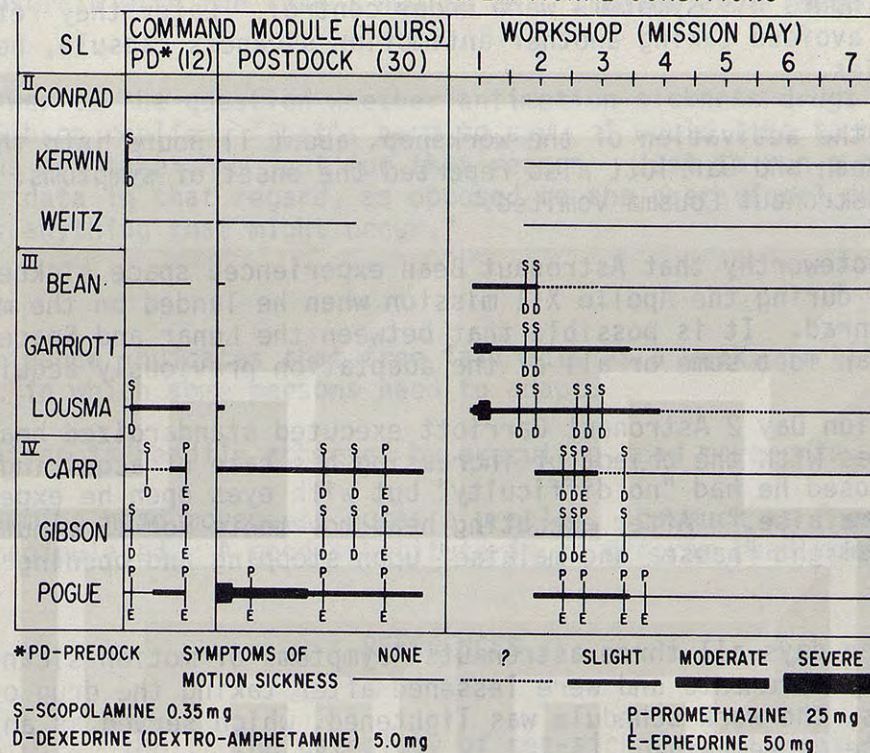


Figure 4 summarizes the findings in Skylab missions under operational conditions. Under experimental conditions conducted on or after Mission Day 8, none of the astronauts participating had symptoms at the end of a test. In the case of astronauts in the third space mission, their extra practice sessions prior to launch rendered them immune prelaunch.

Under operational conditions Astronaut Conrad had demonstrated immunity while participating in Gemini V and XI and in Apollo XII that involved a lunar landing.

Astronaut Kerwin, who took a capsule containing scopolamine 0.35 mg and amphetamine 5.0 mg at launch, did not experience typical symptoms of motion sickness. Theoretically, a person near the borderline between susceptible and insusceptible to space sickness might have profited sufficiently from a single dose to effect a cure by executing head movements during the hours he was protected by the medication.

Astronaut Weitz when asked in a debriefing if he was immune (to motion sickness) during the first week aloft replied, "there (was) no discernable difference to me in how I felt subjectively throughout the flight.

In the second manned mission, prior to launch, the astronauts were quite confident that they would not experience motion sickness in orbit. Nevertheless, Astronaut Lousma reported symptoms within an hour while in the act of doffing

his space suit, the earliest appearance of symptoms on record. He took an anti-motion sickness capsule which abolished his symptoms, and for a period measured in hours his symptoms were under control. Later they returned, and, although he avoided taking another antimotion sickness capsule, he restricted his activities.

During the activation of the workshop, about 11 hours into the flight, Astronauts Bean and Garriott also reported the onset of symptoms. Shortly thereafter Astronaut Lousma vomited.

It is noteworthy that Astronaut Bean experienced space sickness for he was symptom free during the Apollo XII mission when he landed on the moon with Astronaut Conrad. It is possible that between the Lunar and Spacelab missions, Astronaut Bean lost some or all of the adaptation previously acquired aloft.

On Mission Day 2 Astronaut Garriott executed standardized head movements for 30 minutes with the object of increasing his rate of acquiring adaptation. With eyes closed he had "no difficulty" but with eyes open he experienced "developing malaise." After executing head movements for 15 minutes he experienced slight "nausea and malaise" upon stopping and opening his eyes.

For three days all three astronauts' symptoms of motion sickness were intensified by movements and were lessened after taking the drug or restricting movements, the work schedule was lightened, which served as an indicator of performance decrement.

In Skylab IV mission both Astronauts Carr and Pogue, shown in Figure 4 as manifesting symptoms of space sickness, asserted they were not sick.

Astronaut Carr in a debriefing stated, "In one of the debriefings I remarked about epigastric awareness and somebody immediately tagged that as motion sickness. I've seen in certain press releases that I had motion sickness, but I certainly would not characterize it as that because the epigastric awareness that I referred to in that debriefing was the sinking, unwell feeling I had when I was hungry. I don't consider that motion sickness at all. I don't feel that I had any significant motion sickness myself either. I was acutely aware of the fluid shift - - -."

In a debriefing, Astronaut Pogue stated, "I felt that I would not necessarily have thrown up had I not eaten. I started feeling bad, and I ate for the beneficial effect of eating. I think I selected the wrong item, however. If I had taken some aspirin or sedative at that time, it may have helped." In answer to the query "What did you eat?" Astronaut Pogue replied, "A can of tomatoes. - - - It was not nausea that I had at first. I just felt bad - severe malaise and headaches. I think I precipitated nausea by eating."

When Astronaut Gibson in a debriefing was queried about space sickness he replied as follows: "I guess I was fortunate. I just didn't experience anything related to motion sickness at all in the flight. A feeling of head fullness was with me, but while I was in the command module or once we started

the activation, I tried to keep my head motions and body motions down to a minimum. When I first got into workshop I just slowly moved up to a reasonable pace commensurate with the task I had to do. I never experienced any symptoms at all."

In answer to the question whether antimotion sickness drugs were beneficial, Astronaut Gibson replied, "That's hard to say. I would like to have seen one or two of us not take them just for that reason - just to run a good experiment to give you data in that regard, as opposed to the operational press of trying to suppress anything that might occur."

Conclusions

1. The evidence indicates that free fall acts as a weak, partial motion environment in which some persons need to adapt.
2. Adaptation is readily achieved by executing head movements.
3. Programming head movements poses a problem, inasmuch as free fall per se cannot be manipulated. A good substitute is to program head movements under medication.

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SUSCEPTIBILITY TO MOTION SICKNESS DURING

Z AXIS RECUMBENT ROTATION

James R. Lackner and Ashton Graybiel*

Department of Psychology
Brandeis University
Waltham, Massachusetts

*Naval Aerospace Medical Research Laboratory
Naval Air Station
Pensacola, Florida

Two experiments were conducted to evaluate the hypothesis that headward shifts of body fluid are responsible at least in part for the motion sickness experienced in orbital flight. Both experiments involved Z-axis rotation of recumbent subjects. Our approach was to compare intraindividual differences in susceptibility under conditions approximating, in terms of fluid shifts, those to be expected in orbital flight. The head-and-trunk horizontal position was used as a model for zero gravity because Patterson (1) in estimating the likely changes in cerebral circulation on transition into weightlessness 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.

Normal persons rotated about an earth-horizontal axis vary considerably in their susceptibility to motion sickness. In the first experiment, intraindividual differences in susceptibility were measured for 12 subjects each of whom participated in three experimental conditions presented in a counter-balanced design. The three conditions included 10° head-up, head-horizontal, and 10° head-down rotation of the body. These three postures reflect progressively increasing degrees of headward shifts of body fluid and according to a fluid-shift hypothesis of motion sickness should be increasingly stressful.

Subjects assumed the test position 60 minutes prior to rotation thus providing an opportunity for translocation of body fluids. They were then accelerated at $2^\circ/\text{S}^2$ to a constant angular velocity of 30 RPM that was maintained until the subject had reached a pre-determined motion sickness endpoint or one hour had elapsed. The diagnostic criteria developed by Graybiel, Wood, Miller, and Cramer (2) for measuring severity of acute motion sickness were used. A rating of "12 points" was chosen as the level for terminating a run because, although it involves the "nausea syndrome", it generally avoids frank sickness with vomiting. Physiological and psychophysical measurements were conducted throughout the experiment.

There were no intraindividual differences in susceptibility to motion sickness in the three positions tested. Nevertheless, there were significant differences in vital capacity demonstrating the expected fluid shifts. No systematic relationship was present between the appearance of motion sickness symptoms and changes in physiological parameters such as blood pressure, heart rate, and temperature. From these results it was concluded that, in the

sample of subjects tested, short-term effects of fluid shifts greater than those that would be expected in zero gravity had no definite effect on motion sickness susceptibility.

In this first study, subjects had been in the experimental posture for a relatively brief period, one hour, prior to rotation. To cover the possibility that vestibular disturbances caused by fluid shifts might take some time to develop a second experiment was conducted. It differs from the first in extending the period of recumbency before rotation up to 6 hours in one of the experimental conditions. A value of 6 hours was chosen because well within this time period, motion sickness has been manifested in orbital flight (3,4).

The experiment involved measuring intraindividual differences in susceptibility to motion sickness for 14 subjects under two conditions of rotation at 30 RPM in the 10° head-down position. In one condition, subjects were in the 10° head-down position for 6 hours prior to the onset of rotation, in the other condition the delay was only 15 minutes. In both conditions, there were large changes in vital capacity indicating a redistribution of movable body fluids. No correlation was present between the appearance of motion sickness symptoms and changes in heart-rate, blood pressure, or temperature. Subjects tended to be less susceptible to motion sickness when they were recumbent for 6 hours prior to rotation. These results are additional counter evidence for the hypothesis that shifts of body fluid are responsible in large part for the motion sickness elicited in orbital space flight. Such fluid shifts, at least in the early hours in orbit, may actually decrease susceptibility to motion sickness.

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ANIMAL MODELS IN MOTION AND SPACE SICKNESS RESEARCH¹

Nancy G. Daunton
NASA Ames Research Center
Moffett Field, CA

Many problems inherent in human studies of motion and space sickness can be avoided if an animal model is used. Such problems include the usual difficulties with human research (subject cost, procedural restrictions, lack of adequate control over internal and external environments and prior experience, etc.) as well as a problem specific to motion sickness research, i.e., control of level of susceptibility. By using animals which have been rigorously screened for level of susceptibility (e.g., high and low susceptibility), it is possible to achieve a high degree of control over this variable, and thus clarify the effects of any given experimental variable. The use of animal subjects carefully selected for high and low levels of susceptibility to motion sickness also makes it possible to study the etiology of motion and space sickness by determining what structural, biochemical, and/or behavioral differences cause animals with normal vestibular function to respond so differently to the same motion stimuli.

We have been investigating the cat as an appropriate animal model for motion and space sickness research over the past several years. The basic methodology, approach, and the scale for rating motion sickness in cats is presented in detail in Suri, Crampton and Daunton (1979). From these studies it appears that the cat is a good model for use in motion and space sickness research, since: 1) the responses of animals at the extremes of the susceptibility spectrum are quite consistent over time; 2) approximately 40% of the three samples of 20 animals tested to date fall into the extremes of the susceptibility spectrum (i.e., highly susceptible or highly nonsusceptible); and 3) motion sickness susceptibility in cats is generalizable across several different motion environments, including vertical linear acceleration, horizontal rotation, and 0-g parabolic flight.

Because the trait of susceptibility appears to be consistent over time and generalizable across motion conditions in the cat, we have used this animal in several pilot studies of the etiology of motion sickness. In one of these studies, the role of anti-diuretic hormone (ADH) in motion sickness is being investigated. Preliminary data suggest that ADH increases approximately four-fold in susceptible animals undergoing motion stimulation. No such increase in ADH is seen in nonsusceptible animals undergoing the same motion stimulation. In another set of pilot studies the neuroanatomical substrate of motion sickness is being investigated, using the ¹⁴C 2-deoxyglucose technique to identify areas of the brain that are differentially activated in

¹The following individuals have been involved in these studies:
N. Daunton, L. Keil, and K. Suri - NASA ARC, Moffett Field, CA
G. Crampton - Wright State University, Dayton, OH
R. Fox - San Jose State University, San Jose, CA

the activity of the flocculo-nodular area of the cerebellum². Formal experiments are currently being conducted to evaluate further the role of ADH in motion sickness, and to identify the brain areas involved in the motion sickness response.

Using the procedures developed with the cat, we are also evaluating the squirrel monkey as an appropriate model for motion and space sickness research. This animal is highly susceptible to motion sickness in 0- and hypo-g parabolic flights and in rotating environments. However, the squirrel monkey appears to be less susceptible to vertical linear acceleration than is the cat. A major effort is currently underway to develop a rating scale similar to that developed for the cat to evaluate motion sickness responses in the monkey. In addition, behavioral tasks for the monkey are being developed which will allow evaluation of motion sickness levels on the basis of operant behavior, thus eliminating the need for human observation of the animals in the sickness-inducing environments.

Both the cat and the squirrel monkey appear to be promising as models for motion and space sickness research. The animal of choice must be determined on the basis of what specific aspect of motion and/or space sickness is to be investigated in any given experiment. Judicious use of animal models in studies of basic mechanisms of motion and space sickness and in more applied studies involving the development of countermeasures for these maladies should contribute greatly to the understanding and treatment of motion and space sickness.

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THE INCIDENCE AND LATENCY OF VOMITING TO ROTARY MOTION
AND THE EFFECTS OF ABLATION OF THE AREA POSTREMA
(CTZ) IN THE SQUIRREL MONKEY

K. R. Brizzee

Tulane University
Delta Regional Primate Research Center
Covington, Louisiana 70433

Introduction

The central site of mediation of the emetic response to a number of stimuli including the cardiac glycoside and opiate drugs (Borison and Brizzee, 1951) and radiation (Brizzee et al, 1955) has been designated as the chemoreceptor trigger zone (CTZ) (Borison and Wang, 1953) and is located in the area postrema of the medulla oblongate (Borison and Brizzee, 1951). The investigations of Wang and Chinn (1952, 1954, 1955, and 1963) revealed that the integrity of the CTZ is also essential to the occurrence of emesis in response to motion stimuli in dogs. This observation appears to bring the circumventricular organ system, of which the area postrema is an important component, into a functional relationship with the vestibular system.

The susceptibility of the squirrel monkey (*Saimiri sciureus*) to canal sickness was demonstrated by Johnson et al in 1961. However, prior to our present investigations there has been no data available on the possible role of the CTZ in motion sickness in the squirrel monkey. The purpose of the present report is to present our observations to data on the incidence and latency of the emetic response in this species to rotary motion, and the effect of ablation of the area postrema (CTZ) on the incidence of emesis to this motion stimulus.

Materials and Methods

Twelve squirrel monkeys of the Colombian strain were subjected to counter-clockwise phasic rotary motion at 50 r.p.m. The motion was interrupted every 20 seconds for a period of 3 seconds by an automatic electrical timer. Deceleration to zero r.p.m., and acceleration to 50 r.p.m. was accomplished within the 3 second interval. The animals were positioned in a standing or slightly crouching position at the axis of rotation. They were restrained in a well ventilated plastic chamber which allowed them to turn to the right or left in the horizontal plane and permitted free movement of the head and neck. However, they were not able to turn "end for end". The restraining chamber was opaque, but provided with a movable "mask" which could be elevated from the floor to inspect for vomitus.

At least one week following the motion tests 10 animals received 50mg/Kg of 5-hydroxytryptophan subcutaneously, and the incidence and latency of the emetic response was determined.

Bilateral aseptic surgical ablation of the area postrema was carried out by thermal cautery (Brizzee et al, 1955) in six of these animals. Sham operations were performed on 6 animals. At least one month following the surgicals the animals were retested for emetic sensitivity to the rotary motion regimen and 5-HTP injections. The animals were then anesthetized with Ketamine HCl (15 mg/Kg) and pentobarbital sodium (10 mg/Kg) and sacrificed by intracardiac perfusion with Bouin's fluid. The medulla oblongata in each animal was imbedded in paraffin, sectioned at 10 μ m, stained with the Masson trichrome method and prepared for histological evaluation of the lesions.

Table I
Incidence (%) of Emetic Response in
Squirrel Monkey

Rotary Motion				5-HTP			
Rate	Radius	Incidence		Dose	Route	Incidence	
		♂	♀			♂	♀
		(N=16)	(N=15)			(N=4)	(N=10)
50 rpm	0'	43%	58%	50mg/kg	S.C.	75%	80%

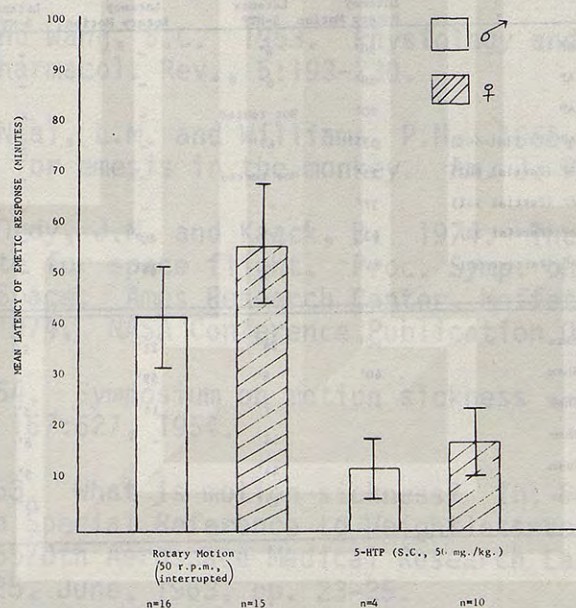


Figure 1. Latency of emetic responses to phasic rotary motion and subcutaneous 5-hydroxytryptophan in squirrel monkeys of the Colombian subspecies.

Results

The incidence and latency of the emetic response to phasic rotary motion and to subcutaneous injections of 5-HTP are shown in Table I. It will be observed that the mean incidence of emesis to the motion test and to 5-HTP was higher in the females than in the males and the difference was significant at the .05 level. However, the difference in the latency of the emetic response to these two types of stimuli was not significantly different in males and females (Fig. 1).

The results of the area postrema (AP) ablation experiments are shown in Table II. Where the ablation of the AP was incomplete the estimated proportion of the structure remaining is given in parentheses. Of the eight animals operated, 6 were refractory to both motion and 5-HTP postoperatively. Two with only a small proportion of the AP remaining responded to the motion test postoperatively, but not the 5-HTP tests.

Table II

Effect of ablation of area postrema on emetic response to rotary motion (50 r.p.m., interrupted for 3 seconds at 20 second intervals) and 5-HTP (50 mg/Kg, 2% solution, injected subcutaneously).

Sex	Ablation	Preoperative tests		Postoperative tests	
		Latency Rotary Motion	Latency 5-HTP	Latency Rotary Motion	Latency 5-HTP
F	AP	50'	6'	-	-
M	AP	38'	6'	-	-
F	AP	90'	Not tested	-	-
M	AP (Partial-40%)	53'	67'	-	-
M	AP (Partial 90%)	25'	Not tested	-	-
F	AP (Partial 14%)	37'	-	-	-
F	AP (Partial 3%)	63'	1'	40'	-
M	AP (Partial 6%)	84'	-	64'	-
M	Sham	60'	24'	21'	2'
F	Sham	40'	5'	59'	-
M	Sham	-	7'	14'	5'
M	Sham	-	11'	-	8'
F	Sham	-	24'	-	5'
F	Sham	-	12'	-	25'

The sham operated animals responded to the postoperative tests in essentially the same manner as in the preoperative tests, with two exceptions. In one case a female which had responded to the preoperative 5-HTP injection failed to respond postoperatively. In the second case a male animal which

had failed to respond to the motion test preoperatively did respond to the postoperative test.

Comment and Conclusions

The observations in this study in the squirrel monkey appear to support the previous observations of Wang and Chinn (1952, 1954, 1955, 1963) which indicated that the integrity of the CTZ in dogs is essential to the occurrence of the emetic response to motion stimuli. The paradoxical results observed in two animals which responded to motion but not to 5-HTP postoperatively, with only a small part of the AP remaining, cannot be explained on the basis of the available data, especially in view of the much higher preoperative incidence of emesis to 5-HTP than to the motion test.

The inconsistencies observed in the sham-operated animals, in which one animal, which responded to 5-HTP preoperatively failed to respond postoperatively, and another animals with a negative preoperative and positive postoperative test formation also cannot be explained on the basis of data presently available.

It appears likely that such inconsistencies may be explained through analyses of data from a much larger series of animals with a more effective motion testing regimen. Such a regimen has now been established (See Appendix B2), and further ablation experiments will be performed with this improved regimen.

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APPENDIX B1
LIGHT AND ELECTRON MICROSCOPE STUDIES ON THE TOPOLOGY, HISTOLOGY
AND HISTOCHEMISTRY OF THE AREA POSTREMA IN THE SQUIRREL MONKEY AND DOG
AND EFFECTS OF SYSTEMIC INJECTION OF 6-HYDROXYDOPAMINE

Examination of the squirrel monkey (*Saimiri sciureus*) area postrema (AP) revealed this circumventricular organ to be primarily composed of two types of glial cells and a single type of neuronal element. No pattern of neuronal arrangement could be discerned, however, this cell type was frequently observed in close relation to the perivascular spaces. The neuronal elements, although slightly larger than the glial cells, were characteristically less electron dense. The neurons routinely displayed an infolded nuclear membrane, a single nucleolus and the normal complement of subcellular organelles. Synaptic terminals were numerous, and both axo-somatic and axo-dendritic varieties were observed with the latter being more numerous. Both clear-cored and dense-cored vesicles could be observed in the same ending. Unmyelinated neuronal processes were the predominant type within the interior of the AP, although myelinated processes were also regularly present.

Non-neuronal elements within the AP resembled CNS astrocytes and were as numerous as the neuronal elements. This cell type appeared to envelope completely the vasculature and separated the parenchyma from the perivascular spaces. The ventricular surface of the AP was covered by modified ependyma which lacked kinocilia but frequently demonstrated microvillar projections. Opposed ependymal cell membranes showed interdigitations, and zonula adherens-type cell junctions connected the ependymal cells near the ventricular lumen. Two types of bulbous projections were observed in the ventricular lumen close to the ependymal surface.

The most characteristic feature of the AP, however, was its vascularity. Perivascular spaces surrounding fenestrated capillaries contained fibroblasts and collagen. The vascular endothelium routinely demonstrated pinocytotic activity, and the basal lamina was prominent.

6-Hydroxydopamine (6-OH-DA) has been shown to produce degenerative changes in noradrenergic nerve terminals and preterminals in the CNS following intracisternal, intraventricular or direct injection into the brain parenchyma. Systemic injection of 6-OH-DA is known to result in degenerative changes in noradrenergic terminals in the peripheral nervous system. However, only a few studies have been carried out on the effects of systemic injections of 6-OH-DA on noradrenergic terminals in the CNS. In the present study cynomolgus and squirrel monkeys were injected intravenously on two successive days with total doses of 350 mg/kg and 150 mg/kg of 6-OH-DA, respectively, and sacrificed at 2 and 24 h following the second injection. Degenerative changes in the area postrema (AP) neurons in all injected animals were characterized by a generalized increase in electron density of cytoplasmic elements in axonal terminals and preterminals. Multilamellar bodies, clusters of clear and dense core vesicles, increased numbers of secondary lysosomes, and an increase in the number of glycogen granules were observed in these structures. In astrocytes

the amount of glycogen increased markedly in injected animals, but no other glial alterations were observed. The number of mast cells in the AP was greater in injected than in noninjected animals, both in the prevascular spaces (PVS) and in parenchymal locations. Cell processes in the PVS were occasionally observed to contain electron dense bodies, and degenerative changes were seen in supraependymal processes in some injected animals.

ATPase reaction product was associated consistently with AP ependymal cells. The product was heavily concentrated along juxtaposed ependymal cell membranes and gave the appearance of filling the intercellular space. Not all ependymal cells however showed the same amount of reaction product. The ventricular surface of the ependymal cells including the numerous microvilli, displayed little or no reaction product. Since the complexity of the AP parenchyma prevents the tracing of basal ependymal processes for any significant distance, it could not be determined if ATPase reaction product appeared along the entire length of the cell process. However, slender processes terminating on the basal laminae of perivascular spaces showed ATPase reaction product. The morphology of these processes included filaments, microtubules and glycogen which would suggest that they were ependymal in nature. However, the possibility that some of these processes represented parenchymal glial elements could not be eliminated entirely. Ependymal cells whose cell bodies abutted directly on superficial vasculature, showed ATPase reaction product extending along the cell membrane adjacent to the basal lamina. It would therefore seem likely that similar activity might be seen associated with ependymal cell processes that extended further into the AP interior.

The distribution of ATPase reaction product in neurons and parenchymal glial elements was significantly less than that seen in association with the ependymal elements. When the reaction product was seen on neuronal or glial cell membranes it appeared 'patchy' and did not cover large areas. The reaction product was also more frequently observed in association with the plasma membrane of the cell soma than the membranes of the cell processes. The Golgi apparatus of both neurons and parenchymal glia contained limited amounts of ATPase reaction product.

Within the perivascular spaces, cells which resembled fibroblasts displayed the presence of ATPase reaction product along the cell membranes.

The basal laminae in the perivascular spaces also showed reaction product. However, this reaction product appeared in a diffuse pattern rather than the more common linear deposits. The vascular endothelium within the AP showed limited lead phosphate, while red blood cell membranes showed ATPase reaction product. Cells that resembled phagocytes frequently showed a conspicuous absence of ATPase reaction product. The overall concentration of reaction product was subjectively much reduced when compared to that seen in association with ependymal cells.

APPENDIX 2

RESULTS OF RECENT TESTS OF EMETIC SENSITIVITY IN BOLIVIAN AND COLOMBIAN SQUIRREL MONKEYS TO COMBINED VERTICAL AND ROTARY MOTION

The motion testing regimen described in the above experiment resulted in an emetic incidence of about 50%. In order to determine a more effective regimen we subjected squirrel monkeys of the Bolivian and Colombian subspecies to combined vertical (6 inch excursion every 2 seconds) and rotary motion regimens at 10, 25 and 50 rpm, with the restraining chamber covered (no visual cues) and uncovered (visual cues present), and reversal of direction every 10 minutes as compared with continuous, uninterrupted rotation. Results to date are shown in Table I. It will be noted that 80% of Bolivian

TABLE I
Incidence of emesis at 10, 25 and 50 RPM

Phenotype	Rotation and Visual Cues								Probability
	Continuous				Reversed				
	Covered Prop.	%	Uncovered Prop.	%	Covered Prop.	%	Uncovered Prop.	%	
Bolivian									Rotation (R)
Colombian									Cues (C)
Combined									Phenotype (P)
10 RPM									
Bolivian	1/3	(33%)	2/5	(40%)	1/3	(33%)	1/3	(33%)	(R)
Colombian	0/3	(0%)	0/3	(0%)	0/3	(0%)	0/3	(0%)	(C)
Total	1/6	(17%)	2/8	(25%)	1/6	(17%)	1/6	(17%)	(P)
Combined*	5/26, 19%								
25 RPM									
Bolivian	4/5	(80%)	4/5	(80%)	2/3	(67%)	1/3	(33%)	(R)
Colombian	2/4	(50%)	2/3	(67%)	2/3	(67%)	1/3	(33%)	(C)
Total	6/9	(67%)	6/8	(75%)	4/6	(67%)	2/6	(33%)	(P)
Combined*	18/29, 62%								
50 RPM									
Bolivian	1/3	(33%)	1/3	(33%)	0/3	(0%)	2/3	(67%)	(R)
Colombian	1/3	(33%)	0/3	(0%)	1/3	(33%)	1/2	(50%)	(C)
Total	2/6	(33%)	1/6	(17%)	1/6	(17%)	3/5	(60%)	(P)
Combined*	7/23, 30%								

* Statistical ranking of 10, 25, 50 RPM percent emesis:

Rotation:	25 RPM	50 RPM	10 RPM
Proportion:	18/29	7/23	5/26
Percent:	62	30	19

Significance: $P < .05$

squirrel monkeys responded to 25 rpm, continuous rotation with concurrent vertical excursions), with and without visual cues. The above monkeys had all been subjected to previous motion tests about 1 month prior to those summarized in Table I.

In more recent tests we have compared emetic sensitivity according to sex and diurnal rhythms at 25 rpm continuous, counter clockwise, combined rotary and vertical motion, with visual cues present in naive animals. While the data have not yet been tabulated, an incidence of 100% has been observed in adult males, in both morning (7 A.M.) and afternoon (2 P.M.) tests. These experiments are continuing, and results will be reported, together with data on effects of ablation of area postrema and/or adjacent structures, at subsequent NASA Conferences and scientific meetings.

AUTOGENIC FEEDBACK TRAINING FOR CONTROLLING VESTIBULAR SYMPTOMATOLOGY

Patricia S. Cowings, Ph.D.

Biomedical Research Division
National Aeronautics and Space Administration
Ames Research Center, Moffett Field, California

I. Research Objectives

The primary purpose of our work is to develop a preventative method for the Zero-Gravity-Sickness-Syndrome. This method is called Autogenic-Feedback training, and it essentially consists of teaching human subjects to control several of their own physiological responses simultaneously. Through this learned control, subjects can voluntarily suppress their own motion sickness symptoms.

In the course of developing this research program, we established a number of overall scientific objectives. First it was necessary to determine if the proposed treatment would be applicable to a wide population of individuals. With the coming of the Space Shuttle era, the complement of scientific mission crews will be **expanded** to include both men and women of diverse professional backgrounds, age, and physical condition. If these individuals are to live and work safely within the space environment, an effective treatment must be developed for many different types of people, rather than for a selected few. Secondly, it was essential that we examine individual differences in performance on motion sickness inducing tests and the corresponding differences in physiological reactions to this stress. If the treatment was to be widely applicable, we would have to determine if training could be modified to meet the requirements of each individual's symptom pattern. Also, we wished to know if the physiological profiles could be used, in any way, to classify or predict susceptibility and adaptability to vestibular stimulation.

The remaining objectives involve several operational requirements for implementing a possible preflight treatment program for astronauts. It was assumed that any therapeutic method for zero-gravity sickness developed with Earth-based tests should be effective under various kinds of motion sickness inducing conditions. In so doing, that treatment would demonstrate a high probability of generalizing to the stimulus condition of zero-gravity as well. A second consideration is that a viable treatment should be capable of being administered in a very short period of time. During experiment integration prior to scheduled Shuttle missions, crew availability for participating in preflight training or preventative therapy sessions is quite limited. What's more, should a crewman require treatment during a flight, it must take effect quickly, allowing him (or her) to return to scheduled flight operations with minimal impairment in efficiency.

II. Treatment Components

Autogenic-feedback training is actually a synthesis of two techniques used for training self-regulation of physiological responses. The first

technique is called biofeedback and is primarily derived from research on operant conditioning. What the word, "biofeedback" literally means is to present a subject with augmented sensory information about some on-going physiological process in his body. We generally tend to be unaware of many of these physiological processes (e.g., the amount of blood volume present in our hands) and so, we don't normally consider the idea of voluntarily controlling them. But, once an external feedback pathway is constructed which allows us to better perceive a response (e.g., a thermometer displaying changes in temperature of a finger tip), it then becomes possible to learn to regulate this response.

The way this "self-control" is learned is very similar to the way a child first learns to walk or a person learns to play the piano. You learn to play the piano by pressing the keys on a keyboard; your ear tells you whether or not you've made a correct response (i.e., pressed the right key). If you press the wrong note, this information is conveyed to your brain through neural pathways and your brain then directs your fingers to move to the correct key on the piano. In this way, an information feedback loop is set up between the muscles of your hand, your brain and your sense of hearing. In a biofeedback experiment, a subject might spontaneously produce a correct response (e.g., vasodilation in the fingers) and this information could be displayed to him with a digital thermometer monitoring the temperature of his hands. An information feedback loop is consequently set up between the vasomusculature of his hands, his brain and his sense of vision. With the aid of this external feedback display, the subject must then figure out the relationships between a given thought or cognitive event and the specific autonomic reaction desired. Like any learning process, this required only repetition and practice before it can be accomplished.

Autogenic therapy is a second, and different training method, yet it also results in learned control of visceral activity. It consists of a series of self-suggestion exercises designed to induce specific somatic sensations. Each exercise in turn, is highly correlated with the production of specific physiological responses. Autogenic therapy utilizes the principle of "ideomotor action": all perceptual and cognitive events are reflected to some extent, physiologically. If you were to monitor the activity of the muscles of your arm as you thought about the movements involved in throwing a baseball, you would register a minute increase in the nervous activity of those muscles. A patient practicing the exercises of Autogenic therapy might suggest to himself that he is experiencing a sensation of heaviness and warmth in his arms and legs. These suggestions have been found to be significantly correlated with increased peripheral vasodilation and a reduction in muscle potential. The standardized exercises are structured in such a way that a predominance in parasympathetic-like activity levels is produced within the patient. This condition can effectively block the emergence of physiological (i.e., sympathetic) or behavioral reactions to stress.

The combination of Autogenic therapy and biofeedback results in a methodology appreciably more effective than either of these two techniques alons. The Autogenic exercises provide the subject with specific instructions about the types of cognitive events and methods of concentration which are likely to produce the desired response. Consequently, the time normally spent by a subject in hypothesis testing is significantly reduced and the initial

probability of his making a correct response is increased. By presenting the subject with immediate feedback about his performance, practice becomes more efficient. Operant conditioning procedures provide a means of "shaping" or strengthening learned autonomic control and enable the subject to discriminate between particular physiological activities produced.

We have found that conditioning can be further enhanced by the inclusion of multiple modality feedback for multiple responses. Several different types of feedback (e.g., visual, auditory, verbal, etc.) are presented for each autonomic variable. When a subject practices control of six physiological responses simultaneously, he may be monitoring as many as eighteen different feedback displays at the same time. This procedure requires the addition of a certain amount of attention training. A subject is considered to be optimally utilizing the feedback when he can use this information to cross-reference his performance and gauge his own learning progress. The experiments described in this report have shown that Autogenic feedback training can enable varied populations of individuals to reliably gain sufficient control of autonomic responses needed to suppress motion sickness symptomatology.

III. Coriolis Tests/Responses Monitored

A Stille-Werner rotating chair was used to induce Coriolis sickness in test subjects. Chair rotation was initiated at 6 rpm for a period of five minutes. At this constant rotational velocity, subjects were instructed to perform 120 head movements at 45° angles in four quadrants. The instructions for the direction of head movements were randomized and they were performed at two second intervals. If at the end of five minutes the subject had not yet reached malaise level III, the velocity of the chair was increased at 2 rpm increments every five minutes. Coriolis tests were terminated at either 30 rpm (65 minutes of rotation) or malaise level III, whichever came first.

The physiological responses monitored were: heart rate, respiration rate, galvanic skin response, peripheral blood volume of the face and hands, and myography of the external intercostal muscle. Biomedical amplifiers were mounted on the back of the chair and their outputs were passed through slip rings to our recording instruments. Consequently, we could observe a subject's activity continuously from a pre-test baseline through to the endpoint of each test.

IV. First Formal Investigation

Our first formal investigation (1,2) examined two primary questions: (a) is it possible to train human subjects to control several of their own physiological responses simultaneously; and (b) will this learned control be of sufficient magnitude as to actually allow them to suppress motion sickness symptoms?

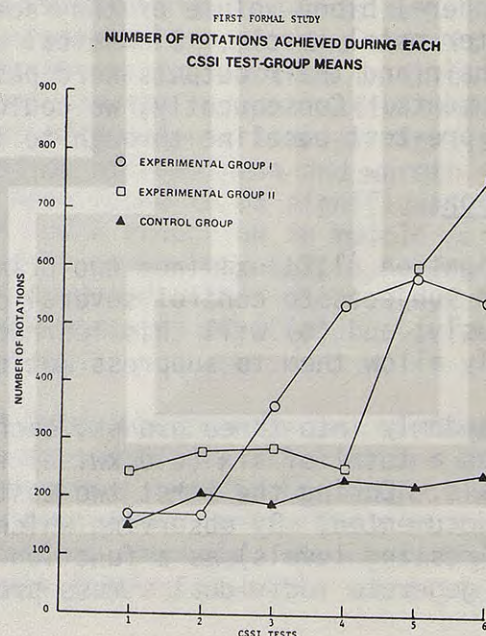
Subjects were divided randomly into three groups, each containing eight men. All subjects were given a total of six (clockwise) rotating chair tests separated by one week intervals. During the first two tests, individual differences in symptom onset were documented. By observing which physiological variable diverged from baseline (resting levels) as a function of exposure to rotation, it was possible to generate individual stress profiles. Since no two

subjects experience motion sickness in precisely the same way, the emphasis of treatment was placed on teaching each individual to control those responses which showed the most liability for him. Subjects receiving treatment were taught to modify their activity levels, essentially "mimicking" their own baseline responses during subsequent Coriolis tests.

There were two Treatment Groups and these differed only in the time in which Autogenic-feedback training was administered. Treatment Group I received 2.5 hours of training prior to the third and fourth rotating chair tests (5 hours total training). Treatment Group II was similarly trained prior to tests five and six. Training sessions were conducted with the subject seated in the rotating chair but without rotation or head movements. Feedback for physiological activity was displayed on a wide-screen oscilloscope, and on digital panel meters. Verbal feedback and auditory tones were presented through speakers mounted above the subject's head. No feedback was given, however, during Coriolis acceleration tests. The Control Group subjects were not given treatment. They were required only to participate in all six Coriolis tests and their data were used to track the course of naturally occurring habituation.

Figure 1 shows the average number of rotations achieved by each group on all six Coriolis tests, before reaching Malaise level III. Subjects in Treatment Group I showed a significant improvement after training on tests 3 and 4. These subjects received no additional training before the fifth and sixth tests and their performance appears to plateau. Treatment Group II subjects were not trained before the first four tests, and show no improvement to this point. However, their ability to withstand Coriolis stress increased significantly after training on tests 5 and 6. The "test-only" Control Group performance did not change significantly across tests.

Figure 1



These data were analyzed using an analysis of variance for repeated measures. Table I shows differences in the average performance of groups across tests as calculated by Scheffe's Post-Hoc Multiple Comparisons Tests.

TABLE I. - Comparisons of Rotations Achieved During Each CSSI Test - Group Means - Using Scheffe's Post-Hoc Multiple Comparisons Test

I. Comparisons Across Tests						
Tests Compared	Obtained t Values and Significance Levels					
	Group 1	Group 2	Group 3			
1 vs 2	0	.40	.68			
2 vs 3	2.73 ****	.05	.41			
3 vs 4	2.38 **	.43	.67			
4 vs 5	.74	4.84 *****	.13			
5 vs 6	.62	2.29 **	.26			
1 vs 6	5.31 *****	8.34 *****	1.06			

II. Comparisons Across Groups						
Groups Compared	Tests					
	1	2	3	4	5	6
Obtained t Values and Significance Levels						
1 vs 2	1.10	1.507	1.17	3.97 *****	.13	3.03 ****
1 vs 3	.08	.59	2.55 **	4.25 *****	5.12 *****	4.25 *****
2 vs 3	1.19	.78	1.39	.29	5.25 *****	7.29 *****

df	Critical Values of t	Significance Levels
10,105	1.91	p<0.05 *
	2.16	p<0.025 **
	2.47	p<0.01 ***
	2.71	p<0.005 *****
	3.24	p<0.001 *****

We conclude from this study that Autogenic feedback training can indeed be used to train human subjects to self-regulate multiple autonomic responses. And, this treatment results in improvements in tolerance to Coriolis stress that are significantly greater and more rapid than that occurring in the course of habituation.

V. Second Formal Investigation

Our second formal investigation (3) was more detailed and addressed more complex issues than the first study. The specific research objectives are outlined below:

1. Replicate the findings of our first study, establishing the efficacy of the treatment effect.
2. Determine whether learned control of motion sickness symptoms transfers across the different stimulus conditions of clockwise and counterclockwise Coriolis acceleration.

3. Standardize the training procedure so that this study may be replicated by other laboratories. Previously, emphasis in training were very much "subject-specific", tailored to meet the needs of the individual. The present study examined the effect of giving all treatment group subjects the same amount of training for the same number of physiological variables, using the same types of feedback.
4. Determine the extent to which a person's initial susceptibility to motion sickness is related to his ability to learn voluntary control of symptom suppression. This was a further attempt to explore the applicability of this treatment to the general population.
5. Determine if this treatment can best be used as either a preventative method or as a countermeasure for motion sickness. A comparison was made between two methods of administering Autogenic-feedback training. Unidirectional conditioning (i.e., training subjects to produce rigidly defined parasympathetic-like activity throughout a test) served as a means of examining the prophylactic effects of treatment. Bidirectional conditioning (i.e., teaching subjects to produce alternating parasympathetic and sympathetic response levels) would better enable subjects to discriminate between these changes in physiological activities and should therefore permit them to "counteract" symptoms as they arose.
6. And lastly, examine the nature of the treatment effect itself. To what degree do experimental factors other than the application of Autogenic feedback training, influence test performance of Treatment Group subjects? It is possible that, by performing the self-suggestion exercises, treatment group subjects are merely being distracted from their symptoms? If so, then concentrating on any cognitive task might enable subjects to improve their tolerance of motion sickness over time. A "Sham" training task was introduced which consisted of instructing control group subjects to play Blackjack with our computer. This particular cognitive task was selected because it was considered to be both interesting yet attention demanding. This task could be presented to subjects visually and verbally in the same way that feedback was presented to Treatment Group subjects; and it could be performed during the Coriolis tests. Further, it was necessary to explore the roles played by expectation and motivation in influencing the performance of treatment group subjects.

Twenty-four men between the ages of 18 and 35 were tested. Subjects were randomly assigned to four equal groups matched for initial susceptibility to Coriolis acceleration (two Treatment groups and two Controls). The procedure for administering Coriolis acceleration tests and the physiological responses monitored were identical to those in the first study. A total of six rotating chair tests, separated by five-day intervals, were administered to all subjects. In the present study, however, the first and second tests were clockwise, the third and fourth were counterclockwise, and the fifth and sixth were clockwise.

Treatment Group I received Autogenic feedback training for bidirectional control of autonomic responses and Treatment Group II for unidirectional control. One Control group was required to participate in Coriolis tests only, allowing us to observe natural habituation rates. The fourth group of subjects received "sham" training and served as a control for examining the effects of performing a cognitive task on stress tolerance. Autogenic feedback training and Sham training were administered prior to the third, fourth, and fifth Coriolis test (total of six hours of training). All subjects in the treatment groups and the Sham training control group participated in the same number of sessions. Table II depicts the standardized procedure for presenting feedback or cognitive task instructions to these subjects.

Table II

TRAINING DAYS	TREATMENT GROUPS I & II AUTONOMIC RESPONSES FEEDBACK MODALITY			CONTROL GROUP IV COGNITIVE TASK PRESENTATION MODALITY		
	VISUAL	AUDITORY	DISTRACTION	VISUAL	VERBAL	DISTRACTION
1	□			X		
2	△			X		
3	●			X		
4	□△●			X		
5	□△●	□	V	X		
6	□△●	□△	V	X	X	V
7	□△○●	□△	V	X	X	V
8	□△○●	□△	V	X	X	V
9		□△	VH		X	VH
10		□△	VH		X	VH
11		△	VR		X	VR
12		□	VR		X	VR

GSR = ●

HR = △

HBVP = □

RR = ○

V = VOICE COMMAND TAPE

H = HEAD MOVEMENTS (NO ROTATION)

R = CHAIR ROTATION (NO HEAD MOVEMENTS)

During training sessions 1 to 4, subjects were presented with visual information only. Verbal and auditory (tone) information were added in sessions 5 to 8, and the relative tasks performed by subjects became more complex. In the last four training sessions (9 to 12), visual information was eliminated and distracting environmental conditions were introduced. The environmental distractions during sessions 9 and 10 consisted of directing treatment group subjects to continue their self-regulatory exercises while simultaneously making head movements (without rotation). Similarly, control group subjects performed head movements while playing Blackjack. Training sessions 11 and 12 were conducted while the chair was rotated (no head movements). In this way, treatment group subjects learned to strengthen their (attention to) learned autonomic control while reducing their dependence on external feedback devices. The control group subjects learned to reliably perform their alternative cognitive task using verbal information only. All subjects learned to divide their attention between respective tasks and the instructions for making head movements during subsequent Coriolis tests.

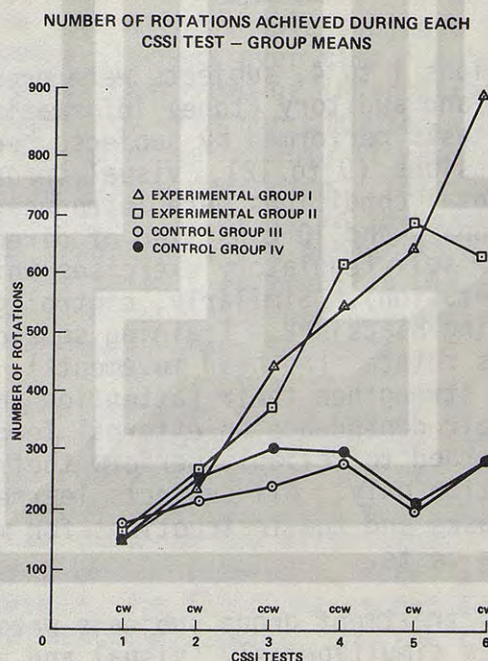
As shown in Table II, treatment group subjects were often presented with several feedback modalities simultaneously (visual and auditory). In addition

to feedback presented in the form of oscilloscope displays, digital panel meters and auditory tones, the experimenter also provided the subject with verbal information. The experimenter therefore could assist the subject by directing his attention to any particular response requiring more control.

In an attempt to control for intervening factors of expectation and motivation, each group of subjects was given a different instructional set at the start of this experiment. Treatment Groups I and II were told that we were interested in determining whether or not learning autonomic control would enable them to suppress their own symptoms and therefore improve their performance on subsequent rotating chair tests. Control Group III (test-only) were told that we were interested in studying changes in autonomic activity during the course of habituation to Coriolis acceleration. We expected that with repeated exposures to the rotating chair, their abilities to withstand this stress would improve. We wished to determine if individual differences in symptom patterns were correlated with differences in rate of habituation. Control Group IV subjects were told that we wanted to examine the effects of performing a cognitive task during motion tests. We expected that as their ability to concentrate on a mental task improved, they would be "distracted" from their symptoms and so should improve their performance across subsequent motion tests. None of the subjects within these groups were aware of the existence of different instructions given to the other groups.

The results of this study are shown in Figure 2, which illustrates the mean number of rotations of each group attained prior to reaching malaise level III. Both treatment groups continued to improve despite changes in the direction of rotation. Neither Control Group improved significantly across tests.

Figure 2



These data were analyzed using a randomized blocks designed for analysis of variance. The blocking factor was level of susceptibility to Coriolis sickness on the first rotating chair test. Table III shows the distribution of subjects' initial susceptibility for each group. Treatment group subjects classified as high or moderate susceptibles demonstrate an equal capability of learning symptom suppression.

Table III
CORIOLIS SICKNESS SUSCEPTIBILITY BASED ON
NUMBER OF ROTATIONS ACHIEVED DURING CSSI TEST I

SPEED, rpm	NUMBER OF ROTATIONS PER STEP	EXPERIMENTAL GROUP I (BIDIRECTIONAL)	EXPERIMENTAL GROUP II (UNIDIRECTIONAL)	CONTROL GROUP III (TEST ONLY)	CONTROL GROUP IV	CATEGORY
6	0 - 30					
8	31 - 70					HIGH
10	71 - 120					
12	121 - 180					MODERATE
14	181 - 250					
16	251 - 330					
18	331 - 420					LOW
20	421 - 520					
22	521 - 630					
24	631 - 750					
26	751 - 880					
28	881 - 1020					
30	1021 - 1170					
• SUBJECTS CAPABLE OF TOTAL SYMPTOM SUPPRESSION (ACHIEVED 1170 ROTATIONS) AFTER TRAINING • SUBJECTS CAPABLE OF SIGNIFICANT SYMPTOM SUPPRESSION (p< 0.05) AFTER TRAINING						

Table IV is a summary of this analysis and also contains the results of planned comparisons (t-tests) of differences between group means, on the third and fifth Coriolis tests (when direction of rotation changes).

Table IV

RANDOMIZED BLOCKS DESIGN FOR ANALYSIS OF VARIANCE							
SOURCE	F	γ	SIGNIFICANCE				
GROUPS	F = 3.95	$p < 0.05$	*				
BLOCKS	F = 8.08	$p < 0.025$	*				
TESTS	F = 7.044	$p < 0.0005$	*				
GROUPS X BLOCKS	F = 0.243	$p > 0.05$	N/S				
GROUPS X TESTS	F = 3.28	$p < 0.001$	*				
BLOCKS X TESTS	F = 1.33	$p > 0.05$	N/S				
PLANNED COMPARISONS [t-TESTS, ONE-TAILED]							
CSSI #3				CSSI #5			
GROUPS	t_{10}	γ	SIG	GROUPS	t_{10}	γ	SIG
I X III	$t = 0.676$	$p > 0.05$	N/S	I X III	$t = 2.39$	$p < 0.025$	*
I X IV	$t = 0.860$	$p > 0.05$	N/S	I X IV	$t = 2.29$	$p < 0.025$	*
II X III	$t = 0.606$	$p > 0.05$	N/S	II X III	$t = 2.21$	$p < 0.05$	*
II X IV	$t = 0.940$	$p > 0.05$	N/S	II X IV	$t = 2.16$	$p < 0.05$	*
I X II	$t = 0.177$	$p > 0.05$	N/S	I X II	$t = -0.202$	$p > 0.05$	N/S
III X IV	$t = 0.950$	$p > 0.05$	N/S	III X IV	$t = 0.077$	$p > 0.05$	N/S

We concluded from these data that we had met each of the research objectives of this investigation. We indeed have a treatment effect; improved performance in treatment groups was due to learned control of physiological responses (i.e., symptom suppression). Practicing an alternative (distracting) cognitive task by Control Group IV was insufficient for enabling them to withstand the stress of Coriolis acceleration. Learned control of symptoms does transfer across opposite direction of Coriolis acceleration, and initial susceptibility is apparently unrelated to overall treatment effectiveness. Bidirectional and unidirectional autonomic conditioning produce comparative results. Consequently, it is safe to conclude that Autogenic feedback training can be applied effectively as either a preventative method or as a countermeasure for motion sickness symptoms.

V. Other Studies Conducted

A number of pilot studies and collaborative investigations have also been conducted as part of our general research program. Results of one pilot study (4) (n=6) suggest that Autogenic-feedback training for symptom suppression transfers across the stimulus conditions of Coriolis acceleration, linear acceleration and optokinetic stimulation. Data of a second pilot study (5) indicate that learned autonomic control is very likely to be remembered by subjects, and that such control is readily re-learned. Significant retention and relearning rates were observed in subjects (n=3) up to two years after receiving treatment.

A recently completed collaborative study (N=18) used a double-blind procedure to examine the effects of Autogenic-feedback training on measures of vestibular function (6). A battery of vestibular tests was administered to subjects (treatment groups and control) before and after training. These tests included two Ataxia tests (the Sharpened-Romberg and the SOLEC-R,-L), oculogyral illusion thresholds, cupulograms, and power functions. The experimenters administering vestibular tests did not know which individuals received treatment. Results showed that neither treatment or control groups subjects showed a significant difference in vestibular test scores at the end of the experiment. Those treatment group subjects who had learned to completely suppress their own motion sickness symptoms were indistinguishable from susceptible subjects. These findings suggest that Autogenic-feedback training may increase a threshold of the facultative linkages proposed by Graybiel, thereby reducing Graybiel's VII responses without affecting VI responses.

The physiological profiles of subjects in all of these experiments are pooled in a continuously updating data base. Thus far, these data provide a strong evidence that physiological profiles can be used to classify individuals' susceptibility and adaptability to motion stimuli. Further, the individual-stress profile produced by a given subject remains essentially unchanged, even when he is exposed to several different types of motion sickness inducing tests. Consequently, by observing the extent to which an individual's physiological responses are modified by the application of Autogenic feedback training, it should be possible to predict that subject's susceptibility to a unique stimulus environment. This finding suggests a possible criteria, based on autonomic response pattern data, for predicting susceptibility to zero-gravity sickness in space.

VI. Conclusions

We feel that the findings of our research program demonstrate several advantages of Autogenic feedback training over the alternative approaches of chemotherapy and habituation training as a prospective treatment for zero-gravity sickness. Anti-emetic drugs have been found to be relatively unreliable, manifesting much variability across individuals and motion environments. Reports on the biomedical results of Skylab indicate that such drugs have had limited therapeutic value in preventing or counteracting symptoms in flight, and deleterious side effects have been noted which interfered with crew operational efficiency (7). Furthermore, chemotherapy has been shown to significantly distort measures of vestibular perception (8). Autogenic feedback training on the other hand, can be tailored to meet the needs of the individual and should produce no side effects whatsoever. Formal investigations have shown that this method does not in any way effect measures of vestibular function and therefore cannot "contaminate" tests of these phenomena as does chemotherapy (6).

The alternative treatment involving preflight habituation training is very time consuming, requiring frequent participation by prospective crewmen in motion tests (debilitating in themselves) using sophisticated facilities. As a result, it may be impractical for a majority of Shuttle passengers to commit to such a program. Habituation tends to be highly specific to the stimulus conditions employed, with poor transfer to other motion environments (9,10). Attempts to prehabituate the Skylab crewmen by rotating chair and parabolic flight exposures were apparently unsuccessful (11). Lastly, not all individuals can clearly benefit from habituation training. Because of this fact, subjects who are highly susceptible to motion tests and those who exhibit a poor adaptational capacity would likely be eliminated from participation in the Shuttle program. This would be the case, even if such individuals possessed scientific qualifications which might make them preferred candidates for a given mission.

Unlike preflight habituation programs, Autogenic-feedback training does not require extensive use of sophisticated facilities and can be administered in a relatively short period of time (approximately 5 to 7 hours of training distributed over several days). Because our treatment acts on the autonomic manifestations of motion stimuli rather than on central (vestibular) mechanisms, the probability of transference across the conditions of Coriolis acceleration, linear acceleration or weightlessness in space should be greater for this method than has been observed for habituation training.

The only unequivocal test of any prospective treatment for the zero-gravity sickness syndrome is to apply that treatment under actual space flight conditions. We feel that Autogenic-feedback training is ready for that test.

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A DOUBLE-BLIND ANTI-MOTION SICKNESS DRUG STUDY

B.A.T. Sauerland, M.F. Reschke, J.L. Homick, J.T. Baker*

Neurophysiology Laboratory
NASA/Johnson Space Center
Houston, Texas

*Technology Incorporated
Houston, Texas

Introduction

Results from previous U.S. manned space programs have indicated that an increase in the mobility of crewmembers in space appears to be directly correlated with an increase in the incidence of space motion sickness. One third of the Apollo crewmembers experienced some degree of motion sickness early in flight (1) while a majority of the Skylab crewmembers experienced symptoms which in some cases were sufficiently severe to affect performance during the first few days of flight (2). Because the Space Shuttle is spacious enough to allow considerable mobility, it can be predicted that space motion sickness will continue to be a biomedical problem of operational significance. Therefore, it is highly desirable to provide countermeasures which allow crewmembers to function unhampered by motion sickness from the onset of the mission.

The most convenient method of preventing or aborting space motion sickness is drug therapy. Studies by Graybiel and colleagues have demonstrated that the most efficacious drugs for the prevention of space motion sickness are either promethazine plus ephedrine or scopolamine plus d-amphetamine (3,4,5). Wood and Graybiel have indicated that the currently effective antimotion sickness drugs belong to sympathomimetic, parasympatholytic, and antihistimimic classes of drugs (6). From these observations, it is evident that the autonomic nervous system plays an important role in the etiology of space motion sickness. On a basic biochemical level, biogenic amines like norepinephrine, serotonin and histamine, and vasoactive substances like the bradykinins and prostaglandins are possible mediators of the motion sickness syndrome in man. They may act as transducers which change neurosensory inputs into responses such as drowsiness, cold-sweating, pallor, nausea, etc.

One approach to the solution of the space motion sickness problem is to attack the problem at the biochemical level. Drugs which act on the central and autonomic nervous systems were used to manipulate these systems.

Method

The participant group consisted of five females and six males ages 20 through 40. All subjects demonstrated normal acoustic and vestibular function as determined by audiometric, postural stability, cupulogram and motion sickness susceptibility testing. The physical status of all participants was within normal limits as determined by Air Force Class III flight physical criteria. All participants underwent extensive pre-drug trial motion sickness testing in order to establish an individualized and reproducible symptom baseline. The provocative stimulation used for inducing motion sickness was stressful coupled angular accelerations generated by requiring the blindfolded subject to execute standard head movements while rotating at a constant velocity in a modified Barany chair. The detection and scoring of the motion sickness symptoms was accomplished by the methods established by Miller and Graybiel (7). The endpoint used for all testing was an MIII level of motion sickness (8 points) or 150 head movements, whichever occurred first. Most trials were terminated when the subject reached a total of

greater than or equal to 8 points.

The drugs and dosages selected for use in this study are:

1. Cyproheptadine (4mg)
2. Perphenazine (4mg)
3. Promethazine (25mg) + d-Amphetamine (5mg)
4. Promethazine (25mg) + Ephedrine (50mg)
5. Scopolamine (0.3mg) + d-Amphetamine (5mg)
6. Thiethylperazine (10mg)
7. Placebo (lactose)

Each drug was presented to a subject twice in a pseudorandom manner interspersed with six placebo trials. For each of the two times a drug was given, the stressor direction of rotation was reversed so that neither the clockwise nor counterclockwise direction was favored. At no time during the study was either the test director, principal investigator, or subject aware of what drug was administered. Four test directors were used in a random format, to remove any bias on the part of a given test director. The time period between any two trials ranged from a minimum of seven days to a maximum of thirty days. Each trial always took place in the am between 0800 and 1100 with each subject having an assigned and consistent start time. The subjects were instructed to refrain from the use of any drugs or alcohol during the twenty-four hour period preceeding each drug trial.

In addition to recording motion sickness symptomatology, vital signs and blood samples were obtained from each subject during each test trial. A pursuit tracking task was also performed. These data were obtained before and immediately after cessation of the stressor profile (chair rotation).

A typical testing sequence was conducted as follows. The subject was given a health questionnaire immediately upon arrival at the laboratory and the vital signs were taken and recorded. The subject performed the tracking task while the questionnaire and vital signs were reviewed by a physician. If the physician determined that the subject was capable of participating in the test that day a blood sample was drawn and the drug was administered. The time was carefully noted. Ninety minutes after drug ingestion the vital signs were taken, the tracking task performed and the second blood draw accomplished. The subject was then placed in the test chair and blindfolded. Exactly 120 minutes after drug ingestion, the stressor profile was started. Symptoms were recorded and scored until a satisfactory endpoint was achieved. After the chair was brought to a stop, vital signs were taken immediately and the final blood draw was accomplished. The tracking task was again performed. The subject was released from the laboratory after it was determined that recovery from symptoms had occurred. The entire time from beginning to end for a typical testing sequence was 2.75 hours. The subjects were prohibited from ingestion of food or drink, (with the exception of water) during the test sequence. Each subject was required to maintain a personal log in which subjective sensations and possible side effects were recorded.

Results

Three primary dependent variables were measured in order to assess the efficacy of the drugs under evaluation. These variables were cumulative symptom points present at the termination of the stressor profile; the total number of head movements required to reach an endpoint; and the Coriolis Sickness Susceptibility Index (CSSI). Computation of the CSSI has been described elsewhere (7). The mean value

obtained for each of these variables for each of the six drugs evaluated, plus the placebo, are summarized in Table I. Also shown for each drug are the percent changes relative to the mean placebo baseline. Examination of these data clearly indicates that the greatest change (i.e., fewer symptoms, highest CSSI scores and greatest number of head movements) were obtained with the three drug compounds containing promethazine, d-amphetamine and scopolamine. A Dunnett t-test, which independently compared each drug to the placebo baseline, indicated that these changes are statistically significant. Cyproheptadine produced modest beneficial effects while thiethylperazine and perphenazine produced little improvement.

TABLE I

(A) Cumulative Symptom Points, (B) Total Head Movements at Motion Sickness Endpoint and (C) CSSI Score for each of the Six Drugs Used and the Placebo (N = 11)

(A) CUMULATIVE SYMPTOM POINTS

Parameter	Number of Samples	Mean $\bar{X}$	Score (a) % Change	S.D.	Variance
Thiethylperazine	22	8.5	1.2	1.4	2.0
Placebo	66	8.4	---	1.0	1.1
Perphenazine	22	7.9	-6.0	2.1	4.3
Cyproheptadine	22	7.0	-16.7	2.5	6.4
Scopolamine/d-Amphetamine	22	6.0	-28.6**	3.1	9.9
Promethazine/d-Amphetamine	22	5.7	-32.1**	2.8	7.7
Promethazine/Ephedrine	22	5.5	-34.5**	3.0	9.2

(B) TOTAL HEADMOVEMENTS

Parameter	Number of Samples	Mean $\bar{X}$	Score (a) % Change	S.D.	Variance
Promethazine/d-Amphetamine	22	108.4	37.6*	23.1	531.6
Scopolamine/d-Amphetamine	22	102.5	30.1*	28.5	811.3
Promethazine/Ephedrine	22	99.8	26.6*	33.7	1133.1
Cyproheptadine	22	93.0	18.0	33.0	1086.0
Placebo	66	78.8	-----	29.9	893.7
Thiethylperazine	22	76.8	-2.5	23.8	565.1
Perphenazine	22	75.5	-4.2	29.0	841.0

(C) CSSI SCORE

Parameter	Number of Samples	Mean $\bar{X}$	Score (a) % Change	S.D.	Variance
Promethazine/Ephedrine	22	23.6	68.6**	20.5	419.1
Promethazine/d-Amphetamine	22	22.7	62.1**	17.6	310.4
Scopolamine/d-Amphetamine	22	21.9	56.4**	21.1	447.1
Cyproheptadine	22	18.7	33.6*	18.7	350.9
Thiethylperazine	22	15.0	7.1	20.5	419.4
Perphenazine	22	14.8	5.7	18.3	337.8
Placebo	66	14.0	-----	14.5	209.3

- (a) % Change Relative to Placebo Baseline
 * Significant at 0.05 Level of Confidence
 ** Significant at 0.005 Level of Confidence

A detailed evaluation of the effects of each drug on individual symptoms within the total motion sickness symptom complex was also performed. The complete results of this analysis are not described here, however, several general findings are noteworthy. Cyproheptadine and the two combinations containing promethazine resulted in a reported increase of drowsiness. Perphenazine and thiethylperazine resulted in a slight increase in the incidence of nearly half of the symptoms monitored. Preliminary analysis of tracking task data, vital signs and some of the blood chemistries indicate no significant change. Further details on these aspects of the drug study will be forthcoming.

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USE OF PAROTID SALIVA IN MONITORING DRUG LEVELS

G. John DiGregorio
Department of Pharmacology
Hahnemann Medical College
Philadelphia, Pennsylvania

For the past ten years our laboratory has utilized human parotid saliva as a biological specimen for the detection and quantitation of drugs taken systemically. We have employed the method of saliva/plasma (S/P) concentration ratios to predict blood values when only salivary concentrations are known. Two experimental models are employed in determining S/P ratios. First a rat model consisting of surgical isolation and cannulation of the parotid ducts and femoral vein. Drugs are administered then blood and saliva collected simultaneously. Both biological specimens are analyzed for the drug administered. The second model utilized the human parotid secretions where a double lumen teflon cup is placed over the Stenson duct. Drugs are taken and blood and saliva collected simultaneously and analyzed for drug concentration. At the present time, the following drugs have been found to be secreted in both animal and human parotid saliva: amphetamine, barbituates, ethanol, narcotics and valium. Present work is being conducted to determine the salivary/plasma concentration ratios of antiemetic drugs such as promethazine and scopolamine in paid human volunteers. The results of this study and other studies will be discussed.

MOVING PLATFORM POSTUROGRAPHY - A PROGRESS REPORT

David J. Anderson and Robert O. Andres

Kresge Hearing Research Institute
The University of Michigan
Ann Arbor, Michigan

Introduction

Justification for a posture test to evaluate flight crews comes from a basic need to know the effects of space flight on the posture control system in general and the vestibular system in particular. The need for a simple test because of limited crew time and a singularly poor environment for the testing (a ship on the open sea) lead to the rail balancing test of Graybiel and Fregly. Considerable valuable data were obtained from the test but unquantified clinical observations of flight crew behavior post-flight provided evidence that the static rail test needed to be supplemented by testing the posture control system in more depth. It was this motivation which led us to develop the moving platform posture measurement system as described in this paper. We are not the first to use a dynamic stimulus for posture testing but the total measurement system approach is unique to the field. The status of the project is such that the test system hardware and software is complete but not all the base line tests have been completed. For convenience of presentation, the total measurement system has been broken down into three basic subsystems: 1) The motion subsystem, 2) The camera subsystem, 3) The data subsystem and the task designs. Criteria for the complete system as well as each of its subsystems will be presented along with the method of implementation for each.

System Overview

The interconnection of the three basic hardware system components is shown in Figure 1. Platform motion is controlled by a single analog line which is delivered from the data system through a digital to analog converter. Several signals containing induced motion information about both the platform and the subject are returned to the data system by way of an analog to digital converter. Platform data are obtained from electromechanical devices in the platform subsystem and subject data come from optical data converted to voltages proportional to silhouette hip and shoulder position in the field from line scan cameras. The data subsystem which both delivers the commands and analyzes the results is the central element of the system. Virtually all of the interaction between the operator and the system is carried out through the data subsystem. The raw data are stored on floppy disks for later recall for display or reduction to parameters useful for summary of the tests. These parameters are transmitted to the University computer center for entry into a large data base which has been designed to contain all the summarized data from all the subjects used on the platform. Organization of this data base allows selected retrieval of the data by a simple set of commands to the University computer.

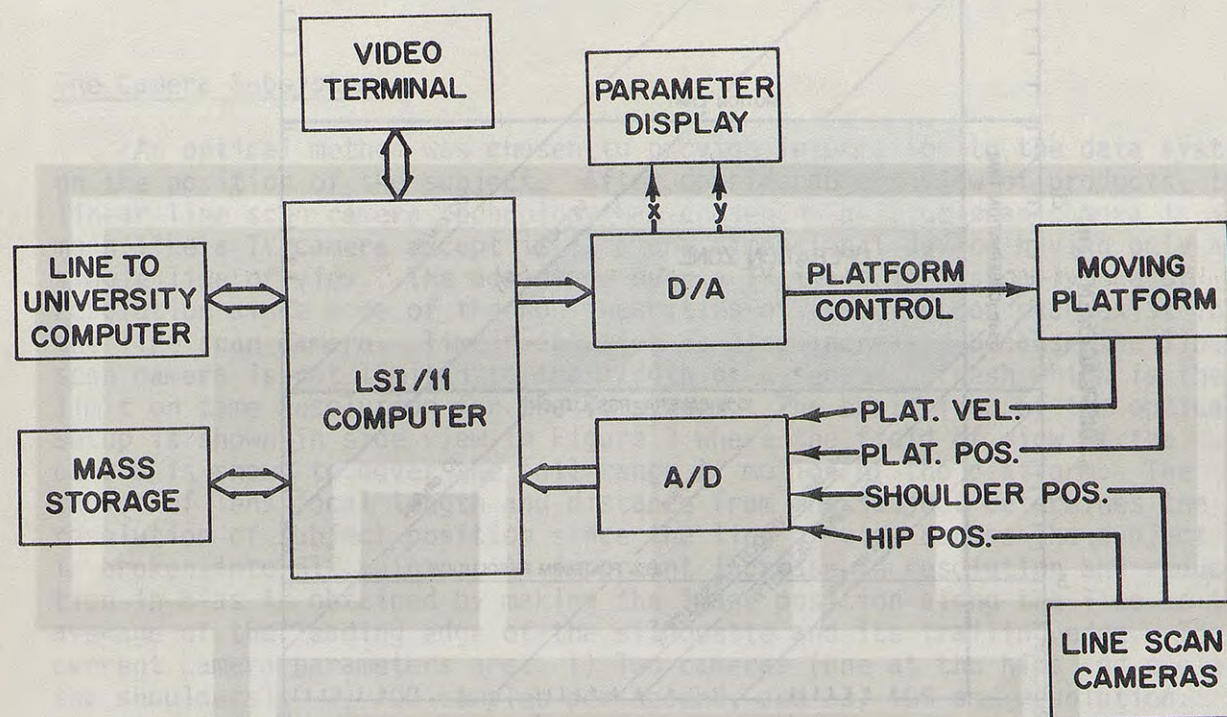


Figure 1. The postural system information flow centers around the LSI/11 digital computer and provides easy communication between the operator and the system.

The Motion Subsystem

The motion system was not the first subsystem to be conceived but it has represented the largest expenditure of resources in the project. Many of the details can be found in Andres et al, 1977. Most of this effort has been expended to assure that the stimulus being delivered to the subject is as free as possible of cues which could confound the intent of the experiment. The motion stimulus is delivered by a rectangular platform which moves in one direction only in the horizontal plane. The subject takes a standing position on the platform facing in the direction of motion. It is therefore his base of support which is moved by the platform. The normal reaction of the subject is to take corrective action to maintain his center of gravity over the new base of support. The physical parameters of the motion are bounded by a number of electro-mechanical realities. The maximum peak-to-peak displacement of our platform is 43 cm. and its maximum velocity is 30 cm/sec. Maximum acceleration which could be a limiting factor is not due to overdesign to overcome large mechanical static friction forces as the motion changes direction. Minimum values for platform parameters such as velocity and position resolution are determined primarily by data system and A/D and D/A hardware resolution. Figure 2 shows the constraints we are now working with when sine wave stimuli are considered. The operational area can be expanded to some extent by hardware adjustments but for the present, the area shown is sufficient for our experiments. In fact, a second model of the platform reduces the peak-to-peak motion to 30 cm.

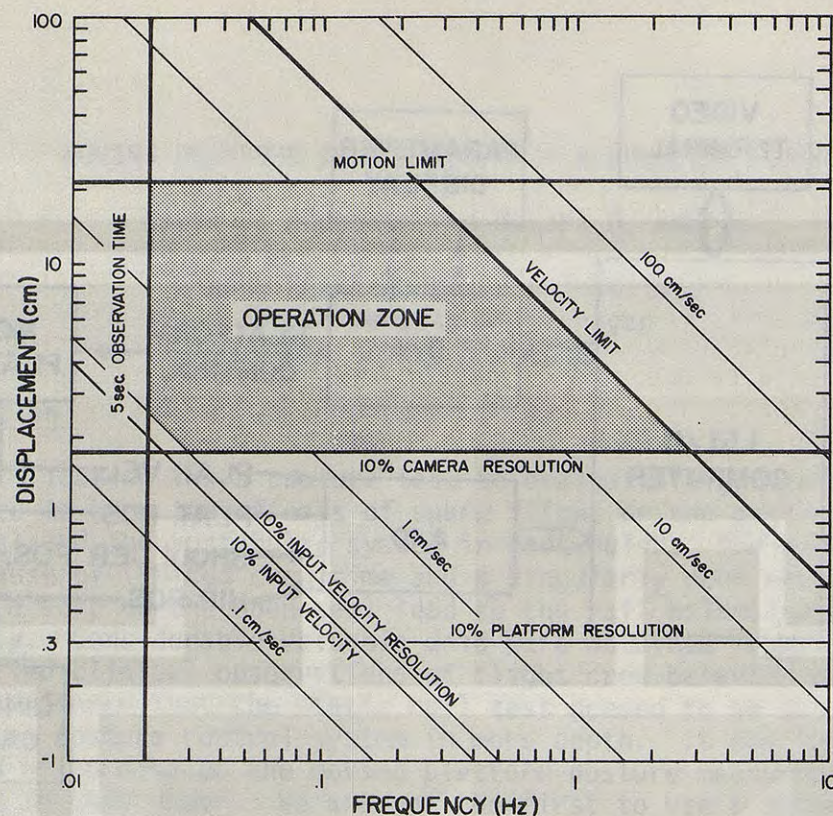


Figure 2. A log-log plot conveniently shows the operational area of the postural platform when it is operated in the sinusoidal mode.

Platform motion is accomplished by rotation of a lead screw under the bed of the platform. A nut mounted on the under-side of the platform causes a mechanical conversion from rotation to linear motion. A torque motor with an attached tachometer and a servo amplifier provides a velocity control loop which receives commands in analog form and returns angular velocity to confirm the motion. The platform motion may therefore be commanded by an arbitrary voltage as long as it stays within the operational limits of the platform.

Of overriding importance to the operation of the platform is the smoothness with which it performs its displacements. The reason for this is, of course, that the platform is the only contact we have with the subject and this contact, therefore, must give as few uncontrolled cues as possible concerning the motion of the platform. We have only subjective measures of the platform roughness of motion but we are constantly retesting it and introducing a new techniques for the reduction of vibration. There is the consideration that changes which increase smoothness of motion act to reduce the stiffness of the linkage between the control and the motion and therefore reduce the preciseness of movement.

The moving platform interfaces with the data system with three signals: 1) The command signal, 2) The angular velocity signal from the tachometer and 3) The position signal which was originally intended only for somewhat coarse measurements but has been upgraded to a higher quality and now becomes part of the data sequence.

The Camera Subsystem

An optical method was chosen to provide information to the data system on the position of the subject. After considerable review of products, the linear line scan camera technology was chosen. The line scan camera is much like a TV camera except it is a one dimensional device having only a single line of view. The advantage over a TV image is basically one of resolution since none of the nonlinearities of the electron scan exist in the line scan camera. Time resolution is also increased because the line scan camera is not limited to the 1/30th of a second refresh which is the limit on time resolution for the TV system. The basic idea of the optical setup is shown in side view in Figure 3 where the field of view of the camera is shown to cover the full range of motion of the platform. The choice of lens focal length and distance from the subject determines the resolution of subject position since the line of view across the subject is broken into 512 points. An important increase in resolution and reduction in bias is obtained by making the image position along the line as the average of the leading edge of the silhouette and its trailing edge. The current camera parameters are: 1) Two cameras (one at the hips and one at the shoulders), 2) 100 samples per second, and 3) 108 cm. resolution. Details of the camera system may be found in Anderson *et al*, 1977.

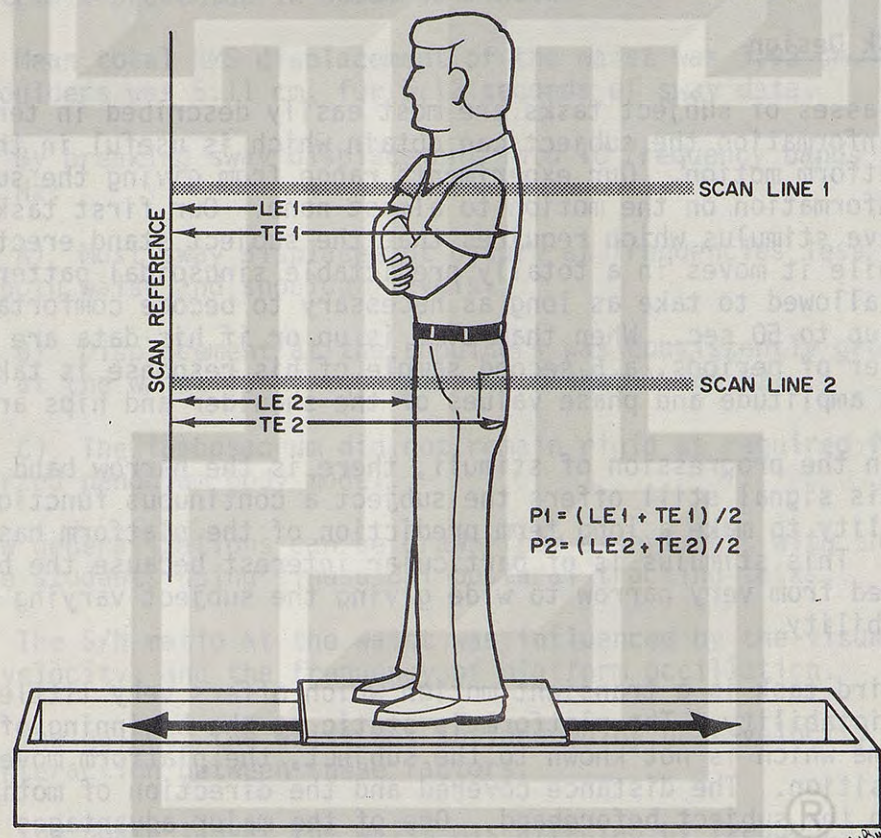


Figure 3. The measurement of subject position by the camera system is done at 2 levels. The center position of the silhouette at each level is obtained by averaging the leading and trailing edge positions.

The Data Subsystem

The functions of the data system can be classified into three major areas: 1) Operator interface, 2) Signal processor and 3) Data storage. All of the programs which operate the platform and receive data from the experiment are operator interactive. That is, there is always a question and answer interaction going on between the data system and the operator to determine the course of the experiment. In a real time environment, the data system is handling both outgoing and incoming signals. Platform motion commands are being sent to the servo loop and data records are being sampled from the input lines. In performing these functions and preparing the data for display, the data system has to do several signal processing functions. These include filtering, time domain to frequency domain conversion, random signal generation and function synthesis. Storage of experiment data requires not only a system with considerable word capacity but also a medium which can accept data on a real time basis. As an example, while a sine wave experiment is in progress, the storage media must be prepared to accept 400 words/sec continuously. To meet all of these needs, the Digital Equipment Corporation LSI-11 was chosen with the RT-11 operating system, floppy disks and a VT-55 video terminal. The system also has the facility to communicate with the University of Michigan computer so that large quantities of subject data can be entered into a data base management system for easy retrieval.

Subject Task Design

The classes of subject tasks are most easily described in terms of the amount of information the subject can obtain which is useful in the prediction of platform motion. Our experiments range from giving the subject complete information on the motion to almost none. Our first task type is the sine wave stimulus which requires that the subject stand erect on the platform while it moves in a totally predictable sinusoidal pattern. The subject is allowed to take as long as necessary to become comfortable with the motion up to 50 sec. When that time is up or if his data are consistent over a number of periods, a 5 second sample of his response is taken. From these data, amplitude and phase values of the shoulder and hips are calculated.

Next in the progression of stimuli, there is the narrow band random signal. This signal still offers the subject a continuous function to track but his ability to make a long term prediction of the platform has been taken away. This stimulus is of particular interest because the band width can be varied from very narrow to wide giving the subject varying amounts of predictability.

The third task is a transient motion which offers very little in the way of predictability. The platform is static at the beginning of the trial and at a time which is not known to the subject, the platform moves quickly to a new position. The distance covered and the direction of motion are not known to the subject beforehand. One of the major advantages of this system is the opportunity just before and just after the test to take static data on the subject. In addition to the parameters which may be adjusted within the system, there are a few which have to do with the instructions

to the subject. These are eyes open verses eyes closed, the type of footwear, the stance and audio cues.

Within all of the above tests, parameters can be adjusted but there are certain subject parameters which cannot be controlled by the system. Among these are sex, weight, height, occupation, age, and medical history. The parameters of each test must be tailored to match these factors.

Results

A full range of results for the completely implemented system have not been obtained but studies have been completed on static and sinusoidal responses. Static responses are the linkage we have with other investigators since most work in posture analysis has been done for this case. The other dynamic studies have not been carried out in a comparable way.

The basis of the static analysis is the conversion of the shoulder position and hip position time series data to the frequency domain. The data are then analyzed frequency band by frequency band. The following points are important observations which we have made so far:

1. The spectrum of sway displacement was not significantly different for trials before the beginning, in the middle, or after a series of active stimulus trials presented in about 45 minutes.
2. Mean total RMS displacement of the waist was 3.93 cm. while that of the shoulders was 5.11 cm. for 5.12 seconds of sway data.
3. By breaking sway displacement into 10 frequency bands ranging from 0. - 3.91 Hz:
 - A) Most sway displacement occurs at frequencies less than .391 Hz for both waist and shoulder levels.
 - B) Displacement at the shoulders was consistently greater than that at the waist for frequencies less than 1.564 Hz.
 - C) The lumbosacrum did not remain rigid as required for an inverted pendulum body model.

A few generalizations can be drawn from experiments with three young adult male students using sinusoidal postural tracking tasks.

1. The S/N ratio at the waist was influenced by the visual situation, the peak velocity, and the frequency of platform oscillation.
2. The gain at the waist was influenced by peak velocity frequency, and the interaction between these factors.
3. The phase lag at the waist was affected by frequency only.
4. The S/N ratio at the shoulders was affected by peak velocity and

frequency of platform motion.

5. Gain at the shoulders was influenced by the visual situation, peak velocity, frequency, and the interaction between velocity and frequency.

6. Phase lag at the shoulders was affected by peak velocity and frequency of platform oscillation.

7. Only frequencies of .195, .391, and .586 yielded positive S/N ratios (dB) at the waist.

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SPECIAL NOTE: SPACE MOTION SICKNESS IN THE
SOVIET MANNED SPACE FLIGHT PROGRAM

Jerry L. Homick
Medical Research Branch
NASA - Johnson Space Center
Houston, Texas 77058

The problem of space motion sickness and related vestibular system disturbances in weightless space flight has not been confined to U.S. astronauts. Problems of a highly similar nature have been reported by Soviet cosmonauts. The following is a brief summary of our knowledge of the Soviet findings in this area. The information presented was derived largely from direct meetings and data exchanges with Soviet vestibular investigators, the most recent of which was the 9th US-USSR Joint Working Group on Space Biology and Medicine held in Leningrad in October 1978.

Incidence of Space Flight Related Vestibular Disturbances

The Soviet cosmonaut, G.S. Titov aboard Vostok 2 in 1962, was the first individual to report symptoms of space motion sickness. Since that time approximately 40% of all Soviet cosmonauts have experienced space sickness of varying degrees. Symptoms reported included loss of appetite, headache, stomach awareness, nausea and vomiting. An episode of vomiting was usually followed by a short period of feeling better. Symptoms were typically most severe during the first 2 days in flight, but often persisted in mild form up to mission day 6 or 7. Symptoms, when they occurred, were usually aggravated by abrupt head movements. Therefore, Soviet cosmonauts are advised to restrict their activities during the first few days of flight.

In addition to the vegetative responses described above Soviet cosmonauts, probably more than U.S. astronauts, have reported a variety of postural and visual illusions. These include tumbling illusions, mild vertigo, and a sense of hanging upside down or falling. These sensations sometimes contributed to their general malaise and were often reported as being different from sensations experienced with motion environments on the ground.

A sensation of head fullness caused by headward shifts of body fluids in zero-g has been experienced by all Soviet cosmonauts. This sensation, or "feeling of blood rush to the head" as it was described, generally persisted throughout the flight. It is of interest to note that during exposure to inflight lower body negative pressure (LBNP) the head fullness sensation would abate, but would return as soon as the lower body negative pressure was terminated.

Data regarding the implementation of inflight vestibular test protocols are scarce. However, on the basis of what we have learned it appears that the Soviets have not flown any type of sophisticated hardware (e.g., a rotating chair or linear accelerator) on board their Salyut space station, nor have they systematically collected any inflight quantitative data on human vestibular system response dynamics in zero-g. It is known that on the 96-day Salyut 6/Soyuz 27 mission an attempt was made to record ocular nystagmus produced by galvanic stimulation of the vestibular receptors. Technical difficulties were

encountered (complaints of burning at the stimulus site) and the experiment was abandoned with no useful data obtained. It appears that the Soviets have to this point in time relied heavily on subjective or phenomenological reporting by their crewmen.

A variety of postflight vestibular related disturbances have been reported by Soviet cosmonauts, particularly following their recent long duration missions. Included are decreased appetite and vertigo, disorientation and nausea associated with abrupt head movements. These symptoms usually persisted no longer than 1 1/2 to 2 days postflight. It has also been reported that cosmonauts returning from long duration flights have experienced difficulty with locomotion and maintenance of postural balance. Quantitative information in this area is sparse, but using stabilometry techniques disturbances in balancing performance lasting up to 10 days postflight have been reported. On the basis of available information it appears that the Soviets have done little quantitative postflight testing of canal and/or otolith receptor sensitivity. In general, subjective reports from crewmen have indicated nearly complete recovery from all vestibular system related disturbances by the 10th day postflight.

Preflight Selection Techniques

Our knowledge of the techniques used by Soviet vestibular investigators for screening cosmonaut candidates for susceptibility to motion sickness is not clear. It is known that on the basis of one or more provocative tests they attempt to place individuals into one of three categories: high susceptibility, moderate susceptibility and low susceptibility. Individuals classified as highly susceptible are eliminated immediately. Individuals in the other two categories are exposed to varying types and amounts of training (some of these training methods are summarized in the following section).

One screening test that appears to have been standardized involves exposure to Coriolis stimulation. This test, which is only five minutes in duration, requires the use of a rotating chair. During the first minute of the test protocol physiological parameters such as pulse rate and respiration are measured. The chair is then rotated at 30 RPM in a clockwise direction for a duration of 1 minute. During rotation the subject is required to execute head movements in the frontal plane only at a rate of one full head movement each 3 seconds. Following 1 minute of such motion exposure the chair is stopped for 1 minute and the subject is observed. After the 1 minute pause the chair is rotated 30 RPM in counterclockwise direction for 1 minute and the head movements repeated. The final minute of the protocol is spent observing the subject and recording responses. Other vestibular assessment techniques involving the use of rotating devices and the measurement of nystagmus have been reported, however, their relationship to motion sickness susceptibility is not clear. In general they have stated that people selected for flight should be those who have demonstrated an ability to adapt to a wide range of vestibular stimuli.

Because a significant number of Soviet investigators firmly believe that hemodynamic alterations (fluid shifts) in zero-g are closely related to space motion sickness, various tests of cardiovascular tolerance to stress are included in their screening of cosmonaut candidates. In other words it is believed that cardiovascular tolerance, especially to situations involving redistribution of blood, is highly related to vestibular tolerance. It is known that the Soviets

make extensive use of head-down tilt to simulate the fluid shifts which occur in zero-g. During these head-down tilt studies various physiological parameters, including vestibular responses, are measured. The degree to which these data correlate with, or are predictive of susceptibility to space sickness is not clear on the basis of information presented by the Soviets. However, they do claim that the assessment of hemodynamic factors is valuable in selecting crewmen for flight, developing countermeasures and accounting for individual variations in susceptibility to motion sickness.

On the basis of the various selection procedures used, especially those involving direct vestibular stimulation, the Soviets have claimed that they can predict with 85% accuracy who will experience space sickness. This claim is suspect, however, in view of the fact that 40% of the cosmonauts have reported inflight symptoms. In fact, it was reported that one of the Soyuz 27 crewmen who exhibited extreme vestibular tolerance by all ground based measurement standards experienced severe symptoms, including vomiting inflight.

Countermeasures

Available information indicates that the Soviets place considerable emphasis on the use of various adaptation training or pre-conditioning techniques which are intended to prepare the cosmonaut to adjust more rapidly to the vestibular stress encountered upon entry into zero-g. These techniques include (a) various methods of vestibular adaptation training, (b) exposure to head-down tilt and (c) a form of biofeedback training. Each of these are briefly described below.

Of the three pre-conditioning techniques referenced above vestibular adaptation training is by far the most extensively used approach. Vestibular training of cosmonauts has traditionally been divided into two categories: active training and passive training. Active training requires participation by the individual in a variety of athletic type activities in which repeated motion of the body in various axis is involved. Thus, active training includes activities such as running, swimming, tumbling and volleyball. Passive training involves repeated exposure of the individual to motion in a single axis or in multiple axis while he is restrained in some type of mechanical device. Included in this category is the use of rotating chairs, parallel swings, optokinetic stimulation devices, parabolic flight and other multiple axis motion simulators. Passive training attempts to capitalize on the sensory conflict theory of motion sickness and is based on the premise that adaptation acquired on the ground will transfer to the zero-g environment. An interesting feature of this form of training is that it is custom tailored to the individual's needs. In other words, if the screening tests indicate that an individual is especially sensitive to canal stimuli, but not other forms of stimulation, then his training program emphasizes the use of canal stimuli. On the basis of what we have learned, it appears that the active and passive training programs are not highly regimented. Each cosmonaut, with recommendations from the flight surgeons, engages in the amount of training he feels is necessary to prepare him for flight. Individuals who are diagnosed as being moderately susceptible to motion sickness do generally receive a greater amount of training than those who are insusceptible to 1-g motion sickness.

In recent years the Soviets have begun to use head-down tilt as a means for pre-conditioning cosmonauts to the headward fluid shift that occurs in zero-g.

The technique, which involves 6° head down sleep during the two week period prior to flight, is claimed to be an important feature of their overall training program. It is not currently known if all of their cosmonauts now go through this training, nor is it known if the efficacy of this form of training has been systematically validated.

Another method mentioned by the Soviets involves the use of auto-regulation or auto-genic training to activate inhibitory mechanisms at an early stage in the development of symptoms of motion sickness. It appears that this technique is not used extensively however, the Soviets claim that crewmen who receive such training are better prepared psychologically to deal with inflight problems.

In general, the Soviets believe their preflight training programs, especially the vestibular training, are effective in reducing inflight symptomatology. They admit that the training is not perfect because cosmonauts continue to experience space sickness. However, they feel that the training has value because it gives the individual a variety of experiences which prepare him to better cope with the novel zero-g environment.

Anti-motion sickness drugs are used very sparingly by the cosmonauts. We have no knowledge that these drugs have ever been used prophylactically. They have used scopolamine as an aid to adaptation during preflight training, but have not used the drug inflight because they believe it fails to eliminate the real source of the disorder in zero-g. They have suggested that scopolamine in conjunction with an anti-hypertensive drug might be better. In a similar vein (i.e., from a fluid shift point of view) they have shown sodium hydrocarbonate to be effective in treating hydrops of the labyrinth and feel that it may be an effective treatment for space motion sickness. They have reported no inflight use of sodium hydrocarbonate. Large doses of B vitamins have also been used with mixed success to prevent motion sickness in laboratory studies, but not inflight.

WORKSHOP SUMMARIES

Brief summaries of each of the four symposium workshops are presented in the following sections. These summaries are based upon transcripts derived from tape recordings of the workshops and written reports submitted by the workshop discussion leaders. For each of the four workshops the discussion leaders were requested by Dr. Sherman Vinograd of NASA to conduct the workshops with several objectives in mind. These objectives were:

- To introduce the problem area and briefly summarize the current status and approaches that have been taken with regard to resolving the problem
- To evaluate potential research programs, especially ground-based research programs, which could contribute to the problems identified
- To indicate what new concepts are available in the area
- To attempt to indicate research priorities
- To provide recommendations for pre-and postflight testing required to validate predictive techniques and countermeasures

In order to promote discussion a number of specific topics for each workshop were pre-defined by NASA and included in the symposium agenda. However, the discussion leaders and other symposium participants were encouraged to introduce and discuss other relevant topics within the context of each workshop.

Unedited versions of summary reports prepared by the workshop discussion leaders appear as appendices in this document. The reader is encouraged to refer to the discussion leaders' summary reports because they contain significant details not included in the following short summaries.

WORKSHOP I: VESTIBULAR/MOTION SICKNESS MECHANISMS*

Evaluation of Fluid Shift Theory

The fluid shift theory states that following orbital insertion, major shifts in body fluids from the legs and torso toward the head, with concomitant changes in cranial pressure, might alter response characteristics of vestibular receptors, contributing to a sensory conflict or directly eliciting motion sickness by unknown neural or receptor mechanisms.

A basic question considered during the workshop was whether or not research in this area should be pursued. It was the consensus of the discussants that unless a new approach was developed which could produce significant new data, research on fluid shifts as a contributing factor to space motion sickness should be abandoned.

Evidence against the theory as a valid explanatory tool can be summarized as follows:

- (1) Recent work by Graybiel and Lackner failed to demonstrate a change in susceptibility to motion sickness following exposure to head-down tilt.
- (2) Space motion sickness dissipates after 3-5 days in orbit while fluid shift is maintained.
- (3) Anecdotal evidence from head-down tilt bedrest studies is generally nonsupportive of the theory.
- (4) Forty percent of the Soviet crews have experienced space motion sickness even though Soviet scientists have adopted the fluid shift theory in attempting to select cosmonauts resistant to the syndrome.

In support of the theory, Ingelstedt's hypothesis involving the association of vertigo and vestibular signs and pressure changes in the inner ear was noted, as well as fluid shift effects on auditory thresholds.

It is clear that the questions of (1) does fluid shift affect the dynamics of the vestibular system and (2) does the change of dynamics in the vestibular system affect susceptibility to space motion sickness remain unanswered. However, the weight of the evidence available at the present time suggests that fluid shifts are of little or no significance in the etiology of the space sickness syndrome.

* The discussion leaders for this workshop were Donald E. Parker and Kenneth E. Money.

Evaluation of Sensory Conflict Theory

The sensory conflict theory as elaborated by Reason and Graybiel (1973) argues that motion sickness symptoms result from a mismatch between the total pattern of information from the spatial senses and that held in a neural store from previous experiences. The basic assumption is that motion sickness is a maladaptation phenomenon which occurs during the period of time that the contents of the neural store are at variance with the prevailing sensory influx. An essential proviso for this theory is the presence of an intact and functional vestibular system. This type of sensory conflict is a subset of one of several sensory rearrangement processes which have been advanced.

The discussants concluded that this theory provided the best available framework for explaining the cause of space sickness even though it has two significant weaknesses. First, the theory predicts more motion sickness than anyone ever detects. Secondly, the uniqueness of the vestibular system is not considered within this approach. The latter aspect, however, appears to be considered by Treisman (*Science*, 197, 493, 1977) in his deductions concerning the evolution of motion sickness.

Three areas needing further investigation were identified in related discussions of the sensory conflict approach. It was clearly noted that no animal has ever been brought to frank vomiting with visual stimuli alone. Perhaps mismatch is not necessarily a powerful variable across species, but the area of sensory conflict, in general, in animal models needs farther elucidation. Secondly, the role of proprioception has not been adequately addressed in terms of its relation to a visual-vestibular mismatch in both humans and animals. Thirdly, the role of olfaction in motion sickness is commonly accepted in terms of certain odors influencing nausea. The smell of toluol was mentioned as a possible inhibitor of motion sickness, but this sensory influence lacks validation. These three areas demonstrate the significant complexity involved in attempting to dissect the intersensory influences on space motion sickness.

New Approaches

A list of suggestions for combating the space motion sickness problem was produced by Dr. Money. The suggestions, which derive largely from the sensory conflict theory, were as follows:

1. Make angular head movements slowly; make linear accelerations short and sharp.
2. If in danger of vomiting, move as little as possible and keep the eyes closed as much as possible.
3. Avoid $-g_z$ which could give rise to an upside down signal.
4. Put pressure on feet.
5. Do not think about orientation.
6. Use a head holder.

7. Use an optimum locomotor strategy, visual reference lines, and tactile cues aligned with visual vertical.
8. Avoid x and y axis head movements.
9. Use optimum pharmacological protection, perhaps i.m. or transdermal. The best drug for most people is not necessarily the best drug for a given individual. The best drug for a brief exposure to motion is not necessarily the best drug for a five-day exposure. Larger and more frequent doses are optimum for some individuals. Combinations of two or even three drugs might be best.
10. Use biofeedback.
11. Use people who have demonstrated their immunity in the shuttle vehicle (or Skylab) previously.

Discussion of some of the above points led to the conclusion that a general approach can be summarized as advising a crewman on Shuttle to experience as much motion as possible without experiencing any (or at most minimum) symptoms of space motion sickness in order to facilitate stepwise adaptation to the weightless environment.

WORKSHOP II: PREDICTION OF SUSCEPTIBILITY*

Evaluation of Motion Sickness Questionnaires

A number of questionnaires have been developed and used as predictors of susceptibility to sickness in different motion environments. Such questionnaires have been shown to yield significant (although not always consistent) correlations with susceptibility in land, water, and air conveyances. It is reasonable to assume that given the same evolution a questionnaire will eventually be developed for persons traveling in spacecraft. Thus, this goal should not be overlooked while presently facing the realization that there is no good questionnaire to predict susceptibility to space motion sickness.

While questionnaires generally offer the obvious advantage of a means of screening large numbers of people in a relatively short period, there are four noteworthy disadvantages. First, people are sometimes unfamiliar with all of the appropriate motion sickness symptoms - hence, inaccurate histories of symptoms are recorded. Secondly, it is difficult to equate motion experiences of different subjects (different conveyances at differing frequencies of exposures). Thirdly, some persons are highly motivated to provide accurate answers and others will suppress information to get through a screening process. And lastly, but perhaps most importantly, a questionnaire assays nothing about an individual's rate of symptom buildup, adaptability, and duration of retention of a given acquired adaptation. These latter concerns indicate that questionnaires should be used only for information gathering.

In conclusion, the discussants expressed the opinion that although it should receive low priority, the development of a motion sickness questionnaire for space flight should still be pursued for several reasons:

1. A systematic record of previous motion exposure would seem to be a natural part of any history of candidates because space motion sickness appears to have been the most common medical problem in space flight.
2. Questionnaires administered after participation in a flight program may achieve more predictive power than questionnaires administered prior to entry into the program. That is, the candidates may become more confident and candid in discussing previous problems.
3. Follow-up questioning on previous candidates must be used to discriminate reluctant candidates from highly motivated ones and thus facilitate future development of good prediction criteria.

* The discussion leaders for this workshop were Fred E. Guedry and James R. Lackner.

Evaluation of Psychodynamic Variables

It was the overwhelming consensus of the discussants that there are no strong correlations between psychodynamic variables and motion susceptibility as determined by provocative tests. Correlations are generally .4 to .5 and they vary with the type of motion parameter.

An interesting example was cited of an old study in which adrenalin was injected into subjects to induce high anxiety levels before administering a provocative test. No significant correlation was found between anxiety level and motion sickness susceptibility.

Evaluation of Provocative Test Methods

The discussion of this topic focused on the identification of an operational need to develop a battery of provocative tests which would measure susceptibility using more than one type of motion environment in terms of the vestibular receptors activated. This type of testing is important because insusceptibility to one form of motion stimulation is not inconsistent with high susceptibility to other forms.

It was noted that with any given battery of tests, there would be some concern over how to evaluate the scores. That is, would an individual who produces inconsistent scores or one who consistently produces scores indicative of moderate motion sickness susceptibility be worse off in space flight? This issue could be resolved by identifying the stressful motion characteristics of the space environment which cause space motion sickness. The information could then be utilized in designing the best ground tests for meaningful prediction of a subject's performance in zero-g.

A preliminary list of provocative tests which could be administered over a period of days was suggested and discussed. This list included the following types of stimuli:

1. Off-vertical rotation
2. Head movements during rotation (Coriolis stimulation)
3. Horizontal axis rotation
4. Parabolic flight
5. Visual-vestibular interaction which involves scanning a complex visual display while being subjected to a strong vestibular stimulation
6. Visual-vestibular interaction in which there is a fairly large phase angle between a strong vestibular input and what the subject's eye is detecting about relative motion in the peripheral field while concentrating on a task
7. Linear acceleration (vertical and horizontal)

Evaluation of Vestibular Reflex Response Correlation

The fundamental question addressed was whether or not there is a relationship between susceptibility to motion sickness and tests of vestibular functional capacity.

The discussants suggested that measures of functional capacity should be included in the assessment of space flight candidates even though there does not appear to be a relationship to space motion sickness susceptibility. Specifically measures of ocular counterrolling (otolith sensitivity), caloric irrigation (canal sensitivity), oculogyral illusions, and nystagmus cupulograms show no evidence of predicting susceptibility. It was noted in biofeedback studies by Cowings, Toscano, and Billingham that no changes in vestibular functional capacity could be measured after subjects adapted to stressful stimuli imposed by coriolis acceleration.

Further discussions revealed that although this area of study should have a low priority, several topics had not been thoroughly investigated. In particular, more data should be obtained on individual differences in rates of decay of nystagmus, ratios of secondary to primary reaction (nystagmus cupulogram), and abilities to both suppress a strong vestibular input and improve response to the same.

New Approaches/Recommendations for Future Investigations

The general views of the participants of this workshop can be summarized by the following recommendations:

1. It is important to recognize the likelihood of an interdependence between selection tests and adaptation procedures.
2. Questionnaires should be used to obtain descriptions of an individual's history of motion exposure and incidence of motion sickness. If they are administered after acceptance into the astronaut program and after exposure to ground testing and inflight training, they will probably be more informative than pre-selection questionnaires.
3. Current information does not indicate that vestibular sensory thresholds are useful predictors of motion sickness susceptibility.
4. There is no specific single modality vestibular function test that can be recommended as an effective predictor of motion sickness susceptibility, but development of a test of dynamics of otolith function (employing frequency domain analysis) should remain a priority item.
5. A battery of quantitative sensorimotor tests, involving interactive sensory inputs from the visual, vestibular, and proprioceptor systems should be used. This battery will have the diagnostic potential for CNS anomalies in the management of interactive inputs and may reveal some specificity of susceptibility.
6. Provocative tests should be patterned after adaptation procedures in order to assess adaptive capacity and retentivity.
7. Retrospective information should be collected from astronauts concerning their histories of motion sickness, especially any recollections of reactions to parabolic flight and any special strategies adopted to cope with space motion sickness symptoms.

WORKSHOP III: TRAINING COUNTERMEASURES*

Evaluation of Vestibular Adaptation Training

Vestibular adaptation training involves an incremental exposure paradigm in which increasing levels of a stressor lead to a heightened level of adaptation. In the laboratory this type of training has often utilized either a slow rotation room or a rotating chair. The ensuing discussion of this approach noted that there were significant individual differences in rate of improvement (time to adaptation) which usually began with a direction specific adaptation and later became a non-direction specific adaptation. A discussion of studies done in this area indicated that the duration of retention of adaptation and the transfer of adaptation acquired in one motion environment to other dissimilar motion are important variables which require further investigation. It was also pointed out that adaptation training schedules should be carefully tailored to each individual's tolerance to motion stress and his rate of adaptability. It was noted that anti-motion sickness drugs might be used to augment adaptation training. That is, by using drugs individuals could be exposed to levels of stress higher than normally tolerated, thereby allowing the adaptation training schedule to progress at an accelerated rate. This approach has yet to be experimentally validated. In general it was agreed by the discussants that vestibular adaptation training, particularly training which involves exposure to sensory conflict, might be an effective countermeasure for space motion sickness. However, it was also agreed that we presently lack the data required to establish the most effective and efficient training methods, and more importantly, we do not know at the present time if training acquired on the ground will transfer to the weightless environment.

Evaluation of Biofeedback Training

In recent years biofeedback training has come under investigation as a method for controlling physiological responses associated with motion sickness. In accordance with techniques developed by Dr. Cowings at the Ames Research Center, the trainer starts by identifying the individual's pattern of autonomic responses. It was reported that in approximately six hours, 80% of the subjects used can be conditioned so that their stress responses (to head movements on a rotating chair) are reduced, becoming more or less automatic for the autonomic nervous system as overtraining is approached. Generally the last four hours of conditioning are devoted to enabling the subject to control his symptoms under distracting conditions. This type of adaptation apparently is not direction specific and may be transferred to other environments because subjects are trained to suppress symptoms rather than respond to specific motion stimuli.

* The discussion leaders for this workshop were Ashton Graybiel, James R. Lackner and Charles M. Oman.

Research areas for biofeedback training were identified in further discussion. Data are needed on retention rates, relearning rates and the subject's stress pattern in the zero gravity environment. It was suggested that the later area could be approached on the ground by testing the effectiveness of the biofeedback technique in parabolic aircraft flight and horizontal axis rotation.

Evaluation of Operational Feasibility of Training Methods

The major focus of this topic was a response to the challenges to determine (1) if there should be preflight training, (2) what is the least time consuming technique for preflight training, (3) can the technique be accelerated, and (4) what facilities will be needed. It was noted that during the early Shuttle flights crew time available for such training might be limited to a total of 20 hours per crewman.

The discussion was initiated with remarks about the Russian approaches to operational training for space flight. Apparently this training is tailored to an individual's weaknesses as determined by a provocative test battery (e.g., those susceptible to linear accelerations are trained with emphasis on linear accelerations). The actual timelines in flight are designed to reduce movement during the early periods of flight.

There was an astronaut recommendation that preflight countermeasures should only be applied to individuals who have flown before and demonstrated space motion sickness symptoms. The concern was voiced because of a belief that persons who may adapt best in a habituation program may indeed be the individuals who would not get sick anyway, hence inconclusive data may result.

The discussants identified experienced astronauts as a valuable resource that should be utilized to validate provocative tests, particularly parabolic flight. It was further elucidated that on two OFT flights there may be some additional "backseat" crewmen acquiring flight experience for future functions as pilot and co-pilot. These individuals may represent good opportunities for the study of space motion sickness if it occurs.

Incremental adaptation training employing rotating chairs and slow rotation rooms, biofeedback training, parabolic flight, and horizontal axis rotation were suggested as feasible operational training methods but there was no consensus on which approach was best.

New Approaches/Recommendations for Future Investigations

The prevalent views of the participants of the workshop are represented in the following recommendations:

- (1) It should be assured that the flight crews for the Shuttle use standard terminology to describe the symptoms of space motion sickness when it occurs.

- (2) Preflight training should include training in symptom management techniques in which the individual learns about his own critical endpoint.
- (3) It is conceivable that there are two adaptation strategies: (1) suppression of symptoms in response to specific motion stimuli, and (2) suppression of symptoms without identifying motion stimuli. Adaptation in a rotating environment (slow rotation room or rotating chair) may not transfer to a zero gravity environment because it involves the first strategy. Biofeedback training procedures may transfer more readily, but this technique needs testing for its generality of application.
- (4) Parabolic flight and horizontal axis rotation are the closest approaches available to simulate intralabyrinthine conflict or a visual-vestibular conflict. Therefore, these methods should also be subjected to further investigation for application as preflight countermeasure.
- (5) The relationship between measurable adaptation (as monitored by vestibular reflex responses) and motion sickness susceptibility has not been examined sufficiently and deserves further study.
- (6) Postflight tests employing a reasonable battery of tests should be performed on both space motion sick and non-sick astronauts. Data obtained from these subjects would be invaluable in not only elucidating the causes of space motion sickness, but also in designing better countermeasures.

WORKSHOP IV: PHARMACOLOGICAL COUNTERMEASURES*

Evaluation of Current Anti-Motion Sickness Drugs

Anti-motion sickness drugs have been shown to raise a subject's threshold for susceptibility to motion sickness, alleviate symptoms already present and facilitate acquisition of adaptation to different motion environments. The most effective drugs, except for amphetamines and ephedrine, appear to be the anticholinergics which are effective across many situations.

The current drugs of high efficacy include the following:

- (1) Oral promethazine (25 mg.) + ephedrine (25 mg.) - beneficial in two-thirds of subjects tested with minimal side effects
- (2) Oral scopolamine (0.3-0.6 mg.) + d-amphetamine (5-10 mg.) - beneficial in 70-80% of subjects tested
- (3) Transdermal scopolamine - under testing
- (4) Intramuscular promethazine (25 mg.) - under testing

Speculative discussions centered about four possible candidates for investigation as anti-motion sickness drugs. These examinations are summarized below:

- (1) A tetrahydrocannabinol (THC) derivative - this substance has been used successfully as an anti-emetic for patients undergoing chemotherapy for cancer. It was suggested that this type of drug might be useful to prevent nausea associated with motion sickness.
- (2) A modifier of cyclic adenosine-5'-monophosphate (cAMP) - increasing cAMP level would increase stability of membrane of the nervous system and may inhibit some of the vestibular problems. It was reported that piracetam (synthesized by UCB in Belgium) does modify cAMP and may be effective in preventing motion sickness.
- (3) The imipramine group - these substances potentiate norepinephrine by blocking reuptake. Increasing levels of norepinephrine or decreasing levels of acetylcholine should decrease the symptoms of motion sickness as suggested by the classical hypothesis concerned with the biochemical basis of vestibular disturbance. Imipramines have been tested, but only one dose was given and the results were not encouraging. The suggestion was offered that multiple doses to develop a build-up of the drug may be necessary to prove efficacy. Therefore, the drug might be good as a prelaunch medication in the prophylactic sense.
- (4) Liver extract - injections of this substance have been reported to prevent motion sickness (British study), but no one was able to offer any explanation of the mechanisms involved.

* The discussion leaders for this workshop were Charles D. Wood, D. Bryant Cramer and Michael A. Moskowitz.

The discussants concluded that it was not likely that a new drug would be identified in the next couple of years which would be as efficacious or better than the current scopolamine-dexedrine and promethazine-ephedrine combinations.

Evaluation of Techniques for Assessment of Drug Efficacy

The utilization of drugs permits three basic ways for combating the motion sickness problem. The one approach is to use the drug as a prophylactic method, either orally or transdermally, to prevent the problem. Another approach is to block motion sickness after achieving a certain symptom level. A third approach is a therapeutic one, applying the drug after the subject is sick to bring him back to a functional level.

Therapeutic failures were discussed in terms of implementing a relatively new technique of monitoring drug absorption via parotid gland saliva. That is, the failures may be due to malabsorption in which the drug is either absorbed too slowly or is metabolized through the liver very quickly. Studies are in progress to sample blood and parotid saliva hourly (up to 12 hrs.) after oral administration of promethazine or scopolamine and after intramuscular injection of promethazine. The objective is to correlate drug concentration to increasing effectiveness in a provocative test (such as the rotating chair) and obtain an indication of whether or not the subject should have a higher concentration of that drug. A suggestion was made to use this technique to compare bioavailability curves of susceptible crewmen who did and did not respond to medication.

The discussants considered the technique of examining the pattern of autonomic responses to help explain intra- and inter-subject variability on drug effectiveness. Conflicting data were cited as to whether or not patterns of autonomic response could be correlated with either blood level of drugs or motion sickness symptoms. Unsuccessful correlations in animal and human studies as well as successful human biofeedback studies were reported. The issue remained unresolved.

A molecular approach to the motion sickness condition was discussed in terms of enhancement of present drugs using pharmacological techniques. The proposition was initiated with an attempt to develop a parallelism between Parkinson's disease and motion sickness. That is, both conditions appear to involve a disturbance between the relationship or balance between two neurotransmitters - dopamine and acetylcholine for Parkinson's disease and norepinephrine and acetylcholine for motion sickness. A variety of drugs are available to amplify a deficiency of norepinephrine. The strategies encompass blocking reuptake, promoting release, and preventing degradation of the transmitter in the nerve terminal. One can also measure metabolites of neurotransmitters in animal models to achieve a more precise understanding of vestibular connections in specific areas at the central nervous system. A structure-activity study was suggested to improve information on the molecular interactions of the present anti-motion sickness drugs.

The discussion concluded with the reminder that animal models used for drug efficacy studies should be species that get motion sick so that both efficacy of different drugs in the motion sickness sense and in the vestibular compensation sense can be investigated.

New Approaches/Recommendations for Future Investigations

Anti-motion sickness drugs offer a significant operational flexibility. These substances can be used to prevent motion sickness, to suppress developing symptoms, or to enhance a subject's adaptation. Areas of investigation, suggested by the workshop participants, which should be actively pursued are as follows:

- (1) Drugs should be tailored to the individual. The effectiveness of three types of medication could be examined in eight to ten days spread over a month. After selecting the best drug, a similar time interval would again be required to optimize dosage or frequency of administration for that individual.
- (2) Dosages should be increased to improve the effectiveness of present drugs. The present doses are minimal from a pharmacological standpoint. The individual's performance level should be monitored as dosage is increased to raise the therapeutic effect without reducing functional capacity.
- (3) Drug facilitated adaptation permits adaptation at a faster rate than achievable without the drug. This is not the same effect as merely taking the drug which leads to symptomatic depression and allows the individual to continue his adaptation schedule. The suggested methodology relates to the state-dependency approach which has been shown to be effective in both animal models and human studies. However, assessing the level of adaptation in this type of investigation is complex. Time must be permitted to allow decay of adaptation so that comparisons can be made for both drug and placebo for the same stimulus magnitude.

APPENDICES

The first four of the following five appendices are comprised of written summaries which were prepared by the various workshop discussion leaders following the completion of the symposium. These summaries represent the discussion leaders' impressions and recommendations and each is presented in an unedited form. The summaries have been re-typed only for the purpose of maintaining consistency of appearance.

VESTIBULAR/SPACE MOTION SICKNESS MECHANISMS

Prepared by: Donald S. Parker and Kenneth E. Money

The mechanisms of space motion sickness were discussed in terms of the sensory conflict theory and the fluid shift theory. A significant majority of the workshop participants apparently agreed with the following views: (a) in spite of limitations, the sensory conflict theory provides the best framework within which space motion sickness phenomena can be comprehended and predicted, and (b) the fluid shift theory of space motion sickness has not been supported by research and observation and probably little is to be gained by further pursuit of research on this theory.

APPENDIX I

WORKSHOP ON VESTIBULAR/MOTION SICKNESS MECHANISMS

The sensory conflict theory as modified by Reason and Brand (1) is called the "sensory rearrangement theory" and it states that motion sickness results from a conflict between expected and actually received information concerning spatial orientation or motion. If the conflict involves the vestibular receptors, a central mechanism ("computer") is thought to compare the pattern of sensory input being experienced with the pattern expected on the basis of past experience; any resulting mismatch signal causes motion sickness. Motion sickness is held to be due to faulty sensory rearrangement phenomena, according to this theory.

Olson presented a control systems analysis re-statement of the sensory conflict theory during the preinitial countermeasures workshop and suggested that, if the "internal model" activities could be determined, his formulation would allow more specific predictions than would the information flow block diagram theories of Reason and Brand or Money. Olson did not, however, have time to present possible techniques for uniquely determining the appropriate values for the internal model matrices.

During the general discussion, the apparently unique role of the vestibular receptors in motion sickness was discussed. Trillman's (2) arguments concerning the evolution of motion sickness appear to offer the best available explanation for this unique role of the vestibular receptors. In contrast to Graybiel's bilaterally labyrinthine defective subjects, from whom motion sickness cannot be elicited, Black noted that the ability to exhibit motion sickness persists in persons who undergo unilateral labyrinthectomy in adulthood.

On the basis of the sensory conflict theory, Money presented 12 suggestions for spacecraft design, training procedures and in-flight activities. Adoption of these suggestions should reduce incidence and severity of motion sickness. Money's suggestions were as follows:

1. Make angular head movements slowly; make linear rotations short and sharp.
2. If in danger of vomiting, move as little as possible and keep the eyes closed as much as possible.

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Sensory Conflict Theory

The sensory conflict theory of motion sickness was summarized by Money. This theory as modified by Reason and Brand (1) is called the "Sensory rearrangement theory" and it states that motion sickness results from a conflict between expected and actually received information concerning spatial orientation or motion, if the conflict involves the vestibular receptors. A central mechanism ("comparator") is thought to compare the pattern of sensory input being experienced with the pattern expected on the basis of past experience; any resulting mismatch signal causes motion sickness. Motion sickness is held to be one of many sensory rearrangement phenomena, according to this theory.

Oman presented a control systems analysis restatement of the sensory conflict theory during the training countermeasures workshop and suggested that, if the "internal model" matrices could be determined, his formulation would allow more specific predictions than would the information flow block diagram theories of Reason and Brand or Money. Oman did not, however, have time to present possible techniques for uniquely determining the appropriate values for the internal model matrices.

During the general discussion, the apparently unique role of the vestibular receptors in motion sickness was discussed. Treisman's (2) arguments concerning the evolution of motion sickness appear to offer the best available explanation for this unique role of the vestibular receptors. In contrast to Graybiel's bilaterally labyrinthine defective subjects, from whom motion sickness cannot be elicited, Black noted that the ability to exhibit motion sickness persists in persons who undergo unilateral labyrinthectomy in adulthood.

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