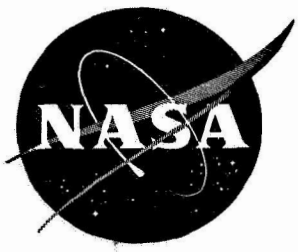
JSC-09275

NASA TECHNICAL MEMORANDUM

NASA TM X-58154
November 1974

16
19



THE PROCEEDING OF THE SKYLAB LIFE SCIENCES SYMPOSIUM

AUGUST 27 - 29, 1974
LYNDON B. JOHNSON SPACE CENTER

VOLUME II

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

LYNDON B. JOHNSON SPACE CENTER

HOUSTON, TEXAS 77058

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
TM X-58154		

4. Title and Subtitle	5. Report Date
The Proceedings of the Skylab Life Sciences Symposium, August 27-29, 1974 Volume II	November 1974
	6. Performing Organization Code

7. Author(s)	8. Performing Organization Report No.
Richard S. Johnston, Lawrence F. Dietlein } Coordinators	JSC-09275
9. Performing Organization Name and Address	10. Work Unit No.
Lyndon B. Johnson Space Center Houston, Texas 77058	951-17-00-00-72
	11. Contract or Grant No.
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address	Technical Memorandum
National Aeronautics and Space Administration Washington, D.C. 20546	14. Sponsoring Agency Code

15. Supplementary Notes

16. Abstract

This document contains the proceedings of the Skylab Life Sciences Symposium held at the Lyndon B. Johnson Space Center 27-29 August 1974. The three manned Skylab missions resulted in biomedical experiment data in the areas of neurophysiology, musculoskeletal physiology, biochemistry, hematology, cytology, cardiovascular and respiratory metabolic functions: as well as detailed test objectives involving crew health and environment procedures. Major emphasis was placed on results from the last mission, Skylab 4, which covered 84 days of in-flight data collection. Many new norms were defined for "normal" man living and operating in a unique environment. While man is quite adaptable to this unique environment, many of the changes observed in Skylab require additional research for future flights lasting very long periods of time such as a Mars mission requiring 18 months.

17. Key Words (Suggested by Author(s))		18. Distribution Statement
• Cardiovascular System • Skylab Program • Hematology • Immunology • Vestibular Tests • Metabolism • Cytology	• Clinical Medicine • Musculoskeletal System • Biomedical Data • Neurophysiology • Biochemistry • Respiratory • Exercise Physiology • Human Performance	STAR Subject Category: 04.

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price*
Unclassified	Unclassified	452	$11.50

*For sale by the National Technical Information Service, Springfield, Virginia 22151

TM X-58154

THE PROCEEDINGS

OF THE

SKYLAB LIFE SCIENCES SYMPOSIUM

AUGUST 27-29, 1974

VOLUME II

National Aeronautics and Space Administration

JOHNSON SPACE CENTER

November 1974

NOTICE

EDITORIAL COMMENTS

This document was prepared by the Life Sciences Editorial Board. The Board consisted of Richard S. Johnston and Lawrence F. Dietlein, M. D., Senior Editors, Sylvia A. Rose, Executive Editor for Publications, and Stanley Jacobsen, Editor for Program Graphics. Other members of the Board were: George G. Armstrong, Jr., M.D., Willard R. Hawkins, M.D., Wayland E. Hull, Ph.D., Joseph P. Kerwin, M.D., Edward L. Michel, M.A., William H. Shumate, Ph.D., and John C. Stonesifer.

Board Of Reviewers

Peer review of papers submitted for presentation at the Symposium was done by panels comprising the Board of Reviewers. Members of the Board of Reviewers were: George G. Armstrong, M.D.; J. Vernon Bailey, M. A.; S. A. Bergman, Ph.D., M.D.; Lawrence F. Dietlein, Ph.D., M.D., James K. Ferguson, Ph.D.; William J. Frome, D.D.S.; Owen K. Garriott, Ph.D.; George W. Hoffler, M.D.; Rudolph A. Hoffman, D.V.M.; Jerry L. Homick, Ph.D.; Wayland E. Hull, Ph.D.; Robert L. Johnson, M.D.; Joseph P. Kerwin, M.D.; Stephen L. Kimzey, Ph.D.; Charles K. LaPinta, M.D.; Carolyn S. Leach, Ph.D.; Edward L. Michel, M.A.; F. Story Musgrave, Ph.D., M.D.; Arnauld E. Nicogossian, M.D.; Sam L. Pool, M.D.; Wayland J. Rippstein, Jr., M. A.; John A. Rummel, Ph.D.; Charles F. Sawin, Ph.D.; William H. Shumate, Ph.D.; Malcolm C. Smith, D.V.M.; Gerald R. Taylor, Ph.D.; William E. Thornton, M.D.; James M. Waligora, M.A.; Harry O. Wheeler, Ph.D.; Michael M. Whittle, M.D.; John F. Zieglschmid, M.D.

Copy Preparation under contract no. NAS 9-13655 with The Boeing Company;
Sylvia A. Rose, Senior Technical Writer/Editor, and
Joanne Bell, Sue Farrow and Sarah Irwin for manuscript preparation.

Graphics by The Boeing Company Audiovisual Department.

INTRODUCTION

The bound copy of *The Proceedings* appears in two volumes. The papers received for reproduction have been grouped into three major sections: Symposium Introduction, Detailed Test Objectives and Medical Experiments, and Symposium Summary. The Detailed Test Objectives and Medical Experiments have been further divided into five subsections: Detailed Test Objectives, Neurophysiology, and Musculoskeletal Changes comprise Volume I; Biochemistry, Hematology and Cytology, Cardiovascular and Metabolic Function, and Symposium Summary comprise Volume II. The papers appear according to the order of presentation at the Symposium, but there are minor variances between contents of *The Proceedings* and the presentation due to the constraint of time imposed by the length of the program. Two papers included in *The Proceedings* were "read by title only" at the Symposium because of late submittal, *i.e.*, Red Blood Metabolism and Determination of Cardiac Size from Chest Roentgenograms Following Skylab Missions. Another paper, Immunity (M112), also "read by title only" has not, as yet, been submitted.

A complete Table of Contents and Index of Authors/Panelists for both volumes are included in each volume for ease of reference. Every attempt has been made to minimize the size of *The Proceedings* and to facilitate reference of an author or his/her paper.

Sylvia A. Rose

November, 1974.

FOREWORD

Good morning ladies and gentlemen; I would like to welcome you to the Skylab Life Sciences Symposium. For the next three days we will present the results of an exhaustive series of medical studies conducted on missions of 28, 54 and 84 days.

Before we move into the business at hand, I might take a few minutes to set the stage for our later presentations.

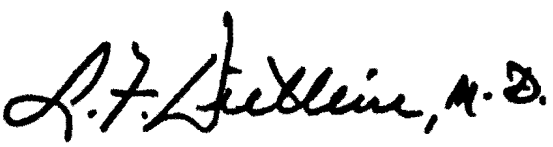
In the history of man's first small steps toward ultimate flight to the planets and to distant stars, some notable milestones have been achieved. As we have moved along, step by step, the impact of our accomplishements has swung from one discipline to another. The successful launch of Alan Shepard into suborbital flight in 1961 was a tremendous boost for rocket specialists. It was, in fact, possible for U.S. rockets to launch a manned spacecraft. In the mid-1960s, the Gemini rendezvous and docking successes were particularly rewarding for guidance engineers and those concerned with space mechanics. In Apollo, the materials brought back from the lunar surface had a special impact for the physical scientist. Now we come to Skylab, and the focus of attention moves to the life scientist. Skylab was, in many respects, our flight. The reams of data returned from these missions provide our first real picture of how man lives in space. We already knew, of course, that man could *exist* in space and that he could *work* in space. Well before Skylab we solved or understood the principal problems of life support, of food service, and of waste management. But it was not until Skylab that we learned that man could truly *live* in space.

I am happy to report that no major medical finding will be presented which might curtail man's dreams of more extensive space exploration, rather we have found that man can adapt to the new and wonderous environment of space.

Many individuals have made a personal commitment to the success of Skylab and previous manned spaceflights, unfortunately all of these people will not be able to take part in these presentations. All of

us with NASA appreciate the outstanding contributions of these individuals from other nations, the aerospace industry, universites, medical schools and other departments of government in making the space program one which we can all look to with pride. It is truely our honor to open this symposium and to have been a part of the Skylab medical team.

Director of Life Sciences



Deputy Director of Life Sciences

Lyndon B. Johnson Space Center

VOLUME I

Table of Contents

Title Page

SYMPOSIUM INTRODUCTION

NEUROPHYSIOLOGY

Table of Contents (concluded)

MUSCULOSKELETAL FUNCTION

VOLUME II

Table of Contents

Table of Contents (concluded)

BIOCHEMISTRY, HEMATOLOGY AND CYTOLOGY

BIOCHEMICAL RESPONSES OF THE SKYLAB CREWMEN

*Principal Investigator: Carolyn S. Leach, Ph. D.**
*Principal Coordinating Scientist: Paul C. Rambaut, Sc. D.**

ABSTRACT

The biochemical investigations of the Skylab crewmen were designed to study the physiological changes that were observed on flight crews returning from previous space flight missions as well as to study those changes expected to result from prolonged weightless exposure. These studies can be divided into two broad categories. One category included routine blood studies similar to those used in clinical medical practice. The second included research-type endocrine analyses used to investigate more thoroughly the metabolic/endocrine responses to the space flight environment. The premission control values indicated that all Skylab crewmen were healthy and were free from biochemical abnormalities. The routine results during and after flight showed slight but significant changes in electrolytes, glucose, total protein, osmolality, uric acid, cholesterol, and creatinine. Plasma hormal changes included adrenocorticotrophic hormone, cortisol, angiotensin I, aldosterone, insulin, and thyroxine. The 24-hour urine analyses results revealed increased excretion of cortisol, catecholamines, antidiuretic hormone, and aldosterone as well as excretion of significant electrolyte and uric acid during the Skylab flights.

The measured changes are consistent with the hypotheses that a relative increase in thoracic blood volume upon transition to the zero-gravity environment is interpreted as a true intravascular volume expansion resulting in a fluid and electrolyte loss. These losses, in association with other factors, ultimately results in a reduced intravascular volume leading to increased renin and secondary aldosteronism. Once these compensatory mechanisms are effective in reestablishing fluid balance, the crewmen are essentially adapted to the null-gravity environment. Although the physiological cost of this adaptation is reflected by the electrolyte deficit and perhaps by other factors, it is assumed that the compensated state is adequate for the demands of the environment; however, this new homeostatic set is not believed to be without physiological cost and, without proper precautions, could reduce the functional reserves of the crewmembers. The general catabolic state found in returning space flight crewmen has been documented with negative calcium, phosphorus, sodium, potassium, and nitrogen balances. Future research efforts will be directed toward the clarification of

*National Aeronautics and Space Administration - Lyndon B. Johnson Space Center, Houston, Texas 77058

the basis for these physiological changes and the procedures required to prevent or lessen these changes on extended space missions.

INTRODUCTION

The ability of man to adapt to new environments has intrigued the physiologist for many years. Underlying this basic adaptability, modern investigators have discerned the action of complex homeostatic control mechanisms. These mechanisms, both neural and hormonal manifest themselves by a resistence to change in the internal milieu of the organism (1, 2). Provided that the imposed stresses are not overwhelming, only slight changes in this internal milieu can be expected. Space flight incorporates unique environmental factors to which the organism has not previously been subjected in the course of its phylogenetic development. To measure the ability of the crewmembers to adjust to this environment, an extensive biochemical investigation was conducted on all three Skylab missions.

METHODS

Continuous metabolic monitoring of the Skylab crewmen began at least 21 days prior to each flight and continued throughout each flight and for at least 17 days after return. Urine was collected on a void-by-void basis before and after flight while the in-flight collections were performed with an automatic urine collection device. An aliquot of each day's in-flight urine was frozen in orbit, stored, and returned to our laboratory for analysis postflight. Table I shows the duration of metabolic monitoring for each mission. The nominal preflight control period of 21 days was extended on Skylab 2 and 4 due to the delays in launch dates. The nominal postflight period of 18 days was shortened by one day on Skylab 2. Following an overnight fast, blood samples were drawn at approximately 7 a.m. c.s.t./d.s.t. according to the schedule shown in table II. Sodium ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant. The more routine clinical biochemical tests were those generally used in laboratory medicine. Radioassay, fluorometric and gas chromatographic techniques were used for most hormonal analyses.

Radionuclide body compartment studies were conducted preflight and postflight. These included dilution studies of total body water (tritium), extracellular fluid (^{35}sulphate), plasma volume (^{125}I-protein) and exchangeable potassium (^{42}K and ^{43}K).

The data have been summarized for presentation. Statistical analyses included the covariant analysis and the paired t-Test. The 24-hour urine data have been grouped according to the dietary cycles.

TABLE I. EXPERIMENT SCHEDULE

Skylab Mission	No. of Preflight Days	No. of Flight Days	No. of Postflight Days
2	31	28	17
3	21	59	18
4	27	84	18

TABLE II. SKYLAB BLOOD SAMPLING SCHEDULE

Skylab Mission	Preflight Day	In-Flight Day	Postflight Day
2	31, 21, 14, 7, 1	4, 6, 13, 27	0, 1, 4, 13
3	21, 14, 7, 1	3, 6, 14, 20, 30, 38, 48, 58	0, 1, 3, 14
4	35, 21, 14, 1	3, 5, 21, 38, 45, 59, 73, 82	0, 1, 3, 14

Table III lists all serum and plasma analyses accomplished on the Skylab crewmen. Analyses conducted on the in-flight samples by micronanalytical techniques are noted. Table IV lists the analyses accomplished on the 24 hour urine samples.

RESULTS

A comparison of each crewman's premission values with values obtained during and after the flight reveals a variety of changes. Tables V, VI, VII and VIII show the results of the plasma and serum biochemical measurements. The in-flight and postflight values are compared with the mean of the preflight values. Those values statistically different from each crewman's own control values are indicated as ($P \leq 0.05$). Elevations in calcium and phosphorus were present throughout the three missions and remained higher than control for several days following flight. Cortisol and Angiotensin I were generally elevated though not

TABLE III. PLASMA AND SERUM BIOCHEMICAL ANALYSES

Substance/Property	Quantitatively Determined
Sodium*	Uric acid
Potassium*	Creatinine*
Calcium*	Total Protein
Magnesium	Alkaline phosphatase
Chloride*	Serum glutamic oxaloacetic transaminase (aspartate aminotransferase)
Phosphorus*	Creatine phosphokinase
Osmolality*	Lactic dehydrogenase
Carbon dioxide	Glucose*
Cholesterol	Total bilirubin
Triglycerides	Growth hormone
Adrenocorticotrophic hormone*	Thyroxine
Cortisol*	Thyroid stimulating hormone
Angiotensin I*	Testosterone
Aldosterone*	Parathormone*
Insulin*	Calcitonin
Blood urea nitrogen	Vitamin D

*Determined during flight

TABLE IV. 24-HOUR URINE BIOCHEMICAL ANALYSES

Substance/Property	Quantitatively Determined
Volume	Antidiuretic hormone
Sodium	Aldosterone
Potassium	Cortisol
Cloride	Epinephrine
Osmolality	Norepinephrine
Calcium	Total 17-Hydroxycorticosteroids
Phosphate-(PO_4)	Total 17-Ketosteroids
Magnesium	Uric Acid
Creatinine	

TABLE V. SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS, (9 Crewmen)

(Mean ± Standard Error)

No.		Sodium* meq/liter	Potassium meq/liter	Chloride meq/liter	Creatinine mg pct	Glucose mg pct	Osmolality mOsmoles	Calcium mg pct	Phosphate mg pct
36	Preflight	141±0.7	4.12±0.04	97.7±0.5	1.26±0.03	86.6±0.03	290±0.8	9.7±0.05	3.4±0.1
	Mission Day								
9	3, 4	139±2	4.26±0.08	96.8±0.7	1.31±0.03	90.3±2.4	289±1	10.4±0.1†	3.7±0.3
8	5, 6	137±2†	4.30±0.14	96.9±0.8	1.27±0.03	86.7±1.8	287±1†	10.2±0.1†	3.6±0.3†
6	13, 14	137±1	4.41±0.15	94.7±1.1†	1.28±0.03	86.7±1.8	286±2	10.2±0.1†	3.9±0.3†
6	20, 21	140±1	4.25±0.11	95.7±0.8	1.35±0.03	87.0±1.8	289±2	10.1±0.2†	3.4±0.1†
6	27, 30	138±0.8†	4.25±0.10	95.2±0.8†	1.27±0.03	84.3±2.3	287±2†	10.4±0.1†	3.9±0.3†
6	38	136±2†	4.05±0.15†	93.5±1.2	1.31±0.07	80.1±2.5†	280±4†	10.1±0.2	3.1±0.5†
6	45, 48	137±2†	4.30±0.13	94.5±0.7	1.34±0.03	84.4±1.4†	287±3	10.1±0.1†	3.8±0.1†
6	58, 59	137±2†	4.19±0.13	94.0±1.5	1.38±0.12	81.8±2.2†	286±4	10.1±0.2†	3.8±0.2†
3	73	139±2	3.75±0.20	94.6±1.2	1.51±0.05	80.9±2.2	284±2	10.1±0.3	3.9±0.2†
3	82	137±0.6	4.19±0.06	95.8±0.2	1.54±0.03	81.0±1.2†	285±2†	10.1±0.1	3.6±0.1
	Recovery (R)								
9	R+0	139±1	4.18±0.05	96.2±1.0†	1.28±0.05	100.5±2.6†	289±1	10.0±0.1†	3.9±0.2†
9	R+1	139±1	4.10±0.08	96.4±1.0†	1.31±0.06	92.3±2.8	289±1	10.1±0.1†	3.6±0.03†
9	R+3, 4	139±1	4.02±0.13	96.9±1.0	1.26±0.06	90.5±1.4†	294±2†	9.8±0.1	3.4±0.2
6	R+14	141±0.8	4.05±0.05	97.7±1.6	1.33±0.09	85.4±0.7	289±2	9.4±0.1†	2.8±0.2

* Corrected for Na-EDTA

† $P \leq 0.05$

TABLE VI. SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS (9 Crewmen)

(Mean ± Standard Error)

NO.		CORTISOL	ANGIOTENSIN I	ALDOSTERONE	ACTH	INSULIN	HGH	PTH
		µg/100 ml	ng/ml per hour	pg/100 ml	pg/ml	µU/ml	ng/ml	ng/ml
39	Preflight	12.2±0.7	0.77±0.14	180±25	35.7± 3.3	17±0.6	1.3±0.2	17±1
	Mission Day							
9	3, 4	12.7±1.6	1.09±0.24	176±58	15.2± 4.9*	15±2	2.1±0.5*	17±2
8	5, 6	14.8±1.0*	1.75±0.42	163±75	26.5± 9.2	18±6	1.2±0.3	16±3
6	13, 14	13.4±1.7	.91±0.28	252±65	33.0± 8	18±3	1.5±0.2	14±1
6	20, 21	12.3±1.5	.52±0.12	163±90	11.9± 4*	8±1*	1.2±0.3	20±4
6	27, 30	13.6±2.1	.45±0.16	204±88	32.0± 7	20±3	3.2±2.0	14±2
6	38	13.7±1.0	.72±0.36	94±17	17.7±11.6	10±1*	1.1±0.3	15±2
6	45, 48	14.3±1.3	.37±0.10	118±7	12.1± 5.3*	9±2*	1.5±0.5	18±4
6	58, 59	13.5±0.7*	1.11±0.51*	148±31	32.3±18.7	9±2*	1.6±0.4	18±3
3	73	14.5±3.4	.27±0.08	117±39	6.5± 6.6*		0.6±0.1	24±2
3	82	16.1±0.6*	.32±0.04	142±17	8.7± 5.2		0.7±0.1	25±2
	Recovery (R)							
9	R+0	13.2±2.1	.71±0.23	215±74	23.8± 6.3	20±3	2.9±0.6*	17±2
9	R+1	10.8±1.0	2.15±0.55*	478±77*	24.0± 7.5*	20±2	2.8±0.8*	19±3
9	R+3, 4	13.7±3.0	.86±0.45	357±65*	23.3± 2.4*	18±2	2.6±0.8*	19±3
9	R+13, 14	10.6±0.7	.14±0.05*	153±35	38.2±13.9	17±3	1.2±0.2	18±4

* $p \leq 0.05$ Key: TV = Total volume
ACTH = Adrenocorticotrophic hormone
HGH = Human growth hormone
PTH = Parathormone

TABLE VII. SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS, (9 Crewmen)

(Mean ± Standard Error)

No.		CHOLESTEROL	SGOT	BUN	URIC ACID	ALK PHOS	MAGNESIUM	BILI T	CPK
		mg pct	mU/ml	mg pct	mg pct	IU	mg pct	mg pct	IU
36	Preflight	205±7	13±0.5	19±0.5	6.4±0.2	24±1	2.1±0.02	0.6±0.02	66±7
	Recovery (R)								
9	R+0	192±25*	12±1	19±1	5.5±0.3*	21±1	2.0±0.03*	0.5±0.1	68±8
9	R+1	178±23*	13±0.3	19±1	6.0±0.3*	21±1	2.0±0.03*	0.8±0.2	85±11
9	R+3, 4	188±14*	13±1	17±1*	6.0±0.3*	20±1	2.0±0.03	0.5±0.1	86±12
9	R+14	204±14	14±0.7	17±1*	6.5±0.3	25±2	2.1±0.03	0.4±0.1	47±7

* $p \leq 0.05$

Key:

SGOT = Serum glutamic oxaloacetic transaminase
BUN = Blood urea nitrogen
ALK Phos - Alkaline phosphatase
BILI T = Bilirubin (total)
CPK - Creatinine phosphokinase

TABLE VIII. SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS (9 Crewmen)

(Mean ± Standard Error)

NO.		LDH	TRIGLY	CARBON DIOXIDE	ALBUMIN	PROTEIN	T_3 TEST	THYROXINE	TSH	VITAMIN D
		mU/ml	mg pct	meq/liter	gm pct	gm pct	pct UPTAKE	µg pct	µU/ml	ng/ml
36	Preflight	200±6	86±5	22±0.7	4.4±0.07	6.8±0.05	32.9±0.4	7.0±0.3	4.5±0.6	43.3± 3.7
9	R+0	181±10	97±15	24±1*	4.5±0.1	7.2±0.1*	33.1±1.3	8.7±0.5*	8.4±2.3	39.6±10.9
9	R+1	167±7	111±23	25±0.5*	4.3±0.1	7.0±0.07*	29.4±3.3	9.0±1.0*	7.5±1.5	43.9± 7.7
9	R+3, 4	231±14*	95±13	26±1*	4.1±0.2*	6.6±0.07	34.2±0.7	8.1±0.8	8.2±1.3*	42.8± 6.6
9	R+14	194±12*	84±6	26±0.5	4.1±0.1*	6.4±0.07	33.4±0.5	6.3±0.3	8.1±0.9*	44.6± 8.8

* $p \leq 0.05$

KEY:

LDH - Lactic dehydrogenase
TRIGLY - Triglycerides
TSH = Thyroid stimulating hormone
T_3 = Triiodothyronine
R+ = Recovery

always significantly. Potassium and creatinine tended to increase in-flight and remain high in the sample obtained immediately after recovery. Plasma aldosterone levels varied in-flight but were significantly increased postflight. Other parameters, not measured in the samples obtained in-flight, were found to be increased postflight. These include total protein, carbon dioxide, thyroid stimulating hormone and thyroxine.

Those plasma measurements which were less than preflight control in-flight and postflight include sodium, chloride, osmolality, and ACTH. Glucose, insulin and aldosterone were decreased in-flight but increased postflight. Other measurements showing decreases postflight which were not measured in-flight included cholesterol, uric acid, magnesium, lactic dehydrogenase, and total bilirubin. Blood urea nitrogen and albumin were not changed at recovery but were decreased the third and fourteenth day.

Those constituents of the 24-hour urine sample which were elevated in-flight and postflight are shown in table IX. All of the electrolytes were increased in-flight along with aldosterone, cortisol and total 17-ketosteroids. Postflight increases were seen in epinephrine, norepinepherine, aldosterone, and cortisol. The data also show trends toward in-flight decreases in antidiuretic hormone (ADH), epinephrine, norepinephrine and uric acid. Postflight significant decreases in sodium, potassium, chloride, osmolality, PO_4, magnesium, and uric acid, ADH and total 17 hydroxycorticosteroids were observed.

DISCUSSION

The environment of space flight with its combination of stresses offers unique challenge to biochemical control mechanisms. That homeostasis has been maintained despite these stresses cannot be taken as evidence of the benign nature of the space environment. Men returning from previous space flights have undergone changes of sufficient magnitude and complexity to warrant detailed study of most endocrinologic and metabolic changes during and after flight. In view of these considerations, this experiment was designed to investigate particular homeostatic response in the areas of (1) fluid and electrolyte balance, (2) regulation of calcium metabolism, (3) adrenal function, and (4) carbohydrate, fat and protein utilization.

Fluid and Electrolyte Balance

It has been consistently demonstrated that exposure to weightlessness produces changes in the distribution of total blood volume (3). It is thought that this redistribution simulates a relative volume expansion

TABLE IX. SKYLAB SUMMARY, URINE BIOCHEMICAL RESULTS (9 Crewmen)

(Mean ± Standard Error)

UNITS		PREFLIGHT DAYS	IN-FLIGHT DAYS			POSTFLIGHT DAYS		
			1-28	29-59	60-85	1-6	7-13	14-18
meq/TV	Sodium	160.0± 3.0	174.0± 3.0	190.0± 7.0	199.0± 6.0	121.0±11.0	170.0± 6.0	173.0± 11.0
meq/TV	Potassium	74.0± 1.0	82.0± 2.0	80.0± 2.0	81.0± 3.0	65.0± 4.0	76.0± 4.0	82.0± 5.0
meq/TV	Chloride	148.0± 4.0	162.0± 5.0	177.0± 6.0	180.0± 5.0	116.0±11.0	160.0± 6.0	164.0± 11.0
mg/TV	Creatinine	1955.0±20.0	2079.0±40.0	2104.0±55.0	2081.0±31.0	2005.0±95.0	2037.0±78.0	1969.0±109.0
mOsmoles	Osmolality	650.0±17.0	789.0±27.0	791.0±19.0	717.0±24.0	593.0±60.0	549.0±49.0	584.0± 66.0
meq/TV	Calcium	8.0± 0.2	14.4± 0.8	14.5± 0.8	11.8± 0.4	11.2± 1.6	8.8± 1.0	8.3± 1.0
mg/TV	Phosphates	1045.0±15.0	1270.0±27.0	1196.0±35.0	1181.0±30.0	934.0±55.0	1029.0±55.0	1031.0± 50.0
mg/TV	Uric Acid	969.0±15.0	899.0±22.0	934.0±38.0	884.0±33.0	884.0±41.0	929.0±50.0	942.0± 53.0
meq/TV	Magnesium	8.9± 0.1	10.8± 0.2	9.4± 0.4	8.7± 0.5	7.7± 0.5	9.1± 0.4	9.1± 0.4
µg/TV	Cortisol	54.3± 4.1	94.4± 4.8	83.6± 4.0	90.2± 5.3	69.5± 5.8	63.3± 6.0	76.6± 8.0
µg/TV	Aldosterone	11.3± 1.1	32.8± 2.2	22.4± 1.7	30.0± 3.1	18.6± 4.3	11.8± 3.0	11.4± 3.3
µg/TV	Epinephrine	27.2± 4.6	24.3± 1.4	21.3± 1.7	38.1± 3.3	37.2± 3.1	33.7± 3.4	37.5± 7.2
µg/TV	Norepinephrine	69.4± 6.0	59.9± 2.0	66.7± 4.0	65.2± 6.4	99.4± 6.2	88.8± 6.4	89.6± 6.6
mµ/TV	Antidiruretic hormone	50.3±10.0	41.9± 4.3	24.1± 2.4	20.3± 2.5	46.5±10.0	25.6± 8.0	31.0± 8.2
mg/TV	Total 17 Hydroxycorticosteroids	6.1± 0.4	6.2± 0.4	6.5± 0.3	6.2± 1.0	5.2± 0.5	5.1± 0.4	5.2± 0.8
mg/TV	Total 17 Ketosteroids	7.0± 0.5	10.3± 0.4	10.8± 0.5	13.5± 1.3	7.0± 0.7	7.4± 0.5	7.6± 0.6

and necessitates compensatory changes in water balance with a net loss of water and electrolytes. A negative water balance is evidenced by nearly universal body weight loss in the returning crews and a rapid regain of body weight on the first postmission day. Some of the weight loss is attributable to a loss of adipose tissue resulting from insufficient caloric intake; however, protein, mineral and electrolyte loss are believed to occur at a proportionately higher rate than can be accounted for on the basis of a hypocaloric regimen (4).

Change in body fluid volume is a sensitive index of homeostatic response. During the first six days in-flight all nine crewmen excreted less urine (average 400 milliliters) than preflight and there was an accompanying decrease of water intake of approximately 700 milliliters. These data support a net loss of water during this period. Sweat and insensible losses are not included but would be expected to be higher at the environmental pressures of the spacecraft (5). It is apparent, however, that a water diuresis did not occur since the osmolality of the urine formed was higher than that of plasma. The urine osmolality (for the first 6-day period in-flight) averaged 300 mOsmoles higher than an equal stable preflight period in spite of decreased electrolyte intake during the first period. These data when totally considered suggest that an increased solute excretion did occur during the initial exposure to weightlessness.

Twenty-four hour urine volume results (fig. 1) indicate that, except for the first period in-flight, the crewmen generally excreted volumes similar to the preflight control values for each man.

A similar pattern to that observed for urine volume is exhibited by urinary antidiuretic hormone (fig. 2). Significant increases in urinary antidiuretic hormone occurred early in-flight in all men. Due to inability to refigerate the urine sample obtained on the first day in-flight, it could not be analyzed for this hormone. Tables X and XI show decreases of about 1.7 percent in total body water, and about 1.9 percent in extracellular fluid volume following recovery; however, when the weight losses are taken into consideration, there is actually a proportional increase in body water on a volume per unit weight basis. These data, along with fluid volumes and osmolality results, indicate that except for Skylab 2 (urine antidiuretic hormone) was minimally stimulated.

Plasma sodium was generally decreased throughout the flight and potassium demonstrated trends toward becoming slightly though not significantly elevated. In-flight, the quantity of urinary sodium excreted each twenty-four hours was elevated above the mean of the 24-hour periods preflight for all nine crewmen (fig. 3). Urinary

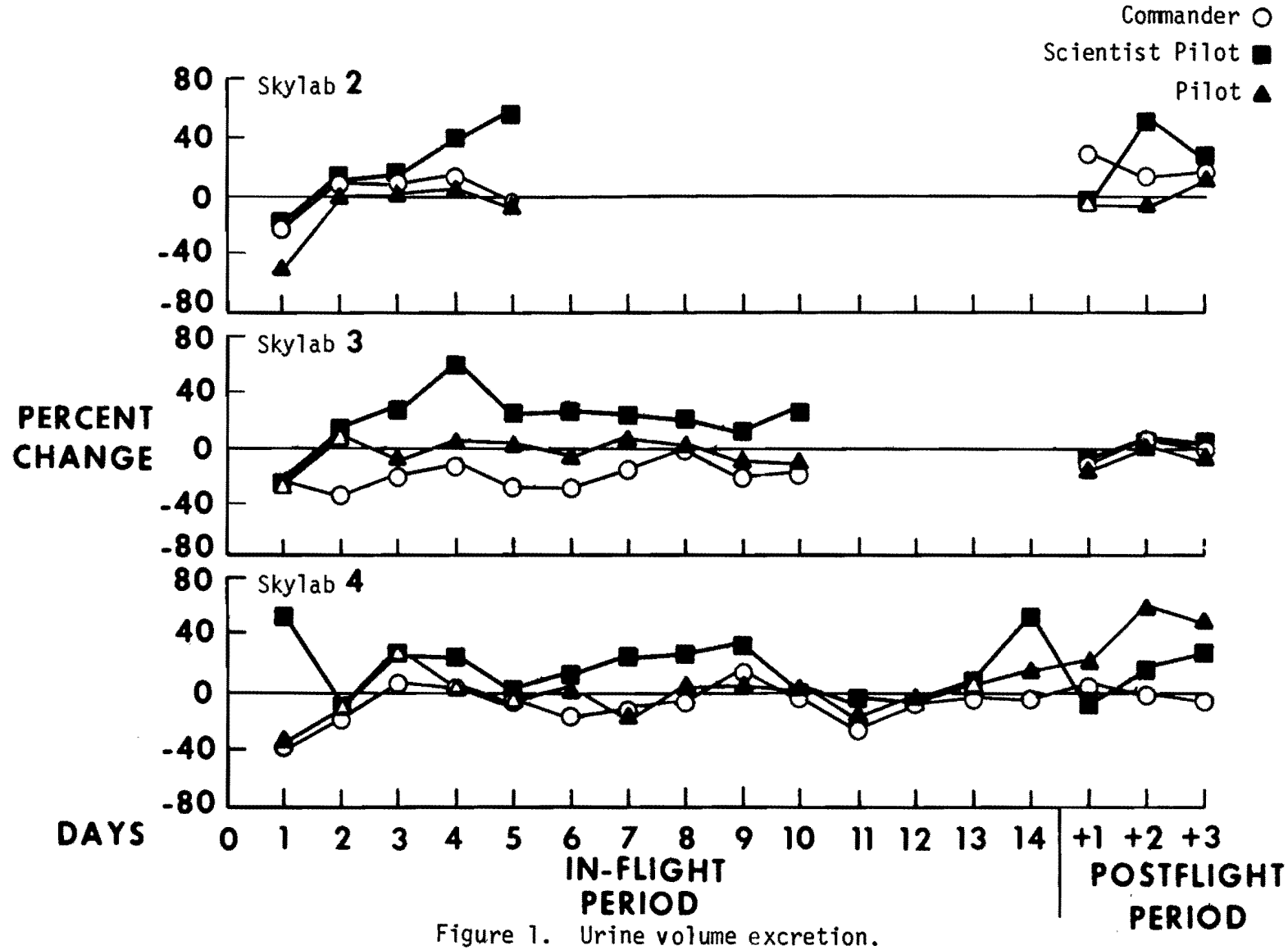


Figure 1. Urine volume excretion.

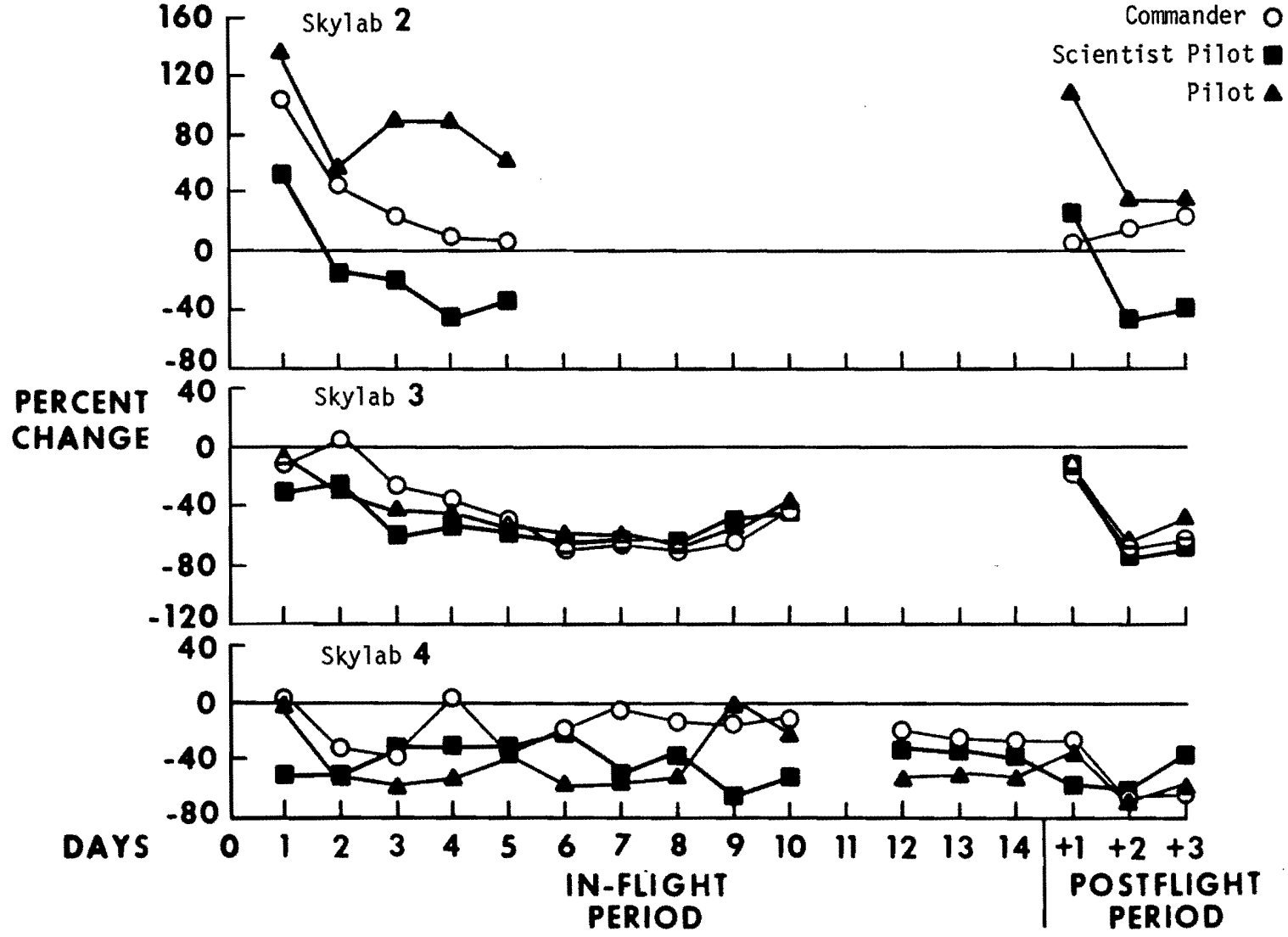


Figure 2. Urinary antidiuretic hormone excretion.

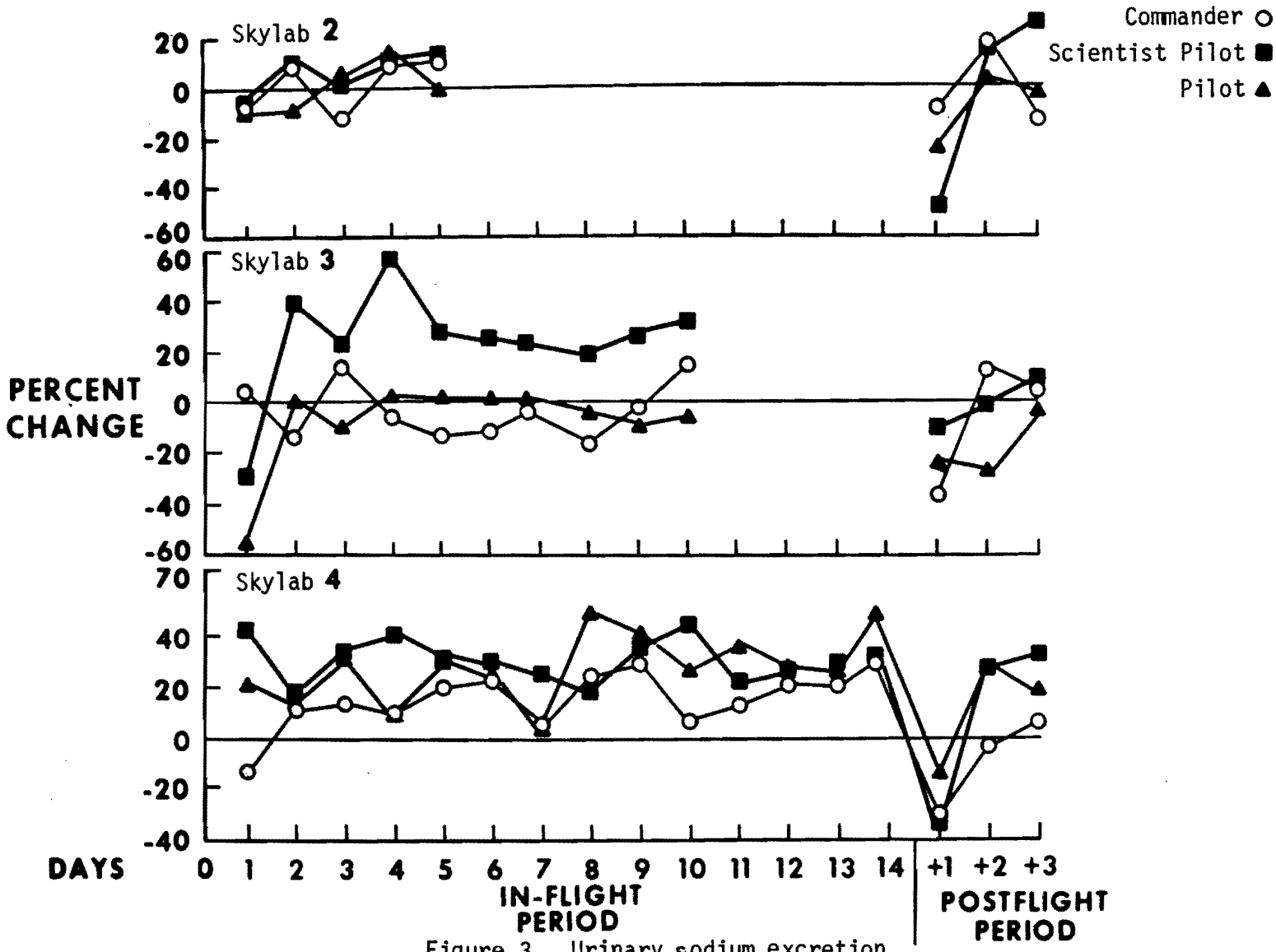


Figure 3. Urinary sodium excretion.

potassium was more variable but, in general, was also elevated (fig. 4). Postflight, both of these electrolytes were significantly decreased in all of the crewmen. The intakes of these two electrolytes were comparable during the three phases of each flight. The loss in potassium was also measured by the decrease in total body exchangeable potassium shown in table XII.

TABLE X. SKYLAB SUMMARY TOTAL BODY WATER

Volume Change (%)

Mission	Commander	Scientist Pilot	Pilot	Mean
2	-2.4	-0.8	-4.4	-2.5
3	-1.4	+1.3	-3.2	-1.1
4	-2.0	-1.1	-1.2	-1.4

TABLE XI. SKYLAB SUMMARY EXTRACELLULAR FLUID

Volume Change (%)

Mission	Commander	Scientist Pilot	Pilot	Mean
2	-1.9	-1.9	+1.3	-0.8
3	-5.6	-10.2	-0.5	-5.4
4	+7.2	-4.5	-1.6	+0.4

TABLE XII. EXCHANGEABLE POTASSIUM

Percent Change (meq)

	Skylab 2	Skylab 3	Skylab 4
Commander	-8.3	-5.6	-3.7
Scientist Pilot	-6.1	-1.1	-8.8
Pilot	-8.8	-3.5	-12.3
Mission Mean	-7.7	-3.4	-8.2

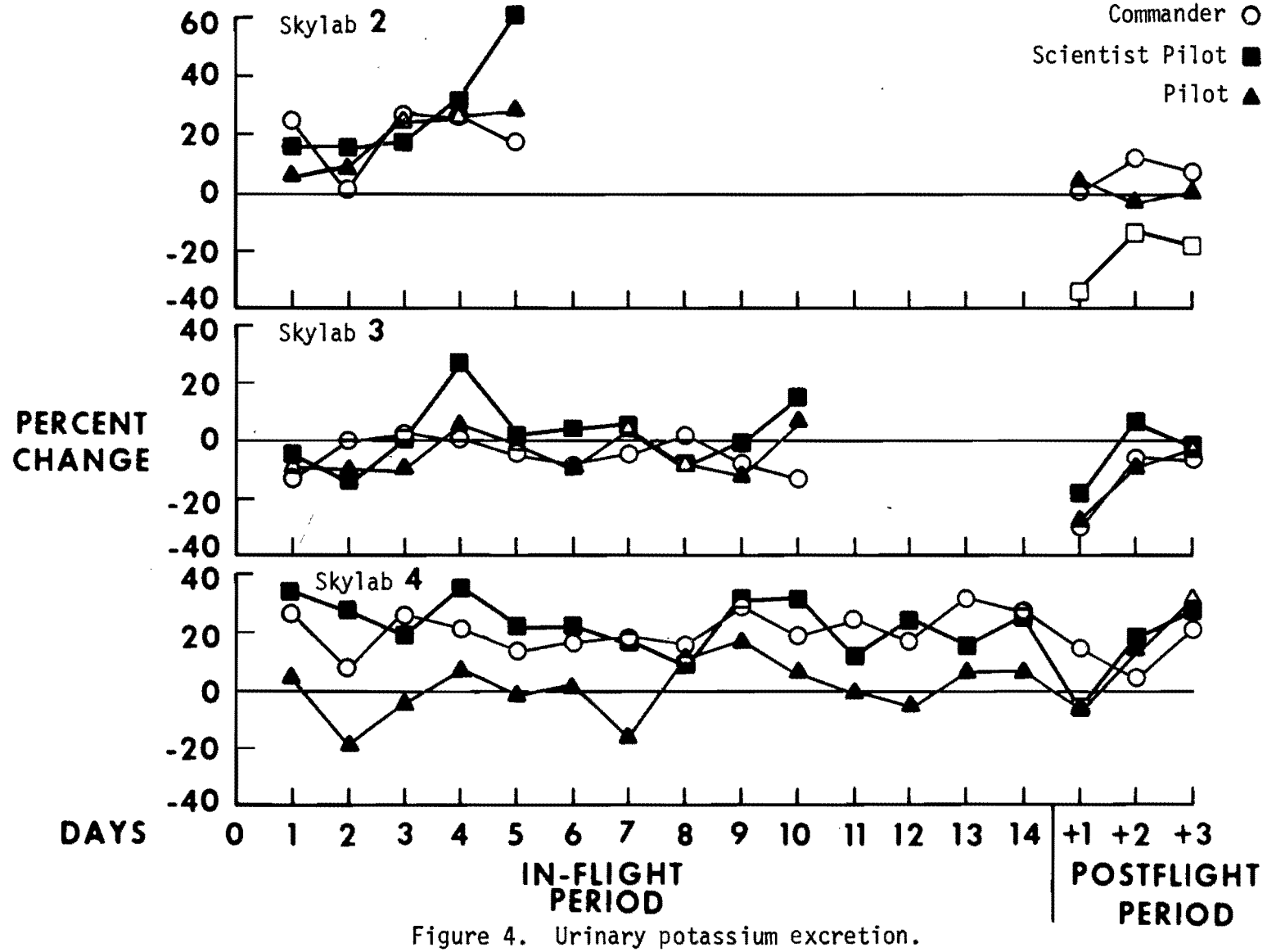


Figure 4. Urinary potassium excretion.

A postflight decrease of as much as 20 percent in total body potassium had previously been shown by measurement of the total body potassium-40 after early Apollo flights. Total body exchangeable potassium, utilizing potassium-42, was measured on the Apollo 15, 16, and 17 crewmen. It was found to be generally decreased postflight even though adequate potassium had been ingested throughout these missions (6). The crewmen of the Gemini 7 mission demonstrated positive potassium balance before and after the flight with a negative balance during the mission.

The Gemini 7 results were accompanied by increased urinary aldosterone excretion (7). During the in-flight phase of the Skylab missions, aldosterone output was increased in all nine crewmen (fig. 5). The aldosterone concentration reached in this period of time could certainly account for the urinary losses of potassium. However, this mechanism is not consistent with the observation that a loss of sodium also occurred. Results of the in-flight metabolic experiment on the thirteen day Apollo 17 mission suggested similar responses by that crew (8). These changes may be explained by functional alterations in the renal tubule proximal to the site of aldosterone action in the distal tubule involving either humoral or physical factors (9, 10). The results of plasma aldosterone measurements on all three missions are shown in relation to preflight baseline values in table XIII. These data, together with changes in plasma renin activity (table XIV) indicate that there was an absolute increase in production of aldosterone. This was probably triggered by increased renin-angiotensin secretion. This elevation could be produced in response to a decrease in effective renal blood flow or in pressure changes in carotid arteries or right heart (11). Increased aldosterone secretion is the probable cause of the potassium loss.

TABLE XIII. PLASMA ALDOSTERONE

	Mean Percent Change				
Skylab 2	+68			+127	-57
Skylab 3	+28	-11		+138	+53
Skylab 4	-62	-44	-2	+ 44	-32
Days					
In-flight	1-28	29-56	57-82		
Postflight				0-4	14

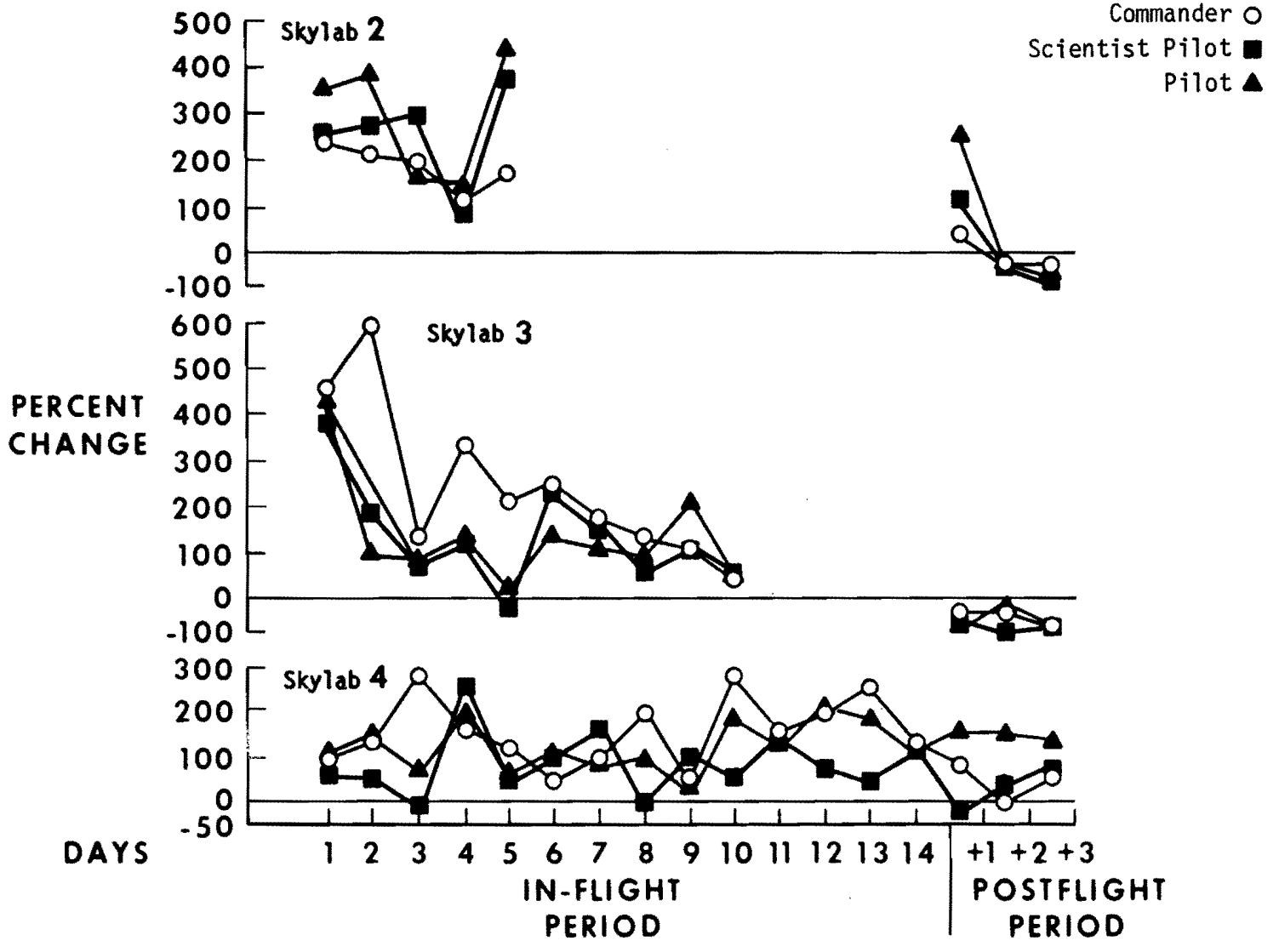


Figure 5. Urinary aldosterone.

TABLE XIV. ANGIOTENSIN I (RENIN ACTIVITY)

	Mean Percent Change				
Skylab 2	+7			-18	-72
Skylab 3	+144	+103		+203	-80
Skylab 4	+203	+30	+25	+56	-61
Days					
In-flight	1-28	29-56	57-82		
Postflight				0-4	14

The decreased blood urea nitrogen values generally found postflight are thought to be indicative of hemodilution and rehydration. The resulting elevations in the rate of urine flow produce a passive increase in urea excretion. The first days' postflight water intake exceeded water intake during equal periods before or during flight. Similar results have been reported from the Soviet space flight of 18 to 24 days during which actual increases in blood urea nitrogen were measured (12). The interpretation of these findings agree with our assumption that the levels of urea nitrogen in blood are a reflection of hydration and renal handling of urea. In Skylab, slight increases were observed in plasma creatinine which are presumably indicative of slight decreases in creatinine clearance. These findings support minor alterations in renal function in-flight, a supposition also advanced by Soviet investigators (12).

The excretion of uric acid was decreased throughout the missions in most of the crewmen. Postflight there were significantly decreased levels of plasma uric acid. These findings confirm earlier Apollo results (13) and are distinctly different from clinical findings where low serum uric acid levels are infrequently observed. In almost all instances such findings are attributed to a failure in the renal mechanism responsible for the return of the metabolite to the systemic circulation.

Regulation of Calcium Metabolism

The threat of bone mineral losses during prolonged weightless exposure has been a constant concern (14). A complete metabolic balance was conducted to ascertain the extent and time course of these losses.

To extend the input/output studies, measurement of plasma levels of 25-hydroxycholecalciferol and hormones implicated in the regulation of calcium were conducted together with plasma calcium and phosphorus. Calcium and phorphorus levels were significantly elevated in the plasma as in the urine throughout the in-flight and early postflight phases. Parathormone levels were more variable in-flight but some were slightly increased with no changes postflight. On the Skylab 4 crewmen, 25-hydroxycholecalciferol was slightly decreased postflight and unchanged in the Skylab 2 and Skylab 3 crewmen. Since calcitonin was below the level of detection for the assay used, it is apparent that no clinically significant increases occurred. In addition to its presence in food, Vitamin D was supplied in supplemental form with a resultant net intake of 400-500 IU/day. These results support the observations of other investigators that the rate of demineralization was slow and is probably attributable to an enhanced resorption possibly mediated by parathyroid hormone.

Adrenal Regulation

The levels of adrenal medullary and adrenal cortical hormones were of particular interest because of changes found in the urinary specimens from the Mercury, Gemini and Apollo flight crews (6, 15). Following these earlier missions, the catecholamines, epinephrine and norepinephrine have been generally increased in the first 24 hours. In addition epinephrine changed to a greater extent than norepinephrine following the entry phase of the missions (16).

In Skylab urinary epinephrine (fig. 6) was generally normal to decreased in-flight and elevated postflight. Norepinephrine (fig. 7) was more variable but did show periods of increase during the flight and significant increases postflight. Adrenal medullary activity is increased by a variety of physical and psychological stimuli. It is well established that epinephrine is most often associated with anxiety responses whereas norepinephrine is more closely related to physical stress (17). Since a primary role of the autonomic nervous system is to maintain adquate blood pressure and flow under conditions of altered gravitational stresses, modification in adrenal medullary activity might be anticipated. The in-flight norepinephrine levels are probably the reflection of the high levels of physical exercise undertaken by each crewman during the flight. Collaborative data from this laboratory suggests that exercise in bedrest is effective in preventing decreases in norepinephrine excretion observed in non-exercised subjects (18).

After the Apollo flights, the plasma cortisol values were below preflight values. However, the pooled urine sample collected during the first 24 hours after recovery did show the anticipated increase in cortisol exretion (6). The cortisol levels were not accompanied by

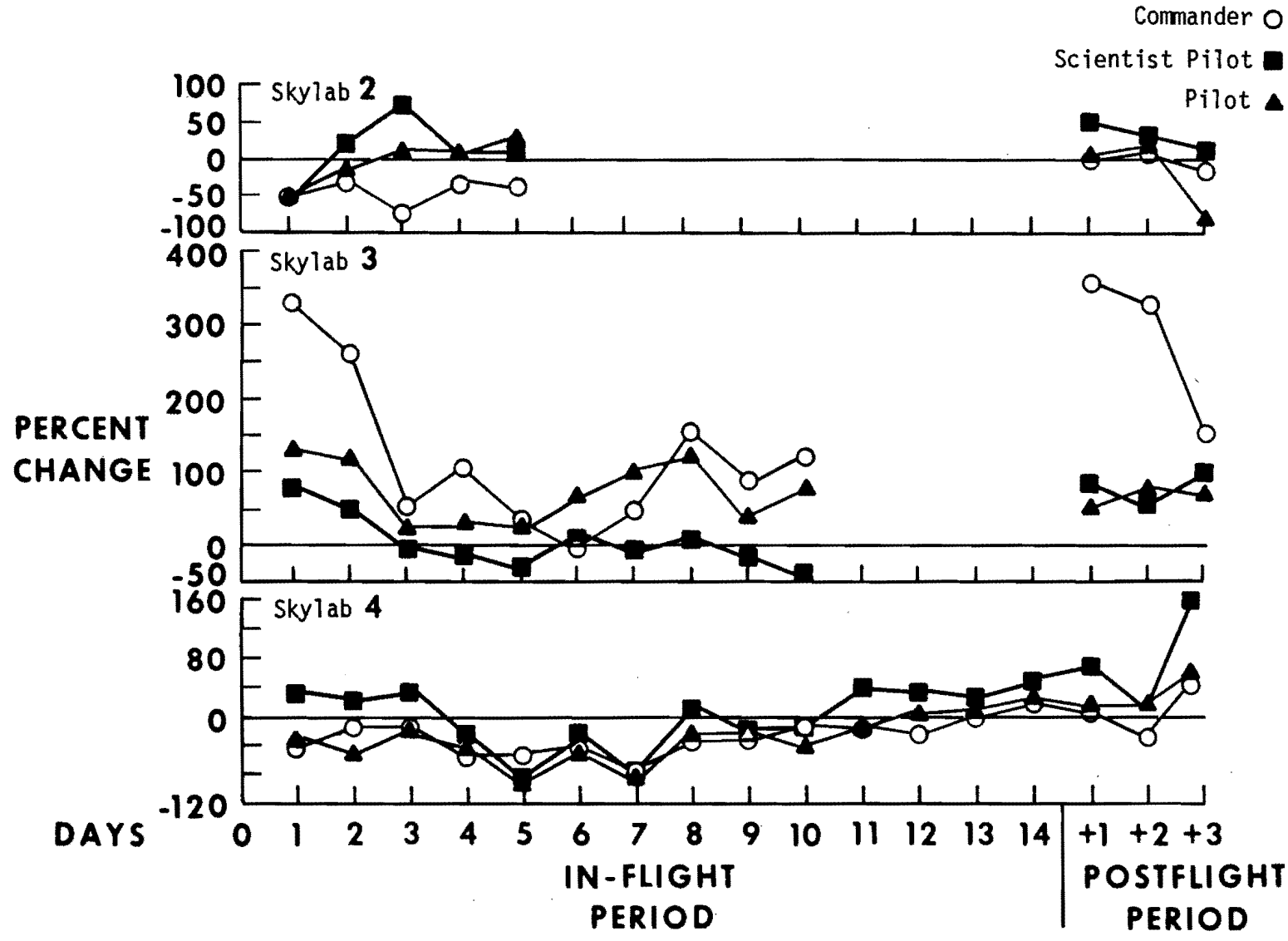


Figure 6. Urinary epinephrine.

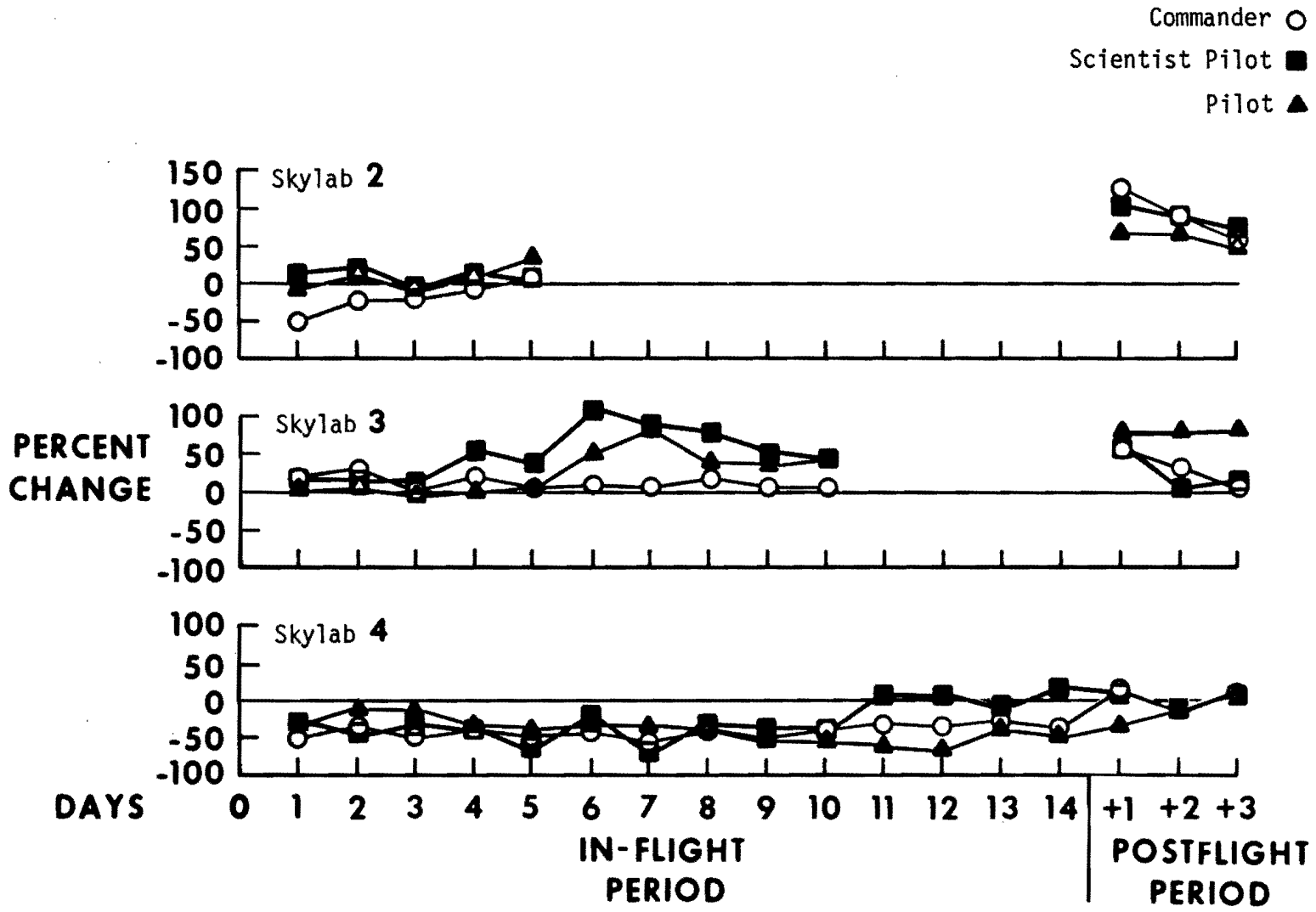


Figure 7. Urinary norepinephrine.

significant decreases in plasma ACTH although there was a slight trend toward such a decrease. It is recognized that the extremely short plasma half-life of adrenocorticotrophic hormone may have obliterated momentary increases during the recovery operations. In Gemini 7 there were decreases in total 17-hydroxycorticosteroid in the in-flight urine samples (7). Balakhovskiy and Natochin also reported decreased total 17-hydroxycorticosteroids in urine collected in space flight. These authors suggested that sample deterioration might account for the decreases observed (12). Our tests, in preparation for the Skylab flights, indicated that the freezing of urine was sufficient to prevent change in steroid concentrations (19). A decrease in 17-hydroxy-corticosteroids was also seen in the one in-flight sample obtained in Apollo 16. In these samples the crewmen exhibited either in "an increase" or "no change" in free cortisol excretion. Elevated in-flight urine cortisol levels and depressed plasma cortisol recovery levels are not a manifestation of alterations in circadian rhythmicity relative to the sampling time during the recovery phase (20).

In Skylab, plasma adrenocorticotrophic hormone values were decreased during the flight and plasma cortisols were elevated. Postflight adrenocorticotrophic hormone remained decreased and cortisol, although more variable, was generally increased. Twenty-four hour urinary cortisol levels were increased significantly through the missions on all crewmen (fig. 8). This was generally accompanied by either no change or slight decreases in daily total 17-hydroxycorticosteroids, even though the summary results indicate no real difference from preflight control values. Decreases in pregnanetriol and tetrahydro-cortisone and slight increases in tetrahydrocortisol accounted for the total 17-hydroxycorticosteroid values. There was an increase in total 17-ketosteroids particularly demonstrated by increases in pregnanediol androsterone and etiocholanolone.

The metabolism or excretion or both of these steroids appears to have been altered. Whether such changes occurred within the adrenal, at the site of liver conjugation or in the kidney is the subject of continuing investigations.

Carbohydrate, Fat and Protein Utilization

Data from the Gemini and Apollo programs show significant loss of lean body mass during the missions. This loss of tissue was evidenced by elevations in nitrogen excretion (7, 21). Whether such losses are due to weightlessness, the hypobaric atmosphere or are merely a result of the psychological stress of the mission is unknown although results of the Skylab Medical Experiment Altitude Test would tend to implicate weightlessness as the primary causative factor in these losses (22).

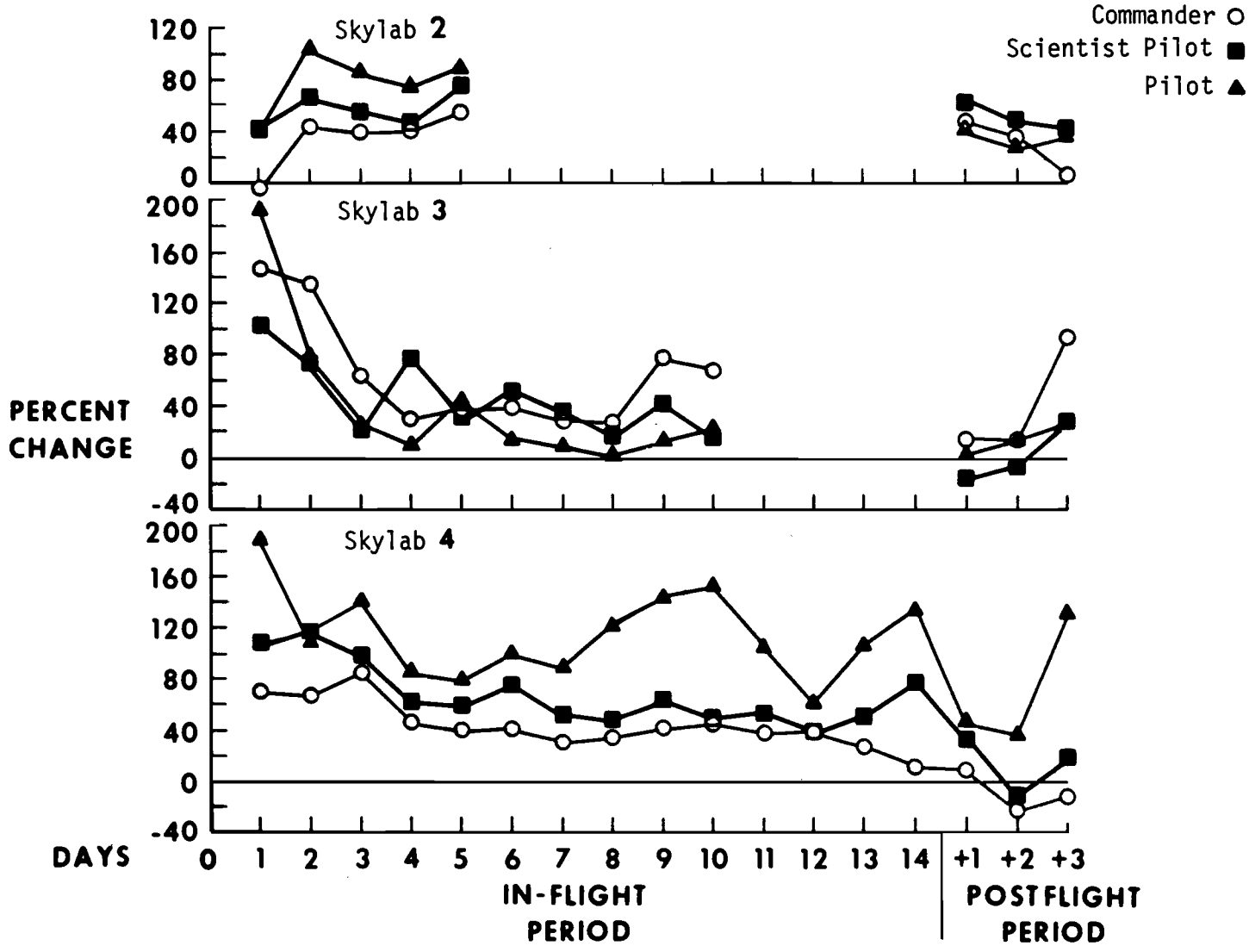


Figure 8. Urinary cortisol.

Similar loss of nitrogen had been observed throughout the Skylab flights and has been accompanied by losses in potassium and water. Moreover, it has been shown that diminution in volume and strength accompanied loss of these components of lean body mass. Urinary amino acids levels were elevated in-flight and postflight. Analysis shows an increase in the ratio-essential:nonessential urinary amino acids during flight. Further attempts to elucidate primary source of protein loss shows evidence of collagen breakdown in-flight as reflected mainly by the increased excretion of total hydroxylysine (fig. 9). Caloric intake has generally been below body requirements so that the weight loss could have been partly caused by an inadequate food intake, in most crewmembers.

In man both hypoglycemia and fasting stimulate growth hormone secretion, the former quickly and the latter more slowly. Growth hormone, an insulin antagonist, raises blood glucose and plasma free fatty acids while lowering plasma amino acids. Growth hormone measurements were made together with measurements of insulin and glucose. Plasma growth hormone levels were quite variable, however, significant elevation occurred during the first days in-flight and the first days after recovery. Insulin and glucose were significantly decreased during the flight and increased after recovery. There was an increase in plasma cholesterol on recovery day. The constancy of the diets preflight, in-flight, and postflight would tend to preclude diet as a significant factor in these changes immediately after flight. Although losses in body fat stores throughout the long missions may account for the mobilization of triglycerides after recovery.

The significant increases in thyroxine and the trend toward higher thyroid stimulating hormone levels correlate well with the decreases in cholesterol for two weeks following recovery. These data confirm earlier Apollo findings that there is increased circulating free thyroxine after space flight (23). Similar findings were reported by the Soviets. They were able to correlate weight loss to cholesterol decreases and suggested without supportive data that the thyroid gland might be implicated (12).

It appears that at recovery blood glucose is raised by the action of catecholamines, cortisol, and growth hormone while the insulin is increased as a response to the elevated blood sugar. The in-flight decreases observed in both glucose and insulin have also been observed in bedrest, although it did not become significant until 56 days in bedrest (24), while the decrease became significant at 38 days in space. The impaired tolerance to a glucose load which has been reported following exposure to bedrest was not measured in this study (25).

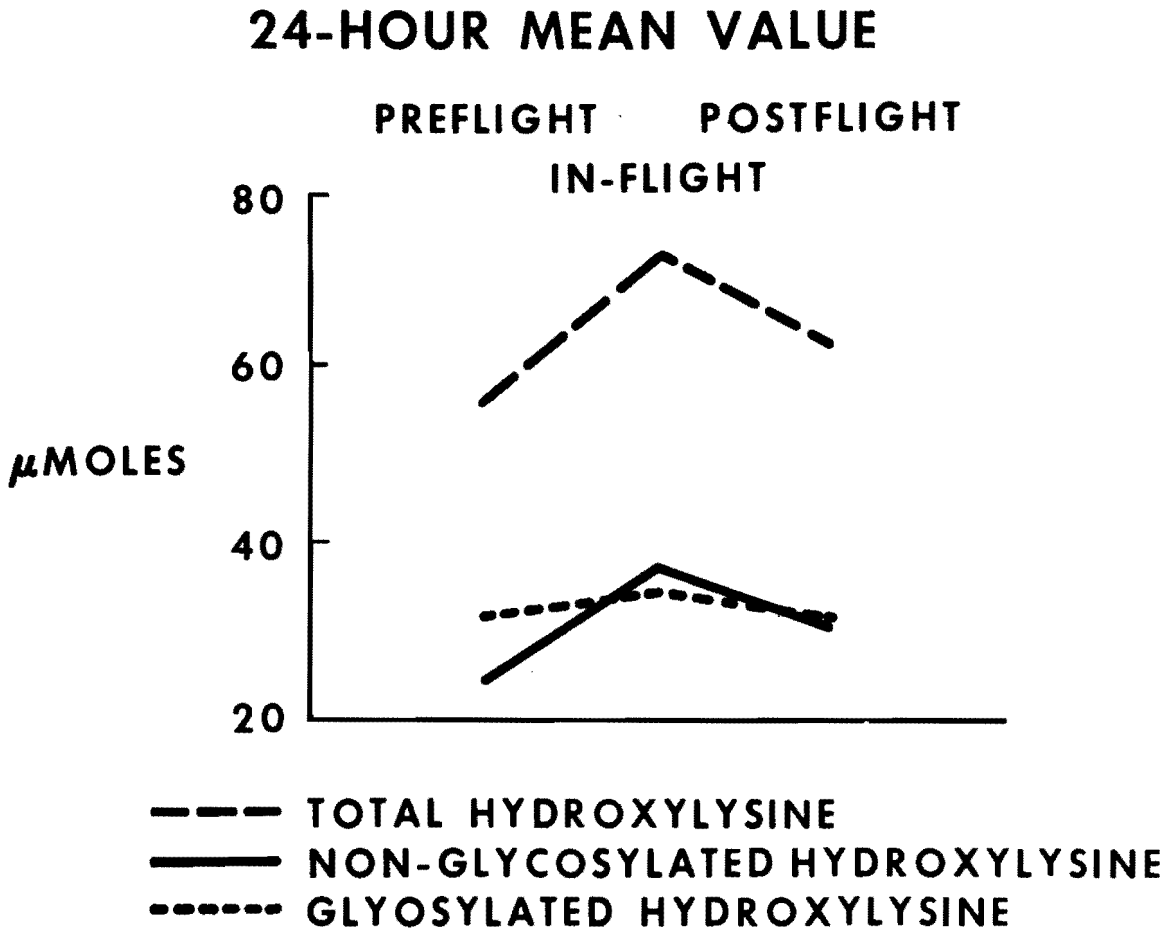


Figure 9. Urinary excretion of hydroxylysine and its glycosides (Skylab 4).

Total plasma protein increased on recovery day as did albumin. Albumin decreased on the third day and fourteenth day after recovery, but not as much as total protein. This is inferential evidence that the glycoproteins were increased immediately postflight. The cholesterol increase seen at recovery may also indicate an elevation in lipoproteins, particularly in high density lipoproteins. Plasma volume increases were recorded during this period due to water and electrolyte retention as the vascular system responded to the effects of gravity. Thus, the decrease in albumin may have been dilutional rather than absolute. Unlike the Apollo results, triglycerides were elevated after flight until the 14th postflight day.

SUMMARY

This experiment, concerened with the biochemical reactions of the body to the stress of space flight, includes both endocrine and metabolic measurements. It is the first comprehensive and integrated study of endocrinology and metabolism during prolonged space flight. Significant biochemical changes were observed. They varied in magnitude and direction but all disappeared shortly after return to Earth.

These changes are for the most part indicative of a successful adaptation by the body to the combined stresses of weightlessness. The transient nature of some of these changes, particularly in fluid and electrolyte metabolism, tend to support the conclusion that a new and stable condition of homeostasis condition has been achieved. In other areas, particularly in those concerned with the metabolism of bone mineral, protein and carbohydrates unstable states appear to persist and it is unclear at this time in which form the ultimate sequelae of these changes will manifest themselves after flight has continued for much longer periods of time.

ACKNOWLEDGMENT

The author gratefully acknowledges the outstanding support provided by the following individuals: Dr. Oliver Lowery, who performed the microanalytical determinations on in-flight plasma; Dr. W. Carter Alexander, for routine clinical, as well as enzymatic and trace element determinations; Dr. Philip C. Johnson, for body fluid compartmental analyses, Dr. John Potts, for parathyroid hormone, calcitonin, and vitamin D radioassays; Dr. Myron Miller, ADH assay; and Dr. B. O. Campbell, ACTH assay.

REFERENCES

1. Cannon, W. B. 1939. The Wisdom of the Body, 2nd Ed., Norton, N. Y.

2. Selye, H. 1973. Stress and Aerospace Medicine. *Aerospace Med.*, 44 (2): 190-193.

3. Berry, Charles A. 1973. Weightlessness in Bioastronautics Data Book, 2nd Ed. NASA SP-3006, Washington, D.C.

4. Johnson, P. C., P. C. Rambaut, and C. S. Leach. 1973. Apollo 16 Bioenergetic Considerations. *Nutrition and Metabolism*, 15: 889-893.

5. Gee, George F., Richard S. Kroneberg, and Roy E. Chapin. 1968. Insensible Weight and Water Loss During Simulated Space Flight. *Aerospace Med.*, 39: 984-988.

6. Leach, Carolyn S., Philip C. Johnson, and W. C. Alexander. In Press 1974. Endocrine, Electrolyte, and Fluid Volume Changes Associated with Apollo Missions, Biomedical Results of Apollo. NASA Special Publication.

7. Lutwak, L., G. D. Whedon, P. H. LaChance, J. M. Reid, and H. S. Lipscomb. 1969. Mineral, Electrolyte and Nitrogen Balance Studies of the Gemini VII Fourteen-day Orbital Space Flight. *Jour. Clin. Endo. Metab.*, 29: 1140-1156.

8. Leach, C. S., P. C. Rambaut, and P. C. Johnson. 1974. Adrenal Cortical Changes of the Apollo 17 Crewmen. *Aerospace Med.*, 45: 535-539.

9. Smith, H. W. 1957. Salt and Water Volume Receptors: An Exercise in Physiologic Apologetics. *Am. J. Med.*, 23: 623-652.

10. Schrier, R. W. and H. E. de Wardener. 1971. Tubular Reabsorption of Sodium ion: Influence of factors other than Aldosterone and Glomerular Filtration Rate. *New Eng. Journal Med.*, 285: 1231-1243.

11. Ross, E. J. 1959. Aldosterone in Clinical and Experimental Medicine. *Blackwell Scien. Pub.*, Oxford, 112: 76-77.

12. Balakhovskiy, I. S., and Yu V. Natochin. 1973. Problemy Kosm'cheskoy Biologii, Tom 22, obmen Veshchestv v Ekstro mal'nykh Usloviyakh Kosmicheskogo Poleta i Pri Yego Imitatsii. Moscow, "Nauka" Press.

13. Alexander, W. C. and Carolyn S. Leach. In Press 1974. Apollo Biochemistry Results, Biomedical Results of Apollo. NASA Publication.

14. Neuman, W. F. 1964. Calcium Metabolism Under Conditions of Weightlessness. In: Florkin, M. and Dollfus, A., Eds., Life Sciences and Space Research, Vol. II: A session of the Fourth International Space Science Symposium, Warsaw, Poland, June 3-12, 1963. North-Holland Publishing Co., Amsterdam, (Sponsored by COSPAR).

15. Leach, C. S. 1971 Review of Endocrine Results: Project Mercury, Gemini Program and Apollo Program, Proc. of the 1970 Manned Space Center Endocrine Conference, Oct. 5-7, 1970, NASA TM X-58068, pp. 3-1 through 3-16.

16. Weil-Malherbe, H., E. R. Smith, Grace Bowlos. 1968. Excretion of Catecholamines Metabolites in Project Mercury Pilots, *J. Appl. Physiol.*, 24: 146-151.

17. Karki, N. 1956. The Urinary Excretion of Noradrenaline and Adrenaline in Different Age Groups, Its Diurnal Variation and the Effect of Muscular Work on it. *Acta Physiol. Scand.*, 39: (Suppl. 132).

18. Leach, C. S., S. B. Hulley, P. C. Rambaut, and L. F. Dietlein. 1973. The Effect of Prolonged Bedrest on Adrenal Function. *Space Life Sciences*, 4: 415-422.

19. Leach, Carolyn S., Paul C. Rambaut, and Craig L. Fischer. In Press. A Comparative Study of Two Methods of Urine Preservation. *Clinical Biochemistry*.

20. Leach, C. S., and B. O. Campbell. 1974. Hydrocortisone and ACTH Levels in Manned Spaceflight. In: Chronobiology, L. E. Scheving, F. Halberg and John Pauly (Eds.), pp. 441-447. Igaka Shoin Ltd., Tokyo.

21. Johnson, P. C., C. S. Leach, and P. C. Rambaut. 1973. Estimates of Fluid and Energy Balance of Apollo 17. *Aerospace Med.*, 44. 1227-1230.

22. Whedon, G. Donald and Paul C. Rambaut. 1973. Mineral Balance-Experiment M071, Skylab Medical Experiments Altitude Test. NASA TMX 58115, pp. 7-1 through 7-12.

23. Sheinfeld, Maxim, Carolyn S. Leach, and Philip C. Johnson. In Press 1974. Plasma Thyroxine Changes of the Apollo Crewmen. *Aerospace Medicine*.

24. Vernikos-Danellis, Joan, Charles M. Winget, Carolyn S. Leach and Paul C. Rambaut. April 1974. Circadian, Endocrine, and Metabolic Effects of Prolonged Bedrest: Two 56-Day Bedrest Studies. NASA Technical Memorandum TMX 3051.

25. Blotner, H. 1945. Effect of Prolonged Physical Inactivity on Tolerance of Sugar. *Arch. Intern. Med.*, 75: 39.

CYTOGENETIC STUDIES OF BLOOD (EXPERIMENT M111)

Lillian H. Lockhart, M.D.
The University of Texas Medical Branch, Galveston, Texas

ABSTRACT

The Skylab M111 experiment is a continuation of the preflight and postflight chromosomal analyses of the flight crews that have been performed since the Gemini III mission. The experiment is designed to determine whether some space flight parameter produces cytogenetic effects in human cells and to provide biological radiation dosimetric capability in the event of significant radiation exposure to a flight crew.

On each of the Skylab flights, blood lymphocytes for analysis of chromosomes for structural defects were obtained from each of the prime crewmembers and from a ground-based control group before and after flight. The cultures were successful except for occasional specimens obtained on recovery day on board the recovery ship. These specimens had to be handled differently than the others. All specimens were in culture for 60 to 70 hours and then were processed by treatemnt with colcemid, a hypotonic solution, followed by fixation and flame-dry slide preparation. On each of the studies, two examiners each counted and analyzed 100 to 150 cells at random for structural defects of the chromosomes. Two types of defects were recorded. The minor defects included the following aberrations: chromatid fragments, chromosome fragments, and deletions. Structural rearrangements such as dicentrics, exchanges, ring chromosomes, and translocations were photographed, and the cells were karyotyped to delineate, when possible, the chromosome or chromosomes involved in the rearrangement.

Except for one study of a control subject, no individual study demonstrated greater than eight percent minor chromosomal structure defects. In considering the more involved structural rearrangements found in individuals, it is apparent that both the astronauts and the controls had one or more such defects on several occasions. These were found both before and after flight, but they were found more consistently in both groups after flight. This result seems to indicate that the flight itself was not a major contributing factor. The influence of repeated isotope injections given to astronauts and to controls must also be considered.

INTRODUCTION

It has been appreciated for some time that increased frequency of chromosomal aberration occurs in man following exposure to ionizing radiation. Information has been obtained by study of persons receiving an external body source, such as therapeutic dosage or of those accidently exposed. Others receiving radiation exposure from an internal source, such as the decay of radioisotopes administered for diagnosis or treatment, have also been analyzed. It is obvious that interpretation of such data may be fraught with many problems. The radiation exposure may be acute or chronic, partial or total body, repeated or a single event. The tissue studied and the time elapsed following exposure have also been quite variable.

Structural chromosomal aberrations are also known to occur following exposure to other environmental factors such as viruses (both DNA and RNA) acquired either through immunization or infection, to various chemicals such as benzene, and to numerous drugs.

Concern over the possible harm of low levels of radiation exposure centers mostly around its association with hereditary damage or malignancy. Essentially no information is available concerning radiation effects on the chromosomes of gonadal or meiotic cells of man and estimates of hereditary damage are based in large part on theoretical views. It should be remembered that we cannot extrapolate findings in somatic cells (in the case under discussion circulating lymphocytes) to gametic chromosomal patterns. On the other hand, concern regarding the cancer hazard in irradiated human populations has been suggested by well founded studies (1). A classic example is that of patients treated with x-rays for ankylosing spondylitis who have on the average a ten-fold increase in mortality from leukemia (2). These patients were reported by Buckton, *et al.* (3) in 1962 to have structural chromosomal damage of cultured peripheral leukocytes some years after the treatment. The fact that many agents which produce tumors in man and animals can also produce chromosomal aberrations in their cells is clearly established. This information coupled with the fact that in several rare human disorders (Bloom's syndrome, Fanconi's anemia and ataxia telangiectasia) there is a constitutional predilection for increased chromosomal aberrations as well as an increased incidence of leukemia and lymphoma has suggested that an increase in structural chromosome aberrations cannot be ignored.

These chromosomal aberrations are structural in nature, that is, they arise through breakage of the strands of chromatin. These breaks may occur either in one or in both chromatids of a single chromosome or multiple breaks may occur in several chromosomes within an individual cell. Following such accidents, the strands may or may not recombine within themselves or the broken ends of several chromosomes may

combine with each other. Two general types of aberrations occur depending on the stage of the cell cycle in which the break occurs. If the cell is in the pre-DNA synthesis period, chromosome strands are single (chromatids) and if the accident occurs after synthesis, the chromosome consists of two chromatids. Chromosomes are technically examined in the metaphase stage of division because that is when they can be separated as individuals, so replication may or may not have occurred when we examine the chromosomes of peripheral lymphocytes, depending in part on the time in culture. In general, these two types of aberrations may be morphologically separated, however, in several instances it is impossible to tell whether the break occurred in the pre-DNA synthesis, and was replicated, or whether both strands were affected after replication. A break will produce a fragment that is generally lost in the next cell division.

Separation of the aberrations into chromatid or chromosome in nature is useful since the type of structural defect occurring in humans as a response to a specific exposure, has varied with the agent to which the person is exposed.

It is with these considerations in mind that the NASA program has wisely considered cytogenetic studies important in past years and has especially concentrated on such aspects in the Skylab program with extended missions and possible increase in radiation exposure.

MATERIALS AND METHODS

This discussion centers on experiments designed for Skylab 2 since results for the other missions are not yet complete. Blood lymphocyte studies were obtained on eleven occasions preflight and eight instances postflight from the three members of the crew, from three controls and from the backup crew until it was apparent that they would not replace the crew. The control group consisted of three persons in the NASA program who would have an environment somewhat similar to the crew over the experimental period except for the flight. A total of 90 cultures were processed and 79 have been analyzed, the remainder being specimens of the backup crew. Venous heparinized blood was drawn either at the Johnson Space Center or the Kennedy Space Center in one to two milliliters aliquots and was obtained at the time of drawing for other medical procedures. The cultures were instituted at the University of Texas Medical Branch on all occasions except for the first two postflight studies which were obtained aboard the recovery ship. Each sample was allowed to settle and five to seven drops of the buffy coat were placed in Chromosome Medium 1A. Four such cultures were initiated on each person from each blood drawing. The cultures were then incubated for a period of 60 to 70 hours at 37° C and processed by a

modified method of Moorehead (4). Colcemid was added to a concentration of 0.1μg/ml for two hours. The cell suspension was then treated with a hypotonic solution followed by numerous washings with fixative (3 methanol:1 acetic acid). Slides were prepared on the same day by flame drying and the cells stained with Wright's stain.

The slides were coded and each of two examiners studied from 100 to 150 cells on each specimen. Cells were selected on low magnification if they appeared to be analyzable and then examined under high magnification; each cell was counted and a search made for any type of structural defect. When a structural defect was found the cell was photographed for further analysis by karyotyping in an attempt to delineate whenever possible the chromosome and/or chromosomes involved in the aberrations.

The cells were scored for the following structural arrangements: chromatid and chromosome constrictions and gaps (not to be considered in this paper); chromatid and chromosome breaks, fragments, and deletions (to be referred to as minor defects); and dicentrics, rings, inversions, translocations, and exchanges (to be referred to as structural rearrangements).

RESULTS AND DISCUSSION

The results of the cyogenetic analysis of lymphocytes of the Skylab 2 astronauts are shown in table I. There were four studies that were unsuccessful. These involved the recovery day specimens of the crew and of one control. These cultures were instituted aboard ship and transported by portable incubator. Several of these specimens had a dark brown appearance upon arrival at the laboratory.

There were no individual studies from this mission that demonstrated greater than 8.0 percent minor structural defects except for one on specimen L, a control. The blood had been drawn aboard ship on the day before recovery. In only 16 studies did such aberrations appear in from 5.0 to 7.9 percent of the cells examined. In our laboratory under similar technical conditions where 13 000 cells a year are counted and analyzed, it is expected that three to four percent of the cells analyzed will show one or more breaks, deletions or fragments. In other laboratories with varying preparation of cells for study, this aberration incidence may even be slightly greater. These defects are known to increase in peripheral leukocyte cultures of persons following a viral illness such as measles or adenovirus, after administration of viral vaccines, after certain diagnostic x-ray studies, and after exposure to certain chemicals. This increase in response to such exposures is in general only temporary, and little can be suggested as to harmful effects.

TABLE I

Skylab 2

Date & Subject	No. Cells Examined	% Minor Defects	Structural Rearrangements
4-2-73 F-53	KSC		
C (26)	268	3.35	
K (43)	239	3.34	1 Exchange
W (34)	250	2.80	
A (80)	259	3.86	
H (55)	260	1.15	1 Inversion
L (14)	271	2.95	
Mc(84)	223	0.44	
M (65)	238	1.68	
S (72)	231	1.73	
4-24-73 F-31	KSC		
L (41)	277	1.44	
S (46)	244	2.45	
4-25-73 F-30	KSC		
A (28)	256	3.90	1 Exchange
H (85)	234	1.28	
L (38)	217	4.60	
4-26-73 F-29	KSC		
C (22)	273	1.83	1 Dicentric
K (12)	263	7.22	
W (59)	241	1.66	
A (7)	255	6.27	
H (89)	234	2.13	1 Dicentric
4-27-73 F-28	KSC		
C (31)	241	1.24	
K (10)	257	4.66	1 Translocation
W (69)	244	4.09	
5-1-73 F-24	JSC		
H (78)	242	0.83	
L (96)	247	4.05	2 Translocations
5-2-73 F-23	JSC		
C (64)	260	5.39	2 Rings, 1 Exchange
K (91)	257	3.89	
W (81)	250	5.20	
A (50)	244	6.56	

Crew: Conrad (C), Kerwin (K), Weitz (W)
Controls: Alexander (A), Hordinsky (H), La Pinta (L)
Backup Crew: McCandless (Mc), Musgrave (M), Schweickert (S)

TABLE I (Continued)

Date & Subject	No. Cells Examined	% Minor Defects	Structural Rearrangements
5-7-73 F-18	JSC		
C (4)	247	3.64	
K (95)	230	3.48	1 Ring
W (13)	243	2.06	
A (29)	238	5.04	1 Dicentric 1 Exchange
5-8-73 F-17	JSC		
H (18)	257	0.78	
L (48)	267	3.74	
5-14-73 F-11	JSC		
C (66)	273	4.03	1 Exchange
K (35)	246	4.47	1 Dicentric 1 Exchange
W (51)	243	5.34	
A (25)	244	7.37	1 Exchange
H (5)	245	2.85	
L (17)	277	1.80	1 Dicentric
5-24-73 F-1	KSC		
C (47)	269	1.86	
K (77)	231	4.76	
W (99)	239	5.43	
A (53)	238	3.78	1 Exchange
H (83)	241	2.90	
L (98)	259	3.47	
Flight= 5-25-73			
6-21-73 R-1	Ship		
A (92)	258	7.75	1 Dicentric
H (67)	Unsuccessful		
L (97)	139	11.51	
6-22-73 R+0	Ship		
C (15)	Unsuccessful		
K (90)	Unsuccessful		
W (56)	Unsuccessful		

TABLE I (Concluded)

Date & Subject	No. Cells Examined	% Minor Defects	Structural Rearrangements
6-23-73 R+1	Ship		
C (23)	257	3.50	
K (32)	234	4.70	1 Chromatid Exchange
W (45)	255	1.57	
A (93)	274	5.11	
H (76)	266	2.25	
L (86)	249	4.01	
6-26-73 R+4	JSC		
C (19)	261	4.21	1 Tricentric 1 Exchange
K (63)	264	2.65	1 Ring
W (57)	290	3.10	1 Dicentric, 1 Ring
A (94)	256	2.73	
H (71)	234	2.99	2 Dicentrics
L (82)	250	2.00	
6-29-73 R+7	JSC		
C (27)	245	1.22	
K (44)	260	6.15	1 Dicentric
W (70)	248	2.02	1 Dicentric
A (87)	239	6.28	2 Exchanges 1 Dicentric
H (3)	232	0.43	
L (52)	248	2.82	1 Dicentric 1 Exchange
7-5-73 R+13	JSC		
C (88)	223	6.72	1 Exchange
K (60)	260	4.62	
W (54)	244	4.91	
A (37)	273	6.23	1 Dicentric 3 Exchanges
7-9-73 R+17	JSC		
K (30)	276	2.90	
7-10-73 R+18	JSC		
C (68)	256	7.03	1 Tricentric
W (73)	246	4.07	1 Dicentric
A (49)	262	3.81	1 Ring
H (33)	255	0.78	
L (42)	238	2.10	

Table II lists the radioisotope injections administered to crew and controls alike in the present study. You will note that only one blood culture was instituted prior to such administration (4-2-74), and no one in the crew, backup crew, or control group had greater than 3.86 percent aberrations on the first study. This may well be chance because at various other occasions throughout the experiment, each person demonstrated such low values. It is quite possible that control L had a viremia at the time in which the 11.51 percent aberrations were found, and throughout the remainder of the study his values returned to expected levels.

TABLE II. ISOTOPE INJECTIONS

1973

4/2	4/24	5/2	5/7	5/14	5/23	6/21	6/22	7/5	8/2	8/28
	^{125}I					^{125}I		^{125}I	^{125}I	^{125}I
	^{51}Cr					^{51}Cr		^{51}Cr	^{51}Cr	^{51}Cr
	^{35}S					^{35}S		^{35}S		^{35}S
	^{3}H				^{3}H	^{3}H		^{3}H	^{3}H	^{3}H
^{14}C										
	^{42}K	^{42}K	^{42}K	^{42}K	^{42}K		^{42}K	^{42}K		
						^{59}Fe				

Speculation as to the significance of structural rearrangements is more difficult. It is noteworthy that in the first culture there was one crewmember and one control with evidence of breakage and recombination. This is not characteristic of the general population. It has been reported that such aberrations as dicentrics, rings, inversions, and exhanges occur very rarely, (fig. 1). Bloom, *et al.* (5) found only one dicentric and no rings in 7188 cells examined. Bender, *et al.* (6) reported 3 dicentrics and no ring chromosomes in 1642 cells from normal, unirradiated individuals. In our experience, it is less common. We would be the first to admit, however, that neither the crew nor the control group under discussion today are members of the general population. As to the crew, we might speculate for a moment what possible exposures occurred prior to chromosome culture. Obviously in such a professional lifetime there are many, varied experiences in comparison to the general population. Perhaps they came to Skylab and even to

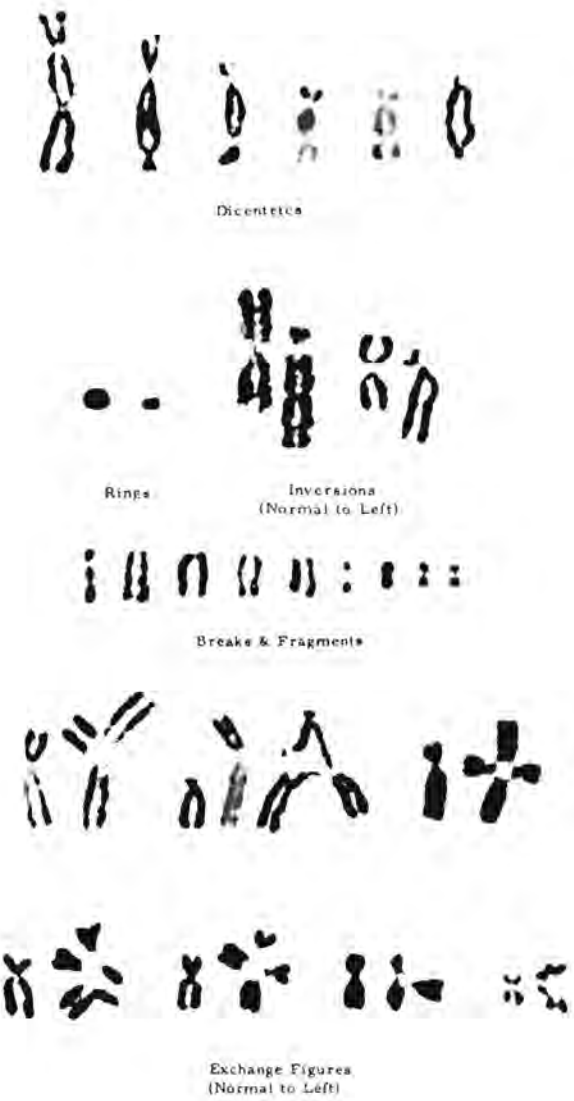


Figure 1. Skylab abnormalities.

NASA with these findings. Gooch and Berry (7) reporting on the chromosome aberrations of the Gemini astronauts also noted an occasional dicentric or ring chromosome.

In reviewing the medical log of this mission, one wonders about such potential problems as exposure to various gases, too high temperatures, to the atmospheric conditions in flight, and in fact, to weightlessness. Prince, *et al.* (8) reported observations on man in an oxygen-helium environment and included chromosome study. They noted up to 4 percent chromatid-type lesions in the subjects. There is otherwise no information relating such variables to chromosome aberration. There is very good documentation regarding illness and drug ingestion in the astronauts of Skylab 2 and comparison of this data with the chromosomal pattern does not suggest a cause and effect relationship.

The appearance of one or more structural rearrangements in 250 cells is unusual, however, in this study there is no difference in the crew and in the control group in regard to such aberrations as they occur sporadically throughout. However, there is one factor common to both groups that cannot be ruled out and this is the administration of radioisotopes for various medical studies. Some subjects from both groups have had such a series on repeated occasions even prior to this mission.

It is indeed impossible to say that the appearance of such aberrations increased in the crew following the mission, and frustrating to admit that what might have been the most important specimens from the crew were unsuccessful. Initially it was thought culture failure may have been the result of transporting the specimens and of difficult culture conditions. In personal communication with Dr. S. E. Ritzman (experiment M112), however, it was realized that the problem may be related to defective lymphocyte transformation and/or DNA synthesis on the day of recovery.

There are several obvious problems in this experiment. Primarily there is no normal control group, that is persons from the general population not receiving isotopes and without previous high altitude or orbital flight experience, analyzed simultaneously. Secondly, we did not have occasion to study the crew over a long period prior to introducing other variables. Arrangements have been made, however, to continue to study them intermittently to determine whether these findings are only temporary. Thirdly, in planning the culture time, a shorter period would have allowed for study of more cells after only one division in culture, and perhaps finding an even greater number of aberrations.

SUMMARY

In summary, I would like to reiterate that the appearance of structural rearrangement in 250 cells examined from one specimen is unusual, that it may only be a temporary finding, and that the data does not seem to suggest that the external sources of radiation to which the crew were exposed in orbit resulted in an aberration increase.

REFERENCES

1. Court Brown, W. M., K. E. Buckton and A. S. McLean. 1965. Quantative Studies of Chromosome Aberrations in Man Following Acute and Chronic Exposure to X-rays and Gamma Rays. *Lancet* I: 1239-1241.

2. Bender, Michael A. 1969. Human Radiation Cytogenetics. *Advanced Radiation Biology* 3: 215-275.

3. Buckton, K. E., P. A. Jacobs, W. M. Court Brown and R. Doll. 1962. A Study of the Chromosome Damage Persisting After X-ray Therapy for Ankylosing Spondylitis. *Lancet* II: 676-682.

4. Moorehead, P. S., P. C. Nowell, W. J. Mellman, D. M. Battips, and D. A. Hungerford. 1960. Chromosome Preparations of Leukocyte Cultures from Peripheral Blood. *Experimental Cell Research* 20: 613.

5. Bloom, A. D., S. Neriishi, A. A. Awa, T. Honda and P. G. Archer. 1967. Chromosome Aberrations in Leucocytes of Older Survivors of the Atomic Bombings of Hiroshima and Nagasaki. *Lancet* II: 802-805.

6. Bender, M. A. and P. C. Gooch. 1966. Somatic Chromosome Aberrations Induced by Human Whole-Body Irradiation: The "Recuplex" Criticality Accident. *Radiation Research* 29:568-582.

7. Gooch, P. C. and C. A. Berry. 1969. Chromosome Analyses of Gemini Astronauts. *Aerospace Medicine* 40: 610-614.

8. Prince, J. E., L. H. Mori, H. J. Zeft, B. E. Welch and A. P. Amarose. 1968. Observations on Man in an Oxygen-Helium Environment at 380 mm Hg Total Pressure: V Chromosome Profiles. *Aerospace Medicine* 39: 111-114.

THE RESPONSE OF SINGLE HUMAN CELLS TO ZERO GRAVITY

P. O'B. Montgomery, Jr., M.D.; J. E. Cook, B.S.E.E.*; R. C. Reynolds, M.D.†; J. S. Paul, Ph.D.*; L. Hayflick, Ph.D.‡; D. Stock, Ph.D.§; W. W. Schulz, Ph.D.*; S. Kimzey, Ph.D.**; R. G. Thirolf, B.S.E.E.**; T. Rogers, Ph.D.**; D. Campbell, M.S.†; and J. Murrell†.*

ABSTRACT

The hardware, Woodlawn Wanderer 9, used to perform the S015 experiment, was fully automated and designed to achieve four major objectives.

- To maintain living cell cultures by supplying them with proper nutrients at a constant temperature of 36° C,
- To produce two phase-contrast time-lapse motion pictures of living cells for 28 days,
- To fix a group of the cultures at predetermined intervals,
- To return some of the cultures of living cells intact for subsequent subculture and preservation.

These living cell cultures were maintained at a temperature of approximately 22° C after the first 12 days of the Skylab 3 mission.

The purpose of the S015 experiment was to extend observations of the effects of zero gravity to include the study of some of these effects on living human cells during and after the 59-day Skylab 3 mission. A strain of diploid human embryonic lung cells, WI-38, was chosen for this purpose. The WI-38 cells were obtained from the laboratory of

*Laboratories for Cell Research, Woodlawn Hospital, Dallas County Hospital District, Dallas, Texas

†Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Texas.

‡Department of Medical Microbiology, Stanford University, Palo Alto, California.

§University of Texas, Health Science Section at Houston, M. D. Anderson Hospital, Houston, Texas.

**Cellular Analytical Laboratory, Johnson Space Center, Houston, Texas.

Dr. Leonard Hayflick, Department of Medical Microbiology, Stanford University. The studies reported here were concerned with observations designed to detect the effects of zero gravity on cell growth rates and on cell structure using light microscopy, studies of cell function and cell cycle were performed using time-lapse motion picture photography, whereas studies for cell deoxyribonucleic acid content were performed using Feulgen staining and microspectrophotometry. Subsequent study of the returned living cells included karyotyping, G- and C-banding, and analyses of the culture media used. Some of the returned living cells were banked by deep-freeze techniques for possible future experiments.

The presentation of the experiment results will include a discussion of all these data in addition to the showing of a time-lapse motion picture of living human cells in the zero-gravity environment.

INTRODUCTION

The advent of satellites has awakened and renewed interest in the effects of gravity on living material. Prior to this time the major interest had been centered on the effects of increased gravity on living material as simulated by acceleration in various types of centrifuges. These studies began as early as 1806 when Knight used water driven centrifuges to demonstrate that it was the direction of the gravitational vector which oriented the growth of plants (1). In 1883, E. Pflüger performed the classic experiment of maintaining a developing frog's egg in an inverted position and demonstrated that this led to abnormalities of development (2). In 1930, Harvey and Loomis working at Princeton, designed and constructed a centrifuge microscope (3). This instrument or modifications of it has been used to study the effects of acceleration on sea urchin eggs and amoebae (4,5,6,7). Because of the buoyant effect of the media in which most specimens have been immersed during the period of acceleration, other investigators such as Matthews and Wunder have used a variety of terrestrial forms of life in their studies (8,9). In general, as might be expected, it takes much larger increases in the gravitational field to produce detectable effects in bacteria (10) than it does to produce detectable effects in amoeba (11), and in the case of the more complex and heavier organisms from the size of rats to man, relatively small increments of gravity may produce measurable and/or lethal effects.

OBJECTIVES

The purpose of the SO15 experiment was to extend our observations of the effects of zero-gravity to living human cells during and subsequent to a 59-day flight on Skylab 3. A strain of diploid human embryonic lung cells, WI-38, was chosen for this purpose[1]. The studies reported in this paper were concerned with observations designed to detect the effects of zero-gravity on cell growth rates and on cell structure as observed by light microscopy, transmission and scanning electron microscopy and histochemistry. Studies of the effects of zero-gravity on the cell function and the cell cycle were performed by time lapse motion picture photography and microspectrophotometry. Subsequent study of the returned living cells included karotyping, G- and C-banding, and analyses of the culture media used. Some of the living cells returned were banked by deep freeze techniques for possible future experiments.

Flight Hardware

The hardware, Woodlawn Wanderer 9, used to carry out the SO15 experiment, was fully automated and designed to achieve four major objectives.

- To maintain living cell cultures by supplying them with proper nutrients and temperature, 36° C.
- To produce two phase-contrast time-lapse motion pictures of living cells for 28 days.
- To fix a group of the cultures at predetermined intervals.
- To return intact some of the cultures of living cells for subsequent subculture and preservation. These cultures were maintained at approximately 22° C after the first 12 days of the mission.

As with most equipment developed for space flight, the hardware design was restricted by limitations of size, weight, and power while high reliability and safety standards were achieved. In this case, biological compatability of materials and the necessity to sterilize some of the components at high temperatures were major constraints not usually encountered in flight hardware design.

[1]WI-38 cells were obtained from the Laboratory of Dr. Leonard Hayflick, Department of Medical Microbiology, Stanford University.

The hardware consisted of a single self-contained package installed in the spacecraft Command Module which supplied the power required to maintain an ambient temperature of between 10° and 35° C. The unit was hermetically sealed to provide an internal pressure of one atmosphere. Figure 1 is a photograph of the exterior of the unit. The fully loaded package weighed 10 kilograms and measured 40 x 19 x 17 centimeters.

Internally, the package was separated into a camera-microscope section and a separately sealed growth curve experiment section. Figure 2 illustrates the interior arrangement with the camera-microscope section on top, the growth curve experiment section below, and the electronic circuitry required to fully automate the experiments located between the two.

In the camera-microscope section there were two independent camera-microscope systems. One system photographed living cells through a 20 power phase-contrast microscope, the other photographed living cells through a 40 power phase-contrast microscope. Each microscope and lamp was miniaturized and measured 7 x 4 x 2.5 centimeters. The phase-contrast image produced by the microscope was projected through an optical system onto the 16 millimeter film. The film was supplied by a film pack which contained two rolls of 16 millimeter film, each 100 meters long. The camera which recorded through the 40 power microscope was operated for a 40 minute period once every 12 hours at the rate of five frames per minute. The 20 power microscope camera operated continuously and exposed one frame every 3.2 minutes.

Each camera-microscope system recorded the images of living WI-38 cells grown on glass in a 0.05 cubic centimeter chamber. The chamber was formed by a gasket sandwiched between two glass discs. Tubes were attached to the gasket for the injection of fresh nutrient and for the removal of the waste medium. The entire chamber was held in a heated block thermostatically controlled to maintain a temperature of 36° C.

In order to fill the chambers, culture medium containing 7000 cells/milliliter was injected into the chamber through a syringe. After a few hours, the cells settled and became attached to the lower glass disc. The chamber was then installed in the microscope stage and the microscope was locked in a focused position.

Fresh medium was supplied by a cylindrical reservoir containing a piston threaded on a screw extending the length of the cylinder. After the screw was automatically rotated 4.5 revolutions every 12 hours, fresh medium was forced into the specimen chamber and waste medium was pulled into the vacuum created on the back side of the moving piston.

Figure 1. External configuration of Woodlawn Wanderer 9.

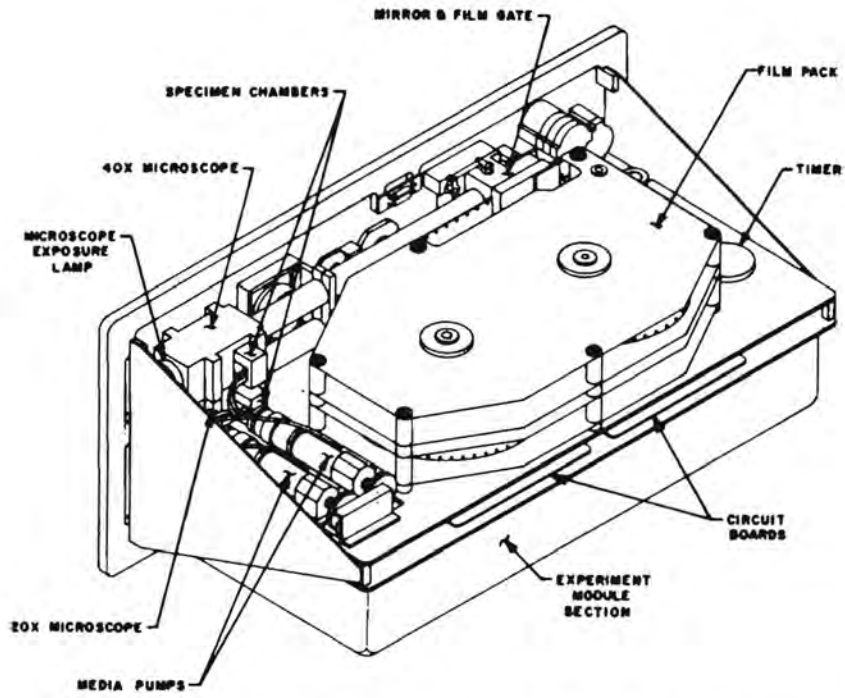


Figure 2. Interior configuration of Woodlawn Wanderer 9.

The growth curve experiment was carried out in a module that was easily removed from the rest of the package for biological servicing. The module was separated into two identical independent assemblies to provide some degree of duplication and control (fig. 3). Each assembly

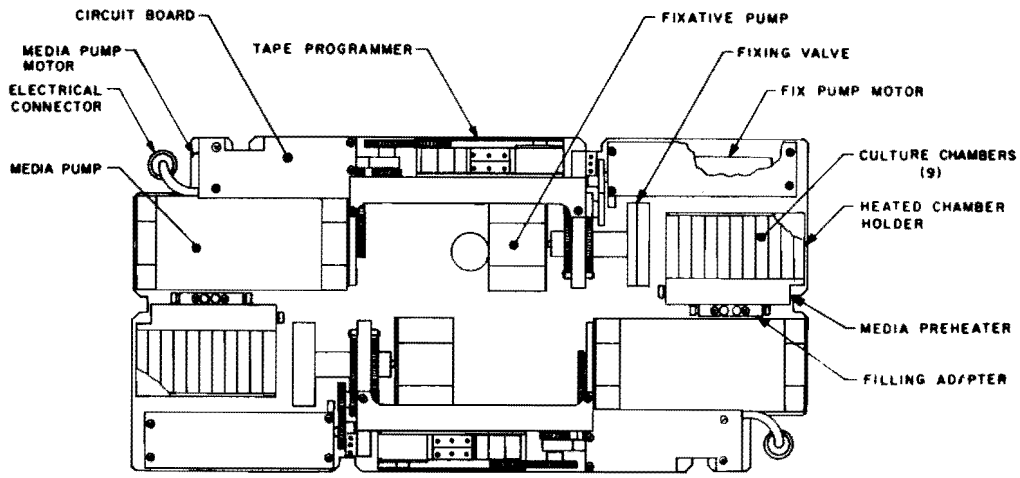


Figure 3. Interior of Woodlawn Wanderer 9.

provided nine miniaturized Rose-type cell culture chambers installed in a temperature-controlled holder. In each assembly the cells were fed automatically by a single nutrient medium pump-reservoir similar in design concept to those used in the camera-microscope systems. In this case, however, the medium passed through a reservoir to be heated before it was injected into the culture chambers in order to avoid temperature shock to the cells in the growth curve module. The culture chambers were connected by tubing in series such that the medium of the first chamber emptied into the second which emptied into the third and so on down the line. At each feeding enough medium was supplied to provide the last chamber in the series with fresh medium.

At programed intervals during the experiment one chamber at a time was removed from the nutrient supply circuit and connected to a fixative supply by a device called the fixing valve. The fixative employed was 5 percent glutaraldehyde in Earle's Balanced Salt Solution. The fixing of cells was accomplished by a motor which, upon signal command by a mechanism using a programed punched tape, rotated the fixing valve 22.5 degrees and then advanced the fixative pump sufficiently to fill one chamber with fixative. Similar commands signaled by the program tape then effected fixation of the other chambers. Each time a culture was fixed it no longer required feeding and, accordingly, the tape-program signaled reduction of the amount of nutrient medium provided by the pump to the remaining culture chambers.

The program tape and nutrient supply pump were driven by the same motor. The tape was programed by two rows of punched holes. Microswitch actuators then rode on the tape and dropped into the holes to activate the motor. One row of holes controlled the release of the correct amount of each nutrient feeding while the other row initiated the cycles which injected the fixative solution into each chamber.

Four of the nine chambers of each assembly were not fixed in-flight and after mission day 12 were maintained at approximately 22° C with reduced feedings throughout the rest of the mission. These cells were returned live for subsequent subculturing.

METHODS

Subcultivation and Cell Counting Procedures

Stock cultures of mycoplasma free WI-38 cells, passage number 13, were trypsinized with 0.125 percent trypsin in phosphate buffered saline with 0.02 percent Versene. The cells were thoroughly agitated and suspended in Earle's BME[2] buffered with 28 millimolar HEPES[3] and supplemented with 10 percent fetal calf serum and 100 units/milliliter each of penicillin and streptomycin. The cells in this suspension were counted in a hemocytometer and then diluted to provide a final concentration of 1000 cells per square centimeter. This concentration of cells was then injected into the chambers and allowed to attach to the glass coverslips. After attachment of the cells, the cell population of each chamber was determined by counting the cells with the aid of phase-contrast microscopy. For

[2]BME = Eagle's basal medium Earle's.

[3]HEPES = N-2-hydroxyethylpiperazine-N2-ethanesulfonic acid.

this purpose a one millimeter grid reticle was placed in the 10X eyepiece of the microscope and only those cells were counted which had their nucleus inside or on the top and left edge of the grid square. A total of 16 such areas were counted by moving the chamber in a 4 by 4 pattern. After counting 16 areas, the average cell number per area and the 2σ standard error were calculated. Areas outside of the 2σ limits were rejected and a new average was calculated. This average was multiplied by a factor of 210 to give the number of cells per square centimeter in each chamber. Since there were no chambers fixed on day one, the average cell count of the five chambers was used as the point on the growth curve for day one.

When the hardware was returned to the laboratory after the flight, the cell population of each fixed chamber was again determined in the same manner as the initial cell count with one exception. When a population of 10 000 cells per square centimeter was attained, counting was performed at a higher magnification by using the same grid reticle in a 15X eyepiece instead of the 10X eyepiece. This procedure was necessary to help eliminate the error in counting cells of high density population. The average number of cells per area was then multiplied by a factor of 400 to give the number of cells per square centimeter.

The final number of cells per square centimeter for each chamber was then plotted on 3-cycle semi-logrithmic paper corresponding to the day on which each particular chamber was fixed. For example, chamber 9-(GCM-1) plotted for day 3, chamber 9-(GCM-2) plotted for day 4, chamber 8-(GCM-1) plotted for day 5, *et cetera*.

Film Analysis Procedures

The time lapse films were analyzed with a projector which permitted projection at 1-8, 16 and 24 frames/second in forward, reverse and still and was equipped with a frame counter. Since the intervals between frames were known, it was possible to calculate the exact time of exposure of each frame.

Cells were counted on the projected image every three hours of recorded 20X film. When the cells reached confluency, counting became difficult because cells in close contact were not clearly distinguishable from each other. Consequently, further cell multiplication was determined by adding up the number of observed mitoses. For this purpose the time and location of every mitosis in the field were recorded.

Mitotic activity was calculated from the average cell density and the number of observed mitoses during a given time interval.

The length of individual cell cycles was determined by projection of the film in reverse. Individual cells undergoing mitosis were followed to their previous mitosis or until they migrated out of the field or until they could not be clearly distinguished because they were in close contact with other cells. The observation in reverse was time-saving since only *one* cell needed to be followed instead of two as in the forward mode. This method also inherently excluded observation of cells which migrated out of the field in forward mode. The length of a cycle was arbitrarily chosen to be the time elapsed between the last frame of metaphase of one mitosis and the last frame of metaphase of the following mitosis.

The rate of cell migration was studied by covering the projection screen with paper and tracing the location of the nucleus of individual cells every hour. The displacements were then measured and tabulated. From these data average rates of migration were calculated for individual cells as well as for a given time interval.

Transmission Electron Microscopy

The whole coverslips with attached cell monolayers in 4 percent glutaraldehyde in a cacodylate buffer[4] were received in the electron microscopy laboratory. The coverslips were scored with a diamond pencil and broken into four quarters. Three of the quarters were stored in 4 percent glutaraldehyde and used subsequently for scanning electron microscopy, phase microscopy, and microspectrophotometry. The remaining quarter was prepared for transmission electron microscopy.

The coverslips portions (quarters) for transmission electron microscopy were arranged in a specially designed Teflon rack and placed in an accompanying tank. The cells were rinsed for five minutes in distilled water and then postfixed in Palade's osmium tetroxide fixative (12) for 20 minutes. After a 5-minute distilled water rinse they were stained secondarily with 2 percent uranyl acetate in 70 percent ethyl alcohol for 20 minutes. Following staining with uranyl acetate the coverslips were dehydrated in graded alcohol solutions followed by two propylene oxide baths for five minutes each. The cells were then placed in a 1:1 mixture of propylene oxide and Maraglas for 30 minutes followed by straight Maraglas solution overnight, in the refrigerator. The following day the cells were allowed to come to room temperature. Beem plastic capsules were filled to within one-eighth inch of the top with Maraglas and the capsules as well as the coverslips were placed in a

[4]Cacodylate buffer is made as follows: glutaraldehyde 8 percent, EM grade, 100 cc; 0.2 M sodium cacodylate, 84 milliliters; and 10X concentrated Earle's Balanced Salt Solution without sodium bicarbonate, 16 milliliters; to make a total volume of 200 milliliters.

bell jar which was evacuated to release any air bubbles which might be present in the Maraglas. After the vacuum treatment, the coverslips were drained and laid cell side up on a thin piece of aluminum foil. The Beem capsules were inverted over the coverslips and the coverslips were then placed in a 60° C oven. After 16 to 17 hours and partial polymerization, the capsules were removed one at a time from the oven and, using a pair of tongs, the lower half of the coverslips was immersed in an acetone dry ice bath at -80° C for about 60 seconds. The coverslip was immediately popped off using the thumb on part of the overlapping coverslip as leverage. This procedure was successful only if the capsules were taken from the oven one at a time since any cooling of the capsule resulted in failure of the coverslip to be removed. When the coverslip was removed, it left the monolayer of cells embedded in the Maraglas. The capsules were returned to the 60° C oven for 48 hours to complete polymerization. The Beem plastic capsule was cut and removed from the plastic block. The surface of the block containing the cell monolayer was then scored with a small radial saw producing one millimeter squares. The scored cell surface was examined under a dissecting microscope and an area selected for sectioning. The remaining squares were sawed off with a jeweler's blade and stored for future use. Sections were cut with a microtome and a diamond knife. Silver colored sections were used. Copper grids of 300 mesh with and without Formvar films were used to hold the sections. Sections were stained with uranyl acetate and lead citrate (13) and examined with a transmission electron microscope.

Scanning Electron Microscopy

Selected coverslip portions (quarters) with attached cell monolayers were prepared for scanning electron microscopy. The cells were fixed in glutaraldehyde and Palade's solution identical to the procedures outlined for transmission electron microscopy. They were dehydrated in graded alcohols and, after the absolute alcohol, they were transferred to a mixture of absolute ethanol and amyl acetate. This was followed by two changes of amyl acetate and subsequent critical-point drying, utilizing liquid carbon dioxide and a critical-point drying apparatus (14). After critical-point drying, the coverslips were removed from the drying chamber and coated with gold and palladium in an evaporator. The dried and coated specimens were examined with a scanning electron microscope.

Phase Microscopy

For phase microscopy the cells were fixed with glutaraldehyde and osmic acid as for electron microscopy. After osmic acid fixation the cells were rinsed in distilled water and mounted in a gelatin phenol mixture (15). The mixture of gelatin and phenol has a refractive index

of approximately 1.041 and is an ideal embedding medium for examination of fixed cells with phase microscopy. The cells were examined with a regular phase and anoptral phase microscope utilizing a W-58 green filter. In addition, the preparations were studied with an interference phase microscope utilizing the W-58 green Wratten filter.

Chromosome Analysis

Chromosome analyses were performed on preflight and flight backup control cultures and on subcultured flight cultures. The cultures were incubated overnight with fresh growth medium, then harvested by standard colchimid arrest and hypotonic treatment procedures. Air dried slides were made for banding analysis. If the cultures were confluent when received they were lightly subcultured and harvested the following day. Cultures were saved and subsequently frozen for storage from all lots of cells received. Air dried slides obtained from the cultures were treated with either urea (16) or trypsin (17) to obtain G-banding patterns. C-band patterns were obtained by the alkaline-SSC denaturation-renaturation procedure (18). All slides were coded before analysis and banding pattern data recorded by number to reduce bias. At least 50 cells were counted from each culture lot to determine the 2n count. Five cells from each control culture were analyzed for G-band pattern and 10 cells were analyzed for C-band pattern. At least 10 cells of the "flight" culture were analyzed for G-band pattern and 20 cells were analyzed for C-band pattern.

Microspectrophotometry

Scanning microspectrophotometry was used to compare semiquantitative data from Feulgen-stained nuclei of human tissue culture cells grown during space flight (Skylab 3) in zero-gravity with matched ground controls (19,20,21,22,23). In-flight and control specimens obtained on mission days 3, 6, 7, 10 and 11 were used for this study.

Scanning microspectrophotometry was performed on selected areas of the nuclei using a scanning microscope photometer having a 1-micron measuring spot at 1 micron intervals at 540 nanometers. For each nucleus scanned, three traverses through the center, or near the center, were made. The edited data provided a raw data matrix of 5 x 3 (15 adjacent optical density values 1 micron apart) from within the nucleus. The data was stored on LINC tape using a PDP-12 computer. Selected area scans of approximately 50 nuclei were obtained for each population of cells. Various computer programs were used for additional editing, raw data print-out matrices, and statistical analysis of the data.

Tissue culture cells stained with Schiff's reagent using a modified Feulgen procedure were used for this study. To identify deoxyribonucleic acid (DNA) Schiff-positive sites in glutaraldehyde-fixed cells, it was necessary to modify the standard Feulgen reaction by addition of a prestaining oxidation with acidified hydrogen peroxide (H_2O_2), a modification of procedure described by Pool (24).

Materials. Schiff's Reagent: Dissolve one gram of basic fuschin (Cert. PF-3, C.I. H2500) in 200 milliliters boiling distilled water. After cooling to 50° C, filter and add 20 milliliters of 1 N hydrochloric acid (HCl) to the filtrate. Cool this solution to 25° C, add 1 gram of sodium metabisulfite and place the solution in the dark for 24 hours. Decolorize with 2 grams of activated charcoal, and filter.

Oxidizing solution (HPSA): Prepare a 10 percent acidified hydrogen peroxide solution by adding 45 milliliters of 30 percent H_2O_2 to 90 milliliters of distilled water. Adjust the pH to 3.2 with 0.1 N sulfuric acid.

Procedure for processing tissue culture cells for DNA Schiff positive sites.

1. Oxidize with HPSA for 20 minutes.
2. Rinse briefly in distilled water.
3. Place in 1 N HCl at 60° C for three minutes.
4. Rinse briefly in distilled water.
5. Transfer to Schiff's reagent for 30 minutes.
6. Rinse in distilled water.
7. Dehydrate in alcohol.
8. Clear in xylene and mount in Permount.

Media Analysis

When the flight hardware and the backup units were returned to the laboratory, samples of the used media were analyzed in the SMA-12 autoanalyzer at the clinical laboratories of Parkland Hospital in Dallas, Texas by Dr. Robert Putnam. Amino acid analyses were performed by Dr. Kenneth Wiggans, biochemist at the University of Texas Health Science Center in Dallas. These results were compared with similar analyses of freshly prepared media.

RESULTS

Growth Curve Analysis

Figure 4 delineates the data for the growth curves of the cells in the flight unit and for the cells in the second backup unit. Inspection of

the two curves show them to be identical S-shaped growth curves. All of the ground based control studies performed yielded identical curves.

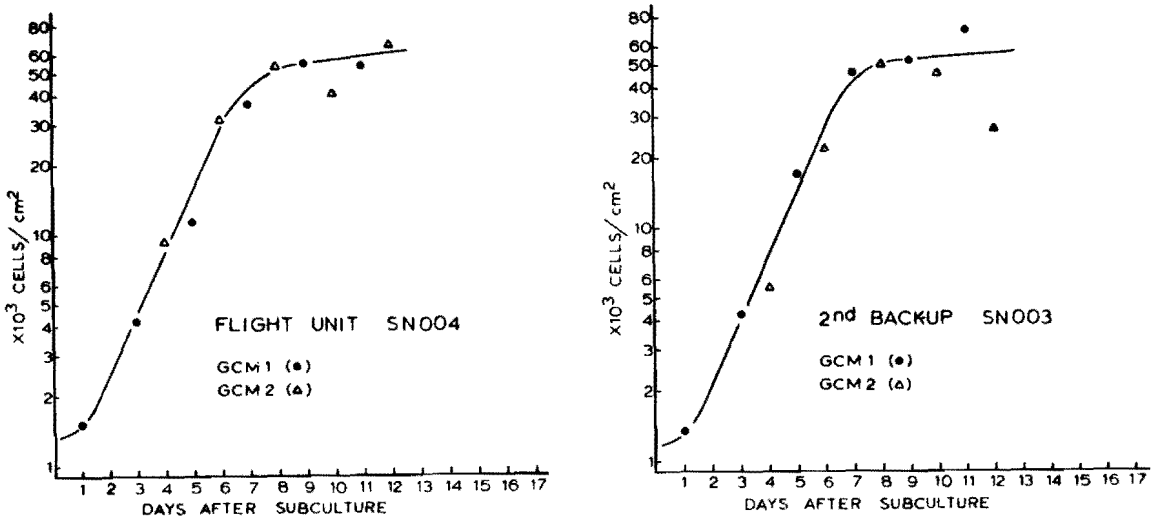


Figure 4. Growth curve data for flight and ground control units.

Film Analysis

Table I is a table of the length of individual cell cycles, in hours, from cells in the flight units and from cells in the backup units. The data indicate that exposure to zero-gravity did not influence the duration of the cell cycle nor the results of mitosis.

TABLE I. LENGTH OF INDIVIDUAL CELL CYCLES, IN HOURS

FLIGHT	CONTROL
28.2	32.4
27.4	22.2
23.7	20.8
22.8	20.7
22.5	19.6
21.3	19.6
21.0	18.8
20.7	17.7
19.9	17.2
19.4	14.5
18.5	
AVERAGE 22.3 ± 3.1	20.4 ± 4.8

Figure 5 is a graph indicating the number of mitoses in the flight units and in the backup units. As can be seen there are no significant differences between the flight units and the control or backup units.

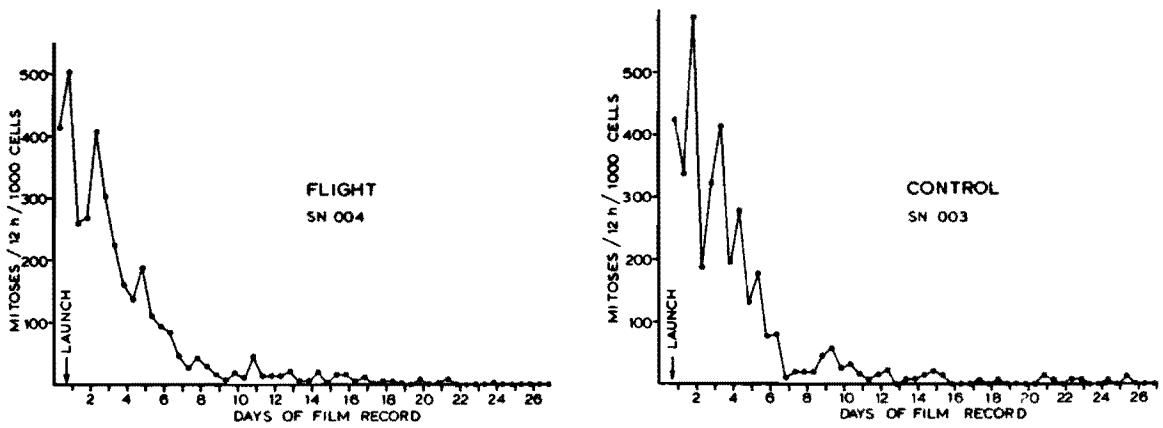


Figure 5. Mitotic Index for flight and ground control cultures.

Table II compares the migration rates of cells in the flight unit with the migration of cells in the backup unit. In each case the migration rates are comparable.

TABLE II. RATES OF CELL MIGRATION IN THE FLIGHT AND GROUND CONTROL CULTURES

	FLIGHT	CONTROL
TOTAL NUMBER OF HOURLY DISPLACEMENTS MEASURED	332	480
AVERAGE RATE OF MIGRATION (microns/h)	37.25	34.7
STANDARD DEVIATION (microns/h)	±20.8	±22.5
LOWEST OBSERVED RATE (microns/h)	3	0
HIGHEST OBSERVED RATE (microns/h)	95	114

The flight and control films were independently reviewed by several scientists. No differences between the flight films and the backup control films were observed for such cellular parameters as vacuole formation, mitosis, cell movement, cell size, nuclear size and location;

nucleolar size, shape, location, and number; presence and location of cytoplasmic organelles, sol-gel state of the cytoplasm and cellular behavior on contact as confluence in each culture was reached.

Chromosome Banding Pattern Analysis

The normal G-band and C-bad patterns were found in all cultures, including the flight material, examined. No abnormalities of banding patterns were observed. The normal G-band pattern is presented in figure 6 and the normal C-band pattern is seen in figure 7. Both figures are from the "flight" culture.

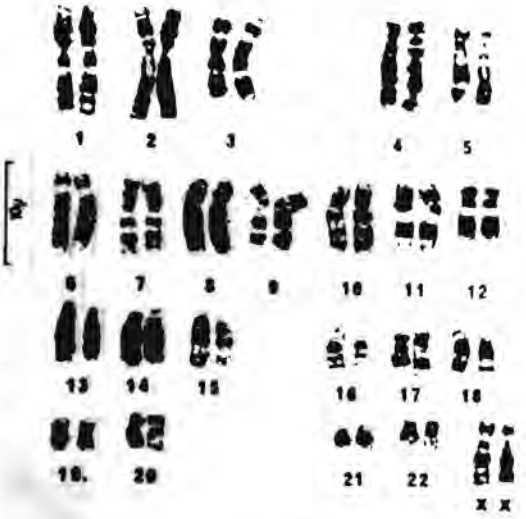


Figure 6. Chromosome G-banding of WI-38 flight cells.

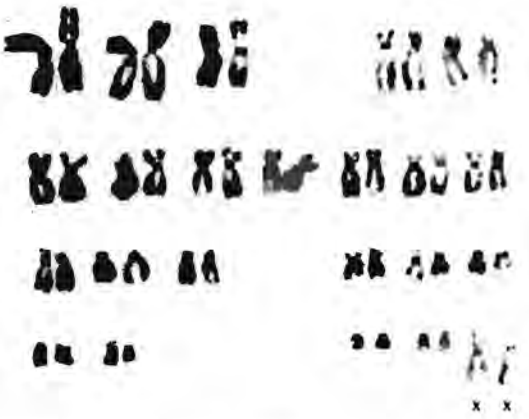


Figure 7. Chromosome C-banding of WI-38 flight cells.

The preflight control culture received from Dr. Montgomery, the control and backup cultures GCM-2053, GCM-2147, GCM-2138, GCM-1808, and the "flight" culture GCM-2052 received from the Hayflick Laboratory all grew well and all were normal diploid lines.

C-banding patterns (constitutive heterochromatin) are known to vary greatly in human populations (25) while G-band patterns are extremely stable. The G-band pattern of man may even be recognized as changed little from those in other higher primates (26, 27). Therefore, we

expected that rearrangements in flight material, if found, would be of the C-band type. However, no C-band changes were noted in any of the cultures.

The results obtained from this study are in keeping with data accumulated by this laboratory from a number of experiments with both human and nonhuman cell cultures. It has been established that diploid cultures, properly maintained, seldom show rearrangements of the chromosomes or changes in banding patterns (28). Cells subjected to radiation (29), chemical stress (30) or other stress factors (31) may develop chromosomal abberations.

Microspectrophotometry

The average optical density value for the 15 determinations from each nucleus was obtained. This value was then used to obtain a mean and ±1 standard deviation (SD) for each population. The results are shown in Table III.

TABLE III. AVERAGE OPTICAL DENSITY OF NUCLEI OF FLIGHT (F) AND CONTROL (C) CELLS

	3-DAY		6-DAY		7-DAY		10-DAY		11-DAY	
	C	F	C	F	C	F	C	F	C	F
Mean	40	44	39	48	41	40	46	45	45	40
±1 SD	14	15	12	12	13	12	12	11	11	7

C = Control
F = Flight

The mean for in-flight specimens is within ±1 SD of the corresponding control. The decrease in the standard deviation with increase in age of the cells is attributed to cell culture growth characteristics. The three-day specimens were characterized by a low population density and the cells were in an asynchronous growth state with all stages of the cell cycle represented.

Figure 8 is a histogram of the frequency of occurrence of the average nuclear optical density value for 3-day, 6-day, 7-day, 10-day, and 11-day control and in-flight nuclei. The distribution of the values shows nuclei in G1, S and G2 phases.

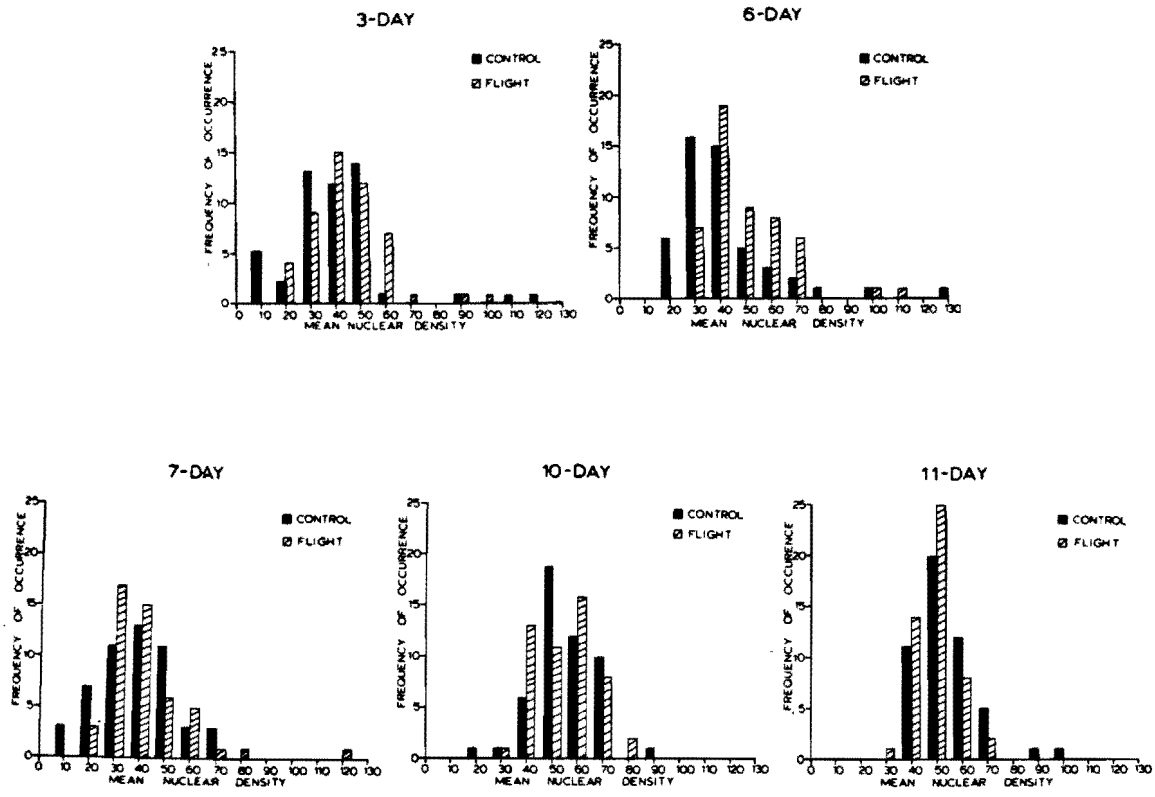


Figure 8. Histogram showing average optical density of flight and control cells.

The 11-day nuclei exhibit a much narrower range in distribution and were also characterized by the lowest standard deviation. This is attributed to the cells having reached a stationary phase since the optical density values indicated a rather uniform population of nuclei in the G1 phase. When the histograms of the populations are compared, the trend from a growth phase (3- and 6-day) to a stationary phase (10- and 11-day) is readily observed.

Whenever possible, mitotic nuclei were scanned in the 3-, 6- and 7-day specimens. On the basis of optical density values, it was determined that all mitotic nuclei contained the 2C complement of nucleoprotein.

None of the scanned yielded data suggesting aneuploidy at the 4C or 8C level. Mitotic nuclei in the 10-day and 11-day specimens were rarely seen and when found, they were usually not in a position to obtain accurate data.

Medium Analysis

Table IV is the result of the SMA-12 analysis of the freshly prepared medium, the used flight medium and the used medium from the backup control unit. The freshly prepared medium differs from the two used medium samples mainly in a higher glucose concentration. There is an unexplained difference in glucose concentration in the used control culture medium (75 mg%) and the flight culture medium (93 mg%). Otherwise, there is no significant difference between the used flight medium and the used control medium.

TABLE IV. SMA-12 ANALYSIS OF FRESH, USED FLIGHT, AND USED GROUND CONTROL CULTURE MEDIUM

	FRESH MEDIA	FLIGHT UNIT		CONTROL	
		GCM1	GCM2	GCM1	GCM2
Na^+ (meq/l)	130.0	131.0	132.0	131.0	130.0
K^+ (meq/l)	5.98	6.22	6.24	6.24	6.20
CO_2 (meq/l)	3.2	0.9	1.2	1.0	1.0
T.P. (g%)	0.7	0.3	0.35	0.3	0.3
Alb. (g%)	0.22	0.06	0.01	0.08	0.08
Ca^{++} (mg%)	7.3	7.35	7.35	7.32	7.35
Glu. (mg%)	124.0	94.0	91.0	71.0	79.0
BUN (mg%)	2.0	1.0	1.0	1.0	1.0
Creat. (mg%)	0.55	0.39	0.42	0.4	0.4
Alk. Phos. (mU/ml)	32.0	9.0	29.0	28.0	28.0
SGOT (mU/ml)	14.0	6.0	7.0	6.0	6.0

Table V gives the results of the amino acid analyses for the freshly prepared medium, the used flight medium and the used backup control unit medium. There appear to be no significant differences between the two samples of used medium.

TABLE V. AMINO ACID ANALYSIS OF FRESH, USED FLIGHT, AND USED GROUND CONTROL CULTURE MEDIA

	FRESH MEDIA	FLIGHT UNIT		CONTROL	
		GCM 1	GCM 2	GCM 1	GCM 2
LYSINE	0.0405	0.0527	0.0502	0.0471	0.0391
HISTIDINE	.0092	.009	.0088	.0085	Trace
ARGININE	.0113	Trace	Trace	Trace	
ASPARTIC ACID	.0057	.0049	.0033	.0062	.0060
THREONINE	.0318	.0318	.0326	.0251	.0280
SERINE	.2825	.280	.277	.222	.266
GLUTAMIC ACID	.0537	.0447	.0442	.0493	.0527
GLYCINE	.0122	.0150	.0197	.0135	.0137
ALANINE	.0160	.0288	.0376	.0283	.0315
CYSTINE (HALF)	.0034				
VALINE	.0379	.0360	.0344	.0298	.033
METHIONINE	.0328	.0153	.0106	.0121	.0085
ISOLEUCINE	.0501	.0282	.0301	.0260	.0280
LUECINE	.104	.0305	.0326	.0283	.0328
TYROSINE		.0137	.0154	.0134	.0124
PHENYLALANINE		.0151	.0171	.0146	.007

Phase, Electron, and Scanning Microscopy of Fixed Cells

A zero-gravity environment produced no observable differences in the flight cells as compared with the ground controls. Both flight and control cells showed identical morphologic changes during the period of the experiment, which we have attributed to age and population density of the cultures. These changes are similar to aging changes in WI-38 cells described by Lipetz and Cristofalo (32). Microvilli are relatively sparse as compared with those present in other cell lines such as Chang liver and Hela cells. As the culture ages and a complete monolayer is formed, the cells become spindle shape and are aligned in a longitudinal direction with other cells to form unidirectional bundles. As these bundles of cells grow and increase in size, they intersect other bundles at varying angles. At the point of junction the two bundles of cells not only interlace but may cross each other at different levels forming a multiple cell layer, rather than a monolayer of cells.

Young cultures at 3 to 6 days of age are rich in ribosomes, filamentous mitochondria, and endoplasmic reticulum, especially in the central portions of the cytoplasm corresponding to the endoplasm. The outer

ectoplasm is rich in microtubules and microfibrils (fig. 9) microfibrils are especially dense adjacent to the plasma membrane where they form distinct bundles which may be demonstrated as light or dark bands with phase microscopy. These bands run in a longitudinal direction just beneath the plasma membrane of the cell (fig. 10).

As the cultures age, a variety of cytoplasmic vacuoles are formed. Transmission electron microscopy shows the vacuoles may be dilated mitochondria, lysosomes, and autophagosomes and fat vacuoles (Fig. 10).

In the 11 to 12 day old cultures filamentous mitochondria and lysosomes are decreased. Endoplasmic reticulum may be decreased and there appears to be a piling up of ribosomes around slightly dilated endoplasmic reticulum tubules. There is a marked increase in the number of microtubules and microfibrils (fig. 11).

Scanning electron microscopy confirms the phase microscopy and transmission electron microscopy observations that these cells have a generally smooth surface and relatively few microvilli. Movies reveal rapid membranous movement of the distal cell surfaces in a beating fashion. This activity was demonstrated in static fashion with the scanning electron microscope (figs. 12 and 13).

CONCLUSION

Twenty separate cultures of WI-38 human embryonic lung cells have been exposed to a zero-gravity environment on a space satellite for periods of time varying from one to 59 days. Duplicate cultures were run concurrently as ground controls. Ten cultures were fixed during the first 12 days of flight. Growth curves, DNA microspectrophometry, phase microscopy, and ultrastructural studies of the fixed cells revealed no effects of a zero-gravity environment on the ten cultures.

Two cultures were photographed by means of phase time-lapse cinematography during the first 27 days of the flight. Analysis of the films revealed no differences in mitotic index, cell cycle, and migration between the flight and control cells.

Eight cultures were not fixed but returned to earth in a viable state after being incubated at 36° C during the first 12 days of the flight and at 22° C for the remainder of the flight. At the present time only karotyping and chromosome banding have been performed in these cells. There are no differences between the flight and control cell cultures.

Minor unexplained differences have been found in biochemical constituents

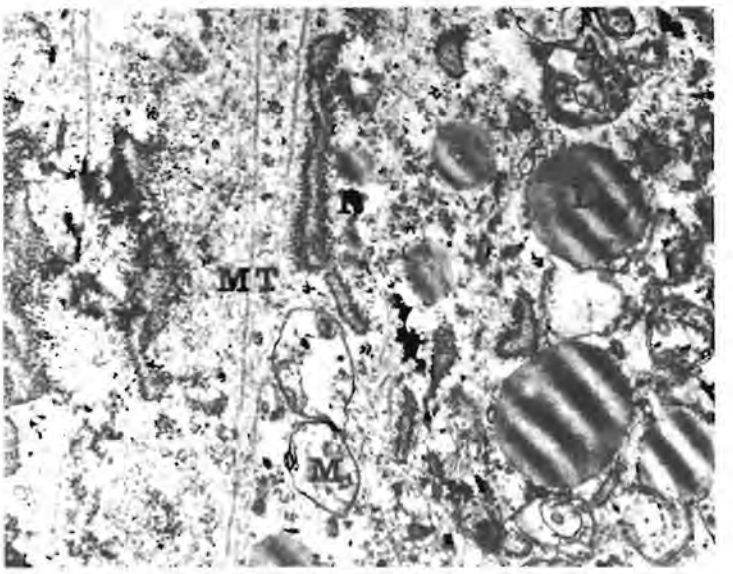


Figure 9. Transmission electron photomicropraph of 6-day old culture at junction of central organelle rich zone of cytoplasm and ectoplasm. Vacuoles in central zone represent swollen mitochondria (M), lysosomes, microtubules (MT), autophagosomes (A) and lipid droplets (L). Endoplasmic reticulum (R). Flight and control cultures are identical. Magnification 50 000X.

Figure 10. Phase photomicrograph of 8-day old WI-38 cell culture. Note overgrowth of one cell over another producing a multilayered colony (O). Numerous clear vacuoles are present (V). A few filamentous mitochondria (M) are present. Glutaraldehyde and osmium tetroxide fixation. Gelatin-phenol mount. Magnification 2000X.

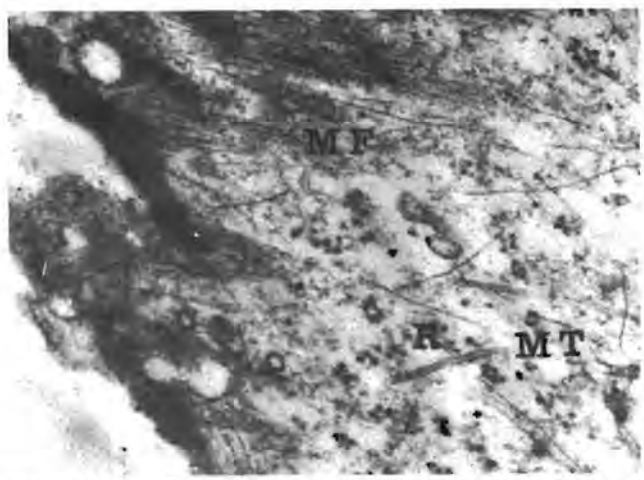


Figure 11. Transmission electron photomicrograph of peripheral cytoplasm showing free ribosomes (R), microtubules (MT) and bundles of microfibrils (MF) beneath plasma membrane. Magnification 100 000X.

Figure 12. Scanning electron photomicrograph of WI-38 cell near end of telophase. Some cytoplasmic bubbling (B) is present. Triangular shaped membranous cytoplasm is beginning to form (T).

Figure 13. High magnification of triangular shaped membranous cytoplasm in previous picture. Note folded cytoplasm (F), static view of the membranous beating of peripheral cytoplasm typical of cells in tissue culture. Microvilli are sparse in the WI-38 cell. Magnification 20 000X.

of the used flight and control media. Our present opinion is that these changes are of no significance.

Within the limits of the experimental design, it was found that a zero-gravity environment produced no detectable effects on Wistar-38 human embryonic lung cells in tissue culture.

REFERENCES

1. Knight, Thomas A. 1806. On the Direction of the Radical and Germen during the Vegetation of Seeds. *Phil. Trans. Royal Soc. London,* Vol. 96, pp. 99-108.

2. Pflüger, Eduard F. W. 1883. Uber den Einfluss der Schwerkraft auf die Theilung der Zellen. *Archiv fur die Gesammte Physiologie des Menschen und der Thiere,* vol. 31, pp. 311-318.

3. Harvey, E. N. and A. L. Loomis. 1930. Scientific Apparatus and Laboratory Methods: A Microscope Centrifuge. *Science,* vol. 72, no. 1854, pp. 42-44.

4. Allen, R. D. 1960. The Consistency of Ameba Cytoplasm and Its Bearing on the Mechanism of Ameboid Movement. II. The Effects of Centrifugal Acceleration Observed in the Centrifuge Microscope. *J. Biophys. Biochemistry Cytology,* vol. 8, pp. 379-397.

5. Allen, R. D. and J. D. Roslansky. 1959. The Consistency of Ameba Cytoplasm and Its Bearing on the Mechanism of Ameboid Movement. I. An Analysis of Endoplasmic Velocity Profiles of *Chaos Chaos* (1). *J. Biophys. Biochemistry Cytology,* vol. 6, pp. 437-446.

6. Harvey, E. N. and D. A. Marsland. 1932. The Tension at the Surface of *Amoeba dubia* with Direct Observations on the Movement of Cyotplasmic Particles at High Centrifugal Speeds. *J. Cell Comp. Phys.,* vol. 2, pp. 75-97.

7. Heilbrunn, L. V. and K. Daugherty. 1932. The Action of Sodium, Potassium, Calcium and Magnesium Ions on the Plasmagel of *Amoeba proteus. Physiology Zoology,* vol. 5, pp. 254-274.

8. Matthews, B. H. C. Proceedings of the Physiological Society, July 24-25, 1953. Adaptation to Centrifugal Acceleration. *J. of Physiol.,* vol. 122, p. 31.

9. Wunder, C. C. 1962. Survival and Growth of Organisms during Life-Long Exposure to High Gravity. *Aerospace Med.,* vol. 33, pp. 355-356.

10. Montgomery, P. O'B., F. Van Orden and E. Rosenblum. 1963. A Relationship Between Growth and Gravity in Bacteria, *Aerospace Med.*, vol. 34, no. 4, pp. 352-354.

11. Montgomery, P. O'B., J. Cook and R. Frantz. 1965. The Effects of Prolonged Centrifugation on *Amoeba proteus*. *Exp. Cell Res.*, vol. 40, pp. 140-142.

12. Palade, G. E. 1952. A Study of Fixation for Electron Microscopy. *J. Exp. Med.*, vol. 95, pp. 285-298.

13. Reynolds, Edward S. April 1963. The Use of Lead Citrate at High pH as an Electron Opaque Stain in Electron Microscopy. *J. of cell Biol.*, vol. 13, pp. 208-212.

14. Anderson, T. E. 1951. Techniques for the Preservation of 3-Dimensional Structure in Preparing Specimens for the Electron Microscope. *Trans. N. Y. Acad. Sci.*, II, vol, 13, p. 130.

15. Dixon, R. Phillippine and J. H. Holmes. October 1962. Teaching Slide Preparations of Urinary Sediment. *Amer. J. of Clin. Path.*, vol. 38, no. 4, pp. 444-448.

16. Shiraishi, Y. and T. H. Yosida. 1972. Banding Pattern Analysis of Human Chromosomes by Use of a Urea Treatment Technique. *Chromosoma* (Berl.), vol. 37, pp. 75-83.

17. Seabright, M. 1972. The Use of Proteolytic Enzymes for the Mapping of Structural Rearrangements in the Chromosomes of Man. *Chromosoma* (Berl.), vol. 36, pp. 204-210.

18. Stefos, K. and F. E. Arrighi. 1971. Heterochromatic Nature of W Chromosome in Birds. *Exptl. Cell Res.*, vol. 68, pp. 228-231.

19. Bartels, P. H., G. F. Bahr, J. Griep, H. Rappaport and G. L. Wied. 1969. Computer Analyses of Lymphocytes in Transformation. A Methodologic Study. *Acta Cytol.*, vol. 13, pp. 557-568.

20. Bartels, P. H., G. F. Bahr and G. L. Wied. 1970. Information Theoretical Approach to Cell Identification by Computer. In Automated Cell Identification and Cell Sorting, G. L. Wied and F. G. Bahr eds., Academic Press, New York, pp. 361-384.

21. Rogers, T. D., V. E. Scholes and H. E. Schlichting, Jr. 1972. Rapid Scanning Microspectrophotometry of Colorless *Euglena grucillis and Astoria longa*. A Basis for Differentiation. *J. Protozool.*, vol. 19, pp. 150-155.

22. Wied, G. L., P. H. Bartels, G. F. Bahr, and D. C. Oldfield. 1968. Taxonomic Intra-Cellular Analytic System (TICAS) for Cell Identification. *Acta Cytol.*, vol. 12, pp. 180-204.

23. Wied, G. L., G. F. Bahr and P. H. Bartels. 1970. Automated Analysis of Cell Images by TICAS. In Automated Cell Identification and Cell Sorting, G. L. Wied and G. F. Bahr eds., pp. 195-360.

24. Pool, Charlotte R. 1973. Prestaining Oxidation by Acidified H_2O_2 for Revealing Schiff-Positive Sites in Epon-Embedded Sections. *Stain Technology*, vol. 48, no. 3, pp. 123-126.

25. Craig-Holmes, A. P. and M. W. Shaw. 1971. Polymorphism of Human Constitutive Heterochromatin. *Science*, no. 174, pp. 702-704.

26. De Grouchy, J., and C. Turleau. 1972. Evolution Caryotypiques de l'homme et du Chimpanze. Etude Comparative des Topographies de Bands Apres Denaturation Menagee. *Ann. Genet.*, vol. 15, pp. 79-84.

27. Stock, A. D., and T. C. Hsu. 1973. Evolutionary Conservatism in Arrangement of Genetic Material: A Comparative Analysis of Chromosome Banding Between the Rhesus Macaque (2n=42, 84 arms) and the African Green Monkey (2n=60, 120 arms). *Chromosoma* (Berl.), vol. 43, pp. 211-224.

28. Hsu, T. C. and J. E. K. Cooper. (in press), 1974. On Diploid Cell Lines. *J. Natl. Cancer Inst.*

29. Fox, M. and A. H. Nias. 1968. The Assessment of Radiation and Chemical Damage in Cultured Mammalian Cells. *J. Physiol.*, vol. 197, pp. 52-53.

30. Bartalos, M. and T. A. Baramki. 1967. Effects of Drugs on Chromosomes. In Medical Cytogenetics, The Williams and Wilkins Company, Baltimore, pp. 400-404.

31. Hampel, K. E. and A. Levan. 1964. Breakage in Human Chromosomes Induced by Low Temperature. *Hereditas*, vol. 51, pp. 315-343.

32. Kipetz, J. and V. J. Cristofalo. 1972. Ultrastructural Changes Accompanying the Aging of Human Diploid Cells in Culture. *J. Ultrastructure Res.*, vol. 39, pp. 43-56.

IMMUNITY (M112)

S. E. Ritzmann, M. D.
University of Texas Medical Branch
Galveston, Texas

(Copy of paper not provided for publication)

BLOOD VOLUME CHANGES

Philip C. Johnson, M.D., Theda B. Driscoll**
*and Adrian D. LeBlance, Ph.D.**

ABSTRACT

Analysis of radionuclide volume determinations made for the crewmembers of selected Gemini and Apollo missions showed that orbital spaceflight has an effect on red cell mass. Because the methods and the protocol developed for earlier flights were used for the crews of the three Skylab missions, direct comparisons are possible. After each Skylab mission, decreases were found in crewmembers' red cell masses. The mean red cell mass decrease of 11 percent or 232 milliliters was approximately equal to the 10 percent mean red cell mass decrease of the Apollo 14 to 17 crewmembers.

The red cell mass drop was greatest and the postrecovery reticulocyte response least for crewmembers of the 28-day Skylab 2 mission. Analyses of data from the red cell mass determinations indicate that the red cell mass drops occurred in the first 30 days of flight and that a gradual recovery of the red cell mass deficits began approximately 60 days after launch. The beginning of red cell mass regeneration during the Skylab 4 flight may explain the higher postmission reticulocyte counts.

INTRODUCTION

Decreased red cell mass has been found regularly among astronauts who return from space flight. This was first documented in the crew of the 8-day Gemini 5 mission and confirmed in the crewmembers of the 14-day Gemini 7 mission. Simultaneously estimated ^{51}Cr red blood cell halftimes were shortened suggesting hemolysis combined with a bone marrow unresponsive to the decrease were the major causes of the observed decrease in red cell mass (1). Similar studies after four Apollo moon landing missions showed that the red cell mass decreases were not associated with decreased ^{51}Cr red blood cell survivals suggesting that marrow inhibition rather than hemolysis may have been the cause of the 10 percent mean red cell mass loss. The crews of both the Apollo and Gemini missions were exposed to at least four hours of 100 percent oxygen at 760 torr (1.0132×10^5 N/m^2) prior to

*Baylor College of Medicine, Houston, Texas

launch and during flight to a hypobaric-hyperoxic atmosphere [100 percent oxygen, 258 torr (0.3440×10^5 N/m^2)]. It has been tempting to explain the decrease in red cell mass as due to the effects of hyperoxia since hyperoxia is known to both inhibit erythropoiesis and cause hemolysis (2,3).

The Skylab missions differ from the Apollo missions by not having hyperoxic environment except for two hours of 100 percent oxygen at 760 torr (1.0132×10^5 N/m^2) prior to launch and for a few hours during the first day when the atmosphere was similar to that of Apollo. The Skylab missions have afforded an opportunity to rule out the hyperoxic hypothesis of the red cell mass decrease while at the same time testing whether changes in red cell mass are progressive with longer periods in weightlessness.

METHODS

Red cell mass measurements were made according to the following schedule. Skylab 2, a 28-day mission: 29 days prior to launch, recovery day and 13, 42 and 67 days later; Skylab 3, a 59-day mission: 20 days before launch, recovery day and 14 and 45 days later; and Skylab 4, an 84-day mission: 21 and 1 day before launch, recovery day and 14 and 31 days later. All specimens were drawn in the morning after an overnight rest with the crewman fasting except for the recovery day samples which were drawn within two hours of the time when the spacecraft landed in the ocean. The 12.5 milliliters of blood drawn for the red cell mass was mixed with 2.5 milliliters of special ACD solution and 25 μCi ^{51}Cr. Sixty milliliters of blood to satisfy the blood requirements of other experiments was drawn prior to the reinfusion of the 10 milliliters of the ^{51}Cr tagged red cells. The cells were incubated for four minutes at room temperature and subsequently 14 milligrams of ascorbic acid was added prior to reinfusion. The red cell mass determination was obtained by averaging the red cell radioactivity of a 30- and 31-minute sample. For each specimen, 2.5 milliliters of blood was drawn. Plasma radioactivity was separated to remove the effect of untagged chromium. The methods used to assure accurate injection and statistically significant counting of the radioactivity are described elsewhere (4).

Thirty days prior to launch, 50 μCi ^{14}C-glycine was injected intravenously for a red cell life span study; the ^{14}C radioactivity was followed for a total of 125 days on the first mission, 131 days on the second mission, and 141 days on the third mission. Blood was generally drawn weekly throughout this period including the time in space. Radioactivity was determined by extracting heme, igniting the dried extract and determining μCi of ^{14}C per milligram heme. At

recovery, 2 μCi of ^{59}Fe citrate was injected for calculation of iron turnover using the 30-, 31-minute samples and a blood sample drawn 2 to 3 hours later. Iron reappearance was obtained from blood samples drawn 1, 3, 7, and 14 days after recovery. Reticulocyte counts were obtained weekly preflight and postmission. Activity of ^{51}Cr red cells was measured to estimate red cell chromium halftime. The total blood drawn for each crewmember is shown in table I.

TABLE I. BLOOD DRAWN FOR SKYLAB CREW MEMBERS AND CONTROL SUBJECTS

Mission Duration (Days)	Preflight ml/days	During Flight ml/days	Postflight ml/days	Total* ml/days	Mean ml/day ml
28	385/30	44/28	365/18	794/76	10
59	344/21	88/59	373/20	805/100	8
84	378/35	88/84	423/21	889/140	6

*Total milliliters blood/days between first and last blood draw. No single blood specimen exceeded 100 milliliters in any 24-hour period.

To insure that the amount of blood drawn did not influence these results, similar amounts of blood were drawn from healthy control subjects. These control subjects were approximately the same age as the crewmembers. Since the control subjects accompanied the medical team to the recovery carriers and Cape Kennedy, their blood results were a confirmation that the remote facilities and delayed final preparation did not affect the results.

RESULTS

Table II shows the red cell mass volume values obtained from the nine crewmembers and the nine control subjects. These are presented as total red cell mass (milliliters) and on a milliliters per kilogram body weight basis.

The mean value of the premission red cell mass of the crewmembers was 2075 milliliters which is not different from the mean values of the controls, 2053 milliliters. The mean values of the red cell mass/kilograms body weight was 28.9 milliliters/kilogram for the crew and

TABLE II. RED CELL MASS AND RED CELL MASS/KILOGRAM BODY WEIGHT OF SKYLAB CREWMEMBERS AND CONTROL SUBJECTS

		Crewmember (milliliters/milliliters per kilogram)			Controls (milliliters/milliliters per kilogram)		
Mission	Day	Commander	Scientist Pilot	Pilot	1	2	3
28-Day	F-29	2097/33.5	2088/26.6	2394/29.3	1918/25.6	2213/27.6	1798/23.0
	R+0	1778/29.5	1763/23.7	2104/27.7	1949/26.0	2299/28.9	1718/21.9
	R+13	1729/28.4	1745/23.3	2088/27.0	1911/26.0		
	R+42	1927/30.0		2340/28.7			
	R+67	2033/31.1	2120/27.3	2441/29.8			
59-Day	F-20	1841/26.9	1780/28.9	2608/30.0	2237/28.0	2250/30.0	1932/29.5
	R+0	1728/26.7	1427/24.3	2332/27.2	2154/27.3	2259/30.2	1899/28.2
	R+14	1792/27.2	1534/25.1	2454/27.6	2122/26.6		1883/28.3
	R+45	1898/27.2	1810/28.9	2690/30.4			
84-Day	F-21	1920/28.4	2030/28.5	1904/28.0	2119/27.4	2197/29.7	1817/24.2
	F-1	1891/27.8	2000/28.0	1962/29.2	2119/27.4	2258/30.5	1766/23.3
	R+0	1813/26.6	1851/26.4	1790/27.0	2096/27.8	2187/29.4	1845/24.2
	R+14	1829/26.6	1941/27.1	1826/27.0	2070/26.7	2175/29.6	1752/23.1
	R+31	1995/28.8	2066/27.8	2010/28.8			

F is days before launch.
R is days following recovery from flight.

27.2 milliliters/kilogram for the controls. These mean values are not different statistically. The recovery mean value of the crew, 1843 milliliters, was different from their preflight mean value and different from the control postflight mean of 2046 milliliters (P = <0.05). The crewmembers showed a mean value decrease of 232 milliliters and the controls showed a decrease of 8 milliliters. Calculated on a milliliters/kilogram body weight basis, the crew's postmission mean value was 26.6 milliliters/kilogram body weight or 2.3 milliliters less than premission while the controls did not change from the premission value of 27 milliliters/kilogram body weight.

Evidence against a hemolytic process is presented in table III where the ^{51}Cr red cell $T_{\frac{1}{2}}$ preflight and postmission values and the ^{14}C-glycine red cell life span mean values are shown. There is no difference of statistical significance between the preflight and postflight crew mean values or the crew and control mean values either for the ^{51}Cr $T_{\frac{1}{2}}$ or the ^{14}C-glycine red cell mean life span.

Table IV shows the iron turnover results. The 0.32 milliliters/kilogram body weight per day for the crew is similar to the 0.30 milliliters/kilogram body weight per day for the control subjects. Statistical analysis indicates no difference between controls and crew in reappearance or turnover indicating that the rate of erythropoiesis was essentially the same for crewmembers and control subjects.

Table V shows the reticulocyte counts arranged according to mission. These are shown as the number of reticulocytes per cubic milliliters of blood X 10^{-3}. The reticuoctye counts were low when drawn at recovery following each mission. Postmission reticulocyte counts greater than premission means were found in only one crewmember of the 28-day mission at 2 weeks, the 3 crewmembers of the 59-day mission at 1 week, and 1 week or less for the 84-day mission's crew. These results indicate that red cell mass regeneration did not occur until fourteen or more days after recovery from the shortest mission. The control subjects did not develop a change in the reticulocyte count at any time indicating that reticulocyte changes found in the crewmembers were not caused by the blood drawing schedule.

DISCUSSION

The red cell mass results of the Skylab studies show that the crewmembers sustained a statistically significant decrease in circulating red cells. The decreases were not found among the ground-based control subjects indicating that the blood drawn for the extensive metabolic studies did not cause the change. Additionally, the second red cell mass

TABLE III.

^{51}Cr RED CELL HALFTIMES IN DAYS OF SKYLAB CREWMEMBERS AND CONTROL SUBJECTS

Mission Duration (Days)	Crewmembers			Controls		
	Preflight	Post-Flight	Change	Preflight	Post-Flight	Change
28	31.2	24.2	-7.0	23.8	23.3	-0.5
	26.6	21.7	-4.9	24.7	23.0	-1.7
	27.9	24.4	-3.5	23.1	21.0	-2.1
59	24.4	22.8	-1.6	26.4	22.0	-4.4
	28.8	27.2	-1.6	21.5	22.0	+0.5
	25.6	23.6	-2.0	24.0	23.2	-0.8
84	24.4	27.4	+3.0	29.0	26.7	-2.3
	22.7	24.5	+1.8	25.6	24.8	-0.8
	23.5	21.8	-1.7	20.0	20.1	+0.1
MEAN	26.1	24.2	-1.9	24.2	22.9	-1.3
±S.E.	±0.9	±0.7	±1.0	±0.9	±0.7	±0.5

^{14}C-GLYCINE RED CELL MEAN LIFE SPAN IN DAYS

	Crewmembers	Controls
28	130	-
	117	-
	116	-
59	128	116
	122	122
	122	107
84	125	130
	131	128
	113	106
MEAN	123	121
±S.E.	±2	±4

TABLE IV. IRON TURNOVER

Mission Duration (Days)	(ml/kg body weight per day) Crewmembers	Controls
28	0.22	0.38
	0.35	0.33
	0.38	0.35
59	0.39	0.29
	0.24	0.30
	0.21	0.29
84	0.30	0.21
	0.38	0.23
	0.42	0.32
MEAN	0.32	0.30
±S.E.	±0.03	±0.01

obtained from the crew prior to the 84-day mission showed that no decrease in red cell mass occurred prior to launch indicating that premission preparations did not cause the change. Iron turnover immediately post recovery was normal. The depressed reticulocyte counts at recovery indicate inhibited reticulocyte release or accelerated loss of reticular material. The lowering of reticulocyte counts was greatest for the crew of the shortest mission and least for the crew of the longest mission. This suggests the 84-day crew may already have been in the recovery or replacement phase of red cell mass prior to their return from weightlessness. The red cell mass mean decrease found after the 28-day Skylab mission was greater than the mean results obtained from the Apollo crewmembers while the mean decrease found after the longest Skylab mission was less (5).

The etiology of the red cell mass drop and lowered reticulocyte counts at recovery is unknown. The red cell mass is the most stable of the various blood constituents. Sudden drops in red cell mass are possible due to hemorrhaging or hemolysis. Gradual decreases are produced by inhibition of bone marrow activity, ineffective erythropoiesis or chronic hemorrhage. There was no clinical evidence of hemorrhage among the crews and haptoglobin levels have tended to be normal or elevated rather than suppressed indicating that intravascular hemolysis did not occur in Apollo or Skylab crews (6). Iron reappearance data gave no clinical evidence to suggest ineffective erythropoiesis. The low reticulocyte counts are additional evidence against ineffective erythropoiesis.

TABLE V. RETICULOCYTE COUNTS OF SKYLAB CREW MEMBERS
(Reticulocytes X $10^{-3}/mm^3$ Blood)

Mission Duration	28 Days			59 Days			84 Days		
Crewmembers	Commander	Scientist Pilot	Pilot	Commander	Scientist Pilot	Pilot	Commander	Scientist Pilot	Pilot
Premission Mean	37	37	27	32	33	43	48	43	44
±SD	2	1	3	6	3	2	5	7	3
Recovery Day (R)	17	19	8	25	21	29	41	38	40
R+1 Day	18	24	12	-	-	-	46	45	67*
R+3 Days	24	30	14	29	24	41	38	48*	31
R+1 Week	29	30	22	42*	55*	102*	66*	55	72
R+2 Weeks	28	38*	21	38	81	126	77	88	83
R+3 Weeks	33	35	26	88	74	91	77	78	88

*First value greater than premission mean.

An age dependent loss of red cells is a possibility and would not be seen in the survival curves obtained if red cells greater than 30 days of age were sequestrated and destroyed selectively during the first few mission days. Loss of cells older than 30 days would not affect the results since the older cell did not contain the ^{14}C-glycine.

Premature loss of older cells without intravascular hemolysis suggests red cell surface and shape changes. This was actually found since all crewmembers showed an increase in abnormal red cell shapes including crenated erythrocytes in the scanning electron microscope evaluation of their blood samples taken at the end of the flight (7). Hyperoxia through lipid peroxidation could cause the red cell shape changes. This may have been the cause of the red cell mass decreases found in Gemini and Apollo crewmembers. It could not explain the red cell mass decrease noted in the Skylab crewmembers. Therefore, other aspects of the environment must have caused this change. A possible but unproven explanation of this combination of abnormally shaped red cells and decreased red cell mass among the Skylab astronauts would be a change in splenic function during the mission. Hypersplenism could start early during the mission when the blood volume was relatively too large perhaps associated with the increased portal pressure and/or decreased portal flow. This would be consistent with the two or three days of nausea and loss of appetite reported by susceptible crewmembers.

The crewmembers' reticulocyte counts were low at recovery indicating increased splenic removal of reticulum or decreased bone marrow production rates. A vitamin E deficiency is one cause of early reticulum loss, but inhibited bone marrow is more likely because the red cell mass stayed low. Bone marrow function would not increase to replace the lost red cells if oxygen delivery to the kidney was maintained. Either hyperoxia or hyperphosphatemia could cause this by shifting the oxygen disassociation curve to the right. In this way net oxygen delivery to the tissues is increased making a lowered red cell mass adequate for tissue oxygen (8). This mechanism helps account for the Skylab results since in-flight blood specimens showed higher phosphorus levels. The red cell mass decrease associated with space flight is not followed by a decrease in hemoglobin concentration since plasma volume decreases occur at the same time (5). The kidneys use both changes in hemoglobin concentration and oxygen delivery to modulate erythropoietin release. Thus, the decreased red cell masses of the Skylab crewmembers might not be followed by compensatory increases in erythropoietin until plasma volume increased. Without increased erythropoietin, bone marrow activity would not increase and should appear inhibited until a new equilibrium is reached.

Both hyperphosphatemia and the decreased plasma volume seem to explain the low reticulocyte counts found at recovery. At recovery iron turnover was normal indicating a possible rebound in bone marrow activity. The rapid expansion in plasma volume during that time could account for the normal iron turnover.

SUMMARY

Taken in its totality with previous flight data, the Skylab data confirm that a decrease in red cell mass is a constant occurrence in space flight. Except in the Gemini missions the decrease does not seem to be caused by intravascular hemolysis. Splenic trapping of red cells is a plausible explanation for the loss of red cells. After the initial loss, there is at least a 30-day delay before the red cell mass begins to reconstitute itself indicating an inhibited bone marrow. Bone marrow function is inhibited because the decrease in red cell mass is associated with a decrease in plasma volume and increased plasma phosphorus levels. This combination probably explains the observed decrease in reticulocyte counts.

REFERENCES

1. Fischer, C. L., P. C. Johnson, and C. A. Berry. 1967. Red blood cell mass and plasma volume changes in manned space flight. *JAMA*, 200, pp. 99-203.

2. Mengel, C. E., H. E. Kann, Jr., A. Heyman, and E. Metz. 1965. Effects of *in vivo* hyperoxia on erythrocytes. II. Hemolysis in a human after exposure to oxygen under high pressure. *Blood*, 25, pp. 822-829.

3. Larkin, E. C., J. D. Adams, W. T. Williams, and D. M. Duncan. 1972. Hematologic responses to hypobaric hyperoxia. *Am. J. Physiol.*, 79, pp. 541-549.

4. Johnson, P. C., T. B. Driscoll, and C. L. Fischer. 1971. Blood volume changes in divers of Tektite I. *Aerospace Med.*, 42, pp. 423-426.

5. Johnson, P. C., S. L. Kimzey, and T. B. Driscoll. Postmission plasma volume and red cell mass changes in the crews of the first two Skylab missions. *Astronautica Acta* (In Press).

6. Fischer, C. L, C. Gill, J. C. Daniels, E. K. Cobb, C. A. Berry, and S. E. Ritzmann. 1972. Effects of the space flight environment on man's immune system: 1. Serum proteins and immunoglobulins. *Aerospace Med.*, 43, pp. 856-859.

7. Kimzey, S. L., L. C. Burns, and C. L. Fischer. Experiment M115--Special Hematologic effects: Dynamic changes in red cell shape in response to the space flight environment. Presented at the Skylab Life Sciences Symposium, August 27-29, 1974, Lyndon B. Johnson Space Center, Houston, Texas.

8. Lichtman, M. A., D. R. Miller, and R. I. Weed. 1969. Energy metabolism in uremic red cells: Relationship of red cell adenosine triphosphate concentration to extracellular phosphate. *Trans. of Associa. of Amer. Physicians,* 82, pp. 331-343.

RED CELL METABOLISM STUDIES ON SKYLAB

Charles E. Mengel, M. D.
University of Missouri,
Columbia, Missouri

ABSTRACT

In previous laboratory experiments on animals exposed to levels of hyperoxia, it was demonstrated that several metabolic effects occurred in red cells during such exposure. The most dramatic of these effects was the occurrence of lipid peroxidation in red blood cells and subsequent hemolysis. Other metabolic alterations noted were some changes of glycolytic intermediates (including increases of adenosine triphosphate and decreases of 2, 3 diphosphoglyceric acid and inhibition of phosphofructokinase. On the basis of these background data, similar metabolic studies were performed on humans involved in space flight. These studies included the Skylab experiences. The primary purpose of the investigations was to study red cells for (1) evidences of lipid peroxidation or (2) changes at various points in the glycolytic pathway. The Skylab missions were an opportunity to study blood samples before, during, and after flight and to compare results with simultaneous controls. No direct evidence that lipid peroxidation had occurred in the red blood cells was apparent in the studies.

Nevertheless, certain metabolic changes in red cells were noted.

° Skylab 2: Increases of hexokinase, glyceraldehyde 3-phosphate dehydrogenase, and pyruvate kinase during flight, and decreases of phosphofructokinase after flight.

° Skylab 3: Decreases of hexokinase, phosphoglyceric kinase, acetylcholinesterase, and increases of pyruvate kinase during flight; and decreases in glutathione, glyceraldehyde phosphate dehydrogenase, and phosphoglyceric kinase, and increased adenosine triphosphate, and pyruvate kinase after flight.

° Skylab 4: Decreases of glutathione, glucose-phosphate dehydrogenase, and phosphofructokinase, glyceraldehyde 3-phosphate dehydrogenase during flight.

The most consistent changes (including laboratory high oxygen pressure studies, Skylab Medical Experiments Altitude Test, and Skylab) have included:

- increased adenosine triphosphate
- decreased phosphofructokinase
- decreased phosphoglyceric kinase
- increased pyruvate kinase
- decreased acetylcholinesterase

The data are consistent with the hypothesis that these conditions of space flight do not produce metabolic changes (lipid peroxidation) that are known to result in hemolysis but do result in significant alterations of glycolytic intermediates and enzymes.

INTRODUCTION

The untoward effects of high oxygen tension for many years had been largely of academic and *in vitro* interest only. Development of the use of oxygen under high pressure for medical purposes, and the use of a hyperoxic environment in the cabins of space vehicles for United States manned space flights increased the practical implications of the potential untoward effects. These situations also provided a special opportunity for study of varying aspects of red cell metabolism. It had been demonstrated that susceptible animals exposed to oxygen under high pressure developed hemolysis due to peroxidation of unsaturated fatty acids in red cell membrane (1). It was also demonstrated that a similar event could occur in humans (2). Subsequent studies under simulated and actual space flight conditions demonstrated variable decreases of the red cell mass.

A major limiting factor in the interpretation of data obtained during the Gemini and Apollo series, however, was that blood samples were analyzed before and after flight. There was no information as to what, if any, changes occurred *during* space flight itself. The Skylab program thus offered a unique opportunity for the study of the possible effects of that environment and flight on red cell metabolism.

The studies carried out included an analysis of red cell componets involved with

- peroxidation of red cell lipids,
- enzymes of red cell metabolism,
- levels of 2, 3-diphosphoglyceric acid and adenosine triphosphate.

MATERIALS AND METHODS

The details and schedules of sampling appear elsewhere.

Blood was kept frozen for transport of samples from the Johnson Space Center to the investigator's laboratory. Samples there remained frozen at -70° F (-39° C) until the time of determination. In all procedures, samples of blood drawn concomitantly from controls were run simultaneously with astronaut specimens.

Details of most analytic procedures used have been previously described (3 through 8).

The procedures employed for 2, 3 diphosphoglyceric acid were basically those described by Oski (9) and Krimsky (10).

A hemoglobin determination as made on blood samples using the cyanmethemoglobin method. The final readings were thus expressed as micromoles of red cell 2, 3 diphosphoglyceric acid per gram of hemoglobin. Simultaneous standards were performed with runs, and also checked against a prepared standard curve. The range used on the standard curve was between 0.1 and 0.4 micromoles (μM).

Abbreviations used:

GSH	Reduced glutathione
ATP	Adenosine triphosphate
2, 3-DPG	2, 3-diphosphoglyceric acid
G6PD	Glucose-6-phosphate dehydrogenase
HK	Hexokinase
PFK	Phosphofructokinase

G3PD	Glyceraldehyde phosphate dehydrogenase
PGK	Phosphoglyceric kinase
PK	Pyruvate kinase
AChE	Acetylcholinesterase

RESULTS

The data obtained from Skylab 2 are shown in table I. Preflight differences between astronauts and controls were not noted.

With the in-flight samples, there were increases of hexokinase, pyruvate kinase, and glyceraldehyde phosphate dehydrogenase. The changes of adenosine triphosphate and 2, 3-diphosphoglyceric acid were not significant.

Postflight there was a significant decrease of phosphofructokinase.

The data obtained from Skylab 3 are summarized in tables II and III. Astronauts and controls were identical preflight.

During flight there were significant decreases of hexokinase, phosphoglyceric kinase, and acetylcholinesterase, and increases of pyruvate kinase.

Postflight the changes noted on recovery day and days 1 and 14 varied.

The results of Skylab 4 studies are shown in table IV through VI.

They show that the only significant change occurred in phosphofructokinase during the early stage of the in-flight samples.

DISCUSSION

The advent of the use of medical hyperoxia and the use of increased oxygen tensions in space capsules prompted the need for further study into changes induced by variable environments and the potential untoward effects on many tissues including red cells. Previous studies in our laboratory had indicated that a mechanism, in fact the only mechanism, responsible for destruction of red cells by hyperoxia was peroxidation of the unsaturated fatty acids in red cell membranes.

TABLE I. SKYLAB 2

Determination †	PREFLIGHT Controls Mean ± 1 SD	PREFLIGHT Astronauts Mean ± 1 SD	IN-FLIGHT* Controls Mean ± 1 SD	IN-FLIGHT* Astronauts Mean ± 1 SD	Sig.	POSTFLIGHT Controls Mean ± 1 SD	POSTFLIGHT Astronauts Mean ± 1 SD	Sig.
GSH (mg %)	195.0 ±30.0	183.0 ±56.0	162.0 ±23.0	169.0 ±24.0		130.0 ± 9.0	148.0 ±19.0	
ATP (μM/g Hb)	5.7 ± 1.3	5.7 ± 0.8	3.7 ± 0.7	4.5 ± 1.7		3.6 ± 0.6	3.5 ± 0.5	
Lipid Peroxides	0	0	0	0		0	0	
2,3-DPG (μM/g Hb)	9.6 ± 2.9	8.1 ± 2.7	9.2 ± 2.7	7.8 ± 3.5		14.4 ± 3.0	14.7 ± 4.6	
G6PD (Eμ/g Hb)	7.0 ± 1.4	7.1 ± 1.6	3.9 ± 1.3	3.9 ± 1.1		4.9 ± 0.7	5.3 ± 0.4	
HK (Eμ/g Hb)	0.50± 0.13	0.46± 0.13	0.65± 0.17	2.4 ± 1.6	$P<0.005$	0.18± 0.09	0.48± 0.4	
PFK (Eμ/g Hb)	26.2 ± 7.5	22.7 ± 5.7	30.4 ± 8.5	28.8 ±11.3		37.0 ± 7.0	25.0 ± 6.0	$P<0.025$
G3PD (Eμ/g Hb)	59.0 ±12.0	65.0 ± 8.0	44.0 ± 8.0	53.0 ± 9.0	$P<0.05$	56.0 ±11.0	53.0 ± 4.0	
PGK (Eμ/g Hb)	28.4 ± 4.0	26.7 ± 8.4	18.5 ± 7.0	20.4 ± 6.3		17.8 ± 3.6	19.5 ± 2.5	
PK (Eμ/g Hb)	12.6 ± 4.0	10.7 ± 5.2	4.0 ± 1.2	5.7 ± 1.4	$P<0.01$	8.6 ± 1.8	7.6 ± 1.8	
AChE (Eμ/g Hb)	62.0 ± 6.0	64.0 ± 8.0	53.0 ± 6.0	55.0 ± 6.0		60.0 ± 6.0	65.0 ± 4.0	

*Data given includes *all* samples. No differences between controls and astronauts were observed at each individual sampling time.

†See pages 3 and 4 for translation of these abbreviations.

TABLE II. SKYLAB 3

Determination*	PREFLIGHT Controls Mean ± 1 SD	PREFLIGHT Astronauts Mean ± 1 SD	IN-FLIGHT Controls Mean ± 1 SD	IN-FLIGHT Astronauts Mean ± 1 SD	Sig
GSH (mg %)	167.0 ±20.0	163.0 ±21.0	119.0 ±74.0	121.0 ±50.0	
ATP (μM/g Hb)	5.9 ± 0.9	5.9 ± 0.5	5.3 ± 0.9	5.9 ± 0.9	
Lipid Peroxides	0	0	0	0	
2,3-DPG (μM/g Hb)	6.1 ± 2.4	7.1 ± 1.3	6.1 ± 3.6	7.9 ± 4.3	
G6PD (*E*μ/g Hb)	9.1 ± 1.0	9.6 ± 1.9	4.7 ± 1.1	4.3 ± 1.3	
HK (*E*μ/g Hb)	0.38± 0.11	0.37± 0.18	0.51± 0.17	0.28± 0.13	$P<0.005$
PFK (*E*μ/g Hb)	25.0 ± 2.0	27.0 ± 1.0	28.1 ± 9.5	28.0 ± 3.7	
G3PD (*E*μ/g Hb)	62.0 ±14.0	61.0 ±14.0	39.0 ± 9.0	42.0 ± 5.0	
PGK (*E*μ/g Hb)	36.0 ± 7.0	33.0 ± 2.0	24.6 ± 5.2	20.1 ± 8.3	$P<0.05$
PK (*E*μ/g Hb)	5.2 ± 1.6	5.9 ± 1.0	5.1 ± 1.6	6.5 ± 2.2	$P<0.05$
AChE (*E*μ/g Hb)	43.0 ± 4.0	45.0 ± 7.0	34.0 ±10.0	27.0 ± 7.0	$P<0.05$

*See pages 3 and 4 for translation of these abbreviations.

TABLE III. SKYLAB 3

POST FLIGHT (DAY)

Determination*	R + 0 Controls	R + 0 Astronauts	Sig.	R + 1 Controls	R + 1 Astronauts	Sig.	R + 14 Controls	R + 14 Astronauts	Sig.	R + 0, R + 1, R + 14 Controls	R + 0, R + 1, R + 14 Astronauts	Sig.
GSH (mg %)	70.0 ± 6.0	37.0 ±13.0	$P<0.01$	104.0 ± 3.0	64.0 ±10.0	$P<0.01$	181.0 ±56.0	183.0 ±12.0		118.0 ±56.0	94.0 ±64.0	
ATP (μM/g Hb)	4.3 ± 0.8	6.1 ± 0.4	$P<0.01$	4.3 ± 6.0	5.4 ± 0.3	$P<0.025$	7.0 ± 0.7	9.8 ± 1.4	$P<0.025$	5.21± 1.5	6.6 ± 1.9	
Lipid Peroxides	0	0		0	0		0	0		0	0	
2,3-DPG (μM/g Hb)	5.6 ± 1.9	6.5 ± 1.8		8.3 ± 4.0	9.1 ± 1.4		4.5 ± 2.0	4.3 ± 1.7		6.1 ± 3.1	6.8 ± 2.2	
G6PD (Eμ/g Hb)	6.0 ± 1.8	6.1 ± 0.6		5.3 ± 1.2	5.5 ± 1.5		5.8 ± 0.5	7.8 ± 0.2	$P<0.01$	5.7 ± 1.2	6.5 ± 1.3	
HK (Eμ/g Hb)	0.49± 0.13	0.67 ± 0.31		0.48± 0.11	0.50± 0.08		0.38± 0.09	0.39± 0.03		0.45± 0.12	0.52± 0.22	
PFK (Eμ/g Hb)	35.0 ±13.0	29.0 ± 4.0		27.0 ± 7.0	27.0 ± 6.0		28.0 ± 2.0	32.0 ± 4.0		30.0 ±10.0	29.0 ± 5.0	
G3PD (Eμ/g Hb)	63.0 ± 4.0	52.0 ± 6.0	$P<0.05$	69.0 ±20.0	54.0 ± 6.0		45.0 ± 1.0	43.0 ± 5.0		59.0 ±16.0	50.0 ± 7.0	
PGK (Eμ/g Hb)	27.0 ± 1.0	19.0 ± 4.0	$P<0.01$	28.0 ± 3.0	28.0 ± 5.0		21.0 ± 3.0	27.0 ± 2.0	$P<0.025$	25.0 ± 4.0	24.0 ± 6.0	
PK (Eμ/g Hb)	6.1 ± 0.8	7.8 ± 2.0		5.5 ± 0.7	7.8 ± 1.2	$P<0.025$	17.0 ± 2.0	18.0 ± 5.0		9.6 ± 5.0	11.4 ± 6.0	
AChE (Eμ/g Hb)	33.0 ± 2.0	29.0 ± 4.0		29.0 ± 3.0	35.0 ± 8.0		29.0 ± 3.0	26.0 ± 3.0		30.0 ± 3.0	30.0 ± 6.0	

*See pages 3 and 4 for translation of these abbreviations.

TABLE IV. SKYLAB 4

PREFLIGHT

Determination*	Controls Mean ± SD	Astronauts Mean ± SD	Sig.
Met Hgb (%)	0.90± 1.08	4.22± 3.67	$P<0.005$
GSH (mg %)	139.55±28.19	128.37±27.90	
ATP (μM/g Hb)	7.11± 0.54	8.29± 1.80	
Lipid Peroxides	0	0	
2,3-DPG (μM/g Hb)	9.24± 3.09	9.18± 4.99	
G6PD ($E\mu$/g Hb)	7.29± 1.12	6.84± 1.32	
HK ($E\mu$/g Hb)	0.72± 0.10	0.73± 0.11	
PFK ($E\mu$/g Hb)	36.04± 9.36	33.80± 9.56	
G3PD ($E\mu$/g Hb)	54.57± 8.64	56.45±10.79	
PGK ($E\mu$/g Hb)	29.74± 6.17	27.76± 3.76	
PK ($E\mu$/g Hb)	10.25± 4.24	10.06± 2.57	
AChE ($E\mu$/g Hb)	54.68±10.89	60.40±10.04	
ATPase	11.17± 1.36	10.35± 0.79	

*See pages 3 and 4 for translation of theses abbreviations.

TABLE V. SKYLAB 4

Determination*	(INF 1-4) Controls Mean ± 1 SD	(INF 1-4) Astronauts Mean ± 1 SD	IN-FLIGHT Sig.	(INF 5-8) Controls Mean ± 1 SD	(INF 5-8) Astronauts Mean ± 1 SD	Sig.
Met Hgb (%)	28.45± 5.92	27.07± 6.13		20.54± 8.20	28.71± 3.16	$P<0.005$
GSH (mg %)	107.77±38.99	88.33±28.08		110.09±38.92	100.86±25.60	
ATP (μM/g Hb)	8.34± 1.83	7.64± 1.48		6.69± 2.13	6.52± 2.39	
Lipid Peroxides	0	0		0	0	
2,3-DPG (μM/g Hb)	3.47± 1.68	3.35± 0.89		4.15± 1.21	4.22± 1.66	
G6PD (Eu/g Hb)	6.42± 1.62	4.80± 1.29	$P<0.025$	4.92± 1.12	4.77± 0.87	
HK (Eu/g Hb)	0.22± 0.10	0.20± 0.09		0.39± 0.09	0.38± 0.07	
PFK (Eu/g Hb)	35.03± 7.75	25.89± 6.68	$P<0.01$	26.30± 9.73	24.92± 4.58	
G3PD (Eu/g Hb)	55.25± 9.31	49.85± 7.02		63.79±17.86	58.32±17.15	
PGK (Eu/g Hb)	14.90± 4.10	15.47± 5.52		18.87± 5.58	18.22± 7.79	
PK (Eu/g Hb)	8.92± 3.63	7.76± 2.67		5.08± 1.20	4.87± 1.00	
AChE (Eu/g Hb)	55.62± 8.67	51.06± 9.45		50.48± 7.37	43.73± 7.86	

*See pages 3 and 4 for translation of these abbreviations.

TABLE VI. SKYLAB 4

POST FLIGHT (DAY)

	R + 0			R + 1			R + 14			R + 0, R + 1, R + 14		
Determination*	Controls	Astronauts	Sig.	Controls	Astronauts	Sig.	Controls	Astronauts	Sig.	Controls	Astronauts	Sig.
Met Hgb (%)	2.96± 2.58	9.33± 5.62		7.05± 4.61	8.04± 4.68		11.35± 3.93	13.39± 3.74		7.12± 5.11	10.25± 5.26	
GSH (mg %)	75.33±17.20	71.42± 6.87		70.16±11.44	56.51±10.12		78.58±12.11	90.96± 2.02		74.69±14.25	72.96±15.82	
ATP (μM/g Hb)	6.60± 0.36	7.68± 1.00		5.25± 0.22	5.30± 0.14		4.47± 0.00	5.53± 0.37		5.53± 0.81	6.17± 1.23	
Lipid Peroxides	0	0		0	0		0	0		0	0	
2,3-DPG (μM/g Hb)	5.17± 1.00	8.86± 2.49		3.14± 0.10	4.27± 1.45		2.31± 0.32	2.57± 0.46		3.54± 1.35	5.23± 3.14	
G6PD (Eμ/g Hb)	7.46± 1.60	8.85± 1.89		3.88± 0.40	4.81± 1.40		4.21± 0.60	4.27± 0.97		5.18± 1.90	5.97± 2.51	
HK (Eμ/g Hb)	0.61± 0.20	0.49± 0.00		0.21± 0.00	0.19± 0.00		0.19± 0.00	0.27± 0.00		0.34± 0.22	0.32± 0.10	
PFK (Eμ/g Hb)	38.26± 2.41	35.64± 7.05		19.38± 5.10	16.40± 8.55		19.31±10.01	18.26± 4.38		25.65±11.11	23.43±11.07	
G3PD (Eμ/g Hb)	79.14± 9.64	82.43± 4.68		39.27± 5.49	39.94± 7.13		46.04± 4.52	42.19± 5.78		54.81±18.74	54.85±20.40	
PGK (Eμ/g Hb)	25.21± 7.63	24.56± 7.37		9.80± 1.12	11.13± 2.91		9.23± 0.83	11.76± 2.36		14.75± 8.65	15.81± 7.81	
PK (Eμ/g Hb)	12.81± 3.10	14.01± 0.55		4.54± 1.46	4.66± 1.48		3.81± 0.30	6.14± 1.13	$P<0.05$	7.08± 4.52	8.27± 4.25	
AChE (Eμ/g Hb)	72.22± 8.48	60.60± 5.41		28.93± 1.01	29.55± 3.83		32.03± 2.65	35.64± 3.16		44.39±20.38	41.93±14.08	

*See pages 3 and 4 for translation of these abbreviations.

In addition to these changes, other studies also demonstrated alterations of glycolytic intermediates and enzymes which, however, could not be linked to concrete evidence of cell damage.

Previous space flight studies were limited by the fact that samples could only be obtained before and after flight, and frequently inappropriate controls existed. The major contribution allowed by the Skylab series of studies was the availability of simultaneous control samples as well as in-flight samples from astronauts. It should be noted, however, that there were progressive gas composition changes as the varied series of Gemini, Apollo, and Skylab flights occurred.

In our present studies, there was no evidence of lipid peroxidation in any of the samples. This may be taken as evidence that the likelihood of overt red cell damage would be slim. There were, however, certain changes observed in glycolytic intermediates and enzymes. For perspective, these may be summarized in Table VII. Included in this table are summary data from the Skylab Medical Experiments Altitude Test (SMEAT) and our own laboratory (OHP) studies using oxygen under pressure. It is apparent that the most consistent change noted, a decrease of phosphofructokinase, had been verified a number of times. It is this enzyme step which is thought to be at the center of the so-called Pasteur effect, and which is susceptible to the effects of oxygen. Other changes have been less consistent and the significance of all of these changes is not understood.

SUMMARY

In summary therefore, it is possible to conclude that there are no evidences of lipid peroxidation, that biochemical effect known to be associated with irreversible red cell damage, and the changes observed in glycolytic intermediates and enzymes cannot be directly implicated as indicating evidence of red cell damage.

TABLE VII. SUMMARY OF RBC METABOLISM CHANGES

DETERMINATIONS*	OHP STUDIES	SMEAT	SKYLAB 2	SKYLAB 3	SKYLAB 4
GSH		+		+	
ATP	+			+	
Lipid Peroxides					
2,3-DPG	+				
G6PD		+		+	
HK			+	+	
PFK	+	+	+	+	+
G3PD			+	+	
PGK		+		+	
PK			+	+	
AChE		+			

*See pages 3 and 4 for translation of these abbreviations.

REFERENCES

1. Mengel, C. E. and H. E. Kann, Jr. 1966. Effects *in vivo* hyperoxia on erythrocytes. III. *In vivo* peroxidation of erythrocyte lipid. *J. Clin. Invest.* 45:1150-1158.

2. Mengel, C. E., H. E. Kann, Jr., A. Heyman and E. Metz. 1965. Effects of *in vivo* hyperoxia on erythrocytes. II. Hemolysis in a human after exposure to oxygen under high pressure. *Blood* 25:822-829.

3. Zirkle, L. G., Jr., C. E. Mengel, S. A. Butler and R. Fuson. 1965. Effects of *in vivo* hyperoxia on erythrocytes. IV. Studies in dogs exposed to hyperbaric oxygenation. *Proc. Soc. Exp. Biol. & Med.* 119: 833-837.

4. O'Malley, B. W., C. E. Mengel, W. D. Meriwether and L. G. Zirkle, Jr. 1966. Inhibition of erythrocyte acetylcholinesterase by peroxides. *Biochemistry* 5: 40-44.

5. Kann, H. E., Jr. and C. E. Mengel. Mechanisms of erythrocyte damage during *in vivo* hyperoxia. Proc. 3rd. Int. Conf. on Hyperbaric Medicine. November, 1966, pp. 65-72.

6. O'Malley, B. W. and C. E. Mengel. 1967. Effects of *in vivo* hyperoxia on erythrocytes. V. Changes of RBC glycolytic intermediates in mice after *in vivo* oxygen under high pressure. *Blood* 29: 196-202.

7. Timms, R. and C. E. Mengel. 1968. Effects of *in vivo* hyperoxia on erythrocytes. VII. Inhibition of RBC phosphofructokinase. *Aerospace Med.* 39: 71-73.

8. Smith, D., R. Timms, C. E. Mengel and D. Jefferson. 1968. Effects of *in vivo* hyperoxia on erythrocytes. VIII. Effect of adenosine triphosphate (ATP) and related glycolytic enzymes. *Johns Hopkins Med. J.* 122: 168-171.

9. Oski, F. A., A. J. Gottlieb, D. Miller and M. Delivoria-Papadopoulos. 1970. The effects of deoxyhemoglobin of adult and fetal hemoglobin on the synthesis of red cell 2,3-diphosphoglyceric acid and its *in vivo* consequences. *J. Clin. Invest.* 48: 400.

10. Krimsky, I. 1963. 2,3-diphosphoglycerate in enzymatic analysis. H. U. Bergmeyer (Ed.) Academic Press, Inc. New York. 1st edition.

EXPERIMENT M115 - SPECIAL HEMATOLOGIC EFFECTS: DYNAMIC CHANGES IN RED CELL SHAPE IN RESPONSE TO THE SPACE-FLIGHT ENVIRONMENT

Stephen L. Kimzey, Ph.D.; Linda C. Burns, M.S.†; and Craig L. Fischer, M.D.‡*

ABSTRACT

Deviations from the normal biconcave discoid shape of red blood cells may be permanent and result from a metabolic or functional disorder of the cell, or may be reversible and result from the influence of plasma-borne factors. The transient alterations are predictable and form the basis for a classification of red cell configurations that may be used as an indicator of body response to unfavorable conditions which have altered the constancy of the plasma milieu. Scanning electron microscopy techniques, with improved spatial resolution and greater depth of focus, have enabled major refinements in the critical interpretation of red cell shape changes.

Blood samples collected during the preflight, in-flight, and postflight phases of each Skylab mission were examined using the scanning electron microscope and the populations of red cells classified according to their surface morphology. Blood samples collected simultaneously from ground-based control subjects were analyzed for comparison. Significant changes in the distribution of red cell shapes did occur in the crew samples collected during the in-flight phase of each mission. Some individual variations among crewmembers were seen but other types of changes observed were generally consistent. The primary changes observed in all samples were increases in the number of echinocytes (crenated cells), stomatocytes, and knizocytes. The Skylab 4 flight crew experienced a substantial elevation in the number of leptocytes (thin, flattened cells); 50 percent of one crewmember's cells were of this type by mission day 82. The magnitude of the major shift in the red cell population classification (discocyte to echinocyte) appears to be correlated to the mission duration; the greatest change occured

*National Aeronautics and Space Administration - Lyndon B. Johnson Space Center, Houston, Texas

†Northrop Services, Incorporated, Houston, Texas

‡Eisenhower Memorial Hospital, Palm Desert, California

in the later in-flight samples from the Skylab 3 and Skylab 4 missions. Most of the changes observed were reversible, and the postflight samples returned to preflight conditions quickly.

This rapid return to preflight values suggests that the alterations in the red cell shape profiles were due to modifications in the plasma environment as opposed to more permanent alterations of red cell metabolic or structural characteristics. The significance of these red cell transformations must be considered with respect to: splenic removal of abnormal cell types that might contribute to the observed red cell mass loss, oxygen-carrying capacity of the cells, changes in the plasma composition during flight, and implications relative to crew selection criteria for future missions.

INTRODUCTION

The familiar biconcave discoid shape of the mature erythrocyte represents a unique structural configuration among cell types. This peculiar shape is so consistent and characteristic of normal erythrocytes that deviations from the discoid form have provided the basis for the detection and diagnosis of a variety of congenital and acquired hematologic disorders (Bessis *et al.*, 1973; Brecher and Bessis, 1972; Bull and Kuhn, 1970; Cooper, 1969; Cooper and Jandl, 1968; Kayden and Bessis, 1970). The mechanisms involved in the maintenance of this biconcave shape have been of considerable interest to physiologists, chemists and mathematicians for a number of years. Several theories have been proposed to explain the physical and chemical bases of this configuration (Adams, 1972, 1973; Bull, 1973; Bull and Brailsford, 1973; Evans and Leblond, 1973), but as yet no single explanation is acceptable to all investigators.

Regardless of the exact mechanism by which the red cell maintains its "normal" discoid shape and regardless of the advantages or disadvantages of this shape relative to the red cell functions (*i.e.*, optimum gas exchange, deformability, survival), it is quite evident that a delicate balance exists between the chemical and physical forces and the metabolic energy and ultrastructual organization of molecules - all interacting to exert a complex array of vectorial forces on the red cell membrane. It is probable that alterations in this balance of forces are responsible for the red cell's exhibiting a variety of different morphological states ranging from a discocyte to a spherocyte with many intermediate shapes. This imbalance may be the result of an intrinsic metabolic or structural defect of the cell usually associated with a hemolytic anemia.

A second class of factors causing alteration in the red cell shape are extrinsic properties of the plasma milieu. This second type of shape change is usually of a less severe nature and, provided the cell is not destroyed by selective removal in the reticuloendothelial system or hemolyzed due to an imbalance of ion and water regulation, these changes are reversible if the causative agent is neutralized or removed from the plasma. The most common and most widely investigated type of red cell shape change due to extrinsic factors is the conversion of the normal discocyte to a spiculed cell, the discocyte-echinocyte transformation. Thus, the evaluation of this type of reversible change in red cell shape may provide an indicator not only of alterations in red cell functional capacity, but may also be used to detect and identify subtle changes in plasma constituents, especially those known to have effects on red cell shape.

As one aspect of the protocol for Skylab Experiment M115, Special Hematologic Effects, samples of blood collected from the crewmen preflight, in-flight, and postflight were critically examined by light and scanning electron microscopy for alterations in the shape of the red blood cells. This study was designed specifically to investigate, detect, and characterize alterations in red cell shape either during or following extended exposure to the space environment. The following report will describe previously unpublished results on the alterations in red cell shape observed during the extended Skylab space flights and the rapid reversal of these changes upon entry into a normal gravitational environment. Possible causes for these modifications in red cell shape will be discussed, as will the significance of these changes to man's functional capacity in space and to other observed hematologic changes.

MATERIALS AND METHODS

Red blood cells from astronaut crews were processed for scanning electron microscopy using the following procedures.

Fixation

Blood samples from preflight and postflight medical examinations were collected in heparin; in-flight samples were collected in ethylenediaminetetracetic acid (EDTA). Approximately 0.1 milliliter (ml) of whole blood per sample was added to 1.0 ml 0.5 percent glutaraldehyde, pH 7.4, 320 mOsmoles, prepared in a standard incubation medium[1].

[1]The standard incubation medium used in these procedures consisted of 10 millimolar (mM) potassium chloride, 141 mM sodium chloride, 1.0 mM magnesium chloride, 1.3 mM calcium chloride, 0.8 mM sodium biphosphate and 5 mM disodium phosphate.

Time in the fixative varied from 1 hour for preflight and postflight samples to 1, 2, 24, 57, and 81 days for in-flight samples. No effect was found on cell morphology as a result of the varying lengths of time the red cells spent in glutaraldehyde. The fixed cell samples were washed twice in a standard incubation medium, pH 7.3, 300 mOsmoles, and then twice in deionized water prior to critical point drying.

Dehydration and Critical Point Drying

Each red cell sample was allowed to sediment for 5 minutes from water onto a clean 9 x 22 millimeter glass cover slip without air-drying. The sample was dehydrated to 100 percent ethyl alcohol by gently adding graded ethyl alcohol solutions dropwise to the water on the cover slip. Three rinses were made with each solution; the third rinse was allowed to remain on the cell sample for 5 minutes prior to replacement with the next solution. A stepwise series of 20%, 50%, 75%, 90%, and 100% ethyl alcohol solutions were used. The ethyl alcohol was then replaced with 50% amyl acetate/50% ethyl alcohol and finally 100% amyl acetate. The samples were critical-point dried from liquid carbon dioxide using a Denton critical point drying apparatus.

Coating

The glass cover slips with the red cell samples were mounted on aluminum stubs using double-edge conductive tape and silver conducting paint. the samples were then coated with approximately 300 angstrom (Å) gold/palladium (60%/40%) in an Edwards evaporator equipped with a rotary/tilt stage.

Scanning Electron Microscope

The red cell samples were examined in an ETEC Autoscan at 20 kilovolt with 2000X magnification. Resolution of the microscope under these conditions is on the order of 200 Å. Magnification and other instrument parameters were held constant for all red cell classification.

Classification

A quantitative, differential classification scheme for red cell shapes was utilized by the Cellular Analytical Laboratory at the Johnson Space Center in ground-based studies [Skylab Medical Experiments Altitude Test (SMEAT) and ground control subjects] and in support of the Apollo 17 mission prior to its implementation in the Skylab Program. The criteria for differentiation of cell shapes and the terminology used are outlined in table I and are consistent with those recently discussed at a workshop on red cell shape at the Institute of Cell Pathology, Hôpital de Bicêtre, Paris, France (Bessis, *et al.*, 1973).

TABLE I. RED CELL SHAPE CLASSIFICATION

DESIGNATION	CHARACTERISTIC	COMMENTS	SCANNING ELECTRON MICROSCOPIC CRITERIA
Discocyte	Disc	Normal Biconcave Erythrocyte	Shallow but visible round depression in central portion of cell.
Leptocyte	Thin, Flat	Flattened Cell	No visible depression and no evidence of cell sphering (cell diameter normal or larger than normal).
Codocyte	Bell	Bell-shape erythrocyte (appearance depends upon side of cell uppermost)	Single concavity with extruded opposite side or flattened ring around elevated central portion of cell.
Stomatocyte	Single Concavity	Various stages of cup shapes	Swollen cell periphery with smaller concavity or concavity flattened on one side, indicating the beginnings of sphering.
Knizocyte	Pinch	Triconcave Erythrocyte	Triconcave depression or cell with pinched area in center.
Echinocyte	Spiny	Various stages of crenation	Deformed and angular cell periphery with spicule formation.

This classification of red cell morphology by shape rather than by disease or origin appears to be desirable from the standpoint that similar or identical shapes may arise from more than one type of disorder or condition. The terminology proposed by Bessis will be used throughout the following discussion.

In each red cell sample, from 500 to 1000 red cells were examined and classified into one of four distinct groups of cells. For the third manned Skylab mission, this classification scheme was enlarged to include two additional categories. Examples of the types of red cell shapes observed in the Skylab samples are illustrated in figures 1 through 11.

Light Microscopy

Red blood cell smears were prepared for routine examination using standard hematological procedures with Wright's stain.

RESULTS

Routine hematologic red cell smears prepared from blood samples collected immediately postflight (within two hours of splashdown) and examined by light microscopy (oil-immersion, 1000X magnification) were by all standard criteria essentially normal. There were no obvious variations

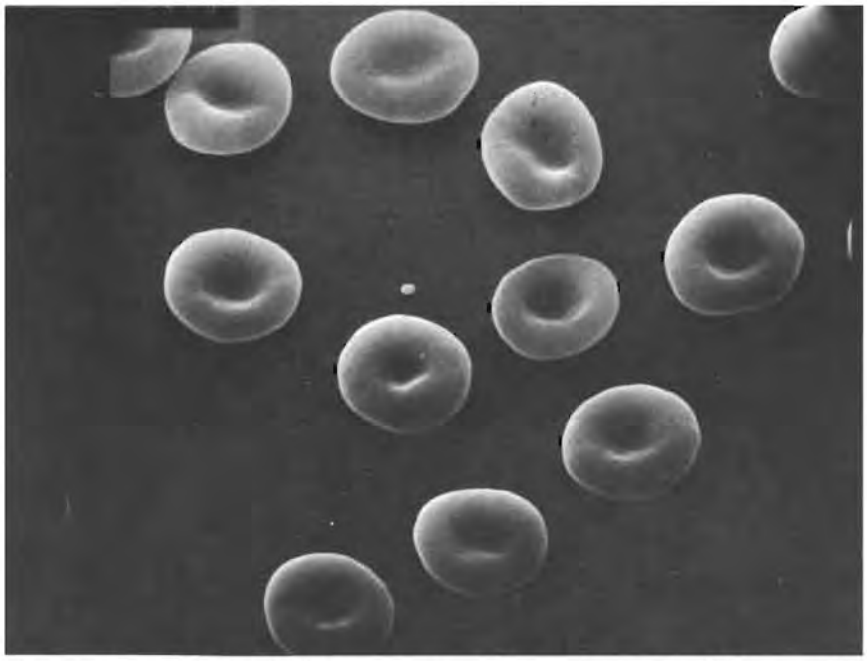


Figure 1. Distribution of normal red cells (Discocytes)
Magnification: 3040X.

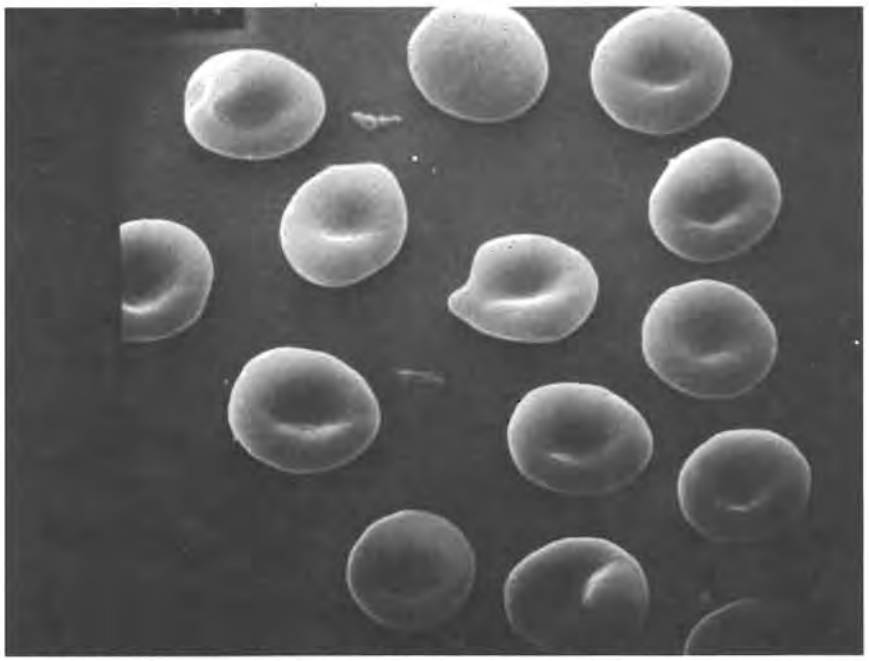


Figure 2. Field containing abnormal red cell types
Magnification: 3120X.

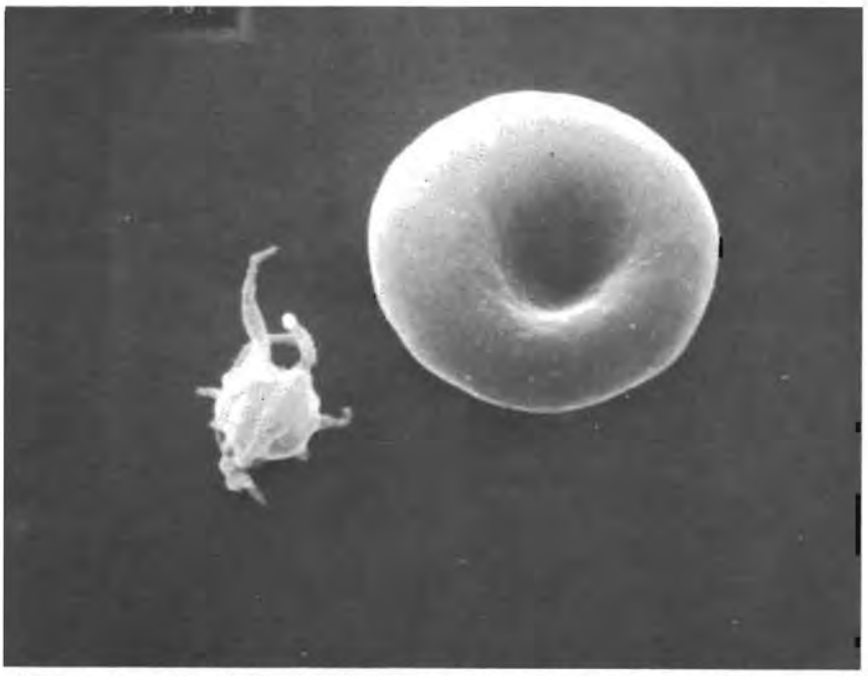


Figure 3. Platelet with normal erythrocyte (Discocyte)
Magnification: 7840X.

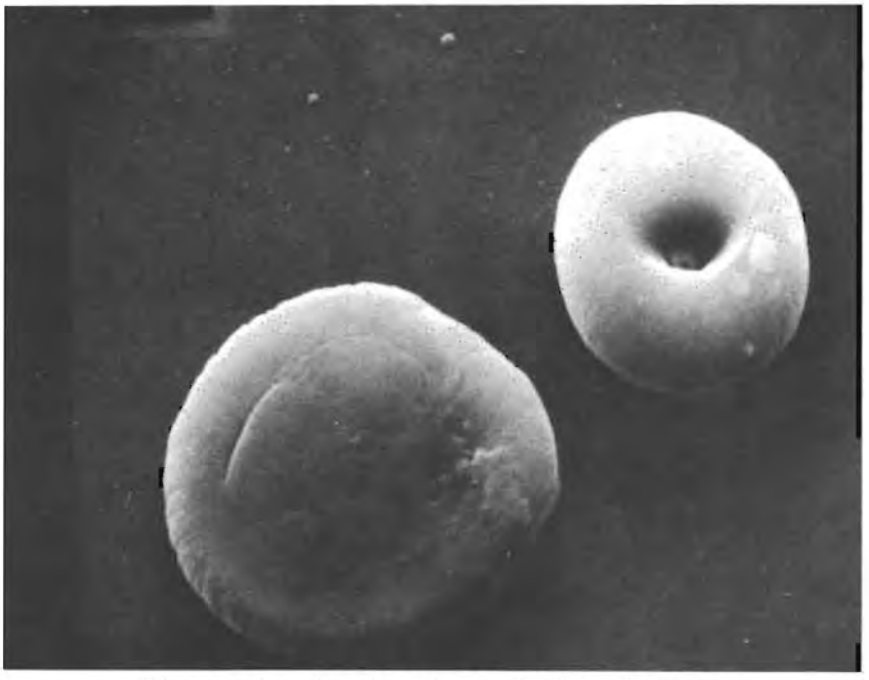


Figure 4. Leptocyte and Stomatocyte
Magnification: 5600X.

Figure 5. Knizocyte
Magnification: 11 920X.

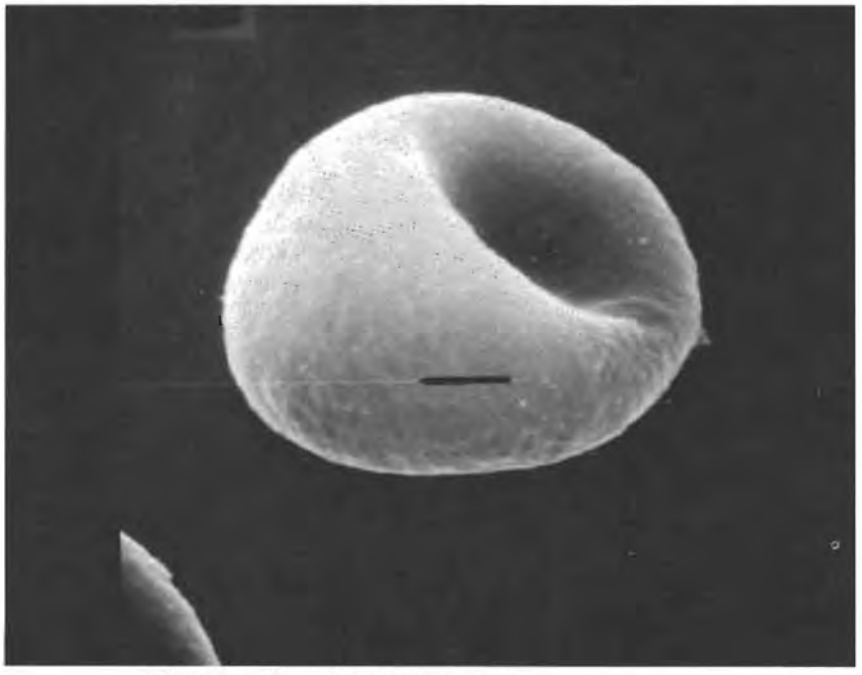


Figure 6. Stomatocyte
Magnification: 11 920X.

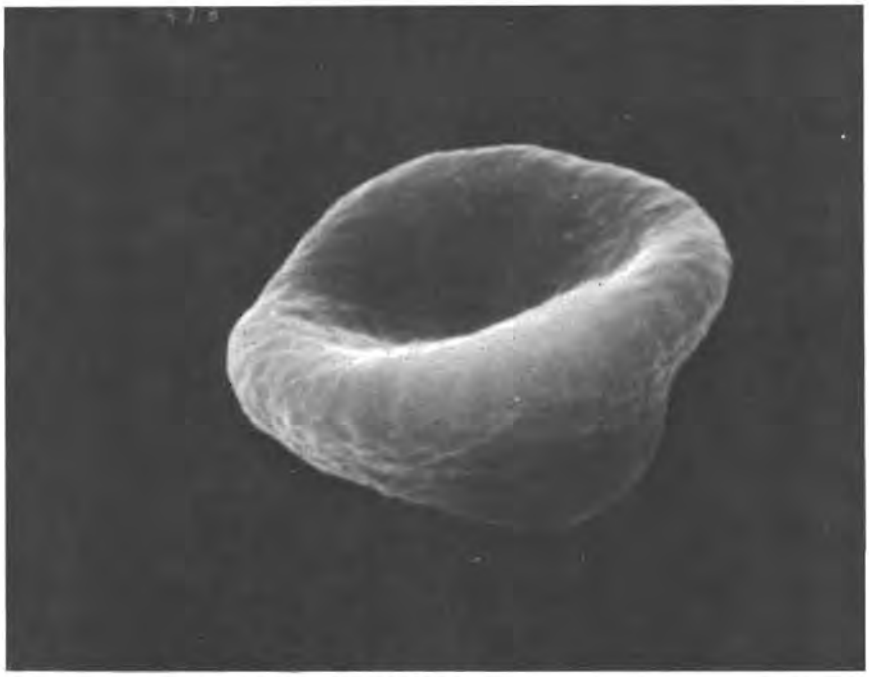


Figure 7. Codocyte
Magnification: 12 560X.

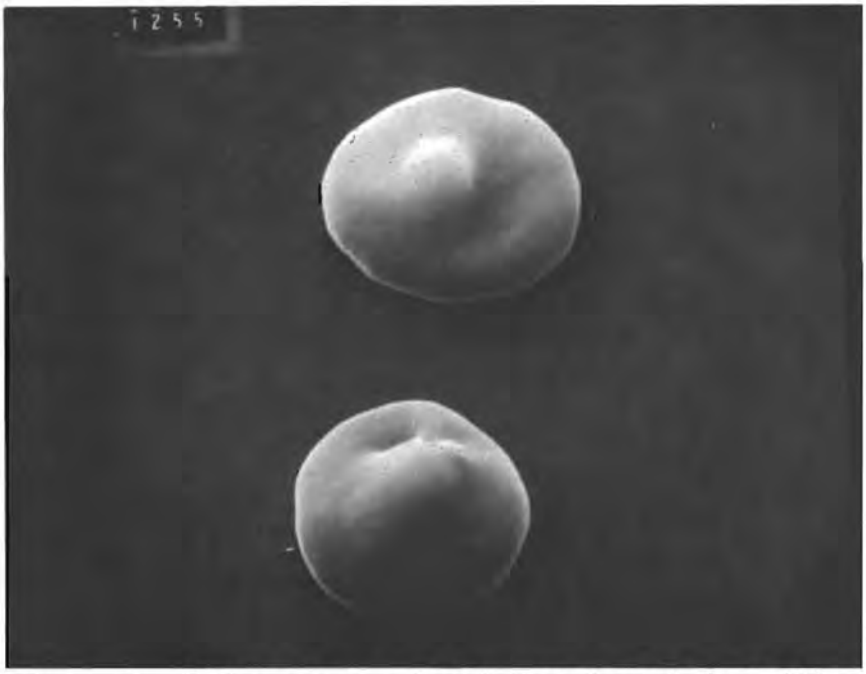


Figure 8. Codocytes as viewed from inverted position (Target Cells) Magnification: 5280X.

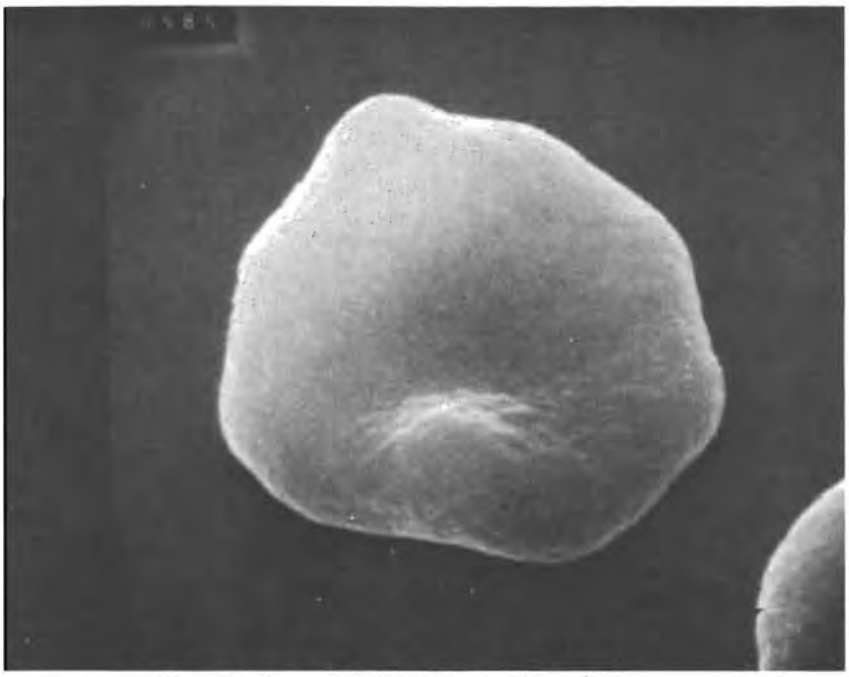


Figure 9. Echinocyte, Stage I
Magnification: 11 840X.

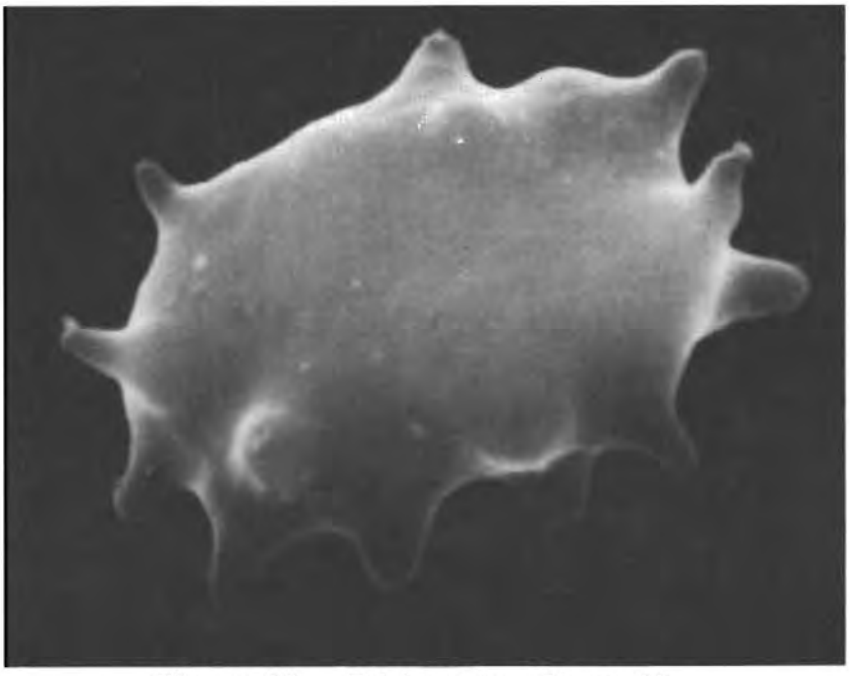


Figure 10. Echinocyte, Stage II
Magnification: 15 840X.

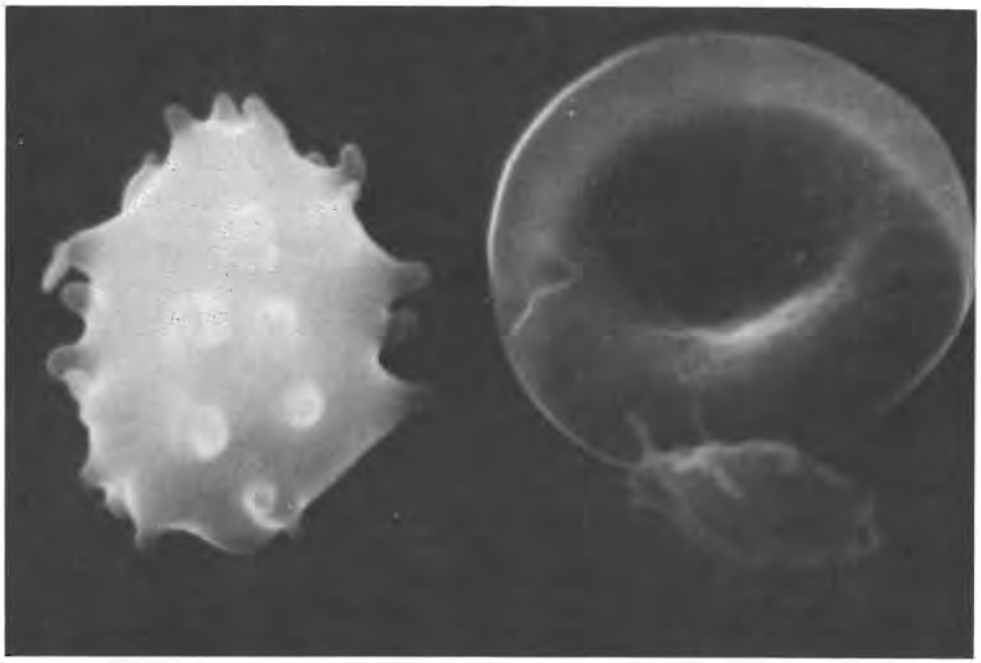


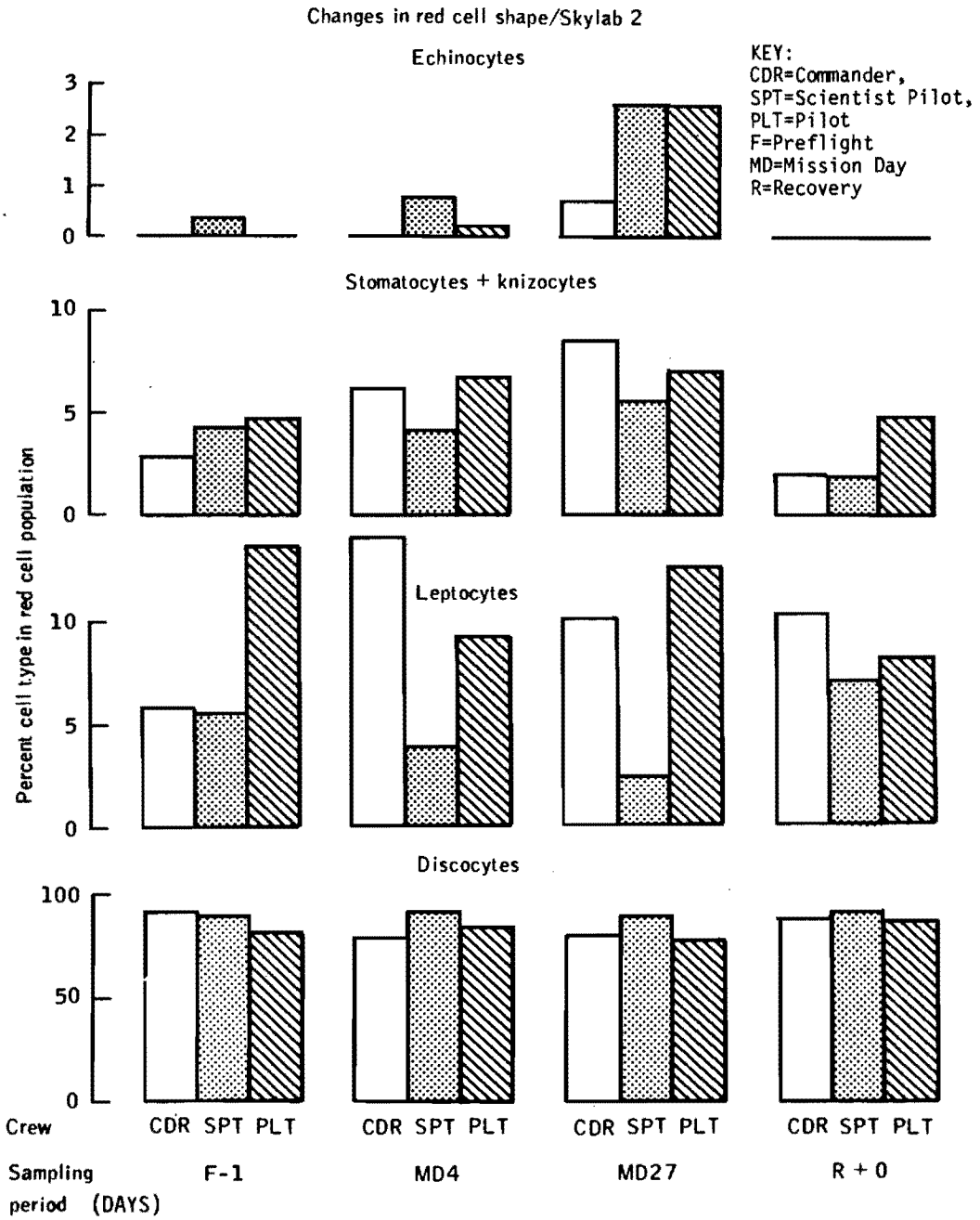
Figure 11. Echinocyte, Stage III, with Discocyte and Platelet
Magnification: 11900X

in the size or shape of the cells as compared to preflight samples. Cell edges were smooth, and the cells were essentially normochromic with no evidence of cytoplasmic inclusions. Quantitative microspectrophotometric examination of single cells indicated no change in the hemoglobin content, and the calculated mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were also normal. No slides were prepared from the blood samples collected during the in-flight phase of the missions for comparison.

However, a quantitative classification of the red cell population, based on variations in cell shape as determined by scanning electron microscopy, indicates a significant variation in the distribution of cell types during the in-flight portions of each mission (figures 12 through 14). During the preflight phase 80 to 90 percent of the circulating red cells were classified as discocytes (mean = 83.4 ± 10.3), but there was considerable variation among individual crewmembers (range, 60.9-92.9 percent). The percentage of discocytes in the blood samples collected immediately postflight (mean = 82.7 ± 7.9) was not significantly different from preflight levels. The remaining 15 to 20 percent of the nondiscoid cells present during the preflight control phase of each mission consisted primarily of leptocytes, stomatocytes and knizocytes (figs. 4 through 6) with the frequency of echinocytes (fig. 9) present being less than one percent. These data are summarized in figures 12 through 14.

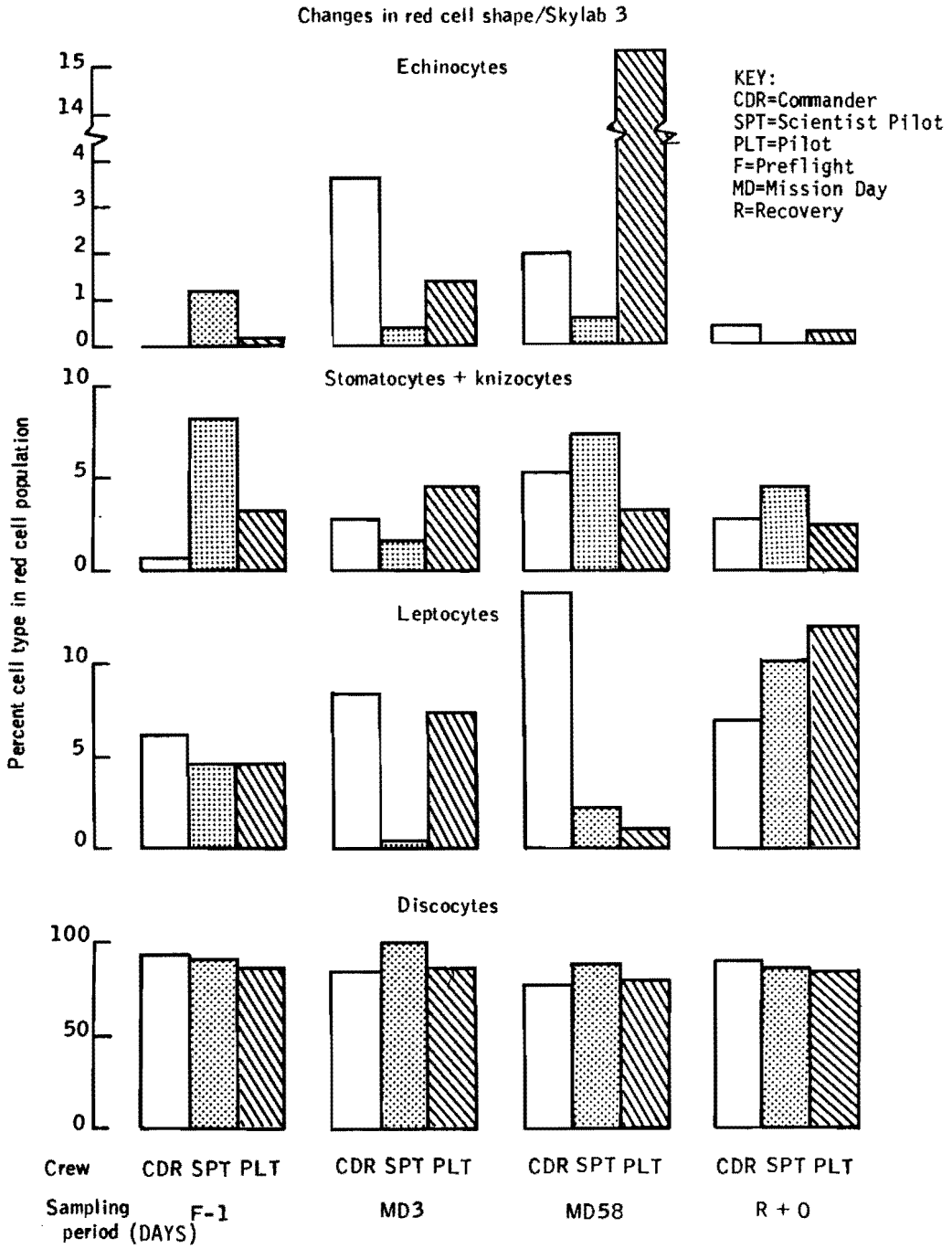
However, during exposure of the crews to the space flight environment, the frequency of echinocytes increased significantly, and this increase appeared to be related to the duration of each mission (fig. 15). Again, considerable individual variation was evident (figs. 16 through 18) but the increase in the numbers of echinocytes, expressed as an average of each crew, was statistically significant after the first sampling period of each mission. The majority of the echinocytes present in these samples were of the stage I type (fig. 9), with few progressing to stages II or III (figs. 10, 11). The first sample collected postflight [Recovery + 0 day, (R+0) was prepared within two hours of entry of the spacecraft. The number of echinocytes observed in this sample represented less than one percent of the red cell population, and was therefore comparable to the preflight value. This rapid reversal of the discocyte-echinocyte transformation is significant and will be discussed in detail.

The pattern of change observed with respect to increases in the numbers of stomatocytes and knizocytes was different from that recorded for transformation to echinocytic shapes. If the data from all three manned missions are considered as a composite there appears to be



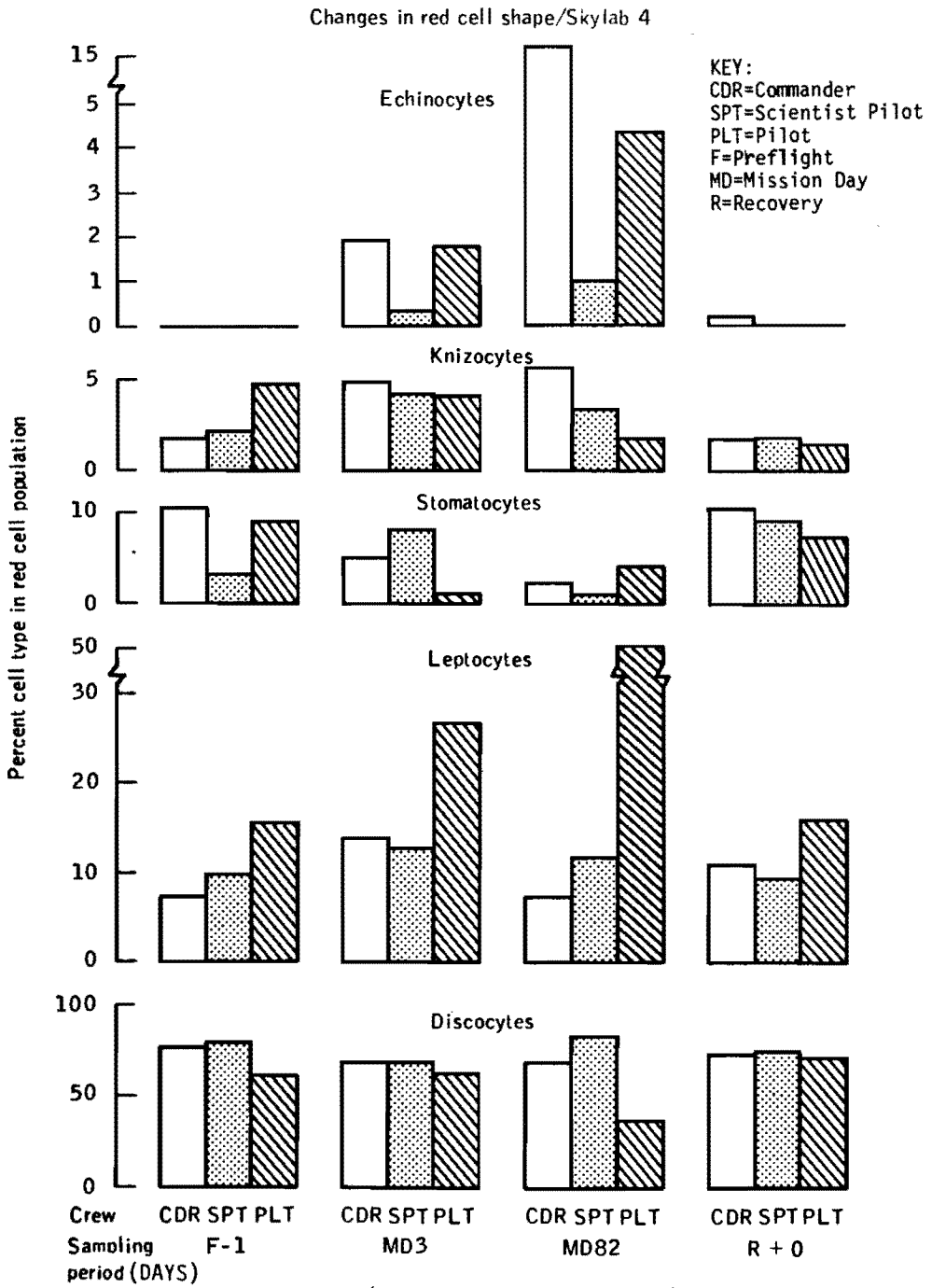
One red cell sample from each crewmember (prepared as described in the Materials and Methods Section) was classified by scanning electron microscopy into five categories of cell types. Mission days 4 and 27 represent blood samples taken during the mission by the crew 4 days and 27 days after launch. F-1 and R+0 represent blood samples taken from the crew during the medical examinations on day 1 preceding launch, and on recovery.

Figure 12. Distribution of red cell shapes during the first manned Skylab mission (Skylab 2).



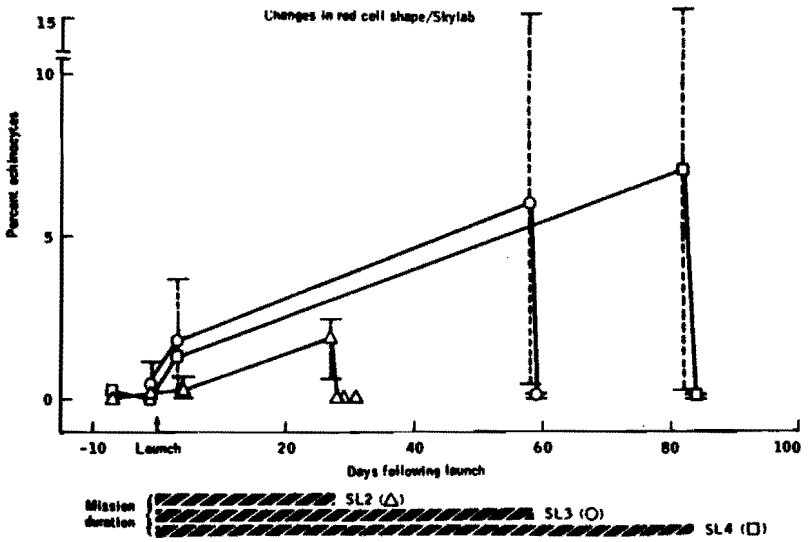
One red cell sample from each crewmember (prepared as described in the Materials and Methods Section was classified by scanning electron microscopy into five categories of cell types. Mission days 4 and 58 represent blood samples taken during the mission by the crew 3 and 58 days after launch. F-1 and R+0 represent blood samples taken from the crew during medical examinations on day 1 preceding launch, and on recovery.

Figure 13. Distribution of red cell shapes during the second manned Skylab mission (Skylab 3).



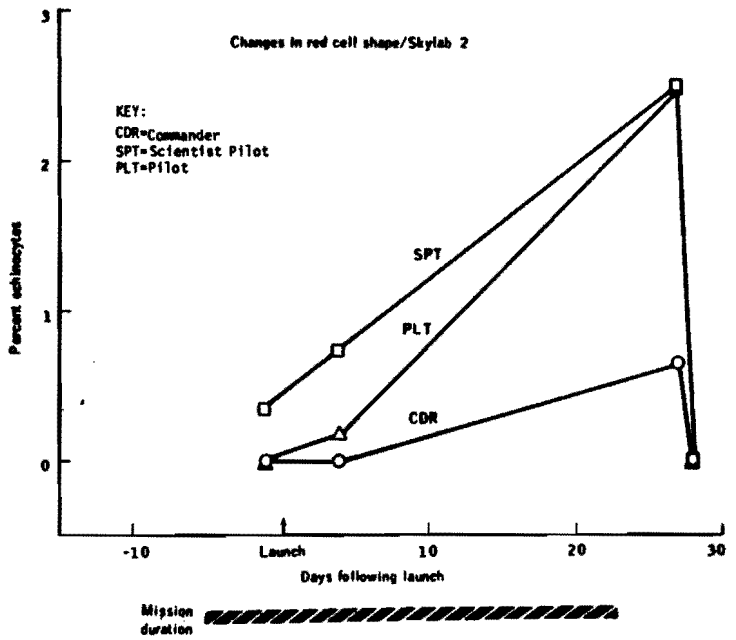
One red cell sample from each crewmember (prepared as described in the Materials and Methods Section) was classified by scanning electron microscopy into five categories of cell types. Mission days 4 and 82 represent blood samples taken during the mission by the crew 4 days and 82 days after launch. F-1 and R+0 represent blood samples taken from the crew during the medical examinations on day 1 preceding launch, and on recovery.

Figure 14. Distribution of red cell shapes during the third manned Skylab Mission (Skylab 4).



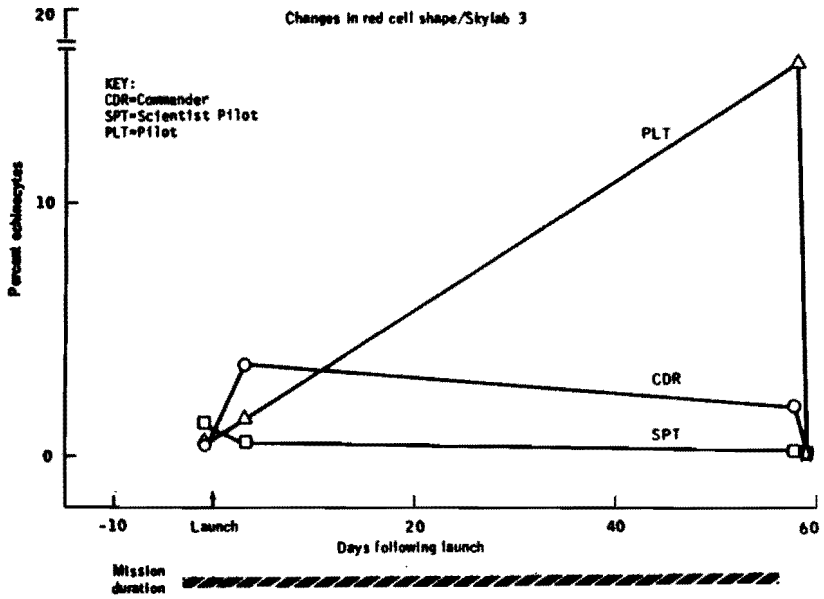
Each point represents the average value of the crew for the mission and sampling day indicated. The dotted lines represent the range of values for the three crewmembers from the mission measured at that period.

Figure 15. Percent of echinocytes in crew red cell samples during the Skylab Missions.



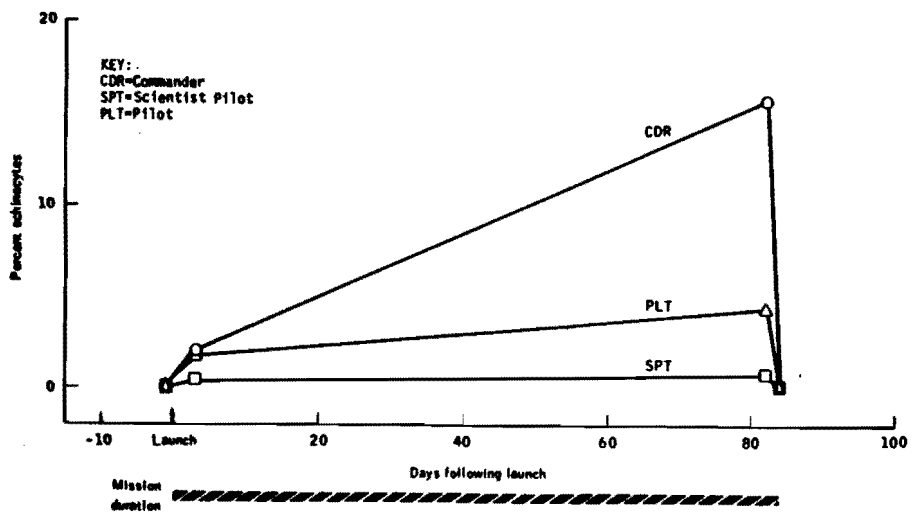
The points for each crewmember are plotted as a function of time after launch. Sampling periods indicated are F-1, MD4, MD27, and R+0.

Figure 16. Percent of echinocytes in crew red cell samples during the first manned Skylab mission (Skylab 2).



The points for each crewmember are plotted as a function of time after launch. Sampling periods indicated are F-1, MD3, MD58, and R+0.

Figure 17. Percent of echinocytes in crew red cell samples during the second manned Skylab mission (Skylab 3).



The points for each crewmember are plotted as a function of time after launch. Sampling periods indicated are F-1, MD3, MD82,and R+0.

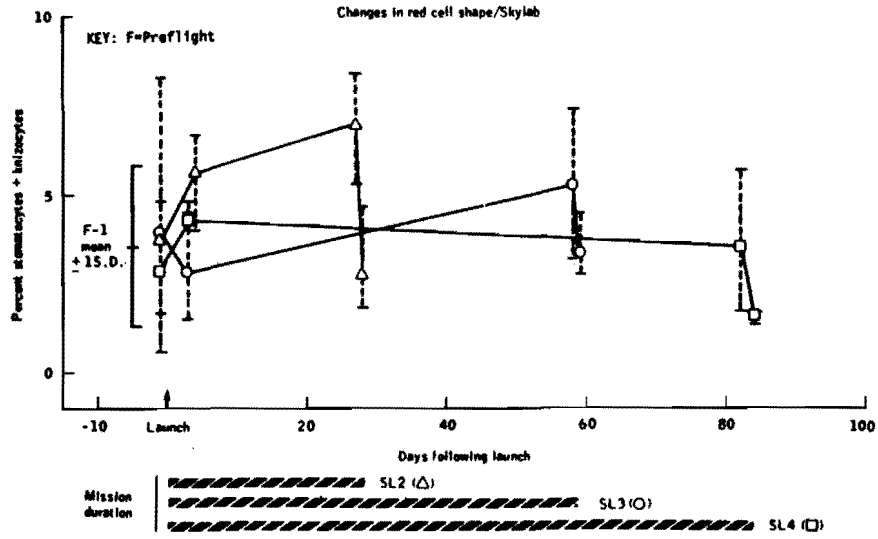
Figure 18. Percent of echinocytes in crew red cell samples during the third manned Skylab mission (Skylab 4).

maximum increase prior to mission day 27 and a gradual reduction with continued time in flight (fig. 19). The percentage of stomatocytes and knizocytes present on mission day 82 is not significantly different from that on recovery day (R+0). It is possible that these altered cells underwent a further transformation to an echinocytic type later in the mission. All Skylab crewmen and particularly those individuals exhibiting the greatest change in the number of echinocytes (Pilot-3, Commander-4, and Pilot-4) did not show a further reduction in their discocyte frequency after the first in-flight sample. (The response of the Pilot-4 is an exception and will be discussed in more detail.) The mean discocyte frequency in 8 of the 9 crewmen was 82.6% ± 10.3 on mission day 3(4) as compared to 81.0% ± 6.8 on the second sampling day (mission day 27, mission day 58, or mission day 82, respectively. However, these values may be somewhat misleading because of the individual variation and relatively small sample size.

The kinetics of the transformation from discocyte to leptocyte demonstrated even a third pattern, with only two of the three crewmen of the 84-day mission (Skylab 4) showing a significant elevation in the frequency of this cell type (fig. 20). Even among the Skylab 4 crew the increased average frequency is due primarily to the response of the Pilot-4 (fig. 21) with the other two crewmen showing only a slight elevation earlier in the mission. It should also be noted that the Pilot-4 had a high percentage (15.5) of leptocytes present during the preflight phase and the lowest percentage (60.9) of discocytes of the nine crewmen examined (figs. 12 through 14).

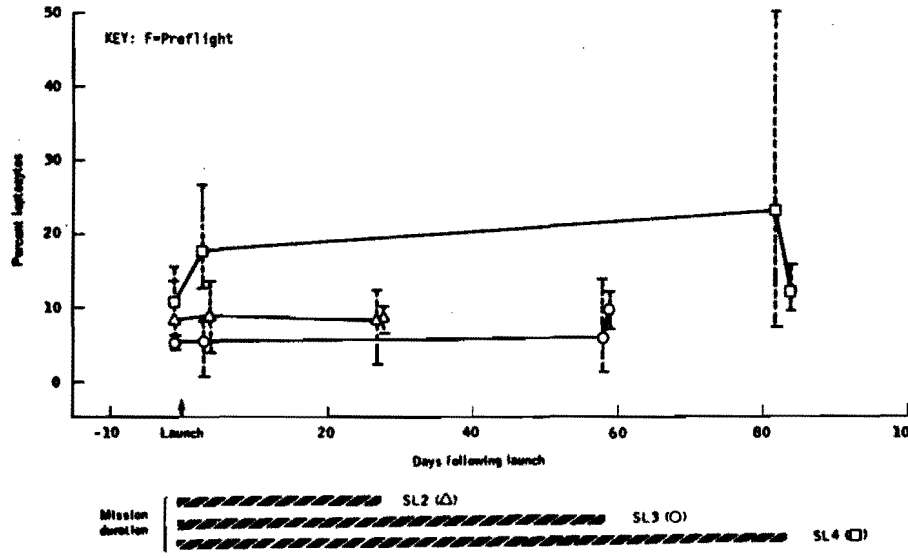
Attempts to compare the degree of change in red cell shape with alterations in several plasma and cellular constituents (sodium, potassium, calcium, magnesium, chloride, osmolality, adenosine triphosphate, and 2,3-diphosphoglyceric acid) failed to demonstrate a significant linear correlation. This finding was not surprising when one considers the sparsity of data values and the inherent characteristics of the mathematical determination of linear correlation coefficients. Data relative to other plasma echinocytogenic factors (especially lecithin and lysolecithin, cholesterol, and free fatty acids) and their cellular concentrations were not available for comparison.

Similar studies were done in support of Apollo 17 and the SMEAT at Johnson Space Center. There were no significant changes in red cell shape distributions during the 56-day SMEAT study in the three-man crew (discocyte mean for entire study = 85.0% ± 3.9) or ground-based control group (mean - 78.9% ± 4.4) either during or immediately following the exposure period (Kimzey, 1973). On Apollo 17 the postflight percentage of discocytes (84.0 ± 6.5) was not significantly different from preflight crew values (90.4% ± 3.6) or those of the control



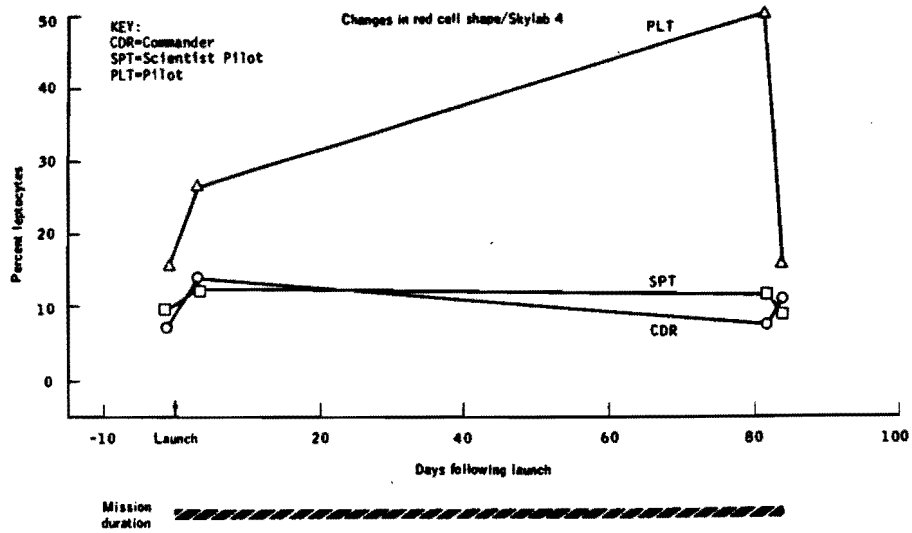
Each point represents the average value of the crew for the mission and sampling day indicated. The dotted lines represent the range of values for the three crewmembers from the mission measured at that period. The solid line preceding the graph represents the mean and standard deviation of all crew samples for all missions from the medical exams taken day 1 prior to launch.

Figure 19. Percent of stomatocytes plus knizocytes in crew red cell samples during the Skylab missions.



Each point represents the average value of the crew for the mission and sampling day indicated. The dotted lines represent the range of values for the three crewmembers from the mission measured at that period.

Figure 20. Percentage of leptocytes in crew red cell samples during the Skylab missions.



The points for each crewmember are plotted as a function of time after launch. Sampling periods indicated are F-1, MD4, MD82, and R+0.

Figure 21. Percent leptocytes in crew red cell samples during the third manned Skylab mission (Skylab 4).

group (preflight mean - 87.3% ± 11, postflight mean - 90.5% ± 3.3). The Skylab ground control group had no changes during the in-flight phase when fixed red cells were maintained exactly as those prepared by the astronauts.

DISCUSSION

The results of this study suggest that during extended exposure to the space flight environment significant alterations occur in the distribution of red cell shapes in the peripheral circulation. The most consistent change observed was the discocyte-echinocyte transformation which was readily reversed following completion of the mission. The kinetics and causes for this type of red cell shape change have been extensively studied in both *in vitro* and *in vivo* systems (Bessis and Lessin, 1970; Brecher and Bessis, 1972; Bull and Kuhn, 1970; Cooper, 1969; Cooper and Jandl, 1968; Deuticke, 1968; Feo, 1973; Kayden and Bessis, 1970; LaCelle, *et al.*, 1973; Leblond, 1973; Shohet and Haley, 1973; Weed and Chailley, 1973). The concept of echinocytogenic plasma, plasma capable of crenating normal red cells, has been well documented by these investigators. Various echinocytogenic factors identified this far are summarized in table II. A detailed discussion of all of the extrinsic, echinocytogenic agents identified in the

Table II. Reversible, Echinocytogenic Factors Affecting Red Cell Shape

Fatty acids:

- oleate
- caprylate

Detergents:

- alkyl sulfonates

Bile acids

Lysolecithin

Hypertonicity

Increased pH

Alcohols:

- ethanol
- butanol

Sedatives:

- barbiturates

Diuretics:

- ethacrynic acid

Coronary vasodilators:

- dipyridamole

Food preservatives:

- substituted benzoates

Metabolic drugs:

- 2, 4-dinitrophenol

Anti-inflammatory drugs:

- indomethacin
- phenylbutazone
- phenopyrazone

Plant glucosides, glycosides and derivatives:

- phloridzin
- phloratin
- tannic acid
- saponins

Modified from Bessis, *et al.*, 1973 2nd Deuticke, 1968.

plasma is outside the scope of this presentation. However, the following points should be emphasized relative to the results of this study and the body of knowledge existing relative to echinocyte formation.

The characteristics of the echinocyte formation observed during the Skylab flights are comparable to those of the discocyte-echinocyte transformation induced by elevations of plasma lecithin, lysolecithin, and/or free fatty acids. Most of the echinocytes observed in the Skylab study were of the state I type (fig. 9) suggesting that the changes in the plasma echinocytogenic factors were moderate. It has been demonstrated by Shohet and Haley (1973) that only a small elevation in the lysolecithin content of the red cell membrane is sufficient to initiate this shape change. The discocyte-echinocyte transformation can occur in seconds when echinocytogenic plasma is added to normal red cells (Bessis, 1973). All of the red cell shape changes, regardless of the cell type or duration of the mission, had almost completely reverted to the preflight levels by the first postflight sampling period (R+0). Thus the modifications in cell shape, which in some cases had occurred over a two to three month period, were neutralized within two to three hours of entry into the Earth's normal gravitational environment.

Most changes in red cell shape induced by intrinsic factors and those related to aged red cells are not readily reversible. This observation would support the concept of a change in one or more of the plasma constituents and its uptake by the cell membrane as being the primary cause of the shape changes.

The magnitude of the red cell shape change was not linearly correlated with any plasma constituent measured in the Skylab studies. However, lecithin, lysolecithin, free fatty acids, and albumin (significant to the clearance of free fatty acids) were not measured in either the in-flight plasma or red cell samples. It has been shown that it is the accumulation of the plasma echinocytogenic agent by the cell membrane which causes the shape change, not merely the addition of the agent to the plasma. This being the case, and because the transformations were all early stages of change, it is possible that extensive chemical analyses of these compounds in the plasma would not provide sufficient information relative to the shape changes.

The significance of the observed red cell shape transformations during Skylab is not readily apparent. Based upon the crews' in-flight exercise performance capacity and based upon their in-flight cardiovascular response to the stress of lower body negative pressure, it seems apparent that these changes in red cell shape do not represent a significant compromise to the body systems' ability to function normally with respect to adequate blood flow and tissue oxygen demand.

However, the impact of alterations in red cell shape with respect to the reduction in circulating red cell mass (Johnson, 1974) might be more significant. Severe deformation of circulating red cells can result in their premature sequestration by the reticuloendothelial system, primarily the hepatic and splenic systems (Rifkind, 1966). The alteration in red cell shape during space flight might provide a sufficient stimulus to the reticuloendothelial system to initiate trapping and eventual removal of these cells from the circulating red cell mass.

Maintenance of normal red cell shape and normal deformability are essential to survival of the cell *in vivo*. A major function of the reticuloendothelial system is to remove from circulation those cells whose structure is abnormal or the membrane too rigid. Since the cells that were examined in this study came from peripheral blood samples, they apparently satisfied the criteria of the reticuloendothelial system for nondestruction. However, the abnormal cells remaining in the circulation may be indicative of a greater degree of shape alteration in other cells which were then removed from circulation.

Sufficient data are not available to answer this question with certainty. As stated earlier, all of the echinocytes observed were of the stage I type. Studies on the deformability characteristics of echinocytes produced by extrinsic plasma echinocytogenic factors have shown that there are no significant differences in the deformability of these cells compared to discocytes (Leblond, 1973). It is only when the crenation progresses to a point where change in the membrane results in loss of effective surface area, that the consequences are different, and the cells have a reduction in their deformability. The absence of stage II or stage III echinocytes would seem to indicate that the changes observed were not progressing to further, more extensive shape alterations.

The magnitude of the echinocyte formation appears to be related to the duration of the flight with no apparent plateau in the curve depicting the response evident after 82 days. The curve describing the combined stomatocyte and knizocyte formation has a peak value between 20 and 30 days after launch, and by 82 days the percent of these types of cells is comparable to the preflight value. This second type of pattern is consistent with that characteristic of the red cell mass loss during these missions. The loss of circulating red cells was also maximal at 20 to 40 days and decreased after that time. However, the recovery of red cell mass was independent of weightlessness or normal gravity after the initial insult (Johnson, 1974). Thus, it is not possible to substantiate a direct relationship between the red cell shape alterations during the Skylab missions to the concomitant loss in red cell mass. However, it is an area that merits further investigation.

CONCLUSIONS

The significance of the transformations in red cell shape observed during the Skylab study must be considered relative to the limitation of man's participation in extended space flight missions. The results of this one study are not conclusive with respect to this question. Based on these examinations of red cells in normal, healthy men and based on other Skylab experiment data relative to the functional capacity of the red cells *in vitro* and the performance capacity of man as an integrated system, the changes observed in this study would not appear to be the limiting factor in determining man's stay in space. However, the results of this experiment and the documented red cell mass loss during space flight raise serious questions at this time relative to the selection criteria utilized for passengers and crews of future space flights. Serious consideration should be given to testing the effectiveness and reserve capacity of the erythropoetic system in those individuals, and until the questions relative to the specific cause and impact of the red cell shape change on cell survival *in vivo* can be resolved, individuals with diagnosed hematologic abnormalities should not be considered as prime candidates for missions, especially those of longer duration.

REFERENCES

1. Adams, K. H., 1972. Mechanical equilibrium of biological membranes. *Biophys. J.*, 12: 123-130.

2. Adams, K. H., 1973. A theory for the shape of the red blood cell. *Biophys. J.*, 13: 1049-1053.

3. Bessis, M., 1973. *Living Blood Cells and Their Ultrastructure* (Translated by R. I. Weed). Springer Verlag, New York, pp. 146-155.

4. Bessis, M. and L. S. Lessin, 1970. The discocyte-echioncyte equilibrium of the normal and pathologic red cell. *Blood*, 36:399-403.

5. Bessis, M., R. I. Weed, and P. F. Leblond, 1973. *Red Cell Shape: Physiol. Pathol., Ultrastructure.* Springer Verlag, New York.

6. Brecher, G. and M. Bessis, 1972. Present status of spiculed red cells and their relationship to the discocyte-echinocyte transformation: a critical review. *Blood*, 40: 333-344.

7. Bull, B., 1973. Red cell bioconcavity and deformability, a macromodel based on flow chamber observatons. In: Red Cell Shape. M. Bassis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 115-124.

8. Bull, B. S. and J. D. Bailsford, 1973. The biconcavity of the red cell: an analysis of several hypotheses. *Blood,* 41:833-844.

9. Bull, B. S. and I. N. Kuhn, 1970. The production of schistocytes by fibrin strands (a scanning electron microscope study). *Blood,* 35:104-111.

10. Cooper, R. A., 1969. Anemia with spur cells: a red cell defect acquired in serum and modified in the circulation. *J. Clin. Invest.,* 48:1820-1831.

11. Cooper, R. A. and J. H. Jandl, 1968. Bile salts and cholesterol in the pathogenesis of target cells in obstructive jaundice. *J. Clin. Invest.,* 47:809-822.

12. Deuticke, B., 1968. Transformation and restoration of biconcave shape of human erythrocytes induces by amphiphilic agents and changes of ionic environment. *Biochim. Biophys. Acta,* 163: 494-500.

13. Evans, E. A. and P. F. Leblond, 1973. Image holograms of single red blood cell discocyte-spheroechinocyte transformation. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 131-140.

14. Feo, C., 1973. The role of lysolecithin formed in plasma on the discocyte-echinocyte transformation, a commentary. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 37-40.

15. Johnson, P. C., 1974. Red cell mass changes of Skylab. Proceedings of the Skylab Life Sciences Symposium. NASA-JSC, Houston, Texas. (In Press).

16. Kayden, H. J. and M. Bessis, 1970. Morphology of normal erythrocyte and acanthocyte using nomarski optics and the scanning electron microscope. *Blood,* 35:427-436.

17. Kimzey, S. L., 1973. Hematology/immunology series experiment report: special hematologic effects (M115). Report on Skylab Medical Experiments Altitude Tests. NASA TM X-58115, pp. 6-21 thru 6-32.

18. Langley, G. R. and C. H. Felderhof, 1968. Atypical autohemolysis in hereditary spherocytosis as a reflection of two cell populations: relationship of cell lipids to conditioning by the spleen. *Blood*, 32:569-585.

19. Leblond, P., 1973. The discocyte-echinocyte transformation of the human red cell: deformability characteristics. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 95-104.

20. La Celle, P. L., F. H. Kirkpatrick, M. P. Udkow and B. Arkin. 1973. Membrane fragmentation and Ca-membrane interaction: potential mechanisms of shape change in senescent red cell. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 69-78.

21. Rifkind, R. A., 1966. Destruction of injured red cells *in vivo*. *Amer. J. Med.*, 41:711-723.

22. Shohet, S. B. and J. E. Haley, 1973. Red Cell membrane shape and stability: relation to cell lipid renewal pathways and cell ATP. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 41-50.

23. Weed, R. I., 1970. The importance of erythrocyte deformability. *Amer. J. Med.*, 49:147-150.

24. Weed, R. I. and B. Chailley, 1973. Calcium - pH interactions in the production of shape change in erythrocytes. In: Red Cell Shape. M. Bessis, R. I. Weed, and P. F. Leblond, Eds. Springer Verlag, New York, pp. 56-68.

25. Weed, R. I., P. L. LaCelle, and E. W. Merrill, 1969. Metabolic dependence of red cell deformability. *J. Clin. Invest.*, 48:795-809.

CARDIOVASCULAR AND METABOLIC FUNCTION

LOWER BODY NEGATIVE PRESSURE: THIRD MANNED SKYLAB MISSION

R. L. Johnson, M. D.; G. W. Hoffler, M. D.*; A. E. Nicogossian, M. D.*; S. A. Bergman, M. D.*; and M. M. Jackson, M. S.**

ABSTRACT

The crew of the Skylab 4 Mission exhibited physiological changes during their 84-day mission that resembled but in several important areas did not reach the magnitude of changes exhibited in crewmen of the two earlier Skylab flights. For example, calf girth diminished rapidly at first and continued throughout the flight, but at a slower rate than in the first two crews. At rest all three crewmen showed, in comparison to preflight levels, elevated mean systolic and pulse pressures and decreased mean diastolic and mean arterial pressures. Similar changes were seen in most Skylab 2 and Skylab 3 crewmen. While mean resting heart rates of both the Skylab 3 and Skylab 4 crews were elevated, those of the Skylab 2 crew were, however, lower than during preflight tests. Stressed heart rates followed previous patterns in being consistently elevated over preflight values. Again, increases of calf volume during lower body negative pressure greatly exceeded preflight increases. Postflight changes in cardiovascular parameters for the most part resembled those seen in previous crewmen of space missions. Their recovery to preflight limits occurred rapidly.

In-flight data and subjective impressions of the crewmen confirmed, as in previous Skylab flights, that lower body negative pressure in weightlessness imposed a greater stress upon the cardiovascular system than in Earth's gravity. Changed relationships in the anatomical distribution of blood volume and extravascular fluids, altered patterns of blood flow, and reduced total circulating blood volume induced by the weightless environment are offered as partial explanations for the changes in cardiovascular responses to lower body negative pressure. The exaggerated in-flight responses to lower body negative pressure generally appeared to decline after the first 30 to 50 days of flight. In-flight data served as a fairly accurate prediction of the postflight status of orthostatic tolerance.

---

*National Aeronautics and Space Administration - Lyndon B. Johnston Space Center, Houston, Texas.

INTRODUCTION

Medical evaluations after Gemini and Apollo flights demonstrated reduced orthostatic tolerance in virtually all crewmen specifically tested (1,2). This diminished ability of the cardiovascular system to function effectively against gravitational stress following exposure to weightlessness, while usually mild and never operationally significant, sometimes resulted in pronounced increases in heart rate and decreases in pulse pressure during orthostatic testing. However, forty-eight hours or less nearly always sufficed for orthostatic responses to regain their preflight status. The magnitude of this postflight loss of orthostatic tolerance showed no clear correlation with flight durations ranging between four and fourteen days. This enigma was compounded by the Russian reports of severe orthostatic intolerance in the Soyuz 9 crewmen after their eighteen-day flight (3). Against this background, concern for postflight orthostatic intolerance in the crewmen of the planned twenty-eight-day flight of the first manned Skylab Mission, Skylab 2, reached greater dimensions.

The objective of the Skylab lower body negative pressure experiment designated M092, was to determine the extent and the time course of changes in orthostatic tolerance during the weightlessness of space flight and to determine whether in-flight data from the experiment would be useful in predicting the postflight status of orthostatic tolerance.

Compared to preflight results, lower body negative pressure produced exaggerated blood pressure and heart rate responses during the first in-flight test of the Skylab 2 crewmen and showed no clear-cut trend toward preflight levels during the twenty-eight-day flight (4). Heart rate responses to the last in-flight test, however, compared quite closely to those of the first postflight test. Postflight orthostatic intolerance was not more severe than that seen after some Apollo flights and differed chiefly in requiring longer periods of time to return to preflight levels.

During the second manned mission, Skylab 3, similar exaggeration of blood pressure and heart rate responses occurred during the first in-flight test (5). Again no definite trend toward preflight values could be seen during the first twenty-eight days but cardiovascular responses to lower body negative pressure appeared to become more stable by the sixth to eighth week of flight. In general, the test results in-flight served to predict quite well the orthostatic tolerance of the individual crewmen in the immediate postflight period. The Skylab 3 crew responded surprisingly well to postflight lower body negative pressure tests. Moreover, the return of orthostatic responses to preflight values occurred more rapidly than after the

twenty-eight-day flight. During both flights the results of lower body negative pressure assumed an important role in assessing the in-flight status of crew health. The experience of the first two missions with the lower body negative pressure and other biomedical experiments greatly reduced apprehension toward extension of the third manned mission, Skylab 4, beyond the 59 days flown by the Skylab 3 crew.

METHODS AND MATERIALS

Preflight baseline data were acquired from the Skylab 4 crewmen over a four and one-half month period from four tests conducted at approximately monthly intervals and three during the last six weeks prior to launch. All tests were carried out in the Orbital Workshop one-g Trainer or the Skylab Mobile Laboratories using flight-type hardware. Training in the techniques of the test and operation of the equipment took place prior to the acquisition of baseline data, most of which was obtained from tests conducted by the astronauts acting both as subjects and observers as they would later do in flight. In-flight tests were conducted usually at three- or four-day intervals while postflight tests were carried out daily at first and then at increasing intervals of time over a period of approximately two months. Table I shows the number of tests on each Skylab 4 crewman during each period of the mission as well as those for the first two manned missions. Scheduling was such that, insofar as possible, each crewman's test was carried out at the same time of day and at least one, but if possible, two hours after meals or vigorous exercise.

TABLE I. LOWER BODY NEGATIVE PRESSURE DURING PREFLIGHT, IN-FLIGHT AND POSTFLIGHT PERIODS OF THE THREE SKYLAB MISSIONS AND TOTAL TESTS FOR EACH PHASE AND EACH MISSION.

Skylab Mission		Preflight	In-flight	Postflight	Total
2	Commander	6	7	8	21
	Scientist Pilot	6	7	8	21
	Pilot	6	8	8	22
		18	22	24	64
3	Commander	6	16	8	30
	Scientist Pilot	5	17	8	30
	Pilot	5	16	8	29
		16	49	24	89
4	Commander	6	22	9	37
	Scientist Pilot	7	22	9	38
	Pilot	7	23	9	39
		20	67	27	114
Total: 3 Missions		54	138	75	267

The lower body negative pressure device, constructed of anodized aluminum, was tubular in shape and could be separated at its center to allow access to the subject's legs (figs. 1 and 2). Movable superior and lateral iris-like templates around the circular opening could be adjusted to fit snugly around the subject's waist. A waist seal of fire-resistant material encircled the end of the device and was fitted closely to the waist by means of a zippered opening and Velcro overlap, and a belt which encircled the waist just outside the metal opening. A padded post, which served as a saddle, could be adjusted footward or headward so that the iliac crests of the subject were at the level of the metal templates. Decreased pressure within the device was provided by a vacuum plenum, or during flight, the vacuum of space. In addition to a valve in this system, a second valve and a pressure gage mounted on the lower body negative pressure device permitted fine adjustment of the pressure within the device to any level between zero and 55 mm Hg below ambient pressure. Safety features included a quick-release valve, easily accessible to subject and observer, and an automatic mechanism to prevent negative pressure from exceeding 55 mm Hg. Sensors mounted inside and external to the device provided internal and ambient temperature records.

Basic measurements during all tests included blood pressure at 30-second intervals from an automatic system which detected and analyzed Korotkoff sounds, heart rate continuously from one component of a Frank lead vectorcardiogram and percentage change in calf volume continuously from capacitance plethysmographic bands encircling the legs (fig. 3). Prior to positioning these bands, a manual measurement was made of circumference of the largest portion of the calves, which also corresponded to the position where the left band was to be placed. Since the right band served solely to measure capacitance changes due to alterations of temperature and humidity within the negative pressure device, it was therefore placed around a rigid metal band which encircled the right leg at the lower level of the calf muscle. Additional measurements carried out during preflight and postflight tests included respiratory excursions from a mercury strain gage across the lower thorax, systolic time intervals from a phonocardiogram and carotid pulse transducer, and, in Skylab 4, echocardiograms. These along with vectorcardiographic findings and preflight and postflight chest x-rays for cardiac size are discussed elsewhere (6-9). Prior to the lower body negative tests, as in Apollo 16 and 17 flight crew evaluations, lower limb volume was estimated from a series of girth measurements taken at three centimeter intervals between ankles and upper thighs. For the first time the latter measurement was also made several times during the Skylab 4 flight (10).

An Experiment Support System provided power and appropriate controls, including those necessary for calibration, to the hardware

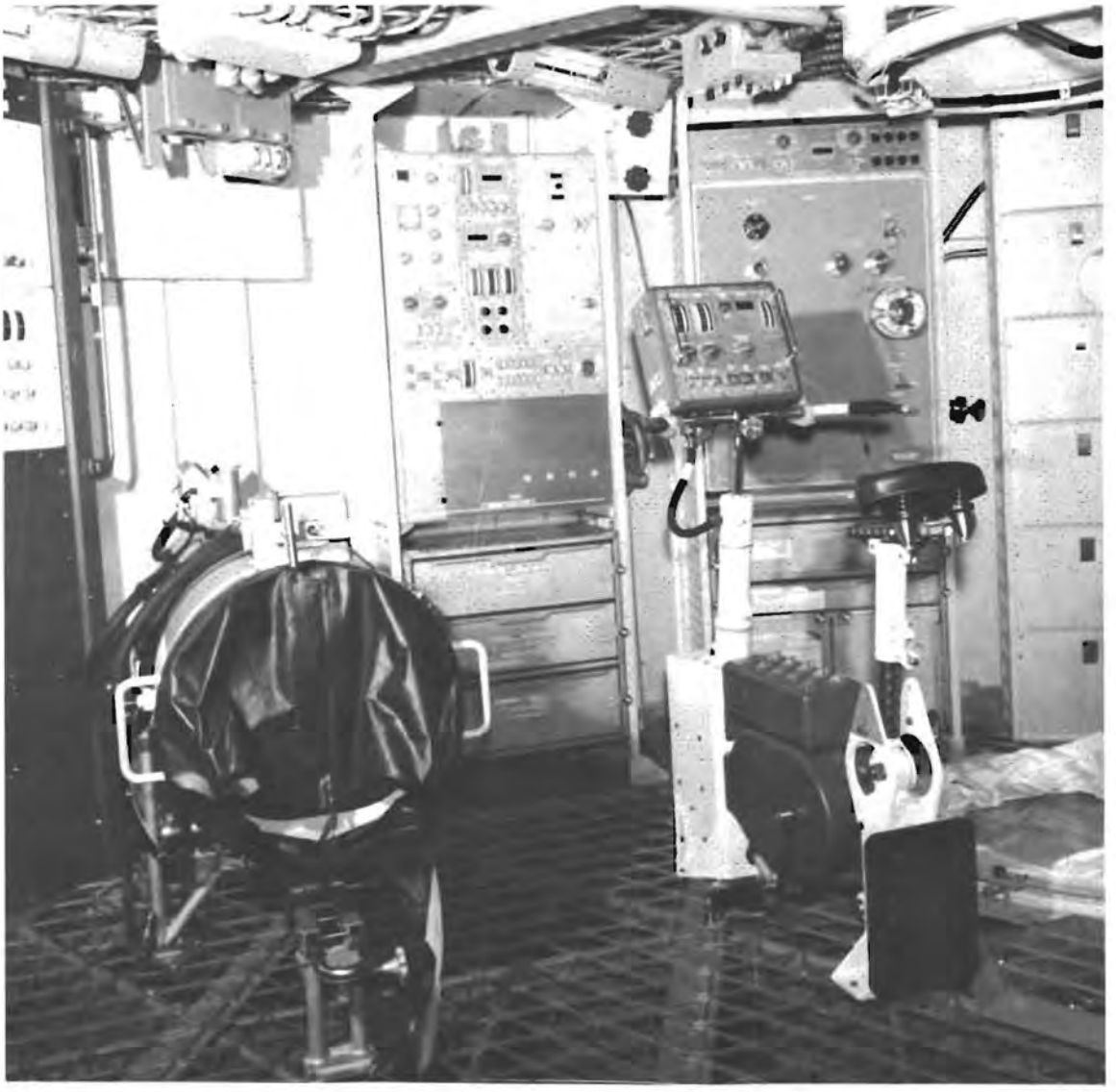


Figure 1. Photograph of the Lower Body Negative Pressure (LBNP) device, showing waist seal with zipper. Movable templates are hidden from view by the seal.

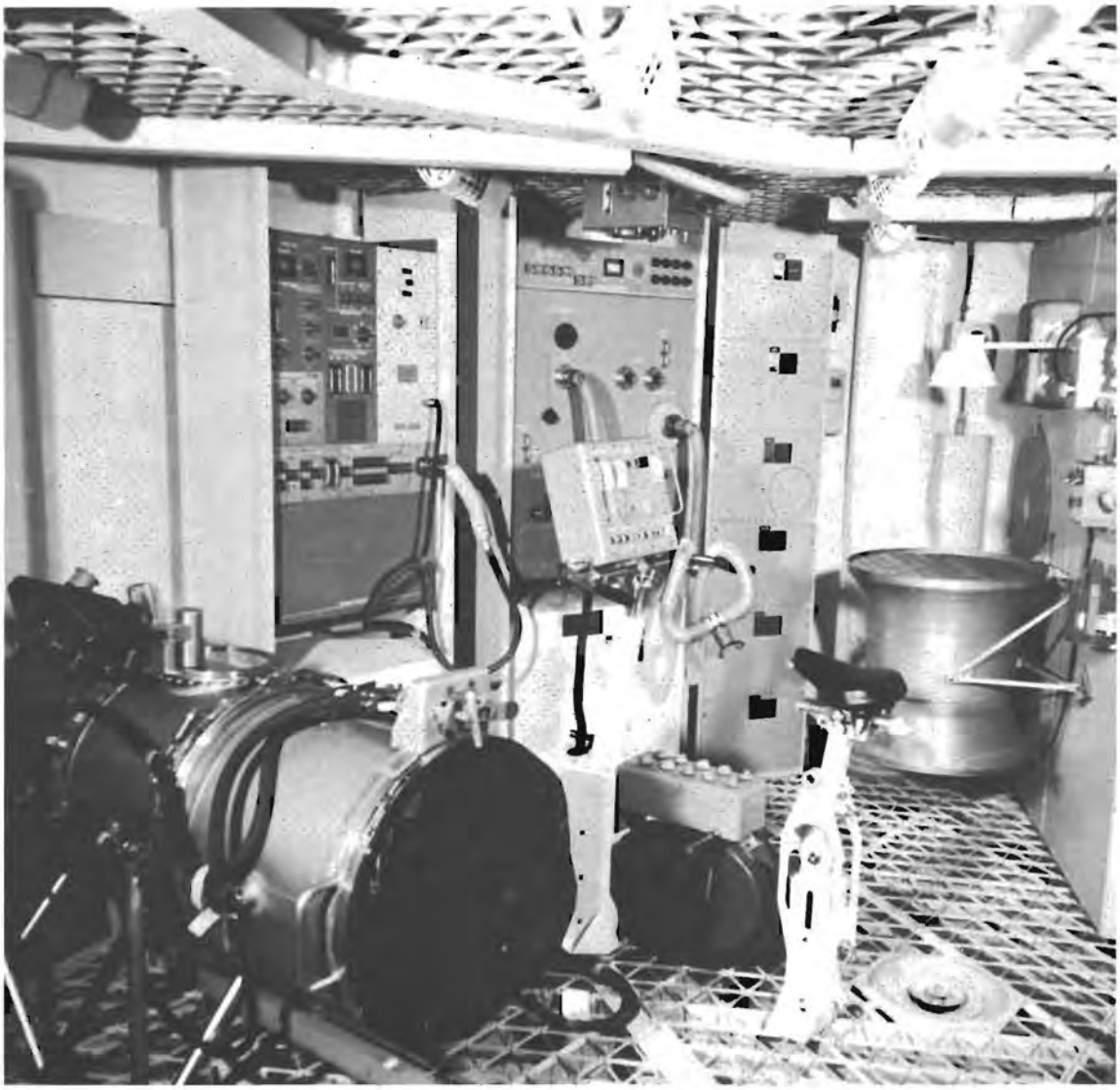


Figure 2. Photograph showing side view of Lower Body Negative Pressure device. The ESS and its displays are in the background.

Figure 3. Photograph of capacitive plethysmographs and plug-in locking connectors.

units already mentioned. The Experimental Support System (ESS) also contained displays for heart rate, which was updated every five beats, systolic and diastolic pressures, percentage changes in calf volume, and temperature within and exterior to the Lower Body Negative Pressure Device.

The lower body negative pressure protocol was identical to that adopted for Apollo studies. The first and last 5 minutes of the 25-minute test were at ambient atmospheric pressure to provide data from resting control and recovery periods, respectively. The 15-minute stress period consisted of five distinct levels of negative pressure applied sequentially: 8 and 16 mm Hg negative pressure for one minute each, 30 mm Hg for three minutes, and 40 and 50 mm Hg negative pressure for 5 minutes each (fig. 4).

Prior to entry, each crewman donned a garment which covered the lower body (see Skylab Medical Program Overview, fig. 6). Garment pressure against the skin was provided by lateral inflatable bladders and capstans. When inflated to gage pressure of 170 to 180 mm Hg, the capstans produced 85 to 90 mm Hg pressure at the ankles and a decreasing gradient of pressure headward which declined to 10 mm Hg at the waist. These garments remained pressurized, except during times when the crewmen could be recumbent, until beginning of the first postflight lower body negative pressure test.

Blood pressure and heart rate data in this paper, unless otherwise specified, refer to mean values during the lower body negative pressure phase, usually the 5-minute periods during resting control and exposure to -50 mm Hg pressure. Mean values from preflight tests established fiducial limits at the $P < 0.05$ significance level for evaluating in-flight and postflight data. The subject of the Results, which follows, applies only to Skylab 4 crewmen except when otherwise specified.

RESULTS

In-flight

Heart Rate

During their first in-flight tests on mission days 5 and 6, resting heart rates of the Commander and the Scientist Pilot showed elevations of resting heart rates above fiducial limits established from preflight tests. The Pilot, on the other hand, on mission day 5 exhibited a resting heart rate that was relatively slow and well within

THE LOWER BODY NEGATIVE PRESSURE PROTOCOL USED FOR SKYLAB CARDIOVASCULAR EVALUATIONS ASSESSING ORTHOSTATIC TOLERANCE

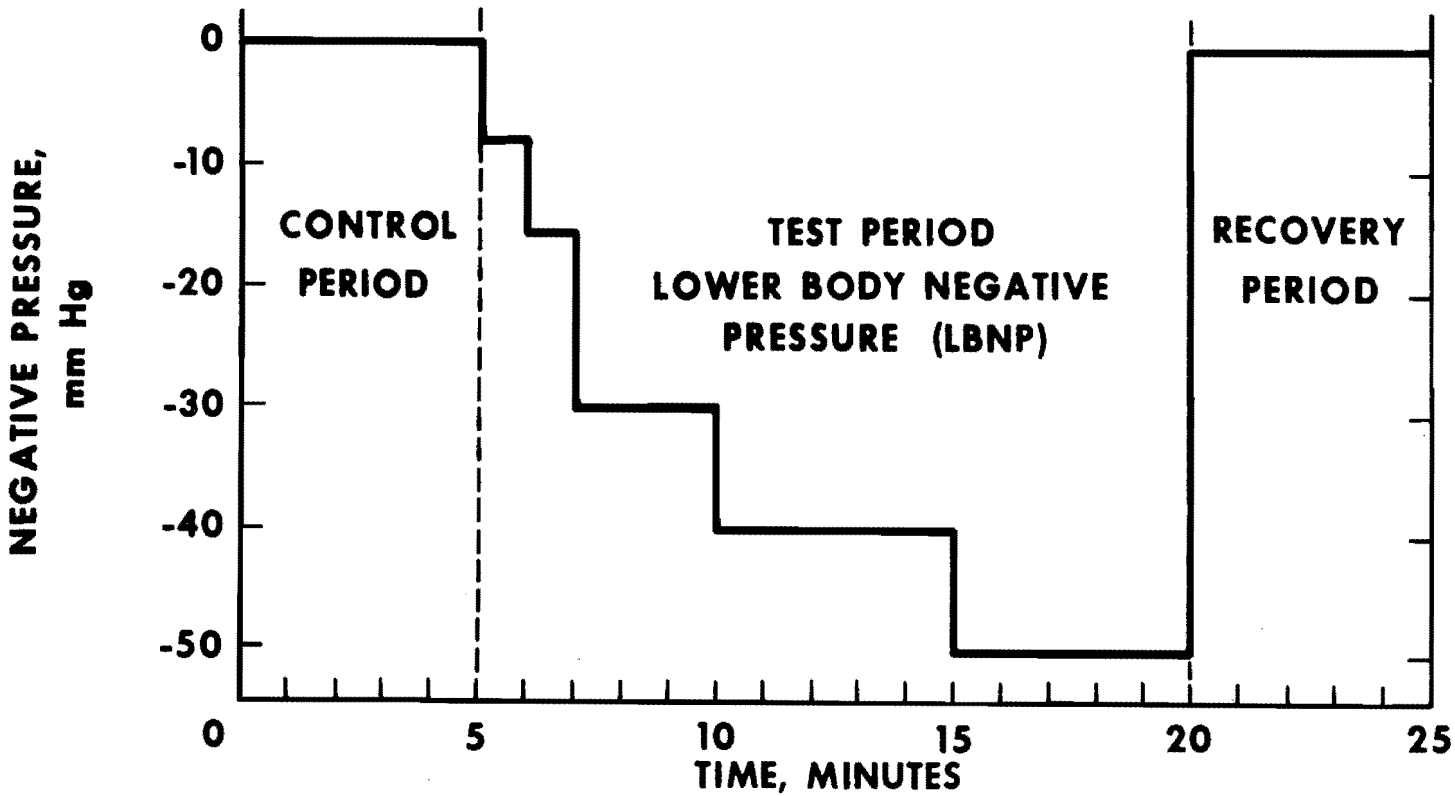


Figure 4. Levels of lower body negative pressure and time of individual phases of the lower body negative pressure protocol.

preflight limits. Typical preflight and the first in-flight tests of each crewman are shown in figures 5 through 10. After mission day 5 resting heart rates were elevated above preflight limits in nearly every test, although a probable trend toward lower rates appeared during the last third of the mission. This was more apparent in the Commander whose resting heart rates fell within preflight limits in three of nine tests after mission day 51 (fig. 11).

During the -50 mm Hg phase of lower body negative pressure heart rates became significantly elevated in all three crewmen in the first and in nearly every subsequent test throughout the flight. The degree of elevation fluctuated rather markedly from test to test. The Commander showed the least fluctuation and, after mission day 39, had no further tests in which stressed (-50 mm Hg) mean heart rates exceeded 81 beats per minute. In the majority of tests after mission day 51, his stressed heart rates remained within preflight limits. Fluctuations of mean stressed heart rates of the Scientist Pilot continued throughout the mission but remained significantly elevated above preflight limits. A slight downward trend may have been present after mission day 34 (fig. 12). Certainly after this time, tests with excessively high heart rate responses occurred less frequently. Stressed heart rate fluctuations of the Pilot became smaller after mission day 29 and a slowly declining heart rate response to lower body negative pressure may have been present after this time (fig. 13).

Blood Pressure

Mean values of systolic blood pressure (SBP) of the Commander during the resting control period of in-flight lower body negative pressure tests were usually within preflight limits. Significant elevations occurred infrequently and sporadically but were more common during the first half of the mission. Conversely, diastolic blood pressure (DBP) at rest was usually significantly lower than preflight values. Resting pulse pressure therefore usually exceeded preflight limits. Calculated mean arterial pressure ($SBP + \frac{SBP - DBP}{3}$) ranged below preflight limits in approximately one-half of the tests, occurring in four successive tests between mission day 11 and mission day 21 and in five of six tests between mission day 47 and mission day 66. The magnitude by which in-flight blood pressure and heart rate means of the Skylab 4 crewmen differed from preflight values appear in table II.

Diastolic pressure of the Commander during lower body negative pressure rose over resting values by significantly greater increments during in-flight tests than in preflight tests (fig. 14). Despite the greater in-flight rise, mean stressed diastolic pressure, while lower than preflight values, was not so to a significant degree. Higher resting levels and smaller falls of systolic pressure characterized in-flight

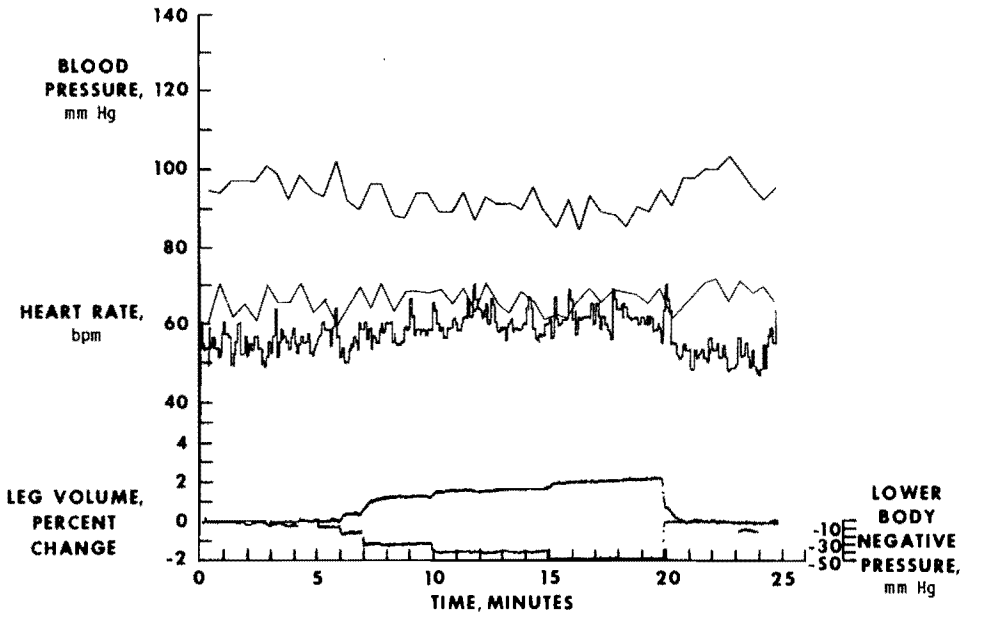


Figure 5. Cardiovascular responses of Skylab 4 Commander during test 50 days prior to flight.

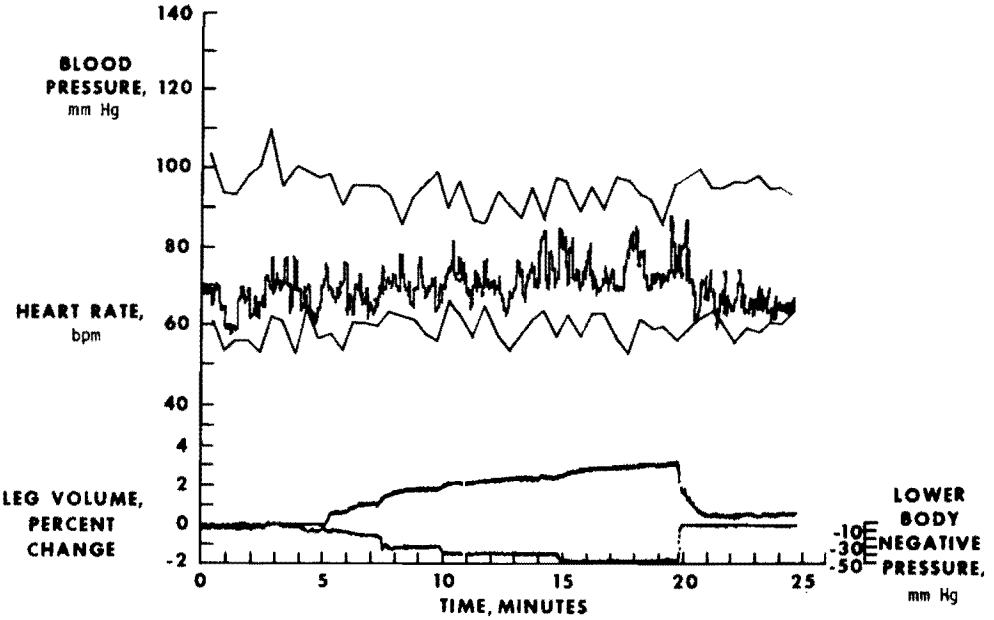


Figure 6. Cardiovascular responses during first in-flight test of Skylab 4 Commander on mission day 5. Moderate depression of diastolic pressure, elevation of systolic pressure during the resting control phase, and increased heart rate and calf volume change during lower body negative pressure are apparent.

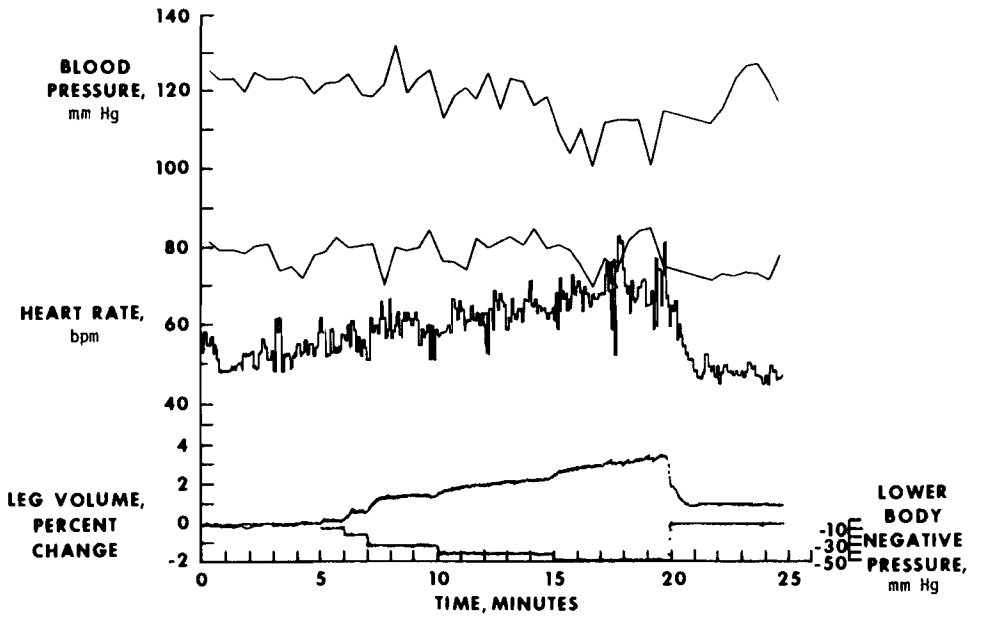


Figure 7. Cardiovascular responses of the Skylab 4 Scientist Pilot during test 21-days prior to flight.

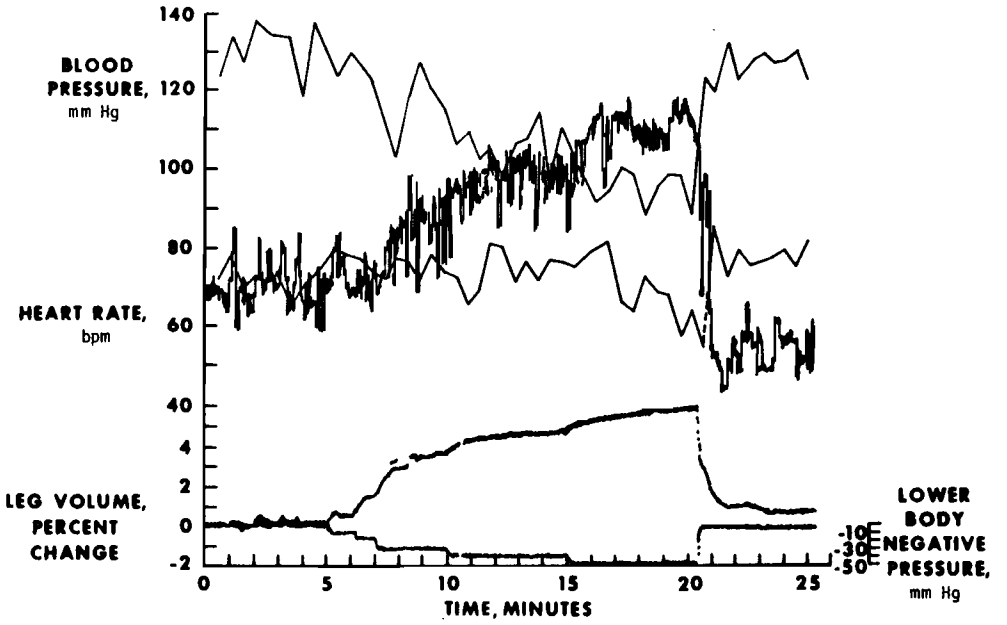


Figure 8. Cardiovascular responses during first in-flight test of the Skylab 4 Scientist Pilot on mission day 6. Changes from preflight values resemble those of the Commander in figure 6 but are more pronounced. The slightly early termination of negative pressure was not due to symptoms.

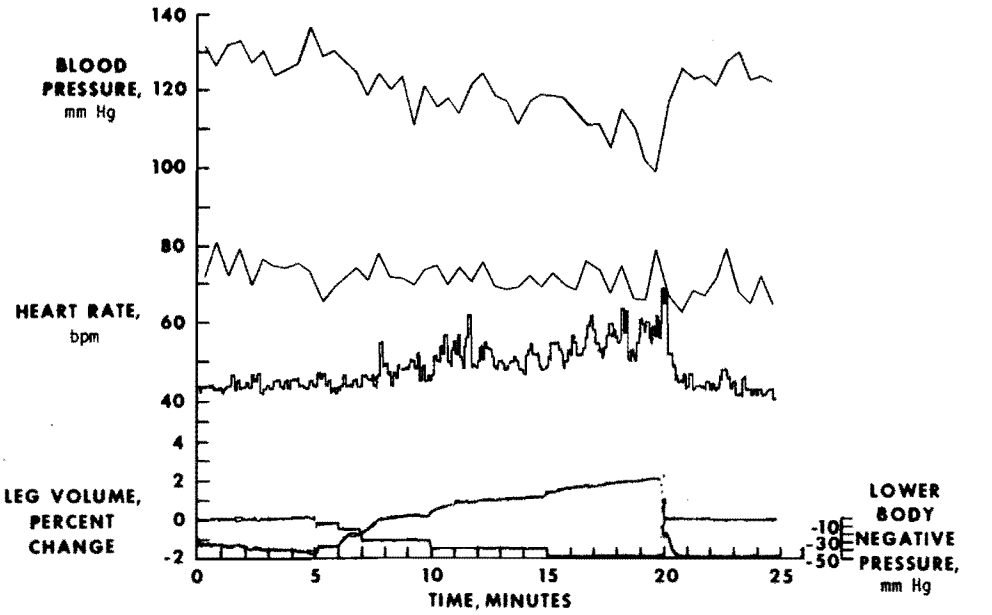


Figure 9. Cardiovascular responses of the Skylab 4 Pilot during test 35-days prior to flight.

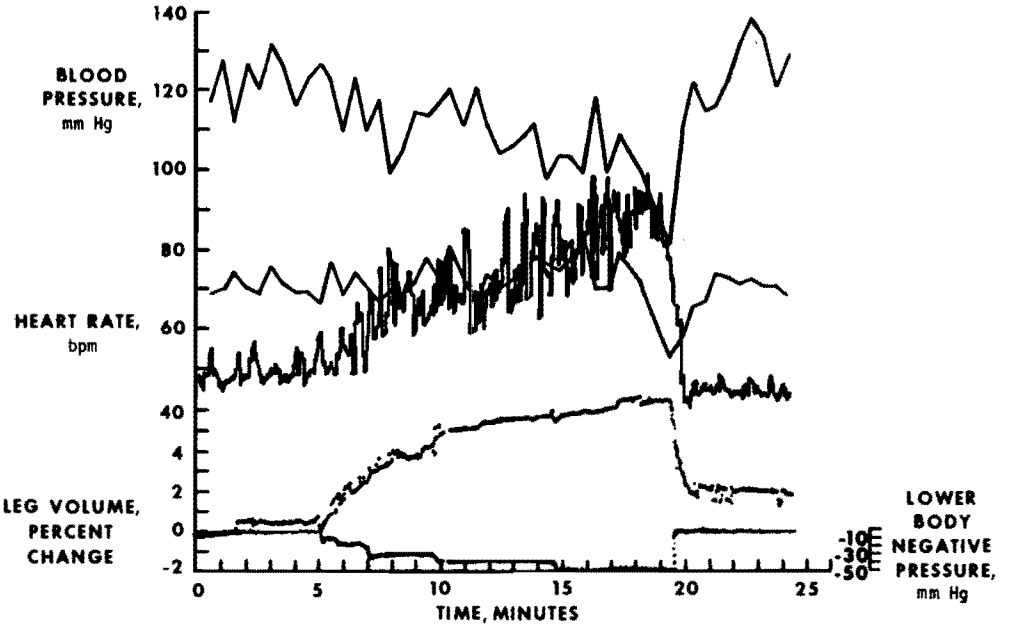


Figure 10. Cardiovascular responses during first in-flight test of the Skylab 4 Pilot on mission day 5 showing changes from preflight responses similar to those of the Scientist Pilot in figure 8.

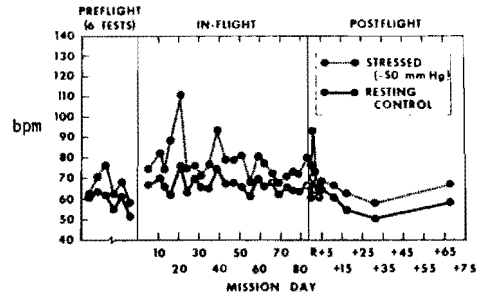


Figure 11. Mean heart rate of the Commander during resting and -50 mm Hg phases of lower body negative pressure.

Note the contracted time scale during the preflight period in this figure and similar figures that follow. Highest heart rate responses occurred on mission days 21 and 39 and post flight on recovery plus one day. A presyncopal episode on mission day 16 probably prevented higher mean heart rate on that day since the test was terminated after a little more than two minutes exposure to -50 mm Hg lower body negative pressure.

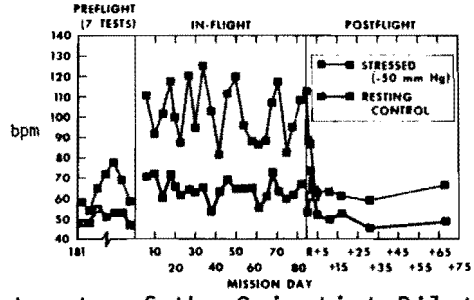


Figure 12. Mean heart rate of the Scientist Pilot during resting and -50 mm Hg phases of lower body negative pressure.

Presyncopal episodes on mission days 14 and 61 may have prevented higher stressed heart rates during these tests although such an effect was not apparent on mission days 34 and 71 when presyncopal symptoms also caused the tests to be terminated. Periodic high stressed heart rates climbed to a peak at mission day 34. Thereafter, these declined in magnitude and also in frequency.

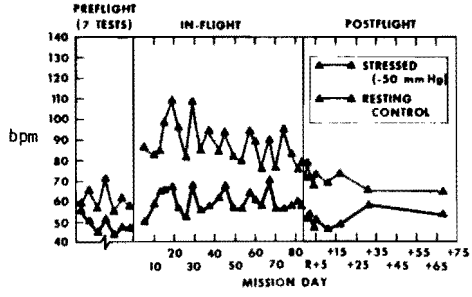


Figure 13. Mean heart rate of the Pilot during resting and -50 mm Hg phases of lower body negative pressure.

The high heart rates that appeared periodically declined in magnitude after the first month in-flight. A slight downward trend in stressed heart rates was apparent during the latter period. A presyncopal episode on mission day 10 may have been associated with the lower mean stressed heart rate on that day.

TABLE II

DIFFERENCES BETWEEN MEAN IN-FLIGHT VALUES FOR HEART RATE AND BLOOD PRESSURE OF THE SKYLAB 4 CREWMEN DURING REST AND -50 mm Hg PHASE OF LOWER BODY NEGATIVE PRESSURE FROM CORRESPONDING MEAN VALUES DURING PREFLIGHT TESTS.

	Commander	Scientist Pilot	Pilot
Resting Control			
Heart Rate (bpm)	+7.8*	+13.3*	+11.3*
Systolic Blood Pressure (mm Hg)	+1.8	+ 2.5	+ 1.0
Diastolic Blood Pressure (mm Hg)	-5.6*	- 2.0	- 2.5
Pulse Pressure (mm Hg)	+7.4*	+ 4.5‡	+ 3.4
Mean Arterial Pressure (mm Hg)	-3.2†	- 0.5	- 1.3
Stressed -50 mm Hg			
Heart Rate	+12.2†	+36.7*	+26.7*
Systolic Blood Pressure	+6.2*	-10.9*	- 1.6
Diastolic Blood Pressure	-1.0	- 4.8	+ 1.3
Pulse Pressure	+7.1*	- 6.1	- 2.8
Mean Arterial Pressure	+1.5	- 6.8*	+ 0.3

* Significant to 0.001 level by paired t-test
† Significant to 0.01 level by paired t-test
‡ Significant to 0.05 level by paired t-test

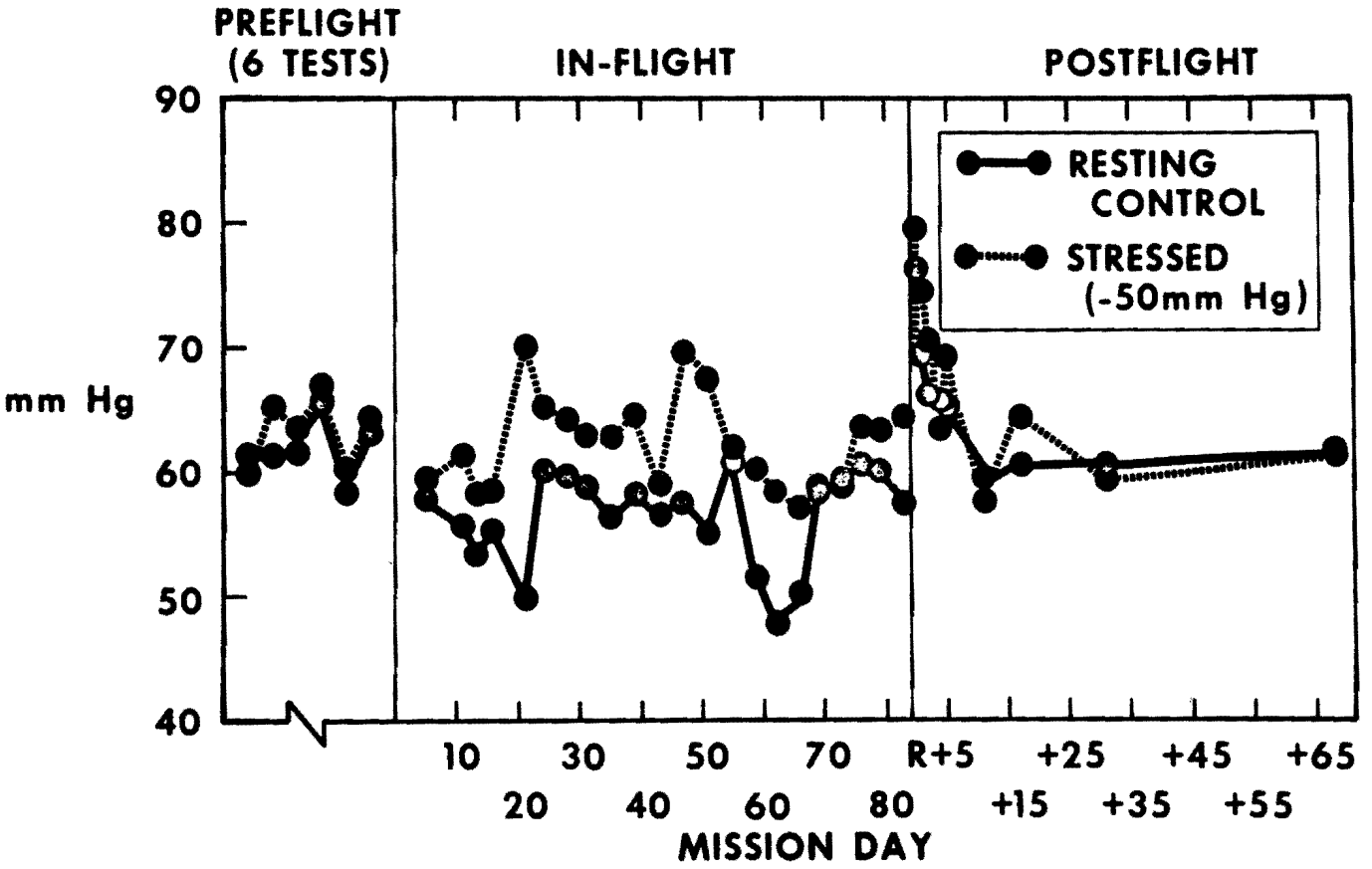


Figure 14. Mean diastolic blood pressure of the Skylab 4 Commander during resting control and -50 mm Hg pressure phases of lower body negative pressure. The marked elevation on mission day 21 was associated with the highest stressed heart rate seen in the Commander's in-flight tests. The elevated diastolic pressure on mission day 39, on the other hand, occurred in association with a heart rate that was only modestly elevated.

lower body negative pressure tests of the Commander as compared to preflight. This combination led to the unusual finding of a significantly higher in-flight mean value of pulse pressure during -50 mm Hg than preflight. Stressed pulse pressure in-flight exceeded preflight stressed pulse pressure in only two other Skylab crewmen, the Commander of Skylab 3 and the Pilot of Skylab 2. In-flight mean values for mean arterial pressure of the Commander during the -50 mm Hg phase of lower body negative pressure differed only slightly from preflight values. Evidence for any trend of change in blood pressure parameters during flight were lacking.

While blood pressure of the Commander showed less variance from test to test in the preflight period than any of the other eight Skylab astronauts, both the Scientist Pilot and the Pilot showed considerable lability of blood pressure during their preflight tests. As a consequence, in-flight changes from preflight values did not achieve statistical significance unless they were of large magnitude.

Even though resting systolic blood pressure of the Scientist Pilot during in-flight tests exceeded preflight limits rather frequently during the first half of the mission, its mean value for all in-flight tests did not depart significantly from preflight values. Diastolic pressure at rest showed little change from mean preflight values. The mean of in-flight values for resting pulse pressure of the Scientist Pilot exceeded preflight means by a significant margin. In addition, most individual tests during the first half of the mission revealed resting pulse pressures significantly higher than preflight fiducial limits. Figure 15 shows mean values of systolic and diastolic pressure of the Scientist Pilot during rest and the -50 mm Hg phase of lower body negative pressure in all tests.

Stressed systolic blood pressure of the Scientist Pilot fell below preflight limits in nearly every in-flight test. Decreases of diastolic pressure below preflight limits during lower body negative pressure occurred less frequently. Stressed pulse pressure and mean arterial pressure frequently declined below preflight limits, and the mean value of mean arterial pressure during in-flight tests were significantly lower than the mean of preflight values. Over the in-flight period there appeared to be a slight downward trend in resting systolic and diastolic pressures and a questionable downward trend in their values during stress.

Resting and stressed systolic and diastolic blood pressures of the Pilot were within the rather wide preflight limits for these values in nearly all in-flight tests. The resting pulse pressure exceeded preflight limits occasionally and sporadically in in-flight tests since systolic blood pressure tended to be higher and diastolic pressure

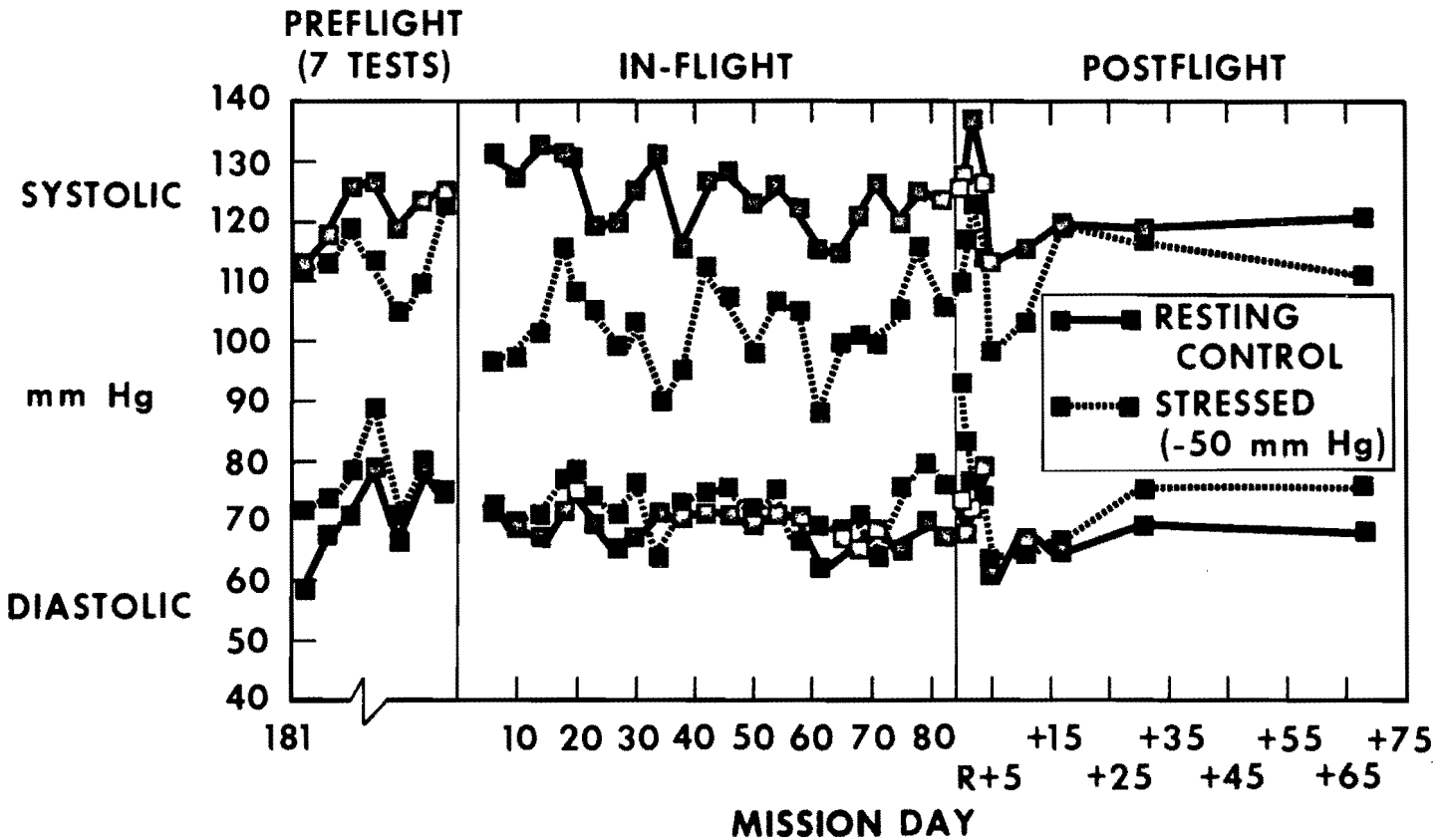


Figure 15. Mean systolic and diastolic blood pressures of the Skylab 4 Scientist Pilot during resting control and -50 mm Hg lower body negative pressure phases of individual tests. The magnitude of falls in systolic pressure during stress tended to decline during the course of the mission.

lower than preflight levels. While pulse pressure showed no definite trend or change during the flight, systolic, diastolic and mean arterial pressures, both at rest and during lower body negative pressure stress, showed definite declining trends (figs. 16, 17).

Calf Volume Increase Induced by Lower Body Negative Pressure

As had been observed in the first two Skylab Missions, calf volume increases during lower body negative pressure greatly exceeded those which had occurred in preflight tests. As illustrated in figures 18 and 19, the rate and magnitude of increase were especially pronounced at the lower levels of negative pressure, -8, -16, and -30 mm Hg. In some tests, calf volume increased so rapidly that the leveling off usually seen before the end of each minute of exposure to -8 and -16 mm Hg pressure did not occur until after the -30 mm Hg level had been reached. This pronounced change in calf volume appeared in the first test and continued, although varying considerably between tests, throughout the mission.

Calf volume increases of the Commander in preflight tests were relatively small in contrast to those of the Scientist Pilot and Pilot, which were larger than usually seen. This same pattern of difference continued throughout the flight. Even when using the least sensitive band available, calf volume of the Scientist Pilot and Pilot rather frequently reached off-scale values after increasing to about 8.5 percent. On mission day 54, following instructions from the ground. the crew made adjustments to reduce sensitivity of the band used by these two crewmen by about 30 percent. Thereafter, the off-scale condition was not reached, even though calf volume increases sometimes exceeded 11 percent. Whereas preflight calf volume increases at the end of the -50 mm Hg phase averaged between 3 and 4 percent, during in-flight tests they reached values usually between 8 and 11 percent in the Scientist Pilot and Pilot. In the Commander, calf volume increases averaged 2.4 percent preflight but usually reached levels ranging between 5 and 7 percent in-flight.

During preflight tests, calf volume decreases indicating venous drainage usually were seen during the five minutes of rest preceding negative pressure. Calf volume during this five-minute period in-flight tests usually shifted upward, indicating an increase in venous inflow. Frequently during the -8 mm Hg and -16 mm Hg phase in preflight tests, evidence of active venous contraction occurred after the initial filling period. This phenomenon was seen more often in the Commander than in either the Scientist Pilot or Pilot. During in-flight tests such indication of venous contraction occurred only infrequently and sporadically.

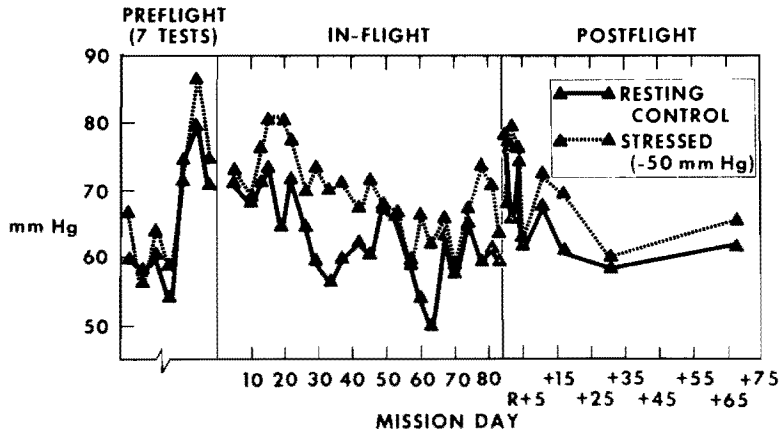


Figure 16.
Mean diastolic pressure of the Skylab 4 Pilot during resting and -50 mm Hg phases of individual lower body negative pressure tests.

In most tests, especially through the first two-thirds of the mission, elevations in diastolic pressure during stress were of large magnitude.

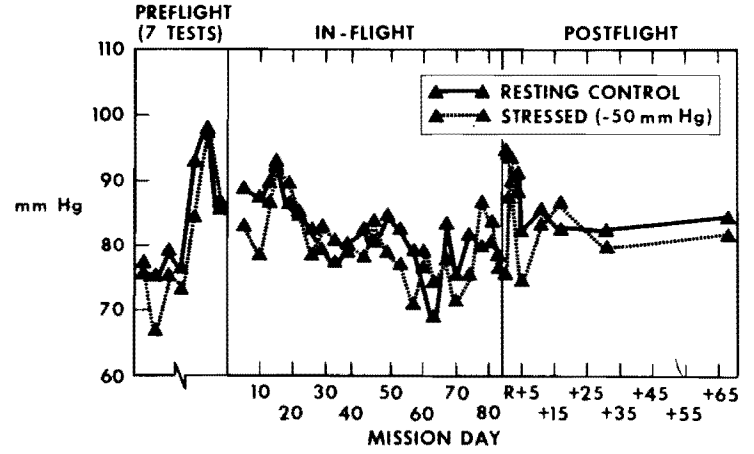


Figure 17.
Mean arterial pressure during resting and -50 mm Hg phases of individual tests of the Skylab 4 Pilot.

A trend toward lower values is extended throughout the in-flight period.

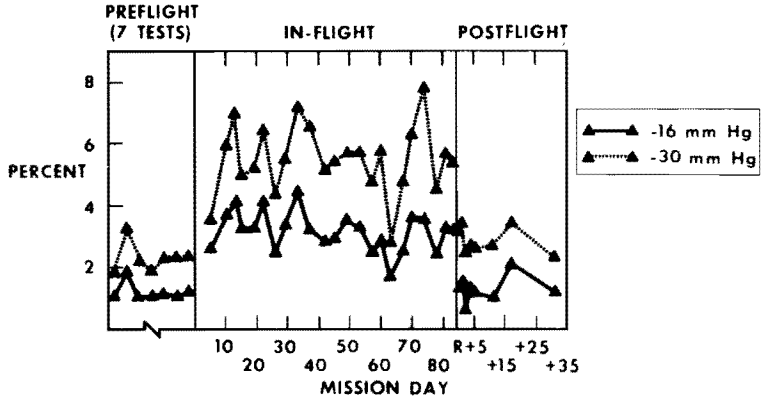


Figure 18.
Increases in calf volume, expressed as a percentage change from resting control volume, during lower body negative pressure tests of the Skylab 4 Pilot.

The values shown indicate percent volume increase at the ends of the one-minute -16 mm Hg and the three-minute -30 mm Hg phases of lower body negative pressure. Resting calf volumes are shown as zero, but actually declined during the course of the flight.

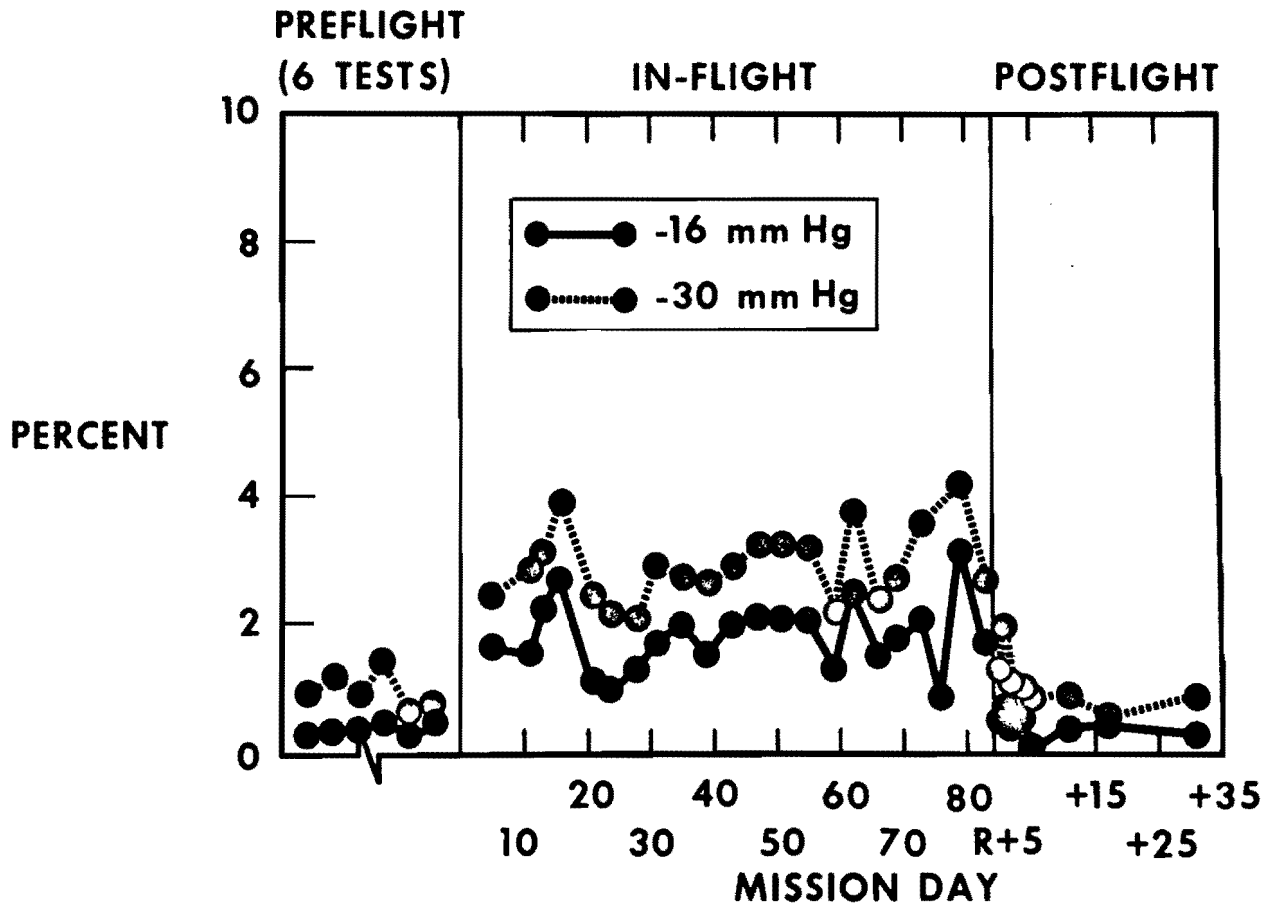


Figure 19. Percentage increase in calf volume of the Skylab 4 Commander at the end of -16 and the -30 mm Hg phases of individual tests of the Commander. Absolute values during both preflight and in-flight periods were lower than those of the Scientist Pilot and Pilot (shown in preceding figure). Proportionate increases of in-flight over preflight values were similar.

Following cessation of negative pressure, calf volume returned usually to within 0.5 percent above or below the resting value in preflight tests. Conversely, during in-flight tests, calf volume at the end of the five minute recovery period usually measured close to two percent above baseline values. In the case of the Commander, there appeared to be an upward trend in this residual volume during the first five weeks of the mission (fig. 20).

Other Measurements and Observations

Resting calf circumference measurements were made by the Skylab 4 crew on mission day 2, three days before the first lower body negative pressure experiment. At this time, both the Commander and the Pilot showed declines of approximately one centimeter from the last preflight measurement. The calf circumference of the Scientist Pilot showed a slight increase, a finding which cannot be adequately explained. These early measurements differed little, if any, from the subsequent measurements on mission day 5 and mission day 6, which showed reductions ranging from 0.8 to 2.0 percent from the last preflight values. This represented a smaller reduction than had occurred in the Skylab 2 and Skylab 3 crewmen whose decreases after comparable times in weightlessness had ranged between 3.5 and 5.0 percent (table III). Subsequent measurements throughout the Skylab 4 flight showed further rapid decreases during the first three weeks and thereafter a slow but steady decline which was apparently continuing at the end of the 84-day mission (fig. 21). The rate of decline was considerably slower than in Skylab 2 and Skylab 3 crewmen, reaching approximately the same level after 84 days that had occurred after 25 to 27 days in crewmen of the first two Skylab flights.

TABLE III

PERCENT DECREASE FROM LAST PREFLIGHT VALUES IN MEAN CALF CIRCUMFERENCES ($\frac{R + L}{2}$) OF THE NINE SKYLAB CREWMEN AT DESIGNATED MISSION DAYS IN-FLIGHT AND AT THE TIME OF THEIR FIRST FIVE POSTFLIGHT EXAMINATIONS.

	Percent Decrease								
	Skylab 2			Skylab 3			Skylab 4		
	Commander	Scientist Pilot	Pilot	Commander	Scientist Pilot	Pilot	Commander	Scientist Pilot	Pilot
IN-FLIGHT									
Mission Day									
2							2.0	-0.8	2.5
4			4.3						
5	3.7	5.0			3.5		2.0		2.5
6				4.5		4.1		0.8	
25-27	6.6	6.8	10.1	6.2	7.6	6.4	2.9	3.1	4.8
57-59				8.4	9.9	8.9	5.8	4.5	6.5
82-83							6.7	5.[illegible]	7.0
POSTFLIGHT									
Recovery									
+0	6.0	6.8	8.3	9.1	10.3	7.3	7.2	5.7	7.7
+1	4.8	5.8	5.6	8.1	8.1	8.6	4.7	4.9	6.1
+2	4.6	5.0	7.5	8.3	8.1	7.5	3.2	3.9	4.9
+4	5.4	4.7	5.6	5.6	7.0	2.7	2.9	1.5	3.5
+5									
+8-11	4.6	2.4	4.5	5.7	3.8	2.7	1.9	0.1	1.0

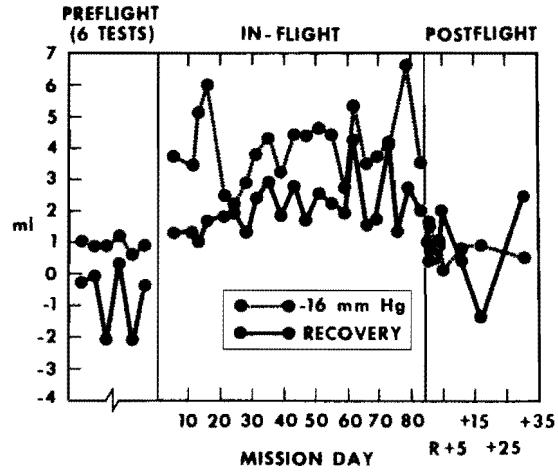


Figure 20. Absolute increases expressed in milliliters, over resting control values of leg volume at the end of the -30 mm Hg and the end of the 5-minute recovery phases of individual tests of lower body negative pressure of the Skylab 4 Commander. The latter measurement, representing residual volume increase, ranged slightly below the volume at -16 mm Hg in in-flight tests but fell below resting volumes preflight.

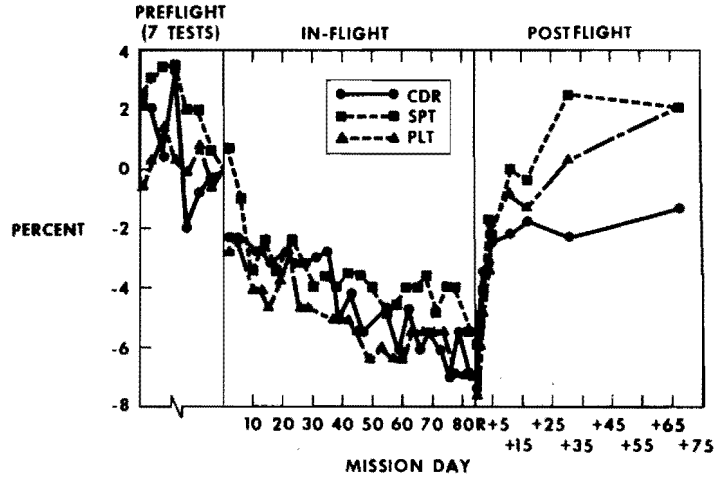


Figure 21. Calf girth of the three Skylab 4 crewmen measured just prior to each lower body negative pressure test. The mean $\frac{R+L}{2}$ of the right and left calf is shown. An eighth measurement, the last of those taken preflight, was made independently 6 days before flight and not in association with a lower body negative pressure test. This last measurement was used as a reference value, 100 percent, from which percentage difference of all other measurements were calculated.

Measurements of lower limbs to estimate volume were also made early, for the first time, in-flight. On mission day 3, estimates of lower limb volume indicated losses of 13.4 and 12.3 percent in the Commander and Scientist Pilot, respectively, compared with the mean of five preflight measurements. The decrease in the Pilot amounted to 9.2 percent on mission day 5. Subsequently, volume of the lower limbs appeared to decrease further as shown in table IV.

TABLE IV

PERCENT DECREASE FROM PREFLIGHT VALUES IN VOLUME OF THE LOWER LIMBS AT THE TIME OF IN-FLIGHT MEASUREMENT, SKYLAB 4

	Volume of Lower Limbs Percent Decrease from Preflight Mean Values		
In-Flight	Commander	Scientist Pilot	Pilot
Mission Day 3	13.4	12.3	
5	12.2*	9.7*	9.2*
8	13.4	13.5	13.1
31	15.8		12.3
37		15.3*	
57-59	17.5	12.4*	13.2
81		12.2*	13.4*

* based on measurement of left lower limb only

Crewmen of the two previous missions had observed that lower body negative pressure in weightlessness forced them further into the Lower Body Negative Pressure Device. To compensate for this and to retain proper positioning of the iliac crests at the level of the iris-like templates, the saddle had usually been adjusted headward one and one-half inches from the position used preflight. This adjustment also became necessary for the Skylab 4 crew. Additionally, like previous crews they experienced abdominal discomfort from contact with the templates and seal that had not occurred on preflight tests. They also reported that the lower body negative pressure test remained subjectively very stressful throughout the flight.

The first test in which it became necessary to terminate the test early because of presyncopal symptoms occurred on mission day 10 during the second in-flight test of the Pilot (fig. 22). After nearly four

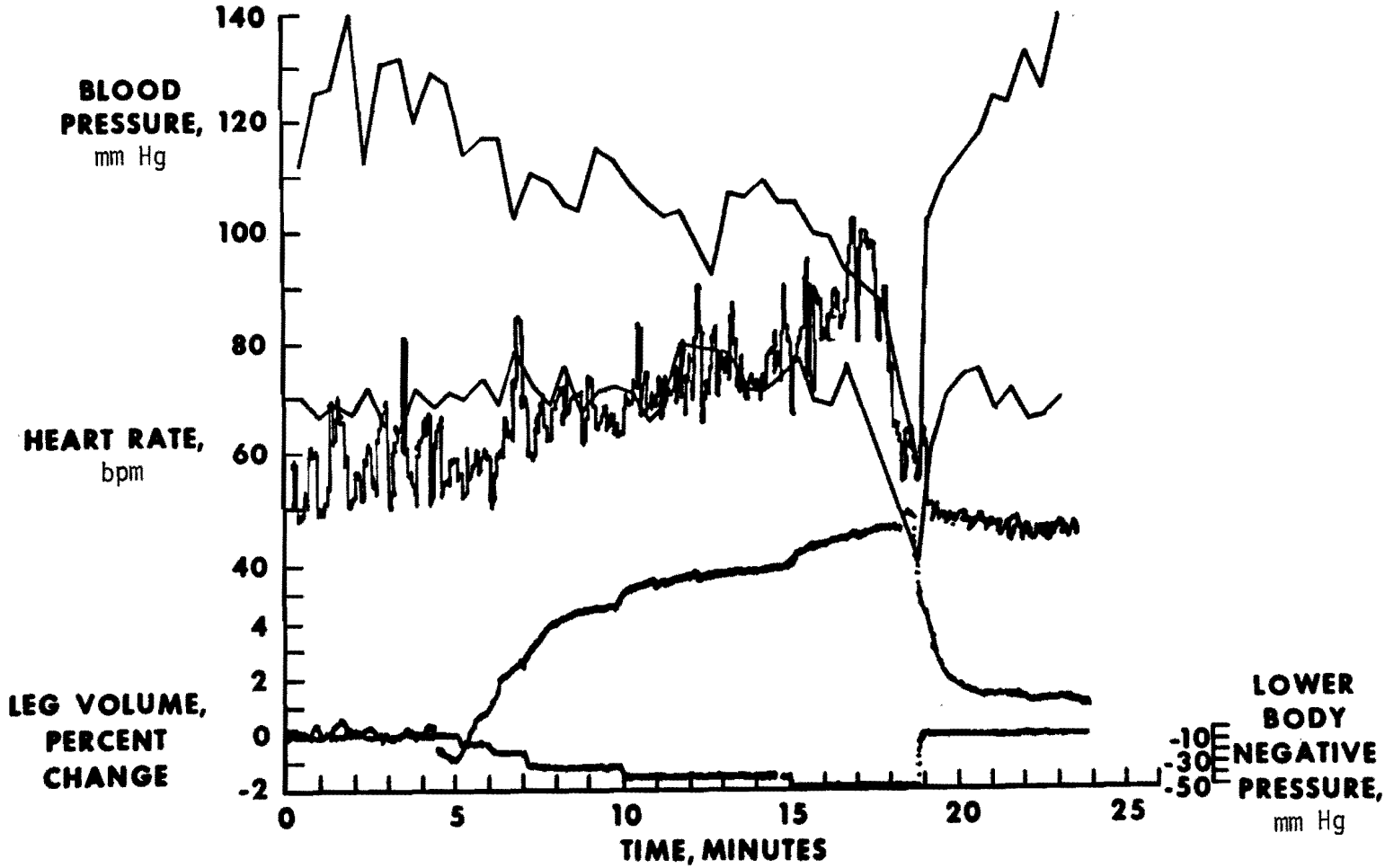


Figure 22. Cardiovascular responses of Skylab 4 Pilot during lower body negative pressure test on mission day 10. Presyncopal symptoms led to termination of the test after nearly four minutes' exposure to the -50 mm Hg phase (Skylab 4).

minutes of exposure to -50 mm Hg pressure he experienced a sensation of dizziness. Associated with this was a further marked fall in systolic and diastolic pressure and narrowing of pulse pressure. Heart rate had reached approximately 100 beats per minute and was falling prior to restoring lower body negative pressure to ambient. In his first in-flight test on mission day 5 (fig. 10), although no presyncopal symptoms had occurred, blood pressure and heart rate were falling just prior to completing the -50 mm Hg phase. In the recovery period following that test, marked sinus arrhythmia, bradycardia and atrioventricular dissociation had occurred suggesting a high rebound vagal tone and that a vasovagal reaction had been imminent. Heart rate had reached about the same level as during the second test although the increase in calf volume had been lower, 6.1 percent, at the end of the -50 mm Hg phase as compared with 9 percent in the test in which symptoms occurred. This test was carried out late in the afternoon following a very busy day in which the Pilot had missed lunch, and a time when he was feeling quite fatigued. Although higher mean heart rates and greater increases in calf volume during lower body negative pressure occurred on many subsequent tests of the Pilot, especially during the first month, symptoms requiring early termination did not recur.

As indicated earlier the blood pressure, heart rate and leg volume of the Scientist Pilot periodically responded quite markedly to lower body negative pressure throughout the mission. On mission day 14 during his third in-flight test, calf volume reached an off-scale condition at slightly over 7 percent increase early in the -30 mm Hg phase. Heart rate climbed rapidly and pulse pressure narrowed gradually during the ensuing minutes (fig. 23). After about two minutes of exposure to -50 mm Hg, systolic pressure fell more rapidly and diastolic pressure also began to fall. Heart rate reached nearly 120 beats per minute and then began to fall. Concurrently, lightheadedness and tingling of the arms occurred and ambient pressure was restored after about 4 minutes of exposure to -50 mm Hg.

Symptoms such as tingling of the arms and shoulders and mild dizziness were commonly experienced by the Scientist Pilot but did not require another early termination of the test until mission day 34. This test terminated about two minutes early when the heart rate was falling from a peak of 140 beats per minute (fig. 24). Presyncopal manifestations including mild faintness and sudden pallor, occurred about 5 seconds before the -50 mm Hg phase was due to end on mission day 61 when ambient temperature in the orbital workshop had climbed from the usual 23.3° C (74° F) to 26.5° C (79.6° F). Again on mission day 71 symptoms led to termination of the test about 30 seconds early. Each of these four episodes were associated with the fatigue of a very busy

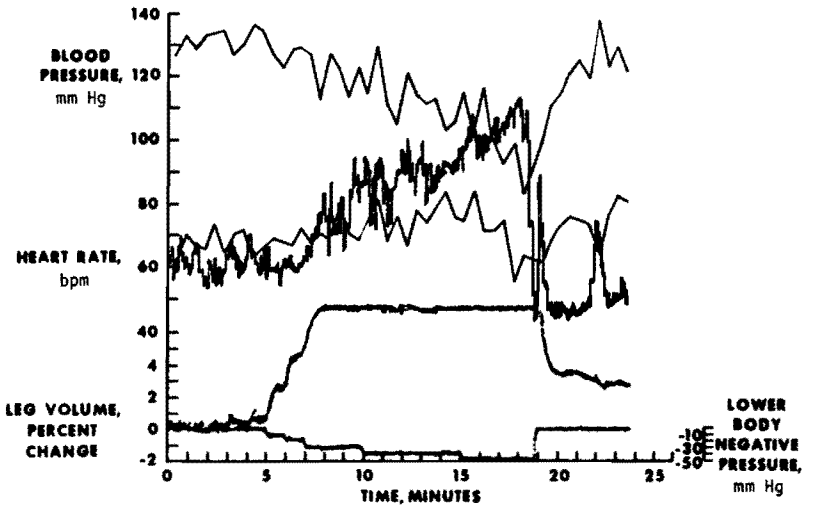


Figure 23. Cardiovascular responses of the Skylab 4 Scientist Pilot during the lower body negative pressure test on mission day 14. Presyncopal symptoms during the -50 mm Hg phase caused the test to be stopped after almost 4 minutes of exposure to this level of negative pressure. The leg volume increase reached the upper limits of transducer output a few seconds after the onset of 30 mm Hg negative pressure.

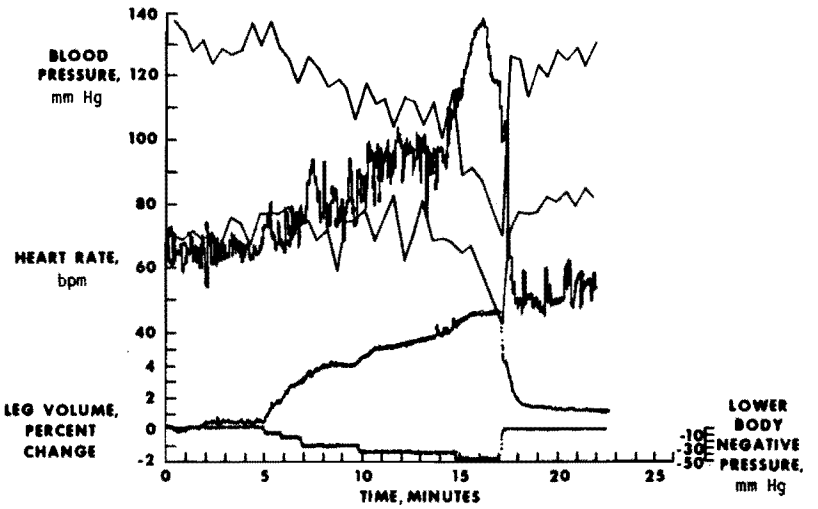


Figure 24. Cardiovascular responses of the Skylab 4 Scientist Pilot during the lower body negative pressure test on mission day 34. Presyncopal symptoms occurred soon after exposure to -50 mm Hg pressure phase which was terminated after approximately 2-1/3 minutes.

day, inadequate sleep during the previous night, and omission of his usual attempts to maintain a high fluid intake.

The only instance in which the Commander experienced presyncopal symptoms was on mission day 16 when mild dizziness and a rapid falling blood pressure after about 2 minutes of the -50 mm Hg phase caused the test to be stopped early (fig. 25). Flight planning difficulties had led to scheduling this test in the afternoon rather than during the usual morning hours. On his next test performed on the morning of mission day 21 he again experienced symptoms including dizziness and the onset of cold sweating of the face but was able to complete the test. This latter test, which was preceded by ingestion of a large amount of water and some toe-rise exercises on the "treadmill", was associated with abdominal and saddle discomfort and also a higher heart rate than in any other of his tests (fig. 26).

Postflight

Heart Rate

Resting and stressed heart rates of the Skylab 4 crewmen followed a somewhat similar pattern of change postflight during their first postflight tests on the day of recovery, all had resting heart rates which were quite slow and within preflight limits. Resting heart rates of the Commander and Scientist Pilot were elevated about 15 and 20 percent, respectively, on the following day over those on recovery. On the second day after splashdown, the Commander's resting heart rate had declined to near recovery day value whereas the Scientist Pilot's rate reached its highest postflight value, 39 percent above the recovery day value. Resting heart rate of the Pilot continued to be low in all postflight tests (fig. 27, 28, 29).

Mean heart rates of the Skylab 4 crew during -50 mm Hg lower body negative pressure at their recovery day examinations were fairly close to their respective values during their last in-flight tests (table V). Stressed heart rates of the Commander followed the same pattern as his resting heart rates with the greatest increase occurring during the day after the recovery day test. Heart rate responses to lower body negative pressure during subsequent tests returned to and remained within preflight limits.

The Scientist Pilot exhibited his highest heart rate response to lower body negative pressure during the recovery day test conducted

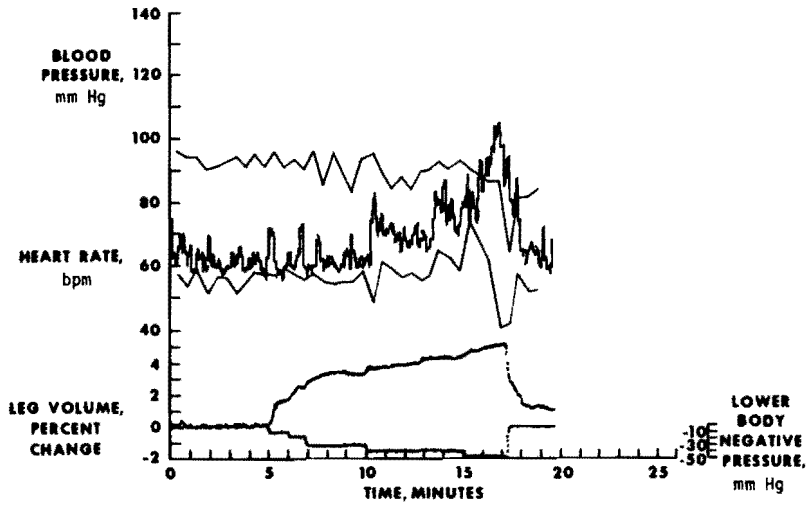


Figure 25. Cardiovascular responses of the Skylab 4 Commander during the lower body negative pressure test on mission day 16. Presyncopal symptoms developed soon after onset of the -50 mm Hg phase and negative pressure was discontinued after a little over 2 minutes at this level.

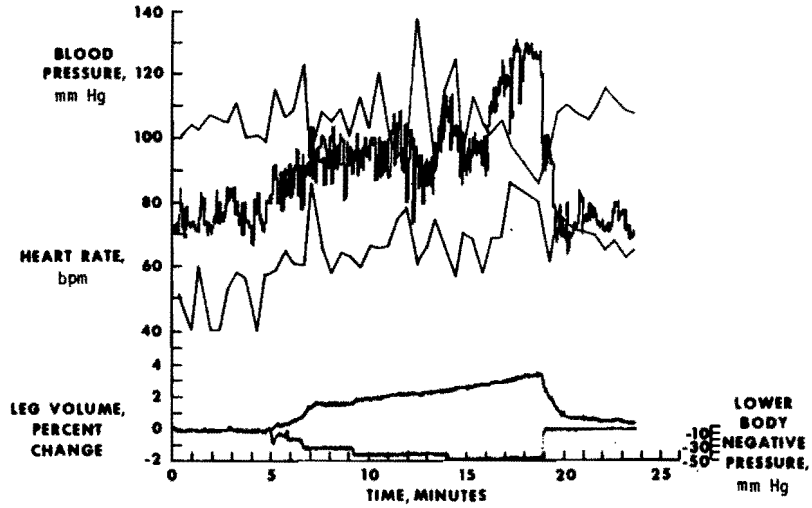


Figure 26. Cardiovascular responses of the Skylab 4 Commander during the lower body negative pressure test on mission day 21. During this test he exhibited a higher heart rate than in any other test. Symptoms did not require the test to be terminated early. The -50 mm Hg phase was continued for a full 5 minutes but the -8, -16, and -30 mm Hg pressure phases were inadvertently shortened.

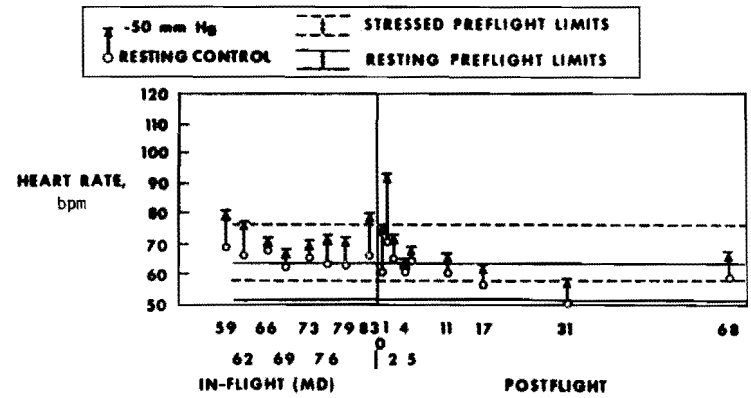


Figure 27. Mean heart rates of the Skylab 4 Commander during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure tests in the last part of the mission and in the postflight period.

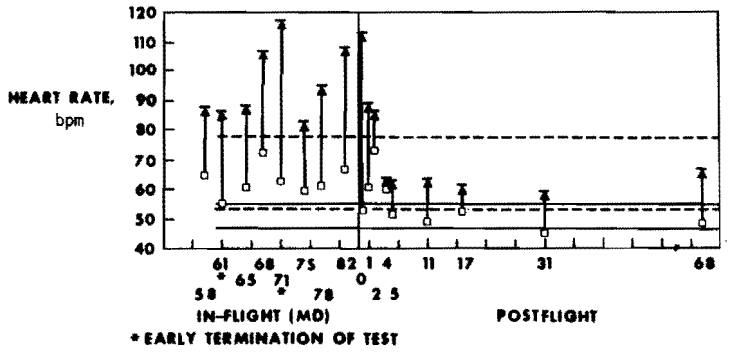


Figure 28. Mean heart rates of the Skylab 4 Scientist Pilot during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure tests in the last part of the mission and in the postflight period.

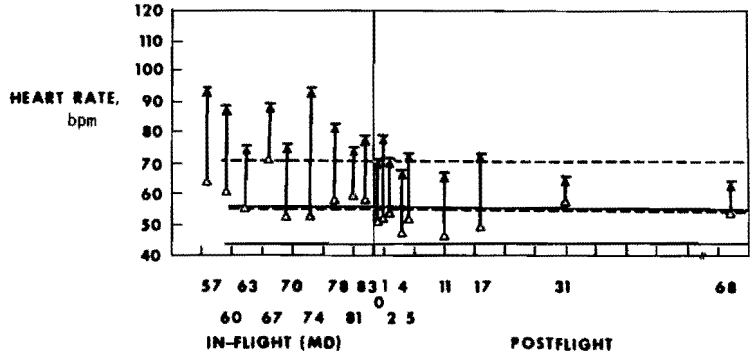


Figure 29. Mean heart rates of the Skylab 4 Pilot during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure tests in the last part of the mission and in the postflight period.

six hours after splashdown. Heart rate during tests on the following day and the second day were elevated over preflight limits by a smaller magnitude, and on subsequent tests returned to and remained within these limits.

Stressed heart rate of the Pilot was slightly elevated above preflight limits on recovery day, climbed to a slightly higher level on the day after recovery, dropped to the recovery day value on the second day after recovery and were within preflight limits on the fourth day post-mission, the heart rate response was again elevated slightly but was within preflight limits on subsequent tests.

TABLE V

MEAN HEART RATES OF THE SKYLAB 4 CREWMEN AT REST AND DURING THE -50 mm Hg PHASE OF LOWER BODY NEGATIVE PRESSURE RESULTS DURING PREFLIGHT AND IN-FLIGHT TESTS, DURING THE LAST IN-FLIGHT TEST, AND DURING EACH OF THE FIRST SIX POSTFLIGHT TESTS.

	Mean Heart Rate (bpm) Resting and Stressed (-50 mm Hg)					
	Commander		Scientist Pilot		Pilot	
	Resting	Stressed	Resting	Stressed	Resting	Stressed
Preflight Mean	58.9	66.3	51.1	64.9	48.0	61.1
In-flight Mean	66.7	78.5	64.4	101.6	59.9	87.8
Last In-flight	66.3	80.2	67.2	108.3	57.4	79.2
Postflight (Days)						
Recovery +0	60.6	68.1	53.0	113.0	51.6	71.2
+1	70.6	82.7	60.9	88.8	51.9	78.7
+2	64.8	68.5	73.8	86.3	53.5	71.6
+4	60.9	62.9	60.4	63.7	46.5	67.8
+5	64.5	65.8	52.0	63.0	51.2	73.4
+11	60.7	61.3	49.7	63.5	46.2	69.1

Blood Pressure

During the first few postflight days, the three Skylab 4 astronauts exhibited marked blood pressure changes both at rest and during lower body negative pressure stress. Although the time course of the postflight pattern differed among the three crewmen, all exhibited pronounced elevation of diastolic and mean arterial pressures both at rest and during lower body negative pressure stress on one or more of the first three post flight tests. Systolic and pulse pressure during rest were also elevated at some time during this period.

On the Commander's first postflight test, begun four hours after splashdown, resting systolic, diastolic and mean arterial pressure were markedly elevated over preflight limits during both resting control and -50 mm Hg pressure phases. Mean arterial pressure both at rest and during -50 mm Hg pressure remained above preflight limits during each test through the fifth post recovery day (fig. 30). Pulse pressure during stress also slightly exceeded preflight limits. Resting and stressed systolic blood pressure and pulse pressure climbed to higher values on the first day after recovery. Thereafter all values declined on successive tests and were within preflight limits by either the fifth or eleventh day postflight.

The Scientist Pilot, during his recovery day test 6 hours after splashdown exhibited resting systolic, diastolic, pulse and mean arterial pressures that fell within preflight limits and quite close to those seen on the last test in-flight. During lower body negative pressure, however, diastolic pressure rose quite markedly above these values and pulse pressure narrowed proportionately (fig. 31). Systolic pressure both at rest and during lower body negative pressure reached its highest post flight value on the second day post flight while diastolic pressure showed little change at rest but during the -50 mm Hg pressure fell from its initially high level on recovery day to progressively lower levels during each of the four following tests.

Resting systolic blood pressure and pulse pressure of the Pilot followed patterns similar to those of the Scientist Pilot in climbing to their highest value on the second day after recovery. Diastolic pressure at rest resembled that of the Commander in exhibiting its highest value during the first test eight hours after splashdown. Mean arterial pressure at rest remained elevated during the first four tests but during lower body negative pressure stress fell markedly during the recovery day test and reached successively higher levels during the following two tests. Stressed systolic, diastolic and pulse pressures showed the same pattern, reaching maximal levels on the second day after recovery (fig. 32).

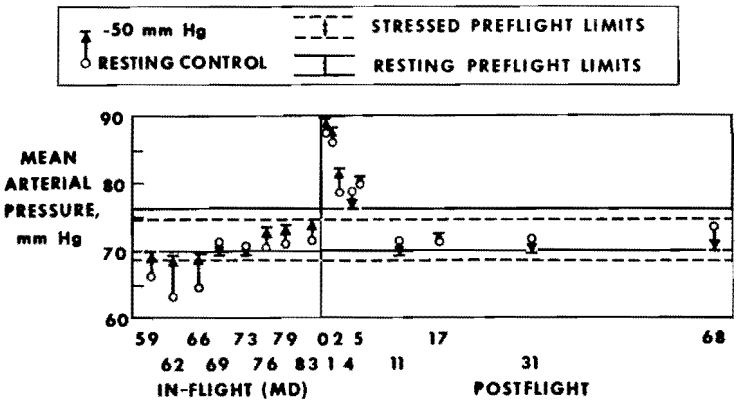


Figure 30.
Mean arterial pressure of the Skylab 4 Commander during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure tests in the last part of the mission and in the postflight period.

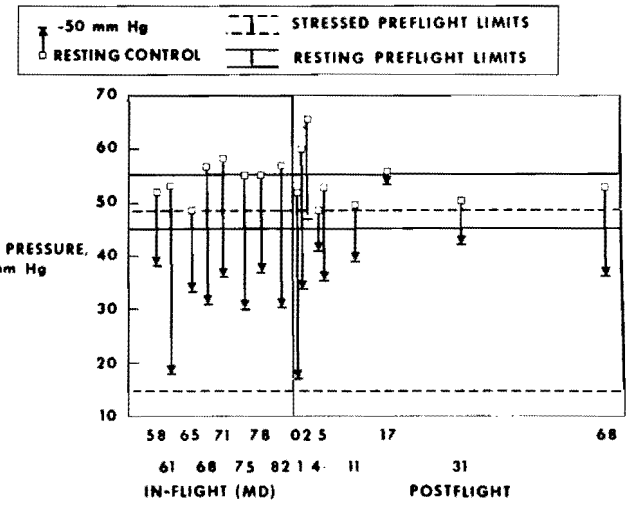


Figure 31.
Mean pulse pressure of the Skylab 4 Scientist Pilot during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure tests in the last part of the mission and in the postflight period.

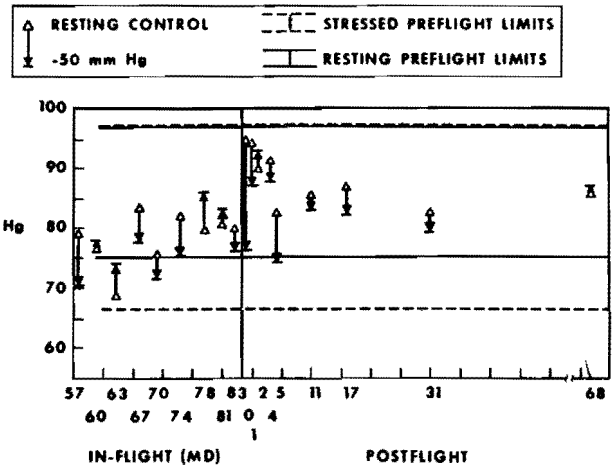


Figure 32.
Mean arterial pressure of the Skylab 4 Pilot during the resting control and the -50 mm Hg pressure phases of individual lower body negative pressure test in the last part of the mission and in the postflight period.

Calf Volume Increase Induced by Lower Body Negative Pressure

Calf volume increases at all levels of lower body negative pressure on recovery day dropped abruptly from the high values that occurred in-flight to approximately preflight values. During the next test on the day after recovery, calf volume increase climbed higher than the recovery day values. While calf volume increase reached their highest postflight value on the day after recovery in the cases of the Commander and Pilot, it climbed slightly higher on the second postmission day in the Scientist Pilot. Thereafter, increase in calf volume induced by lower body negative pressure subsided but remained slightly elevated above preflight mean values.

In contrast to in-flight patterns of increase in calf volume in which over one-half of the total increase had already occurred at the end of the -30 mm Hg phase, the greatest part of the postflight total increase took place usually during the -40 and -50 mm Hg phases. Evidence interpreted as venous drainage during the resting control phase did not appear until tests made several days after splashdown except in the Commander, where calf volume pattern indicated venous drainage in the recovery day test. Volume declines during the lower levels of lower body negative pressure thought to represent active venous contraction was similarly slow to appear. The preflight pattern of nearly complete return of calf volume to resting control values during the five minute recovery period after cessation of negative pressure was first apparent in the Commander. Calf volume during recovery returned nearly to resting levels during the recovery period of the first and most subsequent postflight tests. Similar patterns in the Scientist Pilot and Pilot were considerably delayed.

Other Measurements and Observations

Measured calf circumference after recovery, performed four, six, and eight hours after splashdown in the Commander, Scientist, and Pilot, respectively, was from 0.15 to 0.25 centimeters smaller than when determined during the last in-flight measurements on mission days 82 and 83 (fig. 21). All showed successively larger calf circumferences through the 11 days after recovery with the exception of the Scientist Pilot who showed a slight decrease on the fifth day compared to the fourth day postflight measurment. The Commander and Pilot showed their greatest increment of increase between recovery day and the day after while the increase in the Scientist Pilot was more gradual during the first 48 hours and greatest between the second and fourth day post recovery measurement. All had regained calf girth from six or more percent to approximately two percent below preflight values by the fifth day or in the case of the Scientist Pilot by the fourth day after recovery.

Volume of the lower limbs, calculated as percent change from preflight means, was moderately increased at the time of the first postflight measurement over the last volume measured in-flight a little over 48 hours earlier in the Scientist Pilot and Pilot and 28 days earlier in the Commander (fig. 33). All three postflight volume decreases on recovery day measured approximately the same as that of the Commander of Skylab 2 and slightly less than that of the Scientist Pilot of Skylab 3 at their first postflight measurment three and four hours, respectively, after splashdown.

The postflight pattern of return of lower limb volumes toward preflight values followed a somewhat different pattern than the gain in calf girth. Postflight lower limb volume increased progressively until the second day, leveled off or decreased on the third day and thereafter increased at a generally slower rate. By the second day, or a little over 48 hours after splashdown, a large part of the loss of limb volume had been regained.

During the first postflight test, the Commander exhibited higher systolic and diastolic pressures, narrower pulse pressure and slightly lower heart rates throughout the test than during his last in-flight test on mission day 83 (figs. 34, 35). The recovery day test of the Scientist Pilot produced heart rates quite similar to his last in-flight test on mission day 82 but a higher diastolic pressure and narrower pulse pressure (figs. 36, 37). In the first postflight test of the Pilot, systolic and diastolic pressures remained higher than in his last in-flight test on mission day 83 until the -40 mm Hg phase was reached. At that time, systolic pressure began to fall and pulse pressure to narrow (figs. 38, 39). After the onset of -50 mm Hg, lower body negative pressure systolic and diastolic pressure fell and shortly afterwards mild presyncopal symptoms appeared. The test was terminated after approximately one minute of exposure to the -50 mm Hg level. Of possible significance to the outcome of this test is the fact that the Pilot, because of scheduling difficulties, had performed low levels of supine and upright bicycle ergometry approximately two hours earlier.

The tests after recovery day were all completed without difficulty. Judging by heart rate responses only, preflight limits were attained by the fourth or fifth day after recovery. Blood pressure responses attained these limits by fifth or eleventh day postflight. The striking elevation of systolic pressure and widening of pulse pressure, characteristically greatest on the first day after recovery following Apollo flights and on the first and second day after recovery following Skylab flights, are illustrated in figure 40.

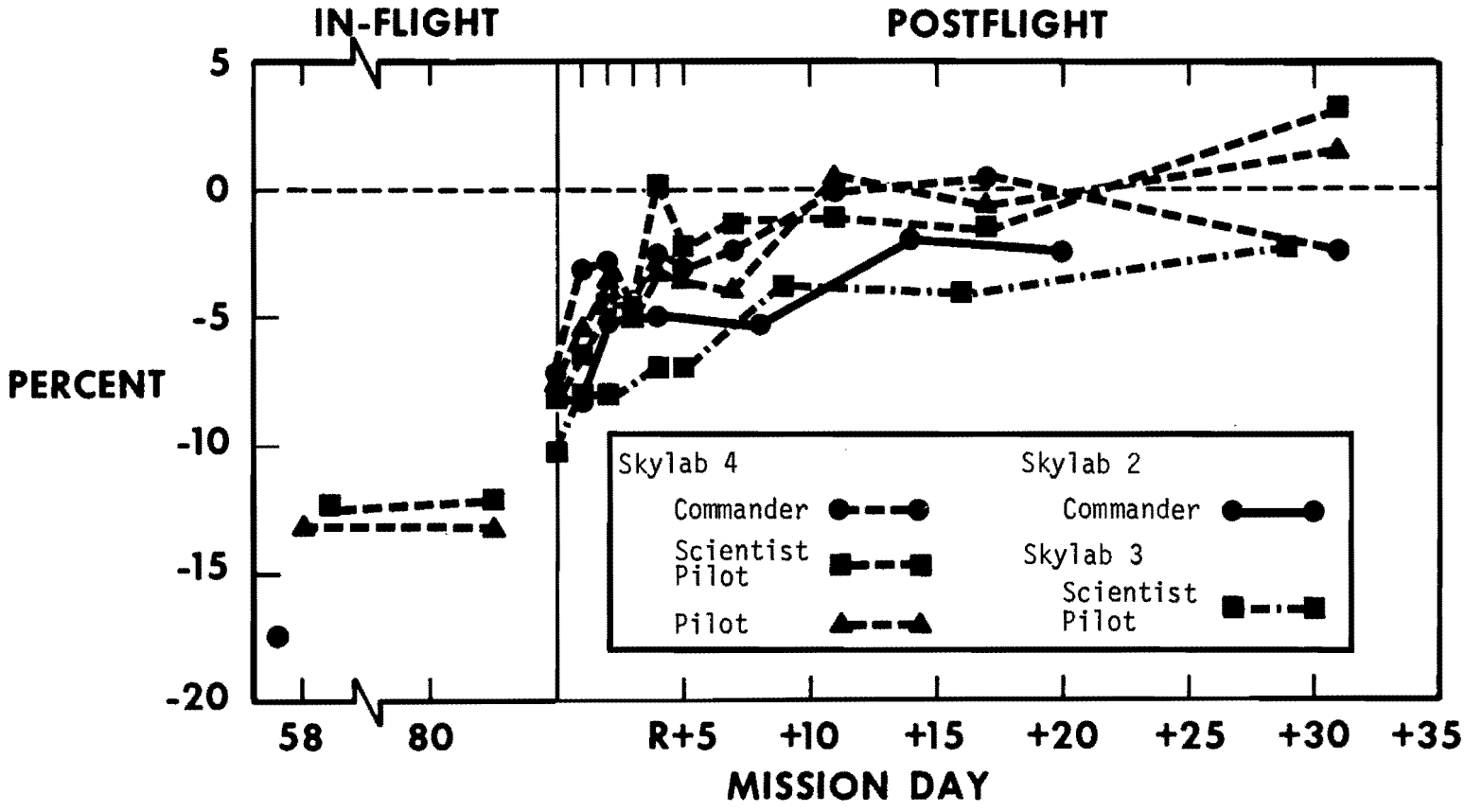


Figure 33. Percentage change in volume of the lower limbs showing volumes measured in the last third of the flight and the postflight return of volume toward preflight values (Skylab 4). Volumes of lower limbs of the Commander of Skylab 2 and the Scientist Pilot of Skylab 3, are shown for comparison.

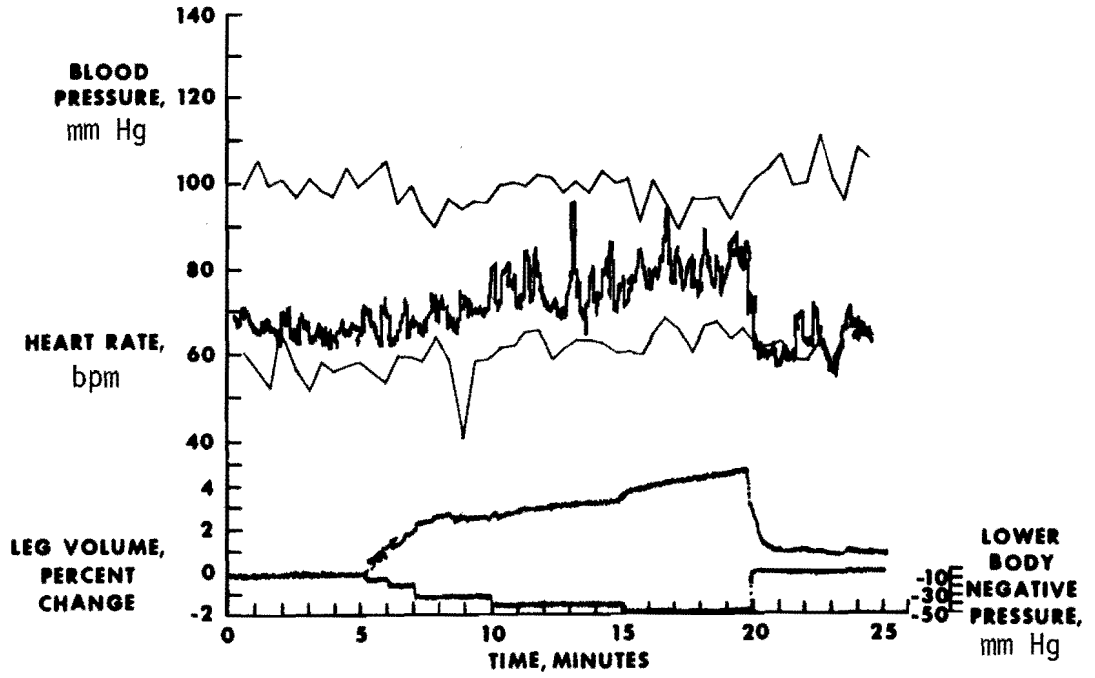


Figure 34. Cardiovascular responses of the Skylab 4 Commander during his last in-flight test on mission day 83.

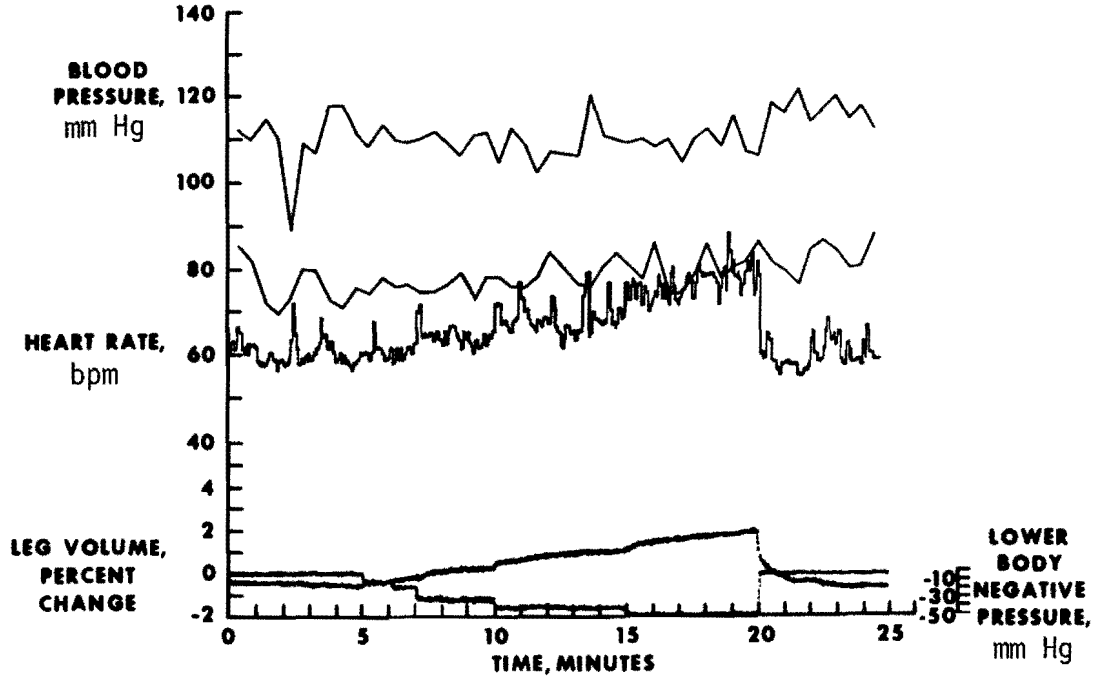


Figure 35. Cardiovascular responses of the Skylab 4 Commander during his first postflight test four hours after recovery.

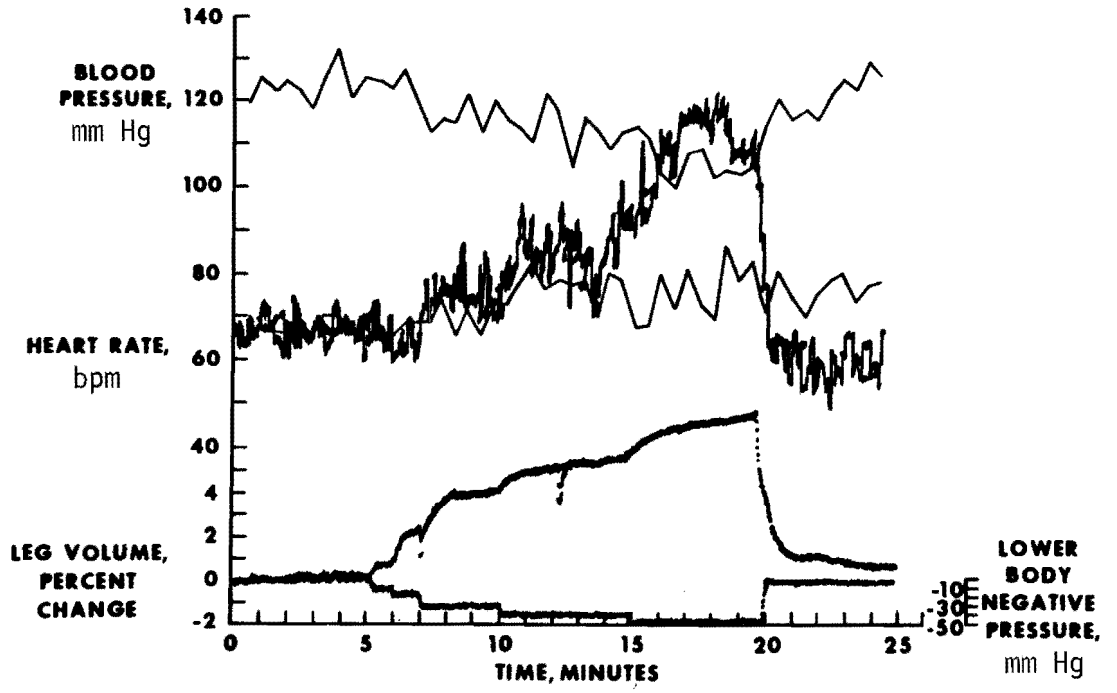


Figure 36. Cardiovascular responses of the Skylab 4 Scientist Pilot during his last in-flight test on mission day 82.

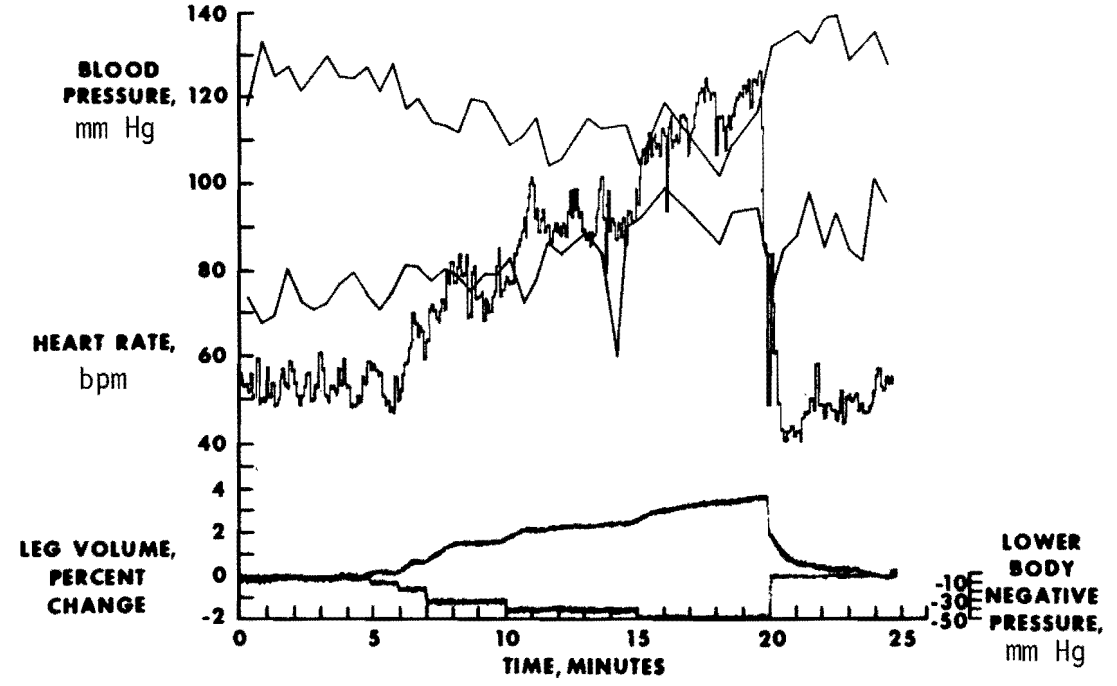


Figure 37. Cardiovascular responses of the Skylab 4 Scientist Pilot during his first postflight test six hours after recovery.

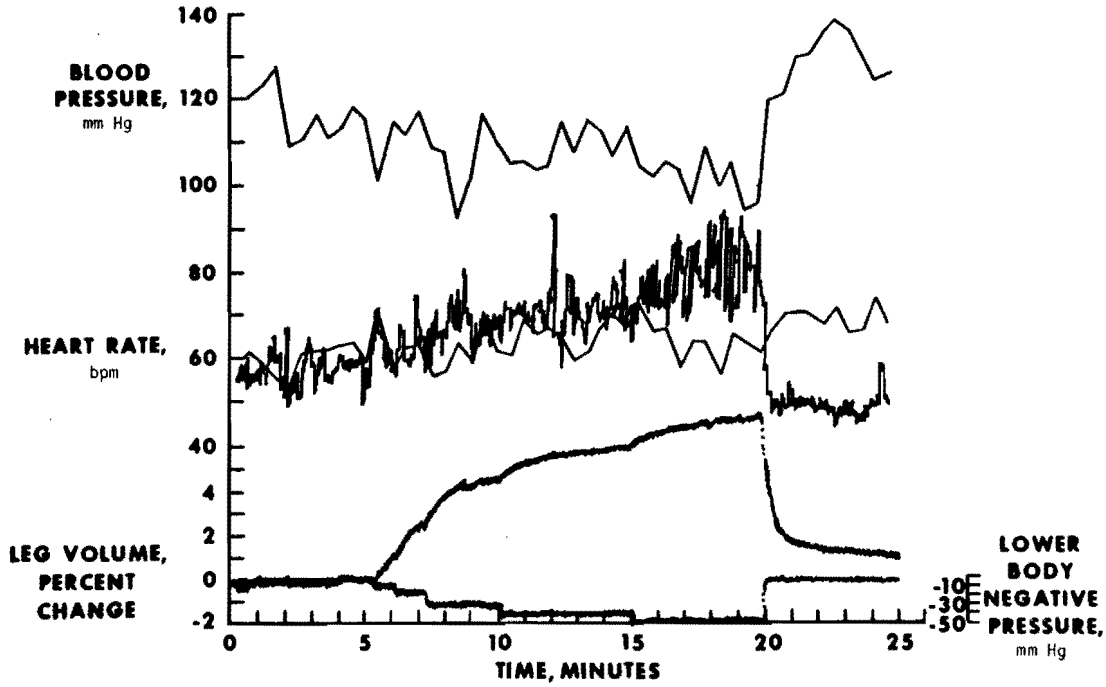


Figure 38. Cardiovascular responses of the Skylab 4 Pilot during his last in-flight test on mission day 83.

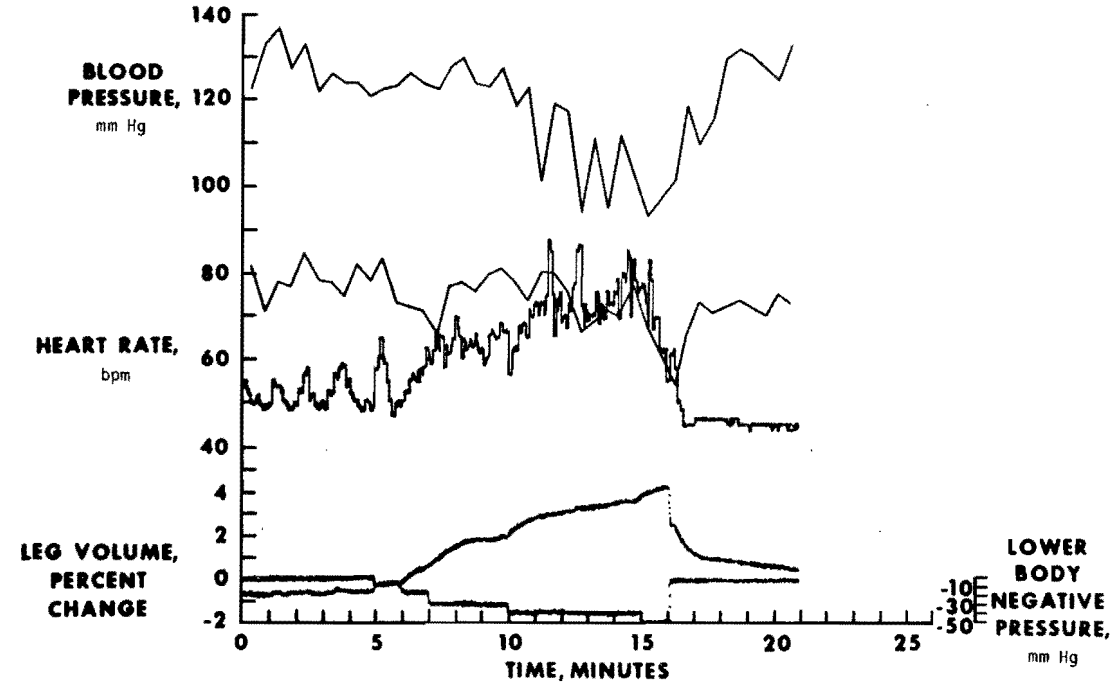


Figure 39. Cardiovascular responses of the Skylab 4 Pilot during his first postflight test eight hours after recovery.

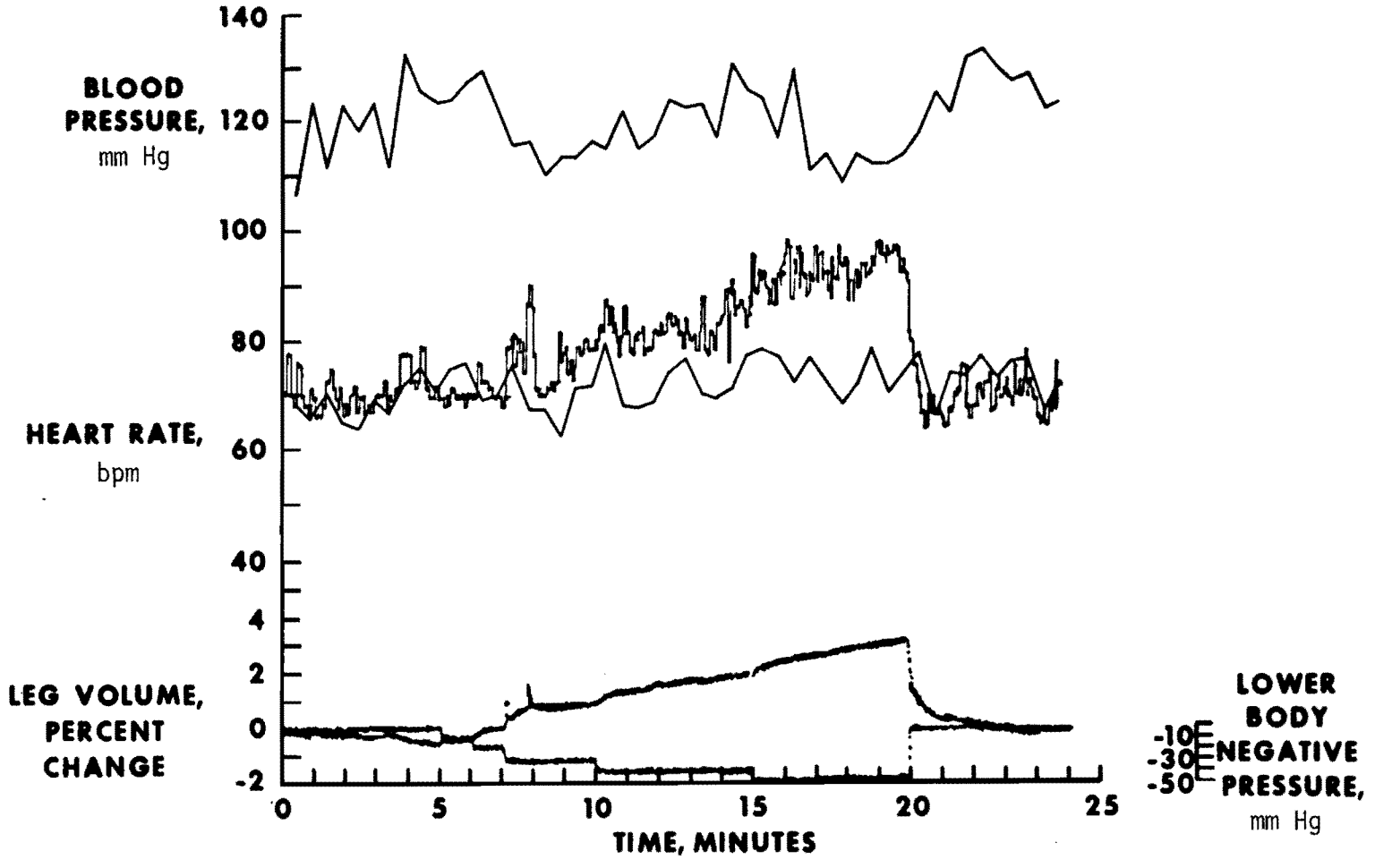


Figure 40. Cardiovascular responses of the Skylab 4 Commander during his second postflight test.

DISCUSSION

An explanation of the changes in cardiovascular responses to lower body negative pressure in a weightless environment requires understanding of the manner in which the systems of the body and their functions adjust to the weightlessness of space flight. A more comprehensive understanding of these adjustments will, in turn, require the correlation of massive volumes of data from all of the Skylab experiments, a task of monumental proportions which has barely been started.

Measurements of calf circumference of Skylab crewmen on the fourth to sixth day of flight revealed decreases of such magnitude that they could only result from loss of fluid. These rapid reductions of calf girth amounted to a mean of 1.1 centimeters or 3.0 percent below preflight values. If volume losses from the measured portion of the lower limbs had declined in proportion to decrease in calf volume a mean estimated loss of more than one liter would have occurred. Volumes of the lower limbs as actually measured in-flight by the Skylab 4 crewmen indicated somewhat greater losses, ranging between 1400 and 2000 milliliters within the first few days of flight. Both types of measurement support a very early loss from the lower limbs of a relatively large volume of fluid. In-flight observations of a full feeling of the head, nasal and ocular congestion, and distention of head and neck veins suggest that this process of headward fluid migration out of the lower extremities must begin simultaneously with achievement of weightlessness.

Increased outflow from veins of the legs tends to reduce local venous pressure and in turn pressure on the venous side of the local capillary bed, a condition which promotes the transfer of interstitial fluid into the capillaries. Capillary exchange of fluids is a highly dynamic process capable of moving large volumes of fluid very rapidly in either direction between capillaries and surrounding tissue. Such transfer of fluid would continue to replenish venous channels as their contents shifted upward until local tissue pressure declined to the level of venous pressure. The flow of lymph toward the central circulation would also be expected to increase. Thus, interstitial fluid, lymph and blood can participate in the rapid outflow of fluid and consequent reduction of lower limb volume.

Veins in regions above the heart are not normally subjected to venous pressure increases of more than small magnitudes and, except during recumbency, are not filled. Photographs and descriptions by the astronauts indicate, however, that cervical and cranial veins became distended early in flight and remained distended throughout flight. These superficial veins and presumably others in the upper part of the body appear then to accommodate a significant portion of the fluids

shifted upward from the lower body. Edema of the eylids and periorbital tissues, also apparent from in-flight photographs, indicate that venous and intracapillary pressure in these regions are at least transiently increased and that interstitial spaces in the upper body also participate in storing fluid displaced to that region.

Whether and to what extent the pulmonary vessels also accommodate blood beyond their normal storage capacity of 700 to 800 milliliters of blood are unanswered and important questions. Modest reductions in vital capacity during flight (11) suggest that they do. In the acute expansion of blood volume by infusion, the lungs appear to be spared and the expanded blood volume is accommodated largely by systemic veins while in chronic circulatory congestion with normal hearts, the lungs seem to share in accommodating the expanded blood volume (12). Whatever the total blood volume in weightlessness, the pulmonary circulation must, at some time during adaptation to weightlessness, react as if total blood volume was increased.

At some time early in the process of these regional shifts of fluid volume, atrial return and cardiac output must transiently increase. Whether atrial distention initiated neurohormonal stimulation of diuresis seems uncertain from available Skylab data at this time. Hemoglobin increases in blood samples taken in-flight suggest that hemoconcentration occurred relatively early in flight (13). Whether plasma volume is reduced chiefly by diuresis or through other mechanisms, is not clear. The low humidity of the Skylab atmosphere and, in the Skylab 2 flight, high environmental temperature, would be expected to lead to large fluid decreases through insensible losses and sweating.

High pressure baroceptors, especially those of the carotid arteries, should initially sense the absence of hydrostatic forces as an elevated arterial pressure and initiate reflexes to reduce pressure and heart rate. Such an event was not observed in Skylab cardiovascular examinations but it would probably have occurred too early and transiently for detection.

Much of the more dynamic changes of the type discussed must have already taken place before the earliest lower body negative pressure tests could be performed. The results of these tests suggest, however, that profound changes in circulatory dynamics continued to occur throughout much of the flight. Vigorous daily activities must also have impacted temporarily any equilibrium that had been reached.

One can postulate with reasonable certainty, however, that by the time of the first in-flight lower body negative pressure tests, total circulating blood volume had been reduced, some hemoconcentration had occurred, and at least a significant fraction of fluids previously

located in the legs was now accommodated by veins and interstitial tissues of the upper part of the body. Whether these fluids were available to supplement circulating blood volume during lower body negative pressure is an unanswered question of great importance to understanding the lower body negative pressure results.

Lower body negative pressure stresses the cardiovascular system by reducing effective circulating blood volume as blood is segregated in the veins of the lower half of the body. Reduced return of blood to the right heart results in reduced cardiac output comparable to that which occurs during orthostasis in a gravity field (13). The volume of blood thus diverted must be a determining factor in the degree of stress produced.

The measurement of calf volume increases during lower body negative pressure should furnish an index to at least estimate the magnitude of this pooled volume. Calf volume increased by considerably greater percentages during in-flight lower body negative pressure than in preflight tests. This change was apparent during the earliest in-flight tests, persisted throughout flight, and diminished again in postflight tests. Moreover, a large fraction of the total volume change in-flight occurred during the first two minutes of lower body negative pressure when negative pressures were least. The most plausible explanation for the latter changes seems to lie in a relatively empty venous system in the legs at the beginning of the tests.

Veins require only low transmural pressures to retain their circular configuration. If lower pressures prevail, they tend to become elliptical or flat (15). In this state, relatively large volumes of blood could be accommodated before any change in venous pressure occurred. This so-called zone of free distensibility, which does not involve stretching of venous wall muscle, probably accounts for the large volume increases in the calf at the slight negative pressure levels as discussed above. The volume of this zone of free distensibility, even during the alterations taking place due to weightlessness, may be expected to vary from time to time under the influence of daily activities. Physical activity in weightlessness requires minimal participation of lower extremity muscles. Such activity might be expected to result in a net loss of venous volume in the lower extremities with venous outflow exceeding arterial inflow. Conversely, due to higher resting venous pressures in the upper body, periods of inactivity such as sleep may allow some filling of leg veins, thus reducing the zone of free distensibility. After periods of inactivity such as sleep, a smaller volume of blood would then be initially displaced by lower body negative pressure than in the former situation.

Pertinent to these considerations is the observation that none of the 13 instances of early termination of tests due to presyncopal symptoms occurred during tests conducted in the morning hours or within seven

hours of arising from sleep, although approximately one-third of all in-flight tests were conducted within that period. These 13 tests were associated with larger than usual calf volume increases during the lowest negative pressure phases of the tests. This suggests that the pooling of large volumes of blood during the first few minutes of the test may so alter the effectiveness of compensatory cardiovascular mechanisms as to render them incapable of adequate responsiveness to the greater stress later in the test.

The higher incidence of presyncopal symptoms in test conducted seven or more hours after arising may be related to the hypothesis mentioned earlier, namely that fluids tend to migrate back to the lower extremities during the inactivity of sleep and that mild activity after sleep tends to empty them again. That this may occur is suggested by the observation of the astronauts that the symptoms of fullness of the head were usually absent on awakening but returned after arising. Similarly, vigorous prolonged exercise on the bicycle ergometer, which should divert a much larger fraction of cardiac output to the muscles of the lower extremities, temporarily relieved these symptoms. If this reasoning is correct, in addition to long-term alterations in fluid volume distributions, fluid volumes in the capacitance vessels and tissues of the lower limbs may be greater in the early hours after arising than later in the day after activity has tended to displace these fluid volumes headward.

Relatively larger proportions of fluid in the lower body early in the day would tend to limit the volume of fluid drawn into the legs and out of the effective circulating blood volume by lower body negative pressure. Other factors being equal, tolerance to lower body negative pressure would then be greater in tests done early than in those conducted late in the day. Among the three astronauts, the Commander of Skylab 2, the Pilot of Skylab 3, and the Commander of Skylab 4, whose in-flight tests were nominally performed in the morning, only one presyncopal episode occurred and this was in the Commander during a test performed in the afternoon over nine hours after arising. In addition, in these three astronauts the heart rate increases induced by -50 mm Hg negative pressure during their 45 in-flight tests, averaged 10.7 beats per minute higher than during preflight tests. The other six astronauts whose tests were nominally scheduled in the afternoons exhibited mean increases of 16.5 beats per minute over preflight stressed values during their 93 in-flight tests. The former difference does not reach statistical significance while the difference between in-flight and preflight stressed heart rates of the six latter astronauts was highly significant ($P<0.001$). While cardiovascular characteristics of individual astronauts may account for these differences they, along with the presyncopal episodes, may also support the hypothesis that headward shifts of fluids occur during the course of daytime

activities, leading to decreasing orthostatic tolerance during the day, and that fluids tend to reaccumulate in the lower body during the inactivity of sleep in a weightless environment.

Although the greatly expanded calf volume changes during the brief -8 and -16 mm Hg phases of in-flight tests were most striking, larger volume changes during the -30, -40, and -50 mm Hg phases also occurred during in-flight tests. At these levels, transmural pressures across venous walls must result in stretching of venous musculature. Increased capacitance of the veins, reduced tone of supporting muscle in proximity to the veins, and diminished tissue pressure must participate to varying degrees in the greater calf volume changes in weightlessness. The relative change in any one of these factors could not be determined, but our current understanding of the effects of weightlessness suggests that all three should be affected. The larger residual volume at the end of the recovery period that occurred in-flight may reflect a greater outflow during lower body negative pressure of fluid from capillaries into tissues. It may also simply indicate that further venous contraction cannot occur, because the zone of free distensibility has been reached. While variations in calf volume increases and residual volume varied from test to test, a definite trend of change during the flight was not seen in the Skylab 4 crew. In this crew the leg volume increase during lower body negative pressure reached higher levels, particularly in the Scientist Pilot and Pilot, than observed in crewmen of the first two flights. Whether the increased exercise, the slower decreases in calf circumference, and the smaller weight losses in the Skylab 4 crewmen were in some way related is not known.

The volume of blood pooled in the lower extremities during in-flight tests did not seem to correlate from test to test with the magnitude of heart rate or blood pressure change during lower body negative pressure. In general, however, those of the nine Skylab astronauts with the greatest increases in calf volume during the in-flight tests also showed the greatest increases in heart rate and changes in blood pressure. In addition, although correlation of heart rate increases with leg volume increases was not evident in preflight tests, the crewmen whose calf volume increases were greatest in preflight tests usually also showed the largest increases during the in-flight tests.

In-flight resting heart rates of the three Skylab 4 crewmen, like those of Skylab 3, were elevated significantly over preflight resting rates. Elevation of resting systolic blood pressure and pulse pressure along with decreases in diastolic pressure and mean arterial pressure, changes seen in the majority of the Skylab 2 and Skylab 3 crewmen, occurred in all three Skylab 4 crewmen, though not always to a statistically significant degree. Such changes are compatible with increased

stroke volume and lowered peripheral resistance due to increased cross section of the resistance vessels (16). If stroke volume was increased, a significant increase in cardiac output was present at rest. There would appear to be no need for increased cardiac output in terms of higher oxygen requirements under these conditions. A plausible and entirely hypothetical explanation of this apparent paradox postulates an alteration in the distribution of cardiac output secondary to weightlessness and the changed distribution of blood volume. If blood flow to the upper body is increased beyond the requirement for oxygen or thermal regulation, opening up and dilatation of normally closed arteriovenous channels in the upper body would lead to a blood pressure pattern of the type observed in the arms and conceivably shunt blood to venous channels in quantities sufficient to elevate cardiac output. Such a condition would be most apt to obtain during rest.

The in-flight mean increase in heart rate during -50 mm Hg lower body negative pressure over resting rates for all nine Skylab crewmen averaged 20.4 beats per minute, a highly significant difference. The increase in heart rate during orthostatic stress has generally proven to be the best single index in the assessment of orthostatic tolerance. According to reports of the Skylab 4 crewmen, -30 mm Hg lower body negative pressure in-flight produced a stress subjectively similar to the -50 mm Hg level preflight. Comparison of mean heart rates for the three crewmen revealed that in-flight heart rates at -30 mm Hg slightly exceeded those in preflight tests at -50 mm Hg, although the difference from resting values in-flight was slightly less than the difference preflight at these negative pressure levels. Greater reductions of mean in-flight stressed systolic pressure and pulse pressure also indicated that -50 mm Hg negative pressure in-flight represented a considerably greater stress than the same level of lower body negative pressure preflight.

The periodic major fluctuations of resting and stressed heart rates and blood pressures observed in previous flights occurred in the Skylab 4 crewmen also. The pattern of these fluctuations varied for each crewman, but their magnitude and frequency were greater during the first part of the mission than later. Their nature and significance is unknown, but, in the case of the Skylab 4 crewmen, their prominence and duration appeared to decrease as cardiovascular responses to in-flight lower body negative pressure stabilized. Adaptation of physiological systems to repetitive acute stress characteristically involves a series of physiological oscillations between overcompensation and undercompensation which gradually declines in magnitude until an optimal accommodation is reached. Oscillating patterns of less pronounced degree were also seen in the three astronauts receiving lower body negative pressure at 3-day intervals in the 56-day Skylab Medical Experiments Altitude Test (SMEAT) (17).

In tests in which presyncopal symptoms required that the test be discontinued, recovery was prompt and complete. In each instance, the subject pushed the emergency relief valve although by then warning declines in heart rate and systolic pressure were usually apparent to the observer. Early forebodings concerning possible harm to the astronaut had assured provision for adequate monitoring displays and hardware safety features.

Postflight findings for Skylab 4 crewmen were remarkable for the relatively small loss of orthostatic tolerance and the rapid return of related cardiovascular parameters to preflight limits. Loss of calf girth was no greater than had been observed in the 59-day Skylab mission. Losses in volume of the lower limb as measured on Recovery day were slightly smaller than in crewmen of the 59-day Skylab 3 mission.

Blood pressure responses were similar to those seen postflight in previous missions with marked elevations of resting systolic and diastolic pressures and, during negative pressure stress, additional large increases in diastolic pressure. Calf volume increases during lower body negative pressure were small during the recovery day test, but thereafter usually somewhat above preflight levels during several successive tests.

The heart rate and blood pressure responses during lower body negative pressure postflight indicated intense sympathetic activity and an adequate cardiac and peripheral arteriolar response. The intensity of these responses paralleled those seen in the first weeks of flight despite evidence that the volume of blood displaced to the lower body was much smaller postflight than in weightlessness which seems probable that even brief periods of orthostasis initiates the process of shifting fluids footward. Relatively dehydrated tissues in the lower body undoubtedly accept large volumes of fluid when venous pressure in the lower extremities rises for even brief periods of time, creating the effect of a sudden hemorrhage in the face of an already contracted blood volume. Baroceptor mechanisms, particularly those involving the carotid sinus, long adjusted to the higher pressures than those experienced in weightlessness, may exhibit increased sensitivity for a time to the reduction in pressure associated with the reappearance of hydrostatic pressures in body fluids. Baroceptor responses may cause intense venoconstriction as well as arteriolar restriction and thus limit both inflow and capacity of the venous system. In addition, during in-flight tests, there was evidence that even though total blood volume was reduced, blood volume in the upper body may actually be expanded and thus furnish a larger available reservoir from which to supply blood to the lower body during lower body negative pressure than in the early postflight period.

The experience of Skylab indicates that protection against orthostatic forces during the first few hours postflight not only serves to prevent orthostatic hypotension but may play an important role in cushioning the cardiovascular effects of return to gravity by preventing sudden large shifts of intravascular fluids to lower extremity vessels and extravascular tissues. Recumbency and the use of external pressure to counteract hydrostatic forces while in the upright position retard these readaptive changes which, if allowed to take place rapidly, can only accentuate the adverse effects of an inadequate circulating blood volume.

The Skylab Missions provided the first American opportunity for detailed studies of the cardiovascular system during the course of prolonged exposure to weightlessness. Basic questions concerning the cardiovascular adaptations to this environment have been answered. For example, a better understanding of the lack of correlation between postflight decrements in orthostatic tolerance and flight exposures of from a few to 14 days was gained. Skylab studies have clearly shown that changes in fluid volume distribution during the first few hours of flight creates profound alterations in cardiovascular functions which in turn, impair orthostatic mechanisms to a marked degree as early as four or five days after entering the weightless environment.

As anticipated, even though the understanding of cardiovascular responses to the conditions of space flight and to stresses resembling orthostasis has been significantly advanced, Skylab studies have raised other questions that have never before been asked; for example, those regarding altered vascular flow and pressure relationships and patterns. Space flight furnishes an environment for cardiovascular study which can be produced in no other way. It is difficult to imagine that increased understanding of cardiovascular function and control mechanisms, as they are altered in weightlessness, will not in the future become relevant to the cardiovascular problems that face us on earth.

CONCLUSIONS

- The Skylab lower body negative pressure experiment demonstrated that loss of orthostatic tolerance had already developed by the time of the first tests after four to six days of flight. Cardiovascular responses to lower body negative pressure showed the greatest instability and orthostatic tolerance the greatest decrement during the first three weeks of flight. After approximately five to seven weeks, cardiovascular responses became more stable and evidence of improving orthostic tolerance appeared.

- In-flight data from the lower body negative pressure experiment proved to be useful not only in predicting the early postflight status of orthostatic tolerance, but also in the in-flight assessment of crew health status.

- The marked increases in calf volume induced by in-flight lower body negative pressure appeared to be secondary to large headward shifts of fluid from the lower body as a result of weightlessness. Judged by objective as well as subjective evidence, in-flight lower body negative pressure presented a much greater stress to the cardiovascular system than the same levels of negative pressure during preflight tests.

- Measurements of calf girth and, in Skylab 4, of the lower limbs confirmed an early, large reduction of lower limb volume. The beginning of this fluid shift appeared to correlate temporally with the onset of signs and symptoms of congestion of the head and neck.

- At rest, in-flight mean resting heart rates, systolic blood pressures and pulse pressures were typically increased while diastolic and mean arterial pressures decreased compared to preflight values in all three Skylab 4 crewmen and in the majority of the other Skylab crewmen. Differences in in-flight responses to lower body negative pressure stress from preflight responses included greater heart rate and leg volume increases in all crewmen and, in most, higher diastolic pressures and mean arterial pressures and lower systolic blood pressures and pulse pressures.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support and assistance of the many unnamed people in multiple disciplines for their contributions to the successful completion of the Skylab Medical Experiments. Particular gratitude and appreciation are due: The Cardiovascular Laboratory Team including Joseph T. Baker, Mary E. Taylor, John A. Donaldson, Donna R. Corey, Karl E. Kimball, Katherine M. Tamer, Donald P. Golden, Roger A. Wolthius, and Thomas A. Beale of Technology, Incorporated, and Karen S. Parker of NASA-JSC; Alma B. Scarborough of NASA-JSC for secretarial assistance; Robert W. Nolte and John Lintott of NASA-JSC; Glen C. Talcott and Martin J. Costello of Martin-Marietta Corporation, Richard J. Gowen, Richard D. Barnett, Fred L. Zaebst and David R. Carroll of the USAF Academy, and other NASA-JSC and NASA-MSFC personnel and their contractor personnel for hardware development; Joseph E. Morgan and his Martin-Marietta one-g trainer

and Skylab Medical Laboratory support teams; the medical support teams who monitored and distributed all in-flight data; the NASA-JSC and contractor computer personnel who implemented the complex computer programs and provided massive volumes of lower body negative pressure data management and reduction; and other members of the NASA-JSC Life Sciences Directorate who provide guidance and assistance to the experiment from the beginning to the end of the Skylab Program.

Finally, the authors express appreciation and gratitude to the Skylab prime and backup crews who contributed not only untold hours and extraordinary expertise, but gave also of themselves in the cooperative and complete spirit of scientific endeavor.

REFERENCES

1. Berry, C. A., and A. D. Catterson. 1967. Pre-Gemini Medical Predictions versus Gemini Flight Results. Gemini Summary Conference NASA SP-138, Washington, D. C., p. 197.

2. Hoffler, G. W., R. A. Wolthius, and R. L. Johnson. Apollo Space Crew Cardiovascular Evaluations. *Aerospace Med.* (in press).

3. Kakurin, L. I. 1971. Medical Research Performed on the Flight Program of the Soyuz-Type Spacecraft. Presented at the 4th International Symposium on "Man in Space". Erevan, Armenia, U.S.S.R.

4. Johnson, R. L., G. W. Hoffler, A. E. Nicogossian, S. A. Bergman,Jr. Skylab Experiment M092: Results of the First Manned Mission. *Acta Astronautica* (in press).

5. Johnson, R. L., A. E. Nicogossian, S. A. Bergman, Jr., G. W. Hoffler. Lower Body Negative Pressure: The Second Manned Mission. Aerospace Medical Association, Annual Scientific Meeting, Washington, D. C., May 6-9, 1974. Preprint, p. 182.

6. Bergman, Stuart A., Jr., G. W. Hoffler, R. L. Johnson. Evaluation of the Electromechanical Properties of the Cardiovascular System after Long-Duration Space Flight. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX. August 27-29, 1974.

7. Henry, W. L., S. E. Epstein, J. M. Griffith, R. E. Goldstein, and and D. R. Redwood. The Effect of Prolonged Weightlessness on Cardiovascular Function in Skylab 4 Astronauts. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX. August 27-29, 1974.

8. Hoffler, G. W., R. L. Johnson, A. E. Nicogossian, S. A. Bergman, Jr. and M. M. Jackson. Skylab Medical Experiment M092 - Lower Body Negative Pressure; Vectorcardiographic Results. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX., August 27-29, 1974.

9. Nicogossian, A., G. W. Hoffler, R. L. Johnson, and R. J. Gowen. Determination of Cardiac Size from Chest Roentgenograms Following Skylab Orbital Missions. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX., August 27-29, 1974.

10. Thornton, William E., G. W. Hoffler, and J. A. Rummel. Anthropometric Changes and Fluid Shifts. Presented at the Skylab Life Sciences Symposium, NASA-JSC, Houston, TX., August 27-29, 1974.

11. Sawin, C. F., A. E. Nicogossian, A. P. Schachter, J. A. Rummel, and E. L. Michel. Pulmonary Function Evaluation During and Following Skylab Space Flights. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX, August 27-29, 1974.

12. De Freitas, F. M., E. Z. Faraco, D. F. De Azevedo, J. Zaduchliver and I. Lewin. 1965. Behavior of Normal Pulmonary Circulation During Changes in Total Blood Volume in Man. *J. Clin. Invest.* 44:366.

13. Kimzey, Stephen L., Linda C. Burns and Craig L. Fischer. Experiment M115 - Special Hematological Effects: Dynamic Changes in Red Cell Shape in Response to Space Flight Environment. Presented at Skylab Life Sciences Symposium, NASA-JSC, Houston, TX, August 27-29, 1974.

14. Stevens, P. M., L. E. Lamb. 1965. Effects of Lower Body Negative Pressure on the Cardiovascular System. *Am. J. Cardiology,* 16:506.

15. Mellander, S. and B. Johansson. 1968. Control of Resistance, Exchange and Capacitance Functions in the Peripheral Circulation. *Pharmacological Reviews.* 20:117.

16. Koch-Weser, Jan. 1973. Correlation of Pathophysiology and Pharmacotherapy in Primary Hypertension. *Am. J. Cardiology,* Special Issue, 32:499.

17. Johnson, R. L., A. E. Nicogossian, M. M. Jackson, G. W. Hoffler, and R. A. Wolthius. Lower Body Negative Pressure - Experiment M092. Skylab Medical Experiments Altitude Test (SMEAT), NASA TMX-58115, NASA-JSC Space Center, Houston, TX. 77058, October 1973.

VECTORCARDIOGRAPHIC RESULTS FROM SKYLAB MEDICAL EXPERIMENT M092: LOWER BODY NEGATIVE PRESSURE

G. W. Hoffler, M.D., R. L. Johnson, M.D., A. E. Nicogossian, M.D.
S. A. Bergman, Jr., M.D. and M. M. Jackson, M.S.
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

ABSTRACT

Vectorcardiograms were recorded via a modified Frank lead system from all crewmen of the three Skylab missions in conjuction with the Lower Body Negative Pressure - M092 Experiment. Data were analyzed by a specially developed computer program (VECTAN). Design of the test sequences allowed direct comparisons of supine resting, Earth based (reference) vectorcardiograms with those taken during lower body negative pressure stress and those obtained at rest in orbit, as well as combinations of these conditions.

Results revealed several statistically significant space flight related changes; namely, increased resting and lower body negative pressure stressed heart rates, modestly increased PR interval and corrected QT_c interval, and greatly increased P and QRS loop maximal amplitudes. In addition, orientation changes in the QRS maximum vector and the J-vector at rest in space seem quite consistent among crewmen and different from those caused by the application of lower body negative pressure. No clinical abnormalities were observed.

Etiology of these findings is conjectured to be, at least in part, related to fluid mass shifts occurring in weightlessness and attendant alterations in cardiovascular dynamics and myocardial autonomic control mechanisms.

INTRODUCTION

Electrocardiographic interval changes suggesting effects of increased vagal tone were observed early in some Gemini crewmembers (1). Preflight versus postflight amplitude differences appeard in electrocardiograms of several of the early Apollo crewmembers. In preflight and postflight crew evaluations of the last three Apollo flights, quantitative postflight vectorcardiographic changes were for the first time determined in American space crews. Changes not considered related to heart rate were mainly those of increased P and QRS vector

magnitudes and orientation shifts. But since most of these postflight findings resembled those observed with the orthostatic stress of lower body negative pressure, it was inferred then that upon their return from space, astronauts exhibited exaggerated responses to orthostasis in the vectorcardiogram as well as in measures of cardiovascular hemodynamics (2). No explicit information on in-flight vectorcardiographic changes or on in-flight influence upon postflight findings existed before Skylab. To help resolve the question, vectorcardiograms have been studied on all nine Skylab crewmen.

The M093 investigators have studied and reported on the vectorcardiograms of exercising Skylab astronauts (3); this M092 report extends our data base with extensive vectorcardiographic recordings on all nine, supine resting astronauts periodically subjected to lower body negative pressure stress.

METHODS

A specially designed Frank lead vectorcardiograph system (4) was used for all Skylab vectorcardiographic recordings (fig. 1). Safety and reliability features commensurate with other space hardware were added; the only other modification was the shifting of leg electrodes to the "presacral" area to obtain greater stability of signals during the exercise experiments M093 and M171. Body sites were permanently marked to assure consistency in repeated application of electrodes (fig. 2). System controls provided individual electrode impedance checks and continual digital heart rate readout selectable from either of the three leads since no onboard display of analog signal was available in the Experiment Support System for crew monitoring. Discrete gain settings for each lead allowed some degree of optimization for individual signal amplitude. All data were recorded primarily on digital magnetic tape with a sample frequency of 320 samples per second per channel (limit of Skylab capability); in-flight data were telemetered from onboard recordings to ground tracking stations as they became accessible. Real-time ground monitoring of in-flight data, therefore, could be randomly available for only relatvely short periods. Data from complete experiment protocols were rarely seen in real time.

Every test protocol consisted of 25 minutes of data recording, broken into five, 5-minute periods for vectorcardiographic analysis. This provided a resting supine control period, three graded levels of lower body negative pressure stress and a final period of recovery at ambient pressure (fig. 3). The first two minutes at lower levels of

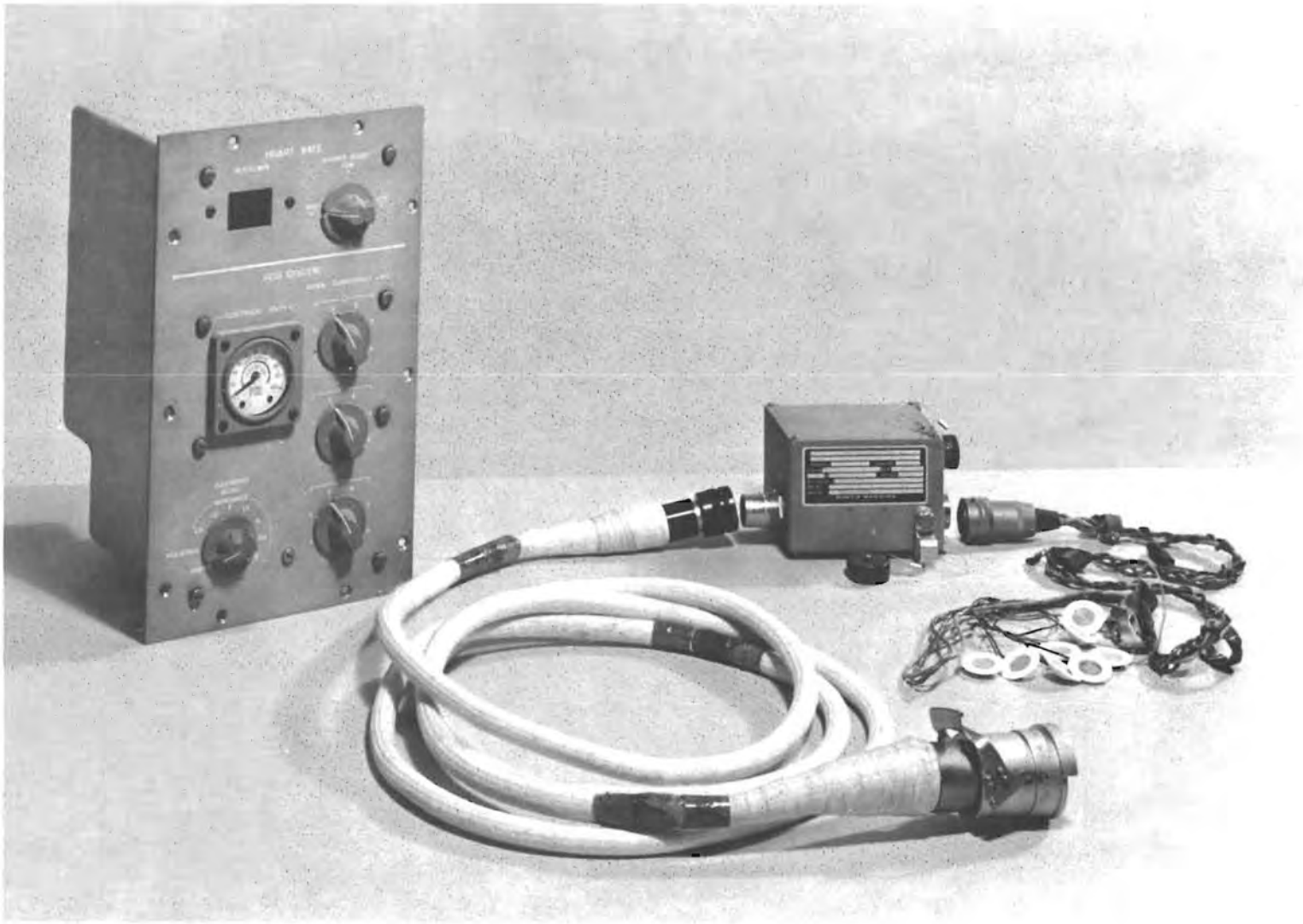


Figure 1. Vectorcardiograph system hardware.

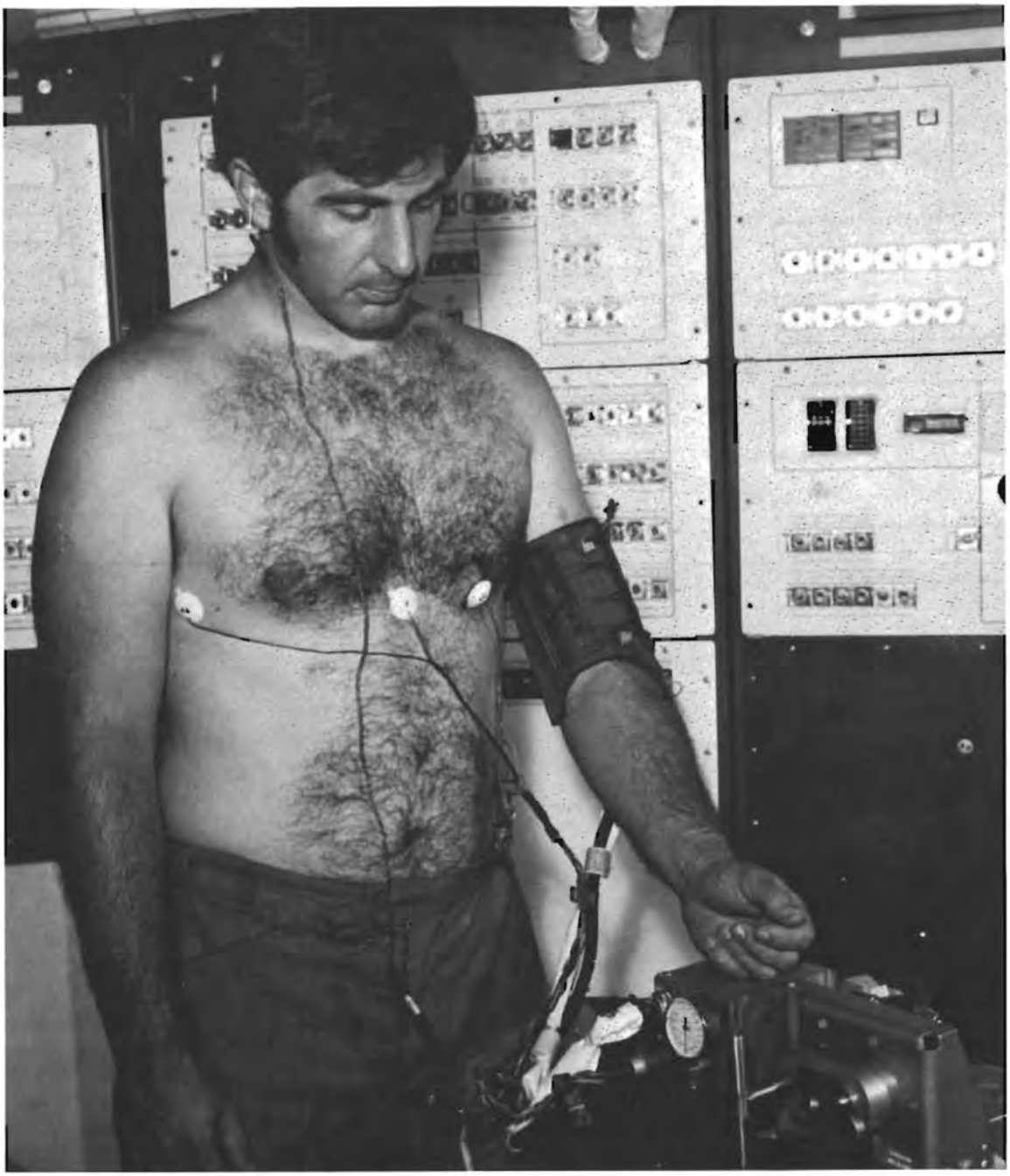


Figure 2. Vectorcardiograph system in place on subject.

lower body negative pressure were included as part of the first major stress period for vectorcardiographic analysis.

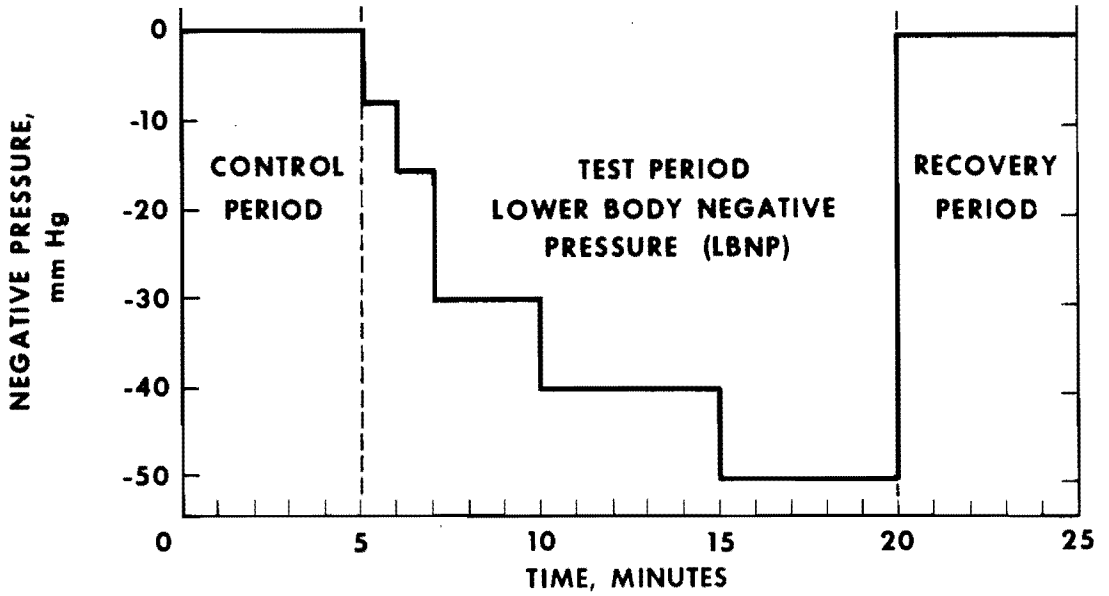


Figure 3. The lower body negative pressure protocol used for Skylab cardiovascular evaluations assessing orthostatic tolerance.

Each astronaut trained both as subject and observer in a one-g flight simulator of the Skylab Orbital Workshop beginning about six months before the launch of his flight. From each crewman, five to seven preflight vectorcardiographic recordings during the lower body negative pressure protocol were obtained during this period to establish his normal vectorcardiogram and variance. Three of these recording sessions were scheduled in the month preceding, with the last approximately five days before, launch.

The earliest in-flight lower body negative pressure tests (fig. 4) were performed on the fourth to sixth day of orbit for each crewman; thereafter in-flight tests were conducted approximately every third day. postflight tests were accomplished on recovery day aboard ship as soon as possible after splashdown and on the succeeding two days. Return to the Johnson Space Center usually occurred on the third day postflight. Subsequent postflight tests were done on fourth and fifth day postflight and on at least three additional days, as late as one to two months after recovery. Flight related test dates were not necessarily the same for all crewmen. All postflight tests utilized Skylab hardware outfitted in a mobile laboratory (fig. 5). The separate systems of hardware were of identical design and departures

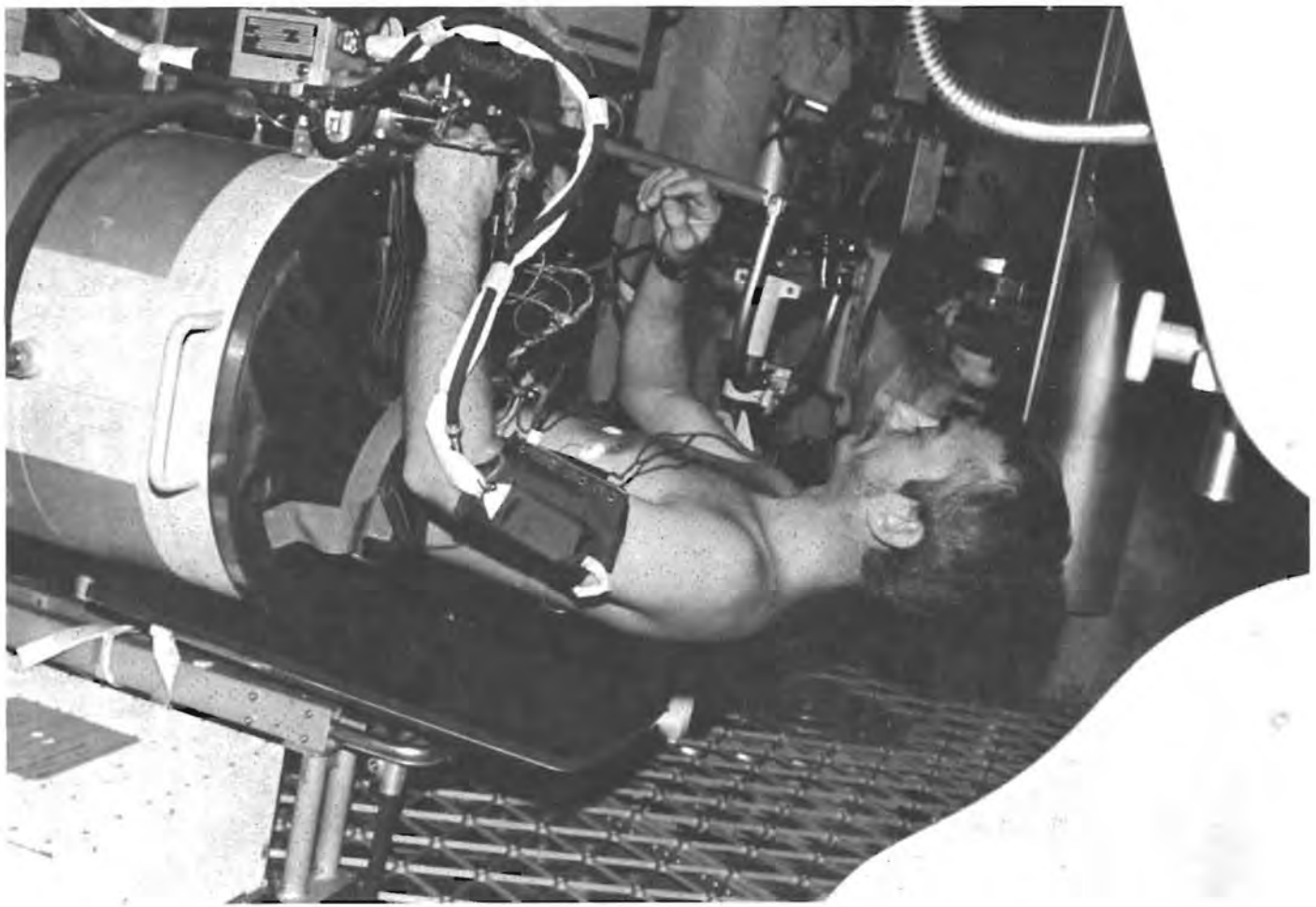


Figure 4. Skylab 3 Scientist Pilot in Lower Body Negative Pressure device. Sensors in place for recording experimental data, including vectorcardiogram.

Figure 5. Skylab Mobile Laboratory. Cardiovascular facility for lower body negative pressure testing.

from equivalence lay only in necessary elements peculiar to one-g or zero-g environment operations, *e.g.*, one-g upper torso support dolly for lower body negative pressure.

All digital recordings were processed by a previously developed computer program called VECTAN (5) which analyzed the three-dimensional spatial entity rather than planar projections in order to obviate perspective distortions. It has been verified with ground-based studies as well as by Apollo and Skylab Medical Experiments Altitude Test usage. The program basically reconstructs the mathematical elements of the spatial P-QRS-T vector loops (fig. 6) which include standard time intervals, vector magnitudes and orientations, calculated areas and circumferences and other quantitative parameters. These data are computed from the spatial vector for every complex analyzed (one every five seconds) (fig. 7) and summarized statistically over discrete protocol periods for every lower body negative pressure test and subsequently for every subject according to flight phase (preflight, in-flight or postflight), test means and/or trends. Finally, group mean values for comparable flight phases have been calculated using the data from all nine crewmen.

Standard statistical procedures have been used to establish in-flight and postflight differences from preflight values for the most part two basic considerations are dealt with by selected vectorcardiographic parameters (table I):

- The effect of space flight itself. Answering this query has been attempted by calculating the in-flight (or postflight) minus preflight difference in the resting phase only, since it has been assumed that the vectorcardiogram recorded on resting, supine subjects in Earth gravity is likely the closest approximation obtainable to the vectorcardiogram recorded on the same resting subject in space. Each subject was thereby his own control; the paired t-test was used to test for statistical significance.

- The effect of lower body negative pressure orthostatic stress. Since the test subject experienced no alterations in body orientation, vectorcardiographic changes evidenced during application of lower body negative pressure should be fairly discretely ascribable to fluidic, footward shifts of body mass, in space or on Earth. Hence differences between -50 mm Hg of lower body negative pressure and resting vectorcardiographic measurements were also amenable to statistical analysis by the paired t-test and were used for these comparisons. Various combinations of condition effects are readily evident in table I which is the comparison matrix used to test for

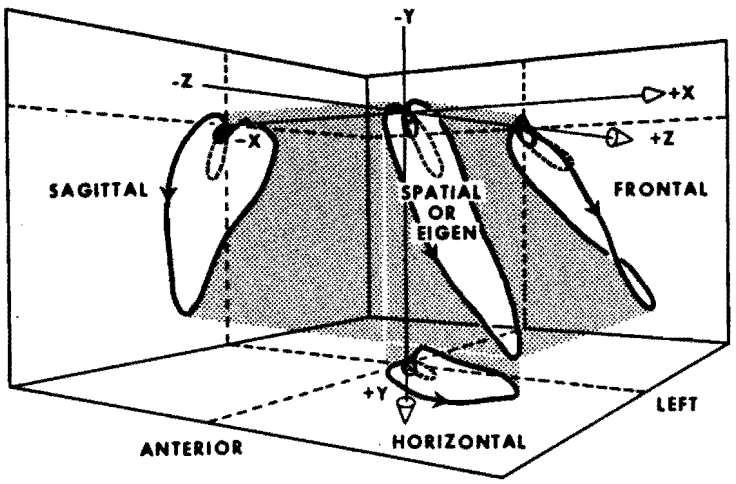
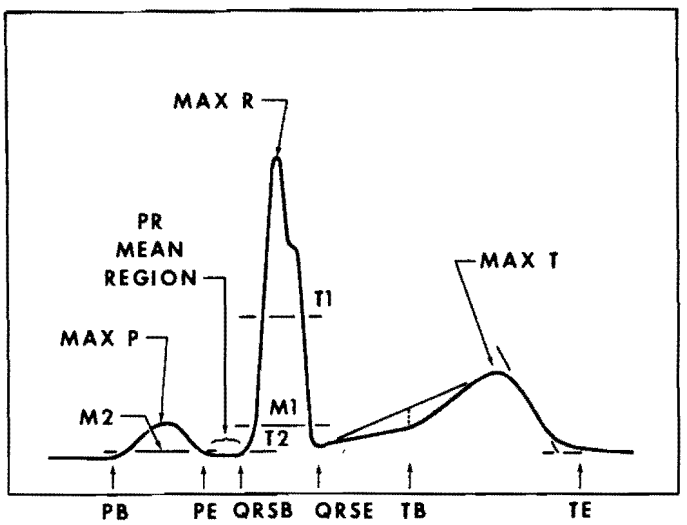


Figure 6. Vectorcardiogram P-QRS-T loops in space with three planar projections.



This derivative from the three orthogonal scalar leads is the basis for all computer analyses in this experiment (M092 VCG).
MAX P, MAX R, and MAX T are respective spatial maxima of the P, QRS, and T loops. PR mean region is the computer null voltage reference. PB, QRS B, and TB are beginning; and PE, QRS E, and TE are ending; fiducial times for the respective loop components. T1, T2, M1 and M2 are respective threshold and modal voltage values employed in the computer program. From these basic elements and the original orthogonal scalar data essentially all aspects of the P-QRS-T complex may be described mathematically in three dimensional space.

Figure 7. Vectorcardiogram spatial vector length in scalar form for one complete P-QRS-T cycle.

vectorcardiographic changes observed after the experimental conditions of lower body negative pressure (LBNP) stress, the space environment itself and entry.

TABLE I. M092 VECTORCARDIOGRAM COMPARISON MATRIX

Reference Values	Percent Change After Designated Condition				
	Condition = LBNP (LBNP Stress Values)			Condition = Flight (Resting Values)	
	PREFLIGHT	IN-FLIGHT	POSTFLIGHT	IN-FLIGHT	POSTFLIGHT
	LBNP	LBNP	LBNP	Space	Space
Preflight Supine Rest	(Alone)	+ Space	+ Space + Entry		+ Entry
In-flight Rest		LBNP (in space)			Entry
Postflight Rest			LBNP (After Space)		

Throughout these data analyses, it has been assumed that all three Skylab crews, despite widely varying mission lengths and initally high ambient temperatures for the Skylab 2 mission, experienced the same space stresses and that their physiologic responses should have been at least qualitatively similar. Using these premises, statistical comparisons have been made primarily on group (nine crewmen) mean values. In recognition of the differences in mission durations, however, and therefore of the possibility of trend changes, in-flight means as well as single test values early and late in each orbital period have been compared separately with preflight mean references.

RESULTS

Heart rate responses to lower body negative pressure (table II) are presented in this report also. It is sufficient to reiterate here that, compared to supine resting preflight values, resting heart rates were elevated in-flight (18%) for the Skylab 3 and Skylab 4 crewmen, and generally in the early postflight period (3%) for all nine Skylab astronauts. The Skylab 2 crewmen, however, differed somewhat in-flight by showing decreased resting heart rates. The average difference between in-flight and preflight resting heart rates of the Skylab 2 crewmen, all of whom showed decreases from preflight values, was significantly ($P<0.001$) different from the same average difference for the other six crewmen, who invariable exhibited higher resting heart rates in-flight than preflight.

During lower body negative pressure stress, heart rates were always elevated, 20 to 50% over their corresponding resting values, regardless of flight phase; however, a tendency toward greater than preflight stressed increases was evident in-flight and immediately postflight.

The PR interval (table II) exhibited moderate, reciprocal changes with heart rate, decreasing significantly (4 to 10%) during lower body negative pressure stress for all but two crewmen (Skylab 2 Commander and Pilot). Though changes in the resting PR interval in-flight were individually sporadic and averaged some 2% less than preflight values for the earliest in-flight tests, mean in-flight values were significantly greater (4%, $P< 0.025$) than preflight. There was, however, no clear time trend throughout the missions nor distinct relationship to duration of flight.

For the QRS duration (table II), although in-flight resting values averaged slightly less than (2%) than the preflight counterpart, no consistent or significant pattern of change with respect to flight phase was seen. A modest but significant ($P< 0.02$) decrease averaging about 5% in absolute value, however, occurred almost universally with the application of lower body negative pressure.

The absolute QT interval (table II) was also uniformly decreased (6 to 15%) during lower body negative pressure stress and whenever the heart rate was elevated, its response following the expected reciprocal relationship to heart rate. Corrected resting QT_C intervals by the Bazett equation (6), however, showed an average increasing trend in-flight, which became significantly different in the late in-flight period from preflight mean values (3% increase, $P< 0.05$). Furthermore, QT_C intervals during lower body negative pressure were elevated (2 to 7%, $P< 0.05$ to 0.001) over resting values at all phases of the mission.

Effects on vectorcardiograph component amplitudes (table III) were greater than those on temporal measurements. The P-wave maximum vector magnitude ($P_{max}MAG$) at rest significantly ($P<0.025$) increased in-flight, averaging about 25%. This increase was greater early than late in flight, was still present on recovery, although already attenuated, but quickly returned to preflight values. Even more marked, however, was the increase in $P_{max}MAG$ during lower body negative pressure (ranging 28 to 55%), again the greater changes being seen in-flight and immediately postflight.

The group average QRS maximum vector magnitude ($QRS_{max}MAG$)(table III) at rest also increased (12%) significantly ($P<0.001$) in-flight with an increasing in-flight trend, returning rather precipitously to preflight levels about three days postflight. Preflight during lower body negative pressure the $QRS_{max}MAG$ decreased from resting

TABLE II. TEMPORAL MEASUREMENTS OF THE VECTORCARDIOGRAM
Percentage changes from the nine crewmen group mean, preflight, supine resting values (as reference) of averages for heart rate, PR interval, QRS duration, and QT interval (basic and heart rate corrected, QT_C) during designated treatment condition.

VECTORCARDIOGRAM MEASUREMENT	PREFLIGHT REFERENCE VALUES SUPINE, RESTING MEAN ± SD	CHANGE AFTER DESIGNATED CONDITION (%)									
		CONDITION = LBNP						CONDITION = FLIGHT			
		PREFLIGHT		IN-FLIGHT		POSTFLIGHT R + 0		IN-FLIGHT		POSTFLIGHT R + 0	
		$\bar{X}$	P	$\bar{X}$	*	$\bar{X}$	*	$\bar{X}$	P	$\bar{X}$	P
Heart rate (bpm)	56 ± 6	+20	<0.001	+54		+57		+9	NS	+2	NS
PR interval (ms)	148 ± 16	-11	<0.01	- 6		- 5		+3	<0.025	+2	NS
QRS duration (ms)	98 ± 8	- 6	<0.001	- 6		- 4		-3	NS	+2	NS
QT interval (ms)	419 ± 20	- 6	<0.001	-13		-14		-2	NS	-1	NS
QT_C interval (ms)	402 ± 13	+ 2	<0.001	+ 7		+ 7		+2	0.01	+0	NS

NS = not significant

*P values were not computed for these comparisons because percentage changes are reckoned from preflight resting references, and compound treatment effects (*i.e.*, LBNP, space and/or entry) are involved. Approximate significance may be judged in relation to the P values for the relatively "pure" treatments of preflight LBNP or flight itself.

TABLE III. AMPLITUDE MEASUREMENTS OF THE VECTORCARDIOGRAM
Percentage changes from the nine crewmen group mean, preflight, supine resting values (as reference) of averages for P-wave maximum vector magnitude ($P_{max}MAG$), QRS complex maximum vector magnitude ($QRS_{max}MAG$), QRS spatial Eigenloop circumference (QRS-E CIRC), and ST-wave maximum vector magnitude ($ST_{max}MAG$) during designated treatment condition.

VECTORCARDIOGRAM MEASUREMENT	PREFLIGHT REFERENCE VALUES SUPINE, RESTING MEAN ± SD	CHANGE AFTER DESIGNATED CONDITION (%)									
		CONDITION = LBNP						CONDITION = FLIGHT			
		PREFLIGHT		IN-FLIGHT		POSTFLIGHT R + 0		IN-FLIGHT		POSTFLIGHT R + 0	
		$\bar{X}$	P	$\bar{X}$	*	$\bar{X}$	*	$\bar{X}$	P	$\bar{X}$	P
$P_{max}MAG$ (mV)	0.122 ± 0.0332	+27	<0.001	+78		+75		+24	<0.02	+16	NS
$QRS_{max}MAG$ (mV)	1.70 ± 0.373	- 6	<0.02	+13		+12		+12	<0.001	+18	<0.001
QRS-E circ (mV)	5.01 ± 1.027	+ 3	NS	+24		+32		+19	<0.005	+21	<0.001
$ST_{max}MAG$ (mV)	0.646 ± 0.206	-15	<0.01	-32		-37		-10	NS	- 6	NS

NS = not significant

*P values were not computed for these comparisons because percentage changes are reckoned from preflight resting references, and compound treatment effects (*i.e.*, LBNP, space and/or entry) are involved. Approximate significance may be judged in relation to the P values for the relatively "pure" treatments of preflight lower body negative pressure or flight itself.

values (7%, $P< 0.02$) but showed no significant response to lower body negative pressure in-flight. This appears to be a differential response to lower body negative pressure preflight versus in-flight, or perhaps an overriding dominance due to the effect of space flight alone.

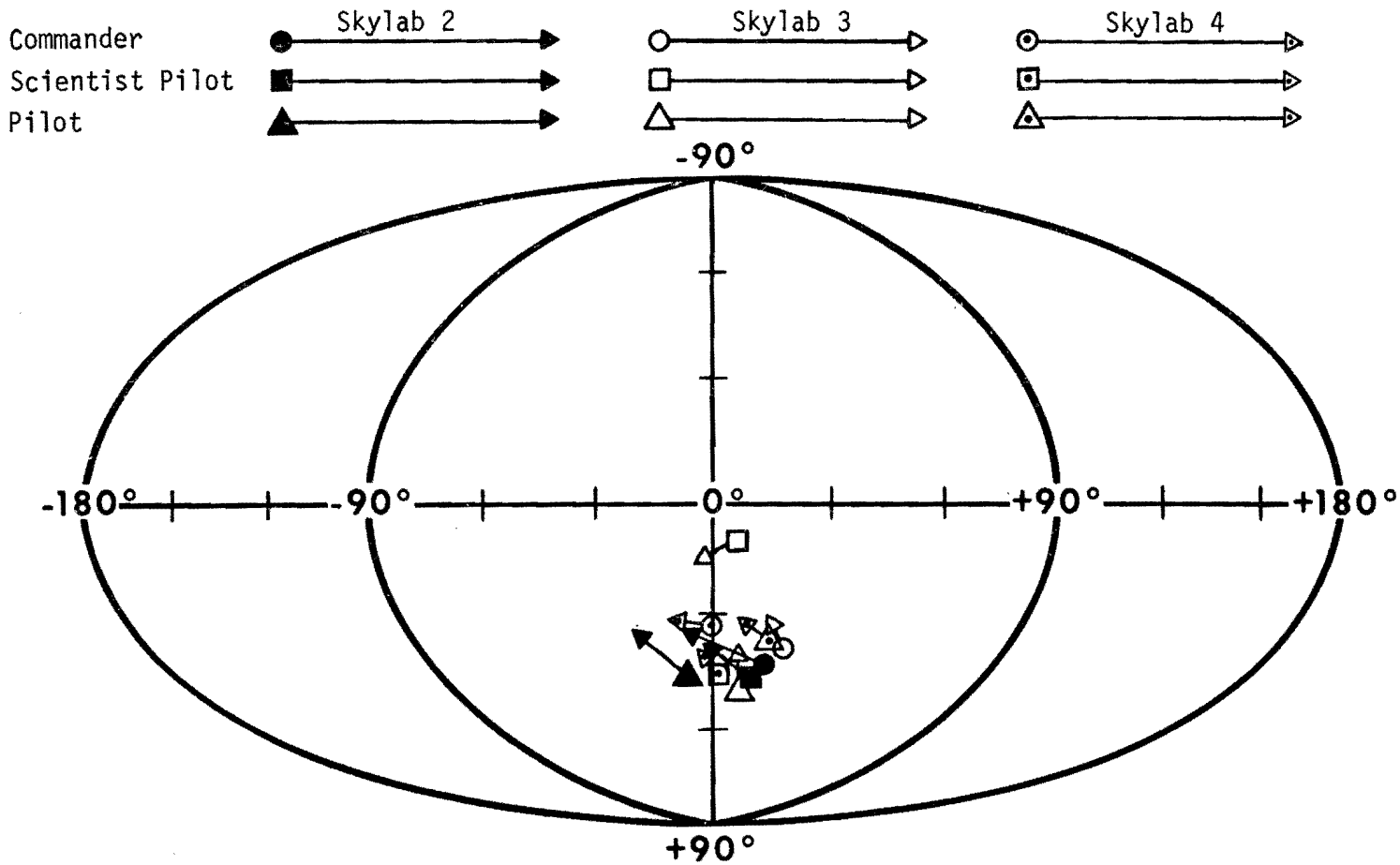
Perhaps a better indicator of change in the overall QRS depolarization complex, the total QRS Eigenloop* circumference (table III) reflected highly significant in-flight increases also (19%, $P< 0.005$), which generally progressed during the in-flight phase. In-flight increases and precipitous postflight return to preflight values caused this measurement to exhibit a "square wave" phenomenon during the in-flight phase. Somewhat paradoxically, however, the QRS Eigenloop circumference also increased during lower body negative pressure, insignificantly preflight, but to around 10% in-flight ($P< 0.0025$).

The resting ST maximum vector magnitude ($ST_{max}MAG$) (table III) for the group underwent nonsignificant decrements in-flight ($\sim$ 10%). But here, as with the heart rate, a distinctly different pattern prevailed in the Skylab 2 crewmen compared to the other two crews such that the question of significantly different stressors may be considered a possible explanation. The effect of lower body negative pressure was always to increase $ST_{max}MAG$, 14% preflight ($P< 0.01$) up to 25% in-flight ($P< 0.001$) and 30% immediately postflight ($P< 0.0001$).

Alterations in orientation of the $P_{max}MAG$ vector at rest in space were quite variable and nonuniform; lower body negative pressure produced a slightly greater and more consistent effect of a general shift of the $P_{max}MAG$ vector terminus inferiorly and rightward.

In contrast to $P_{max}MAG$ orientation, the resting $QRS_{max}MAG$ vector terminus showed a rather consistent, though not large, shift toward more anterior orientation in-flight, with a nearly equivalent return on the day of recovery (fig. 8). Figures 8 and 9 depict the QRS maximum vector termini on a spherical surface (Aitoff equal area projection) representing the body thorax with equatorial azimuth at heart level, 0° being the left axilla, and minus and plus 90°, anterior and posterior, respectively. Negative elevation angles represent headward, and positive, footward, declinations from the horizontal reference plane. A slight superior component is also seen in this orientation shift. Almost universally the $QRS_{max}MAG$ vector terminus shifted in the opposite direction (posteriorly and inferiorly) upon application of lower body negative pressure (fig. 9). The net effect of lower body negative pressure in-flight, therefore, was less than either effect alone.

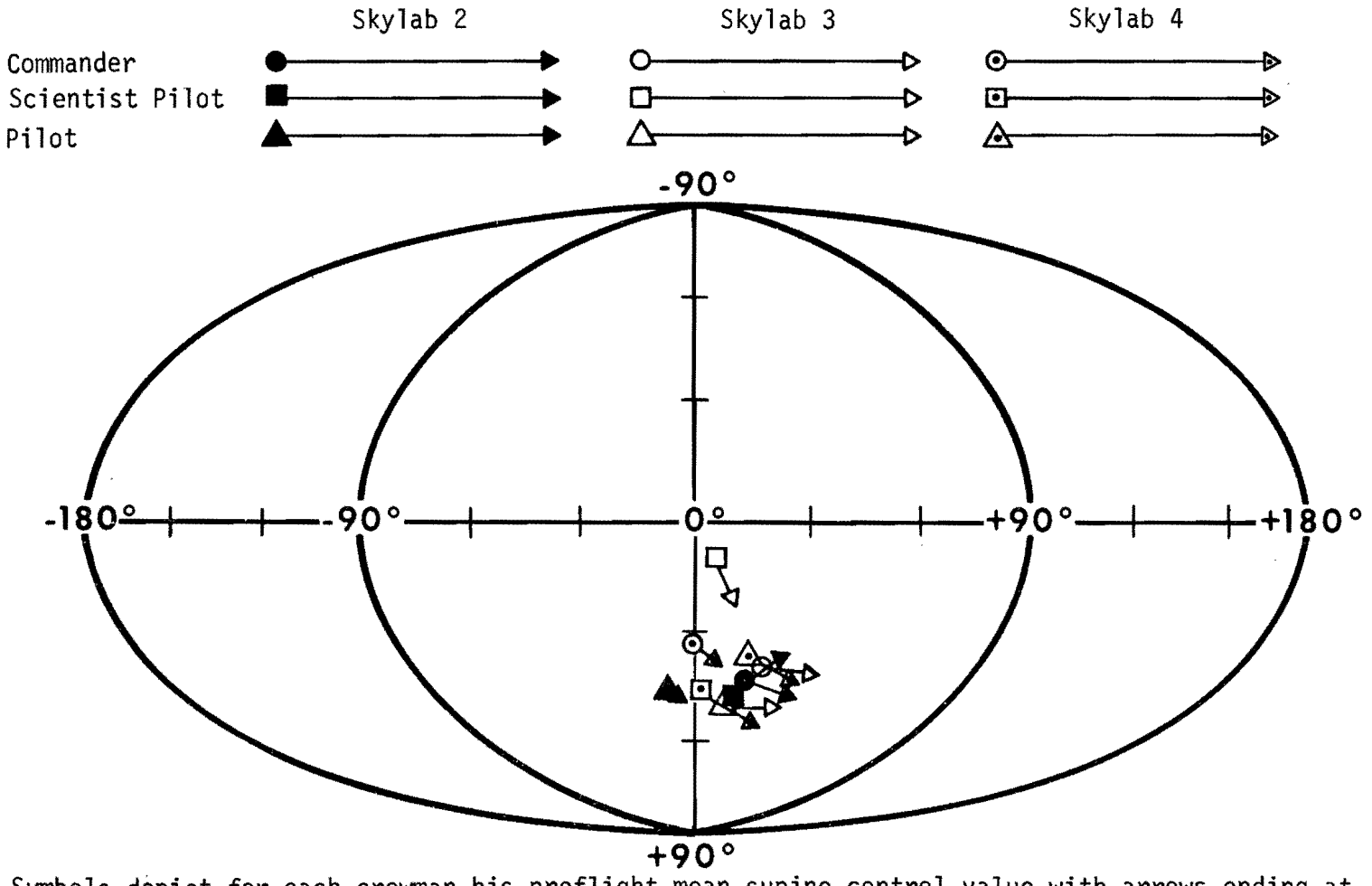
*The QRS Eigenloop is that unique spatial entity representing the net summation of all instantaneous vectors throughout the QRS depolarization cycle. It is normally fairly planar and is quantified and oriented within standard orthogonal reference axes.



Symbols depict for each crewman his preflight mean supine control value with arrows ending at the first in-flight shifted location, still in the resting state.

The spherical grid (Aitoff equal area projection) represents the body surface where myocardial voltages are measured. The center (0°) is the left axilla, -90° is anterior center chest, +90° is posterior center back, and ±180° is the right axilla; these azimuthal angles are in the horizontal plane at the level of the fifth intercostal space. Negative elevation angles from the horizontal reference plane represent superior (headward) direction and positive elevation angles, inferior (footward) direction.

Figure 8. Skylab M092 QRS_{max} orthogonal orientation. The effect of space.



Symbols depict for each crewman his preflight mean supine control value with arrows ending at his preflight shifted location under the stress of -50 mm Hg lower body negative pressure. Spherical grid is the same as for figure 8.

Figure 9. Skylab M092 QRS_{max} orthogonal orientation. The effect of lower body negative pressure.

The resting $ST_{max}MAG$ vector orientation shifted slightly rightward in-flight, but always remained in the left anterior inferior octant. Lower body negative pressure produced a similar and somewhat larger shift, with an accompanying modest superior distortion.

In table IV resting J-vector magnitude (the spatial distance between origin and end of the QRS loop) shows no significant in-flight changes, but a postflight increase of 18% was significant at $P< 0.05$. Much greater augmentation occurred during lower body negative pressure stress preflight (30%, $P< 0.001$) and in-flight (up to 41% in the early part of the orbital phase).

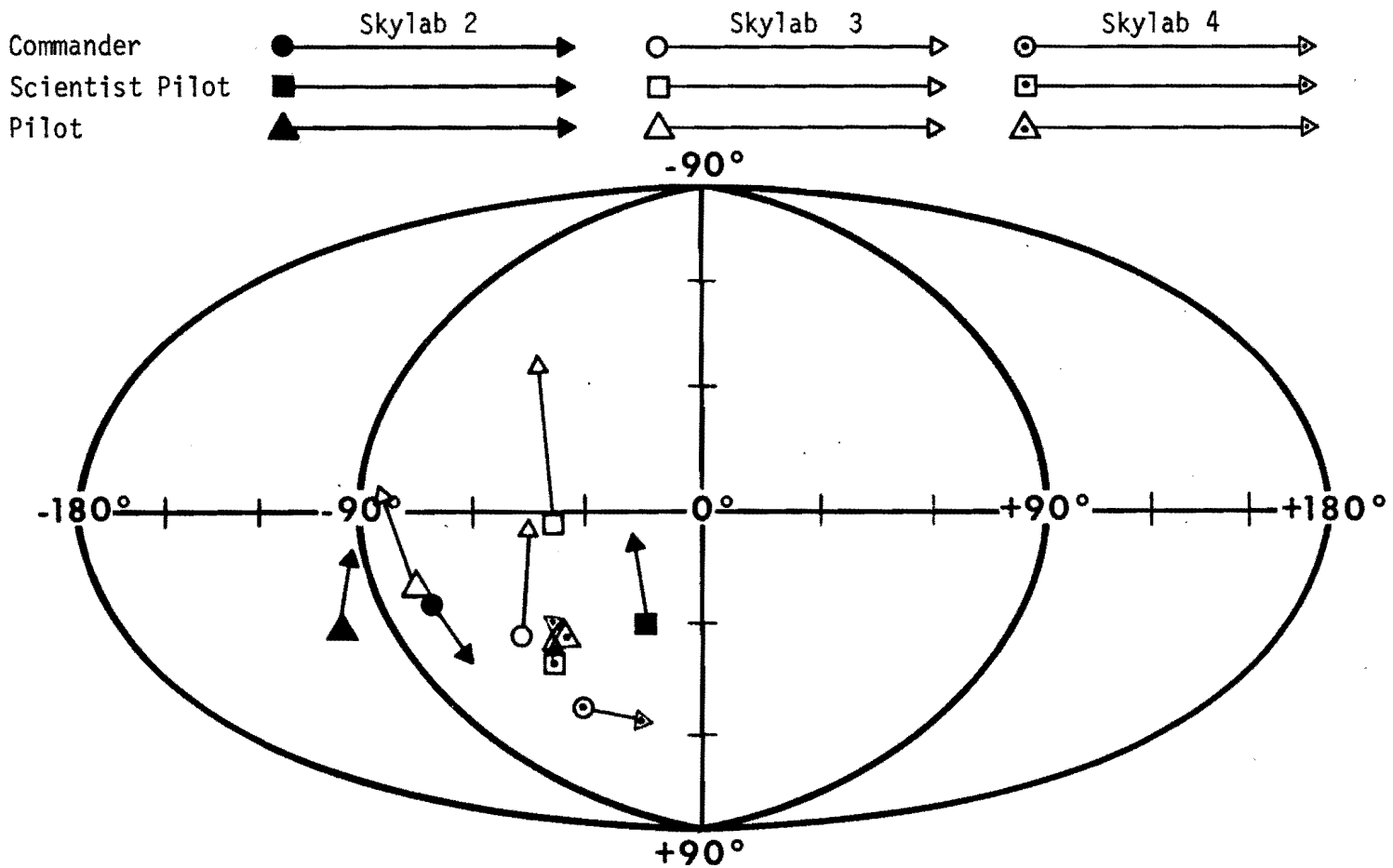
TABLE IV. DERIVED MEASUREMENTS OF THE VECTORCARDIOGRAM
Percentage changes from the nine crewmen group mean, preflight, supine resting values (as reference) of averages for J-VECTOR magnitude, ST slope, and QRS-T spatial angle.

VECTORCARDIOGRAM MEASUREMENT	PREFLIGHT REFERENCE VALUES SUPINE, RESTING MEAN ± SD	CHANGE AFTER DESIGNATED CONDITION (%)									
		CONDITION = LBNP						CONDITION = FLIGHT			
		PREFLIGHT		IN-FLIGHT		POSTFLIGHT R + 0		IN-FLIGHT		POSTFLIGHT R + 0	
		$\bar{X}$	P	$\bar{X}$	*	$\bar{X}$	*	$\bar{X}$	P	$\bar{X}$	P
J Vector (mV)	0.074 ± 0.024	+28	<0.001	+13		+26		+ 6	NS	+18	<0.05
ST Slope (mV/s)	1.28 ± 0.528	- 1	NS	-21		-18		+ 5	NS	+ 7	NS
QRS-T angle (deg)	38 ± 14	+61	<0.001	+13		+105		-17	NS	+12	NS

NS = not significant

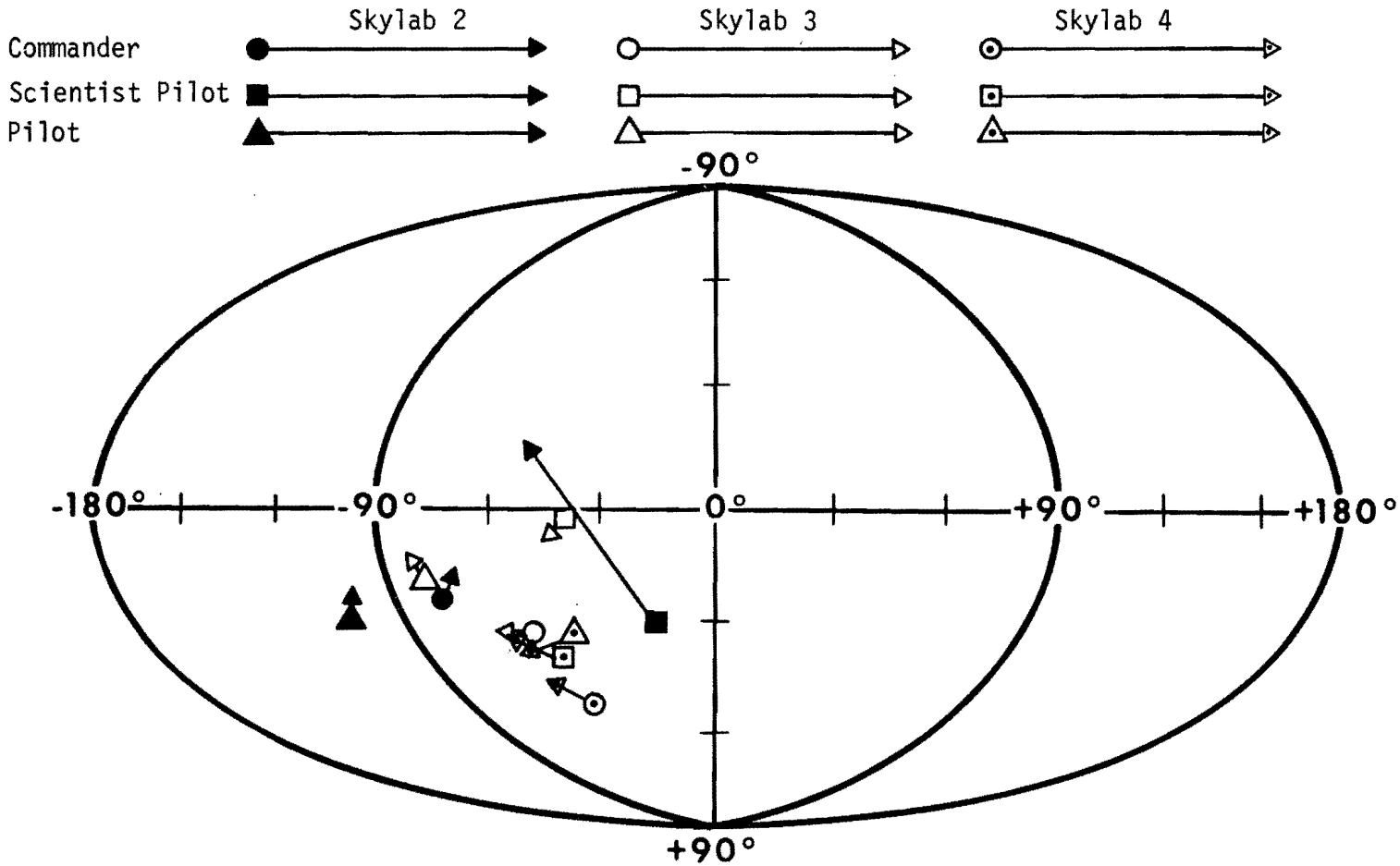
* values were not computed for these comparisons because percentage changes are reckoned from preflight resting references, and compound treatment effects *i.e.* lower body negative pressure, space and/or entry) are involved. Approximate significance may be judged in relation to the P values for the relatively "pure" treatments of preflight lower body negative pressure or flight itself.

Orientation changes of the J-vector terminus were perhaps the most consistent and striking. At rest early in-flight seven of nine crewmen (excepting the Commanders on Skylab 2 and 4) displayed considerable shift superiorly (figure 10). All nine crewmen by late in-flight produced a further leftward shift, while immediately on recovery day all resting J-vector orientations moved dramatically toward their respective preflight positions. Preflight lower body negative pressure stress produced very minor J-vector shifts (fig. 11), mostly rightward, but in-flight and postflight reorientations during lower body negative pressure were marked, especially in the superior direction; the terminus of several moved to the left superior, anterior and posterior octants, well separated from their normal resting position in the left anterior inferior octant. This was most striking immediately postflight.



Symbols depict for each crewman his preflight mean supine control value with arrows ending at the first in-flight shifted location, still in the resting state. Spherical grid is the same as for figure 8.

Figure 10. Skylab M092 J-Vector orthogonal orientation. The effect of space.



Symbols depict for each crewman his preflight mean supine control value with arrows ending at his preflight shifted location under the stress of -50 mm Hg lower body negative pressure. Spherical grid is the same as for figure 8.

Figure 11. Skylab M092 J-Vector orthogonal orientation. The effect of lower body negative pressure.

Resting values for the ST slope (table IV) averaged 1.3 and ranged 0.5 to 2.1 millivolt/second. In-flight and postflight changes were rather variable and not statistically significant, though the group average was augmented in-flight above the preflight reference. Latest in-flight tests were on mission day 25 for Skylab 2; average values for all nine crewmen taken on or near mission day 25 in their respective flights were elevated only 1% over the preflight reference, while a corresponding average 4% increase occurred on the Skylab 3 and Skylab 4 six crewmen around mission day 58. The Skylab 4 crew did not show further increases later in orbit, but an average (nine crewmen) immediate postflight elevation of 7% required up to several days to disappear.

The effect of lower body negative pressure on the ST slope was likewise variable. A preflight increase of 2% was not statistically significant. An average, but not significant, decrease of 21% early in-flight augmented to a statistically significant 41% decrement ($P< 0.01$) late in-flight. On recovery day, however, this reduction in ST slope due to lower body negative pressure was already diminished to 15% with no statistical significance.

The spatial angle between $QRS_{max}MAG$ and $ST_{max}MAG$ vectors is a close approximation to the true QRS-T spatial angle. The average resting value of this QRS-T angle (table IV) decreased 17% in-flight (not statistically significant). A distinct mission trend in reduction of the angle was seen by an early in-flight decrease of only 3% progressing to an average 25% ($P< 0.005$) decrement in the late mission vectorcardiograms. Even so, on recovery day a complete reversal had already occurred with the group averaging a 12% increase over the preflight mean QRS-T angle.

The effect of lower body negative pressure was large and highly variable, but almost always caused an increase in the QRS-T angle which was greater preflight and postflight (69%, $P< 0.001$ and 96%, $P< 0.005$, respectively) than in-flight. The average in-flight increase due to lower body negative pressure was only 47% ($P< 0.02$); a trend toward a lesser in-flight increase due to lower body negative pressure was evident with longer orbital stay.

Concerning lower body negative pressure related arrhythmias, rare ectopic beats of both ventricular and supraventricular origin were noted at some time or other in all crewmen, but frequency appeared unrelated to mission phase. The only other notable occurrences were atrioventricular junctional rhythm seen primarily in all three Scientist Pilots and the Skylab 4 Pilot. These usually manifested themselves during higher levels of lower body negative pressure or immediately upon release, but occasionally were present even at initial rest. They

were seen preflight, in-flight and postflight, perhaps slightly more often in the Skylab 4 Pilot, a representative scalar strip of whom is shown in figure 12. No arrhythmias of clinical concern were ever recorded during lower body negative pressure tests, although the Skylab 3 Commander did exhibit a short episode of atrioventricular dissociation on mission day 21 at release of lower body negative pressure; this never recurred. Additionally, the Skylab 4 Pilot demonstrated considerable distortion of his ST-T waveform occasionally during lower body negative pressure, both in-flight and postflight; restoration was prompt after release of negative pressure.

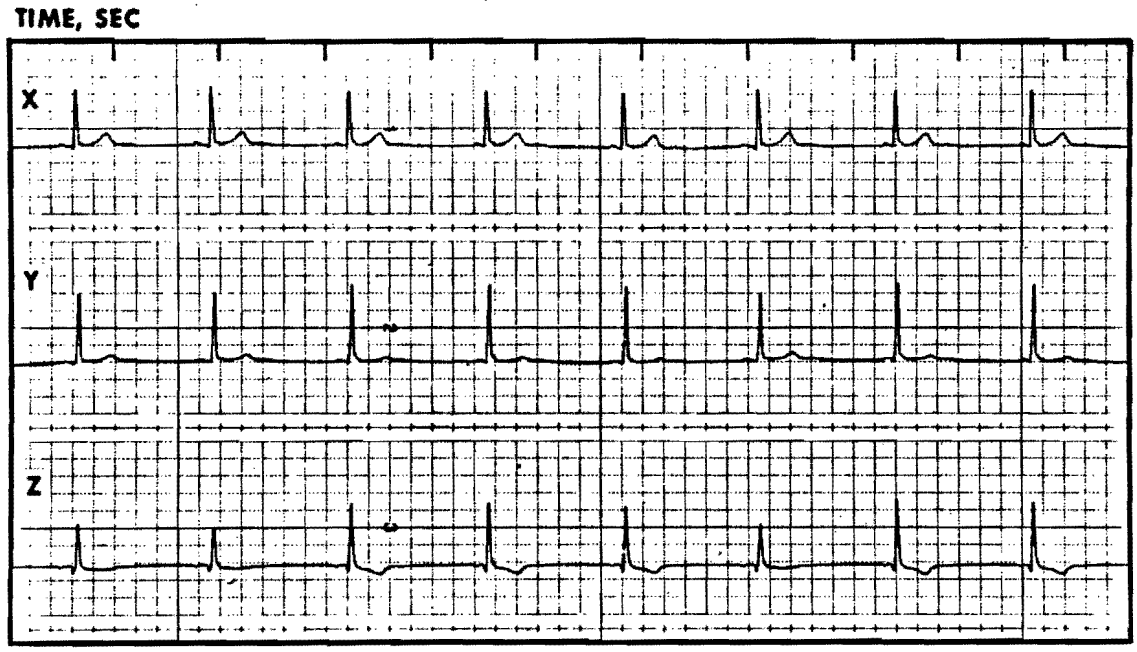


Figure 12. Scalar XYZ vectorcardiogram leads of Skylab 4 Pilot showing intermittent junctional arrhythmia shortly after release of lower body negative pressure on the day of entry.

It should be further pointed out that in no measurement described here did changes exceed the accepted clinical limits of the normal for that measurement. Changes are, therefore, not considered in the pathological context, but as normal physiologic variants of the cardiac electrical phenomena affected by the stresses of the Skylab space environment or of lower body negative pressure. As such they may shed light on basic physiologic mechanisms.

DISCUSSION

Since heart rate is perhaps the best measure of orthostatic stress and is also a pivotal element in considering vectorcardiographic findings, the in-depth discussion of heart rate presented in another paper (7) is an essential to the understanding of the mechanisms involved. Uniformily lower body negative pressure stress produced heart rate elevations in one-g and in orbit, before and after flight. The normalized differential, however, is greater in-flight and immediately postflight than prior to flight. Average percentage increases in heart rate during lower body negative pressure over resting heart rate are: Preflight = 20%, early in-flight = 50%, around mission day 25 = 42%, around mission day 58 (six crewmen only) = 40%, late in-flight = 43%, and immediately postflight = 54%. Even though these differentials are significant in themselves, they are even further exaggerated by the fact that resting heart rates were generally elevated in-flight and postflight over preflight values. Of further importance is the high correlation of stressed heart rate with respective resting rates at any given test session. Therefore, whatever the conditions, stresses or events which affect an individual's resting heart rate must certainly reflect their effects in other physiologic and electrocardiographic measurements.

A modest reciprocal relationship between PR interval and heart rate is generally accepted (8). However, the data from Skylab indicate a more direct relationship; in-flight (especially late) resting heart rate elevations were usually accompanied by increases in the PR interval also. Conversely, the inverse response was observed during lower body negative pressure stress at all flight phases. This conceivably might indicate an in-flight alteration in cardiac autonomic control at rest which was overridden by the stress of lower body negative pressure. Altered autonomic control also might be related to the junctional rhythm observed not infrequently in several crewmen.

Since the only significant changes in QRS duration were seen during lower body negative pressure stress, little difference across the flight phases occurred, and resting differences were insignificant, it is inferred that space flight produced no noteworthy effects on this measurement.

Though the expected reciprocal relationship of QT interval and heart rate was evidenced throughout all flight phases, the trend tendency for the corrected QT_C interval to increase through the orbital phase favors a space related effect upon this measurement independent of heart rate. The effect was directionally the same as that due to lower body negative pressure, though of somewhat lesser magnitude. Since the QT interval represents total ventricular electrical systole

(depolarization and repolarization) and the QRS duration (depolarization) was essentially unchanged, this in-flight lengthening of the QT_C interval must be chiefly due to prolongation of the repolarization process. This conceivably might be related to changes in autonomic balance, but could as likely involve basic cellular metabolic processes.

A seeming paradox in P_{max}MAG is difficult to explain. Lower body negative pressure increases in this measurement have long been observed, sometimes attributed in part to more nearly synchronous depolarization of both atria with increased heart rate and relative adrenergic dominance. Experimental data on dogs by Nelson and co-workers (9) supports an increase in P-wave amplitude upon removal of blood. A space related increase in this measurement at rest, even for those crewmen of Skylab 2 who had decreased resting heart rates in-flight seems to address another mechanism. The fact that early in-flight vectorcardiograms exhibited the greater increases would point to a possible etiology related to fluid shifts which are felt to be operative early following orbital insertion. That fluid is shifted in the opposite direction during lower body negative pressure, when even greater P_{max}MAG values are observed, compounds the paradox. Physiologically, positional changes in this vector do not appear relatively significant.

Even more striking were the QRS_{max}MAG and QRS Eigenloop circumference changes. These measures of increased ventricular depolarization voltage imply a definite space effect, since lower body negative pressure produced actual decreases in the former and nonsignificant increases in the latter preflight. End diastolic ventricular blood volume is considered by Nelson, *et al.*(9) to be a major factor affecting the QRS complex. Manoach, *et al.*(10), and others (11) have demonstrated in dogs a significant direct correlation of blood volume and QRS amplitude during controlled hemorrhage, volume replacement, vena caval occlusion and direct intracardial infusion overload. One might also consider the potential effect in space of relative hemodilution (12) which, according to Rosenthal, *et al.*(13), augments QRS magnitude by lowering intracavitary blood resistivity.

In the hypothesized events occurring in space, a large fluid shift from the lower body centripetally would very likely produce initially a relatively increased intravascular and intracardiac volume. Subsequent transfer of fluid from other compartments to the vascular tree could dilute the original hematacrit as well as increase total blood volume. This interactive complexity could also account for the modest vector orientation shifts observed, particularly as the two ventricular chambers may experience nonidentical alterations. Trying to relate these vectorcardiographic findings to hemodynamic events is enticing, but difficult (14). Our data and the study by Brody (15), who asserted

That intracavitary blood exerts a powerful effect upon surface lead electrical potentials of the heart by differentially decreasing tangential while augmenting radial dipoles seem to give our hypothesis practical and theoretical support. Another perhaps less likely consideration is that these increased surface potentials in-flight do in fact represent increased myocardial work, which might logically be considered due to increased stroke volume and/or elevated systemic pressure.

Finally, since the J-vector and ST slope give important information on myocardial oxygenation, the absence of a significant space related alteration in these two measurements is encouraging. The increased J-vector magnitude and decreased ST slope during lower body negative pressure stress, however, need further investigation.

CONCLUSIONS

°Vectorcardiograms taken on all crewmen during the Lower Body Negative Pressure Experiment (M092) on the Skylab flights have shown several consistent changes apparently related to space flight. Principally involved among these changes are temporal intervals, vector magnitudes and their orientations, and certain derived parameters, presumably as a consequence of altered autonomic neural imputs upon the myocardial conduction system and/or of major fluid shifts known to have occurred in flight.

°Correlations of these electrocardiographic findings with other hemodynamic and related changes appear reasonable and consistent, especially as regards the concept of headward fluid shifts in space.

°All observed measurements have been well within accepted limits of normal and are considered to represent adaptative phenomena rather than pathological conditions.

°These findings have, in a predictable fashion, opened new questions which will direct future ground-based and in flight researches - particularly in the area of cardiovascular electro-hemodynamic studies for the Shuttle era.

ACKNOWLEDGEMENTS

The contributions to these medical findings from Skylab are acknowledged to many people in multiple disciplines. Particular recognition and thanks are due:

Members of the Cardiovascular Laboratory Team: Joseph T. Baker, Thomas A. Beale, Donna R. Corey, John A. Donaldson, Donald P. Golden, Karl E. Kimball, Katherine M. Tamer, Mary E. Taylor, and Rodger A. Wolthuis of Technology Incorporated, and Karen S. Parker and Marion M. Ward of NASA - Johnson Space Center.

Hardware development: John A. Lintott of NASA - Johnson Space Center and Martin Costello of Martin-Marietta Corporation.

One-g trainer and Skylab Mobile Laboratory support team: J. Morgan and his Martin-Marietta Corporation.

The medical support teams who monitored and routed all in flight data.

The NASA - Johnson Space Center and contractor computer personnel who implemented the complex software programs which provided the massive data reductions to the investigators.

All other unnamed and unknown participants whose efforts contributed in whatever manner to the success of this Herculean team effort.

Last, but in no respect least, the authors shall be ever grateful to the Skylab prime and backup crews who gave not only untold hours and extraordinary expertise, but also themselves in the full spirit of scientific endeavor.

REFERENCES

1. Vallbona, C., and L. F. Dietlein, Measurements of the Duration of the Cardiac Cycle and Its Phases in the Gemini Orbital Flights, in A Review of Medical Results of Gemini 7 and Related Flights, held by the National Aeronautics and Space Administration at the John F. Kennedy Space Center, Florida, August 1966.

2. Hoffler, G. W., R. L. Johnson, R. A. Wolthuis and D. P. Golden, Results of Computer Reduced Vectorcardiograms from Apollo Crewmembers. Preprints of the 1973 Scientific Meeting of the Aerospace Medical Association, Las Vegas, Nevada, May 1973.

3. Smith, R. F., K. Stanton, D. Stoop, D. Brown, W. Janusz, and P. King. Vectorcardiographic Changes during Extended Space Flight, proceedings of Skylab Life Sciences Symposium, NASA-JSC, Houston, Texas, August 1974.

4. Frank, Ernest. 1956. An Accurate, Clinically Practical System for Spatial Vectorcardiography, *Circulation*, 13: 737-749.

5. Golden, D. P., G. W. Hoffler, R. A. Wolthuis, and R. L. Johnson, VECTAN II: A Computer Program for the Analysis of Skylab Vectorcardiograms. Preprints of the 1973 Scientific Meeting of the Aerospace Medical Association, Las Vegas, Nevada, May 1973.

6. Bazett, H. C. 1918. An Analysis of the Time-Relations of Electrocardiograms. *Heart*, 7:353-370.

7. Johnson, R. L., G. W. Hoffler, A. E. Nicogossian, S. A. Bergman and M. M. Jackson, Lower Body Negative Pressure: Third Manned Mission. Proceedings of Skylab Life Sciences Symposium, NASA-JSC, Houston, Texas, August 1974.

8. Schlamowitz, I. 1946. An Analysis of the Time Relationships within the Cardiac Cycle in Electrocardiograms of Normal Men. *Amer. Heart J.*, 31:329-342, 464-476.

9. Nelson, C. V., P. W. Rand, E. T. Angelakos, and P. G. Hugenholtz. July 1972. Effect of Intracardiac Blood on the Spatial Vectorcardiogram I - Results in the Dog. *Circulation Res.*, 31:95-104.

10. Manoach, Mordechai, S. Gitter, E. Grossman, D. Varon and S. Gassner, 1971. Influence of Hemorrhage on the QRS Complex of the Electrocardiogram, *Amer. Heart J.*, 82:55-61.

11. Angelakos, E. T. and N. Gokhan. 1963. Influence of Venous Inflow Volume on the Magnitude of the QRS Potentials *in Vivo*. *Cardiologia*, 42:337-348.

12. Kimsey, S. L., L. C. Burns, and Craig L. Fischer. Experiment M115-Special Hematologic Effects: Dynamic Changes in Red Cell Shape in Response to the Space-Flight Environment. Proceedings of Skylab Life Sciences Symposium, NASA - JSC, Houston, Texas, August 1974.

13. Rosenthal, A., N. J. Restieaux, and S. A. Feig. 1971. Influence of Acute Variations in Hematocrit on the QRS Complex of the Frank Electrocardiogram. *Circulation*, 44:456-465.

14. Hugenholtz, P. G. The Accuracy of Vectorcardiographic Criteria as Related to the Hemodynamic State. Proceedings of Long Island Jewish Hospital Symposium Vectorcardiography, North-Holland Publishing Company, c. 1966.

15. Brody, Daniel A. 1956. A Theoretical Analysis of Intracavitary Blood Mass Influence on the Heart-Lead Relationship. *Circulation Research*, 4:731-738.

HEMODYNAMIC STUDIES OF THE LEGS UNDER WEIGHTLESSNESS

William E. Thornton, M.D., G. W. Hoffler, M.D.
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

ABSTRACT

Following exposure to weightlessness, alterations in the return of blood from the legs play a crucial role in orthostatic tolerance and may be an important factor in work tolerance. To investigate some of the hemodynamic mechanisms involved, an experiment was performed on the Skylab 3 and Skylab 4 missions to study arterial blood flow, venous compliance, and muscle pumping of blood. Skylab 4 results are presented.

Venous compliance and arterial blood flow were determined by occluding venous flow with a pressure cuff above the knee and recording the resulting change in volume from a midcalf segment by means of a capacitance volume transducer. For flow measurements, the cuff was inflated to 30 mm Hg pressure for three 10-second periods. This sequence was repeated at 50 mm Hg cuff pressure. Flow was calculated from the initial rate of volume change. Compliance curves at 30 mm Hg pressure were obtained by inflating the cuff to this pressure for 3 minutes and recording the volume change as outlined previously; two such determinations were made at each recording. Compliance (differential volume/differential pressure) was calculated from the known pressure point on the curve.

Muscle pumping action was studied by placing the subject in lower body negative pressure at -30 mm Hg and recording volume change from a calf segment as before. After 3 minutes, the crewman made 10 maximum effort isometric contractions of the leg, waited one minute, and repeated the procedure. The amount of blood collected in the segment from the negative pressure and the amount remaining after pumping were determined.

This entire sequence of studies was performed three times before flight, seven times during flight, and three times after flight. Blood flow showed a marked average increase in all crewmen throughout the in-flight phase; wide variations were seen but no clear trend. After flight, an immediate sharp reduction, virtually to preflight values, occurred. Venous compliance demonstrated a slowly increasing compliance which reached a fivefold increase in two of the three crewmen by mission day 15, a slowly decreasing trend in all three crewmen after mission day 40, and a precipitous drop to less than preflight

values at recovery. The values for the Commander of Skylab 4 showed little change. After muscle pumping, the relative amount of blood remaining in leg veins was approximately the same during flight as before flight, but the absolute amount collected and remaining was increased several times.

It was concluded that the most likely cause of increased blood flow was an increase in cardiac output secondary to increased central venous pressure caused by blood redistribution. Changes in venous compliance are thought to be primarily changes in somatic musculature which is postulated to primarily determine venous compliance of the legs. This was also thought to be demonstrated by the changes in muscle pumping. It is thought that these compliance changes, when taken with the decreased blood volume; provide a basis for the changes seen in orthostatic tolerance, work capacity and lower body negative pressure response.

INTRODUCTION

In the next two reports I shall describe experiments which were added to the original Skylab experiment protocol long after the schedule had been fixed. Only those of you familiar with space flight scheduling and operations can appreciate the problems this causes. At the same time, the scheduling flexibility which was developed as the mission progressed produced far more valuable data than was originally hoped for. These changes became a tribute to the flight crews and management team and again illustrated the outstanding characteristic of manned space flight, the flexibility to optimize returns from an experiment or from a mission. Scheduling under such situations was critical, and if there are recognized holes in the data or crucial data points missing, it was not due to the investigators oversight but to a matter of mission priorities.

Significant among the medical findings following prolonged space flight have been reduced orthostatic tolerance and ergometric work capacity. Changes in hemodynamics of the legs with increased blood pooling and reduction in cardiac output must be considered one of the most probable causes of these effects. Concern for the above plus the observed marked tissue changes occurring in the legs during flight prompted the addition of several procedures to evaluate hemodynamic changes in the leg; resting arterial blood flow, venous compliance and muscle pumping were investigated.

The Lower Body Negative Pressure experiment recorded leg volume changes and this inherently contains compliance information. However in measuring such changes, stress is applied to a considerable portion of the body and affects many body systems capable of altering the primary leg

volume response. In so far as possible, we looked at the initial reaction to pressure in the smallest possible vein segment.

Impromptu studies were implemented during the latter portion of the Skylab 3 mission. Results were of sufficient value to include more comprehensive studies on Skylab 4 which will be subsequently described fully; for convenience, each aspect of the experiment will be completely discussed in turn, except for conclusions.

The entire series of procedures was actually performed three times preflight, seven times in-flight, and three times postflight. The minimal original in-flight schedule was further reduced by other scheduling requirements during periods critical to the experiment. Several trials were lost or severely compromised by artifacts which appeared to be electrical. Other than these problems, the data were collected without difficulty.

PROCEDURE

If an occlusive cuff placed around a limb segment is inflated somewhat above venous pressure, arterial flow will be little affected, but venous flow will be stopped until its pressure exceeds cuff pressure. If volume change is also measured, its initial rate of change with time, before appreciable back pressure develops, approximates arterial inflow (fig. 1).

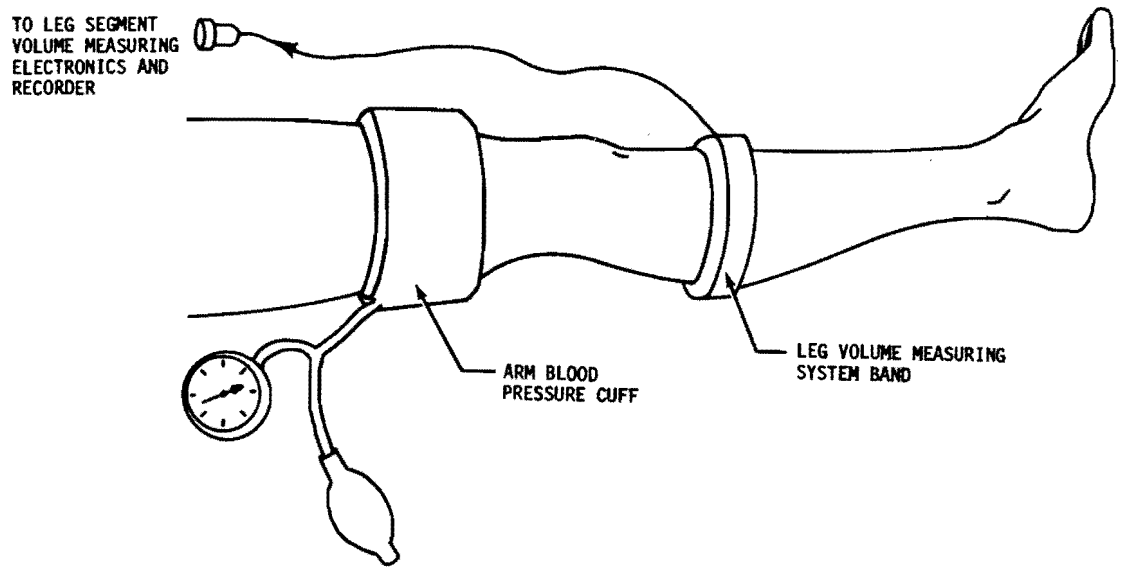


Figure 1. Arterial flow - measurement experimental arrangement.

There are several assumptions and sources of potential error in this measurement.

By waiting until the volume reaches a plateau, *i.e.*, until venous pressure equals cuff pressure and venous flow resumes, a single known value of compliance can be determined, figure 2.

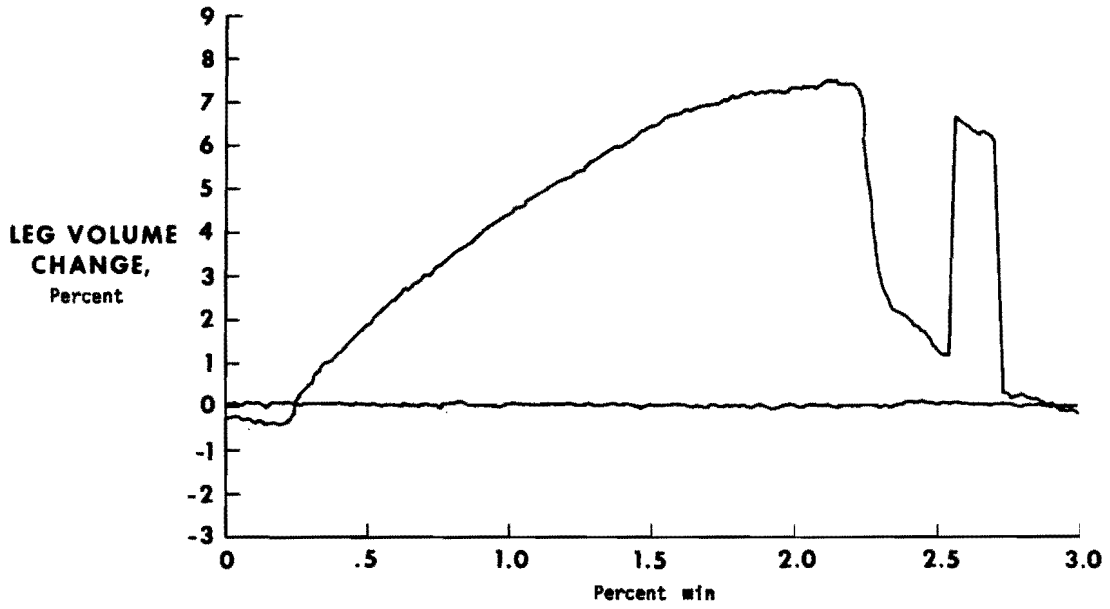


Figure 2. Venous compliance record.

Data for these two studies were obtained, as shown here, with an arm blood pressure cuff above the left knee and a capacitance limb volume measuring system band around the maximum girth of the calf. Volume changes actually measured are only those in the segment directly beneath the cuff. Volume changes of the entire leg or even calf cannot be inferred from this measurement.

Blood flow was recorded by rapidly inflating the cuff to 30 mm Hg for 20 seconds for three trials. This sequence was repeated at 50 mm Hg cuff pressure. Subjects are supine when measured under one-g.

In-flight curves from such a series at 30 mm Hg are shown in figure 3. The first volume change probably caused a small sensor position artifact which in turn shifted the baseline slightly.

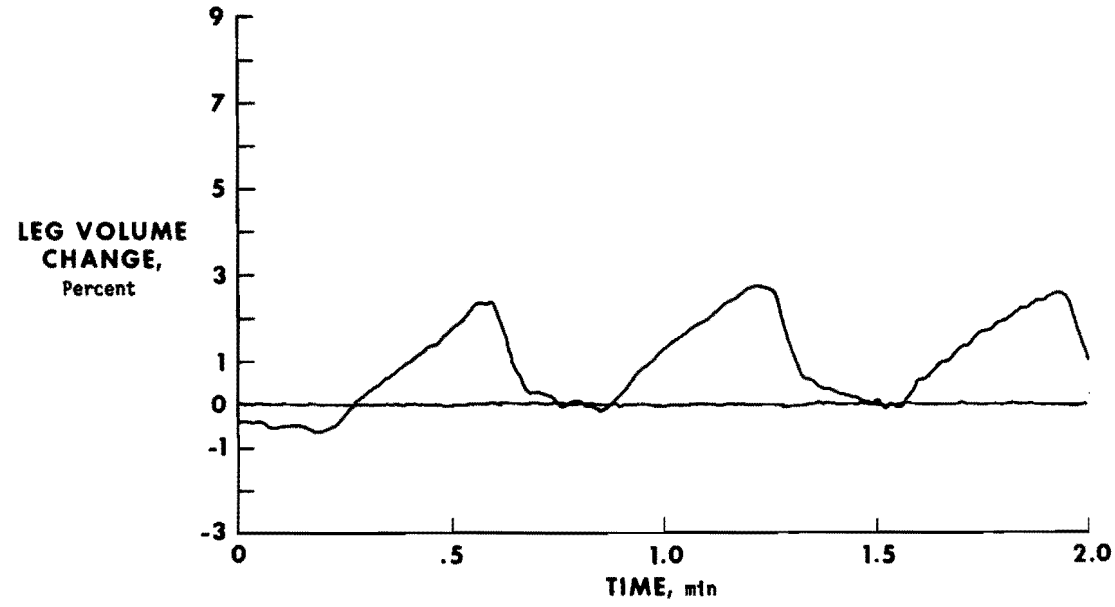


Figure 3. Arterial flow record.

Blood flow was calculated by manually drawing a tangent to the slope and measuring this slope in terms of changed volume/changed time. Usually there was an unexpected increase in volume change during cuff inflation which, in spite of the distance between plethysmograph segment and cuff, must be venous reflux. This initial slope and artifact were avoided during measurement. Another possible but unavoidable error was flow of blood from or into areas not typical of the segment under measurement, *e.g.*, the foot. Blood and fluid flows were calculated in terms of 100 milliliters of tissue under the capacitance band.

Measurements were made at both 30 and 50 mm Hg pressure (figs. 4a and 4b) to indicate the effectiveness of occlusion of the leg vessels by an arm cuff (a leg pressure cuff was not available in-flight) and which was used in all measurements. The curves generally correspond well except for the last two postflight tests from the Scientist Pilot.

DISCUSSION OF DATA

There is great variability in the in-flight data, some of which probably resulted from changes in temperature and in relationship of the time of measurement to ingestion of food and exercise. None of these

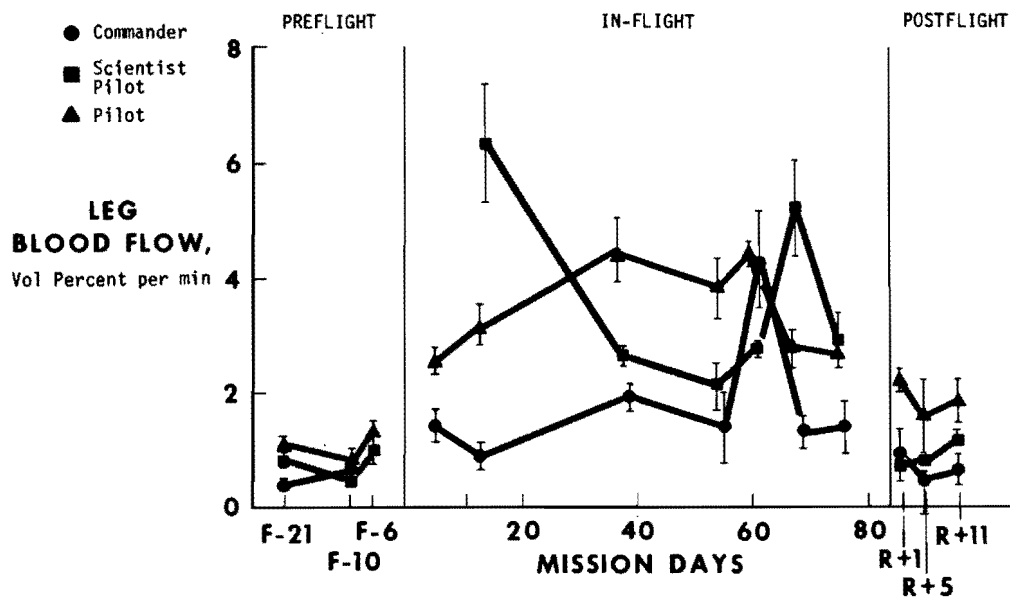


Figure 4a. Skylab 4 leg blood flow, 30 mm Hg pressure.

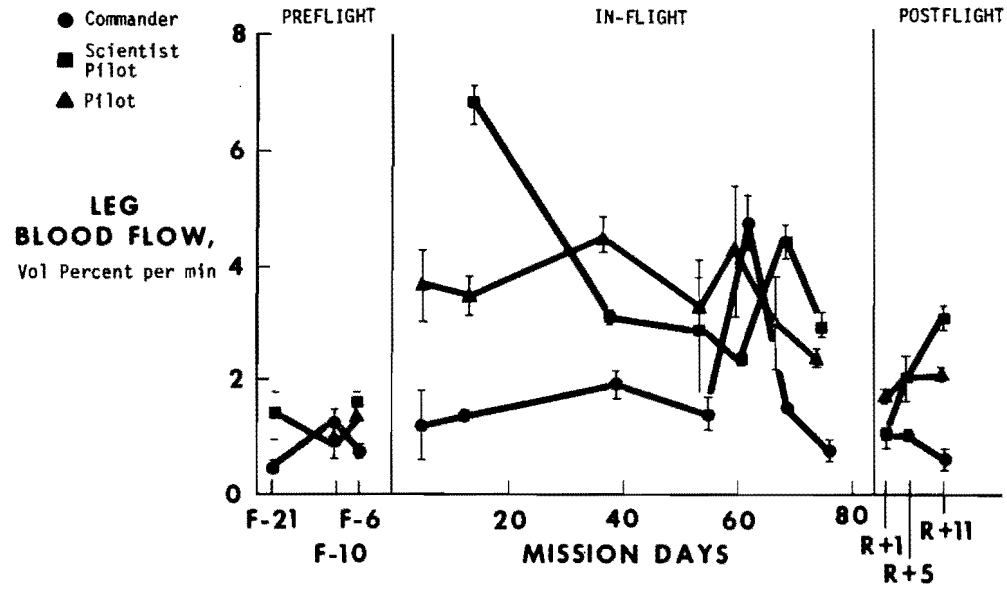


Figure 4b. Skylab 4 leg blood flow, 50 mm Hg pressure.

factors were controlled or adequately known to be properly accounted for. In spite of the variability, it seems safe to say that blood flow was elevated above preflight and postflight levels throughout the flight, and probably remained slightly elevated in the Scientist Pilot postflight.

Several possibilities should be considered for this increase in blood flow. Under one-g, an increase in muscle blood flow is seen in elevation of the legs while supine, or in other maneuvers which increased intrathoracic venous pressure, a mechanism which apparently releases sympathetic vasoconstrictor action. It will be shown in our next report (Anthropometric Changes and Fluid Shifts) that fluid and blood from the legs were shifted cephalad on exposure to weightlessness and this must have produced transient increase in venous pressures which may not have been completely restored to "normal" throughout the flight. Decreases in transmural pressure could have allowed increase in vessel size and flow, but the changes required to do this in the legs are too large to be considered under the circustances.

My own hypothesis is that cardiac output is increased secondary to an increase in the central venous pressure. While there is no hard supporting evidence for this hypothesis, several observations indicated that it may have happened.

In-flight variation was too large to allow any statements about trends. Note, however, a marked difference between the Commander of Skylab 4 and the other two crewmen. This difference was rather obvious in lower body negative pressure testing and it will be seen again in several experiments. Postflight there was an abrupt drop to just above preflight levels. This is consistent with any of the possible causes of increased blood flow which were mentioned.

Compliance is the change in volume for a given change in pressure and, in this case, it is assumed to be a change in venous volume produced by cuff pressure of 30 mm Hg or more simply stated, how much blood will be pooled in the veins at any one pressure. Let me emphasize that the compliance curve is alinear, and that this measurement is only one point on the curve from a vessel which was not completely empty at the start. Further, the exact starting pressure is not known.

Compliance for the three Skylab 4 crewmen are plotted in figure 5 in terms of volume percent change (milliliters/100 milliliters of tissue). It is obvious that more points are needed on these curves, especially in the 2 to 3 week period. It should be noted in all crewmen there was an increase in compliance that required *10 days or more* to reach a maximum. It then appeared to decrease slowly, possibly cyclically in two crewmen, until recovery, when there was an immediate fall to or

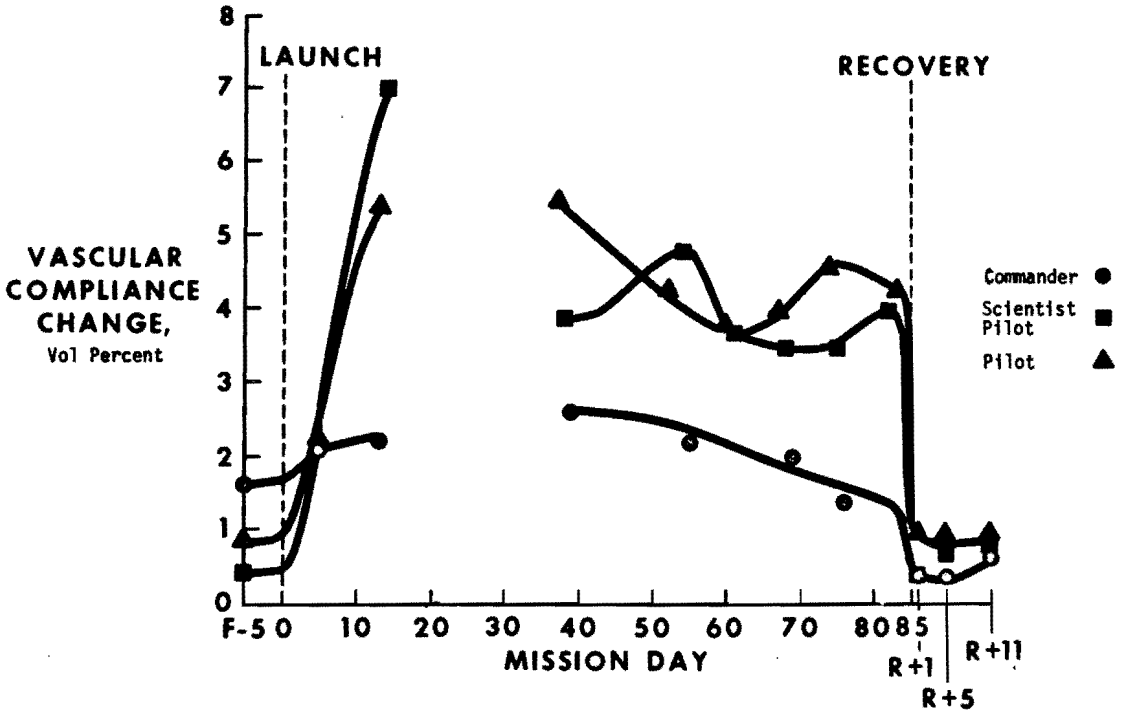


Figure 5. Skylab 4 crew vascular compliance.

even below preflight levels, with again a marked difference in Commander's response.

Before attempting to explain these results, let me give you my views of veins in the leg -- veins which may differ and behave differently from those encountered elsewhere in the body.

Figure 6 is an obviously exaggerated schematic of leg anatomy. The foot and skin of the leg are drained by unsupported veins with thick muscular walls, walls that will even go into spasm when irritated. The leg muscles are drained by much larger thin-walled conduits with little muscle or innervation; in some areas they are described as sinuses and are little more than a sac attached to the surrounding muscles. Response of such vessels should be more dependent upon the surrounding somatic muscles than upon its wall. These deep veins comprise the major venous volume - 85 percent is a commonly used value - the response that we see from the mid-calf is predominantly the response of these deep veins. There is no evidence for an increase in superficial venous volume in-flight.

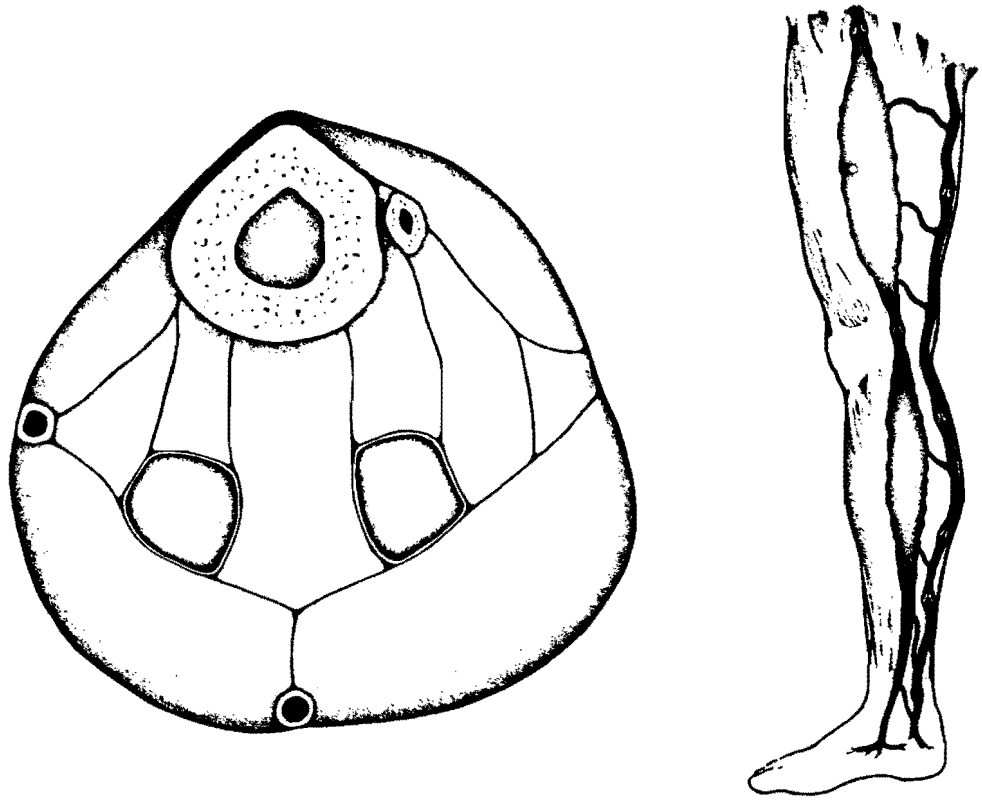


Figure 6. Distorted schematic of leg anatomy. Veins are in black.

Referring back to the responses measured, my interpretation of the changes lie in the condition of the surrounding muscles. There was a slow loss in volume of the calf segment during the first 20 days of weightlessness in contrast to the sudden loss of volume of the legs as a whole. A part of this loss was in the muscle itself. Further, with the unloading of external forces, there must have been some atrophy and a loss in muscle tone.* As the mission progressed, I suspect the body, as it always seems to do, tended to reestablish equilibrium, or "take up the slack" if you will, such that effective tone was increased in-flight and very sharply increased on being resubjected to one-g. Working a muscle, as it was experienced on recovery, causes an increase in fluid volume which may have been effective here.

Additional hemodynamic information was obtained by having the crewmen perform muscle pumping under negative pressure (fig. 7). After an experiment M092 test, the subject was left in the lower body negative pressure device and -30 mm Hg pressure was applied for three minutes causing blood to pool, again assumed to be primarily in the deep veins.

*It may be coincidence but work on the treadmill with heavy calf loading did not start until mission days 8 to 10.

At the end of this time, the subject made ten maximum effort isometric contractions of his legs. These contractions caused large pressure forces to develop against the blood in the deep veins which forced it into the central circulation through one-way vein valves. Time was allowed for an additional pooling to occur and the procedure was repeated.

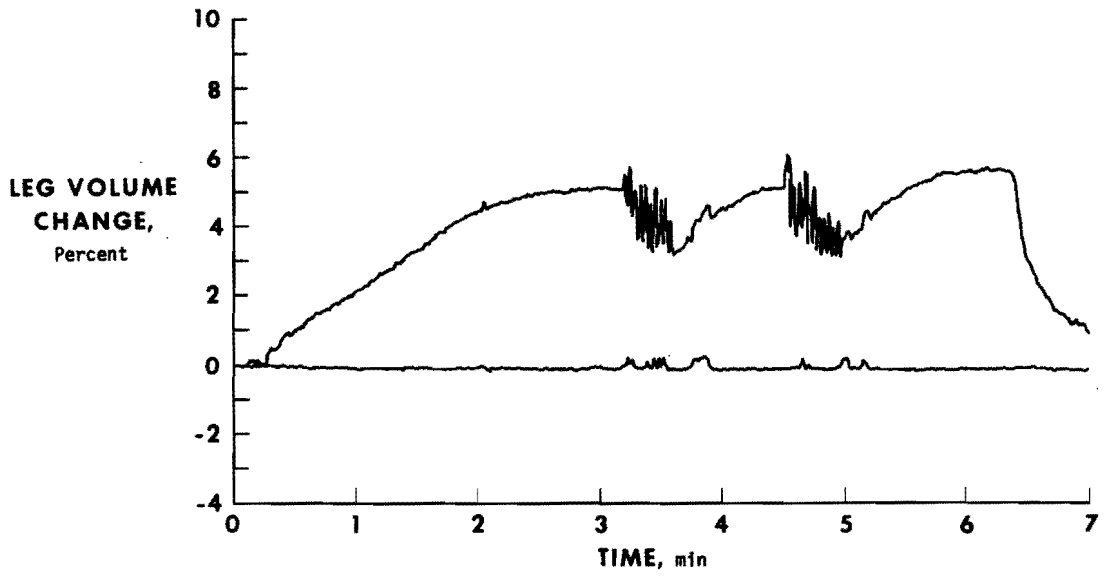


Figure 7. Muscle pumping record.

The volumes of blood accumulated and the amount remaining are plotted in figure 8, for two subjects in-flight - the Scientist Pilot and Commander. The Pilot's responses, which are not shown, were generally similar to those of the Scientist Pilot. The amount of blood pooled was generally comparable to that pooled by cuff occlusion at 30 mm Hg pressure (figs. 4a, 5). The one "wild point" of the Scientist Pilot bothers me; try as I might, I cannot discredit it, so it remains. Again, the amount of blood pooled by the Scientist Pilot is roughly two times that of the Commander; however, after muscle pumping both have the same volume remaining. While this may be sheer coincidence, I suspect there is an anatomical difference in the Commander's deep venous structure. Postflight there was a marked and immediate decrease in the amount of blood pooled while effective pumping action was still present.

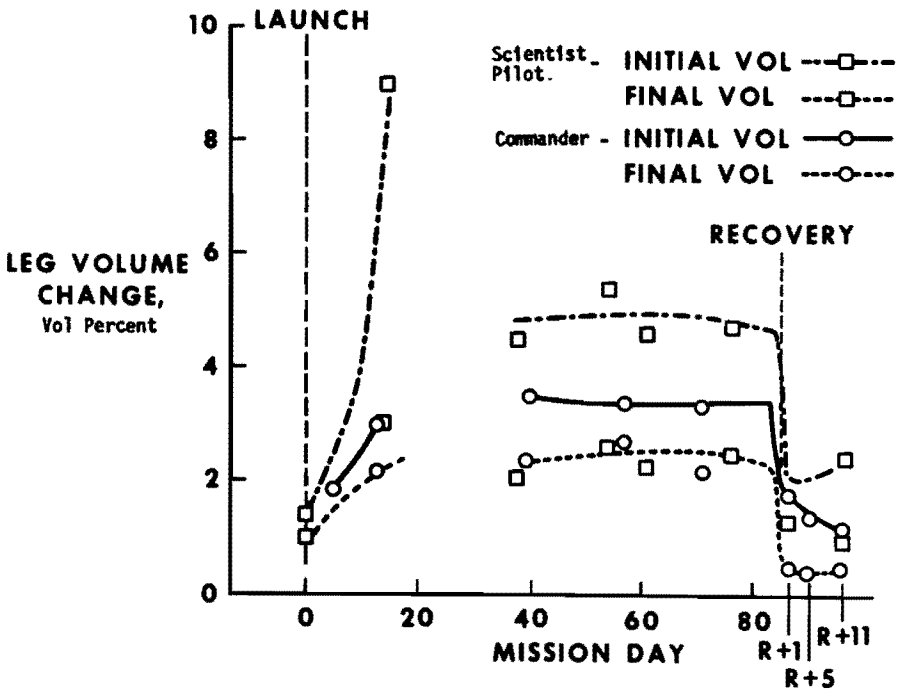


Figure 8. Skylab 4 crew leg volume changes from muscle pumping.

Under one-g, a subject typically removes about 50 percent of pooled volume from his calf, while thigh pumping is relatively less effective. About the same percentage is removed in-flight. The Commander's postflight pumping was less effective than his preflight average, and preflight and postflight efforts were relatively less effective than his in-flight pumping, which suggests that he has less deep venous volume capacity. This variance is further supported by blood volume studies and is discussed under anthropometry.

How do these findings relate to crewmen in space flight? The Skylab 4 crew confirmed the prompt postflight return to baseline seen in the measurements of this experiment by standing and walking easily for long periods on the day after recovery. The deficiencies were only detectable by the lower body negative pressure and ergometric tests and these also quickly returned to normal.

It would appear that the general shape of the compliance curve for this flight (fig. 5) agreed with the experience of the crew and with the number of times the runs were prematurely ended. The crew felt that the test became increasingly stressful and then the stress declined. Abortion of lower body negative pressure tests also appeared to cluster within this one four-week period. The effects of a decreasing blood volume and red cell mass and increased compliance are probably the two fundamental parameters in lower body negative pressure response.

However, there are a host of factors, even and especially psychological factors, that can affect the compliance curve, to say nothing of final systemic responses.

While it was gratifying to have the importance of venous changes and especially compliance so impressively recognized in the paper on lower body negative pressure, compliance and fluid volumes should not be over-emphasized at the expense of other mechanisms. Although I consider these fundamental, a great host of others remain to be explored.

I would question the concept of significant changes in compliance being caused by empty and flattened veins. As I will show in the next report on Anthropometry, leg veins were not empty, at least the superficial leg veins were not.

Secondly, I question the concept of compliance or potential volume spaces being changed by sleep in weightlessness which seems counter to common experience and to measurements done during Skylab, when muscular activity was shown to increase muscle volume. This activity would reduce potential venous volumes, especially of the deep veins enclosed with the muscles in fascial compartments. Muscle pumping is a very transient phenomena and removes only a portion of the blood. Thus I would look elsewhere for the short term variations in response to lower body negative pressure.

CONCLUSION

In summation: Changes in blood flow were demonstrated, which I think make the problem of obtaining cardiac output data in space even more imperative.

Venous compliance changes were demonstrated which, with blood volume changes, should provide an initial and primary point of departure for investigation of the complete response to lower body negative pressure. Time course of the compliance changes should be considered by mission planners. Shuttle reentry, for example, will fall within the zone of increased sensitivity to orthostatic stress. There was a demonstration of a marked difference in individual response on Skylab 4, which might also be considered in some flight operations. Since compliance of the leg vessels appears to be intimately related to leg muscle, this relationship should be properly investigated. Muscle condition may have played a major role in the slower return to normal of the crews of Skylab 2 and 3. In the future, proper cognizance should be given to such venous studies in bed rest, especially of the deep veins as both the medical community and NASA stand to benefit by such studies.

In conclusion, another portion of man's body has been demonstrated to be capable of making adaptations to weightlessness, which produces both stability under weightlessness and rapid re-adaptation on return to one-g. This bodes well for future manned flights.

ACKNOWLEDGEMENTS.

Great appreciation is due the Skylab 3 and 4 crews on this experiment for they performed the in-flight measurements in an excellent fashion with little training on Skylab 4 and no training at all on Skylab 3. Col. Richard Gowen gave a good deal of aid in insuring accurate calibration of the leg bands. Without the support of Bill Schneider and others in the flight management team this work could not have been scheduled.

ANTHROPOMETRIC CHANGES AND FLUID SHIFTS

William E. Thornton, M.D., G. W. Hoffler, M.D. and J. A. Rummel, Ph.D.
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

ABSTRACT

Several observations of body size, shape, posture, and configuration were made to document changes resulting from direct effects of weightlessness during the Skylab 4 mission. These measurements constitute two broad, overlapping categories: anthropometric changes and fluid shifts. Direct anthropometric measurements of limbs and trunk were made from each crewman before, during, and after flight. At the same time, photographs were made of each crewman in the anatomic and relaxed position. Infrared augmented film, which emphasized superficial venous patterns, was used for these photographs. Center-of-gravity and center-of-mass determinations were also made.

After the crewmen were placed in orbit, a number of anatomical and anthropometric changes occurred including a straightening of the thoracolumbar spine, a general decrease in truncal girth, and an increase in height. Relaxed posture resembles that of a quadruped. Some slight trends toward preflight morphology were seen during the latter half of the mission with a prompt return to preflight configuration on recovery.

The series of accurately located limb girth measurements allowed volume determinations of arm and leg segments. By the time of the earliest in-flight measurement on mission day 3, all crewmen had lost more than two liters of extravascular fluid from the calf and thigh. The puffy facies, the "bird legs" effect, the engorgement of upper body veins, and the reduced volume of lower body veins were all documented with photographs. Center-of-mass measurements confirmed a fluid shift cephalad. This shift remained throughout the mission until recovery, when a sharp reversal occurred; a major portion of the reversal was completed in a few hours.

The anatomical changes are of considerable scientific interest and of import to the human factors design engineer, but the shifts of blood and extravascular fluid are of more consequence. It is hypothesized that the driving force for the fluid shift is the intrinsic and unopposed lower limb elasticity that forces venous blood and then other fluid cephalad. This shift may be the driving force for a number of other phenomena, including blood volume loss and changes in leg hemodynamics, and should be considered in the vestibular area and

other problem areas. This phenomenon should also receive proper cognizance in bed-rest and other future simulation studies.

INTRODUCTION

Man's body, both as a species and as an individual, has been shaped by continuous exposure to gravity and a large portion of it is dedicated to more or less continuously opposing gravitational forces. One could confidently predict that placing the human body in weightlessness would produce changes in size, shape, and composition. Many of these changes and their effects were described by astronauts from the earliest days of space flight, for example; puffy faces, stuffy noses, engorged head veins, low back discomfort, and the "bird legs" of space.

The anthropometric studies in American space programs prior to Skylab were:

- Preflight and postflight leg volume measurments on the later Apollo flights.
- Stereophotogrammetry of the crew preflight and postflight on Apollo 16.

On Skylab only leg volume measurements, and stereophotogrammetry preflight and postflight, and maximum calf girths in-flight were originally scheduled.

In an effort to obtain the most comprehensive and coherent picture of changes under weightlessness, we initiated a set of measurements on Skylab 2 and, at every opportunity, added additional studies. All pertinent information from ancillary sources, even news photographs was gleaned and collated.

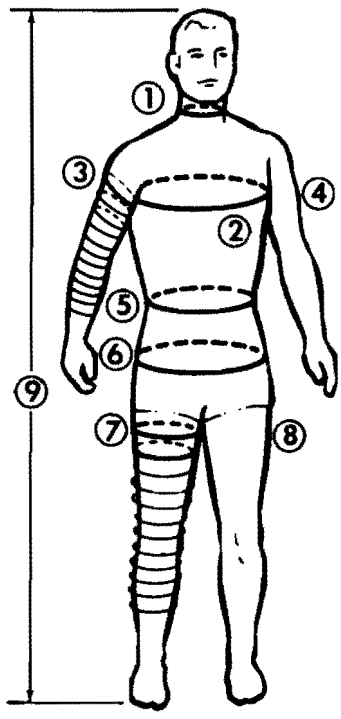
On Skylab 2, the initial anthropometric studies were scheduled in conjunction with the muscle study presented at the session this morning and consisted of direct limb girth measurements for limb volume and trunk girths. A single set of facial photographs was made in-flight. Like measurements were continued on Skylab 3, with additional photographs and truncal and limb girth measurements in-flight.

Prior to Skylab 4, a few of us felt there was considerable evidence for large and rapid fluid shifts, so a series of in-flight volume and center of mass measurements and infrared photographs were scheduled to be conducted as early as possible in the Skylab 4 mission.

A number of changes were properly documented for the first time, most important of which were the fluid shifts. The following description of Skylab anthropometrics will address work done on Skylab 4 primarily.

PROCEDURE

The series of direct anthropometric measurements shown in figure 1 were made preflight and postflight on all missions, and in-flight on the Skylab 4 mission. Leg and arm girth measurements were made every three centimeters by means of a calibrated tape jig attached to the limb to insure accurate location. As part of their experimental protocol, Drs. G. W. Hoffler and R. L. Johnson made such leg measurements preflight and postflight on Apollo and Skylab and, to avoid repetition, data from these measurements were shared on Skylab. We extended their technique of measurement to include the arms on all Skylab missions and preflight and postflight. The in-flight limb measurements on Skylab 4 were made with an unattached single tape and a calibrated longitudinal tape.



① NECK-CIRCUMFERENCE AT LARYNX

② CHEST-CIRCUMFERENCE AT NIPPLE (INSP AND EXP)

③ ARM VOLUME (GIRTH EVERY 3 cm)

④ ARM VOLUME (GIRTH EVERY 3 cm)

⑤ ABDOMINAL CIRCUMFERENCE AT UMBILICUS

⑥ HIP CIRCUMFERENCE AT GREATEST DIAMETER

⑦ LEG VOLUME (GIRTH EVERY 3 cm)

⑧ LEG VOLUME (GIRTH EVERY 3 cm)

⑨ HEIGHT

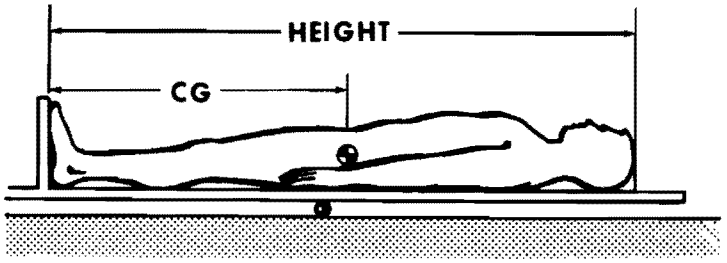
Figure 1. Anthropometric measurements of Skylab crewmen.

For general documentation, a series of preflight, in-flight and postflight front, side and back photographs were made with the crewmen in standard anatomical position; and to note postural changes, an in-flight series of photographs were made with the crewman completely relaxed and free-floating. An infrared sensitive color film was used in an attempt to document the superficial venous blood distribution.

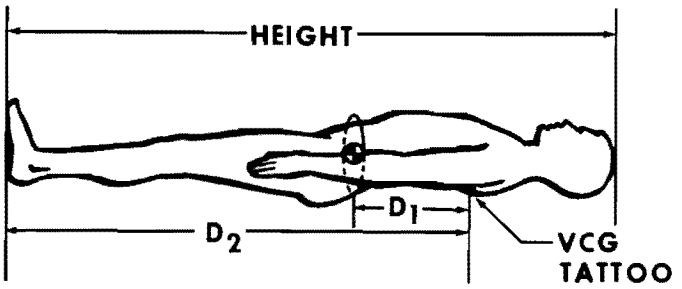
The infrared film had poor resolution and at the last minute, 35 mm was substituted for 70 mm film further reducing resolution. Quality of the in-flight anatomical and postural photographs suffered. However, with diligence, a good deal of vascular detail could be determined that would not have been available on ordinary film.

In an effort to devise a simple way to indicate fluid shifts, center of mass and center of gravity measurements were made (fig. 2). A teeter board was used for these measurements on Earth.

In-flight it was possible to obtain center of mass directly by tying a cord around the subject and then pulling the cord at right angles to the subject. If the cord was anywhere off the center of mass the subject would tilt. The crew claimed this scheme was accurate to a few millimeters.



ONE-G CENTER OF GRAVITY MEASUREMENT



ZERO-G CENTER OF MASS MEASUREMENT(in Weightlessness)

Figure 2. Techniques used to measure center of gravity and center of mass at one-g and in weightlessness (Skylab 4).

Let's look first at the in-flight changes that occur.

OBSERVATIONS AND DATA

Figures 3 and 4 show a preflight and postflight front view of a Skylab 4 crewmen. Although these are third generation copies, one is able to see arm venous pattern clearly.

The Commander of Skylab 3 is shown in-flight in figure 5. In one of the anatomical films, I thought that he had done a military brace in spite of his denials, for he isn't that trim and erect under one-g. Note the abdomen and ram rod spine. Also note, the jugular full to the angle of the jaw and other head veins.

Figure 6 is an in-flight photograph of the subject free-floating and relaxed. Relaxed postural changes varied somewhat throughout the flight and from individual to individual; tracings, figure 7, from in-flight photographs of the Scientist Pilot of Skylab 4 are typical of changes seen.

The spinal column was flexed with loss of the thoracolumbar curve but with retention of the cervical curvature, such that the head is thrust forward. Both upper and lower limbs have moved toward a quadruped position. Postflight, there was surprisingly little change from preflight posture.

Figure 8 are plots showing what gravitational unloading does to truncal size. The Pilot of Skylab 4 had the largest changes with gain of some two inches in height and loss of four inches in abdominal girth. Chest girth was also initially reduced in both inspiration and expiration, but trended toward "normal" in-flight. Postflight, which is poorly shown in these figures, there was a more or less rapid trend toward preflight values. It seems that most of the increase in height was caused by expansion of the intervertebral discs which were unloaded. This stretched the torso and probably aided in reduction of abdominal girth. Abdominal viscera may be considered semiliquid, and when their weight was removed the normal tone of abdominal muscles moved them in and upward. Changes in chest girth are not so easily explained, but if the spinal column moved upward without a similar anterior elevation of the sternum, then the rib (costovertebral) angles is increased, effectively reducing thoracic girth. Changes noted in the Commander were virtually the same as those noted in the Scientist Pilot.

There was considerable evidence of large and rapid shifts in fluid from the lower to upper body prior to Skylab 4. Indeed, no subject has

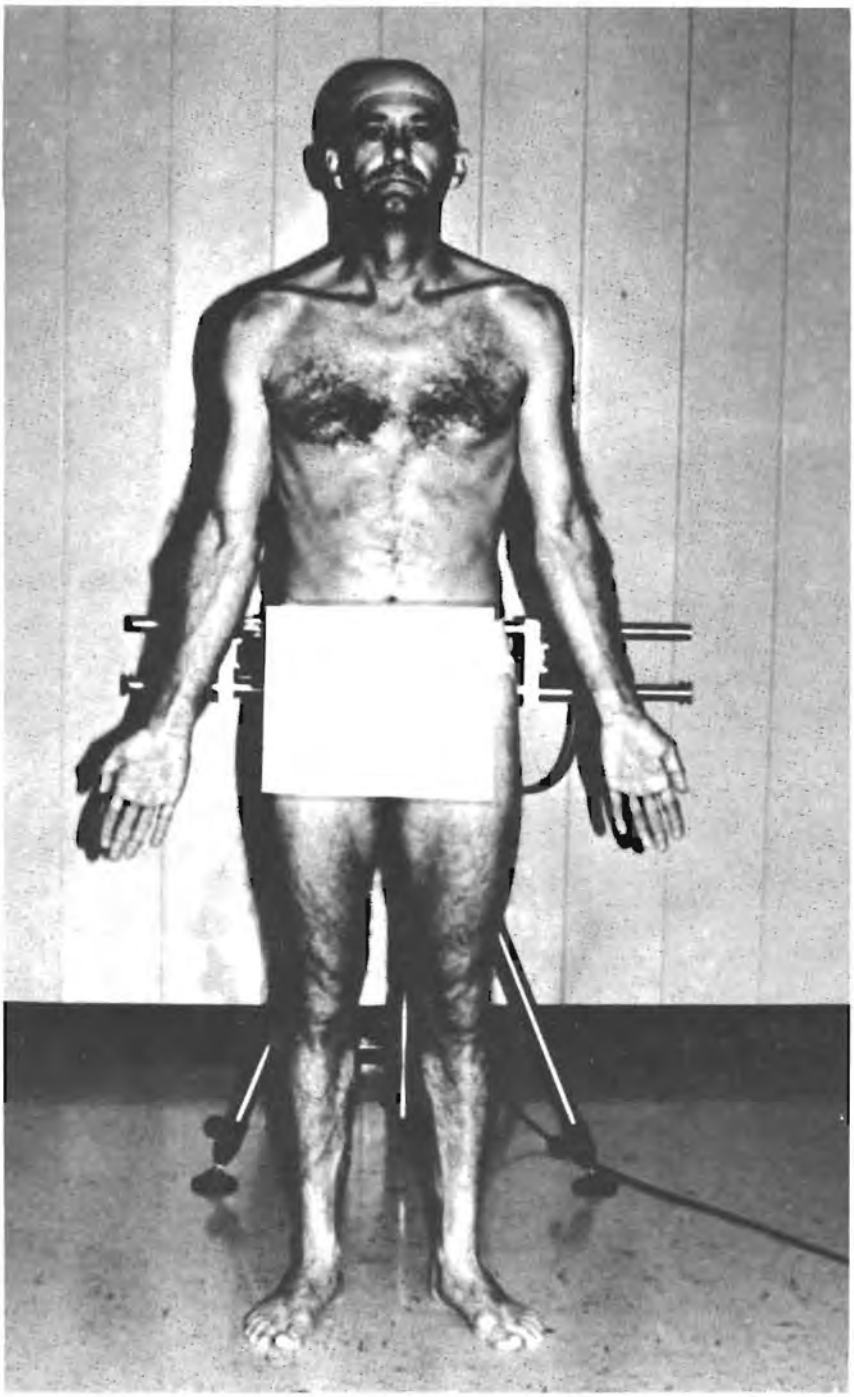


Figure 3. Preflight (color) anatomical photograph of Skylab 4 crewmen with infrared augmented film to enhance superfical venous pattern.

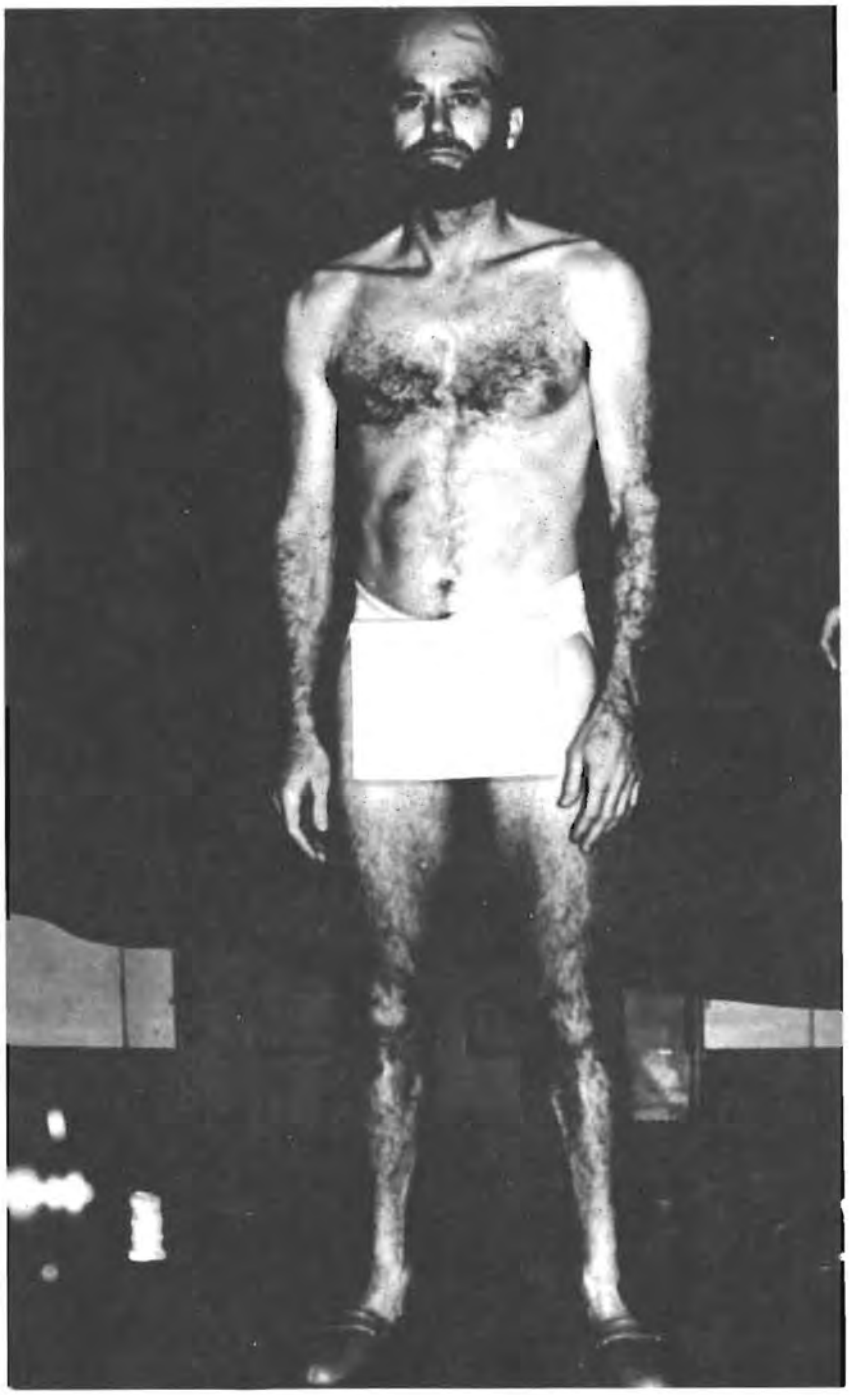


Figure 4. Postflight anatomical photograph, Skylab 4 crewman.

Figure 5. Photograph of the Skylab 3 Commander showing posture and full head and neck veins.

Figure 6. In-flight astronaut free floating and relaxed.

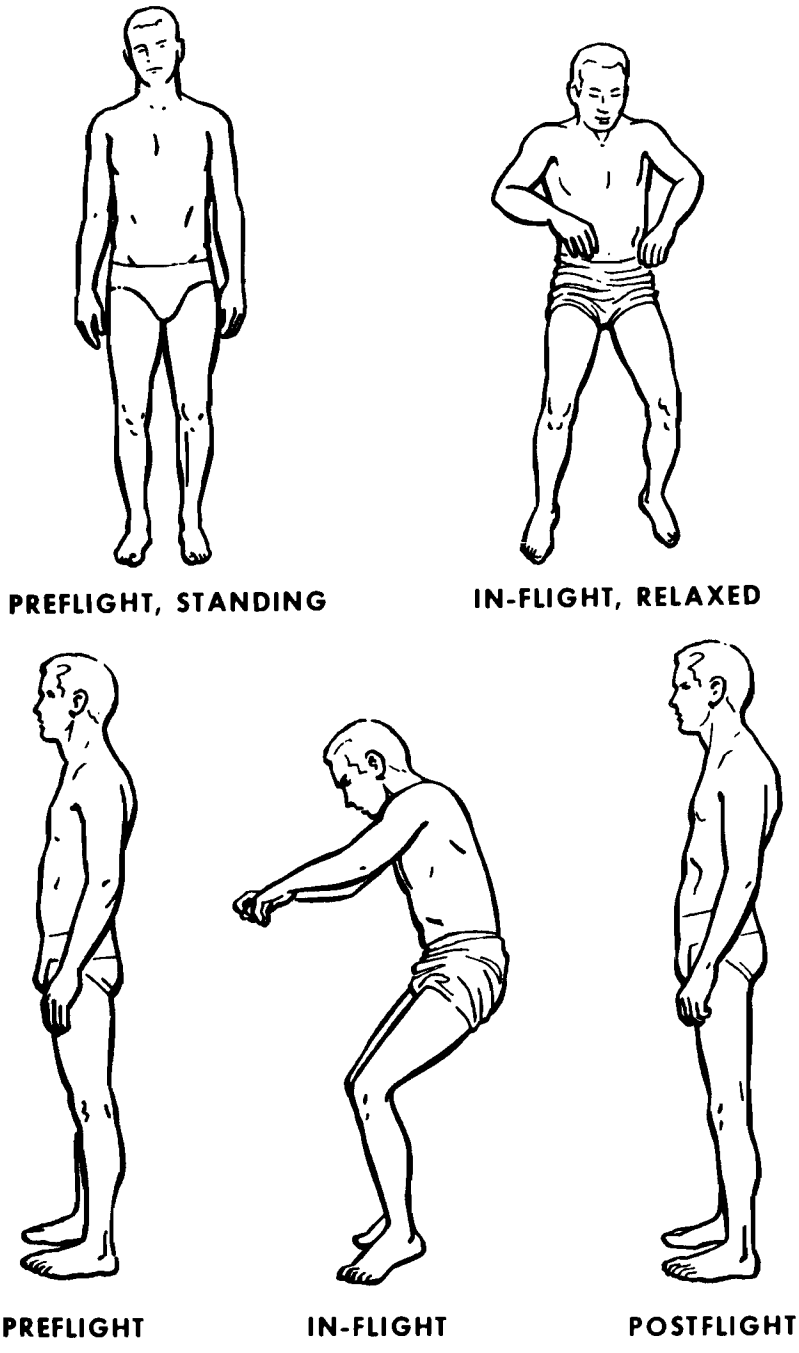


Figure 7. Postural changes, Skylab 4 Scientist Pilot.

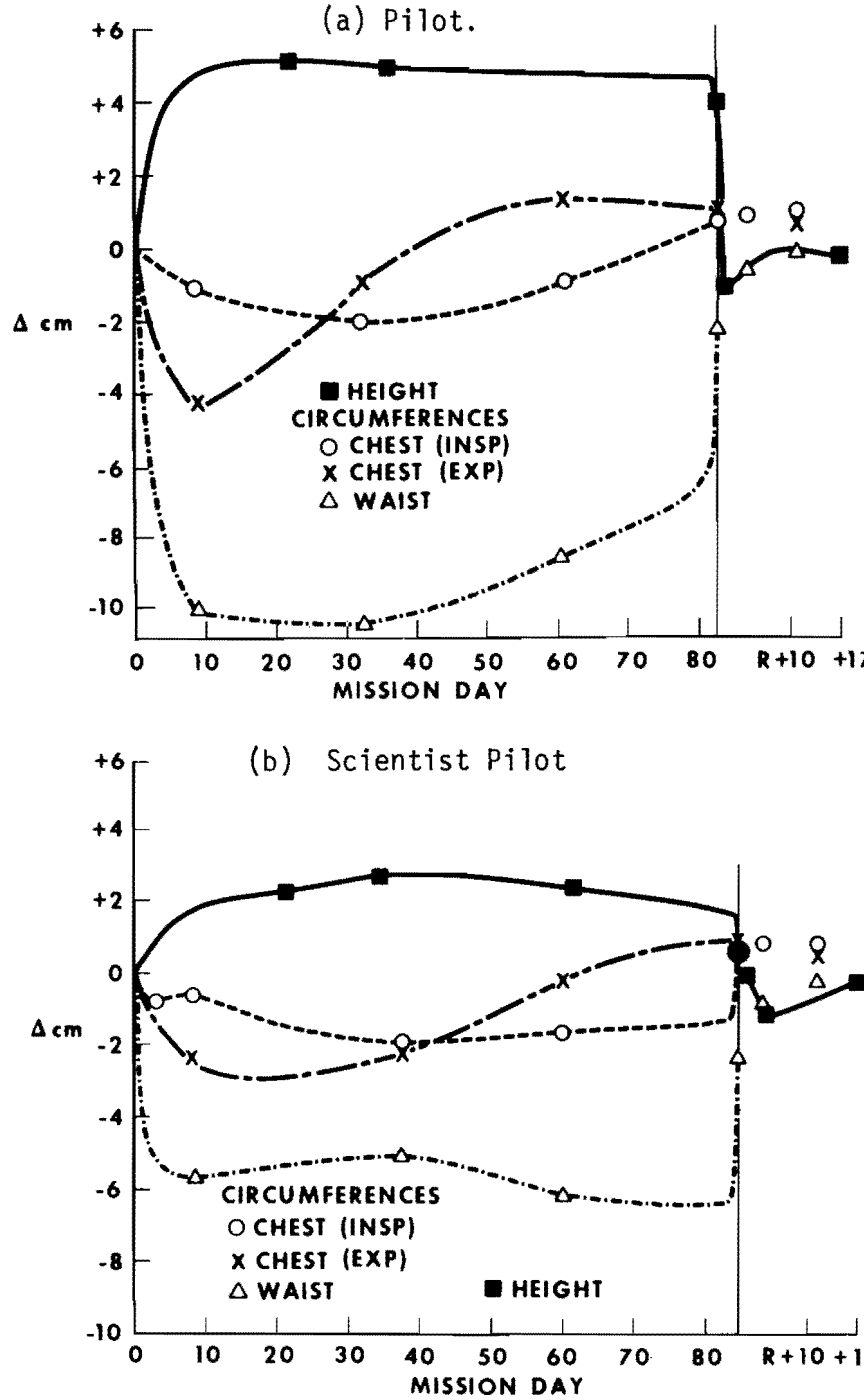


Figure 8. Plot showing in-flight and postflight anthropometric changes, Skylab 4.

been discussed more in space physiology; nevertheless, virtually no one was willing to accept it. Such large and rapid shifts seemed to be contradicted by the relatively small gains in postflight leg volume which obviously contained tissue increases. Single midcalf girth measurements on Skylab 2 and 3, in-flight were also misleading for they indicated much smaller and slower changes consistent with a predominant component of muscle atrophy.

There was obviously no way to prove the point without data and to do this during activation of an already overscheduled mission was the toughest job I tackled. Thanks to Messrs. Richard Johnston, Kenneth Kleinknecht and others, and above all, the crew, this data was gathered - not as much as desired, but to gather from the papers presented today, apparently enough to convince all concerned. Leg and arm volumes were calculated by measuring the girth of each three-centimeter segment and treating it as a tapered cylinder, then summing these volumes.

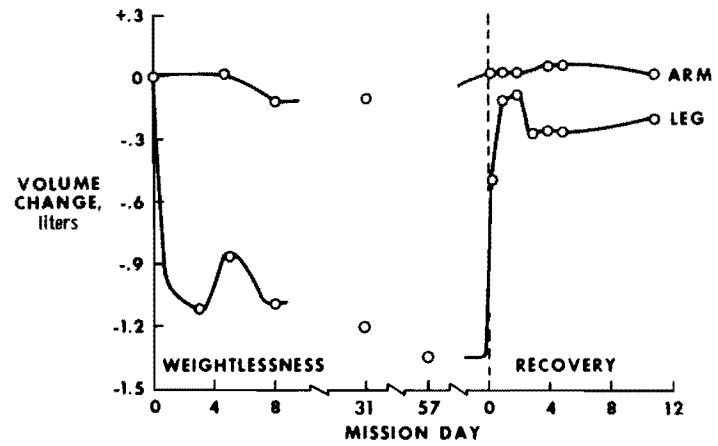
Mission day 3 was the earliest possible that these measurements could be scheduled, although it is a measurement which should have started within hours of orbital insertion; even then, only two crewmen performed these measurements on mission day 3. Figure 9 shows that there is a rapid loss in leg volume; the curves on these plots are only estimates, and I suspect the shift was essentially over by the first day. Remember these are changes in one leg only and on mission day 8 total change was approximately 2 liters and 13 percent of total leg volume for each crewman.

Note that on recovery the majority of the increase in leg volume was complete by the time of first measurement on the day of recovery; or within a matter of hours after reexposure to one-g.

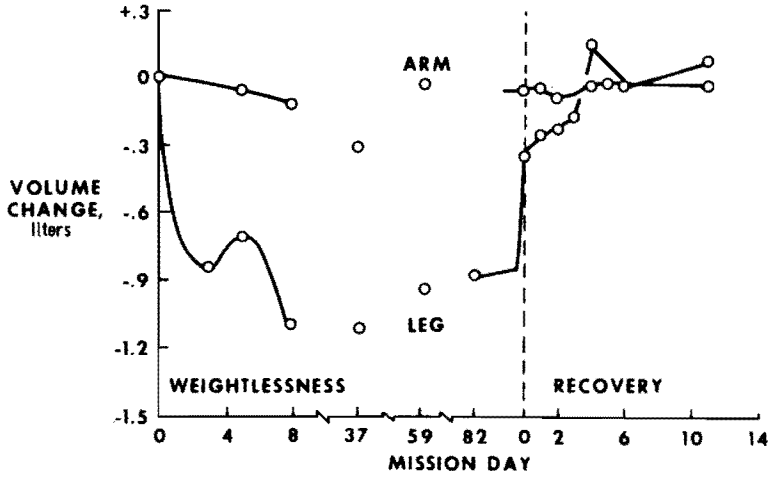
I agree with Dr. Michael Whittle that the slower postflight trends show tissue replacement. Somewhat to my surprise, the arms showed no evidence of fluid shift and the changes seen were small and probably related to metabolism.

Where did this fluid go? There was no weight loss in two of the three crewmen compatible with loss of this amount of fluid.

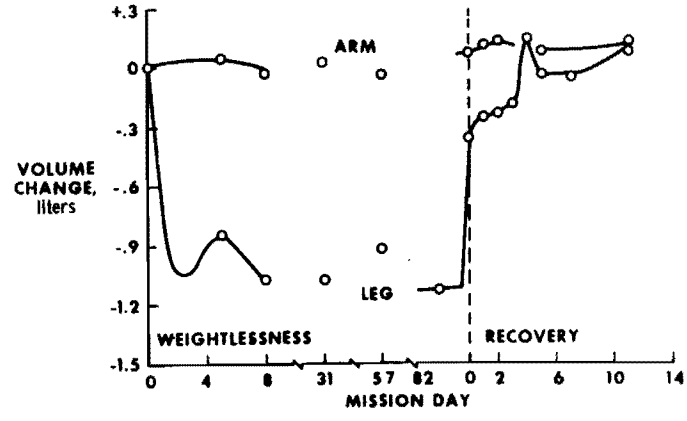
Center of mass measurements were scheduled on this flight primarily to follow the time course of fluid shifts, since only minutes were required for the measurement. Unfortunately, schedules were changed such that the points of real interest were over before the first measurement could be made. Figure 10 is a plot of the center of mass, the upper curve shows the center of mass changes and the complication by the increase in height, shown in the lower curve. Center of mass



(a) Commander



(b) Scientist Pilot



(c) Pilot

Figure 9. Change in left limb volumes, Skylab 4.

shifted cephalad more than could be accounted for by the height increase which is another small confirmation of fluid shift.

We have long had astronaut objective and subjective descriptions of puffy facies, head fullness and other symptoms of increased fluid in the head.

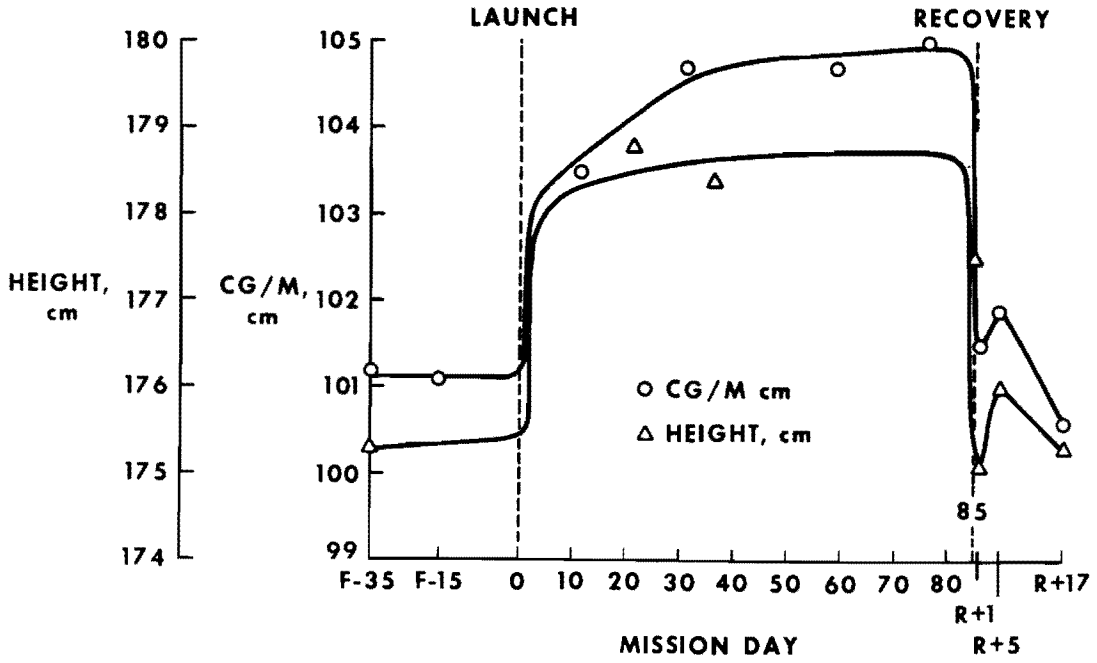


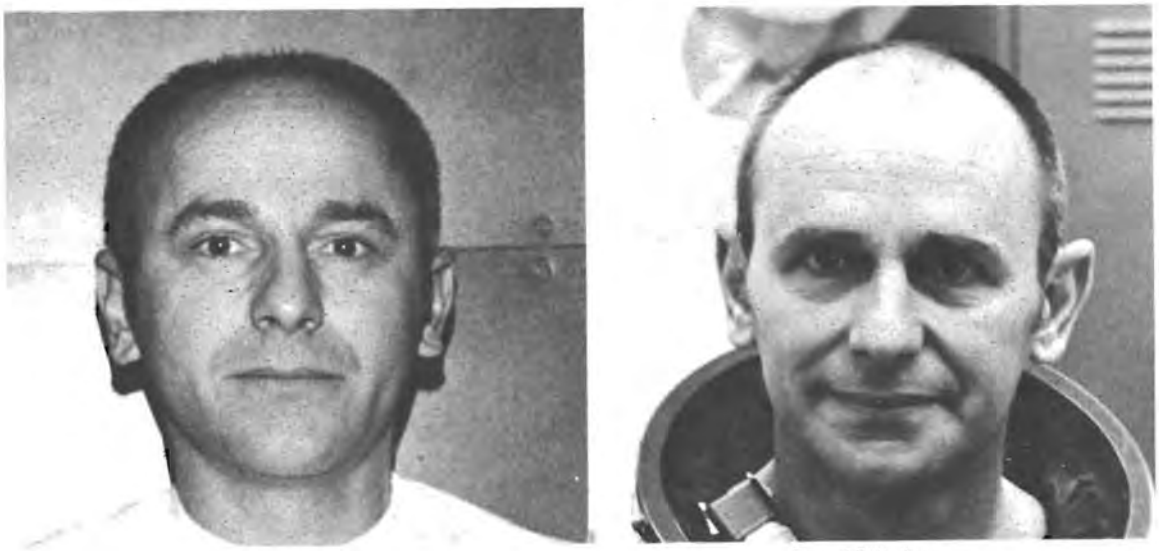
Figure 10. Center of gravity/center of mass, Skylab 4 Pilot.

Finally, there are the photographs. While these do not allow quantitation, they provided powerful evidence for increased fluid in the head and neck region.

Figure 11, a photograph of the Pilot on Skylab 2, was the first taken for this purpose. Although it is slightly distorted it still demonstrates the puffy facies - note the thickened eyelids. This in-flight photograph was made near the end of the mission and demonstrates that this type of edema and venous congestion still remained.

Next, figure 12, is a picture of the Commander of Skylab 3 with the preflight view on the right-hand side; again the in-flight photograph was made near the end of the mission. Although angle and lighting differ, I believe the difference in facies are apparent.

Figure 11. Skylab 2 Pilot showing the puffy facies still present toward the end of the mission.



In-Flight Preflight

Figure 12. Skylab 3 Commander comparing the puffy facies in-flight to the normal facies preflight.

Finally, we have the assessment of the infrared photographs. Original plans were to machine analyze the superficial venous pattern, but the quality was too variable, therefore, only a qualitative assessment was made. However, several features were obvious. From first through the last mission the following was observed in all in-flight photographs of the crewmen:

- Only superficial veins were visualized
- Foot and lower leg veins were not distended as they are when standing under one-g.
- They were not completely empty for the dorsal arcade of the foot and digital branches were easily seen with the infrared film.
- Calf veins were not distended but were still visible.
- Several superior branches in the anterior thigh were moderately full.
- Little difference could be seen between preflight and in-flight patterns of the trunk and upper arms. Hand and forearm veins were well filled and distended in-flight. This surprised me since superficial arm veins, like those of the leg have increasing amounts of wall muscle as they become more distal.
- Jugular veins were always completely full and distended as were veins of temple and forehead.
- Postflight, there was a prompt reversion to preflight pattern, however, foot and lower leg filling appeared to be less in the early recovery period.

Changes in mass have already been discussed and are obviously related to the changes seen here.

It was not possible to document body composition changes with specific gravity and other measurements. Observation of all crews, and especially those on Skylab 2 and 3, left the impression that loss of fat had occurred, except for the Commander of Skylab 4. Radioisotopic studies by Drs. P. C. Johnson and C. S. Leach confirmed an increased loss of fat by all crewmen except the Commander of Skylab 4.

DISCUSSION

What is the importance of the changes observed under weightlessness? The major changes are reviewed in table I.

TABLE I. MAJOR ANTHROPOMETRIC CHANGES

Truncal

	Cause	Effect
Change in Height	°Reduced load on spine with	°Pressure suit entry and fit
	Loss of thoracolumbar curvature	°Fit of other personally fitted gear
	Expansion of intervertebral discs	°Possibly changes thoracic cage
Reduction in Waist Girth	°Weightless abdominal contents are pushed "in" and "up" by unopposed tone of abdominal muscles	°Probably alteration in respiratory function and capacity
		°Change in internal structural relations
Reduction in Chest Girth	°Possible increase of costal angle from increase in spinal length	°Possible alteration in respiratory function and capacity

Change in height is as much a conversation piece as anything else. One crewman, for example, is shorter than his wife and was elated to find in flight that he was finally taller. Postflight there was an undershoot, and he came home to her on the third day postflight shorter than ever. Such changes provide new data points for those studying the human skeleton and, hopefully, will add to the knowledge of it.

In future flight, allowances may have to be made in custom fitted gear. For example, small height increases greatly increase the difficulty of donning pressure suits; these difficulties may show up in the time and motion studies on Skylab.

Reduction in waist girth with cephalad shift of abdominal viscera probably alters maximum lung volumes but to no great extent. Vital capacity is reduced by lying down in one-g and the effects are somewhat analagous. Apparently it did alter some internal relationships for at least one crewman felt that running and jumping on the treadmill produced unpleasant jouncing of gastric contents. One could speculate on the effects that such shifts would have on pathological processes of the bowel - *e.g.*, hiatus hernia or a perforation. It is hardly necessary to comment on the changes in chest girth which were small.

In-flight postural changes are listed in table II. These postural changes have two significant considerations. Human engineering should allow for the most efficient work positions in the future. For example, a chair designed for use in one-g to support the weight of legs and torso, is not shaped to provide good passive support in weightlessness. The body has to be forced into such a position by use of a tight waist restraint. Secondly, these changes under weightlessness should be of interest to those making theoretical studies of postural mechanisms and the like and provide them with new data points.

TABLE II. IN-FLIGHT POSTURAL CHANGES

Relaxed

	Cause	Effect
Flexion of thoraco-lumbar spine with cervical curvature preserved	°Removal of anterior center of gravity with unopposed forces of vertebral musculature	°Pushes head anteriorly and inferiorly making new position
Legs are semiflexed	°Tilt of pelvis secondary to flexion of spine - unbalanced weightless legs with imbalance of resting muscle forces	°Renders one-g seating unsuitable for zero-g since body must work to maintain such positions
Arms are elevated	°Weightless arms with imbalance of resting muscle forces	°This with flexion of back puts arms and head in unusual relationship for work or study

Fluid shifts are of more importance. Although tissue fluid and blood shifts are so closely interrelated as to be difficult to separate, I feel something is gained by treating them separately. Blood shifts occur rapidly; they begin seconds after change in forces but their long term effects may last months.

Standing upright under one-g, veins and arteries below the heart have increasing hydrostatic pressure as the veins descend toward the feet where the force may be 80 to 100 mm Hg. Shortly above the heart, the venous pressure becomes zero and the vessels are virtually empty and at least partially collapsed. Under weightlessness, without this superimposed hydrostatic pressure, venous pressure, except for negligible flow pressures, are the same throughout the body. Volumes are now shifted only in response to the compliances, the tension if you will, of the various areas of the venous systems. The result is that we have essentially central venous or right atrial pressure throughout the entire venous system. Veins such as head and neck which are normally empty, fill until their back pressure is equal to that of the pressure in, for example, a foot vein, which develops the same pressure

at a much smaller volume. When a subject stands from a lying position under one-g, a nominal 700 milliliters of blood goes into the legs and probably a comparable volume is shifted centrally. Most of this blood volume moves to that undefined "central volume" and produces a small increase in pressure with a probable effect of increasing cardiac output.

A second result of the fluid shift produces results that are more obvious and therefore more easily to document. Certain body sensors detect this as an abnormally large volume and cause plasma to be reduced thus leaving high hemoglobin and hematocrits in the circulating blood. An as yet unknown sensor is activated to detect and reduce over a matter of weeks red blood cell production such that red cell mass becomes appropriate to the new volume. Such readjustment to altered volumes are also seen under one-g; for example, individuals with leg varicosities have increased blood volumes. I think that the reduced loss of red cell mass in the Skylab 4 Commander is further evidence of reduced leg venous volume. Table III illustrates this.

TABLE III. FLUID SHIFTS

Blood - Exposure to Weightlessness

- °Removal of hydrostatic forces produces essentially uniform pressure throughout venous system
- °Differing tensions throughout the venous system redistributes blood
    - °Higher effective tension of leg veins force a quantity of blood out of the legs
    - °Lower effective tension of head and neck veins accept a small volume of blood which increases pressure and distension
    - °Remainder of blood increases central venous volume and pressure
- °Sensors reduce volume by reducing plasma volume
- °Unknown sensors detect "excess" red blood cells and reduce production until normal values are reached
- °Reduced blood volume is appropriate for effective reduction of total venous volume in weightlessness but inappropriate for one-g or one-g simulations
- °Increased filling pressure may increase cardiac output

On return to one-g, a reverse process ensues. After the first day repeated blood tests show an anemia which is slowly replaced by an increasing red cell mass. These changes are delineated in table IV.

TABLE IV. FLUID SHIFTS

Blood - Reexposure to one-g

°Hydrostatic pressures increase effective venous capacity by expansion of leg veins

°Central volume and pressures are decreased

°Plasma volume expands reducing hematocrit

°Red blood cell production is resumed or increased until new equilibrium is reached

Tissue fluid shifts are larger in volume than blood shifts but somewhat slower acting. For sentimental purposes, I must show my old campaign slide (fig. 13), poor as it is. When standing under one-g there is a hydrostatic column of up to 80 to 100 mm Hg pressure on arteries, veins, and capillaries in the foot; this is illustrated by the internal arrows. This pressure is opposed by tissue pressures and after a period of extravasation they equalize. Under weightlessness, the reverse occurs with resorbtion of fluid by the tissues until transmural pressures are again balanced. In the upper body areas and particularly the head, we have the opposite effect from increased transmural pressure which produces edema. These processes are simultaneous. Tissue fluid shifts are delineated in table V.

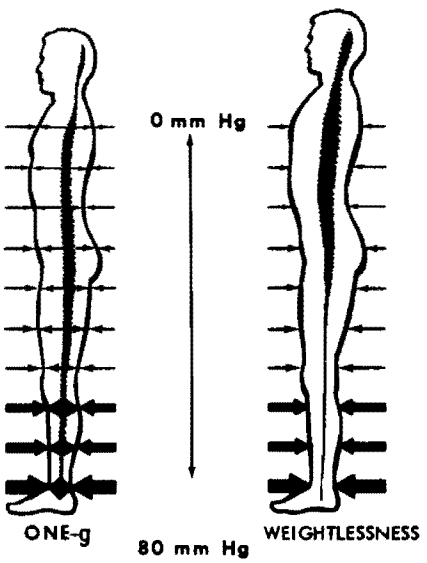


Figure 13. Fluid pressure/volume changes under weightlessness.

TABLE V. FLUID SHIFTS

Tissue

A. Below the heart:

°Hydrostatic forces removed from blood column, venous and arterial, cause:

increased transmural resorbtion from decreased pressure in legs with resultant rapid loss of fluid from legs,

Reduction in tissue pressures in leg which may effect venous compliance.

°Change in hydrostatic forces may be caused by small to moderate loss of fluid through diuresis or decreased intake.

B. Above the heart:

°Hydrostatic forces removed from blood columns and increased transmural pressures cause:

edema to tissues of body above heart,

possible effects on vestibular apparatus.

Whether this shift of fluid produces an increase in intravascular volume or not depends upon how rapidly fluid is regained from some areas and lost to others. It is at least theoretically possible that fluid is lost more rapidly than it is gained, with a reduction of intravascular volume. I do not think this happens and expect there may be a very slight expansion of intravascular volume which, coupled with the blood from leg veins, may result in a small fluid loss via the Gauer-Henry scheme (increased atrial pressure and diuresis), or some other mechanism. However, remember that tissue fluid shifts occur under one-g without undue diuresis. Legs are smaller in the morning and eys are puffy, and a shave lasts longer if made an hour or so after arising.

Fluid shifts should be investigated as a possible participant in the vestibular upsets that have occurred. Time course and other aspects of these vestibular upsets are suggestive and I have no hard evidence for or against this.

SUMMARY

In summary we have documented for the first time anthropometric changes and the correct magnitude and time course of fluid shifts under weightlessness that have implications for future human factors engineering and that explain some medical phenomena. More importantly these data provide a fundmental point of departure for future research.

Bed rest studies for example have not properly considered such fluid shifts. We now have better criteria for evaluating the fidelity of weightless analogs such as bed rest and water immersion.

Most importantly we again find the human body capable of making stable adaptation to two widely differing environments in an amazingly short time. In the course of these experiments, I think data has been offered to justify the title "Earth man - Space man".

ACKNOWLEDGEMENTS

Any listing of individuals here is bound to omit several who made contributions. Above all the Skylab 4 crew is to be commended for gathering the data with surprising accuracy under trying conditions which included virtually no training for the tasks. The work could not have been implemented without the support of Dick Johnston, Bill Schneider, Kenneth Kleinknect and others in Skylab management. Jack Ord greatly influenced the direction of this and my other experiments by our previous collaboration during the Manned Orbiting Laboratory project.

Post Scriptum

During the Question and Answer session, Dr. Otto Gauer's interesting comments and slides corroborated our findings with data from his independent research, hitherto unknown to us. These comments and reproductions of the slides have been included in the Panel Discussants portion.

VECTORCARDIOGRAPHIC CHANGES DURING EXTENDED SPACE FLIGHT

Raphael F. Smith, M.D.; Kevin Stanton, M.D.†; David Stoop, M.D.†; Donald Brown, M.D.†; Walter Janusz, M.D.† and Paul King, Ph.D.**

ABSTRACT

To assess the effects of space flight on cardiac electrical properties, vectorcardiograms were taken on the 9 Skylab astronauts during the flights of 28, 59, and 84 days. The Frank lead system was used and observations were made at rest; during 25%, 50%, and 75% of maximum exercise; during a short pulse of exercise (150 watts, 2 minutes); and after exercise. Data from 131 in-flight tests were analyzed by computer and compared to preflight and postflight values. Statistically significant increase in QRS vector magnitude (six of nine crewmen); T vector magnitude (five of nine crewmen); and resting PR interval duration (six of nine crewmen) occurred. During exercise the PR interval did not differ from preflight. Exercise heart rates in-flight were the same as preflight, but increased in the immediate postflight period. No major changes in QRS, T, or ST vector direction occurred. There were sporadic (usually isolated) ectopic ventricular beats in-flight and one astronaut had a brief episode of ventricular tachycardia 21 days after the first mission. Conclusions: with the exception of the arrhythmias, no deleterious vectorcardiographic changes were observed during the Skylab missions. The increase in QRS and T magnitude resembles the electrocardiographic changes associated with athletic conditioning and may be related to increased ventricular volume secondary to centripetal shifts of fluid and/or the in-flight isotonic exercise program. Prolongation of the PR interval at rest with normalization by exercise suggest that there was increased vagal tone in those crewmen exhibiting this response.

INTRODUCTION

The objectives of Skylab Experiment M093 were to measure electrocardiographic signals during space flight, to elucidate the electrophysiological basis for the changes observed, and to assess the effect of the change on the human cardiovascular system. Vectorcardiographic methods were used to quantitate changes, standardize data collection,

*Vanderbilt University, School of Medicine, Nashville, Tennessee 37232.

†Naval Aerospace Medical Institute, Pensacola, Florida 32512.

and to facilitate reduction and statistical analysis of data. Since the Skylab missions provided a unique opportunity to study the effects of prolonged weightlessness on human subjects, an effort was made to construct a data base that contained measurements taken with precision and in adequate number to enable conclusions to be made with a high degree of confidence. Standardized exercise loads were incorporated into the experiment protocol to increase the sensitivity of the electrocardiogram for effects of deconditioning and to detect susceptibility for arrhythmias.

Vectorcardiography provides a comprehensive, three dimensional approach to the analysis of electrocardiographic data which has proven to be useful in both clinical (1, 2) and research applications (3, 4). Vectorcardiographic techniques have been utilized to quantitate electrocardiographic changes during bedrest experiments (4) and Keplerian parabola flights (5). In-flight vectorcardiograms were not obtained during the Mercury, Gemini, or Apollo missions, although preflight and postflight vectorcardiograms were obtained during Apollo 15, 16, and 17.

The purpose of this report is to describe the M093 experiment design, the data transmission system, data reduction methods, and to report the analysis of data from the three Skylab missions.

METHODS

Experiment Design

Vectorcardiograms were taken at rest, during exercise, and after exercise in each crewman during preflight, in-flight, and postflight phases of the Skylab missions. Experiment M093 was designed primarily to obtain electrocardiographic data. In a second Skylab experiment, M171 Metabolic Activity, the Frank lead system (6) was applied for the purpose of obtaining electrocardiographic data during more strenuous exertion. In both experiments vectorcardiograms were obtained from the crewmen at rest for five minutes. In experiment M093 the subject exercised on the bicycle ergometer at a work load of 150 watts for two minutes; during M171 the subject exercised on the ergometer at levels equivalent to 25, 50, and 75% of his maximum aerobic capacity determined prior to the flight. The subject exercised for five minutes at each work load for a total of 15 minutes. After the single exercise load in experiment M093, vectorcardiograms were obtained for 10 minutes. In experiment M171, postexercise vectorcardiograms were obtained for five minutes. The exercise profiles are depicted in figure 1 and the

ergometer is shown in figure 2. Mechanical problems in the orbital workshop during the early portion of Skylab 2 caused scheduling conflicts which resulted in the deletion of the M093 protocol during that flight. However, the M093 protocol was performed throughout Skylab 3 and Skylab 4.

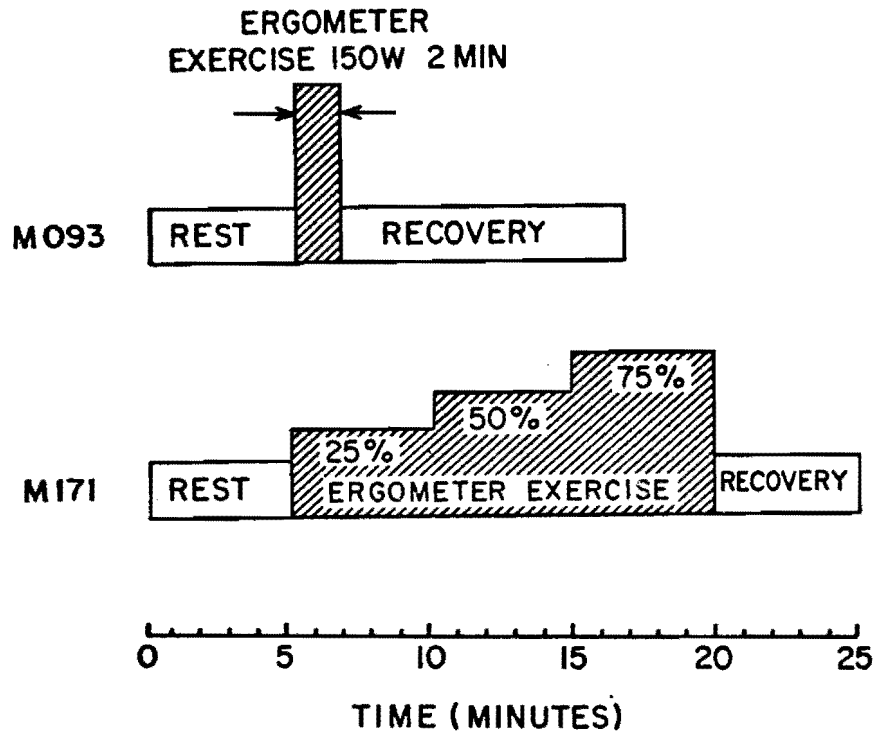


Figure 1. Ergometer exercise profiles for Experiment M093 and Experiment M171. For the M171 protocol, the maximum aerobic capacity of each astronaut was determined prior to the flight and the work levels were 25, 50, and 75 percent of this value.

Instrumentation

Eight electrodes were applied to the crewmen in a modified Frank lead configuration. To lessen muscle noise during exercise, the lead system was modified by transferring the left leg electrode to the left sacral region since the potential difference between the left leg and the left sacrum is negligible. The resistor network proposed by Frank (6) was utilized to correct for the distortion of the cardiac dipole field that

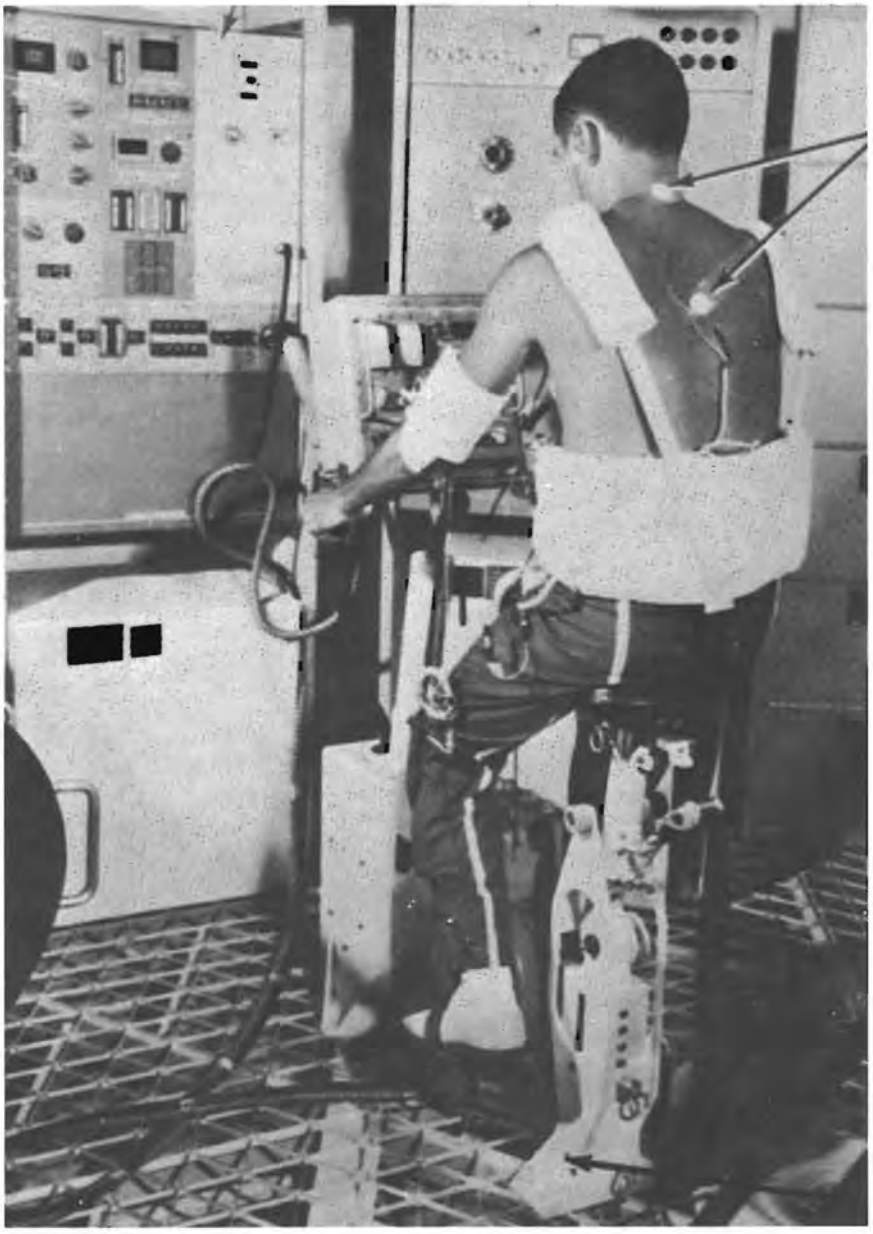


Figure 2. Orbital Workshop bicycle ergometer. The Experiments Support System and Vectorcardiographic subpanel can be seen in the background. The arrows show the positions of two electrodes of the Frank lead system.

results from the shape of the torso and the eccentric location of the heart in the chest. The output of the network is theoretically proportional to the orthogonal components of the cardiac dipole. In the preflight period the electrode sites were marked on each crewman's body by a small tattoo and immediately before the run the electrode site was prepared with benzalkonium chloride. The electrodes were well-type disks and a sponge impregnated with a conductive electrolyte gel served as an interface between the silver-silver chloride electrode and the skin. After attaching the electrodes to the body, the ground reference electrode was tested to determine if there was proper isolation of the subject from the spacecraft ground, then each electrode was tested in sequence to determine the impedance of the skin-electrode interface. The electrode contact was considered to be satisfactory if the impedance was less than 100 000 ohms. To prevent the electrocardiographic signals from exceeding the dynamic range of the recording system, the proper signal conditioner gain for each crewmen was determined prior to the flight and the appropriate switch position selected for the individual at the start of the experiment run.

The signal conditioners had differential input with input impedance greater than 40 megohms. The frequency response of the signal conditioners was flat from 0.14 Hz to 90 Hz, at 0.05 Hz and at 100 Hz the frequency response was less than 3 dB down from the flat portion of the frequency response curve. The harmonic distortion of the signal conditioners was less than one percent over the frequency range of the unit. The phase angle difference between vectorcardiographic amplifiers did not exceed one degree over the frequency range of the unit. The three vectorcardiographic channels were simultaneously calibrated by a 10 Hz square wave. The Experiment Support System conditioned and distributed electrical power to experiment equipment, received experiment data in analog and digital form, displayed heart rate data for the crewmen, and routed analog signals to the Airlock Module telemetry system.

The spacecraft recording and telemetry system consisted of two pulse code modulation programmers, pulse code modulation interface box, a data storage and playback system, and remote multiplexers and signal conditioners. This equipment was located primarily in the Airlock Module. The system accepted analog signals from the vectorcardiographic amplifiers and arranged these data into binary coded words at a rate of 320 samples per second. Tape recorders were used to record data for delayed transmission to Lyndon B. Johnson Space Center. The units recorded reduced bit rate segments of the pulse code modulation outputs from the pulse code modulation programmer together with voice data from the crewmen. The recording speed was 1-7/8 inches per second (0.048 meters/second) and the tapes were played back 41-1/4 inches per second (1.05 meters/second) thus allowing four hours of data to be

transmitted in less than 11 minutes. Data were transmitted at "greater-than-real time" rates during passes over receiving stations, a procedure referred to as data "dumps". Due to the volume of data from Skylab experiments it was necessary to compress the vectorcardiographic data and eliminate redundant samples. A zero order predictor algorithm was selected as the data compression technique. In essence, a digital sample of a parameter was tested to determine if it differed from the value of the sample last transmitted. If there was no difference between the current sample and the previous sample, the value was considered to be redundant and not transmitted to L. B. Johnson Space Center.

Computer Analysis Program

The pattern recognition logic of the M093 program is based on a statistical method of identifying components of the vectorcardiogram rather than utilizing empirically derived fiducial values. The program consists of a main program and 10 subprograms that scale and analyze the data. The main program initializes constants, enters identifying information, enters data pertaining to the length of calibration and length of experimental data, generates a digital filter, and serves as a control program for the subroutines. The subroutines compute scale factors from the calibration pulses, apply digital filtering, define the baseline, determine onset and end of waves and segments, and generate a tabular and graphical output of vectorcardiographic items. An optional subroutine derives the 12 conventional electrocardiograms from the three orthogonal vector leads or derives any lead for which spatial coordinates are given. The following vectorcardiographic items are measured or calculated:

- P, QRS, T duration; start and end time
- P, QRS, T maximum voltage X, Y, Z leads; time of occurence
- P, QRS, T vector loop length
- P, QRS, T maximum vector magnitude, azimuth, elevation; time of occurrence
- P, QRS, T maximum vector velocity; time of occurence
- P, QRS, T, ST area X, Y, Z leads
- P, QRS, T, ST spatial mean vector magnitude, azimuth, elevation
- Ventricular gradient magnitude, azimuth, elevation

- QRS instantaneous vector magnitude, azimuth, elevation at 10 millisecond intervals
- Angle between spatial mean QRS-T vectors
- Slope and curvature ST segment
- Heart rate

A program for statistical analysis of intra-experiment data has been used in series with the M093 analysis program. The statistical program provides tabular output and graphic displays of both standard statistical parameters and special statistical metrics for directional measurements.

Data Management

For crew safety during the flights, the electrocardiographic signals from each experiment were examined within 24 hours for changes of clinical importance. Occasionally when the orbital workshop was in communications range and an experiment was in progress, electrocardiographic signals were available for immediate analysis. However, due to the gaps in ground station coverage, in most cases the complete data from the experiment were not available until 12 to 24 hours following the run. An analog version of the lead transformation algorithm was available to convert the three orthogonal vectorcardiographic leads to a conventional 12 lead electrocardiogram. Combinations of electrical resistance were chosen to provide the best match between electrocardiographic signals obtained from the standard clinical leads and the derived electrocardiographic signals. Circuit boards were constructed for each astronaut and inserted into the synthesizing unit when an experiment was in progress. Figure 3a is an actual 12-lead electrocardiogram from the Commander of Skylab 2. Figure 3b shows the 12 leads that were derived from the vectorcardiographic signal. Microfilm copies of the computer analysis of experiment data were available within 48 hours after the experiment was performed. These reduced data were reviewed and after inspection of an analog reconstruction, spurious values were deleted from the data base.

RESULTS

Vectorcardiographic parameters from 131 in-flight tests were analyzed by digital computer and compared to pre-flight and postflight values. The vectorcardiographic items examined were heart rate, QRS duration, QRS maximum vector magnitude and direction, T maximum vector magnitude and direction, PR interval, QT interval, area of ST segment X lead, and the spatial angle between QRS and T mean vectors.

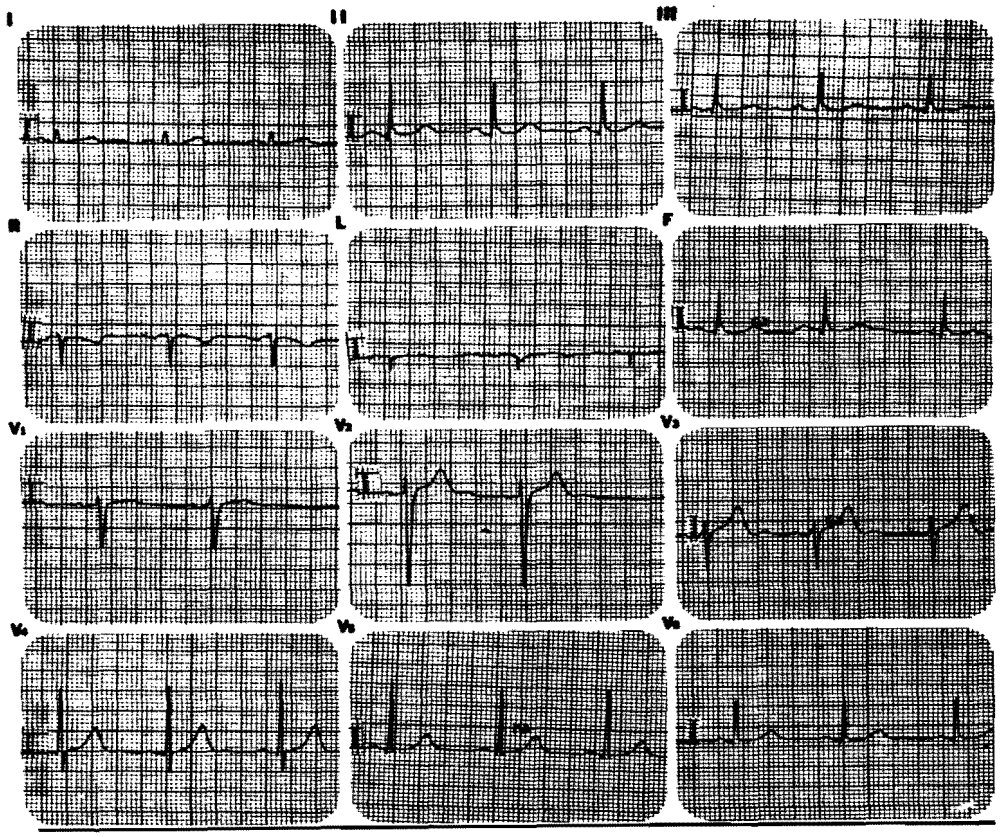


Figure 3a. Conventional 12-lead electrocardiogram from Skylab 2 Commander.

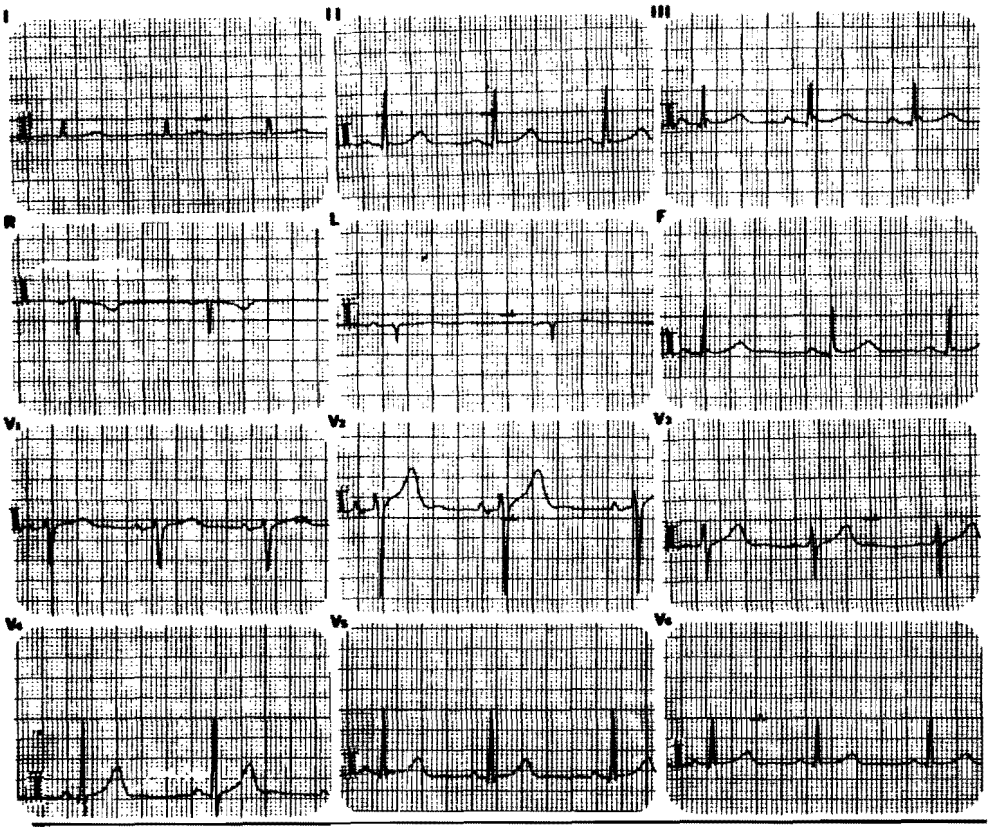


Figure 3b. Twelve lead electrocardiogram derived from Frank orthogonal leads.

A statistically significant increase in QRS maximum vector magnitude occurred in six of the nine crewmen. Crew trends plotted as a percentage change from the mean preflight value are shown for the three Skylab missions in figures 4, 5, and 6 respectively. Although crew trends were similar during the three Skylab missions, there were interesting individual differences in the time course of the magnitude changes.

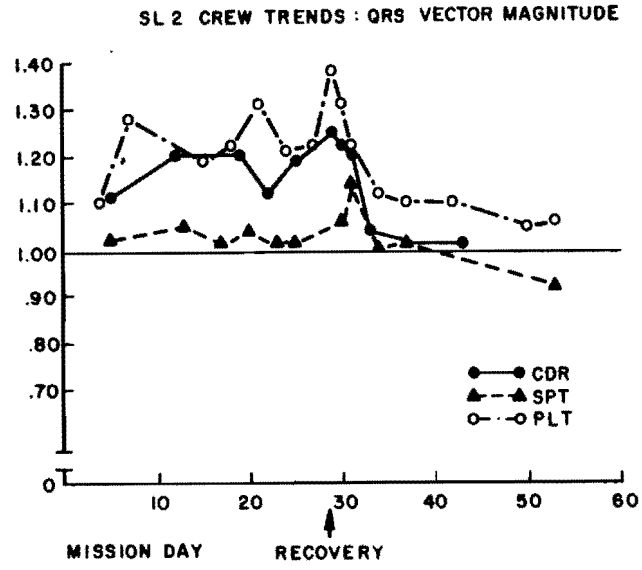


Figure 4. QRS vector magnitude during Skylab 2 mission. Data plotted as percentage change from the mean preflight value.

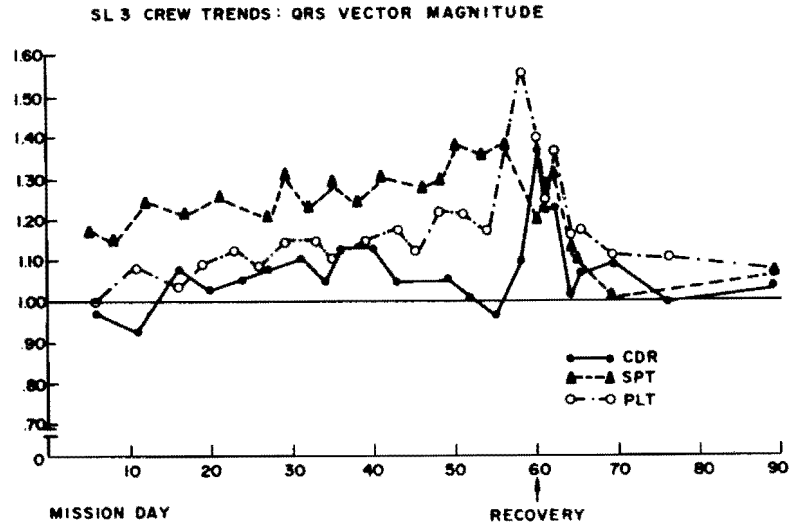


Figure 5. QRS vector magnitude during Skylab 3.

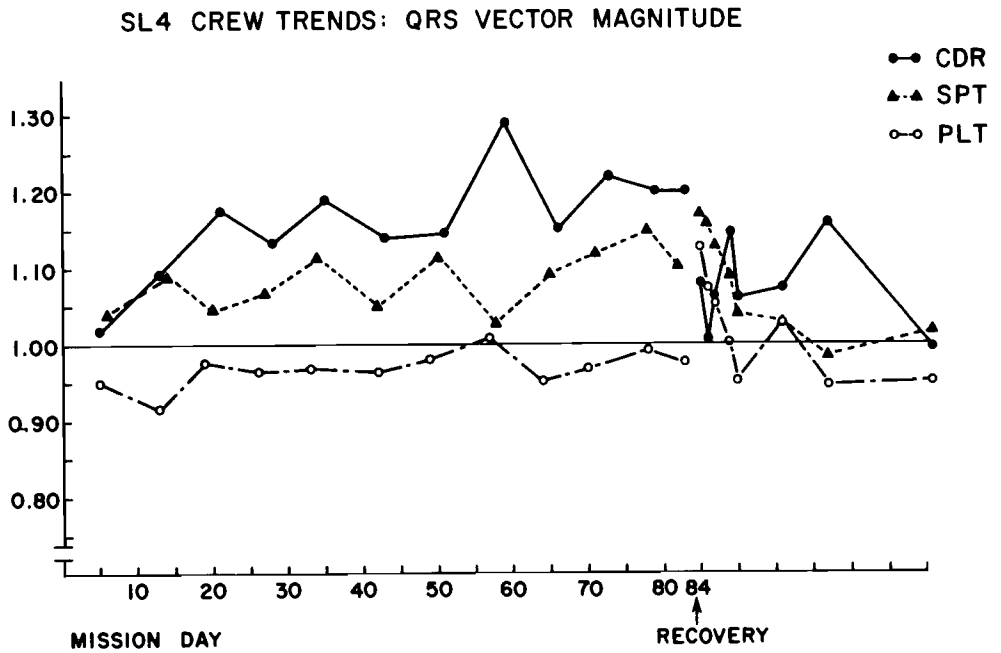


Figure 6. QRS vector magnitude during Skylab 4.

For example, in some astronauts the increase in QRS maximum vector magnitude began in the preflight period as depicted in figures 7 and 8 and in other crewmen the preflight increase was not evident, as shown in figure 9. It should be noted that the data points are spaced equally on the abscissa of figures 7, 8, and 9 although the actual time intervals between the experiments were not equal. The preflight data collection period for Skylab 2 was approximately six months; thus, the rate of QRS maximum vector magnitude increase was considerably greater during the flight than in the preflight period. The magnitude of the spatial T vector increased in five of the nine Skylab crewmen and although the increase was statistically significant, variation in the measurements was large. The angle between the spatial QRS and T mean vectors did not increase significantly in any crewmen during the flights and there were no major changes in QRS, T, or ST vector direction.

The duration of the PR interval measured at rest increased in six of nine crewmen during the three flights and the crew trends for Skylab 3 and Skylab 4 are shown in figures 10 and 11. However, the average

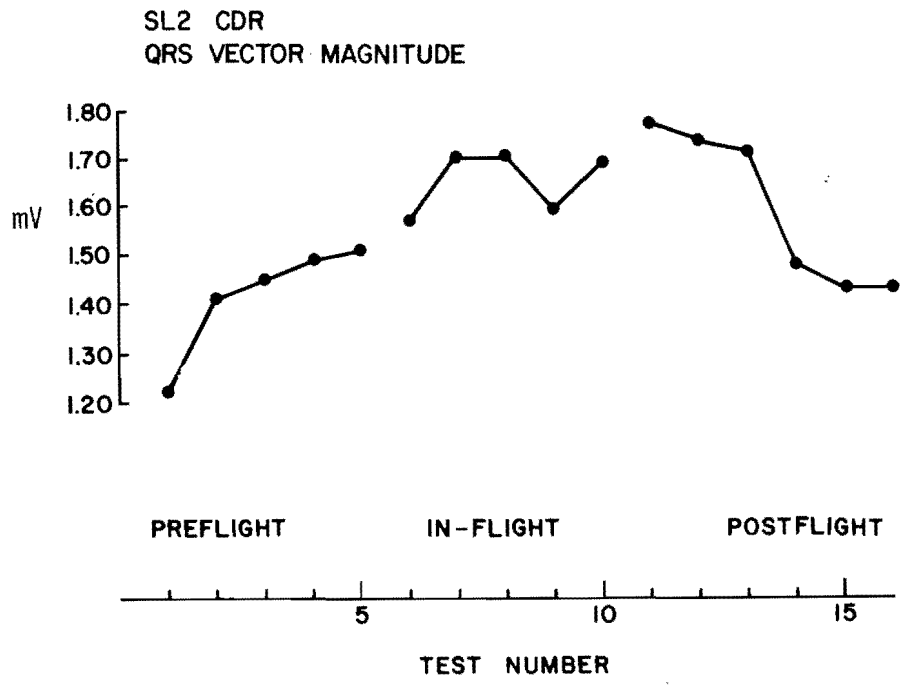


Figure 7. Evolution of QRS vector magnitude change in the Commander of Skylab 2. Experiments are spaced equally on absicissa although the time intervals between the experiments were not equal.

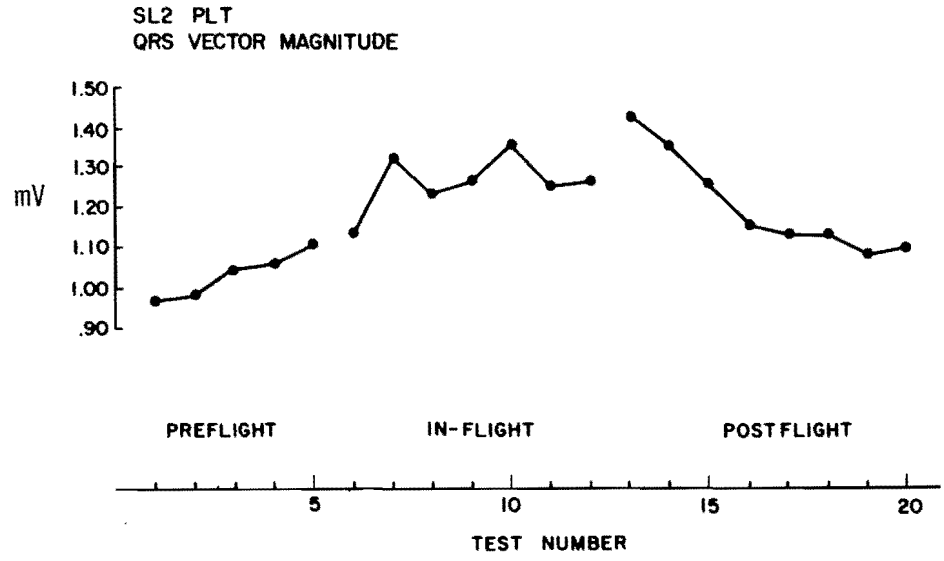


Figure 8. Evolution of QRS vector magnitude change in the Pilot of Skylab 2.

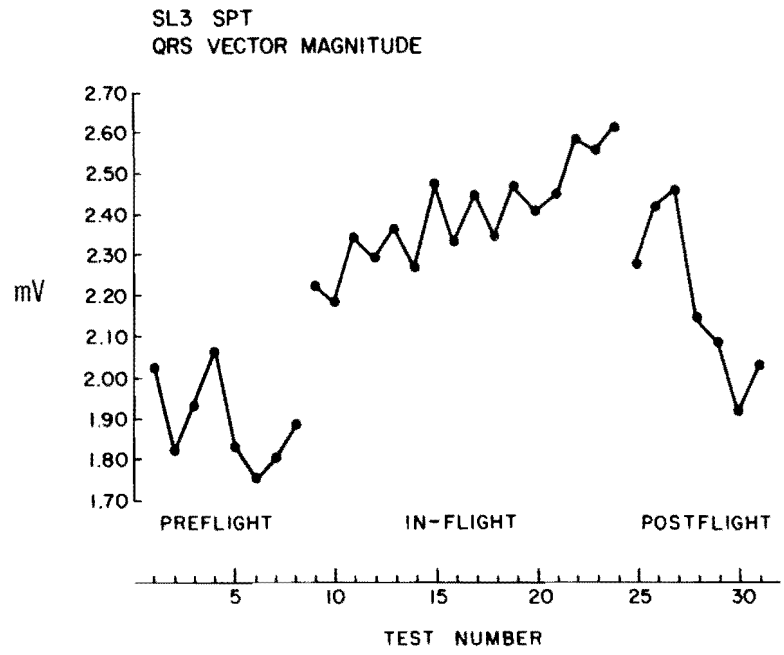


Figure 9. Evolution of QRS vector magnitude changes in the Scientist Pilot of Skylab 3.

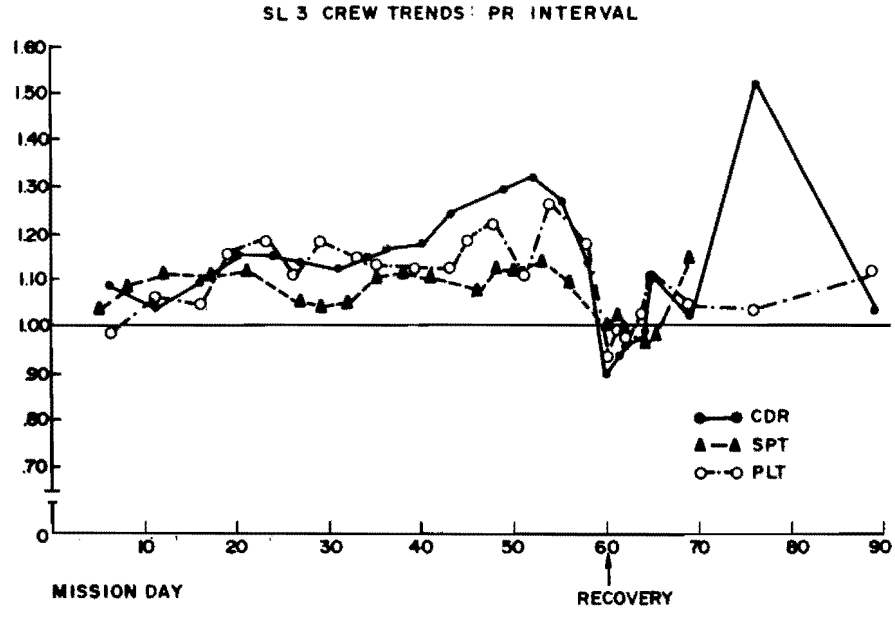


Figure 10. PR interval duration during Skylab 3. Data plotted as percentage change from the mean preflight value.

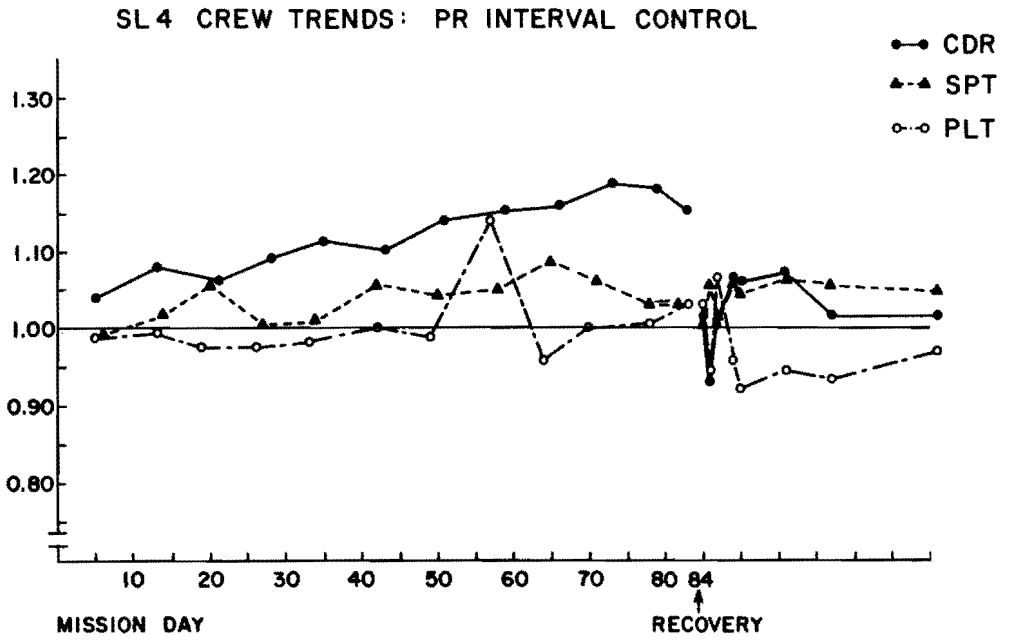


Figure 11. PR interval duration during Skylab 4.

PR interval in-flight did not exceed the clinical standard for the upper limit of normal (0.20 seconds) in any crewmen. During exercise the PR interval did not show a significant difference from the PR interval duration for comparable exercise in the preflight period. A significant decrease in the resting heart rate was observed in the Skylab 2 crew during the flight. However, a significant change in resting heart rate was not a crew trend in the later missions. In general, the average heart rate during the third level of exercise, M171 protocol remained the same as preflight or tended to decrease slightly during the flights. In the immediate postflight period there was a marked increase in the resting heart rate and heart rate response to a given exercise load. As an example, the heart rate responses during Skylab 4 are shown in Figures 12 and 13.

The scalar analog reconstructions of the digital vectorcardiographic signals, the twelve-lead electrocardiograms obtained with the transformation circuitry, and instantaneous vector loop displays were reviewed to check the technical quality of the data and to detect changes of clinical importance. During the three Skylab missions there were no ST segment abnormalities that suggested myocardial ischemia or other changes in the configuration of the electrocardiographic waveforms that were considered to be adverse. During the three flights cardiac arrhythmias were occasionally observed. The Commander

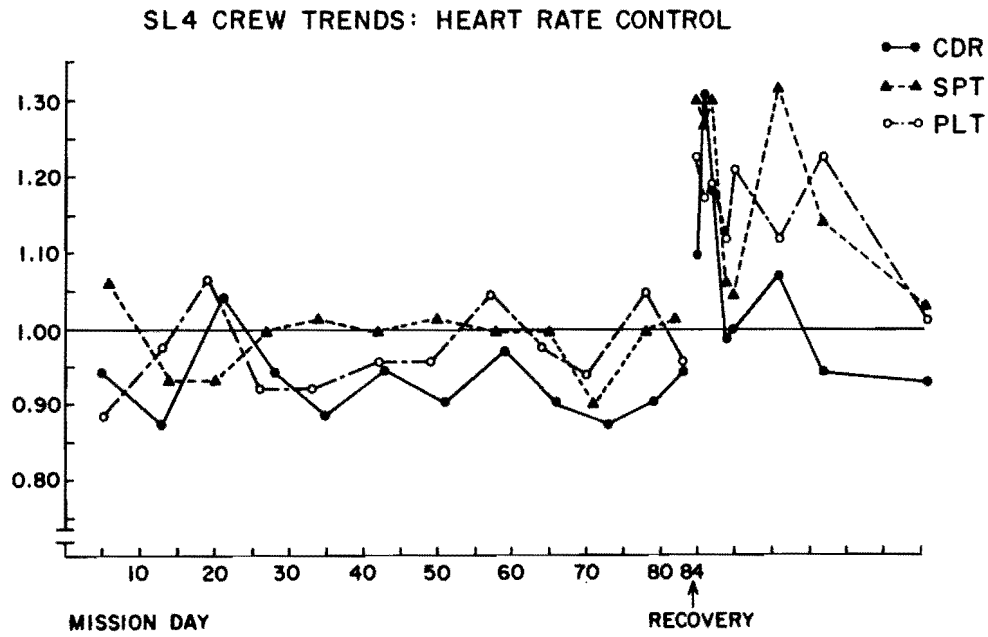


Figure 12. Resting heart rates Skylab 4 crew plotted as a percentage of the mean preflight value.

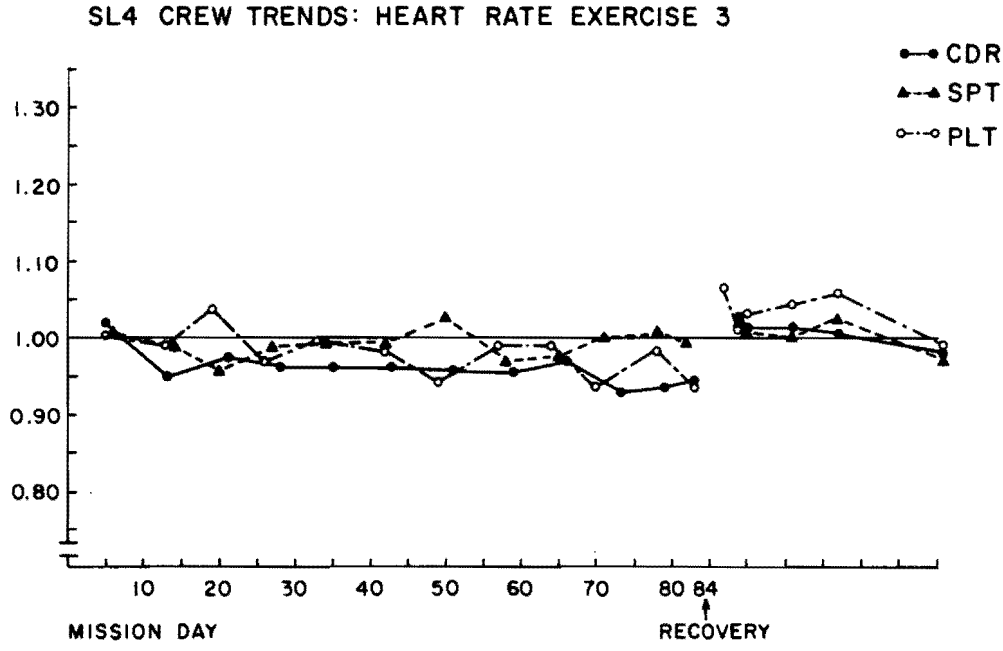


Figure 13. Average heart rate during the highest level of exercise M171 protocol. The data are plotted as a percentage of the mean preflight value. It should be noted that the exercise loads were decreased in the immediate postflight period.

of Skylab 2 had multiple ventricular ectopic beats during the third level of exercise on the initial in-flight M171 test but no arrhythmias were evident in the exercise tests that the Pilot of Skylab 2 performed in the preflight period and during the mission. However, during the third level of exercise (M171 protocol) 21 days after recovery he had salvos of ectopic ventricular beats for approximately 1-1/2 minutes. A representative segment of the arrhythmia is shown in figure 14. The ectopic beats were considered to be ventricular in origin because because the initial beat in the salvo was often a ventricular fusion beat, the isolated ectopic beats did not alter the sinus rhythm, and the degree of QRS aberration was not clearly related to the coupling interval of the premature beat. Furthermore, the ectopic complexes had a monophasic configuration in lead V_1 which suggests a ventricular origin for the arrhythmia. He was monitored for 72 hours, no arrhythmias were detected and he has had no difficulty on subsequent heavy-load exercise tests.

The Scientist Pilot of Skylab 3 had premature ventricular beats sporadically during the second Skylab mission. On mission day 8 during a long extravehicular activity period he was noted to have 80 premature ventricular beats over a 6-1/2 hour period of observation. These ectopic beats were isolated in occurrence and had a configuration suggesting a unifocal origin. This astronaut also had intermittent periods of atrioventricular junctional rhythm at rest throughout the flight. On mission day 21 the Commander of Skylab 3 had a three-beat run of atrioventricular dissociation presumably due to advanced atrioventricular block. The atrial rate was 50 and the junctional escape rate was approximately 39. The episode occurred during the recovery phase of experiment M092 and was not observed in later tests. The crew of Skylab 4 had premature ventricular beats sporadically throughout the mission. On mission day 43 the Commander had two consecutive ectopic ventricular beats during the third level of exercise M171 protocol and on mission day 83 he had three successive ventricular fusion beats during the first exercise level of an M171 test. The Pilot of Skylab 4 had atrioventricular junctional rhythms at rest and after release of lower body negative pressure. There was no impairment of function during the arrhythmia.

DISCUSSION

Elucidation of the mechanisms that underly the cardiac electrical changes is made difficult by the large number of uncontrolled environmental and physiological variables that were operative during the Skylab flights. It is known that electrocardiographic changes occur when there are shifts in the anatomical position of the heart, with hypokalemia, with perturbations of the autonomic nervous system, with changes in the volume of intracavitary blood, and with physical

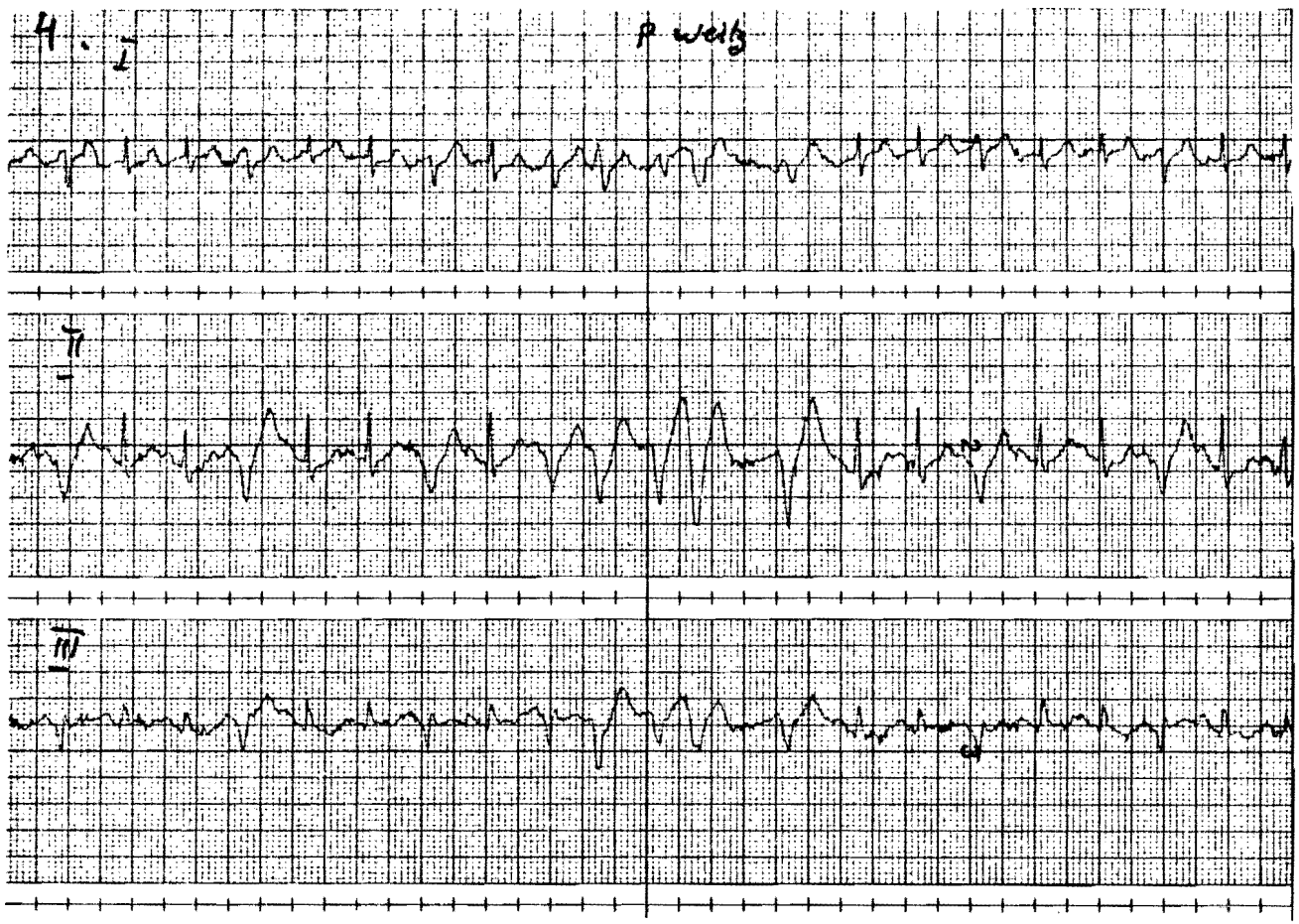


Figure 14. ECG during arrhythmia experienced 21 days postflight by the Pilot of Skylab 2. The ECG was taken during exercise and six frontal plane leads are shown. The analysis of the arrhythmia is discussed in the text.

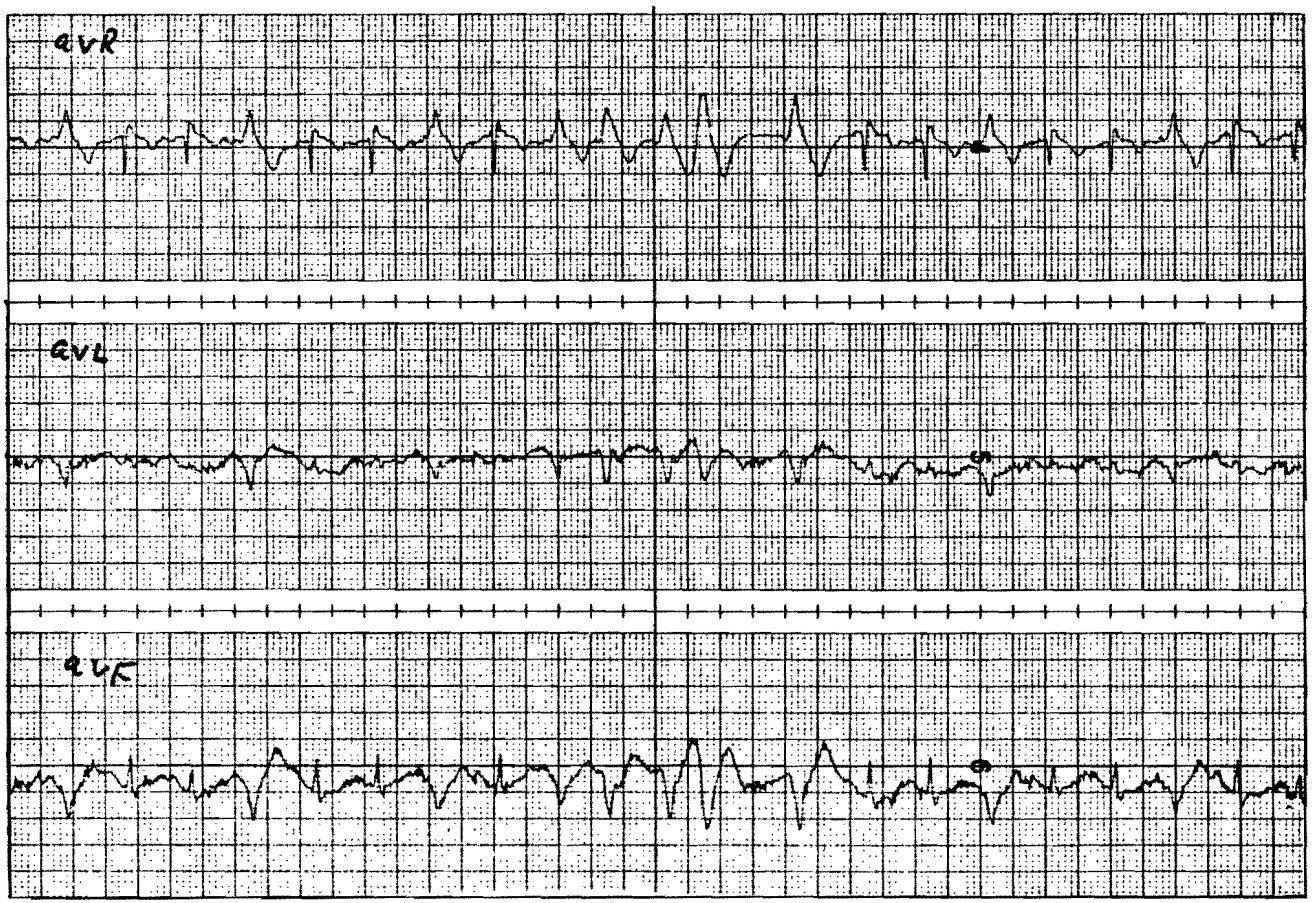


Figure 14. Concluded.

conditioning and "deconditioning". These factors have either been shown to vary during space flight or alterations in these factors would intuitively be expected in a weightless environment.

The increase in the magnitude of the QRS maximum vector is an especially interesting change because this has been a crew trend in each Skylab flight. In the majority of the astronauts the QRS maximum vector magnitude has progressively increased during the flight and in several the upward trend began prior to the flight. The T maximum vector magnitude also tended to increase but variation between measurments was greater. The changes observed during the Skylab flights differ from left ventricular hypertrophy encountered clinically in that the angle between the spatial QRS and T vectors was unchanged or decreased in the astronauts and with pathological left ventricular hypertrophy the angle characteristically increases. The QRS and T magnitude increase and the directional relationship between the QRS and T vectors resemble those changes seen in athletes whose electrocardiograms are followed during a physical conditioning program (7). Similarly in dogs given heavy exercise loads over a 12 week period, Wyatt and Mitchell observed a decrease in resting heart rate, a decrease in heart rate response to a standard work load, and an increase in QRS spatial vector magnitude (8).

Increased intracavitary blood due to the centripetal shift of volume during weightlessness may be another mechanism that contributed to the increase in QRS maximum vector magnitude. From a theoretical analysis Brody (9) predicted that an increase in intravavitary blood would augment potentials from radially oriented cardiac dipoles and attenuate those from tangentially oriented dipoles. Since the radially oriented dipoles have the most marked influence on the QRS vector, the net effect of increased diastolic volume would be to increase QRS vector magnitude. Millard, Hodgkin, and Nelson (10) using a series of physiological interventions in experimental animals have confirmed the validity of the Brody effect. Morganroth *et al.* (11) determined left ventricular volumes, wall thickness, and mass by echocardiograph in 26 actively competing college athletes. Athletes competing in events requiring strenuous isotonic exercise had increased left ventricular volume without increased wall thickness and athletes competing in isometric events had increased wall thickness without increased left ventricular volume. Thus, centripetal shift of fluid and isotonic exercise may have had an additive effect in causing the increased QRS vector magnitude that has been observed during the Skylab flights. Measurement of cardiac diastolic dimensions by echocardiography during the preflight and postflight period of Skylab 4 suggested that there was a decrease in the transverse cardiac dimension on the first day after recovery in two of the three crewmen (12). However, after each mission the QRS maximum vector magnitude has remained increased for five to ten days.

An increase in the PR interval duration was a common observation during the three Skylab missions. The PR interval duration is a composite of the conduction time through intra-atrial pathways, the atrioventricular node, and the bundle of His. Since conduction in the atrioventricular node is longer than in the other components, for clinical purposes the PR interval duration serves as an estimate of atrioventricular node conduction. Although drugs such as digitalis, beta-adrenergic blockade, and nodal ischemia can cause prolongation of atrioventricular conduction time, an increase in vagal tone is a more likely explanation of the prolongation of the PR intervals seen in the Skylab astronauts. Further support for this explanation comes from the observation that the PR duration during exercise in-flight was the same as the PR interval duration measured in the preflight period during comparable exercise. Thus the adrenergic influence of exercise tended to overcome the increased vagal influence observed when the men were at rest.

Ventricular ectopy occurred throughout the three Skylab missions. In general this was sporadic, did not alter hemodynamic function in a detectable manner, and electrocardiographic signs of myocardial ischemia were not associated. On three occasions the crewman involved was under extraordinary stress: the first in-flight M171 exercise test of Skylab 2, during a long extravehicular activity in Skylab 3, and during the last in-flight M171 test in Skylab 4. In the case of the more serious ventricular ectopy observed in the Skylab 2 Pilot on the twenty-first postflight day, the relationship of the arrhythmia to the flight is conjectural. He had been in another city on the evening prior to the test and had returned to Houston early on the day of the test. No arrhythmias were observed during the 72 hours following the test and the exercise protocol has been repeated on multiple occasions and the arrhythmia has not recurred during the testing.

With the exception of the arrhythmias, no adverse electrocardiographic changes were observed in the Skylab crews that could be attributed to long exposure to a weightless environment or to the other stresses of extended space flight. Specifically, there was no evidence of myocardial ischemia or changes in the electrocardiogram that would suggest vasoregulatory abnormalities or the emergence of patterns that have been observed in deconditioning experiments (4). The vectorcardiographic techniques utilized in the M093 experiment added both accuracy and precision to the data acquisition and facilitated both scientific investigation and monitoring for crew safety.

REFERENCES

1. Massie, E. and T. J. Walsh. 1969. Clinical Vectorcardiography and Electrocardiography. The Year Book Publishers, Inc., Chicago.

2. Smith, R. F. and R. J. Wherry, Jr. 1966. Quantitative interpretation of the exercise electrocardiogram. Use of computer techniques in the cardiac evaluation of aviation personnel. *Circulation* 34: 1044-1055.

3. Smith, R. F., K. C. Stanton and P. H. King. 1974. Applications of the Frank lead system in clinical and aerospace medical research. H. A. Miller and D. C. Harrison, Eds., Biomedical Electrode Technology, Theory and Practice, pp. 387-404. Academic Press, Inc., New York, N. Y.

4. Saltin, B., G. Blomqvist, J. H. Mitchell, R. L. Johnson, Jr., K. Wildenstahl and C. B. Chapman. 1968. Response to exercise after bedrest and after training. *Circulation* 38, suppl. 7, pp. 1-78.

5. Allebach, N. W. 1966. The Frank lead system as an electrophysiological monitor at 1g, 2g, and 4g. Proceedings of the Second Annual Biomedical Research Conference, NASA Publication (unnumbered) pp. 321-338.

6. Frank, E. 1956. An accurate clinically practical system for spatial vectorcardiography. *Circulation* 13: 737-749.

7. Rautaharju, P. M. and M. J. Karvonen. 1967. Electrophysiological consequences of the adaptive dilatation of the heart. M.J. Karvonen and A. J. Barry. Eds. Physical Activity and the Heart, pp. 159-183. Charles C. Thomas, Springfield, Ill.

8. Wyatt, H. L. and J. H. Mitchell. Influences of physical training on the heart in dogs. *Circulation Research* (in press).

9. Brody, D. A. 1956. A theoretical analysis of intracavitary blood mass influence on the heart lead relationship. *Circulation Research* 4: 731-738.

10. Millard, R. W., B. C. Hodgkin and C. V. Nelson. End-diastolic volume changes reflected in the electrocardiogram. *Circulation* (supplement) (in press).

11. Morganroth, J., B. J. Maron, W. L. Henry and S. E. Epstein. 1974. The athlete's heart: Comparative left ventricular dimensions of collegiate athletes participating in sports requiring isotonic or isometric exertion. *Clinical Research* 22: 291.

12. Henry, W. L., S. E. Epstein, J. M. Griffith, R. E. Goldstein and D. R. Redwood. The effect of prolonged weightlessness on cardiovascular function in Skylab 4 astronauts. Skylab Life Sciences Symposium, Lyndon B. Johnson Space Center, Houston, TX. August 27 to 29, 1974 (in press).

EVALUATION OF THE ELECTROMECHANICAL PROPERTIES OF THE CARDIOVASCULAR SYSTEM

Stuart A. Bergman, Jr., M.D., G. W. Hoffler, M.D., and R.L. Johnson, M.D.
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

ABSTRACT

Cardiovascular electromechanical measurements were collected on returning Skylab crewmembers at rest and during both lower body negative pressure and exercise stress testing. These data were compared with averaged responses from multiple preflight tests. Systolic time intervals and first heart sound amplitude changes were measured. Clinical cardiovascular examinations and clinical phonocardiograms were evaluated.

Postflight, in all crewmen there were significant changes in ejection time index, in pre-ejection period, and in the ratio, pre-ejection period/ejection time. These changes were present at supine rest as well as during lower body negative pressure stress testing. All systolic time intervals had returned to preflight values within one month. There were decreases in first heart sound amplitude responses to lower body negative pressure by all Skylab 4 crewmen. This response was markedly depressed in one crewman who had a presyncopal episode during the lower body negative pressure test on recovery day.

Two of the three crewmen exhibited depressed first heart sound amplitude responses to submaximal exercise on the day after recovery. Skylab 4 crewmen had altered systolic time intervals during upright rest and during exercise compared with preflight values. The systolic time intervals data were consistent with a reduced stroke volume and possibly a reduction in contractility and/or Frank-Starling effect.

Clinical cardiovascular examinations revealed a reduction in all heart sounds, reduction in precordial movement, and a marked reduction in arterial pulsations. Trace to one plus pretibial edema was noted in the Skylab 3 and Skylab 4 crewmen in the early postflight period. The causes for this transient edema are complex.

The persistent alterations in the systolic time intervals in the face of a replenished blood volume and no consistent correlation with afterload or with change in leg volume during lower body negative pressure suggest that there is a functional impairment to venous return and

perhaps a myocardial factor in the overall decreased tolerance to this stress in the postflight period. Systolic time intervals data collected during exercise support the above hypothesis and are consistent with decreased stroke volume. Clinical studies also support the contention. All changes noted returned to normal within 30 days postflight so that the processes appear to be transient and self limited. The cardiovascular system seems to adapt quite readily to zero-g, and more importantly it is capable of readaptation to one-g after long duration space flight. Repeated exposures to zero-g also appear to have no detrimental effects on the cardiovascular system.

INTRODUCTION

It is well known that after short duration space flights, such as the Apollo flights, crewmen exhibited cardiovascular instability in response to orthostatic and exercise stresses (1, 2). Although through preflight and postflight stress testing several other physiologic variables associated with the decreased tolerance were documented, in-flight timing of the changes were impossible. The measurements were simple, *e.g.*, electrocardiograph and blood pressure. There were wide unexplained interindividual variations between crewmen of the same flight and different flights in their responses to the tests.

The Skylab program offered an opportunity to study man during long duration space flight. The medical test protocols were an established part of this program in the preflight, in-flight and postflight periods. Because payload and flight qualified hardware were and are a high-cost portion of the NASA programs, there had to be a limit to the number of devices allowed for in-flight biomedical experiments. Devices and techniques which enhanced or embellished the core experiments in-flight were encouraged instead to be a part of the preflight and postflight evaluations. Therefore, most of these items were designed for testing in the Skylab Mobile Laboratories and became an item on the preflight and postflight schedules.

Devices and techniques for measuring and analyzing systolic time intervals and quantitative phonocardiograms were initiated during Apollo 17, the last lunar mission. This first generation hardware was utilized as well for the Skylab 2 mission as part of the lower body negative pressure experiment. The data show that the systolic time interval from Apollo 17 crewmen remained elevated longer postflight than the response criteria of heart rate, blood pressure, and percent change in leg volume all of which had returned to preflight levels by the second postflight. Although the systolic time interval values were only

slightly outside the preflight fiducial ($P<0.05$) limits, this finding suggested that: the analysis of systolic time interval may help to identify the mechanisms of postflight orthostatic intolerance by virtue of measuring ventricular function more directly and, the non-invasive technique may prove useful in determining the extent and duration of cardiovascular instability after long duration space flight.

The systolic time intervals obtained on the Apollo 17 crewmen during lower body negative pressure were similar to those noted in patients with significant heart disease.* Although similar changes in systolic time intervals occur with a decreased ventricular filling secondary to a decreased venous return in normal young subjects (3) and although a decreased blood volume was noted in the Apollo crewmen, a progressive myocardial deterioration during long exposure to zero-g could not be ruled out. Based on Apollo and Gemini experience, a firm stance was taken by the biomedical scientists that during flight daily exercise sessions would be provided for Skylab astronauts - the excerise was to be provided by an in-flight cycle ergometer.

Postflight evaluations of systolic time intervals were accomplished after all Skylab missions. During Skylab 4 additional noninvasive techniques were allowed so that after this mission echocardiography, semi-bloodless (radioisotopically determined) circulation times and resting cardiac outputs, and peripheral venous pressure were performed. Results from these techniques are presented in other papers of this symposium (4, 5).

METHODS

General

Preflight examinations for the lower body negative pressure experiment (M092) were conducted over a four to ten month period prior to launch. The last three preflight tests were accomplished at F-30, F-15, and F-5 days, respectively. During these final baseline tests full data collections were performed including the systolic time intervals and absolute amplitude measurements.

Postflight lower body negative pressure test were performed with the few hours of splashdown (recovery day tests). Both lower body negative pressure and the vectorcardiograph exercise tests were done on the day after and on eleven days after recovery. Lower body negative pressure tests were done on several subsequent days after each Skylab flight up to two months postflight on Skylab 4.

*(Unpublished results)

The lower body negative pressure protocol consisted of five minutes supine rest, 15 minutes of incrementally applied negative pressure to -50 mm Hg and a five minute recovery period. The Exercise-Vectorcardiograph test included a five minute rest period in the upright position, a two minute exercise period at 150 watts and a ten minute upright recovery period. The data presented in this paper will include only the control and end of maximal stress periods.

Systolic time intervals were calculated from the vectorcardiograph X-lead, phonocardiogram, carotid pulse trace, and pneumogram during all three missions (fig. 1). However, data acquisition problems in the preflight period of Skylab 2 made the systolic time intervals data difficult to inerpret, and therefore these data are not presented. Also, for similar reasons quantitative phonocardiographic data from Skylab 2 and Skylab 3 are not available for this document. Amplitude of the first heart sound (S_1 Amp) data during exercise and during lower body negative pressure stresses (preflight and postflight) are presented for Skylab 4 only. Systolic time intervals information is presented from Skylab 3 and Skylab 4 for lower body negative pressure and exercise stress tests.

Equipment

The following list of transducers, signals, and types of analyses are provided for a clearer understanding of the data. A more comprehensive description of the system used will be made available at a later date.

Phonocardiographic System. The system used for phonocardiograms included a 20 gram Elema EMT-25C piezo-electric crystal accelerometer transducer which is coupled with a high pass filter network of 25, 50, 100, 200 and 400 Hz central frequencies (-12 dB roll off). The raw output from the transducer which has a high pass characteristic was recorded onto analog tape and subsequently played back through a NASA-designed filter system for analysis. The analyzed signals were reproduced upon light sensitive paper at 100 mm/second using a Brush (Mark 2300) light beam recorder.

Vectorcardiogram. The X-lead of a vectorcardiograph system was used for timing of electrical events of the heart and the characteristics of this system are described elsewhere (5). Tattoos on the crewmen insured reproducible placement of the electrodes.

Pneumogram. A mercury-in-silastic strain gage was used to measure quantitative rate and qualitative depth of respiration. Used mainly to determine the phase of respiration the output was used in determining other measurements such as systolic time intervals.

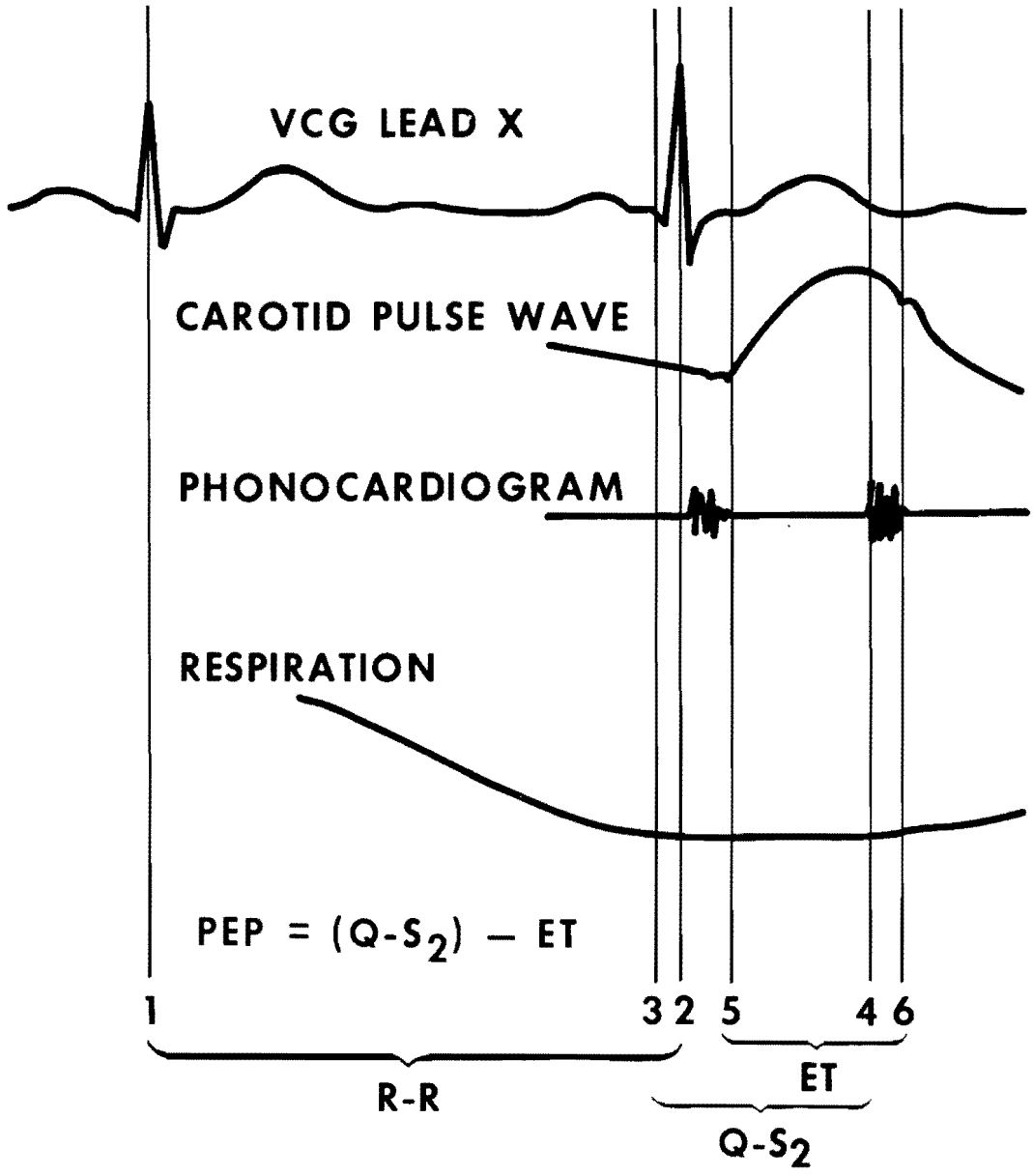


Figure 1. Signals used to measure systolic time intervals. Note that PEP is calculated from the $Q\text{-}S_2$ and ET measurements.

Carotid Pulse. A Sanborn/Hewlett-Packard APT-16 displacement transducer was used to measure carotid pulsations. This transducer had a flat frequency response from d.c. to approximately 60 Hz and has been shown to reproduce arterial pulses faithfully at high and low heart rates (7).

Apexcardiogram. Apexcardiograms were collected on the Skylab 4 crewmen only. The same displacement transducer used for the carotid pulsations was used for the apex cardiogram.

Other Equipment. The Skylab blood pressure measuring system, Lower Body Negative Pressure Device, leg volume measuring system, the cycle ergometer, vectorcardiograph, experiment support system, analog tape recorders, and the various other Skylab equipment are included in other documents or in other papers of this symposium.

TECHNIQUES

Systolic Time Intervals

Systolic time intervals were measured in the following manner: signals from the vectorcardiograph (X-lead), carotid pulse, phonocardiogram, and pneumogram were recorded during the tests on analog tape (Ampex, Model 1260). Replay and analysis of all signals were accomplished via a small computer with software developed jointly between the Cardiovascular Laboratory at the Johnson Space Center and the Massachusetts Institute of Technology. Corrections for heart rate were employed after Weissler, *et al.* (6). Basically, the program user scanned the four data channels which had been digitized at 200 to 1000 samples per second, and chose samples which met predetermined criteria (8). By use of movable cursors the systolic time intervals were determined semiautomatically. Computations were performed according to the program and the entire summary was stored.

First Heart Sound Amplitude

Absolute amplitude of the first heart sound was measured manually from the phonocardiographic signals. Because there is no standard reference such as voltage for phonocardiograms (as there is for electrocardiogram and vectorcardiogram) the stressed S_1 Amp was always compared with the control resting amplitude of the first heart sound of each individual for each test. Each individual served as his own control, both preflight and postflight. The microphone was placed in the fourth left intercostal space just to the left of the sternum in all crewmen, during all tests. Amplitude of the first heart sound was expressed as a percent change from control state. In general,

20 consecutive beats were chosen in the control period of the exercise or Lower Body Negative Pressure test protocols, and the amplitudes of the first heart sound (S_1) were measured in millimeters. At maximal steady state stress, ten consecutive beats were measured and compared with the control mean S_1 Amp. Comparison of the S_1 Amp at maximal stress was expressed as percentage change in amplitude from control.

Clinical Evaluations

In addition to systolic time intervals and S_1 Amp measurements clinical cardiovascular examinations which included phonocardiography, apexcardiography, and carotid pulse analyses were performed. The results of these clinical evaluations are given in order to add more information about the postflight cardiovascular condition of the Skylab astronauts.

RESULTS

Reports on the data from in-flight cardiovascular tests for the Skylab crewmen are contained in the papers being presented by Drs. R. L. Johnson, G. W. Hoffler, and R. Smith at this symposium. The following results reflect only information from preflight and postflight studies which were conducted during the lower body negative pressure, and exercise-vectorcardiograph experiment (M093) experiments. Because the most extensive measurements were made on the Skylab 4 crewmen, these data dominate the results and discussion. However, comparisons are made with the other Skylab missions and with Apollo.

Lower Body Negative Pressure

Figures 2 through 4 show the postflight systolic time intervals responses of the Skylab 4 (84 days) crewmen to lower body negative pressure over time. Heart rate was elevated postflight.

In general, the results of the postflight tests show that there was no change in total electromechanical systole ($Q\text{-}S_2$), ejection time index was decreased at rest and during lower body negative pressure, and pre-ejection period and the ratio of pre-ejection period to uncorrected ejection time (PEP/ET) were both increased significantly. Table I shows the percent change in systolic time intervals postflight for Skylab 4 and Skylab 3 crewmen. It is clear from this table that Skylab 3 crewmen had greater increases in pre-ejection period and pre-ejection/ejection time than did the Skylab 4 crewmen. This finding was present at rest, at -50 mm Hg lower body negative pressure and for a longer duration postflight at rest and during maximal stress.

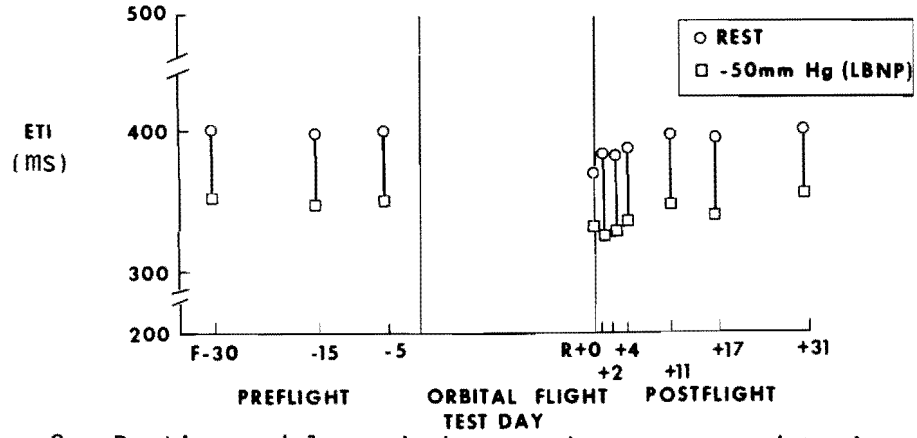


Figure 2. Resting and lower body negative pressure (LBNP) stressed mean ejection time index (ETI) for all Skylab 4 Crewmen.

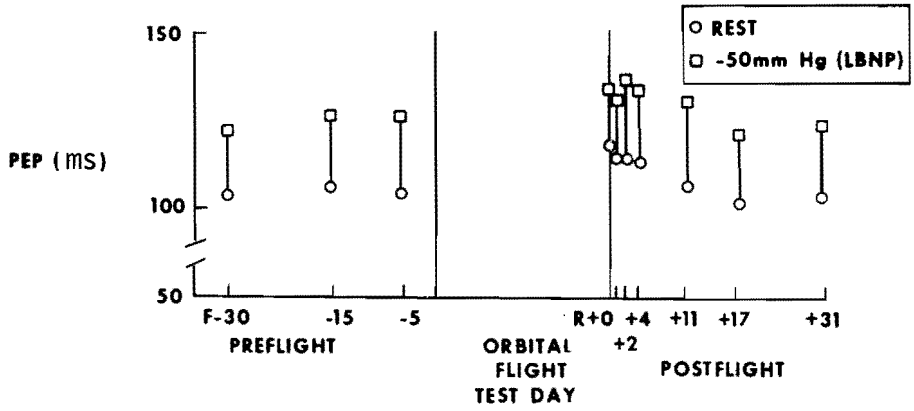


Figure 3. Resting and lower body negative pressure (LBNP) mean pre-ejection period (PEP) for all Skylab 4 crewmen.

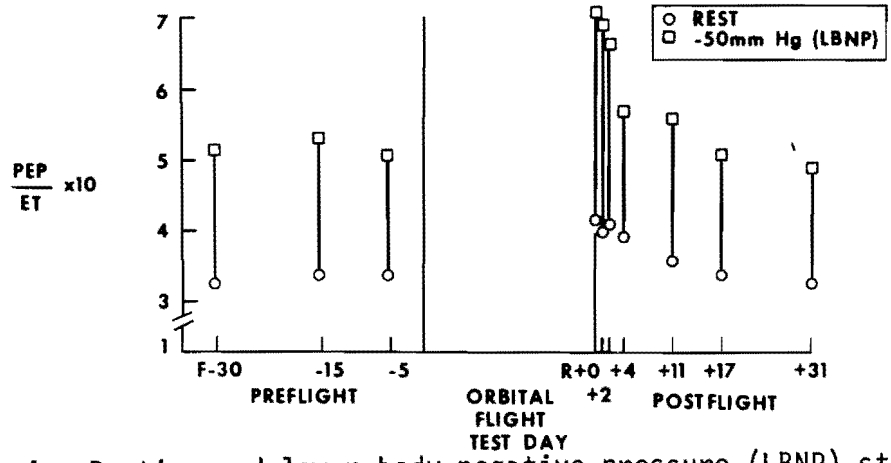


Figure 4. Resting and lower body negative pressure (LBNP) stressed pre-ejection period/ejection time (PEP/ET) - mean values for Skylab 4 crewmen.

TABLE I. PERCENT CHANGE IN SYSTOLIC TIME INTERVALS DURING LOWER BODY NEGATIVE PRESSURE - SKYLAB 3 AND SKYLAB 4 CREWMEN

Recovery Day, Percent Change From Preflight

SKYLAB MISSION	TEST	$(Q - S_2)$ INDEX	EJECTION TIME INDEX %	PRE-EJECTION PERIOD %	PRE-EJECTION PERIOD / EJECTION TIME %
3	REST	NO CHANGE	↓ 7	↑ 18	↑ 28
	LBNP	NO CHANGE	↓ 10	↑ 14	↑ 33
4	REST	NO CHANGE	↓ 7	↑ 15	↑ 20
	LBNP	NO CHANGE	↓ 7	↑ 10	↑ 28

All systolic time interval changes were back within preflight values by two to four weeks in all crewmen. Most resting systolic time intervals had returned within a week to 11 days. Most systolic time intervals at -50 mm Hg had returned by 9 to 16 days on Skylab 4. However, all three of the Skylab 3 crewmen had abnormal pre-ejection period/ejection time until the tests 31 days after recovery because of both abnormal ejection time interval and borderline high pre-ejection period during stress.

Mean of the diastolic pressures (one determinant of systolic time intervals) for the Skylab 3 and Skylab 4 crewmen are shown in figure 5. Diastolic pressure tended to be elevated during the first or second day after splashdown and then returned to preflight values; the Commander on Skylab 4 maintained an elevated diastolic pressure until 11 days after recovery. Also, the Pilot on Skylab 3 had an elevated diastolic pressure until 4 days after recovery. No crewman exhibited frank pathologic blood pressures during supine rest (control) phase of the lower body negative pressure tests. Stress heart rates had returned to preflight levels by the fourth day after recovery.

Percent change in leg volume (fig. 6) during lower body negative pressure was within preflight values on recovery day. With the exception of the Commander's test on the fourth day postflight, the Skylab 3 crewmen's response remained within baseline limits. The percent change in leg volume for two Skylab 4 crewmen (Scientist Pilot and Pilot) appeared to be elevated on days one to four after recovery, while the Commander's response was within preflight levels during this period. In spite of these findings the Skylab 4 crewmen regained their preflight systolic time intervals more quickly than did the Skylab 3 crewmen; these findings will be addressed again in the discussion.

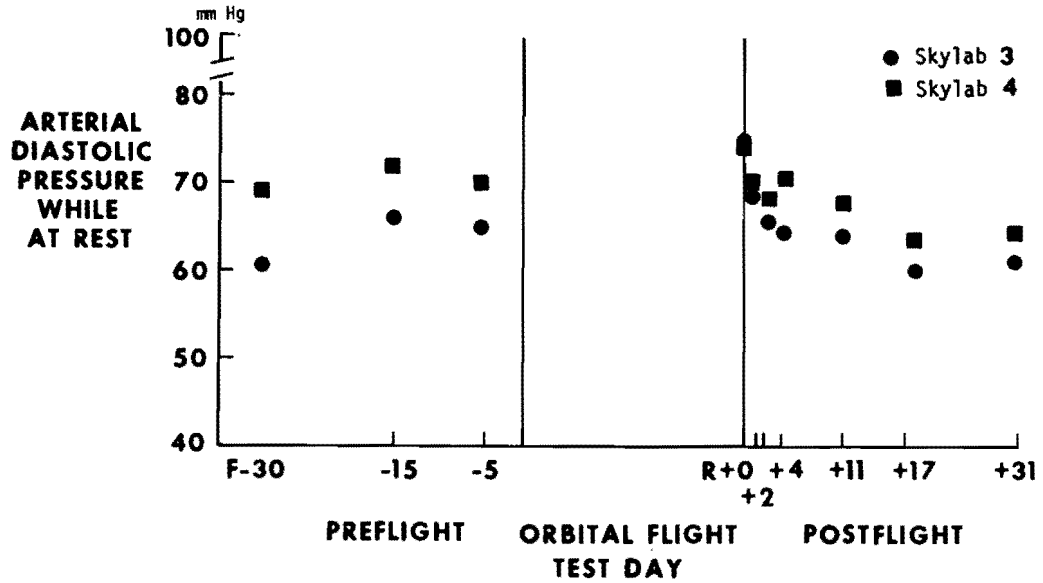


Figure 5. Resting diastolic pressures, mean values for Skylab 3 and Skylab 4 crewmen.

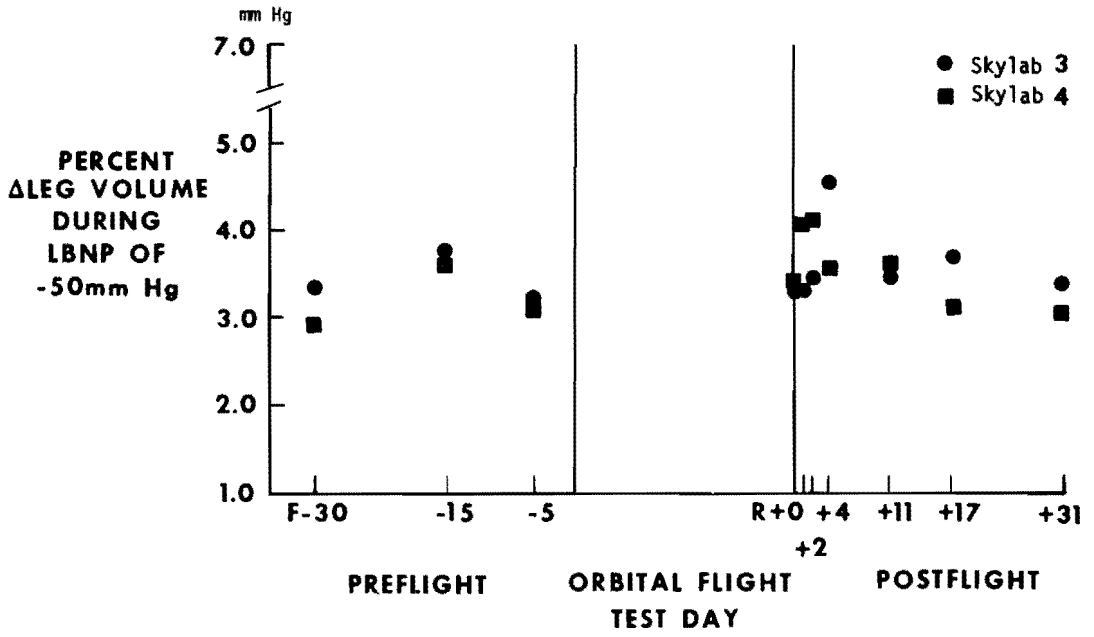


Figure 6. Mean percent change in leg volume during preflight and postflight lower body negative pressure (LBNP) tests at -50 mm Hg negative pressure.

The S_1 Amplitude responses of all Skylab 4 crewmen were depressed post flight as shown in figure 7. Figure 8 shows a typical S_1 Amp response by the Skylab 4 Pilot preflight versus the day after recovery. Notice the progressive reduction in S_1 Amp with increase in negative pressure in the first postflight day test as compared to a preflight test. Heart rates are also shown in figure 8.

During his recovery day lower body negative pressure test the Pilot's S_1 Amp response fell to 30 percent, a value which during Apollo was uniformly associated with syncope (9). The Pilot exhibited presyncope during this recovery day test at approximately one minute into the maximal stress level. His S_1 Amp response to lower body negative pressure was back to preflight limits only by 31 days postflight compared to 11 days postflight for the Commander and Scientist Pilot.

Exercise Results

Preflight systolic time interval responses to the two minute bout of exercise at 150 watts were typical of those reported by other workers (8, 10). Figures 9, 10, 11, and 12 reflect the Skylab 4 mean systolic time interval responses on the first and eleventh days postflight, compared with three preflight tests. Supine resting values were obtained from the lower body negative pressure test data which were collected approximately one hour before exercise. Compared to preflight responses the first day postflight test can be summarized as follows: Total electromechanical systole ($Q\text{-}S_2$) corrected for heart rate $(Q\text{-}S_2)I$ increased and ejection time index decreased during upright rest and exercise by four percent in the Scientist Pilot and Pilot with the Commander showing no significant change in $(Q\text{-}S_2)I$ or in ejection time index. Mean pre-ejection period increased 15 percent at rest and increased 14 percent during excerise. The pre-ejection period/ejection time increased by 22 percent at rest and 26 percent during exercise compared with the preflight values. Table II shows individual crewmen results.

TABLE II. PERCENT CHANGE IN STI - REST AND EXERCISE - POSTFLIGHT COMPARED WITH PREFLIGHT IN SKYLAB 4

CREWMAN	STATE	$(Q\text{-}S_2)I$	ETI	PEP	$\frac{PEP}{ET}$
Commander	Rest	↑ (NC)	↓ (NC)	↑ 6	↑ 19
	Exercise	↑ (NC)	↓ (NC)	↑ 5	↑ 18
Scientist Pilot	Rest	↑ 4	↓ 4	↑ 22	↑ 24
	Exercise	↑ 4	↓ 4	↑ 16	↑ 31
Pilot	Rest	↑ 4	↓ 4	↑ 18	↑ 22
	Exercise	↑ 4	↓ 4	↑ 22	↑ 30

NC = No significant change

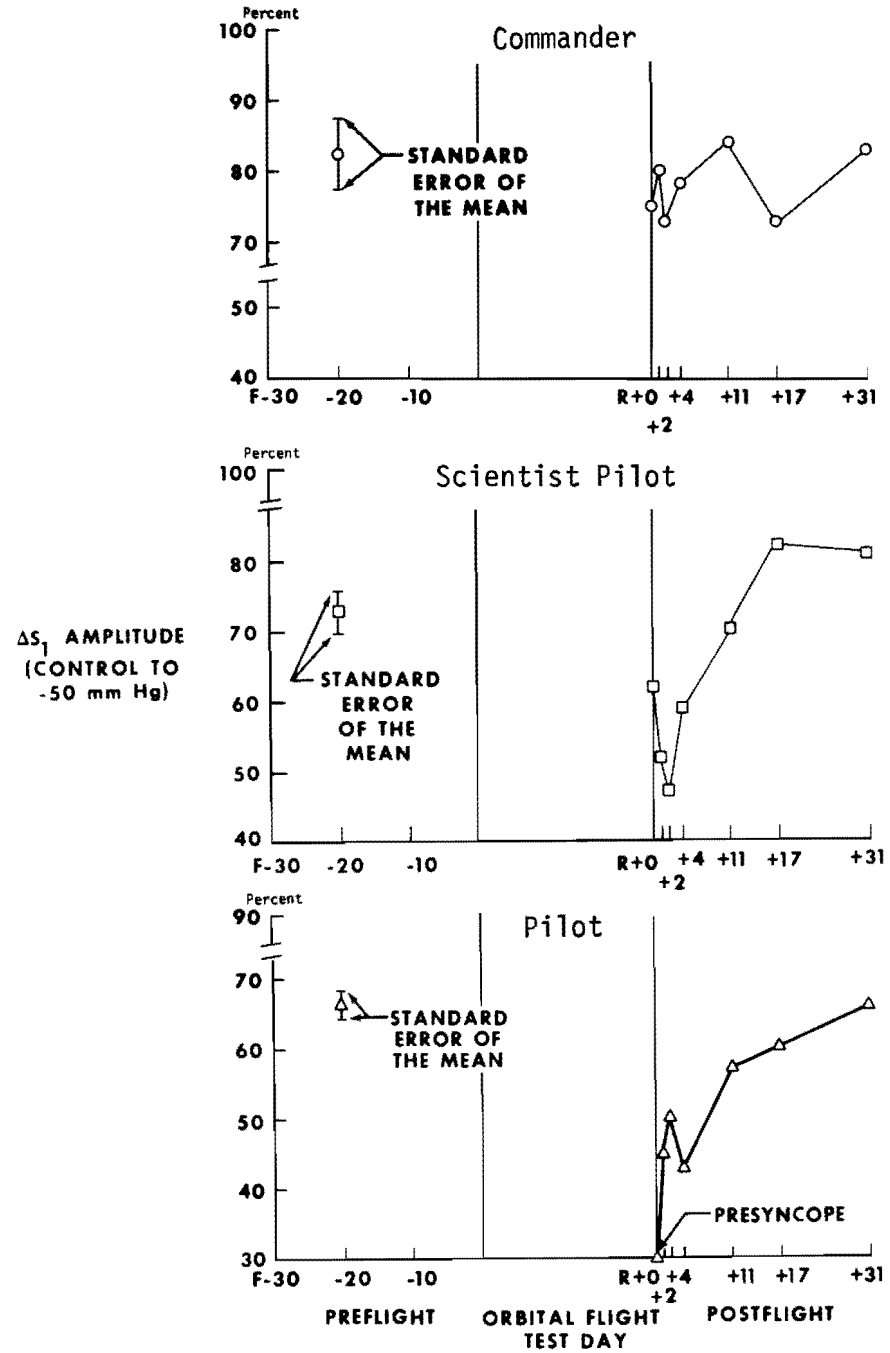


Figure 7. Percent change in first heart sound amplitude from control to -50 mm Hg lower body negative pressure for Skylab 4 crewmen.

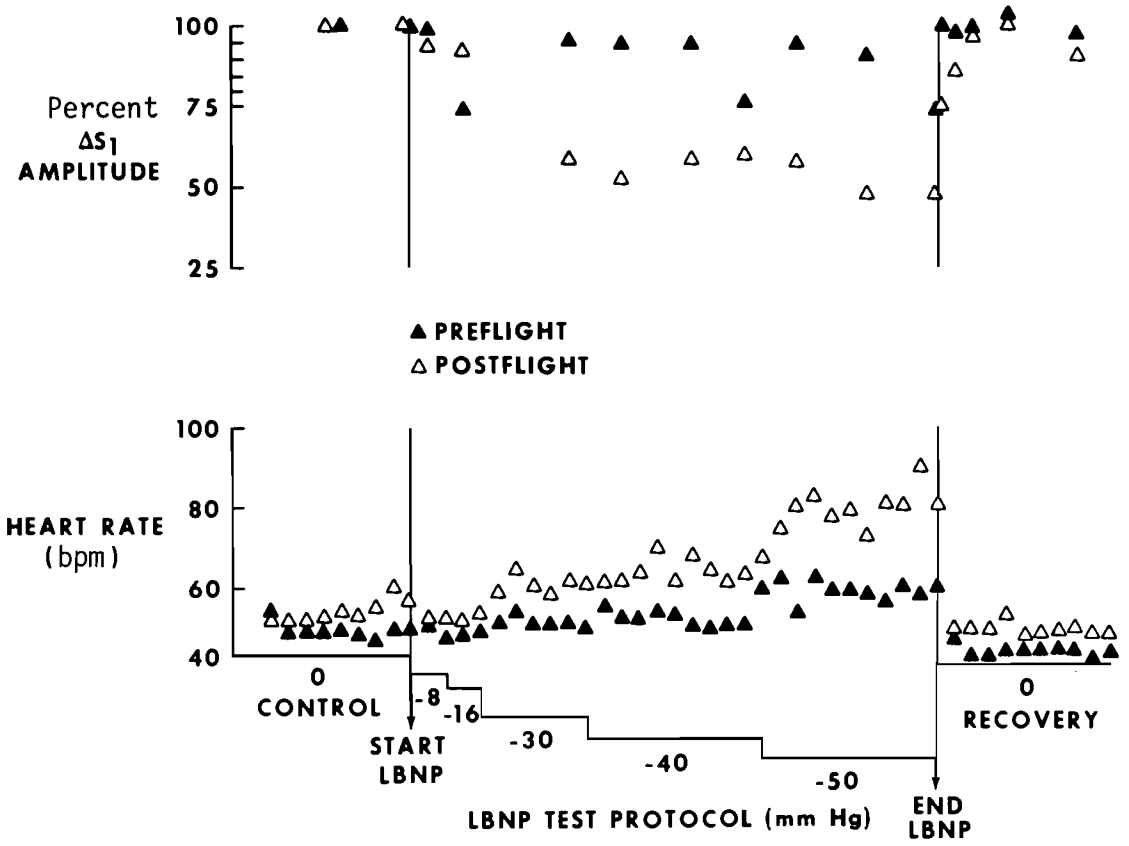


Figure 8. Heart rate and first heart sound amplitude response to lower body negative pressure (LBNP) by Pilot of Skylab 4 - preflight versus day 1 postflight.

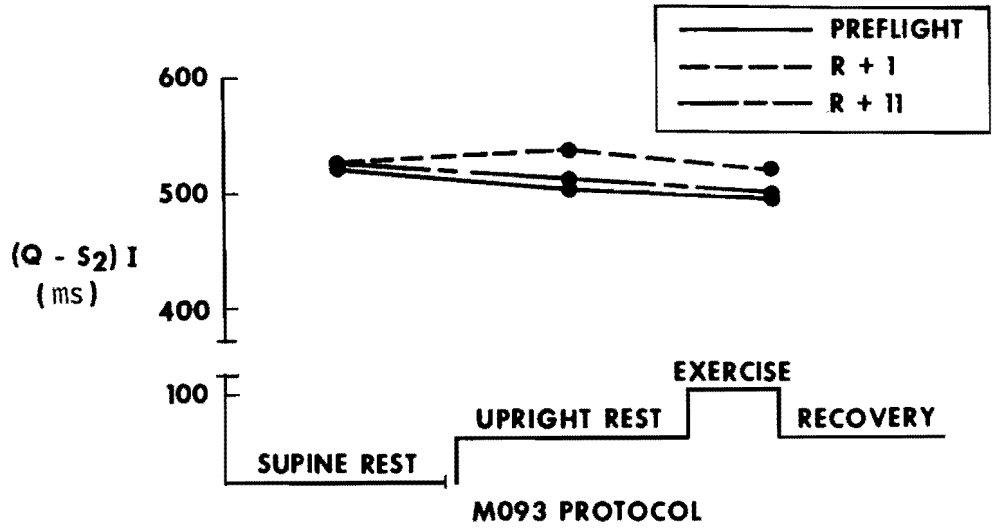


Figure 9. Response of all Skylab 4 crewmen to exercise - total electromechanical systole. Mean $(Q-S_2)I$ at rest and after 150 watts exercise.

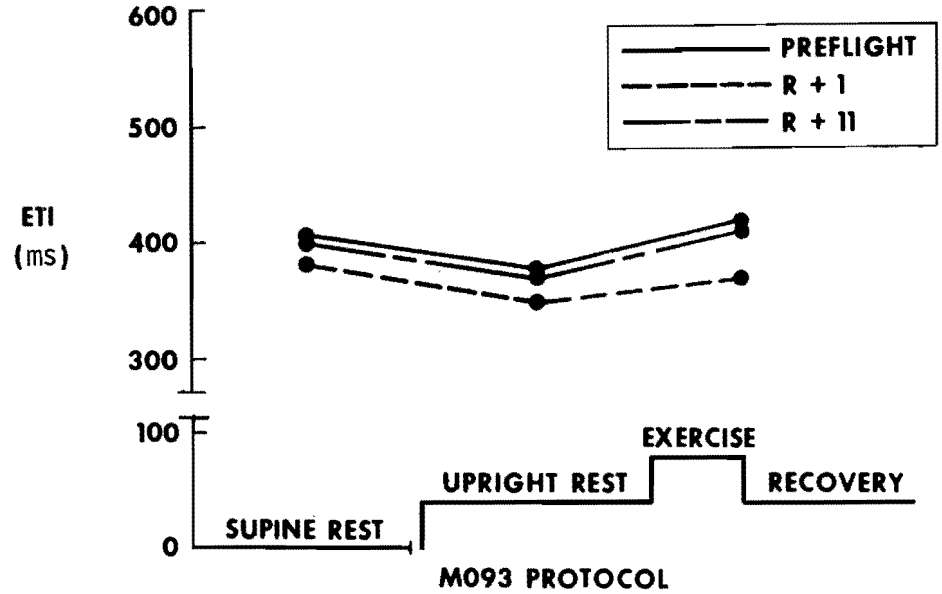


Figure 10. Response of all Skylab 4 crewmen to exercise - mean ejection time index (ETI) at rest and after 150 watts exercise.

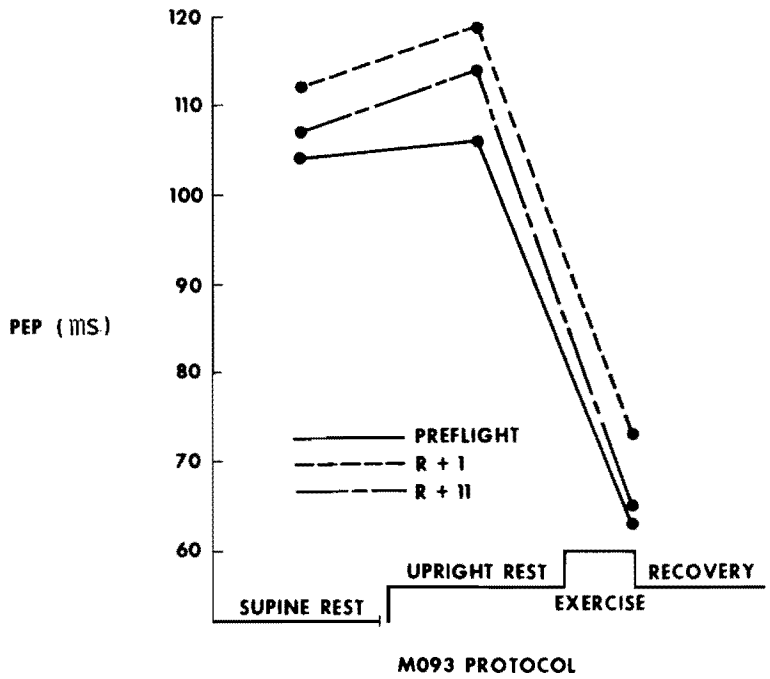


Figure 11. Response of all Skylab 4 crewmen to exercise - mean pre-ejection period (PEP) at rest and after 150 watts exercise.

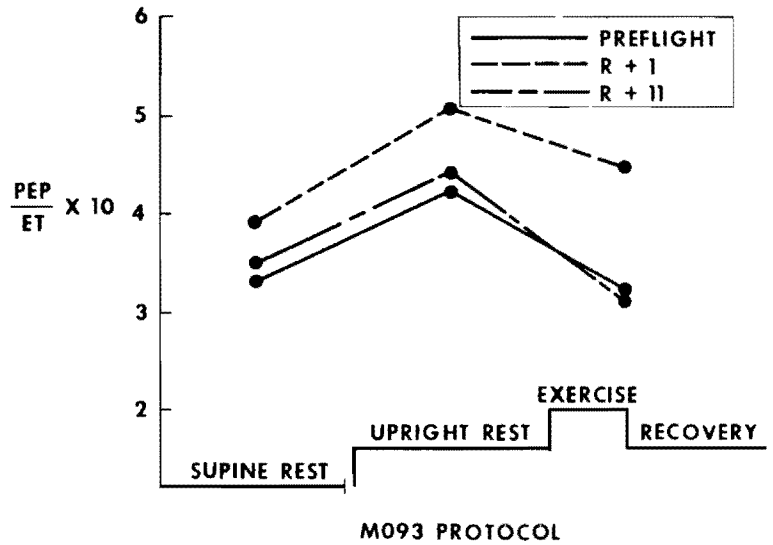


Figure 12. Response of all Skylab 4 crewmen to exercise - mean pre-ejection period/ejection time (PEP/ET) at rest and after 150 watts exercise.

First heart sound amplitude responses to exercise of the individual Skylab 4 crewmen are shown in figure 13. The Commander had very little if any change in the S_1 Amp for given heart rate at 150 watts postflight. The Scientist Pilot had a depressed S_1 Amp response on the first day postflight, but an apparently normal one on the eleventh day postflight. The Pilot's S_1 Amp response was low compared with the other crewmen on two of the three preflight tests. His response appeared to be depressed further postflight with no differences between the first and eleventh day postflight tests. These data have not been analyzed statistically as of the writing of this paper so that full interpretation of this data is not possible at this time. No evidence for a training effect was apparent.

Clinical Findings, Phonocardiography and Apexcardiography

The crewmen of Skylab 3 and Skylab 4 were given thorough cardiovascular examinations which included phonocardiograms. Apexcardiograms were done on Skylab 4 crewmen only. Although fourth heart sounds (S_4) were present on some crewmen preflight these sounds are not abnormal (11). All heart sounds were diminished postflight. Several crewmen had prominent S_4 with exercise (12). However, even heart sounds and arterial pulsations obtained during exercise were attenuated in the immediate postflight period. By 11 day postflight these findings disappeared. Apexcardiography was normal preflight. Postflight the point of maximal impulse was not palpable and no apexcardiograms could be obtained. This was true as late as the eleventh day postflight on Skylab 4 crewmen. This finding is consistent with the other data and probably reflects diminished ventricular action.

One finding which was of concern at first, but which is now accepted as not being of clinical importance was trace to one plus pretibial edema in all crewmen. This finding appears to begin on day 1 or day 2 postflight. The edema is usually "trace" after one or two hours of ambulation. In Skylab 3 the edema lasted to day 16 postflight On Skylab 4 it was absent on day 18 postflight. Although the systolic time intervals data were abnormal and it is known that usually edema is a common sign of a compromised left ventricle, the causes for this postflight edema are probably more complex than those of pure cardiac dysfunction.

The facies caused by cephalad fluid shifts, seen on television and in photographs which are so obvious during flight, are peculiarly absent within an hour after splashdown. It is interesting that the in-flight facies, described elsewhere appear quite similar to subjects who are studied in the head down tilt position (1).

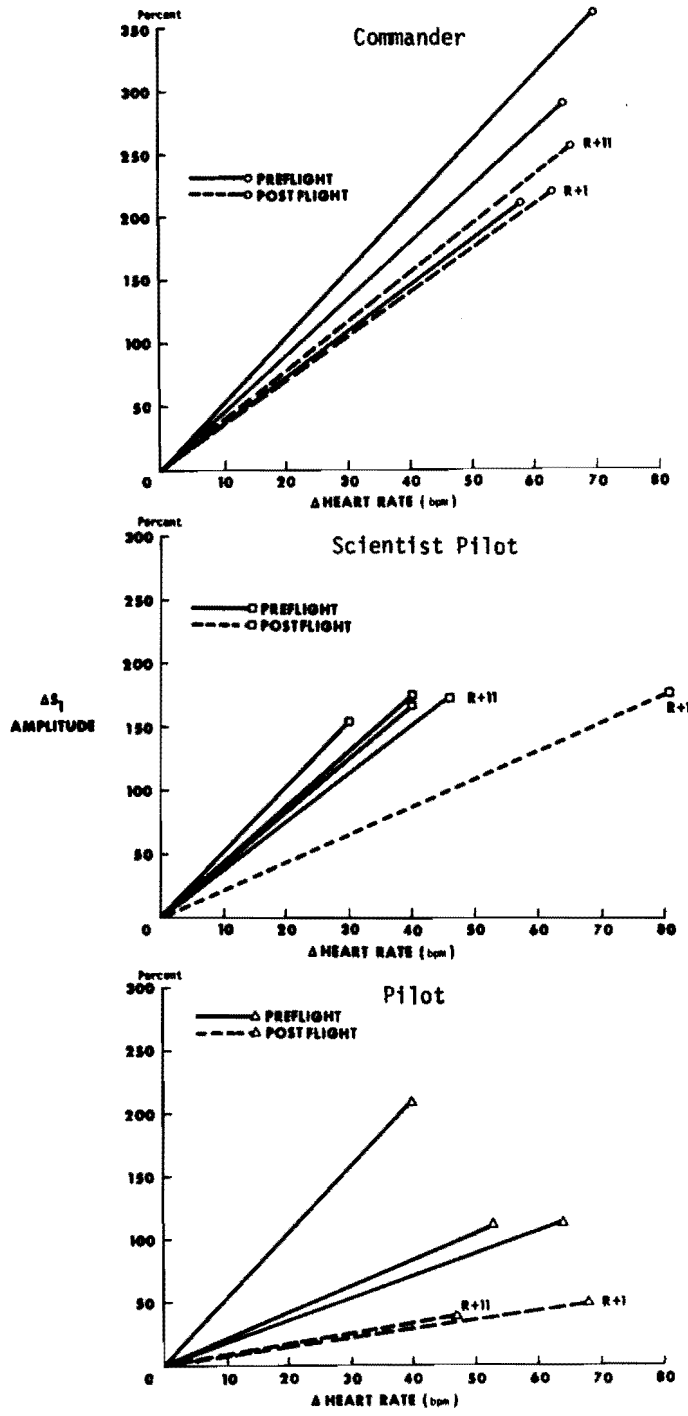


Figure 13. First heart sound amplitude response to exercise - Skylab 4 Crewmen.

Immediately postflight, the Skylab crewmen appeared to be relatively dehydrated and the skin on the face was wrinkled rather than being puffy and fluid filled. Clinically, it appears that the fluid is redistributed rapidly postflight, but the pattern of distribution is such that plasma volume (and blood volume) is not replaced immediately. This decreased blood volume is probably a major cause for abnormal systolic time intervals during the recovery day testing at rest and during lower body negative pressure stress (as is afterload). The Skylab 4 crewmen did not appear to be as dehydrated upon recovery as were the Skylab 3 crewmen.

DISCUSSION

Sytolic time intervals and S_1 Amp data are difficult to interpret in man. Interpretation is even more difficult when some of the hemodynamic variables are possibly unknown. However, a better interpretation of these data is possible if one knows the hemodynamic events which occur in response to a known stress (13, 14). The intervals of systole have been described and interpreted for certain stresses such as lower body negative pressure (3, 15, 16); and exercise (10, 8). The availability of additional information such as blood volume, diastolic or mean blood pressure, and posture are needed when one attempts to interpret systolic time interval information (8). The externally measured intervals have been shown to correlate quite well with those measured directly (17).

Actually there are two problems to the analysis of systolic time intervals and S_1 Amp data. One problem involves accuracy of measuring the various parameters. Another, more difficult problem, is interpretation of the obtained results. The data presented in this paper is subject to both of these problems. However, every attempt has been made to choose the proper transducers and recording equipment and to measure as accurately as possible the intervals and amplitudes.

The systolic time interval data obtained from the Skylab astronauts during the preflight period reflect good reproducibility of these measurements. During this controlled period the intervals do not vary a great deal as can be seen in figures 1 through 7 which present the results of the three preflight tests. Conversely, one recognizes that the postflight, as well as in-flight, period is not nearly as controlled (18). However, the reproducibility of postflight from several missions allows some confidence that these data do represent the responses of individuals after space flight.

The preflight (control) rest and lower body negative pressure data obtained from the Skylab astronauts are quite similar to the systolic time interval data obtained from younger men (3). The postflight systolic time interval data at rest and during lower body negative pressure (especially on recovery day and days 1 and 2 post recovery) reflect changes one would expect from a decrease in total blood volume, but also from myocardial dysfunction (19, 20, 13, 21). In the face of a constant total electromechanical systole (corrected for heart rate) with a decreased ejection time index and an increased pre-ejection period one is presented with three possibilities, or combinations, to explain the results:

- a decrease in preload,
- an decrease in contractility, and/or
- an increase in afterload (22).

A decrease in preload was suggested by measurements of significant decreases in blood volume on all Skylab crewmen (5). There were deficits in both red blood cell mass and plasma volume. The blood volume is reportedly back to preflight levels by one week with some fluctuations in plasma volume although the red blood cell mass remains depressed for a longer duration (23). The decrease in preload associated with lower body negative pressure stress or with upright posture is well established (14, 16, 24).

If decrease in absolute blood volume were the only factor influencing the systolic time interval findings after space flight one would expect the systolic time intervals to return to preflight values along with the blood volume repletion (24). However, this is not the case. The systolic time intervals remain abnormal for a longer period. Skylab 3 crewmen took longer to return to baseline systolic time intervals than did the Skylab 4 crew although the decreased blood volume and the duration of this decrement were similar. The differences between the crews may be related to activities of the crewmen in-flight, *e.g.*, the amount of exercise performed; or they may be related to postflight activities as well.

The systolic time interval during lower body negative pressure stress remains abnormal longer than did the systolic time intervals at rest. This finding is not surprising since one goal of stress testing is to elicit cardiac malfunction when none is apparent at rest. Additionally, because the stressed systolic time intervals remained depressed after blood volume repletion, it could be argued that perhaps more blood is pooled at -50 mm Hg postflight than is pooled preflight. Therefore, a decreased preload by virtue of increased pooling could account for

the results of postflight lower body negative pressure induced changes in systolic time intervals. The percent change in leg volume does not support this hypothesis. The Skylab 3 crewmen exhibited abnormal systolic time intervals for one month after return although there was little deviation in percent change in leg volume during lower body negative pressure between preflight and postflight periods. No consistent pattern of percent change in leg volume and systolic time interval response was noted for the Skylab 4 crewmen either (fig. 6).

Afterload, a potent determinant of the intervals of systole, if consistently elevated could cause the systolic time interval changes noted in the astronauts' postflight tests (22). The Commander of Skylab 4 had significant elevation in diastolic pressure through day 11 postflight. The Pilot demonstrated a similar picture after Skylab 3. However, these crewmen did not differ in their systolic time interval responses to lower body negative pressure, or at rest, from the other crewmen of their respective missions. The systolic time interval response appears to be only partially accounted for by changes in afterload with the exception of recovery day testing. A summary of these data are given in figure 5.

Contractility, the other independent determinant of systolic time intervals (in particular pre-ejection period) (25, 22, 26) could be considered as a cause for the changes in systolic time intervals observed postflight. Patients with primary myocardial disease, as well as patients with other forms of chronic heart disease whose ventricles are abnormal, exhibit changes in systolic time intervals which are identical to those noted in Skylab crewmen postflight (22, 6, 13). However, these patients' hearts are usually enlarged, *i.e.*, increased preload is a sign of the problem. Ejection fraction is quite low in these patients (20, 28). The total electromechanical systole (corrected for heart rate) of these patients are either normal or slightly prolonged. Although preload is more than adequate, a condition which would be reflected by an abbreviated pre-ejection period, contractility is decreased and pre-ejection period is markedly prolonged. The stroke volume is decreased as is the ejection fraction, the ejection time index is shortened. Consequently, pre-ejection period/ejection time is elevated in these patients. In compromised hearts, administration of a positive inotropic drug such as digitalis shortens the total electromechanical systole (corrected for heart rate) mainly by virtue of a decreased pre-ejection period. Ejection time index is either unchanged or prolonged. These systolic time intervals reflect the increase in contractility, stroke volume, and ejection fraction. No exact causal relationship can be applied to ventricular function, given a set of systolic time interval alone, because of the complex variables. However, ancillary information makes their interpretation a valuable method for the evaluation of cardiac function.

The above example of how systolic time interval reflects cardiac function, although not directly applicable to the Skylab results does point out the kind of reasoning one must go through in order to intrepret a set of systolic time intervals. However, the astronauts could have had a slight decrease in contractility in addition to the decrease in preload. The systolic time interval responses to the exercise-vectorcardiograph test postflight reflect possible decreases in stroke volume which may be due to decreased left ventricular function (28, 21, 29). Significant increases in total electromechanical systole (corrected for heart rate) and pre-ejection period with decreases in ejection time index are consistent with myocardial decrements in the Skylab 4 crewmen in response to a 150 watt exercise challenge on day 1 postflight. Also, the systolic time intervals and first heart sound amplitude data obtained during post flight lower body negative pressure tests are suggestive of myocardial dysfunction, *e.g.*, the recovery day test on the Pilot. This data is also suggestive of a bedrest response, where significant losses of blood volume exist and a myocardial factor could not be ruled out as a cause for cardiovascular decrements (30). We are confronted with the fact of a true decrement in performance without a clear indication that the decrement is due to a decrease in preload or to a mixture of decreased preload and decreased heart muscle function. Neurohumoral factors are also possible.

Note

Studies on the amplitude of the first heart sound during lower body negative pressure and exercise stresses provide analysis of ventricular function from a slightly differenct view. It had been shown as with systolic time intervals that during stress testing patients or animals with cardiac dysfuction show a lower increment in first heart sound amplitude than do normal organisms (31, 27, 29, 23, 33). First heart sound amplitude can be used as an index of cardiac performance, expecially during stress testing.

In reviewing the data from Skylab 4 astronauts certain correlations are apparent between the systolic time interval and first heart sound amplitude data. For example, the first heart sound amplitude responses of the Pilot to lower body negative pressure and to exercise are quite similar. Of the Skylab 4 crewmen the Pilot exhibited the lowest increment in first heart sound amplitude per increment in heart rate during the exercise tests on days 1 and 11 postflight. His first heart sound amplitude responses to lower body negative pressure was lowest and its return to preflight took longer than did the other two crewmen's responses. Resting value of ejection time index, an index of stroke volume, took longest to return of the Skylab 4 crewmen (day 11 postflight). Lower body negative pressure stressed pre-ejection

period/ejection time was above preflight limits until day 18 postflight (the same, however, as the Commander). During postflight exercise on day one postflight, pre-ejection period was 17 percent and 6 percent higher than the Commander and Scientist Pilot, respectively. Lengthening of total electromechanical systole (corrected for heart rate) and pre-ejection period/ejection time during this exercise stress was equal to that of the Scientist Pilot, but greater than these values in the Commander (4 percent and 12 percent). Also, on recovery day, when he exhibited a presyncopal episode during lower body negative pressure, the Pilot's first heart sound amplitude fell to 30 percent (25). His percent change in ejection time index was lowest and pre-ejection period highest of the crewmen during this test.

These close correlations of systolic time interval and first heart sound amplitude responses to postflight stress testing add assurance that these techniques, each proven by direct methods to reflect ventricular function, point to a decrease in ventricular function as being a definite cause for the observed decrements in post flight orthostatic and exercise tolerance, whether or not peripheral mechanisms are responsible for the decreased ventricular performance. It is unfortunate that noninvasive methods are not available which can allow one to give an exact accounting of the specific roles played by the heart, the peripheral circulatory system, and neurohumoral systems in causing these decrements. Such techniques would certainly allow us to develop *definite* dose-response curves for cardiovascular countermeasures during longer duration space flight.

The postflight noninvasive measurements including echocardiography (4), which were accomplished at rest and during stress testing on Skylab 4, present as near complete a picture of cardiovascular status as was possible to obtain. Furthermore, the additional accuracy which might have been provided by invasive methods may well have lead to less conclusive results on several experiments if complications of these invasive procedures had occurred. To our knowledge, no measurements made on any of the Skylab crewmen including stress testing had any affect on the natural course of readaptation to one-g.

CONCLUSIONS

Although much of the decrement in cardiovascular functioning seen postflight is due to decreased blood volume, there is evidence in the systolic time interval, first heart sound amplitude, and clinical data to suggest that there was at least a functional impediment to venous return and possibly a myocardial factor as well. Whatever the causes, the impairments were not of gross pathologic porportions. If ability to take care of oneself is considered, the astronauts appeared to be quite capable of this task postflight.

Systolic time intervals and phonocardiographic data, at rest and during stress, indicate that decrements in cardiovascular function are not related necessarily to mission duration. However, this statement must be interpreted with the knowledge that each crew was handled slightly different. For example, on the longest mission much more time was alloted to various exercises than on the 28 or 59 day missions.

Functional impairment of the cardiovascular system as a result of space flight appears to be self limited. Readaptation to one-g is complete and probably requires one to two months. Many readaptations including systolic time interval and first heart sound amplitude responses to lower body negative pressure and submaximal exercise require less time.

The use of noninvasive techniques to study the cardiovascular responses after space flight is useful in determining hemodynamic changes quantitatively over time. Such techniques would definitely be worthwhile during zero-g exposure of future missions in order to define cardiovascular status from first exposure to steady state adaptations. Sensitive noninvasive techniques coupled with ground based analogs of weightlessness would serve to establish dose-response curves for the cardiovascular system so that exact countermeasures could be used operationally during the Space Shuttle era and beyond.

Supplemental Comments Regarding Cardiovascular Adaptations

It is difficult to discuss the preflight and postflight finding of Skylab without speculating on what happens to the body upon exposure to zero gravity and upon the ensuing adaptations the body makes to this environment. It is equally difficult to discuss the postflight findings without speculating on the condition of the body during long duration space flight just prior to, during, and upon entry into the Earth's gravitational field. Comments in this section will be limited to cardiovascular responses.

Upon entry into the zero-gravity environment the right heart is provided with an increased venous return by virtue of the lack of a gravity field and the relatively abundant capacity of the upper body vasculature. The abundance of blood available to the heart under these circumstances must lead to an increase in cardiac output as the healthy heart ejects as much blood as it is presented. The increased right ventricular filling may be partially compensated for by an increase in pulmonary blood volume, but at some filling pressure is channeled directly to the left ventricle, creating an increase in Starling Effect (increased preload). If *no* exercise is performed, the oxygen needs of the body are easily satisfied by the increased cardiac output compared with one-g and heart rate decreases as the adrenergic stimuli subside in the wake of a daily routine, which is established after launch. It is of interest that a progressive decrease in heart rate was noted during Apollo missions.

During exercise as on the Skylab cycle ergometer the first few trials are likely to be awkward secondary to lack of zero-g experience. There is probably a decreased mechanical efficiency until the crewman learns how to master the zero-g induced difficulties of holding on and pedaling. Once these mechanical problems are mastered, however, the zero-g environment allows one to accomplish higher workloads than was possible during one-g cycle ergometry because the venous return is increased and the problems of supine exercise in one-g are absent. Oxygen consumption is increased also because the arms play a more active role during zero-g exercise on the ergometer as the crewman begins to work against his arms.

An increase in $\dot{V}_{O_2}$ Max is recognized generally as reflecting a training effect. However, in zero-g an increased $\dot{V}_{O_2}$ Max must be interpreted with caution. Use of the arms contributes to $\dot{V}_{O_2}$. Also, the increase in cardiac output caused by the increased availability of blood in zero-g will cause the appearance of a training effect by causing an increased $\dot{V}_{O_2}$ and allowing greater work capacity.

Fixed submaximal work loads (from one-g testing) present less of a challenge in zero-g (once learning has occurred) by the above mechanisms, which mimic a training effect, so that such parameters as heart rate and blood pressure are decreased compared with one-g testing. The recovery heart rate is also decreased since blood from the working muscles is returned more quickly in zero-g and does not stagnate as happens in one-g in the upright position. The rapid return of heart rate after exercise is a common finding after a training effect, and one could reach this latter conclusion if not aware of the possible behavior of body fluids, and especially blood, in zero-g.

Exercise induced increases in blood pressure apparently do not significantly effect any symptoms of increases in intercranial pressure. Crewmen failed to recognize any differences in head fullness during isometric as opposed to dynamic exercise although both were used frequently during each in-flight day. It is known, however, that by comparison with dynamic exercise, isometric exercise causes a much greater increase in both systolic and diastolic pressure with only small increments in heart rate. The dynamic exercise, rather than causing an increase in the symptom of head fullness, actually caused relief of this symptom. Additionally, the secondary effects of the cephalad fluid shifts, *i.e.*, nasal and sinus congestion were also abated by strenous dynamic exercise. The mechanisms for relief of these symptoms are probably related to redistribution of the cardiac output to the exercising muscles (arms and legs) and to an outpouring of vasoactive catecholamines which constrict mucosal blood vessels and reduce mucosal tissue swelling.

In contrast to exercise responses, the lower body negative pressure test is more stressful in zero-g than in one-g (1). Blood volume may be decreased, plus the crewman is forced deeper into the Lower Body Negative Pressure Device by lack of gravity. Crewmen quickly discover this discrepancy and learn how to make the stress more comparable to the one-g tests (1). Although of no clinical importance several crewmen noticed the recoil from the heart's contractions. This sensation is more apparent in the head and neck during complete relaxation. Ballistocardiography could be more useful in zero-g.

Postflight, there are definite decrements in the ability of the cardiovascular system to withstand orthostatic and metabolic stresses. These decrements can be measured (24, 34, 19). There is an immediate decrement in exercise performance to a given workload (35, 36, 2). Maximal aerobic capacity was not evaluated postflight although the M171 experiment utilizes moderate to heavy workloads. Decreases in ability to perform heavy exercise such as jogging may be depressed for several weeks postflight. At least part of this lag time is due to postflight schedules and to weakened musculoskeletal structures. Orthostatic intolerance has already been discussed (1). The crewmen are usually surprised by the decreased stress of this test postflight compared to in-flight sensations.

In the postflight period readjustment to one-g probably begins with the opening of the parachutes. The cardiovascular decrements noted shortly after this time probably are related to a decrease in absolute blood volume, a functional impairment to venous return (which lasts beyond the volume deficit) and possibly to a transient primary myocardial dysfunction. Fortunately, the decrements appear to be transient and self-limited.

ACKNOWLEDGMENTS

The authors wish to thank Dr. A. E. Nicogossian, Miss M. M. Jackson, and Mrs. M. Ward for their support of the experiments. Special appreciation is extended to Mr. Joseph Baker, Mr. John Donaldson, Mrs. Mary Taylor and Miss Karen Parker for their diligent and dedicated effort in making the data analysis possible in a very short period of time. The authors are grateful to Dr. Roger Wolthuis, Mr. Donald Golden, Mr. Thomas Beale, and Mr. Karl Kimball for their support in developing the computer programs. In addition Mr. T. W. Holt of Technology Incorporated is to be commended for his leadership and expert management in assembling the team which made this analysis possible. The Skylab mission surgeons, Drs. Charles Ross, Paul Buchanan, and Jerry Hordinsky along with Dr. William Shumate, leader of the Skylab Life Sciences Mission Managers, are also to be congratulated for their contributions to this effort.

REFERENCES

1. Johnson, R. L., G. W. Hoffler, A. E. Nicogossian, S. A. Bergman, Jr. and M. M. Jackson. Lower Body Negative Pressure: Third Manned Skylab Mission. Presented at Skylab Life Sciences Symposium, NASA Johnson Space Center, Houston, Texas, August 1974.

2. Rummel, J. A., E. L. Michel and C. A. Berry. 1973. Physiological Response to Exercise after Spaceflight. *Aerospace Med.*, 44.

3. Grayboys, T. B. and F. J. Forlini. Systolic Time Intervals in Subjects Exposed to Progressive and Sudden Lower Body Negative Pressure (LBNP). Presented at the Aerospace Medical Association Scientific Meetings, Las Vegas, Nevada, May 1973.

4. Henry, Walter L., Stephen E. Epstein, James M. Griffith, Robert E. Goldstein and David R. Redwood. Effects of Prolonged Space Flight on Cardiac Function and Dimensions. Presented at Skylab Life Sciences Symposium, NASA Johnson Space Center, Houston, Texas, August 1974.

5. Johnson, Philip, Theda B. Driscoll and Adrian D. LeBlance. Blood Volume Changes. Presented at the Skylab Life Sciences Symposium, NASA Johnson Space Center, Houston, Texas, August 1974.

6. Weissler, A. M. and C. L. Garrard. 1971. Systolic Time Intervals in Cardiac Disease. *Modern Concepts of Cardiovascular Disease*, XL: 1-4.

7. Johnson, J. M., W. Siegel and G. Blomqvist. 1971. Characteristics of Transducers Used for Recording the Apexcardiogram. *J. of Appl. Physiol.* 31: 796-800.

8. Spodick, D. H. and V. M. Quarry-Pigott. 1973. Effects of Posture on Exercise Performance - Measurement by Systolic Time Intervals. *Circulation*, XLVIII: 74-78.

9. Bergman, S. A. Jr., R. A. Wolthuis, G. W. Hoffler and R. L. Johnson. Analysis of Phonocardiographic Data From Apollo Crews: A Pre- and Post flight Evaluation During LBNP. Presented at the Aerospace Medical Association Scientific Meetings, Las Vegas, Nevada, May 1973.

10. Debacker, G. 1974. Effect of Posture on Exercise Performance. *Circulation*, XLIX: 594.

11. Craig, E. 1967. Gallop Rhythm. *Prog. Cardiovascular Dis.*, 10.

12. Bergman, S. A. Jr. and G. Blomqvist. 1972. The Significance of atrial gallops during Exercise. Abstracts of the 45th Scientific Sessions, Supplement II to *Circulation*, XLV and XLVI.

13. Spodick, D. H., V. M. Pigott and R. Chirife. 1972. Preclinical Cardiac Malfunction in Chronic Alcoholism: Comparison with Matched Normal Controls and with Alcoholic Cardiomyopathy. *New England J. of Med.*, 287: 677-680.

14. Stafford, R. W., W. S. Harris and A. M. Weissler. 1970. Left Ventricular Systolic Time Intervals as Indices of Postural Circulatory Stress in Man. *Circulation*, XLI: 485-492.

15. Stevens, P. 1966. Cardiovascular Dynamics during Orthostasis and the Influence of Intravascular Instrumentation. *Amer. J. Cardiol.*, 17: 211.

16. Wolthuis, R. A., S. A. Bergman, Jr. and A. E. Nicogossian. July 1974. Physiological Effects of Locally Applied Reduced Pressure in Man. *Physiological Reviews*, 54: 566-595.

17. Martin, C. E., J. A. Shaver, M. E. Thompson and P. S. Reddy. 1971. Direct Correlation of External Systolic Time Intervals with Internal Indices of Left Ventricular Function in Man. *Circulation*. XLIV: 419-431.

18. Aronow, W. S., P. R. Harding, V. Dequattro and M. Isbell. 1973. Diurnal Variation of Plasma Catecholamines and Systolic Time Intervals. *Chest*, 63: 722-726.

19. Weissler, A. M., W. S. Harris and C. D. Schoenfeld. 1968. Systolic Time Intervals in Heart Failure in Man. *Circulation*, XXXVII: 149-159.

20. Garrard, C. L., A. M. Weissler, and H. T. Dodge. 1970. The Relationship of Alterations in Systolic Time Intervals to Ejection Fraction in Patients with Cardiac Disease. *Circulation*, XLII: 455-462.

21. Limas, C. J., H. H. Guiha, O. Lekagul and J. N. Cohn. 1974. Impaired Left Ventricular Function in Alcoholic Cirrhosis with Ascites. *Circulation*, XLIX: 755-760.

22. Talley, R. C., J. F. Meyer and J. L. McNay. 1971. Evaluation of the Pre-Ejection Period as an Estimate of Myocardial Contractility in Dogs. *Amer. J. Cariol.*, 27: 384-391.

23. Kimzey, S. L., P. C. Johnson, S. E. Ritzmann and E. E. Mengel. Hematology and Immunology: The Second Skylab Mission. Presented at the Aerospace Medical Association Scientific Meetings, Washington, D. C., May 1974.

24. Burch, G. E. and P. Depasquale. 1964. Cardiac Performance in Relation to Blood Volume. *Amer. J. of Cardiol.*, 14: 784-795.

25. Epstein, S. E. 1968. Role of the Capacitance and Resistance Vessels in Vasovagal Syncope. *Circulation*, XXXVII.

26. Harris, W. S., C. D. Schoenfeld and A. M. Weissler. 1967. Effects of Adrenergic Receptor Activation and Blockade on the Systolic Pre-ejection Period, Heart Rate, and Arterial Pressure in Man. *J. of Clinical Investigation*, 46: 1704-1714.

27. Adolph, R. J. and J. F. Stephens. 1970. The Clinical Value of Frequency Analysis of the First Heart Sound in Myocardial Infarction. *Circulation*, XLI: 1003-1014.

28. Sugimoto, T. and T. Inasaka. 1973. Relationships of Left Ventricular Systolic Time Intervals to Hemodynamic Variables in Intact and Failing Hearts. *Japanese Circulation J.*, 37: 711-712.

29. Sakamoto, T., R. Kusukawa, D. M. Maccanon and A. A. Luisada. 1965. Hemodynamic Determinants of the Amplitude of the First Heart Sound. *Circulation*, XVI: 45-57.

30. Saltin, B., G. Blomqvist, J. H. Mitchell and R. L. Johnson. 1968. Response to Exercise after Bed Rest and After Training. *Circulation*, Supplement VII, XXXVII and XXXVIII: VII-1-VII-78.

31. Bergman, S. A., Jr., J. Houston, and G. Blomqvist. 1971. Intensity of the First Heart Sound in Normals and Patients with Coronary Heart Disease. *Clinical Res.*, 19.

32. Luisada, A. A., D. M. Maccanon, B. Coleman and L. P. Feigen. 1971. New Studies on the First Heart Sound. *Amer. J. of Cardiol.*, 28: 140-149.

33. Van Bogaert, A. 1966. New Concept on the Mechanism of the First Heart Sound. *Amer. J. of Cardiol.*, 18: 253-262.

34. Jorgensen, C. R., K. Wang, Y. Wang and F. L. Gobel. 1973. Effect of Propranolol on Myocardial Oxygen Consumption and Its Hemodynamic Correlates during Upright Exercise. *Circulation*, XLVIII: 1173-1182.

35. Michel, E. L., J. A. Rummel, C. F. Sawin, M. C. Buderer, J. D. Lem. Results of Skylab Medical Experiment M171 Metabolic Activity. Presented at the Skylab Life Sciences Symposium, NASA Johnson Space Center, Houston, Texas, August 1974.

36. Rummel, J. A., E.L. Michel and C. F. Sawin. Metabolic Studies During Exercise: The Second Manned Skylab Mission. Presented at the Aerospace Medical Association Scientific Meetings, Washington, D. C., May 1974.

EFFECT OF PROLONGED SPACE FLIGHT ON CARDIAC FUNCTION AND DIMENSIONS

Walter L. Henry, M.D.; Stephen E. Epstein, M.D.; James M. Griffith, Robert E. Goldstein, M.D.; and David R. Redwood, M.D.
National Institute of Health, Bethesda, Maryland

ABSTRACT

Echocardiographic studies were performed preflight 5 days before launch and on recovery day and 1, 2, 4, 11, 31 and 68 days postflight. From these echocardiograms the following measurements were made:

° left ventricular transverse dimension at end-diastole,

° left ventricular tranverse dimension at end-systole,

° ventricular free wall thickness at end-diastole.

From these primary measurements, left ventricular end-diastolic volume, end-systolic volume, stroke volume, and mass were derived using the accepted assumptions. Preflight measurements in the Commander revealed the left ventricular end-diastolic volume, stroke volume, and mass to be at the upper limit of normal, while those of the Scientist Pilot and Pilot were increased significantly above the normal range. These findings in the Scientist Pilot and Pilot resemble those seen in trained distance runners. Wall thickness measurements were normal in all three crewmembers preflight. Postflight basal studies were unchanged in the Commander on recovery day through 68 days postflight In both the Scientist Pilot and Pilot, however, the left ventricular end-diastolic volume, stroke volume, and mass were decreased slightly. These decreases were noted on recovery day through 11 days postflight but had returned to near normal by 31 days postflight. Wall thickness measurements were unchanged. Left ventricular function curves were constructed for the Commander and Pilot by plotting stroke volume versus end-diastolic volume. In both astronauts, preflight and postflight data fell on the same stright line demonstrating that no deterioration in cardiac function had occurred. These data indicate that the cardiovascular system adapts well to prolonged weightlessness and suggest that alterations in cardiac dimensions and function are unlikely to limit man's future in space.

INTRODUCTION

Future space programs call for the exposure of man to prolonged periods of weightlessness. From previous NASA studies of astronauts returning

from relatively brief duration space missions, it is clear that profound but apparently reversible changes occur in various body functions. However, the effects of prolonged weightlessness on cardiac structure and function is largely unknown. Several observations have raised the suspicion that the heart might be affected adversely. These include:

- heart size - as determined radiographically the heart is smaller immediately postflight as compared to preflight,
- postural hypotension - occurs early postflight, and
- compared to control preflight studies, cardiac output during exercise often is reduced shortly after splashdown (1).

One of the problems in assessing the significance of diminished heart size, postural hypotension, and reduced exercising cardiac output is that space flight results in a decreased blood volume and this may cause a diminution in cardiac filling. Since the magnitude of most parameters of cardiac function is dependent on left ventricular end-diastolic volume (*i.e.*, left ventricular end-diastolic fiber length), deviations from normal, without reference to existing left ventricular end-diastolic volume, may merely reflect diminished cardiac filling rather than a primary aberration of cardiac function (2). By taking advantage of the capabilities of echocardiography to measure noninvasively left ventricular volume, stroke volume, and ejection fraction, (3-8) and of the fact that the astronauts were routinely subjected to lower body negative pressure (whereby cardiac filling is progressively decreased), we were able to construct classic ventricular function curves noninvasively, thereby obviating the difficulties encountered in comparing cardiac function at different end-diastolic volumes preflight and postflight. In this manner, the effect of an 84-day period of weightlessness on cardiac structure and function was evaluated in the Skylab 4 astronauts.

METHODS

Equipment and Technique

Studies were performed with a standard transducer (2.25 megahertz, 10 centimeter focus, 1.25 centimeter diameter), and a modified commercial ultrasound unit. The ultrasound signal was connected via a custom-built video amplifier to a strip-chart recorder and recorded continuously on light-sensitive paper. The T-scan technic was used to visualize the ventricular septum and posterobasal left ventricular wall (9). The thickness of the ventricular septum was measured inferior to the distal margins of the mitral leaflets. Posterobasal left ventricular

free-wall thickness was measured with the transducer oriented so that part of the ultrasound beam was reflected from the posterior mitral leaflet. Both thickness measurements were made just before atrial systole. Left ventricular transverse dimensions at end-diastole and end-systole were measured using the T-scan technique to identify maximum transverse dimension just caudal to the tip of the mitral leaflet (fig. 1). Left ventricular volumes were estimated by cubing the left ventricular transverse dimensions (3-5). Stroke volume was calculated by subtracting the end-systolic volume from the end-diastolic volume while ejection fraction was determined by dividing stroke volume by end-diastolic volume (3, 4). Left ventricular mass was calculated by the method of Troy *et al.* (10).

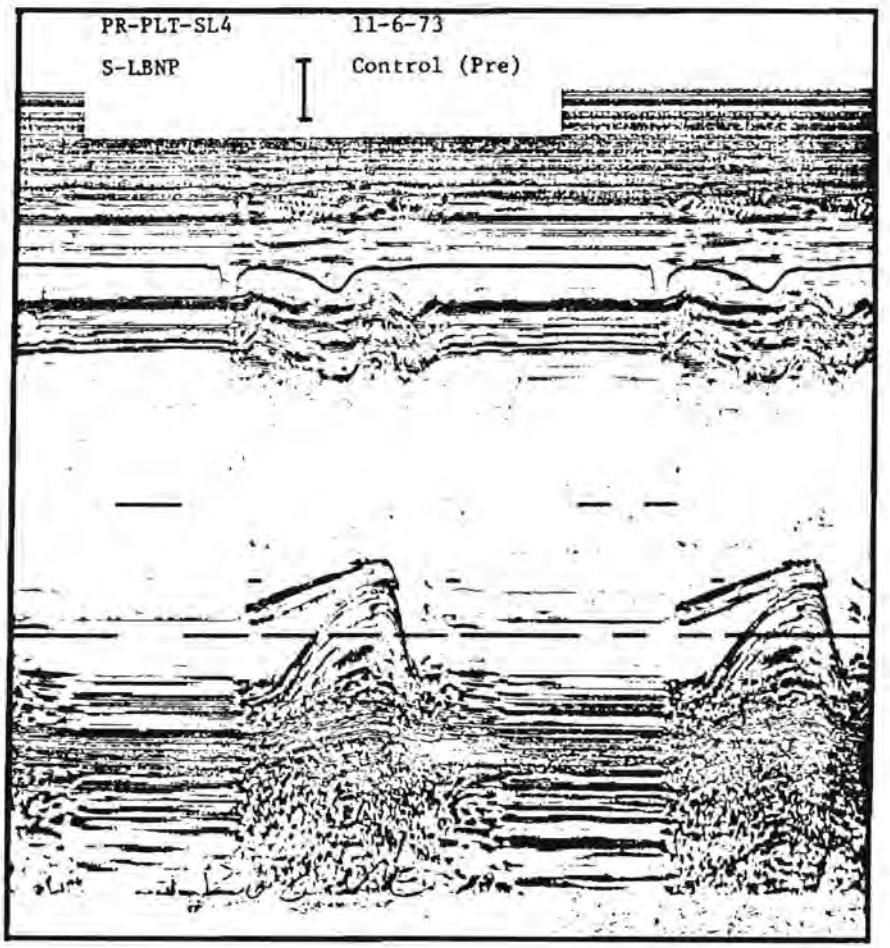


Figure 1. Measurement for left ventricular dimensions at end-diastole and end-systole, Skylab 4.

Study Protocol

Echocardiographic studies were performed with each Skylab 4 astronaut supine and rolled slightly onto his left side. Data were collected preflight on day 5 and postflight on recovery day and days 1, 2, 4 11, 31 and 68. On each of these days a standard procedure was followed. First, control measurements were made prior to the standard protocol for application of lower body negative pressure. The same measurements were repeated five minutes after the end of the standard lower body negative pressure protocol, and successively followed by an echo devoted lower body negative pressure study which consisted of seven consecutive 1-1/2 minute periods. Control values were obtained during the first period. The middle five periods occurred during the application of an increasing amount of lower body negative pressure, beginning with -8 mm Hg, proceeding through -16 mm Hg, -30 mm Hg, -40 mm Hg, and ending with -50 mm Hg. A post lower body negative pressure 1-1/2 minute control period followed the release of the -50 mm Hg negative pressure. Echocardiographic data were recorded during the final 30 seconds of each period. The echocardiograms from each astronaut were randomized and coded so that the investigator who derived the dimensions was unaware of the day the data were collected. In addition to the echocardiographic data, systemic blood pressure (obtained with an automated sphygmomanometer system) and heart rate were recorded.

RESULTS

Control Values

Figure 2 is a plot of the estimated left ventricular volume at end-diastole in milliliters versus time in days for all three astronauts. Preflight, the Scientist Pilot and Pilot had volumes that were above the normal upper limit of 141 milliliters; immediately postflight, the left ventricular end-diastolic volume was reduced by 15 percent in these same two astronauts. This reduction persisted through day 11 postflight but had returned to near preflight values by the postflight 31-day study. Left ventricular end-diastolic volume was altered little in the Commander.

Preflight left ventricular wall thicknesses were as follows: Commander: septum 10 millimeters, posterior wall 11 millimeters; Pilot: septum 10 millimeters, posterior wall 10 millimeters; Scientist Pilot: septum 11 millimeters, posterior wall 11 millimters. These values were all within the normal range of 9 to 12 millimeters and were unchanged postflight.

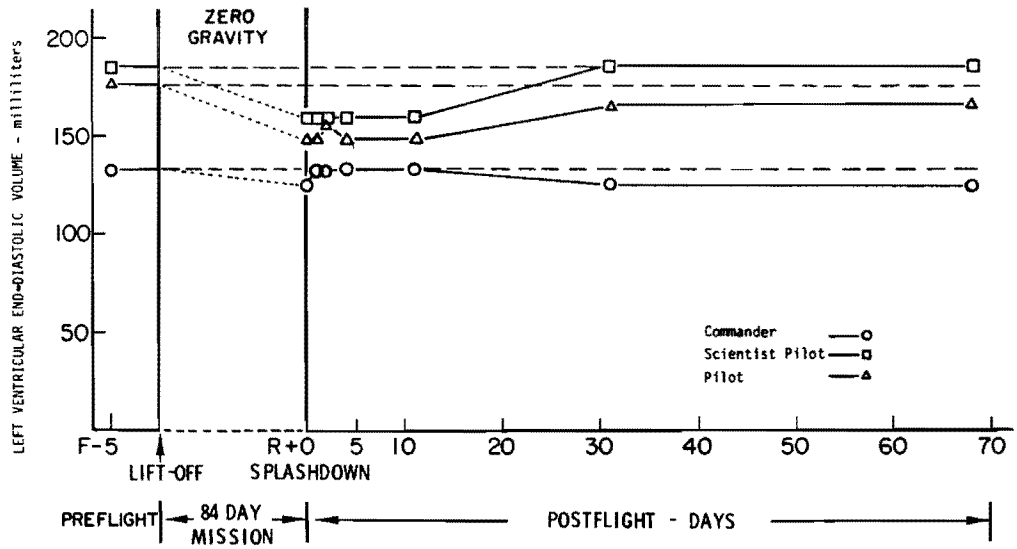


Figure 2. Estimated left ventricular volume at end diastole in mililiters *vs.* time, Skylab 4.

Figure 3 is a plot of estimated left ventricular mass in grams versus time in days for the three Skylab 4 astronauts. Preflight, all three were at or above the upper normal limit. Postflight, on recovery day the mass was slightly (8 percent) reduced in the Scientist Pilot and Pilot. These reductions persisted through day 11 postflight but had returned toward the preflight values by the thirty-first day postflight.

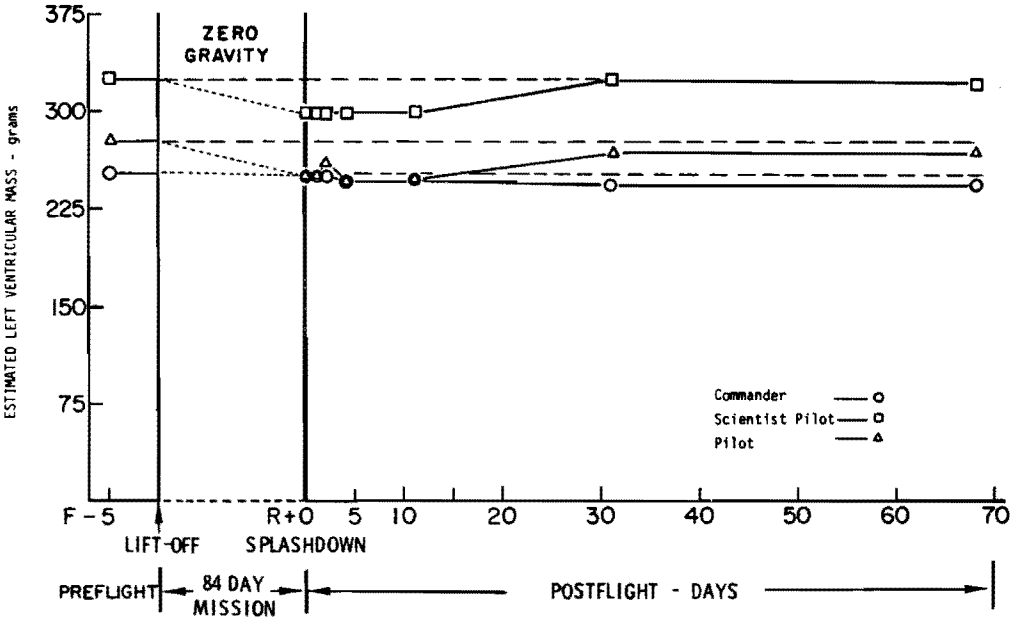


Figure 3. Estimated left ventricular mass in grams *vs.* time in days, Skylab 4.

Stroke volume in milliliters per beat is plotted versus time in days for all three Skylab 4 crew members in figure 4. Compared to normal values, the preflight volume of the Scientist Pilot and Pilot were significantly elevated, while that of the Commander was within normal limits. Postflight, stroke volume diminished in the Scientist Pilot and Pilot and was unchanged in the Commander. The reduction in stroke volume persisted through day 11 postflight but had returned to near preflight values by 31 days postflight.

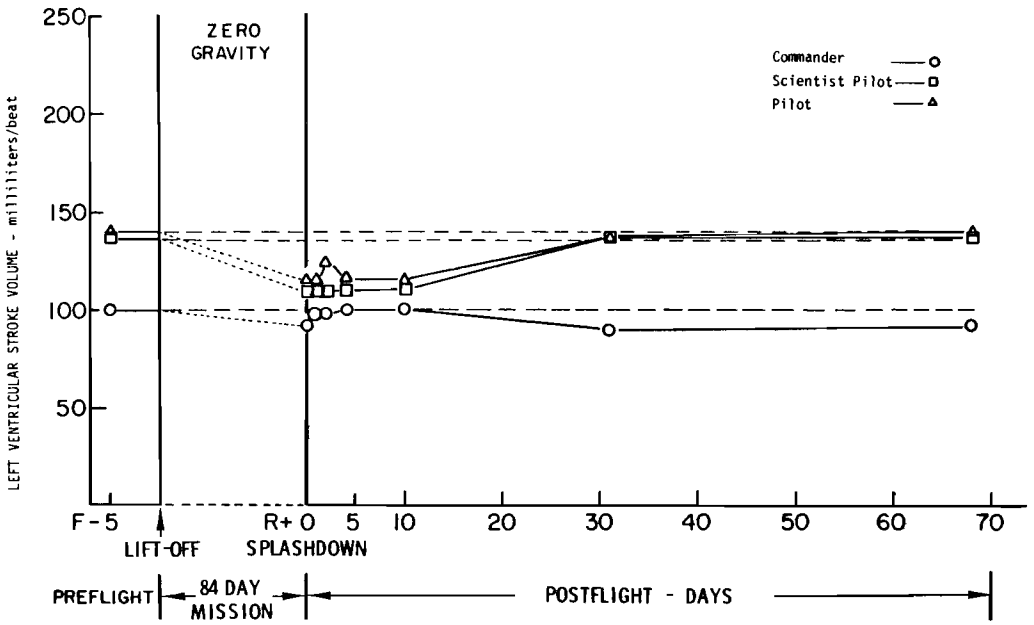


Figure 4. Stroke volume in milliliters/beat *vs.* time in days, Skylab 4.

Lower Body Negative Pressure Data

Satisfactory echocardiographic data were obtained during the echo-devoted lower body negative pressure protocol for the Commander and Pilot but not for the Scientist Pilot (tracings from the Scientist Pilot were of marginal quality, probably due to chest wall configuration).

Figure 5 is a plot of the left ventricular end-diastolic volume (solid line) and the stroke volume (dotted line) at the various levels of lower body negative pressure for the Pilot preflight. Similar curves were constructed for the Commander preflight and for both the Commander and Pilot postflight.

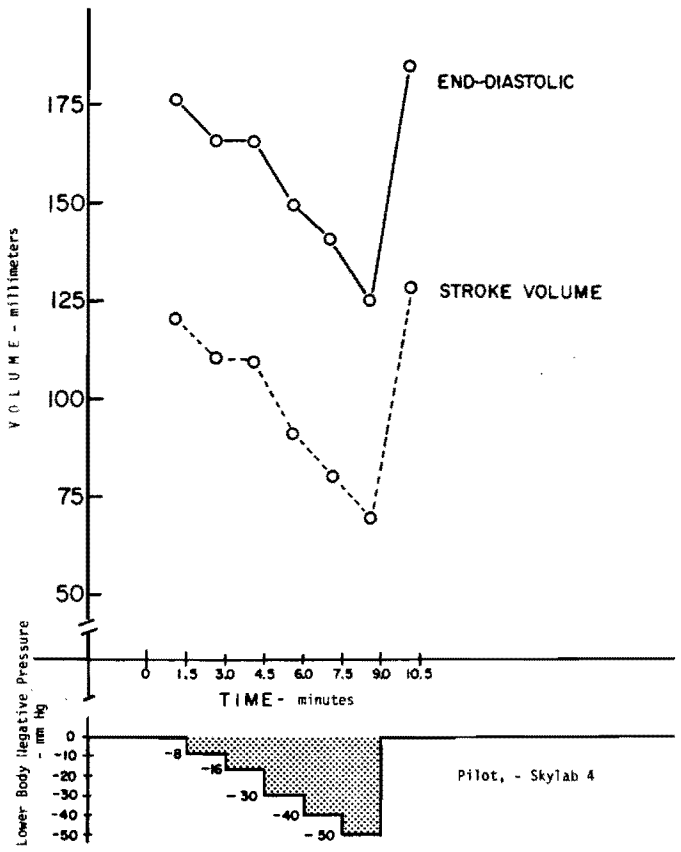


Figure 5. Left ventricular end-diastolic volume and stroke volume at the various levels of lower body negative pressure, Pilot of Skylab 4.

Using these data, ventricular function curves were constructed by plotting left ventricular end-diastolic volume versus stroke volume for the Commander (fig. 6) and the Pilot (fig. 7). Preflight values are shown by the solid lines and the immediate postflight data by the dotted lines. These figures illustrate that no deterioration in ventricular function occurred since the preflight and postflight data fall on the same straight line.

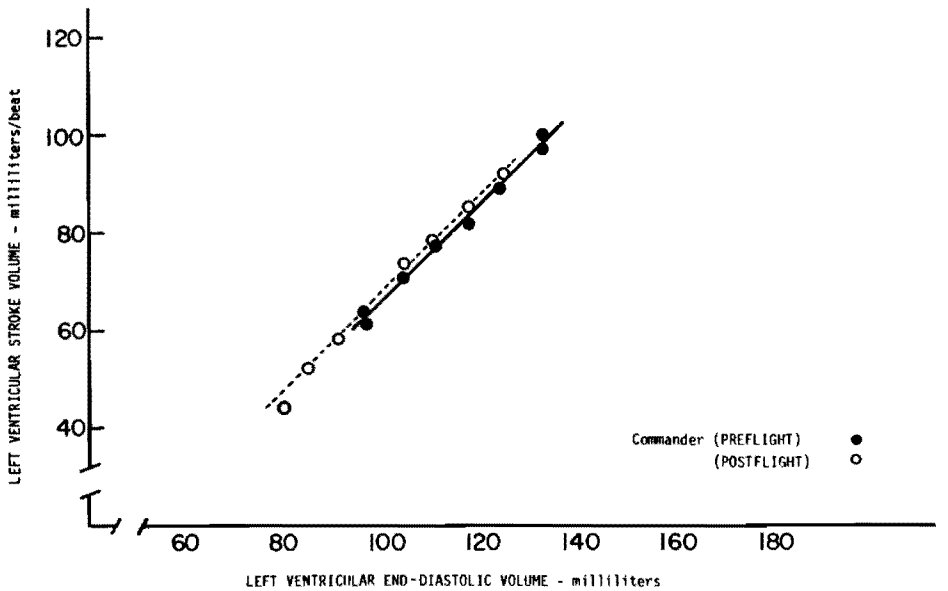


Figure 6. Ventricular Function Curve, Commander of Skylab 4.

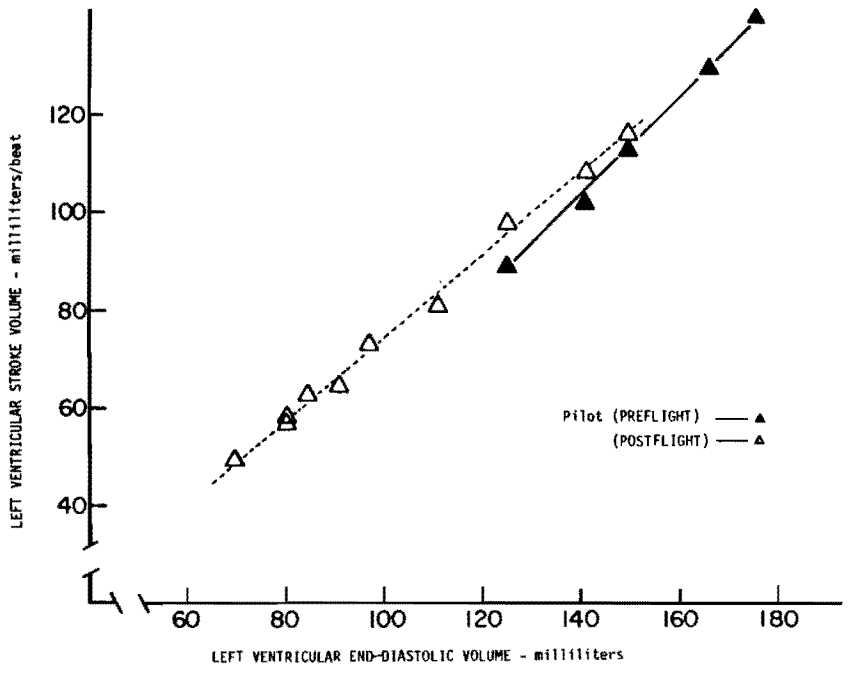


Figure 7. Ventricular function curve, Pilot of Skylab 4

DISCUSSION

The results of the present investigation demonstrate that small but significant decreases in stroke volume occurred in two of the three Skylab 4 astronauts immediately following an 84-day period of weightlessness. Although this could be interpreted as an impairment of cardiac function, echocardiographic measurements demonstrated that left ventricular end-diastolic volume also was slightly diminished postflight in the same two astronauts. Since end-diastolic volume is an important determinant of stroke volume, it is obvious that comparisons of parameters of cardiac performance must be made at comparable end-diastolic volumes. When this was done (by constructing ventricular function curves), it was clear than no significant alteration in cardiac *function* occurred in any astronaut. Moreover, the small decreases in left ventricular end-diastolic volume, stroke volume and left ventricular mass that did occur were demonstrated to be reversible postflight over a 30-day period.

It is interesting to speculate on the mechanism of the alterations in left ventricular volume and mass seen in the Skylab 4 astronauts. One mechanism that could account for the dimensional changes is the profound change in plasma volume that occurs with weightlessness (1). The mechanism undoubtedly explains at least some of the changes observed in left ventricular end-diastolic volume. However, it is possible that other factor(s) are involved. Of interest, the two astronauts (Scientist Pilot and Pilot) in whom decreases in left ventricular end-diastolic volumes were observed had end-diastolic volumes preflight that were significantly greater than the usually accepted normal range. In this regard, echocardiographic data of the Scientist Pilot and Pilot were very similar to those seen in trained athletes involved in endurance events (*i.e.*, swimmers, runners) (11) in that the echocardiograms of such athletes reveal a dilated, nonthickened left ventricle that ejects an increased stroke volume. In contrast, the left ventricular end-diastolic volume and stroke volume of the Commander were at the upper limits of normal. Of note, the Scientist Pilot and Pilot ran much longer distances during their preflight training than the Commander. If these differences in cardiac dimensions are due to the differences in the amount of preflight distance running performed by the three astronauts, then it is possible that at least some of the changes seen immediately following the 84-day space mission merely reflect the inability to continue distance running while in space. It should be emphasized that despite the decreases in left ventricular dimensions observed in the Scientist Pilot and Pilot immediately postflight, their echocardiograms postflight were still in the trained athlete range, and the Commander was still at the upper limit of normal. That more striking changes did

not occur may be at least partly a result of the bicycle exercises performed in space during the 84-day mission.

While the results of the present study cannot be extrapolated to longer duration space missions, it is clear that 84 days of weightlessness did not produce any deterioration in cardiac function. Moreover, the changes in cardiac volume and mass observed were minimal and reversible. The data indicate that the cardiovascular system adapts well to prolonged weightlessness and suggest that alterations in cardiac dimensions and function are unlikely to limit man's future in space.

REFERENCES

1. Johnson, Philip C., Theda B. Driscoll and Adrian D. LeBlanche. Blood Volume Changes. Presented at the Skylab Life Sciences Symposium, NASA - JSC, Houston, Texas, August 1974.

2. Braunwald, E., J. Ross, Jr., and E. H. Sonnenblock. 1968. Mechanisms of contraction of the normal and failing heart. Little Brown & Co., Boston, Mass.

3. Feigenbaum, H. 1972. Echocardiography. Lea and Febiger, Philadelphia, Pa.

4. Feigenbaum, H. 1972. Clinical applications of echocardiography. *Prog. Cardiovasc. Dis.* 14: 531-558.

5. Popp, R. L., D. C. Harrison. 1970. Ultrasonic cardiac echocardiography for determining stroke volume and valvular regurgitation. *Circulation*, 41: 493-502.

6. Pombo, J. F., B. L. Troy, and R. O. Russell, Jr. 1971. Left ventricular volume and ejection fraction by echocardiography. *Circulation*, 43: 480-490.

7. Fortuin, N. J., W. P. Hood, Jr., and E. Craige. 1972. Evaluation of left ventricular function by echocardiography. *Circulation*, 46: 26-25.

8. Cooper, R. H., R. A. O'Rourke, and J. S. Karliner, *et al.* 1972. Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation*, 46: 914-923.

9. Henry, W. L., C. E. Clark and S. E. Epstein. 1973. Asymmetric septal hypertrophy: Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation*, 47: 225-233.

10. Troy, B. L., J. Pombo, and C. E. Rackley. 1972. Measurement of left ventricular wall thickness and mass by echocardiography. *Circulation*, 45: 602-611.

11. Morganroth, J., B. J. Maron, W. L. Henry and S. E. Epstein. 1974. The athlete's heart: Comparative left ventricular dimensions of collegiate athletes participating in sports requiring isotonic or isometric exertion. *Clinical Research* (Abstract) 22: 291A.

RESULTS OF SKYLAB MEDICAL EXPERIMENT M171 -- METABOLIC ACTIVITY

E. L. Michel, J. A. Rummel, Ph.D.*, C. F. Sawin, Ph.D.*, M. C. Buderer, Ph.D.†, and J. D. Lem**

ABSTRACT

The experiment was conducted to establish whether man's ability to perform mechanical work would be progressively altered as a result of exposure to the weightless environment of space flight. The Skylab crewmen exercised on a bicycle ergometer at workloads approximating 25, 50, and 75 percent of their maximum aerobic capacity. The physiological parameters monitored were respiratory gas exchange, blood pressure, and vectorcardiogram/heart rate. The results of these tests indicate that the crewmen had no significant decrement in their responses to exercise during their exposure to zero gravity. Immediately after the flight, however, all crewmen demonstrated an inability to perform the programed exercise with the same physiological effectiveness as they did both before flight and in-flight. The most significant changes were elevated heart rates for the same workload and oxygen consumption (decreased oxygen pulse), decreased stroke volume, and decreased cardiac output at the same oxygen consumption level. It is apparent that some adaptive changes in physiological function must have occurred in flight, but these did not become evident until the crewmen attempted to readapt to the one-g environment.

The results of the third manned Skylab mission (Skylab 4) are presented and a comparison is made of the overall results obtained from the three successively longer Skylab manned missions. The Skylab 4 crewmembers' 84-day in-flight respones to exercise were no worse and were probably better than the responses of the crewmen on the first two Skylab missions. Indications that exercise was an important contributing factor in maintaining this response are discussed.

As stated previously, an immediate postflight readaptation period was observed in all crewmen during which a decrement in response to exercise was evident. This period was of a short duration, was not intensified by the duration of the mission, and resulted in no lasting

*National Aeronautics and Space Administration - Lyndon B. Johnson Space Center, Houston, Texas.

†Life Sciences Division, Technology Incorporated, Houston, Texas.

effects. It appears that the observed responses are a result of a decreased venous return caused by an altered fluid balance/blood volume state as well as a possible reduction in vascular tone of the venous system.

INTRODUCTION

When the metabolic activity experiment was first submitted for consideration in the proposed medical investigations associated with the Skylab Program, it was hypothesized that man's ability to do work would be compromised as a result of exposure to the weightless environment of space flight. At that time ground-based bed rest studies were the only data to support this hypothesis (1, 2, 3, 4). Exercise response tests conducted on some of the Gemini crewmen about this same time indicated trends but showed no statistically significant alterations postflight as compared to preflight. The Gemini Program postflight tests were conducted approximately 24 hours after splashdown when the crews returned to J. F. Kennedy Space Center. It was not until the Apollo Program that we were able to document a significant decrement in the crews' postflight response to excerise (5, 6, 7). During the Apollo Program, operational constraints were modified to permit postflight medical testing of the crew on board the recovery aircraft carrier within two to eight hours after splashdown. Twenty of the 27 Apollo crewmen tested exhibited a statistically significant decrease in their tolerance for exercise. Although this response was reversible within 24 to 36 hours, it became obvious that man could not be committed to long-duration space flight until the magnitude and time course of these changes could be established and the underlying physiological mechanisms understood. The eventual acceptance of the M-171 metabolic activity experiment for all three Skylab Missions provided us with an opportunity to attempt to do this. The primary objective of the experiment was to determine whether man's metabolic effectiveness in doing mechanical work was progressively altered by exposure to the space environment. The secondary objective was the evaluation of the M-171 bicycle ergometer as an in-flight crew personal exerciser.

The results of the first (Skylab 2) and second (Skylab 3) manned missions have been reported in detail previously (8, 9). This manuscript will report the results of the third (Skylab 4) manned mission and then attempt to summarize what has been learned from all three Skylab Missions about the physiological response to exercise during and after periods of 28 days, 59 days, and 84 days of weightlessness.

MATERIALS

A detailed description of the experimental hardware has been reported (8). The main items of hardware associated with the performance of the M-171 experiment are shown in figure 1 and include the bicycle ergometer, the metabolic analyzer, and the experiment support system. The experiment support system supported common and special requirements of a number of medical experiments. It provided data management with event time and subject and test identification, and regulated power for these experiments. It also provided visual readouts and controls for the blood pressure measuring system and the vectorcardiograph/heart rate system.

The ergometer is a hand- or foot-driven electromechanical bicycle-type exercise device designed to allow a test subject to exercise in the zero-g environment. A restraint system consisting of a shoulder and waist harness and foot restraints was developed, but the upper torso harness was found ineffective and was discarded during Skylab 2. The foot restraints were most effective and upon the recommendation of the first crew, modified wrap-around handlebars were installed by the Skylab 3 crew (fig. 2). Although these were, in general, well accepted by the crewmen some preferred to put their hands on the ceiling or to place padding between their head and the ceiling.

In the manual work-load mode of control of the ergometer, which was utilized in the conduct of the M-171 experiment, a continuous range of 25 to 300 watts was available. The loading of the erogmeter was independent of the pedalling rate - between 50 to 80 cycles/minute. In addition to being the M-171 experiment stressor, the ergometer was the principal device for personal exercise during the mission.

A ground support calibration system consisting primarily of a torque motor, torque sensor, and power computer was developed to provide accurate calibration of the ergometer prior to installation in the workshop. Additionally, electronic calibration was performed prior to each in-flight test.

The metabolic analyzer consists of a rolling seal dry spirometer for the measurement of volume, a mass spectrometer for the measurement of the four respiratory gases and an analog computer to calculate minute volume, oxygen consumption, carbon dioxide production, and respiratory exchange ratio. Figure 3 is a functional schematic of the metabolic analyzer.

End-to-end calibrations utilizing a hand pump and known gas mixtures were performed prior to installation of the metabolic analyzer in the

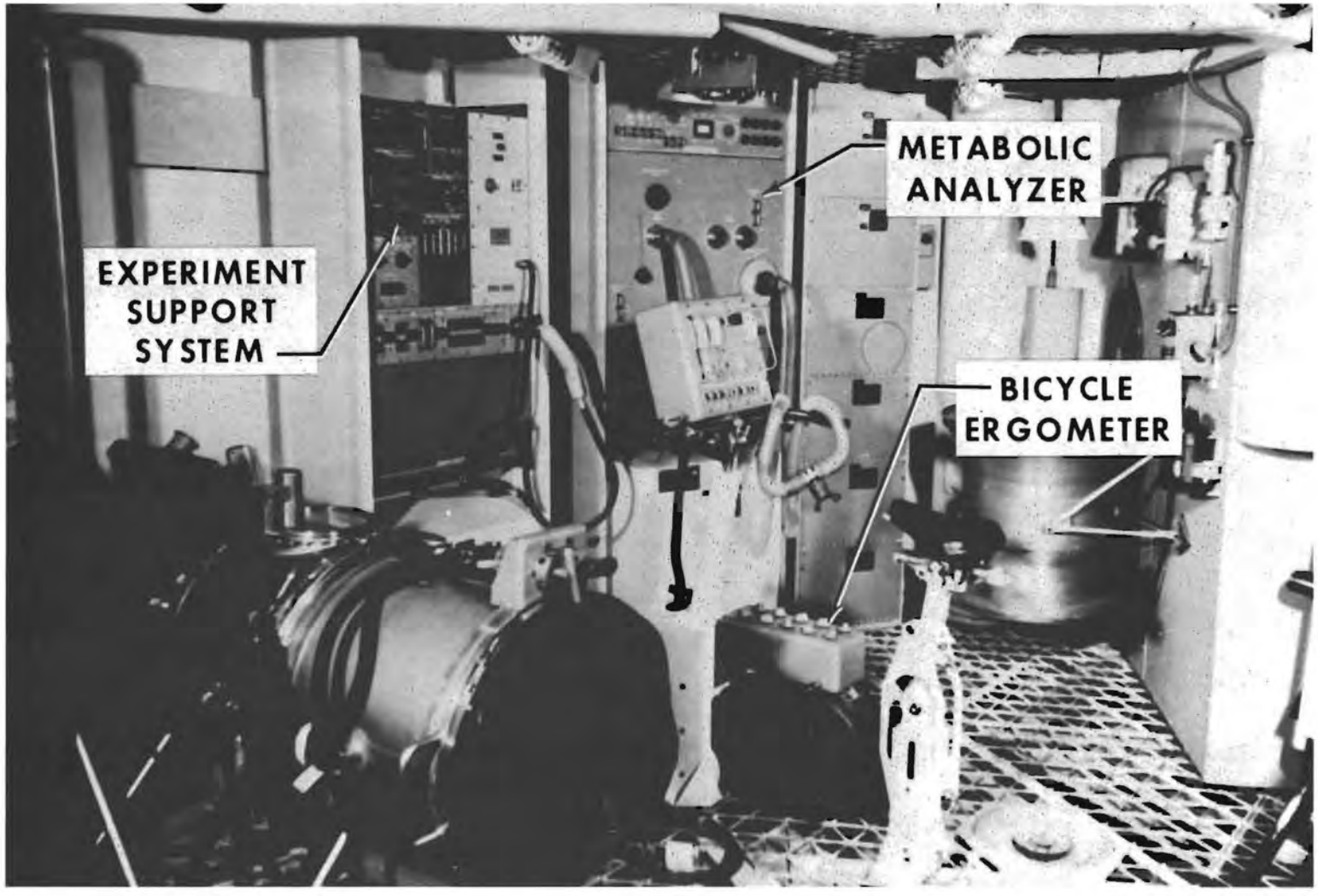


Figure 1. Skylab in-flight experiments.

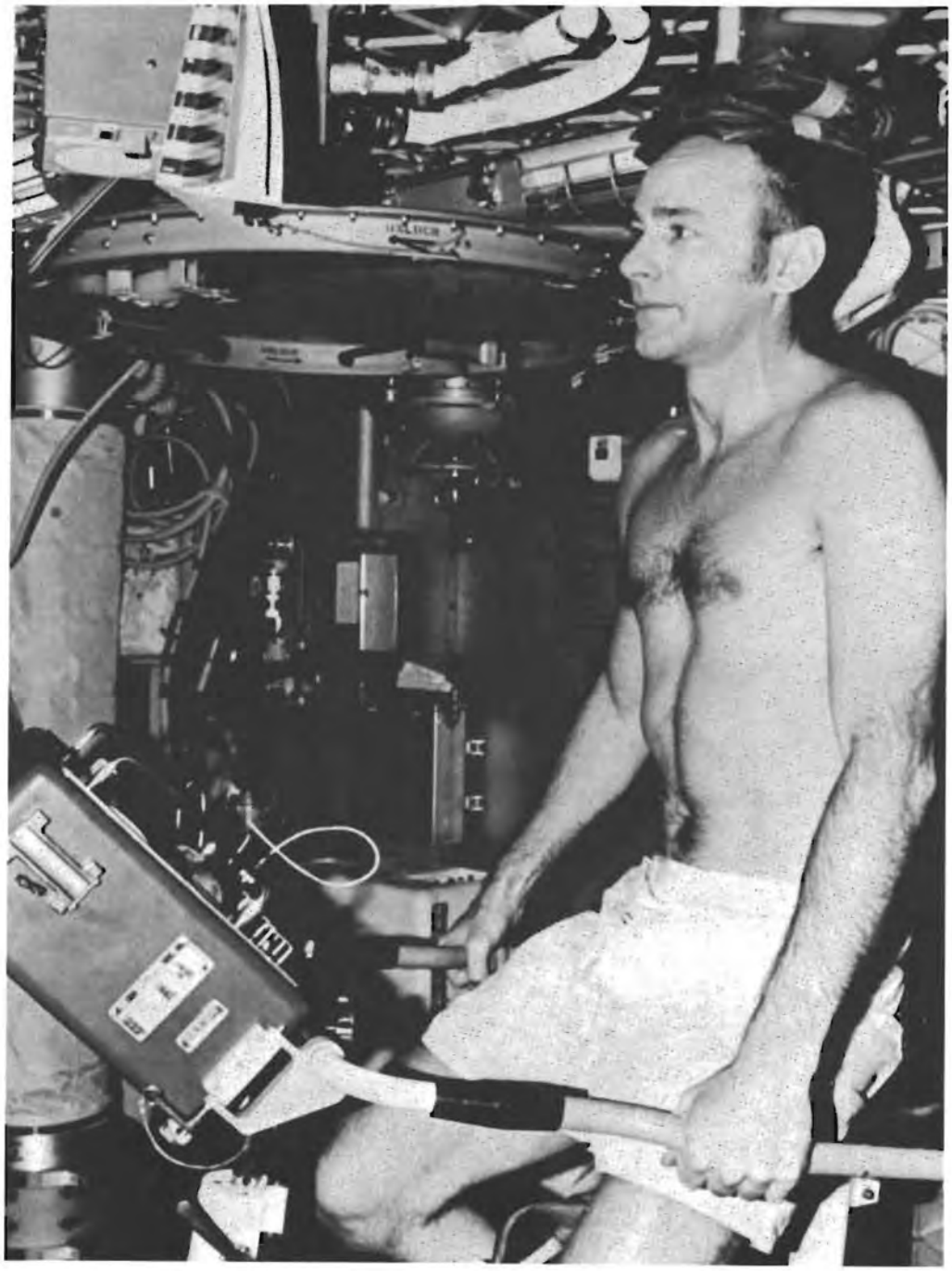


Figure 2. M-171 ergometer restraint methods.

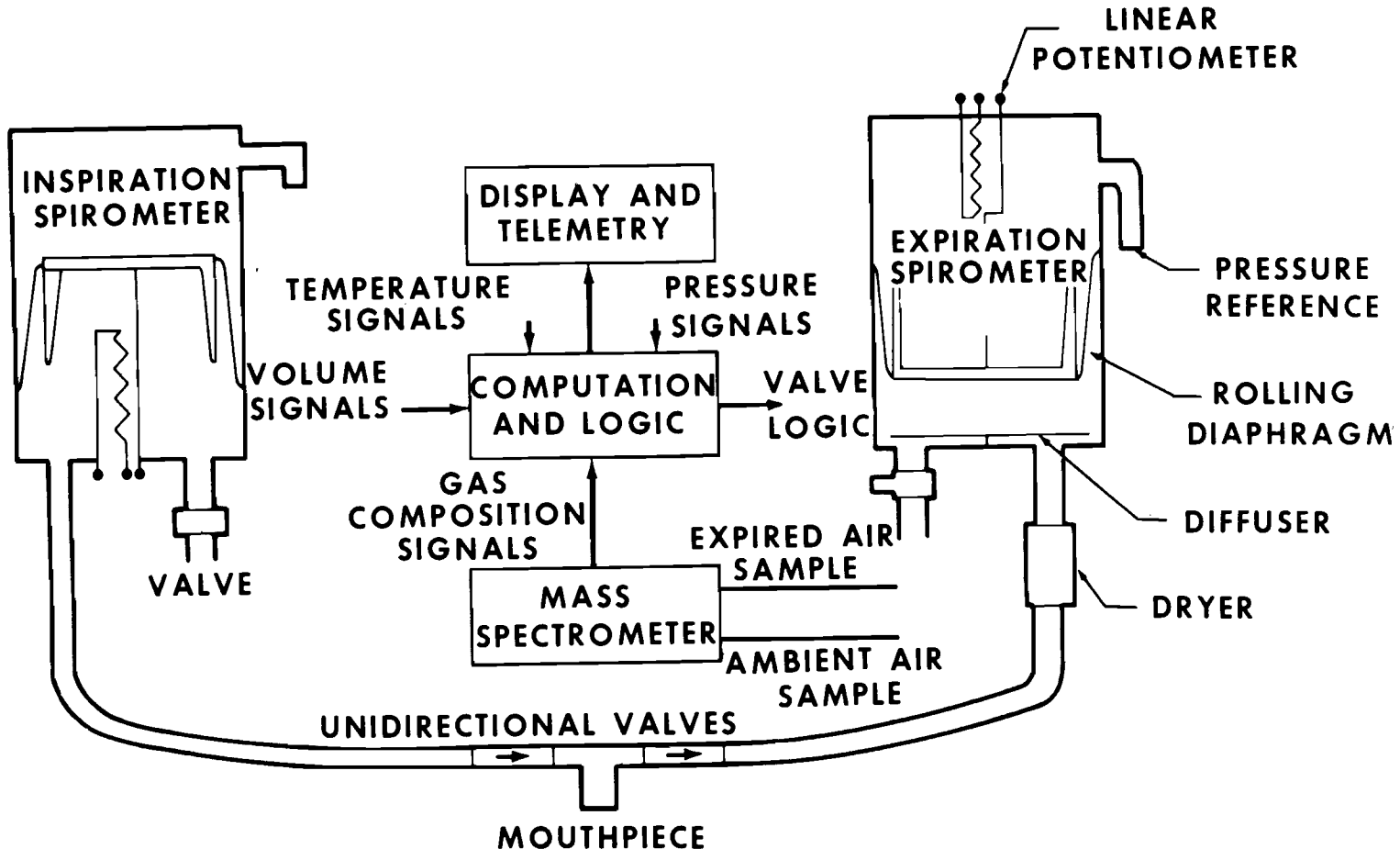


Figure 3. Schematic for respiratory gas analyzer.

workshop and during activation of the workshop at the beginning of each mission. No change in calibration was evidenced throughout the entire program.

METHODS

The experiment protocol, as shown in table I, consisted of measuring metabolic expenditures during rest and calibrated exercise. Each crewman's aerobic capacity was determined at approximately 12 months and again at six months prior to launch. Based upon these tests, a three-step workload protocol was established as follows:

- After obtaining a five-minute resting metabolic rate, the crewman exercised on the bicycle ergometer at fixed work levels approximating 25, 50, and 75 percent of his maximum oxygen uptake ($\dot{V}_{O_2}$ max) for a period of five minutes at each level.
- This was followed by a five-minute recovery period.
- The experiment protocol was scheduled to be repeated every 5 to 6 days by each crewman during all three Skylab Missions.

The acquisition of significant baseline data for each crewman was implicit in our experimental approach. Each subject served as his own control.

The physiological measurements (table II) which were made during the conduct of the experiment were oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), minute volume ($\dot{V}_E$), vectorcardiogram/heart rate, and blood pressure. These measurements, with the exception of the vectorcardiogram/heart rate, were updated every minute. Heart rate was updated every 5 beats but only minute averages were utilized in the analysis of M171 data. Environmental conditions, ergometer work load and vectorcardiogram were measured continuously during each experiment run. An oral body temperature was obtained prior to each test. During the preflight and postflight tests single breath cardiac output (10, 11), vibrocardiographic and carotid pulse measurements were made. The derived respiratory data included respiratory exchange ratio, oxygen pulse, and mechanical and pulmonary efficiency. The derived cardiovascular data were mean arterial pressure, pulse pressure, and in the preflight and postflight tests, total peripheral resistance, A-VO_2 difference, and stroke volume. Not all of these derived data have been reduced and analyzed at this time.

In performing the M-171 experiment, each Skylab 4 crewman had eight preflight baseline tests, six spaced at approximate monthly intervals

TABLE I. M171 EXPERIMENT PROTOCOL

Time	Exercise Protocol
5 minutes	Rest
5 minutes	25 Percent of Maximum $\dot{V}_{O_2}$
5 minutes	50 Percent of Maximum $\dot{V}_{O_2}$
5 minutes	75 Percent of Maximum $\dot{V}_{O_2}$
5 minutes	Recovery

Legend:

Performed by each of three Crewmen

Five times in 28-day mission
Eight times in 59-day mission
Twelve times in 84-day mission

TABLE II. M-171 PHYSIOLOGICAL MEASUREMENTS

Raw Data	Derived Data
Ergometer Work Level (Watts)	Respiratory
Respiratory	Respiratory Exchange Ratio
Oxygen consumption	Oxygen pulse
Carbon dioxide production	Pulmonary efficiency ($\dot{V}_E/\dot{V}_{O_2}$)
Minute volume	Mechanical efficiency ($\dot{V}_{O_2}$/Watt)
Cardiovascular	Cardiovascular
ECG/VCG	Mean Arterial pressure
Systolic/Diastolic blood pressure	Total Peripheral Resistence
*Cardiac output	Arterial-Venous Oxygen Difference (A-$\dot{V}_{O_2}$)
*Vibrocardiogram	Stroke Volume
*Carotid Pulse	

*Preflight and Post flight only

ECG = Electrocardiograph
VCG = Vectorcardiograph

over a 6-month period prior to launch and two additional tests at 15 and 5 days before flight. The first six baseline tests were conducted by the crew on themselves utilizing the one-g trainer. The last two baseline tests were conducted in the Skylab Mobile Laboratories by the principal investigators who subsequently performed the postflight tests in the Skylab Mobile Laboratories onboard the recovery ship. Each crewman was tested approximately every 6 days during the 84-day mission for a total of 12 tests per man.

As a result of the experience gained from the Gemini and Apollo programs, a concerted effort was made during the planning for Skylab to perform the postflight tests on the crew as soon as possible after splashdown. To insure the best possible comparison between the preflight and postflight experiment data with those obtained in-flight the Skylab Mobile Laboratories were outfitted with a set of M-171 experiment instrumentation and transported intact to the recovery ship. Postflight, eight M-171 tests were conducted on each crewman: at recovery and on days 1, 2, 3, 5, 11, 17 and 31 following recovery. Prior to the Skylab 4 launch and based on data obtained from the first two Skylab manned missions, the principal investigators decided to perform preflight and postflight tilt ergometry exercise tests (30° from horizontal) on the crew in an attempt to better understand the previously observed postflight decrements in response to exercise. Since the recovery medical testing day was already excessively long, we elected to substitute the supine/upright ergometry testing for the standard M-171 protocol. The standard protocol was conducted on the day after recovery and on all subsequent postflight test days. The protocol used for the modified test on the day of recovery, consisted of five minutes supine rest, five minutes upright rest, five minutes upright exercise, five minutes supine exercise and five minutes supine recovery. The exercise level used was identical to the first level of work (25 percent maximum) of each crewman's standard M-171 protocol. This modified protocol was accomplished 15 and 5 days preceding launch, on recovery day, on the first day after recovery prior to M-171 standard protocol, and on 17 and 31 days post recovery.

RESULTS OF SKYLAB 4

The next three tables (tables III, IV, V) summarize the Skylab 4 results for the Commander, Scientist Pilot, and Pilot, respectively, utilizing the physiologic variables which were routinely monitored during all performances of the M-171 experiment. Resting, level-3 exercise, and recovery mean values are presented for each variable during the three phases of the mission. Those values outside the preflight 95 percent confidence levels are marked with an asterisk. The values

TABLE III. SKYLAB 4 M171 DATA SUMMARY

Commander

VARIABLE	PREFLIGHT $\bar{X}$	IN-FLIGHT $\bar{X}$	POSTFLIGHT $\bar{X}$
Heart Rate (bpm)			
Rest	66	66	76*
Level 3	157	152	163
Recovery	112	87*	109
$\dot{V}_{O_2}$ (l/min STPD)			
Rest	.237	.283*	.203*
Level 3	2.26	2.20	2.14
Recovery	.603	.632	.717
$\dot{V}_{CO_2}$ (l/min STPD)			
Rest	.234	.301*	.187*
Level 3	2.14	2.13	2.05
Recovery	.721	.776	.839
SBP (mm Hg)			
Rest	96	97	106
Level 3	192	195	195
Recovery	149	131	170
DBP (mm Hg)			
Rest	67	59*	72
Level 3	71	56*	67
Recovery	66	61*	78
$\dot{V}_E$ (l/min BTPS)			
Rest	8.90	11.79*	9.27
Level 3	64.43	62.04	60.04
Recovery	25.98	24.65	29.18

Key:

* = Outside the 95% confidence limit
STPD = Standard temperature, pressure dry
bpm = Beats per minute
BTPS = Body temperature, pressure saturated
$\dot{V}_{O_2}$ = Oxygen consumption
$\dot{V}_{CO_2}$ = Carbon dioxide production
$\dot{V}_E$ = Minute volume
SBP = Systolic blood pressure
DBP = Diastolic blood pressure

TABLE IV. SKYLAB 4 M171 DATA SUMMARY

Scientist Pilot

VARIABLE	PREFLIGHT $\bar{X}$	IN-FLIGHT $\bar{X}$	POSTFLIGHT $\bar{X}$
Heart Rate (bpm)			
Rest	64	62	74*
Level 3	164	166	167
Recovery	104	92*	102
$\dot{V}_{O_2}$ (l/min STPD)			
Rest	.269	.289	.263
Level 3	3.07	3.01	3.00
Recovery	.676	.745	.763
$\dot{V}_{CO_2}$ (l/min STPD)			
Rest	.255	.279	.221
Level 3	2.88	3.03*	2.91
Recovery	.791	.982*	.893
SBP (mm Hg)			
Rest	127	119*	123
Level 3	204	200	198
Recovery	186	174	189
DBP (mm Hg)			
Rest	84	74*	78*
Level 3	55	52	51
Recovery	66	61	63
$\dot{V}_E$ (l/min BTPS)			
Rest	7.51	9.98*	10.33*
Level 3	84.18	97.24*	102.69*
Recovery	24.6	31.44*	34.07*

Key:

* = Outside the preflight 95% confidence limit
STPD = Standard temperature, pressure,dry
bpm = Beats per minute
BTPS = Body temperature, pressure saturated
$\dot{V}_{O_2}$ = Oxygen consumption
$\dot{V}_{CO_2}$ = Carbon dioxide, production
$\dot{V}_E$ = Minute volume
SBP = Systolic blood pressure
DBP = Diastolic blood pressure

TABLE V. SKYLAB 4 M171 DATA SUMMARY

Pilot

VARIABLE	PREFLIGHT $\bar{X}$	IN-FLIGHT $\bar{X}$	POSTFLIGHT $\bar{X}$
Heart Rate (bpm)			
Rest	54	53	65*
Level 3	147	147	156*
Recovery	114	91*	118
$\dot{V}_{O_2}$ (l/min STPD)			
Rest	.238	.283*	.253
Level 3	2.86	2.59*	2.63*
Recovery	.849	.754	.849
$\dot{V}_{CO_2}$ (l/min STPD)			
Rest	.216	.247	.222
Level 3	2.72	2.65	2.68
Recovery	1.22	1.08	1.08
SBP (mm Hg)			
Rest	115	115	125*
Level 3	204	200	213
Recovery	188	186	204
DBP (mm Hg)			
Rest	72	64*	74
Level	60	51*	59
Recovery	65	60	69
$\dot{V}_E$ (l/min BTPS)			
Rest	6.69	8.47*	10.73*
Level 3	98.51	90.61*	95.12
Recovery	40.97	34.77*	45.02

Key:

* = Outside the preflight 95% confidence limit
STPD = Standard temperature, pressure dry
bpm = Beats per minute
BTPS = Body temperature, pressure saturated
$\dot{V}_{O_2}$ = Oxygen consumption
$\dot{V}_{CO_2}$ = Carbon Dioxide production
$\dot{V}_E$ = Minute volume
SBP = Systolic blood pressure
DBP = Diastolic blood pressure

for each test data point in the case of resting values were based on the average of the entire five minute period. The exercise values were based on the average of the last three minutes of the five minute period and the recovery values were those obtained for the second minute during the five minute recovery period.

As can be seen in the case of the Commander, significant changes observed in-flight were decreased recovery heart rate, decreased resting, exercising, and recovery diastolic blood pressure and increased resting minute volume, oxygen consumption and carbon dioxide production. Postflight, the Commander exhibited a significant elevation in resting heart rate and decreases in both resting oxygen consumption and carbon dioxide production.

The in-flight response of the Scientist Pilot showed a decreased recovery heart rate and increased ventilation not only during rest but during exercise and recovery. Additionally, decreases in resting systolic and diastolic blood pressures were observed as well as increased carbon dioxide production during both exercise and recovery. Postflight, the Scientist Pilot demonstrated significant elevation in resting heart rate and in resting, exercising, and recovery ventilation accompanied by a decreased resting diastolic blood pressure.

The in-flight response of the Pilot was similar to the other crewmembers in that he also exhibited a significant reduction in both recovery heart rate and diastolic blood pressure as well as an increase in resting minute volume. Unlike the others, though, he had a significant decrease in exercising oxygen consumption and exercising minute volume. The significant changes observed in the Pilot's postflight response were elevated resting and exercising heart rates, systolic blood pressure, and resting minute volume. The decreased oxygen consumption observed in-flight in the Pilot during exercise remained so during the immediate postflight test period.

Because of the immense quantity of data, we elected to report the mean values obtained during the various phases of the mission. However, this type of presentation precludes following transients and/or trends in these data. Using only the Pilot's data, the individual plots representative of the most common significant alterations seen in the Skylab 4 crew will be presented. The rest of these pertinent data are presented in the appendix. Figure 4 deals with alterations in heart rate. All three crewmen displayed a decreased in-flight recovery heart rate. Additionally, all crewmen exhibited a significantly elevated resting and exercising heart rate immediately postflight Figure 5 is a plot of the ventilation response. All crewmen exhibited a significantly elevated in-flight resting minute volume which continued

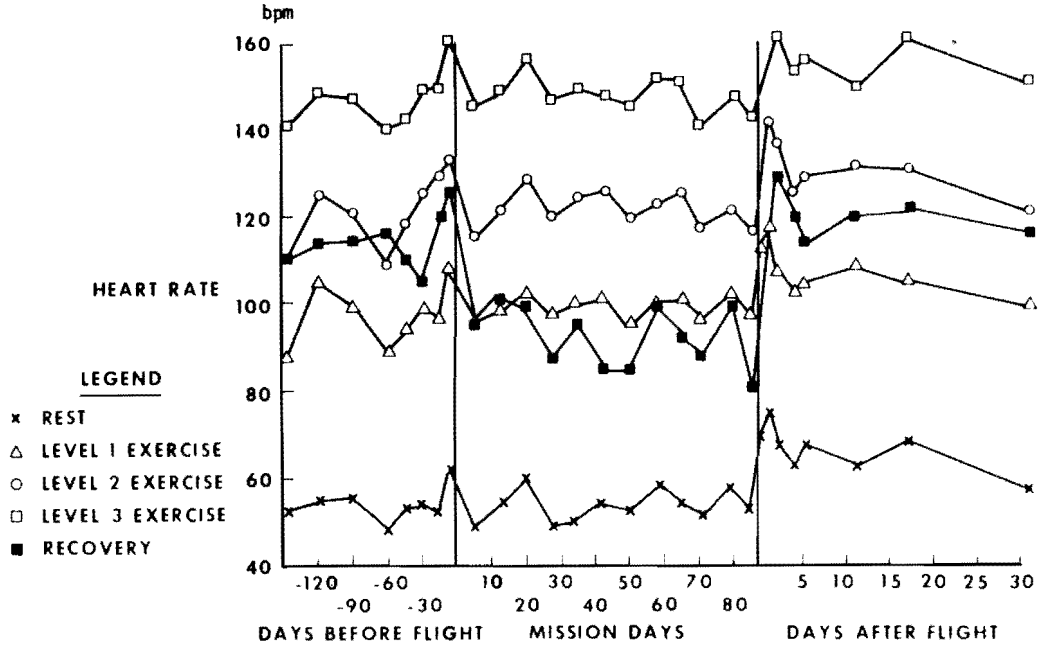


Figure 4. Heart rate, Skylab 4 Pilot.

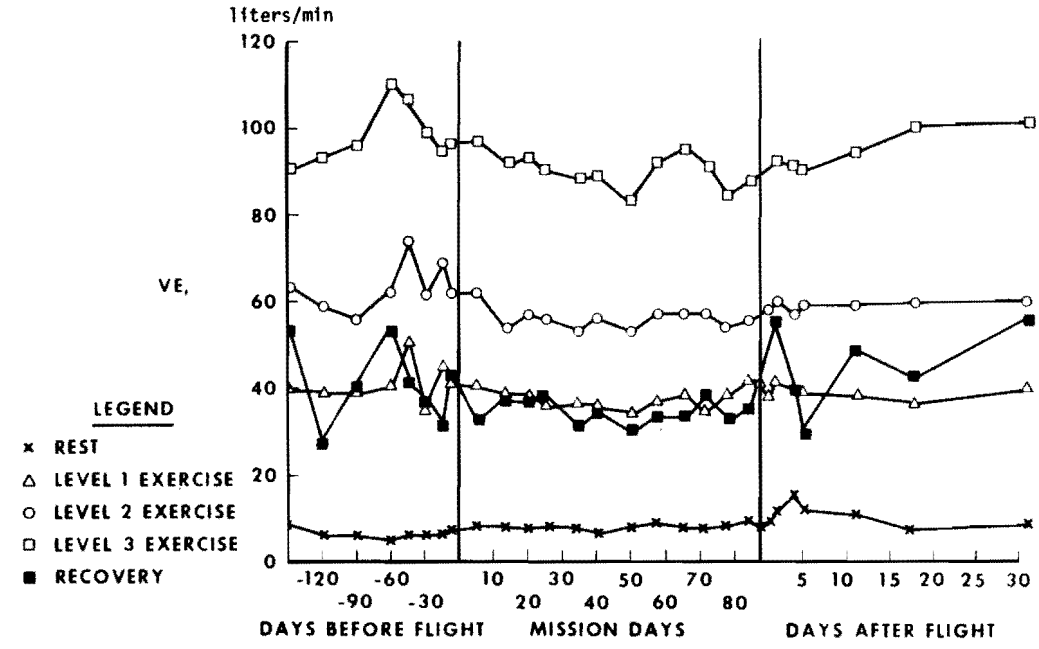


Figure 5. $\dot{V}_E$, Skylab 4 Pilot.

during the postflight testing for both Scientist Pilot and Pilot. Figure 6 shows the decreased in-flight, resting and exercising diastolic blood pressure pattern observed in all Skylab 4 crewmen.

Figures 7 and 8 show the results of the preflight and postflight cardiac output and stroke volume measurements. As stated previously, the first standard M-171 protocol was done on the first day after recovery. On that day only the Commander exhibited a decrease in cardiac output (41 percent) and stroke volume (41 percent); these values showed a prolonged but gradual increase back toward normal and both parameters were within 15 percent of normal by 31 days after recovery. The cardiac output values for the Scientist Pilot and Pilot were slightly increased over preflight while their stroke volume values were slightly decreased. The cardiac output and stroke volume levels of the Scientist Pilot gradually increased from the first day after recovery to 31 days postflight when both of these levels were significantly increased over preflight values. The Pilot showed a slight downward trend in cardiac output after the first day following recovery but his postflight stroke volume showed no particular trend. As would be expected based on the cardiac output and stroke volume data, the Scientist Pilot and Pilot had no change in their A-V_{O_2} differences while the Commander exhibited an increased A-V_{O_2} difference of about the same percent magnitude as his observed reduced cardiac output. The interpretation of these results will be addressed later in conjunction with the results from the Skylab 2 and Skylab 3 missions.

The tilt ergometry studies demonstrated that resting heart rate increased when subjects were placed upright from the supine position. Preflight, the average increase was from 54 to 61 beats per minute (12.6 percent) while in the immediate postflight period the increase was from 65 to 83 beats per minute (27 percent). Thus, not only was the resting level slightly increased in the supine position postflight but the change in heart rate when positioned upright was significantly greater. The late postflight values were similar to preflight.

Figure 9 summarizes the response of Skylab 4 crewmen during the 25 percent maximum exercise in the supine and upright positions. For data comparison, the six tests obtained on each crewman were categorized into preflight, immediate postflight, and late postflight periods. During preflight tests there was very little change in exercising heart rate when the subject was placed supine after five minutes in the upright position. Preflight mean supine and upright values were exactly the same at 103 beats per minute while the immediate postflight change was only from 117 beats per minute to 114 beats per minute. For

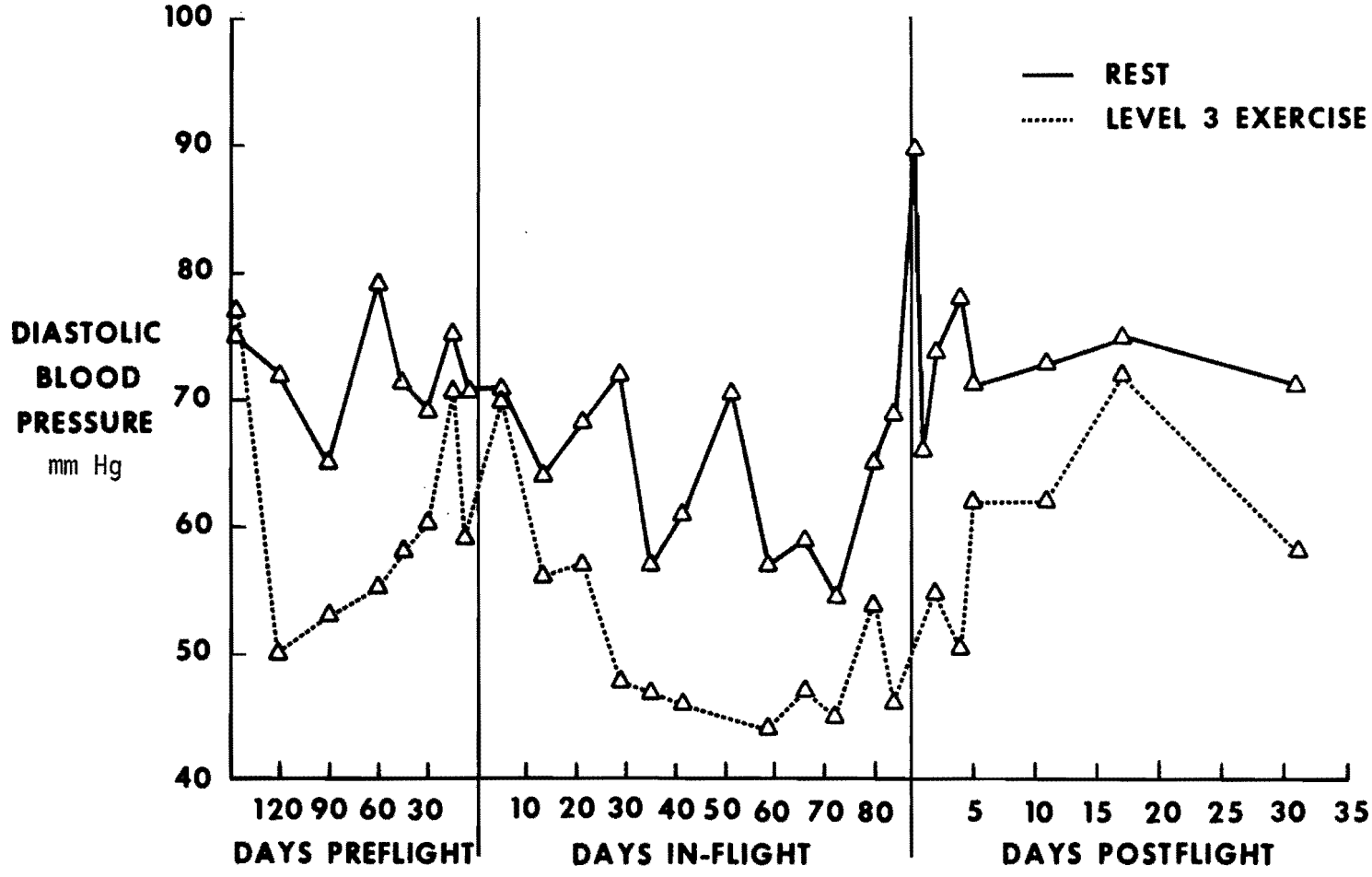


Figure 6. Diastolic blood pressure; Skylab 4 Pilot.

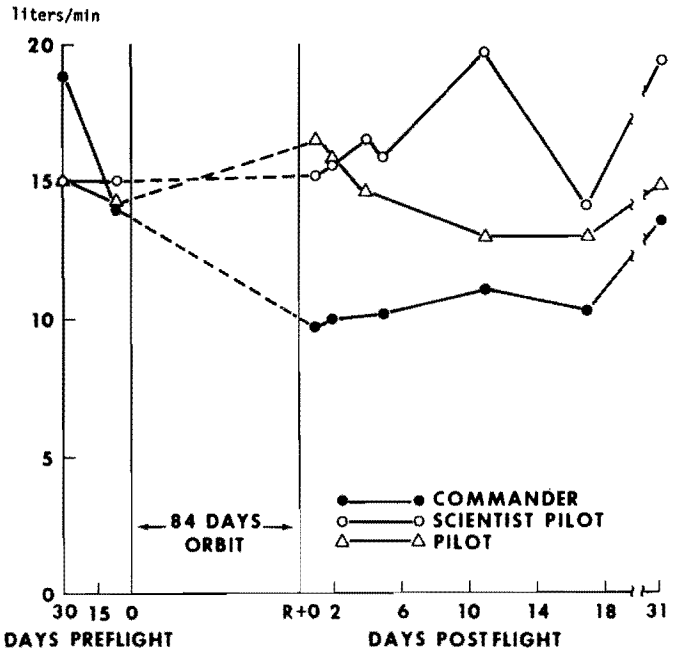


Figure 7. Cardiac output during submaximal exercise (Skylab 4).

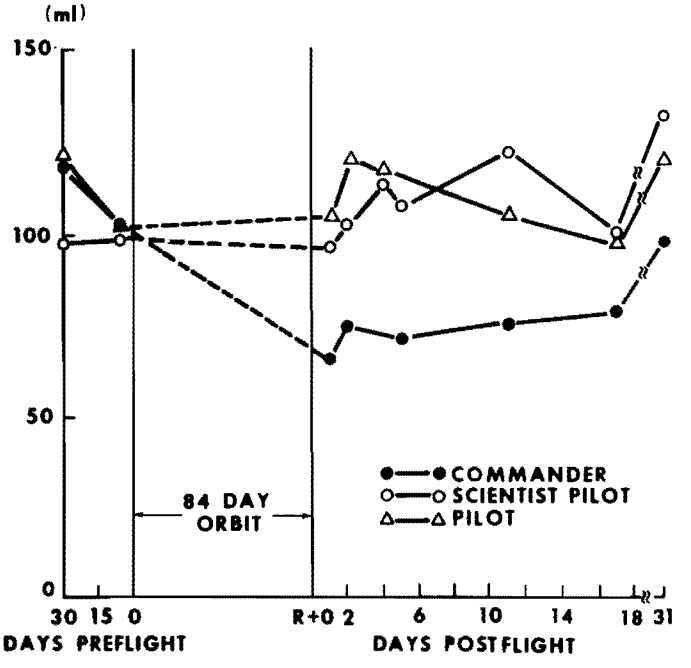


Figure 8. Mean stroke volume during submaximal exercise (Skylab 4).

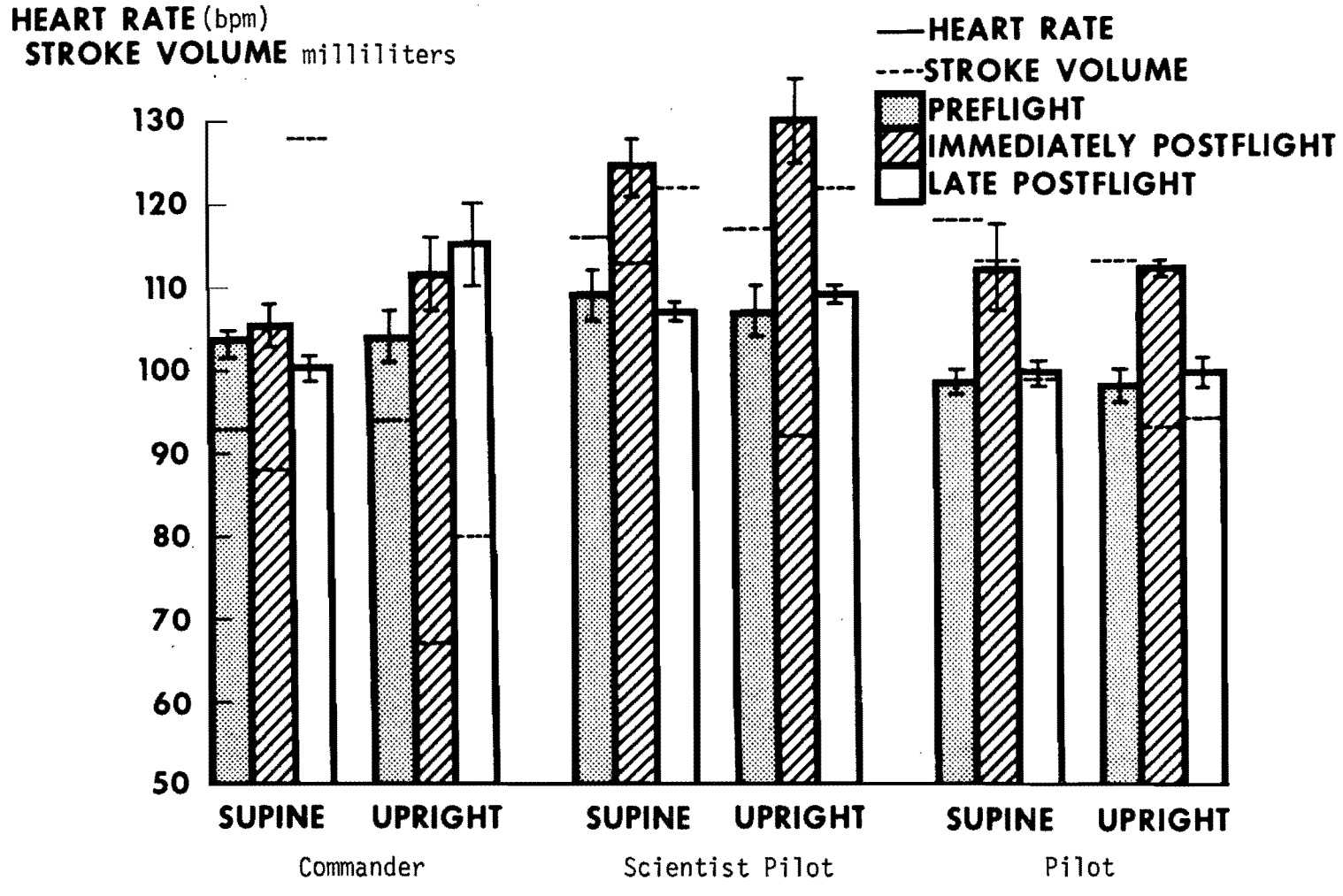


Figure 9. Skylab 4 supine ergometry (25 percent of maximum).

some yet unexplained reason the Commander exhibited a very marked response on one of his late postflight tests. All other late postflight tests were similar to baseline. On the other hand, stroke volume, as depicted by the dotted line, did show significant changes when the subject was positioned from the upright to the supine during immediate post flight exercise. Whereas the supine exercising values immediately postflight were within 5 milliliters of preflight, stroke volume decreased approximately 24 milliliters in all three crewmen upon assuming the upright position.

Table VI depicts what each Skylab crewman elected to do for personal exercise. After mission day 23 the crew reverted to negative reporting and only reported deviations from their selected protocols. As can be seen, each crewman selected a very vigorous personal exercise program which involved not only quantitative bicycle ergometry for stressing of the cardiovascular system but also the minigym, extensor springs, and "treadmill"; these exercises and exercise devices are described elsewhere (12). The latter three exercise devices were placed aboard for exercise of arm and leg antigravity muscles not adequately conditioned by bicycle ergometer exercise. These data will be further addressed when summarizing the differences in personal exercise habits of the various crewmen. Additionally, during Skylab 4 we obtained instrumented personal exercise periods on all crewmen (table VII). There had been no requirement for any instrumentation during personal exercise, however, in preflight discussions with the Skylab 4 crew they agreed to periodically instrument (vectorcardiograph/heart rate, blood pressure and metabolic analyzer) themselves. Measured heart rates and oxygen consumptions revealed that the crew had no difficulty in performing maximum levels of exercise during their personal exercise periods. Heart rates in the range of 180 to 185 beats per minute were observed during crew work loads of 240 to 286 watts. With regard to the $\dot{V}_{O_2}$ values normalized for body weight, there can be no doubt that the Skylab 4 crew did improve their physical condition during the course of the mission.

SUMMARY OF SKYLAB EXERCISE RESPONSE TESTING

Table VIII summarizes the performance of experiment M-171 during three Skylab Missions. A total of 82 tests were performed in-flight on the nine crewmen. All in-flight tests were completed as programed with the exception of the first in-flight tests on the Pilot and Scientist Pilot of Skylab 2. The Pilot's test was terminated two minutes and the Scientist Pilot's test four minutes into the third level of exercise due to ergometer restraint and environmental thermal problems.

TABLE VI. DAILY PERSONAL EXERCISE PROTOCOL
SELECTED BY EACH SKYLAB 4 CREWMAN

EXERCISE	Commander	Scientist Pilot	Pilot
LEG ERGOMETRY (Watt min)	5000	8337	6000
MINIGYM (TOTAL REPETITIONS)	100	200	200
SPRINGS (TOTAL REPETITIONS)	75	0	120
TORSO ISOMETRICS (TOTAL REPETITIONS)	20	0	20
TREADMILL			
WALK (min)	10	0	0
RUN (min)	1	0	0
SPRINGS (REPETITIONS)	300	1000	100
TOE RISES (REPETITIONS)	200	200	75

TABLE VII. INSTRUMENTED MAXIMUM IN-FLIGHT ERGOMETRY

CREWMAN	MISSION DAY	WORKLOAD, Watts	$\dot{V}_{O_2}$ (liters/min)	$\dot{V}_{O_2}$ (cc/kg per min)	HEART RATE, (bpm)	$\dot{V}_E$ (liters/min)
Commander	(PREFLIGHT)		2.716	40	183	83
	21	240	3.041	45	181	106
	66	244	3.149	46.2	183	121
	79	242	2.930	42.5	184	115
Scientist Pilot	(PREFLIGHT)		3.423	48.9	183	89
	20	286	3.692	53.3	184	>142
	27	286	3.910	56.3	185	>138
	42	286	3.855	55.3	183	>150
	65	286			183	>140
	82	286	3.801	54.2	185	>147
Pilot	(PREFLIGHT)		3.182	47	183	119
	33	238	2.932	44.6	176	103
	37	230	2.932	44.2	178	137
	63	244	3.584	53.8	183	>150
	83	286	3.366	50.5	185	>150

TABLE VIII. EXPERIMENT M171 PERFORMANCE SUMMARY

	Commander	Scientist Pilot	Pilot
Skylab 2			
PREFLIGHT TESTS	5	5	5
IN-FLIGHT TESTS	6	6	7
POSTFLIGHT TESTS	8	7	9
Skylab 3			
PREFLIGHT TESTS	7	7	7
IN-FLIGHT TESTS	9	9	9
POSTFLIGHT TESTS	8	8	8
Skylab 4			
PREFLIGHT TESTS	8	8	8
IN-FLIGHT TESTS	12	12	12
POSTFLIGHT TESTS	8	8	8

Tables IX and X summarize the results for pulmonary efficiency ($\dot{V}_E$ at $2L\dot{V}_{O_2}$) or mechanical efficiency ($\dot{V}_{O_2}$ at 150 watts). The only significant changes in pulmonary efficiency in flight were observed in the Skylab 2 Pilot and the Skylab 4 Scientist Pilot. Postflight, only the Skylab 3 Scientist Pilot and Skylab 4 Scientist Pilot demonstrated a significant difference in pulmonary efficiency relative to preflight baseline. Thus, there appears to be no trend in these data that would indicate that space flight changes the pulmonary efficiency of the crews during submaximal exercise. Conversely, six of the nine crewmen demonstrated a small but statistically significant increase in in-flight mechanical efficiency and four of these six maintained this increased mechanical efficiency during the postflight test period. The exact reason for this is not known, but it might be a result of a training effect. This was unexpected in that one would expect mechanical efficiency, if changed, to decrease because of the restraint problems expected in the weightless environment.

TABLE IX. PULMONARY EFFICIENCY

$\dot{V}_E$ AT 2Liters $\dot{V}_{O_2}$

SKYLAB MISSION	TIME PERIOD	Commander $\bar{X}$	Commander SD	Scientist Pilot $\bar{X}$	Scientist Pilot SD	Pilot $\bar{X}$	Pilot SD
2							
	PREFLIGHT	51.8	3.78	59.8	3.68	59.6	2.16
	IN-FLIGHT	50.9	3.32	64.9	3.49	68.4	2.30*
	POSTFLIGHT	40.9	3.65	61.2	2.89	67.5	4.06
3							
	PREFLIGHT	57.6	7.73	49.4	3.46	56.8	3.69
	IN-FLIGHT	56.8	5.56	51.9	5.21	57.9	4.19
	POSTFLIGHT	55.3	3.66	54.8	1.96*	59.3	2.05
4							
	PREFLIGHT	54.7	3.15	48.8	1.80	60.4	2.53
	IN-FLIGHT	54.8	4.41	55.6	2.93*	62.9	3.71
	POSTFLIGHT	53.3	3.10	54.5	2.94*	62.4	2.67

*SIGNIFICANT AT $P<0.05$

$\dot{V}_E$ = Minute volume

$\dot{V}_{O_2}$ = Oxygen consumption

SD = Standard deviation

TABLE X. MECHANICAL EFFICIENCY

$\dot{V}O_2$ AT 150 watts

SKYLAB MISSION	TIME PERIOD	Commander $\bar{X}$	Commander SD	Scientist Pilot $\bar{X}$	Scientist Pilot SD	Pilot $\bar{X}$	Pilot S
2							
	PREFLIGHT	2.07	0.09	2.07	0.22	2.10	0.069
	IN-FLIGHT	1.87	.10	1.83	.14	1.84	.05*
	POSTFLIGHT	2.05	.08	2.06	.08	2.00	.07
3							
	PREFLIGHT	2.04	0.11	2.01	0.07	2.02	0.17
	IN-FLIGHT	1.93	.08*	1.79	.27*	1.87	.07*
	POSTFLIGHT	1.93	.10	1.89	.05*	1.86	.06*
4							
	PREFLIGHT	1.96	0.09	1.94	0.05	2.11	0.11
	IN-FLIGHT	1.85	.09*	1.89	.08	1.88	.08*
	POSTFLIGHT	1.83	.05*	1.98	.10	1.90	.04*

*SIGNIFICANT AT $P<0.05$

$\dot{V}_{O_2}$ = Oxygen consumption

SD = Standard deviation

Generally, the in-flight and postflight responses to exercise by the crews of Skylab 2, 3 and 4 were similar. In-flight, some subtle, isolated differences were seen. However, there were no trends observed which would indicate a degradation in the exercise response of the crews. The Skylab 4 crew exhibited a significant in-flight decrease in recovery heart rate but not in resting (sitting position) heart rate. The Skylab 2 crew, on the other hand, exhibited decreases in both parameters while the Skylab 3 crew exhibited no changes in either. Figure 10, shows six of the nine crewmen had elevated resting ventilation in-flight which was maintained in five of these same individuals during the immediate postflight period. "Exercising" diastolic blood pressures were significantly decreased in flight in five of the crewmen while "exercising" in-flight oxygen consumption was slightly decreased in six crewmen (fig. 11 and 12).

Postflight, a significant decrement in response to exercise was noted in all crewmen. The degradation was evidenced by a decreased oxygen pulse (increased heart rate for a given oxygen consumption) as seen in figure 13. Additionally, a decreased cardiac output for the same oxygen consumption, and a decreased stroke volume were found. Significantly elevated resting ventilation was evidenced immediately postflight in both the Scientist Pilot and Pilot on Skylab 4 and the Commanders of Skylab 2 and 3.

Figures 14 and 15 summarize the cardiac output and stroke volume data for all three crews. Changes in blood flow during exercise subsequent to prolonged exposure to weightlessness were among the most consistent and striking findings of the Skylab medical experiments. The six astronauts who comprised the crews of Skylab Missions 2 and 3 exhibited large decreases in both cardiac output and stroke volume during exercise on the recovery day M-171 tests. At this time, the Skylab crewmen showed an average cardiac output deficit of 28 percent coupled with a 47 percent decline in stroke volume as compared to preflight values. For the Skylab 3 crew on the day of recovery, cardiac output was decreased by 35 percent and stroke volume was 45 percent lower than preflight. For both crews, the cardiac output values returned to within 15 percent of preflight by the second day after recovery while the stroke volume deficit required 8 to 16 days to return to within 15 percent of preflight values. However, stroke volume increased rapidly to within 80 percent of preflight during the first four postflight days. The percent changes in cardiac output and stroke volume were accompanied by changes in A-VO_2 differences of approximately equal magnitude but opposite direction.

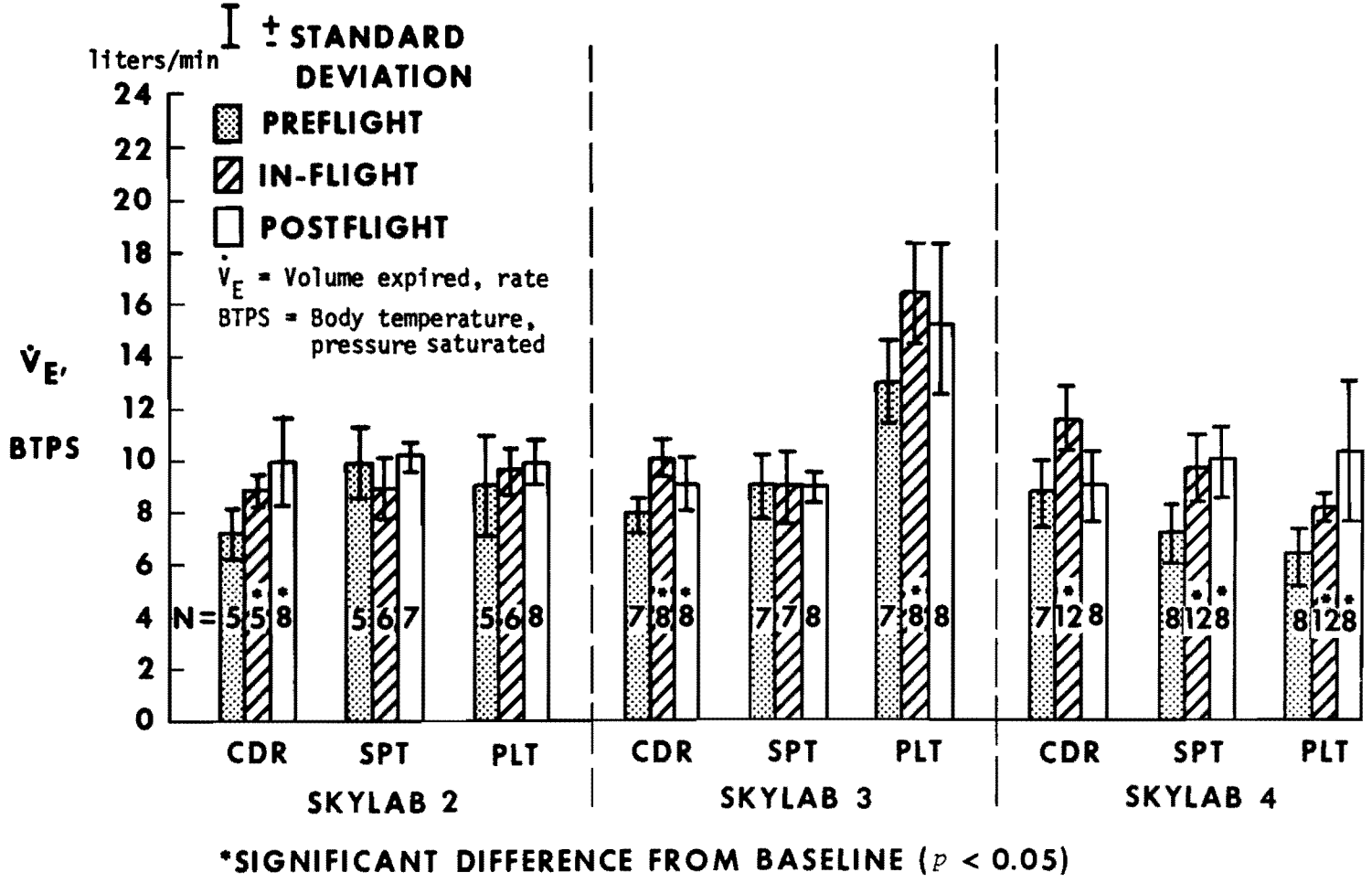


Figure 10. Resting minute volume.

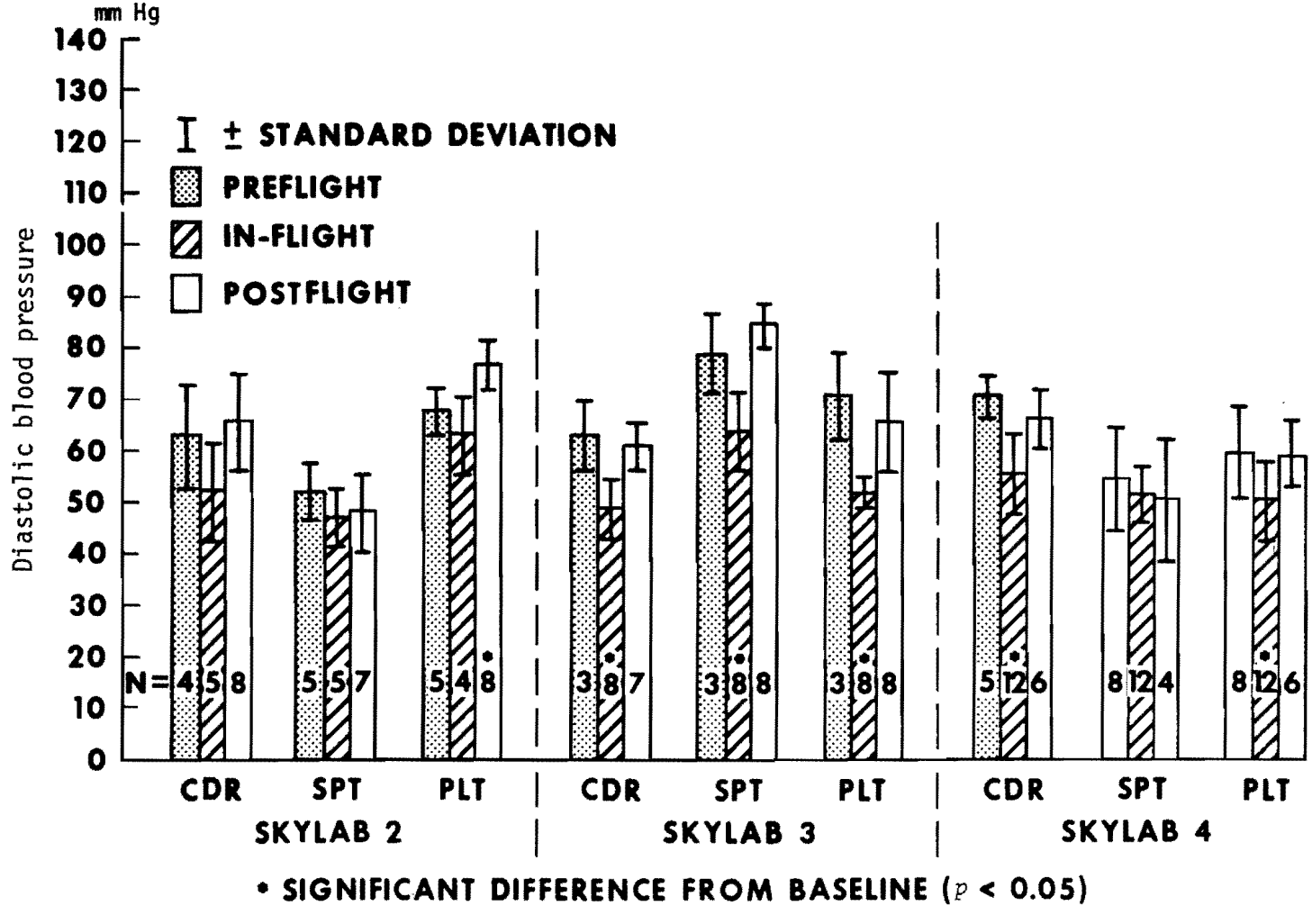


Figure 11. Diastolic blood pressure (level 3 exercise).

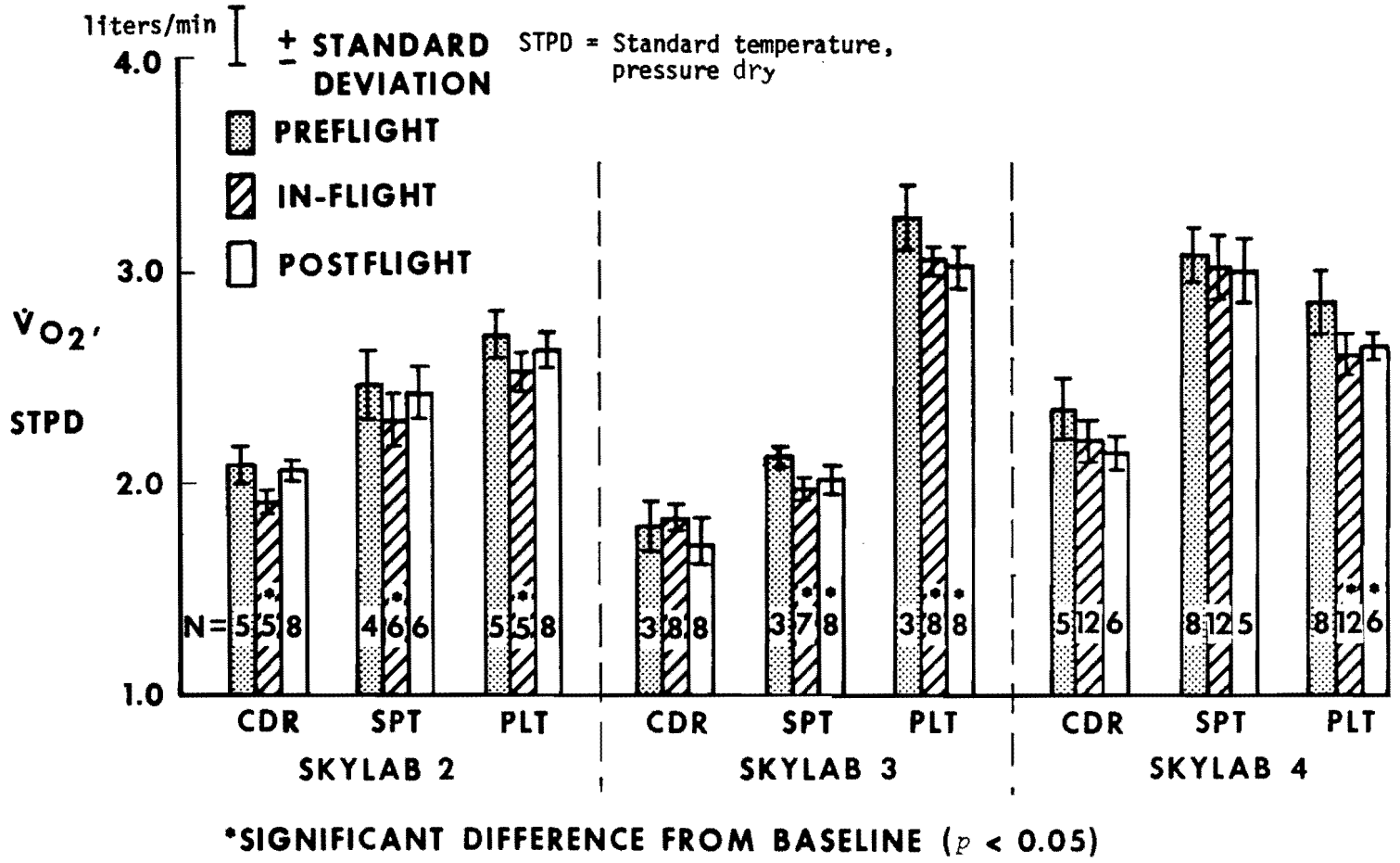


Figure 12. Oxygen Consumption, level 3 exercise.

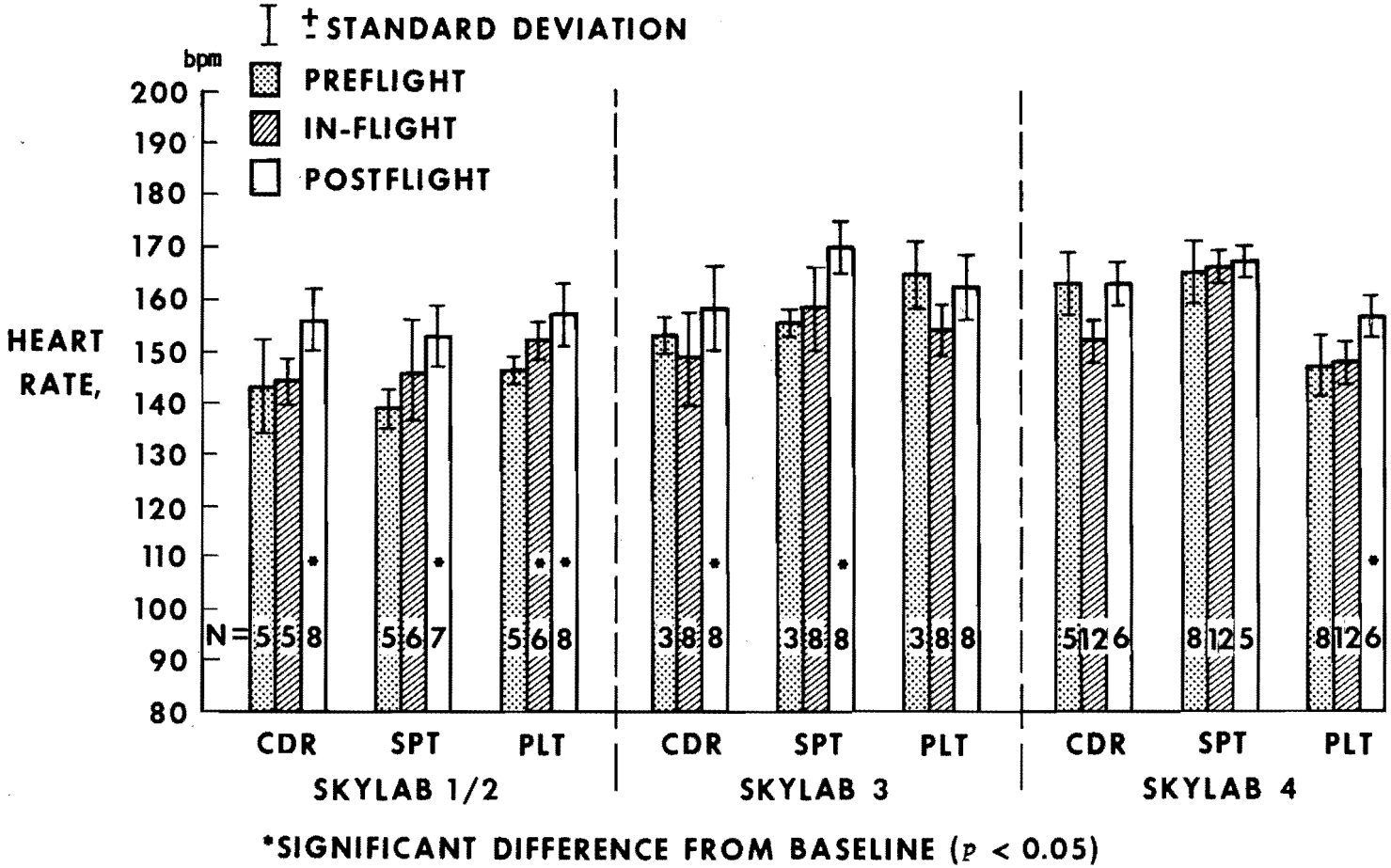


Figure 13. Heart rate, level 3 exercise.

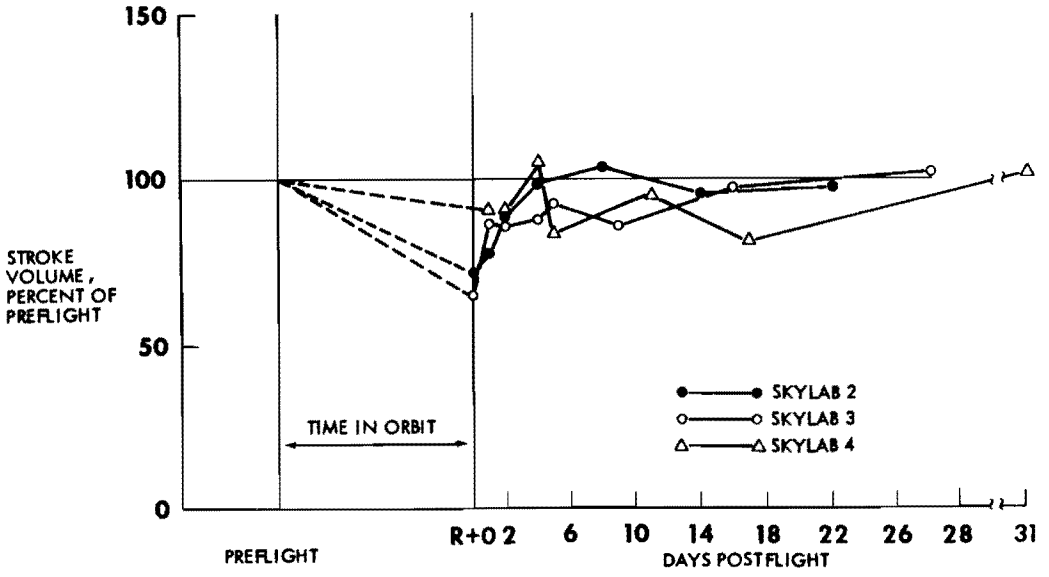


Figure 14. Cardiac output during submaximal exercise.

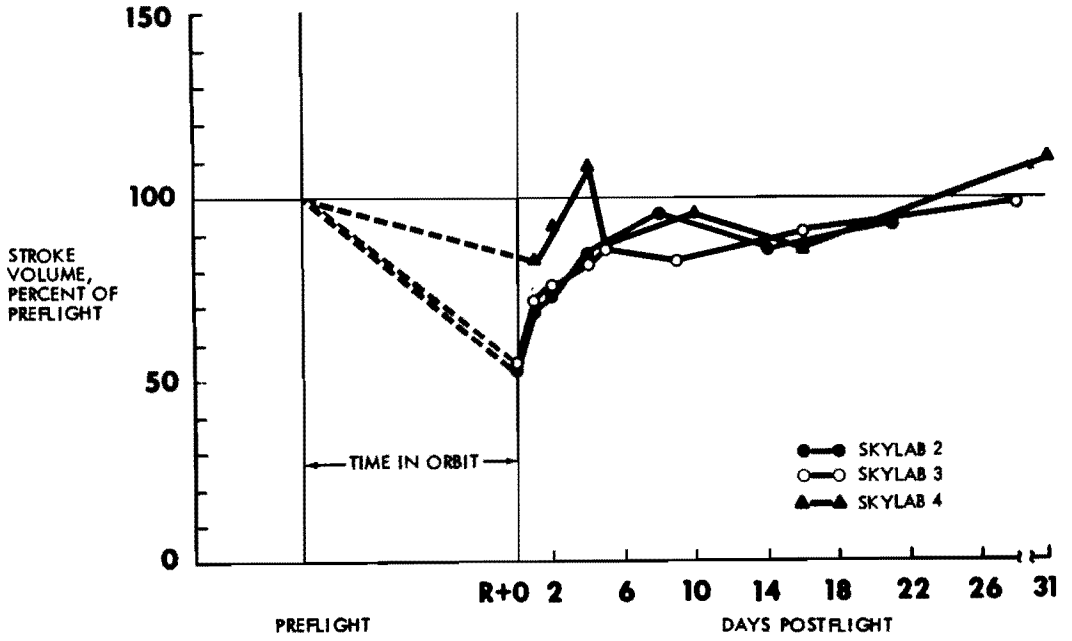


Figure 15. Stroke volume during submaximal exercise.

The present data collected on the Skylab crew would tend to implicate altered venous return as the cause of decreased cardiac output. The augmented stroke volumes noted during 30° tilt exercise reduce the likelihood that decreased myocardial function was the limiting process. Also, the rapid initial rise in both cardiac output and stroke volume over the first four postflight day would better parallel presumed readjustments in blood volume and vascular competence than would be expected if restorative processes were occuring in the myocardium.

In comparing the personal exercise levels of the various crews it becomes obvious that the amount of exercise accomplished in-flight was effective in maintaining a normal crew exercise response in-flight as well as in shortening the length of the postflight readaptation period. Table XI compares the quantitative bicycle ergometer exercise accomplished by the crews. Reference to the far right-hand column, showing these data normalized to the crewman's body weight, reveals that the Skylab 3 crew exercised about 107 percent more than the Skylab 2 crew and the Skylab 4 crew exercised 130 percent more than the Skylab 2 crew. Except for some isolated individual responses in the cardiac output and stroke volume data, all other parameters returned to normal in approximately 18 to 21 days for the Skylab 2 crew, 5 days for the Skylab 3 crew, and 4 days for the Skylab 4 crew. Based on these data there appears to be no correlation between the length of the postflight readaptation period and mission duration. It is interesting to note that the amount of exercise performed in-flight was inversely related to the length of time required postflight to return to preflight status.

TABLE XI. IN-FLIGHT QUANTITATIVE PERSONAL EXERCISE SUMMARY

SKYLAB MISSION		(1) TOTAL (watt min)	(2) DAILY avg (watt min)	(3) DAILY avg (watt min/kgm Body Weight)	
2					
	Commander	62 810	2 855	47	
	Scientist Pilot	45 307	1 618	21	31.3 avg
	Pilot	55 795	1 993	26	
3					
	Commander	228 581	3 874	58	
	Scientist Pilot	214 645	3 638	62	65 avg
	Pilot	386 193	6 545	75	
4					
	Commander	349 210	4 108	62	
	Scientist Pilot	469 420	5 523	80	72.3 avg
	Pilot	414 760	4 879	75	

(1) Includes M171 Experiment tests and personal exercise.

(2) Based on 28-day Skylab 2 mission, 59-day Skylab 3 mission, and 84-day Skylab 4 mission.

(3) Based on mean in-flight body weight.

As stated previously, the Skylab 4 results were somewhat different and are more appropriately depicted by examining the response of the individual Skylab 4 crewmen shown in figures 7, 8.

The data from the Skylab 4 Commander are similar to those seen in Skylab 2 and Skylab 3 crewmen although his return to normal was slower than the astronauts of Skylab missions 2 and 3.

The consistent postflight elevation in cardiac output and stroke volume for the Scientist Pilot of Skylab 4 may be a reflection of in-flight physical conditioning in this individual. His in-flight exercise regimen was rigorous, and it is likely that his measured preflight cardiac output and stroke volume values were not representative of his improved physical condition at the end of the orbital period. Thus, his immediate postflight values might well have been depressed and only fortuitously appeared to be the same as his preflight values. The upward trend in stroke volume during the latter days of postflight testing would seem to lend credance to the idea that his postflight "normal" levels were somewhat higher than preflight.

The results from the Skylab 4 Pilot are perhaps even more difficult to explain. His cardiac output and stroke volume values showed little or no change from preflight values during any of the postflight tests. From the first through the 17th day postflight both parameters showed a small downward trend but the overall magnitude of the trend is small enough to be of questionable significance. It is possible that his cardiovascular system was inherently nonresponsive to the weightless environment due to factors which we cannot define at this time.

The tilt ergometry testing accomplished preflight and postflight in the Skylab 4 mission demonstrated that immediate postflight supine heart rates were elevated both during rest and exercise. Although a tachycardia was observed in the upright position, the change in "exercising" heart rate was not nearly as pronounced as during rest. Both systolic and diastolic blood pressures were elevated in the upright position in at least two of the three Skylab 4 crewmen while data for the third crewman were not as clear-cut due to technical problems with the blood pressure measuring system postflight. During both the supine and upright postions reduced cardiac output was observed immediately postflight for the same stress level. However, the decrease was less in the supine position. These results on highly active crewmen cannot be directly compared with the limited studies accomplished after complete bed rest in which supine exercising stroke volumes were greatly reduced (2, 4).

The secondary objective of the M-171 experiment was to evaluate the bicycle ergometer as an in-flight exerciser for long-duration missions. Upon exposure to the weightless environment, the crews commented on a "fullness in the head" feeling and sinus problems which never really subsided. The crews have reported that the bicycle ergometer exercise provided relief from these subjective feelings, which partially explains the strong desire for the crewmen to exercise. The heavy leg exercise evidently facilitated the return of the blood to the lower extremities thus relieving their symptoms. The bicycle ergometer proved to be a very effective stressor of the cardiovascular system. If it were to be the exerciser chosen for long-duration missions, additional provision would have to be made for maintaining muscular strength in those anti-gravity muscles not adequately exercised by the bicycle ergometer.

CONCLUSIONS

Immediately postflight all crewmen showed a significant decrement in submaximal exercise response. The degradation was, in large part, evidenced by decreases in oxygen pulse, cardiac output, and stroke volume. Since similar in-flight effects were neither observed nor suspected, it is apparent that these physiological responses were a result of readaptation to one-g. Furthermore, it appears that the responses we observed resulted from decreased venous return due to re-adjustments in fluid balance/blood volume state or vascular tone. This postflight readaptation period was of short duration, was not intensified by the duration of the mission, and resulted in no irreversible effects.

Although personal exercise was not experimentally controlled during the Skylab Program, qualitative comments by the crewmen indicated that they derived some psychological benefits from these activities. In addition, given the known physiological effects of high levels of physical activity that occur in normal gravity, it would not be unreasonable to assume that in-flight exercise had a beneficial effect not only in the maintenance of a normal in-flight response to exercise and well being but also in reducing the period of time required for readaptation post flight. However, this hypothesis must be evaluated by proper experimentation. In the meantime, we will recommend exercise as a beneficial adjunct to space flight.

The successful completion of the 28-, 59-, and 84-day Skylab Missions showed that man can perform submaximal and maximal aerobic exercise in the weightless environment without detrimental trends in any of the physiologic data.

ACKNOWLEDGEMENT

Evaluation of the bicycle ergometer hardware used for the Skylab Program M171 Experiment and personal exercise showed that it was utilized approximately 248 hours in flight and the metabolic analyzer was utilized approximately 100 hours in-flight without malfunction in either device; thus, all experimental data were obtained as programed without failure. The outstanding performance of these pieces of hardware was further amplified by the successful usage of these two devices by the crewmen in their in-flight performance of 82 M171 experiment tests by and on themselves. The outstanding performance of the crewmen indicates their dedication in light of the complexity of the hardware operation and their extremely busy schedules.

This retrospective review of the successful completion of the Metabolic Activity portion of the Skylab Program experiments prompts the authors to express, here, their appreciation to the Skylab astronauts and to Mssers. R. E. Heyer, J. M. Waligora, D. J. Horrigan, H. S. Sharma, P. Schlottman of NASA-JSC and Messers. P. Schachter (Ph.D) and D. G. Mauldin of Technology Incorporated for their respective contributions and invaluable assistance in the six years of effort in design, development and performance of this experiment for Skylab. We also wish to acknowledge the counsel and encouragement of Dr. U. C. Luft of the Lovelace Foundation for Medical Education and Research.

REFERENCES

1. Cardus, D. 1966. Effects of 10 days recumbency on the response to the bicycle ergometer test. *Aerospace Med.*, 37: 993-999.

2. Hyatt, K. H., L. G. Kamenetsky, and W. M. Smith. 1969. Extravascular dehydration as an etiologic factor in post-recumbency orthostatism. *Aerospace Med.*, 40: 644-650.

3. Miller, P. B., R. L. Johnson and L. E. Lamb. 1965. Effects of moderate physical exercise during four weeks of bed rest on circulatory functions in man. *Aerospace Med.*, 36: 1077-1082.

4. Saltin, B., G. Blomquist, J. H. Mitchell, R.L. Johnson, Jr., K. Wildenthal and C. B. Champman. 1968. Response to exercise after bed rest and after training. A longitudinal study of adaptive changes in oxygen transport and body composition. *Circulation*, 38: 1-78.

5. Berry, Charles A. 1969. Preliminary clinical report of the medical aspects of Apollos VII and VIII. *Aerospace Med.*, 40: 245-254.

6. Berry, Charles A. 1970. Summary of medical experience in the Apollo 7 through 11 manned space flights. *Aerospace Med.*, 41: 500-519.

7. Rummel, J. A., E. L. Michel and C. A. Berry. 1973. Physiological response to exercise after space flight - Apollo 7 to Apollo 11. *Aerospace Med.*, 44: 235-238.

8. Michel, E. L., J. A. Rummel and C. F. Sawin. 1974. Skylab Experiment M-171 "Metabolic Activity": Results of the First Manned Mission, *Acta Astronautica*, (in press).

9. Rummel, J. A., E. L. Michel, C. F. Sawin and M. C. Buderer. 1974. Metabolic Studies During Exercise: The Second Manned Mission, *Aerospace Med.*, (in press).

10. Kim, T. S., H. Rahn and L. E. Farhi. 1966. Estimates of true venous and arterial P_{CO_2} by gas analysis of a single-breath. *J. Appl. Physiol.*, 21: 1338-1344.

11. Buderer, M. C., J. A. Rummel, C. F. Sawin and D. G. Mauldin. 1973. Use of the single-breath method of estimating cardiac output during exercise-stress testing. *Aerospace Med.*, 44: 756-760.

12. Thornton, W. and J. Rummel. 1974. Measurement and Prevention of Muscle Deconditioning on Skylab. Presented at Skylab Life Sciences Symposium, Johnson Space Center, Houston, Texas.

APPENDIX

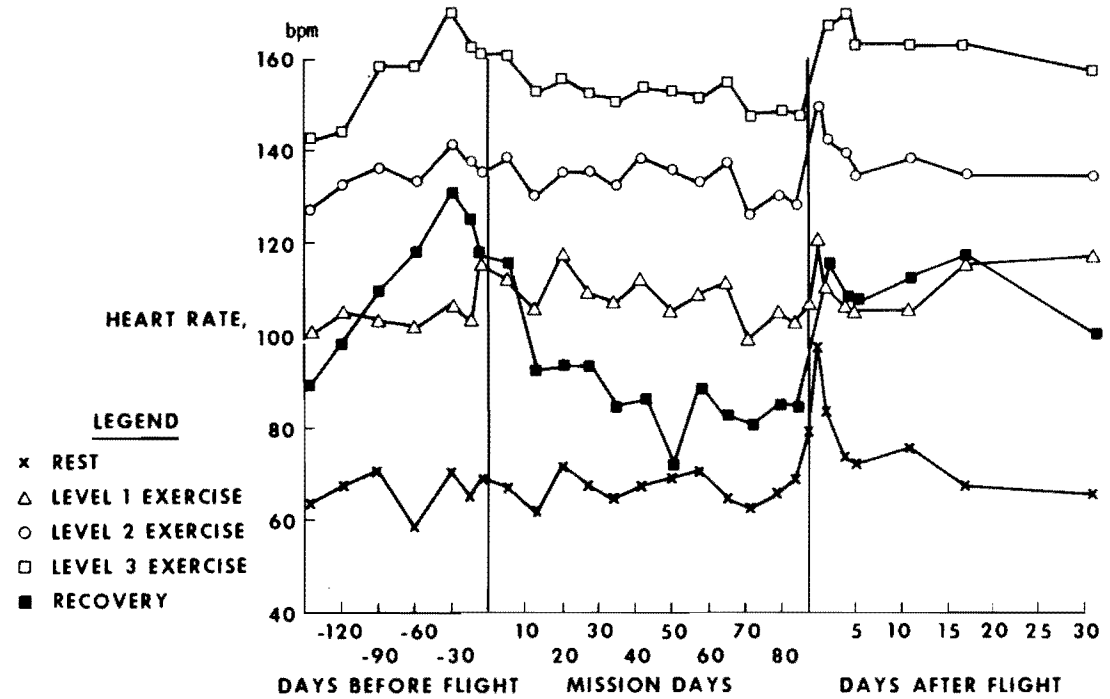


Figure 1A. Heart rate, Skylab 4 Commander.

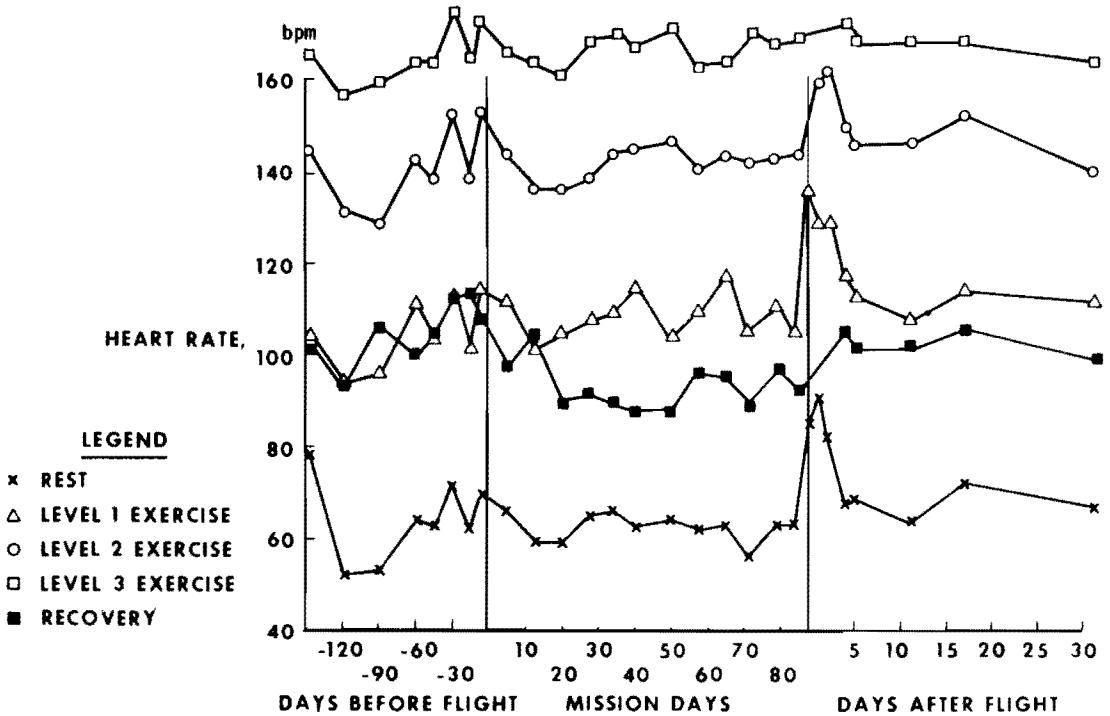


Figure 1B. Heart rate, Skylab 4 Scientist Pilot.

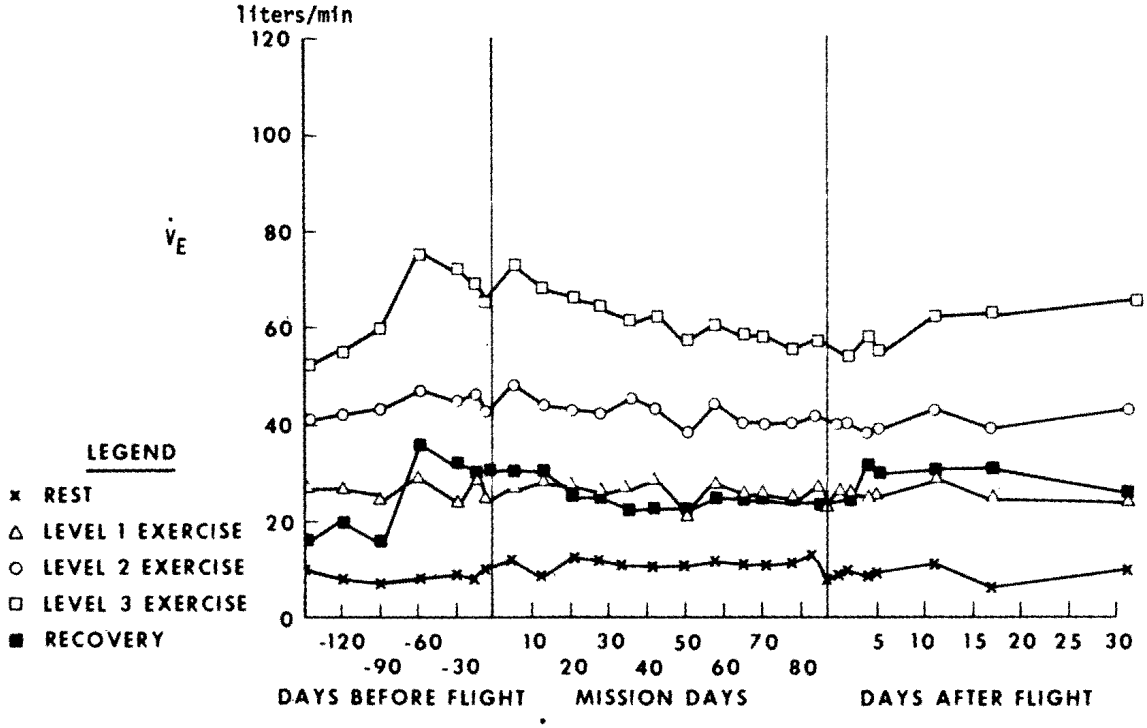


Figure 2A. $\dot{V}_E$, Skylab 4 Commander.

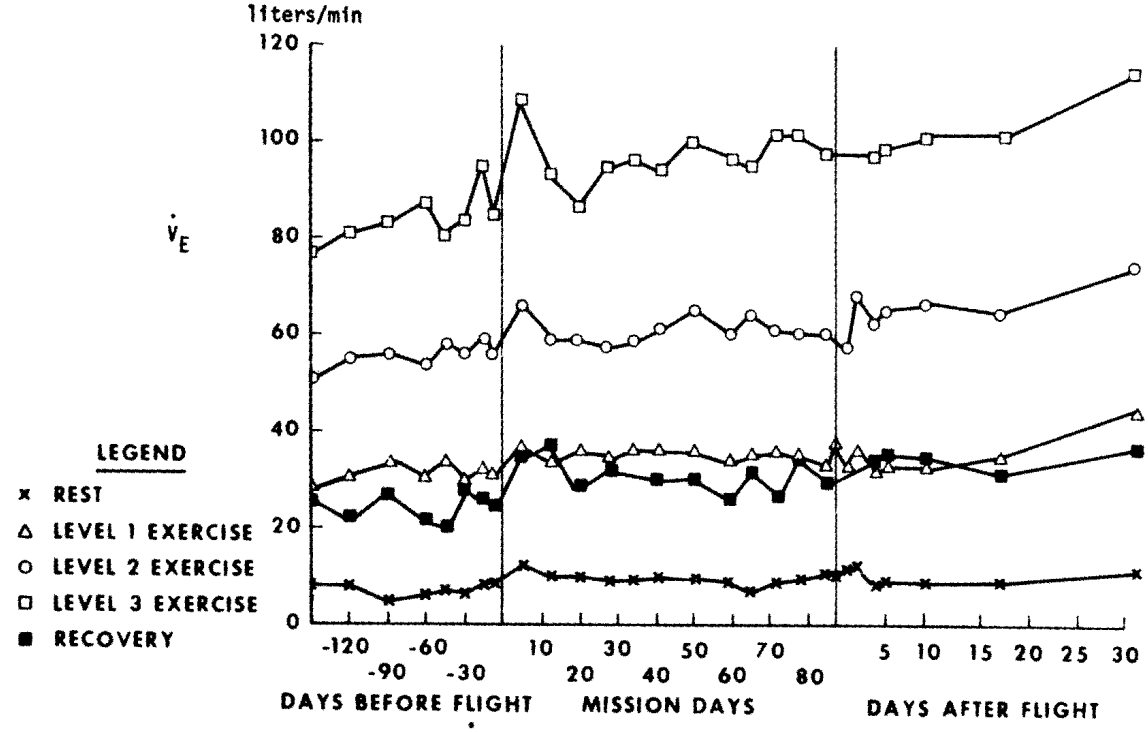


Figure 2B. $\dot{V}_E$, Skylab 4 Scientist Pilot.

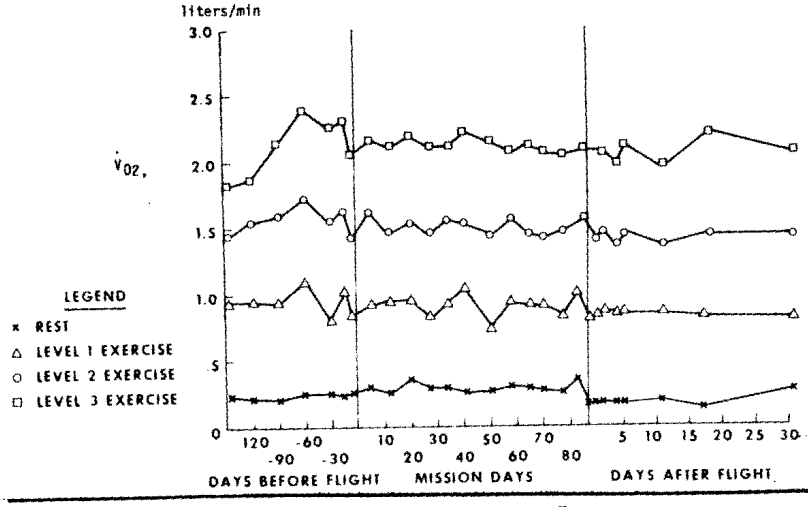


Figure 3A. $\dot{V}_{O_2}$, Skylab 4 Commander.

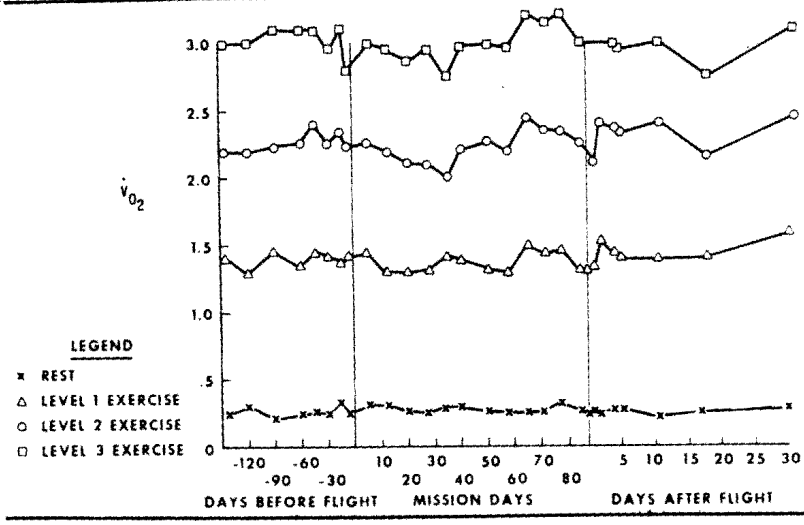


Figure 3B. $\dot{V}_{O_2}$, Skylab 4 Scientist Pilot.

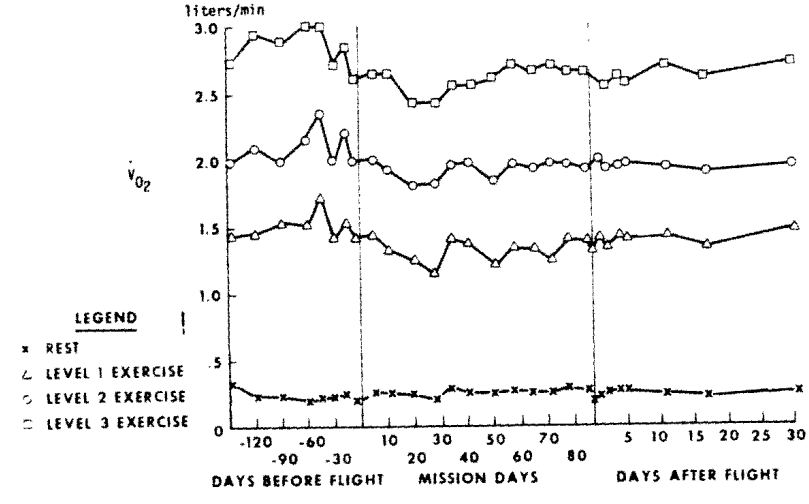


Figure 3C. $\dot{V}_{O_2}$, Skylab 4 Pilot.

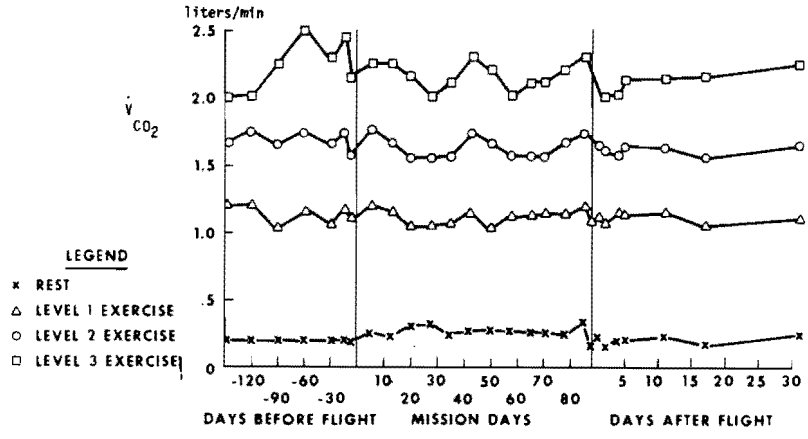


Figure 4A. $\dot{V}_{CO_2}$, Skylab 4 Commander.

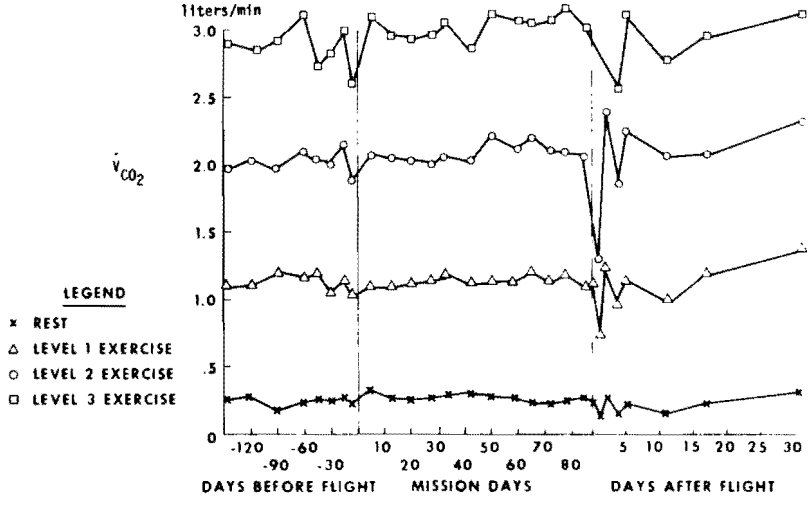


Figure 4B. $\dot{V}_{CO_2}$, Skylab 4 Scientist Pilot.

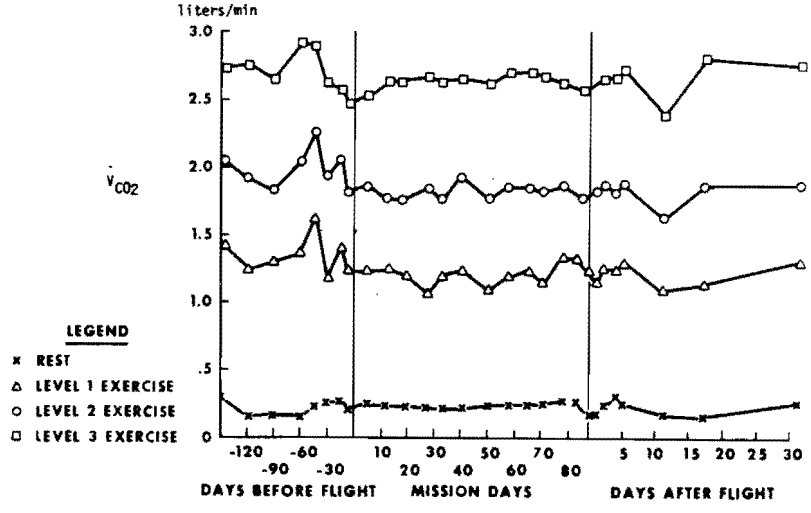


Figure 4C. $\dot{V}_{CO_2}$, Skylab 4 Pilot.

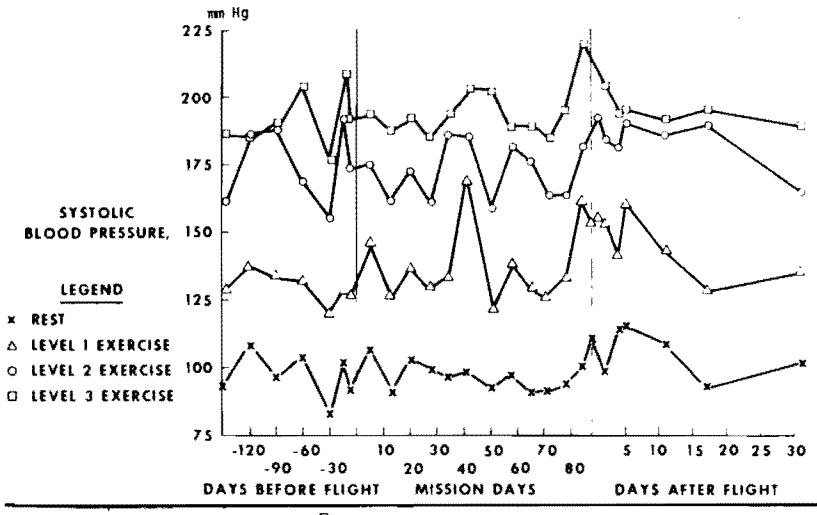


Figure 5A.

Systolic blood pressure, Skylab 4 Commander.

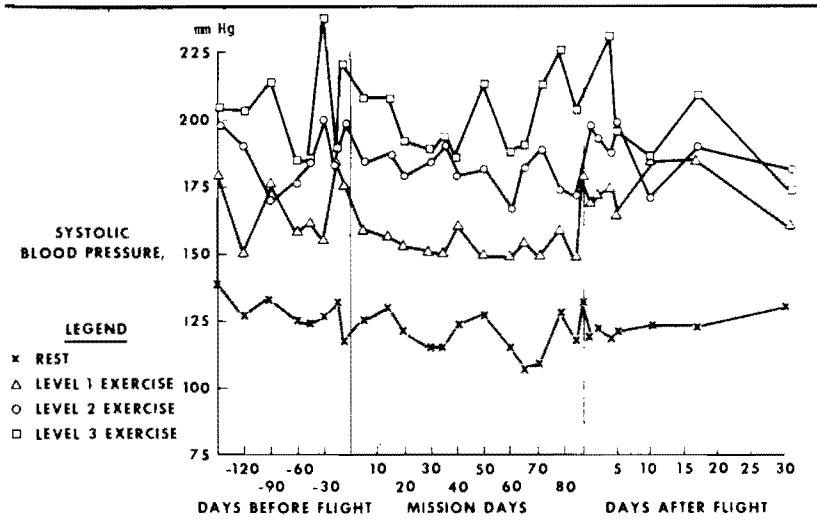


Figure 5B.

Systolic blood pressure, Skylab 4 Scientist Pilot.

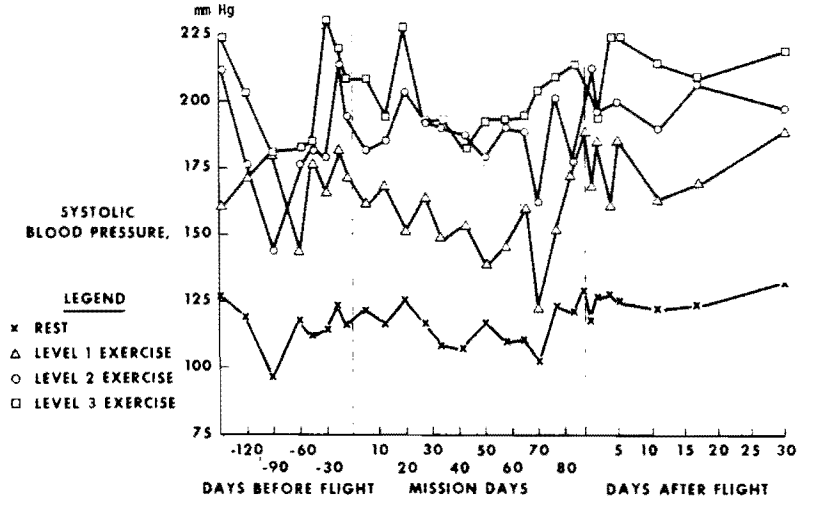


Figure 5C.

Systolic blood pressure, Skylab 4 Pilot.

PULMONARY FUNCTION EVALUATION DURING AND FOLLOWING SKYLAB SPACE FLIGHTS

C. F. Sawin, Ph.D.; A. E. Nicogossian, M.D.*; A. P. Schachter, Ph.D†; J. A. Rummel, Ph.D.*; and E. L. Michel**

ABSTRACT

Previous experience during the Apollo postflight exercise testing indicated no major changes in pulmonary function. Although pulmonary function has been studied in detail following exposure to hypoxic and hyperoxic environments, few studies have dealt with normoxic environments at reduced total pressure as encountered during the Skylab missions.

Forced vital capacity was measured during the preflight and postflight periods of the Skylab 2 mission. Initial in-flight measurements of vital capacity were obtained during the last two weeks of the second manned mission (Skylab 3). Comprehensive pulmonary function screening was accomplished during the Skylab 4 mission. The primary measurements made during Skylab 4 testing included residual volume determination, closing volume, vital capacity, and forced vital capacity and its derivatives. In addition, comprehensive in-flight vital capacity measurements were made during the Skylab 4 mission. Vital capacity was decreased slightly during flight in all Skylab 4 crewmen. No major preflight to postflight changes were observed in the other parameters.

INTRODUCTION

Previous experience during the Apollo Program showed no major changes in pulmonary function when evaluated by postflight exercise testing (1). Although pulmonary function has been studied in detail following exposure to hypoxic and hyperoxic environments, few studies (2, 3, 4, 5, 6) have dealt with normoxic environments at reduced total pressure as encountered during Skylab. The absence of a gravity vector would be expected to facilitate ventilation/perfusion relationships and result in better overall gas exchange in the weightless state. Because of this and the absence in previous history of postflight pulmonary problems, vital capacity was initially proposed as the only functional screening test for Skylab.

*National Aeronautics and Space Administration - Lyndon B. Johnson Space Center, Houston, Texas.

†Life Sciences Division, Technology Incorporated, Houston, Texas.

Cardiac output measurements were made in our laboratory (7) during preflight and postflight exercise tests using the technique of Kim *et al.* (8). Due to the magnitude of decreases in cardiac output following the first and second manned Skylab missions and because the method of Kim *et al.* is based upon normal pulmonary function, it was decided to perform more thorough pulmonary function screening in conjunction with the final and longest duration Skylab mission. This paper summarizes pulmonary function data obtained during all three Skylab missions.

METHODS

The Skylab Program consisted of three manned, earth-orbital flights of progessively increased duration (28, 59, and 84 days). Each Skylab crew included a Commander, a Scientist Pilot, and a Pilot. The average composition of the spacecraft gas atmosphere during Skylab was: inspired oxygen partial pressure equal to 170 torr (226×10^2 N/m^2), inspired nitrogen partial pressure equal to 75 torr (10×10^3 N/m^2), inspired water partial pressure equal to 10 torr (13×10^2 N/m^2), and inspired carbon dioxide partial pressure equal to 5 torr (67×10^2 N/m^2), although the nominal composition was inspired oxygen partial pressure equal to 181 torr (241×10^2 N/m^2) and inspired nitrogen partial pressure equal to 77 torr (103×10^2 N/m^2) at a total pressure equal to 258 torr (344×10^2 N/m^2). This atmosphere was planned to provide approximate sea level equivalent of alveolar oxygen partial pressure.

The Skylab 4 pulmonary function test equipment layout is shown in figure 1. Skylab metabolic analyzers (9) were used for all Skylab 2 and Skylab 3 pulmonary function studies. Briefly, these units were designed to measure vital capacity and respiratory gas exchange ($\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$). Each unit had rolling seal spirometers, a mass spectrometer, and an analog computer.

Forced vital capacity and its derivatives were measured during the preflight and postflight periods of the first manned mission (Skylab 2). Initial in-flight measurements of vital capacity were obtained during the last two weeks of the second manned mission (Skylab 3). Comprehensive pulmonary function screening was accomplished during the final manned mission (Skylab 4). One metabolic analyzer was modified to support the Skylab 4 preflight and postflight pulmonary function screening. This unit was modified to compute the volume of nitrogen washed out as: $\dot{V}_{N_2} = (\dot{V}_E \times F_{E_{N_2}} - \dot{V}_I \times F_{I_{N_2}})$.
Oxygen was supplied to the inspiration spirometer via a demand regulator. These modifications permitted residual volume determination by open circuit washout of pulmonary nitrogen during oxygen breathing (10,11,12).

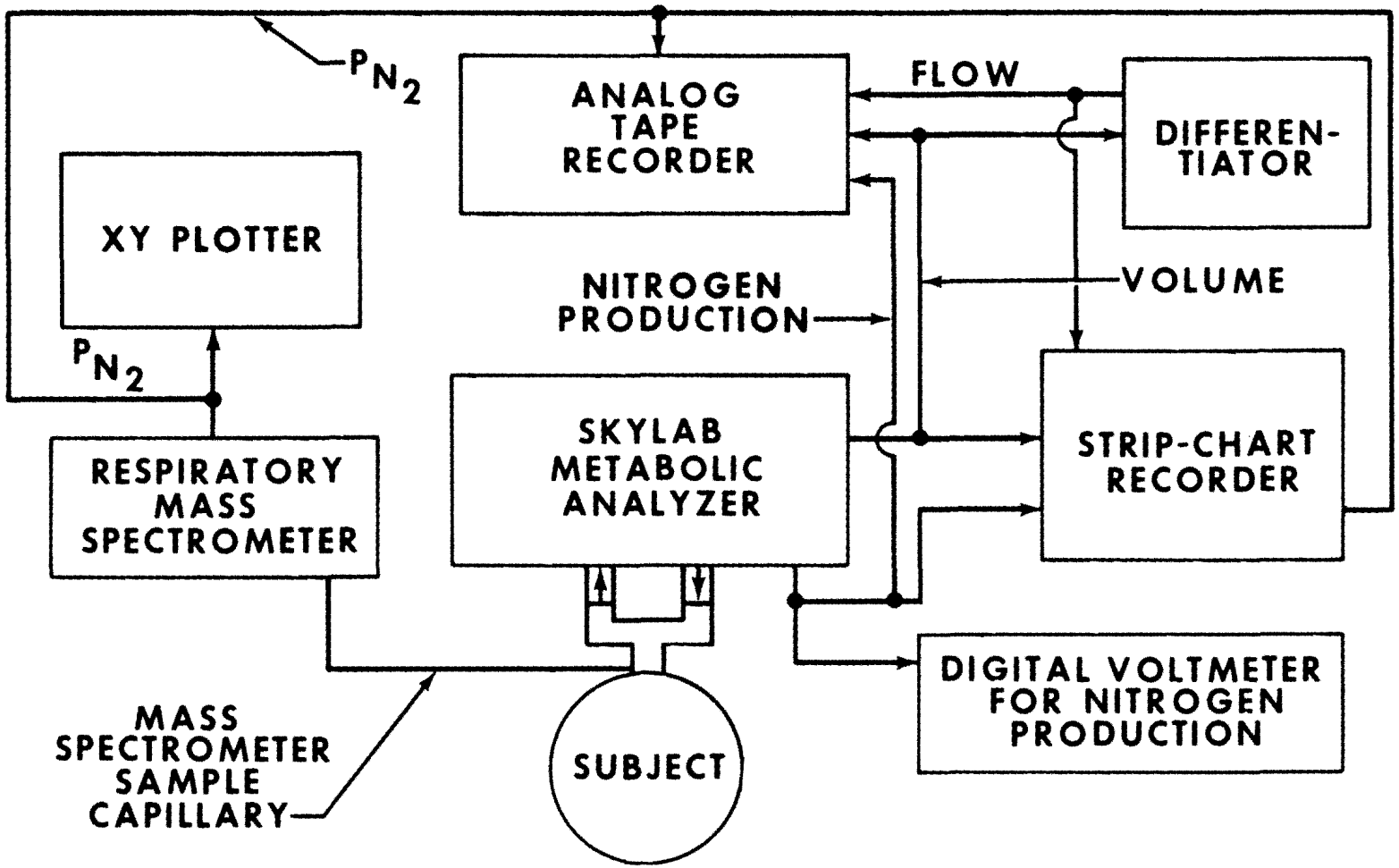


Figure 1. Skylab 4 Pulmonary Function Test Equipment.

A respiratory mass spectrometer monitored nitrogen partial pressure continuously at the subject interface. An XY plotter provided continuous nitrogen partial pressure (ordinate) as a function of time (abscissa) during residual volume determinations.

Closing volume and closing capacity together with their ratios to vital capacity and total lung capacity, have been proposed as indicators of small airway mechanics (13, 14). These indices were computed from data obtained from the single-breath oxygen washout test and residual volume. Vital capacity and forced vital capacity were measured to obtain commonly reported flow and volume parameters (15, 16, 17, 18). Residual volume and closing volume measurements were made with the subject in the sitting position. Vital capacity and forced vital capacity measurements were made with the subject standing.

An analog tape recorder and stripchart were used during all Skylab 4 preflight and postflight testing to provide permanent, synchronous records of nitrogen partial pressure at the mouthpiece, tidal volume, flow rate, and nitrogen washout. The Skylab 4 preflight pulmonary function examinations were conducted five days preflight. Vital capacity was measured at six day intervals in-flight. Complete postflight examinations were conducted on recovery day and 1, 2 and 5 days after recovery. Vital capacity measurements were continued at 11, 17, and 31 days postflight.

RESULTS AND DISCUSSION

Pulmonary function data for Skylab crewmen obtained in the Cardiopulmonary Laboratory at Johnson Space Center during annual astronaut physical examinations are summarized in table I. Vital capacity and flow rate data for the Skylab 3 Scientist Pilot were low relative to reported normal values (16, 18); however, the Scientist Pilot demonstrated adequate pulmonary reserve during numerous bicycle ergometer exercise tests in our laboratory. With the exception of pulmonary function data for the Skylab 2 Scientist Pilot and the Skylab 4 Pilot, table 1 contains the means and standard deviations of data from each crewman's three or four annual physical examinations preceding Skylab.

Skylab 2 Forced Vital Capacity Determinations

Table II summarizes the preflight, recovery day, and first day post recovery forced vital capacity data. No data were obtained for the Scientist Pilot postflight due to orthostatic intolerance complicated by sea sickness. The values shown for each crewman represent the best effort of two trials. The Commander's forced expired volume in 1-second on the first day postflight was significantly reduced. Based on his

normal forced vital capacity, it is possible that his decreased forced expiratory volume in 1-second was due to less than maximal subject effort.

TABLE I. PREFLIGHT ANNUAL PHYSICAL EXAMINATION SUMMARIES

	Age (yr)	Height (m)	Weight (kg)	Vital Capacity (liters, BTPS)	Residual Volume (liters, BTPS)	FEV_1 (liters, BTPS)	MMFR 25-75% (liters/sec, BTPS)
Skylab 2							
Commander	43	1.7	62	4.77±0.21	2.18±0.42	3.71±0.14	3.27±0.32
Scientist Pilot	41	1.83	77	6.95*	2.66*	5.07*	4.06*
Pilot	41	1.78	80	5.31±0.09	2.10±0.24	3.94±0.14	3.05±0.11
Skylab 3							
Commander	41	1.75	69	5.03±0.06	2.12±0.25	4.16±0.05	4.34±0.33
Scientist Pilot	42	1.75	62	4.04±0.13	1.54±0.22	3.27±0.04	3.07±0.34
Pilot	37	1.83	89	6.95±0.10	2.02±0.15	5.21±0.18	4.33±0.75
Skylab 4							
Commander	41	1.75	68	6.05±0.21	1.95±0.32	4.65±0.18	4.17±0.25
Scientist Pilot	37	1.75	71	6.26±0.08	1.77±0.01	4.78±0.06	3.93±0.25
Pilot	43	1.75	68	6.30*	1.99*	5.30±0.35	7.43±0.22

All values are mean ±SD with the exception of those with one test only (*). Most values are from annual exams on the preceding 4 years.

BTPS = Body temperature, pressure saturated
FEV_1 - Forced expiratory volume in one second
MMFR = Maximum midexpiratory flow rate

TABLE II. SKYLAB 2 POSTFLIGHT FORCED VITAL CAPACITIES

	FVC (liters, BTPS)			FEV_1 (liters, BTPS)		
	Preflight	Postflight		Preflight	Postflight	
	F-5	R+0	R+1	F-5	R+0	R+1
Commander	4.95	4.74	4.88	3.56	3.57	2.51
Scientist Pilot	7.0	NA	NA	5.02	NA	NA
Pilot	5.28	5.41	5.35	4.03	3.89	4.22

FVC = forced vital capacity in one second
FEV_1 = Forced expiratory volume in one second

F- = Preflight days to launch
R+ = Postflight days after recovery
NA = Not applicable
BTPS = Body temperature, pressure saturated

Skylab 3 Vital Capacity Determinations

In-flight vital capacity measurements were made during the last two weeks of the Skylab 3 mission. Results of preflight, in-flight, and postflight measurments are shown in table III. The Commander showed no changes except a slight increase in vital capacity five days post recovery. Vital capacity of the Scientist Pilot was slightly higher in-flight but normal postflight relative to preflight values. The Pilot exhibited decreased vital capacity in-flight but normal vital capacity postflight relative to preflight.

TABLE III. SKYLAB 3 VITAL CAPACITIES

Vital Capacity (liters, BTPS)

	Preflight*	In-flight			Postflight			
		MD45-47†	MD50-52	MD58	R+1	R+2	R+4	R+5
Commander	5.03±0.06 SD	5.07	4.96	4.87	4.95	-	5.16	5.30
Scientist Pilot	4.04±0.13 SD	4.24	4.36	-	-	3.92	4.11	4.19
Pilot	6.95±0.10 SD	6.10	6.35	6.17	6.91	6.90	6.94	7.01

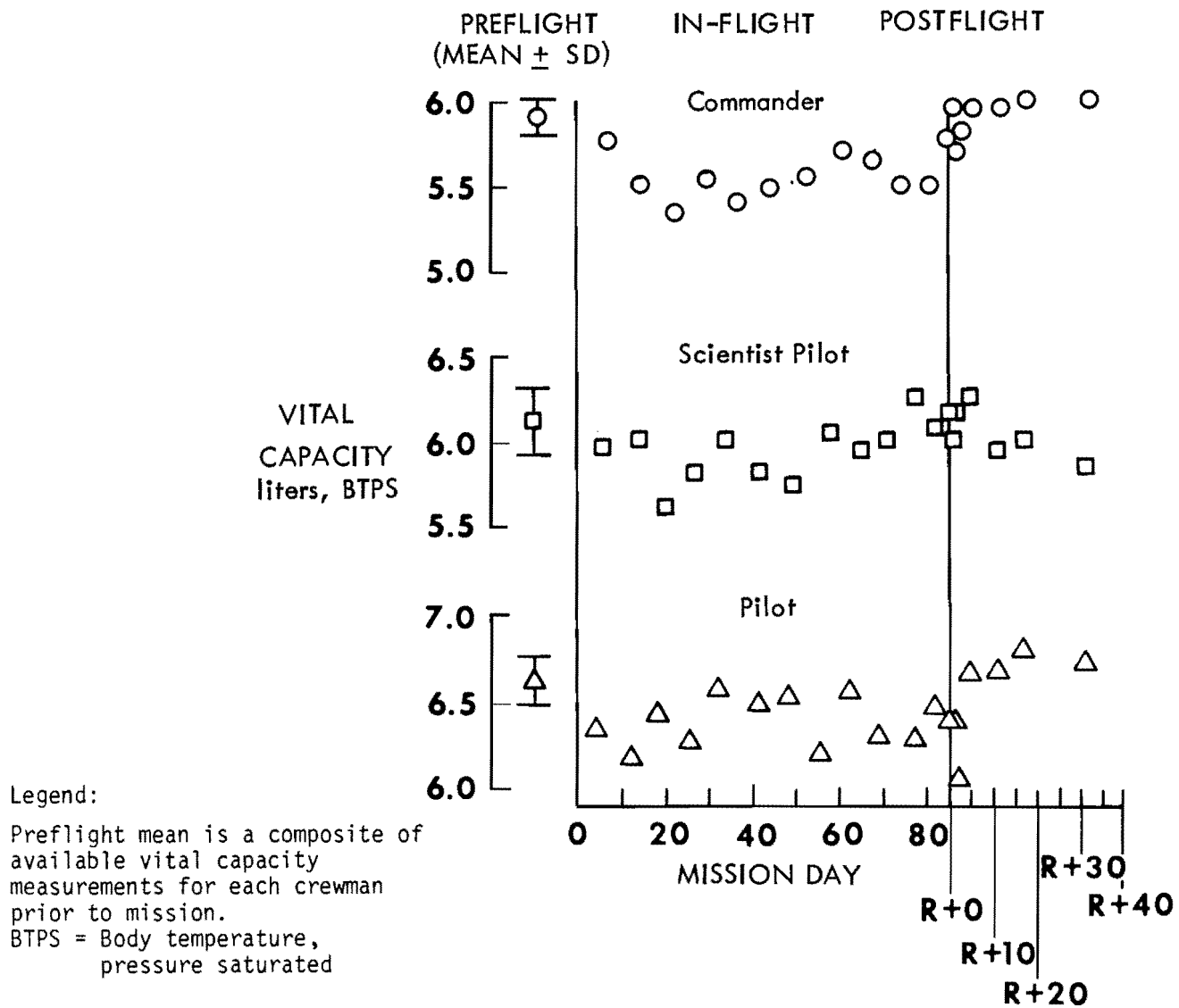
*Data from table I
†MD - Mission Day
BTPS = Body temperature, pressure saturated
SD = Standard deviation

Skylab 4 Vital Capacity Determinations

Vital capacity data for the Commander, Scientist Pilot, and Pilot are shown in figure 2. Vital capacities were generally observed to be lower in-flight relative to preflight. Vital capacity for the Commander remained below preflight for the entire in-flight period. All data presented in figure 2 were obtained using experiment M171 metabolic analyzers.

Skylab 4 Pulmonary Function Screening Tests

Nitrogen washout curves showed no indications of trapping. All washout curves appeared to reflect the anticipated two time constants representing washout of pulmonary and total body nitrogen spaces.



Legend:

Preflight mean is a composite of available vital capacity measurements for each crewman prior to mission.
BTPS = Body temperature, pressure saturated

Figure 2. Skylab 4 vital capacity data.

The Commander had a pronounced vasovagal response following maximal oxygen inspiration during the first closing volume determination on recovery day and further testing was curtailed until the next day. A hardware failure resulted in loss of residual volume measurement for the Commander on the first day following recovery. All other measurements on the first day following recovery, and all measurements on days two and five postflight were within normal ranges. The composite results for Skylab pulmonary function screening tests are presented in table IV.

Residual volume in the Scientist Pilot was slightly increased immediately following recovery and on day two compared to preflight. Residual volume/total lung capacity percent indicated that these changes were probably insignificant. Ventilatory equivalents were variable and reflected the Scientist Pilot's irregular respiratory pattern during washouts.

Although vital capacity for the Pilot was slightly decreased on the second day following recovery relative to preflight, forced vital capacity was normal. Maximum midexpiratory flow rate (between 25 percent and 75 percent of the forced vital capacity) values for the Pilot are the highest recorded in our laboratory for any individual.

Skylab 4 provided the first opportunity for extensive, noninvasive pulmonary function screening on astronauts before and following an extended zero-g exposure. No physiologically significant quantitative decrement in pulmonary function was shown by any crewman during examinations following this 84-day Earth-orbital mission.

Postflight chest films for all crewmen were compared to preflight films to detect changes, if any, in the pulmonary vessels, parenchyma, or heart size. No significant pulmonary vasculature or parenchymal changes were observed in any instance.

Vital capacity, the only parameter measured preflight, in-flight, and postflight, showed in-flight decreases approaching 10 percent in the case of the Skylab 3 Pilot and for the Commander, Scientist Pilot, and Pilot on Skylab 4 (table III and figure 2). These decreases in vital capacity apparently resulted from one or a combination of the following factors:

- cephalad shift of the diaphragm in zero-g,
- body fluid redistribution into the thoracic cavity, or
- a direct result of decreased ambient pressure.

TABLE IV. PULMONARY FUNCTION SCREENING*

	COMMANDER					SCIENTIST PILOT					PILOT				
PARAMETER	F-5	R+0	R+1	R+2	R+5	F-5	R+0	R+1	R+2	R+5	F-5	R+0	R+1	R+2	R+5
VC (liters)	5.83	5.94	5.72	5.82	5.94	6.11	6.16	6.00	6.16	6.26	6.49	6.38	6.38	6.05	6.64
RV (liters)	1.40	1.53	- -	1.31	1.43	1.53	2.18	1.27	2.43	1.65	2.20	1.67	2.00	2.20	1.53
TLC (liters)	7.23	7.47	- -	7.13	7.37	7.64	8.28	7.27	8.59	7.92	8.69	8.05	8.38	8.24	8.17
RV/TLC (%)	20	21	- -	18	19	20	26	18	28	21	26	21	24	27	19
TV (liters/breath)	1.07	1.20	1.00	1.15	0.92	2.48	2.83	1.87	- -	1.48	2.23	0.92	0.94	0.82	0.80
V_A/RV	30	23	- -	33	16	48	28	48	27	16	23	21	17	18	16
FVC (liters)	5.61	- -	5.56	5.71	6.05	5.83	5.77	5.39	5.88	6.21	6.22	6.22	5.72	6.27	6.32
FVC/VC (%)	99	- -	97	98	102	96	94	90	96	99	96	97	90	104	95
FEV_1 (liters/sec)	4.62	- -	4.29	4.59	4.70	4.35	4.61	4.24	4.37	4.54	5.50	5.50	5.39	5.49	5.29
$MMFR_{25-75}$ (l/sec)	4.32	- -	4.30	4.39	4.14	3.17	5.15	3.69	3.43	3.65	6.61	7.06	7.73	6.82	5.10
MET (sec)	0.65	- -	0.64	0.65	0.73	0.92	0.56	0.73	0.86	0.85	0.47	0.44	0.37	0.46	0.62
MEFR (liters/sec)	12.4	- -	12.0	12.4	12.3	10.5	11.0	10.5	10.9	10.8	11.6	11.6	11.0	12.2	11.4
V (60% TLC) (l/sec)	4.74	- -	3.88	4.61	5.50	3.70	4.74	3.67	3.73	4.87	7.76	7.55	7.33	7.46	5.72
CV (liters)	0.80	0.88	0.83	0.56	0.76	1.02	0.99	0.99	0.49	0.81	0.72	0.89	0.50	0.45	0.59
CC (liters)	2.20	2.41	- -	1.87	2.18	2.55	3.18	2.26	2.92	2.46	2.91	2.56	3.43	2.64	2.12
CV/VC (%)	14	15	16	10	13	17	16	17	8	13	11	14	8	7	9
CC/TLC (%)	30	32	- -	28	30	33	38	31	34	31	34	32	32	33	25

*A summary of measured and derived values obtained 5 days preflight (F-5), immediately following recovery (R+0), 1 day (R+1), 2 days (R+2) and 5 days (R+5) following recovery.
All volume and flow measurements are reported at BTPS conditions.

VC = Vital capacity
RV = Residual volume
TLC = Total lung capacity
V_A/RV = Ventilatory equivalents
FVC = Forced vital capacity
FEV_1 = Forced expiratory volume in 1 second
MMFR = Maximum midexpiratory flow rate
MET = Midexpiratory time
MEFR = Midexpiratory flow rate
CV = Closing volume
CC = Closing capacity

KEY;
CDR=Commander
SPT=Scientest Pilot
PLT=Pilot

Foley and Tomashefski (2) showed a decrease in flow rate with no significant decrease in forced vital capacity when performed during the zero-g portion of Keplerian maneuvers in KC-135 aircraft. Ulvedal *et al.* (6) showed forced vital capacity to be reduced 3 to 8 percent by exposure to equivalent 18 to 33 500 foot altitudes without concomitant hypoxia. Robertson and McRae (4) similarly observed a 4 percent decrease in forced vital capacity in subjects exposed to a 5 psia, oxygen-helium gaseous environment with inspired oxygen partial pressure of 175 torr (233×10^2 N/m^2) for a period of 56 days. Vital capacities returned to normal upon chamber descent to near sea level ambient pressure. Vital capacities were measured during Skylab Medical Experiments Altitude Test (SMEAT) (5), a ground-based 56-day simulated Skylab mission in which the environment was comparable to Skylab with the important exception of the presence of Earth's gravity. A standard vitalometer was used for both the pre-altitude and the 5 psia measurements. Mean vital capacity values for the SMEAT Commander, Scientist Pilot, and Pilot were decreased by -4.5, -2.9, and -4.9 percent, respectively, during this 56-day exposure to barometric pressure equivalent to a 27 000 foot altitude without hypoxia. Post SMEAT, vital capacities returned to baseline values. Our in-flight Skylab data are in general agreement with all reported studies (4, 5, 6).

CONCLUSIONS

In summary, the vital capacity changes observed in-flight may be partially explained as a response to 5 psia ambient pressure. However, the proportion of vital capacity decreases directly attributable to other factors such as body fluid shifts and a cephalad shift of the diaphragm cannot be determined from the present data. Regardless of the cause(s) of decreased in-flight vital capacities, a review of post-flight data shows that these changes revert to normal within two hours following recovery without significant impact on crew health status.

Further in-flight comprehensive pulmonary function testing will be necessary during future manned missions in order to substantiate observed decreases in vital capacity and increase our knowledge concerning the physiological effects of the weightless state upon the human body. The Space Shuttle will have a sea level equivalent atmosphere. Therefore, it will provide the first opportunity to evaluate pulmonary function where the primary environmental change will be the weightless state (zero-g).

REFERENCES

1. Rummel, J. A., E. L. Michel and C. A. Berry. 1973. Physiological response to exercise after space flight - Apollo 7 to Apollo 11. *Aerosp. Med.* 44:235.

2. Foley, M. F. and J. F. Tomashefski. 1969. Pulmonary function during zero-gravity maneuvers. *Aerosp. Med.* 40:655.

3. Robertson, W. G., H. J. Zeft, V. S. Behar, and B. E. Welch. 1966. Observations on man in oxygen-helium environment at 380 mm Hg total pressure. II. Respiratory. *Aerosp. Med.* 37:453.

4. Robertson, W. G. and G. L. McRae. 1966. Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm Hg total pressure. VII. Respiratory function. *Aerosp. Med.* 37:578.

5. Skylab Medical Experiments Altitude Test (SMEAT). 1973. Chapter 10-Metabolic Activity. Table 10-2. NASA TMX-58115. Lyndon B. Johnson Space Center, Houston, TX.

6. Ulvedal, F., T. E. Morgan, Jr., R. G. Cutler, and B. E. Welch. 1963. Ventilatory capacity during prolonged exposure to simulated altitude without hypoxia. *J. Appl. Physiol.* 18:904.

7. Buderer, M. C., J. A. Rummel, C. F. Sawin, and D. G. Mauldin. 1973. Use of the single-breath method of estimating cardiac output during exercise-stress testing. *Aerosp. Med.* 44:756.

8. Kim, T.S., H. Rahn, and L. E. Farhi. 1966. Estimation of true venous and arterial P_{CO_2} by gas analysis of a single-breath. *J. Appl. Physiol.* 21:1338.

9. Sawin, C. F., J. A. Rummel and E. L. Michel. March 1973. Physiological verification of an automated in-flight respiratory gas analyzer. Presented at A.A.M.I. Annual Meeting, Washington, D.C.

10. Bateman, J. B., W. M. Boothby and H. F. Helmholz, Jr. 1949. Studies of lung volumes and intrapulmonary mixing. Notes on open-circuit methods, including use of new pivoted type gasometer for lung clearance studies. *J. Clin. Invest.* 28:679.

11. Cournand, A., E. D. Baldwin, R. C. Darling and D. W. Richards, Jr. 1941. Studies on the intrapulmonary mixture of gases. IV. Significance of pulmonary emptying rate and simplified open circut measurment of residual air. *J. Clin. Invest.* 20:681.

12. Darling, R. C., A. Cournand and D. W. Richards, Jr. 1940. Studies on the intrapulmonary mixture of gases. III. An open circuit method for measuring residual air. *J. Clin. Invest.* 19:609.

13. Buist, A. S., D. L. Van Fleet and B. Ross. 1973. A comparison of conventional spirometric tests and the test of closing volume in an emphysema screening center. *Am. Rev. Resp. Dis.* 107:735.

14. Buist, A. S. 1973. Early detection of airways obstruction by the closing volume technique. *Chest* 64:495.

15. Fry, D. L. and R. E. Hyatt. 1960. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gas flow in the lungs of normal and diseased human subjects. *Am. J. Med.* 29:672.

16. Kory, R. C., R. Callahan, H. G. Boren and J. C. Syner. 1961. The Veterans Administration-Army Cooperative Study of Pulmonary Function. I. Clinical spirometry in normal men. Review in *Amer. J. Med.* 30:243.

17. Nicogossian, A. 1972. Lung mechanics during exercise at a stimulated altitude of 3962 meters. A Thesis. Ohio State University.

18. Morris, J. F., A. Koski, and L. C. Johnson. 1971. Spirometric standards for healthy nonsmoking adults. *Amer. Review Resp. Disease* 103:57.

METABOLIC COST OF EXTRAVEHICULAR ACTIVITIES

James M. Waligora and David J. Horriagan, Jr.
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

ABSTRACT

The data on metabolic rates during Skylab extravehicular activities are presented and compared with prior experience during Gemini and Apollo. Difficulties experienced with Gemini extravehicular activities are reviewed. The effect of a pressure suit on metabolic rate is discussed and the life support equipment capabilities of each life support system are reviewed. The methods used to measure metabolic rate, utilizing bioinstrumentation and operational data on the life support system, are described. Metabolic rates are correlated with different activities. Metabolic rates in Skylab were found to be within the capacities of the life support systems and to be similar to the metabolic rates experienced during Apollo lunar 1/6-g extravehicular activities. They were found to range from 100 kcal/h to 500 kcal/h, during both 1/6-g and zero-g extravehicular activities. The average metabolic rates measured during long extravehicular activities were remarkably consistent and appeared to be a function of crew pacing of activity rather than to the effort involved in individual tasks.

INTRODUCTION

The prospect of pressure suit operations outside of space vehicles and on the lunar surface was the source of much speculation prior to Gemini. Prediction varied from the prospect of almost effortless activity to the fear that without the stabilization provided by Earth gravity useful activity would be very difficult. The Skylab zero-g extravehicular activity data is of particular interest when it is considered in combination with the Apollo and Gemini data. This paper covers the energy cost of extravehicular activity from Gemini through Skylab.

Gemini

A summary of the Gemini extravehicular activities, their length, the difficulties experienced by the crewmen, and the average and peak heart rates, is presented in table I. There was no attempt to measure metabolic rates. It was apparent that on several occasions, the metabolic rates were above the capacity of the life support systems, both for thermal control and carbon dioxide washout.

TABLE I. GEMINI EXTRAVEHICULAR ACTIVITY EXPERIENCE

5 Gemini extravehicular activity missions - 6 hours total extravehicular activity time

Flight	Experience	Duration (hours)	Heart Rates (beats per minute) $\bar{x}$	Peak
Gemini 4	Overheating during hatch closing - objectives completed	0.60	155	175
Gemini 9	Visor fogging - hot at ingress - objectives incompleted	2.11	155	180
Gemini 10	No problem with heat or work rate - objectives completed	0.65	125	165
Gemini 11	Exhausting work - no specific mention of heat - objectives incompleted	0.55	140	170
Gemini 12	Good restraints - no problems - objectives completed	2.10	110	155* 130

Metabolic rates - not determined but in excess of life support system capability at times

*Voicing a message to Houston

The energy cost of extravehicular activities is dependent to a large extent on the pressure suit and life support system. The Gemini pressure suit had a fixed resting position and had minimum mobility for extravehicular activity. Considerable energy was expended working against the suit. The heat removal capacity of the life support system was limited physically to about 225 kcal/h in Gemini 4. The gas cooling life support system used on the later Gemini units had an increased physical capacity, but at acceptable body temperatures the system was limited to about 250 kcal/h. The emphasis in the earlier Gemini extravehicular activities was in the use and evaluation of propulsive maneuvering units. Beginning with Gemini 12 increased emphasis was placed on extravehicular activity technology and improved restraint and systems. In summary, the Gemini Program indicated that extravehicular activities could be much more difficult and physically taxing than had been anticipated and that more emphasis should be placed in crew training and restraint technology.

Apollo

The lunar portion of the Apollo Program presented entirely different extravehicular activity problems, *i.e.*, 1/6-g and an unknown terrain. The effect of 1/6-g on the cost of work in a pressure suit had been investigated by several researchers using 1/6-g simulators (1, 2, 3). Indications were that the cost of walking would be reduced while the cost of other activities would be increased; however, the results and conclusions were by no means uniform. An additional factor of uncertainty was the terrain and surface composition of the moon and its effect on the metabolic cost of walking. In response to these uncertainties, conservative biomedical estimates of the life support requirements were defined based on the available data, and methods to measure metabolic rate during the extravehicular activities were developed utilizing operational data from the life support system and bioinstrumentation.

To handle high workloads during Apollo extravehicular activities and the resulting high heat production in the suit, a liquid cooling system was used. The liquid cooled garment used in this system could suppress sweating at work rates up to 400 kcal/h and allow sustained operations at rates as high as 500 kcal/h without thermal stress.

Real-time estimates of metabolic rate were made during the lunar surface extravehicular activities using three parameters: oxygen bottle pressure, the heat removal by the liquid cooled garment, and heart rate. The noise experienced in the telemetered oxygen-bottle-pressure data made it difficult to obtain reliable oxygen utilization rates for time periods of less than 30 minutes, particularly at low metabolic rates. The oxygen utilization rates included the suit leakage which had

to be estimated. The maximum leakage rate of oxygen allowed by the pressure suit specification was equivalent to a metabolic rate of approximately 50 kcal/h.

Because of the limitations of the oxygen-bottle-pressure method, correlation of liquid cooled garment data to metabolic rate was also used during the mission. Using a thermoregulatory mathematical model and empirical data on the liquid cooled garment, a relationship was defined between liquid cooled garment heat removal and metabolic rate for each liquid cooled garment inlet temperature. This method was verified with test data obtained during altitude chamber training.

Correlations between heart rate and metabolic rate were obtained for each individual from a series of preflight exercise response tests on the ergometer. The heart rate method was used only as a relative measurement because of its known sensitivity to psychological and environmental factors. The heart rate method, however, when related to total energy expenditure as determined by oxygen and liquid cooled garment methods, permitted an estimate of the cost of specific activities on a minute-by-minute basis.

The average metabolic rates experienced during these extravehicular activities, as shown in table II, were lower than had been predicted prior to Apollo, and the crewmen were able to move easily and confidently on the lunar surface. Within the operational classification of activities the most energy consuming were those classified as overhead. These activities included egress, offloading and setup of equipment around the lunar module vehicle, and ingress and stowage of lunar samples. The highest metabolic rates experienced during the performance of discrete activities (350-450 kcal/h) were associated with steep uphill walking traverses, transporting of the Apollo Lunar Scientific Experiment Package pallet, ingressing the lunar module with lunar samples, drilling, and removing of drill bits. The Apollo Lunar Scientific Experiment Package deployment and geologic survey activities resulted in lower metabolic rates than the overhead activity. These activities as a group were less predictable and required more time for judgment and in some cases for precise manual manipulation. The lowest metabolic rates and the most clearly defined operation activity was observed while riding the Lunar Rover. The metabolic rates for this activity approached rates reported for shirtsleeve riding in an automobile.

The highest average rate of 300 kcal/h was experienced by the Lunar Module Pilot on Apollo 11. This crewman had been assigned to the task of evaluating modes of locomotion during what was the shortest extravehicular activity, and he was quite active in performing this task. Several crewmen experienced the minimum average metabolic rates of approximately 200 kcal/h on different missions.

TABLE II. APOLLO LUNAR SURFACE EXTRAVEHICULAR ACTIVITIES

Flight	EVA	Crewman	Scientific Package Deployment	Geological Station Activity	Overhead	Lunar Rover Vehicle Operations	All Activities	EVA Duration (hours)
Apollo 11	1	Armstrong	195	244	214	---	227	
		Aldrin	302	351	303	---	302	2.43
Apollo 12	1	Conrad	206	243	294	---	246	
		Bean	240	245	267	---	252	3.90
	2	Conrad	---	218	215	---	221	
		Bean	---	253	248	---	252	3.78
Apollo 14	1	Shepard	182	294	220	---	202	
		Mitchell	226	174	259	---	234	4.80
	2	Shepard	118	238	214	---	229	
		Mitchell	203	267	213	---	252	3.58
Apollo 15	1	Scott	282	275	338	152	276	
		Irwin	327	186	293	104	246	6.53
	2	Scott	243	293	287	149	253	
		Irwin	265	189	266	99	204	7.22
	3	Scott	261	242	311	138	260	
		Irwin	230	188	234	107	204	4.83
Apollo 16	1	Young	207	216	273	173	220	
		Duke	258	268	275	159	255	7.18
	2	Young	---	223	249	112	198	
		Duke	---	244	236	105	208	7.38
	3	Young	---	231	235	124	205	
		Duke	---	242	264	103	208	5.67
Apollo 17	1	Cernan	285	261	302	121	275	
		Schmitt	278	300	285	113	272	7.20
	2	Cernan	---	261	302	121	207	
		Schmitt	---	300	285	113	210	7.62
	3	Cernan	---	261	302	121	234	
		Schmitt	---	300	285	113	237	7.25
	Average		244	244	270	123	234	
Total Time (hours)			28.18	52.47	52.82	25.28	158.74	

Particular efforts were made to relate walking speed to metabolic rate during Apollo 14 which included the most extensive walking traverses. The data are presented in figure 1.

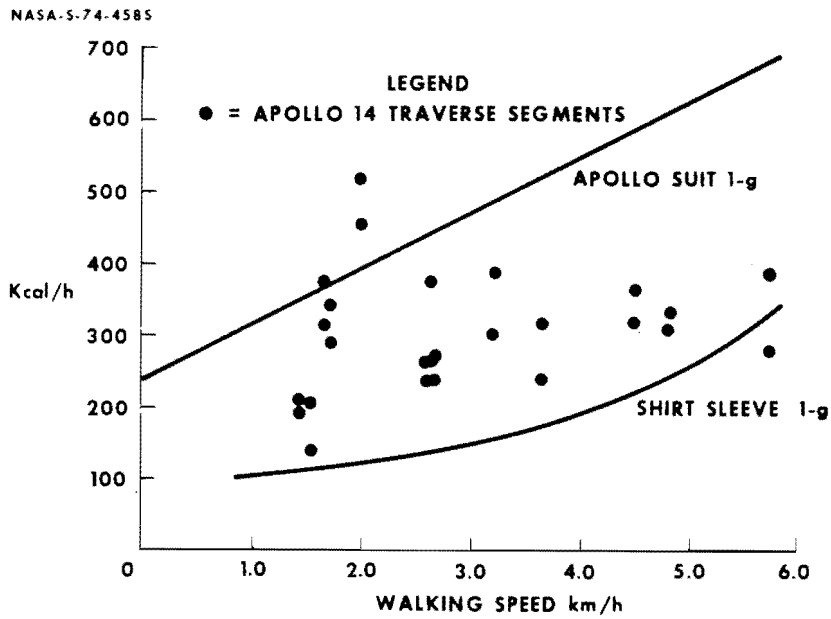


Figure 1. - Metabolic cost of lunar walking.

The data exhibited a very poor correlation between traverse rate and metabolic rate. During these operational traverses it appeared that the crewman maintained a comfortable walking effort and to a large extent the rate of travel at this level of effort varied with the terrain and the requirements of each traverse. The average speed for the 2.9 kilometers covered was 2.4 km/h at a metabolic rate of 300 kcal/h. The speed and efficiency of lunar walking were both greater than could be achieved wearing a pressure suit at one-g while neither speed nor efficiency was the equivalent of shirtsleeve operation at one-g.

A time and motion study (4 and 5) was carried out on Apollo 15 and 16 utilizing operation motion picture film and kinescope. This study compared the facility and energy cost of performing several specific activities at one-g during suited training and at 1/6-g on the lunar surface. One of the observations of this study was that manipulative tasks were completed more rapidly at one-g than at 1/6-g, but at greater metabolic cost.

In addition to the 14 lunar surface extravehicular activities, there were 4 zero-g extravehicular activities. The first was a standup extravehicular activity on Apollo 9 utilizing a portable life support system and on this extravehicular activity we have data (table III) similar to that obtained during the lunar surface extravehicular activities. During the Command Module extravehicular activities of Apollo 15, 16, and 17 the only data available were the heart rates. The metabolic rates estimated from heart rate were not used to constrain these extravehicular activities and it appears that in some cases the heart rates were elevated due to psychogenic causes.

TABLE III. APOLLO ZERO-G EXTRAVEHICULAR ACTIVITIES

Flight	Crewman	Metabolic Rate (kcal/h)	Duration-hours
Apollo 9	Schewickart	151	0.98
Apollo 15	Worden	<237	0.66
	Irwin*	<117	0.66
Apollo 16	Mattingly	<504	1.41
	Duke*	not measured	1.41
Apollo 17	Evans	<302	1.11
	Schmitt*	<143	1.11
		Total Time (hours)	7.38

*Standup extravehicular activities

Skylab

Despite the large quantity of 1/6-g extravehicular activity data collected during Apollo, when the Skylab Program began, the experience with zero-g was limited to six hours of Gemini experience during which considerable difficulty was encountered and four hours of Apollo Command Module extravehicular activity consisting of a standup extravehicular activity and three repetitions of a comparatively simple film retrieval task. The original extravehicular activities planned for Skylab were six 3- to 4-hour extravehicular activities primarily to

replace film in the ATM cameras. The umbilical life support system of Skylab had a heat removal capability equivalent to the Apollo portable life support system. The metabolic rate data were limited to the liquid cooled garment data and the heart rate data because of the different life support system. The correlation of heart rate and metabolic rate was based on the most recent in-flight experiment M171 bicycle ergometer test. The Skylab data are presented in table IV.

TABLE IV. SKYLAB EXTRAVEHICULAR ACTIVITIES

Metabolic Rates

Mission	Duration (hours)	Metabolic Rate (kcal/h) CDR	PLT	SPT
SL2 EVA-1 (Gas cooling only)	0.61		330	260
SL2 EVA-2	3.38	315		265
SL2 EVA-3	1.56	280		
SL3 EVA-1	6.51		265	240
SL3 EVA-2	4.51		310	250
SL3 EVA-3 (Gas cooling only)	2.68	225		180
SL4 EVA-1	6.56		230	250
SL4 EVA-2	6.90	155	205	
SL4 EVA-3	3.46	145		220
SL4 EVA-4	5.31	220		185
Total Time	83.6 h	$\bar{x}$	230 kcal/h	

man-hours

The first Skylab extravehicular activities were done to deploy the solar panels. After success was achieved, and a considerable capability to perform work in zero-g was demonstrated, the number of extravehicular activities was increased to 10 and the duration of these extravehicular activities was lengthened. These additions included the deployment of the solar panels, erection of a solar canopy, repair of an Earth resource antenna, replacement of a gyro six-pack and other vehicle and experiment repairs. An additional extravehicular activity was done to make observations on the Comet Kohoutek. Because of problems with one of the vehicle coolant loops all three crewmen operated from a single coolant supply but the comfort cooling capacity at the loops remained at about 400 kcal/h steady-state. No problems were experienced from overheating. Because of the problem with the vehicle coolant system, the last extravehicular activity on Skylab 3 was conducted with gas cooling only. It was of limited scope and duration and no problems were experienced.

The metabolic rates were similar to those on the Apollo 1/6-g extravehicular activities. The highest metabolic rate, 500 kcal/h, was reached while the Commander on Skylab 2 was trying to cut a strap that was keeping the solar panels from deployment. The lowest rates were resting rates and these were reached several times during the extravehicular activities, particularly at the times when there was not enough light to continue an ongoing activity during a night pass. Crew comments during extravehicular activities indicated that it was easier to maneuver themselves and their equipment in zero-g than in water tank simulations, but that adequate restraints were even more important.

CONCLUSIONS

- With adequate life support equipment and adequate restraints the capability was demonstrated to perform varied and extensive extravehicular activity tasks both in zero-g and 1/6-g with considerable real-time flexibility.
- The capability to work at relatively high levels, up to 500 kcal/h, when required was demonstrated without physiologic problems provided the life support capability is adequate.
- The average energy cost of long extravehicular activities was remarkably consistent at about 200 to 250 kcal/h, and appears to be a function of the crew pacing its activity rather than to the effort involved in performing individual tasks.

REFERENCES

1. Wortz, E. C. and E. J. Prescott. Dec. 1966. Effects of Subgravity Traction Simulation on the Energy Costs of Walking. *Aerosp. Med.*, Vol. 37, No. 12, pp. 1217-1222.

2. Margaria, R. and G. A. Cavagna. Dec. 1964. Human Locomotion in Subgravity. *Aerosp. Med.*, Vol. 35, No. 12, pp. 1140-1146.

3. Shavelson, R. J. Aug. 1968. Lunar Gravity Simulation and its Effect on Human Performance. *Human Factors*, Vol. 10, No. 4, pp. 393-402.

4. Kubis, J. F., *et al.* 1972. (Final Report) Apollo 15 Time and Motion Study, NASA CR-128695.

5. Kubis, J. F., *et al.* 1972. (Final Mission Report) Apollo 16 Time and Motion Study. NASA CR-128696.

DETERMINATION OF CARDIAC SIZE FROM CHEST ROENTGENOGRAMS FOLLOWING SKYLAB MISSIONS

A. Nicogossian, M.D., G. W. Hoffler, M.D.*, R. L. Johnson, M.D.* and R. J. Gowen, Ph.D.†*

ABSTRACT

Decreased cardiothoracic transverse diameter ratios following Mercury, Gemini and Apollo space flights have been reported previously. To evaluate further changes in cardiac size, standard posteroanterior chest films in systole and diastole were obtained before flight and within a few hours after recovery on each of the Skylab astronauts. Postflight chest X-rays were visually compared to the preflight roentgenograms for possible changes in pulmonary vasculature, lung parenchyma, bony or soft tissue structures. From these roentgenograms the following measurements were obtained: cardiac and thoracic transverse diameters, cardiothoracic transverse diameter ratio, cardiac area from the product of both diagonal diameters, cardiac silhouette area by planimetry, thoracic cage area and cardiothoracic area ratio. The postflight frontal cardiac silhouette sizes were significantly decreased when compared with the respective preflight values ($P<0.05$ or 0.01). The observed changes are thought to be related to postflight decrease in the intracardiac chamber volume.

INTRODUCTION

Determination of size is a major factor in the clinical evaluation of the healthy or failing heart. Knowledge of heart size assists the interpretation of both electrocardiographic and hemodynamic information. The evaluation of changes in cardiac size has been important in the overall cardiovascular assessment of orthostatic intolerance observed among the majority of astronauts following space missions.

Decreased cardiothoracic transverse diameter ratios following Mercury, Gemini and Apollo flights have been reported earlier from our laboratory (1, 2). More recently similar data following space missions of

*National Aeronautics and Space Administration - Lyndon B. Johnson Space Center, Houston, TX.

†U.S.A.F. Academy, Colorado Springs, Colorado.

longer duration have been presented (3). The majority of crewmembers who exhibited postflight decreases in the cardiac silhouette size also showed a decreased orthostatic tolerance to lower body negative pressure. Similar findings were also reported by the Soviet investigators following 30-day bed rest studies (4) and in cosmonauts upon return from space missions. This paper presents further radiological data from all three Skylab manned missions and discusses the physiological factors possibly involved in the cardiac silhouette changes.

METHODS AND MATERIALS

Standard posteroanterior chest films were obtained before and as soon as possible after flight on each of the Skylab astronauts following extended space flights of different durations: 28, 59 and 84 days. All X-ray exposures were 150 milliseconds in duration. Systolic and diastolic exposures were triggered electronically from the electrocardiographic R-wave peak by a special device interposed with the X-ray equipment control. The electronic trigger device delayed the roentgenographic exposures from the R-wave peak according to the instantaneous heart rate (the preceding RR interval). For systole the delays were 175 to 325 milliseconds, corresponding to heart rates ranging from 140 to 40 beats per minute, and for diastole 385 to 1165 milliseconds for heart rates ranging from 140 to 44 beats per minute.

Postflight chest X-rays were visually compared with the preflight films for possible changes which might have occurred in pulmonary vasculature, lung parenchyma, bony or soft tissue structures. One or two additional postflight films were taken several days following splashdown to assess trends. While many of the film pairs showed readily apparent postflight decreases in heart size (fig. 1), several measures have been adopted to determine this change quantitatively. Figure 2 shows the geometry utilized in determining thoracic and cardiac areas. The thoracic cage area was obtained by a modified method as described by Barnhard (5) and by Loyd (6). After the inner border of the ribs was outlined, the thoracic center was determined by drawing the line (CL) along the vertebral column. Next, perpendicular lines to (CL) were drawn at 2.5, 5.0 and 15.0 centimeters from the first thoracic intervertebral space - point of origin (a) creating three upper polygonal segments. A horizontal line (k-m) drawn halfway between the level of the apices of the right and left hemidiaphragms delineated the lower border of the fourth segment. The last segment was delimited by a horizontal line (n-p) drawn at mid-distance between the two costophrenic angles; actual area of this segment was modified by circular deductions for infra diaphragm space. The total thoracic area was summed from the computed area of each of the above five segments.

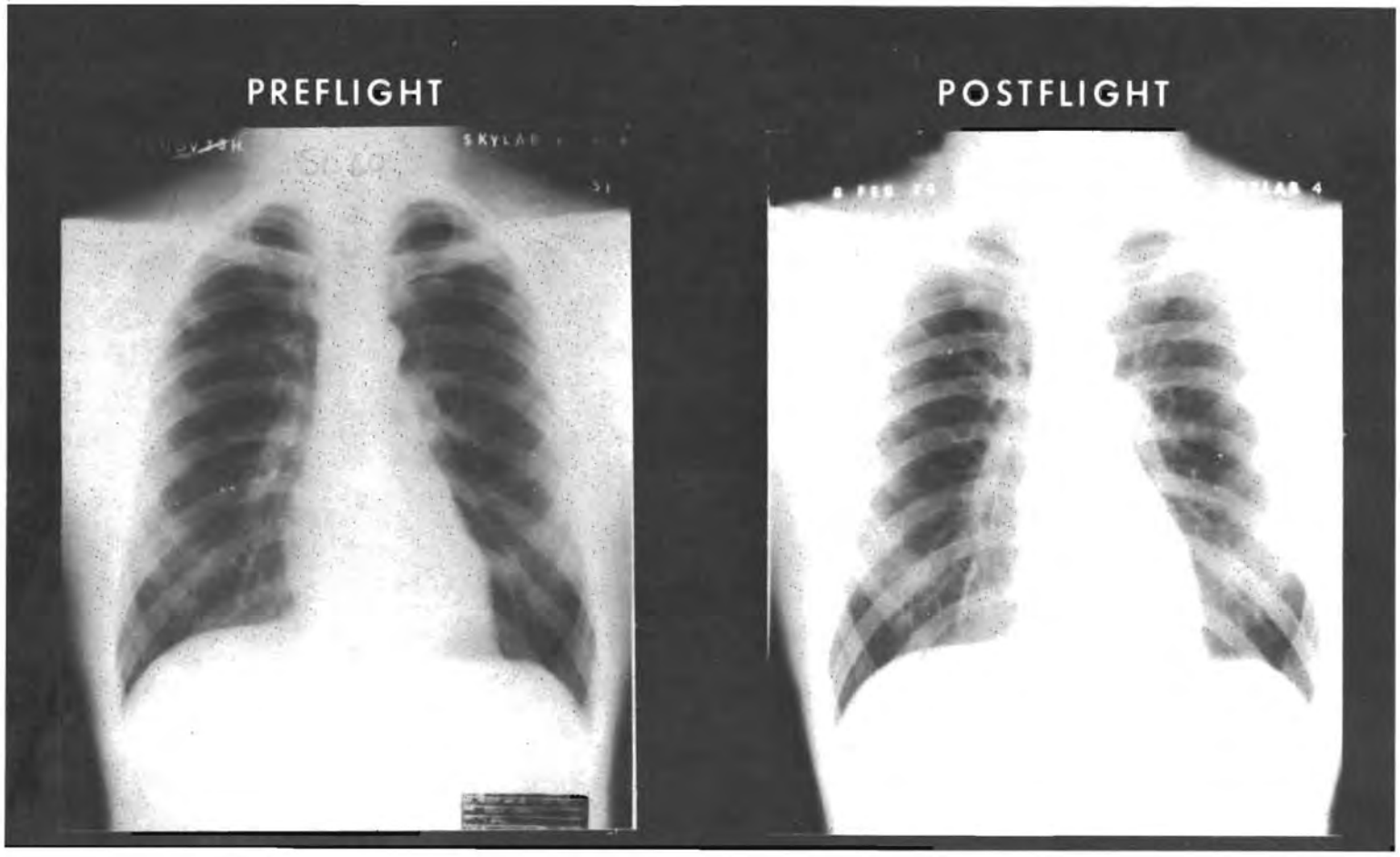


Figure 1. Systolic Chest X-ray of the Skylab 4 Scientist Pilot. (Preflight and on the day of Recovery)

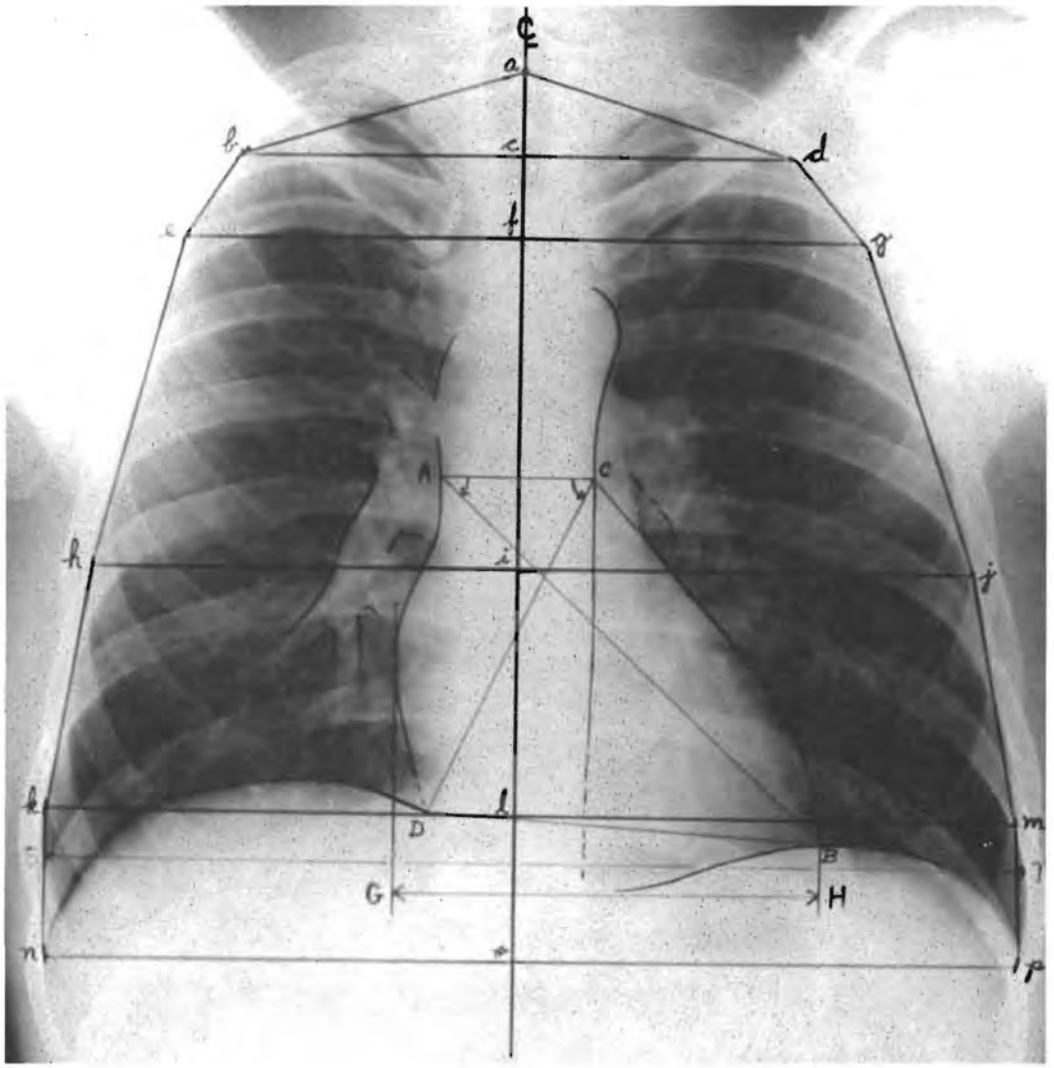


Figure 2. Geometry of cardiothoracic measurements.

To obtain uniform evaluation of the cardiac area, the heart silhouette was outlined in the following manner.

- The lower border of the heart was defined as the line (B-D) between the intersections of the right and left cardiac borders and the respective hemidiaphragms,
- the right cardiac border (A-D) followed the right atrium and superior vena cava,
- the left cardiac border (B-C) was completed by drawing a regression line of the left heart border intersecting with the left margin of the descending aorta,
- the upper cardiac border was outlined by a perpendicular (A-C) to the center line at the level of the upper left heart border.

The following parameters were measured and/or computed:

- Cardiothoracic transverse diameter ratio (C/T_D).
- Cardiac silhouette area, by planimetry.
- Cardiothoracic area ratio (C/T_A).
- Cardiac area from the product of long and short diagonal diameters.

It is hoped that the additional information inherent in this technique will reflect more accurate size values and help compensate for slight variations in body position and inspiratory level. All postflight data were compared to the respective preflight values using the Student's t-test and regression analysis.

RESULTS

No roentgenological abnormalities were observed on either preflight or postflight films. The chest X-rays of the Skylab 3 Pilot on the day of recovery were of poor quality and not amenable to analysis; all other X-rays were of acceptable quality. Differences between preflight and postflight systolic and diastolic cardiothoracic diameter and area ratios are presented in tables I and II. Both C/T_D and C/T_A showed a decrease in the individual values postflight. In general there was

more variability in the C/T_D responses postflight, some cases in diastole showing a modest increase in the immediate postflight ratios. Comparison of the preflight and postflight cardiac silhouette area differences showed a fairly consistent decrease in the cardiac area on the day of recovery (tables III and IV). The Skylab 3 Commander, however, showed a postflight increase in the systolic cardiac area as determined from the products of minor and major diameters (19.76 cm^2) and a very slight increase in the diastolic cardiac area as measured by the planimetric method (0.30 cm^2).

TABLE I. SYSTOLIC CARDIOTHORACIC RATIO DIFFERENCES
PREFLIGHT VERSUS POSTFLIGHT

Skylab Mission	Crewman	POSTFLIGHT ROENTGEN EXAMINATION FIRST Date (Days)	FIRST C/T_D*	FIRST C/T_A†	SECOND Date (Days)	SECOND C/T_D	SECOND C/T_A	THIRD Date (Days)	THIRD C/T_D	THIRD C/T_A
2	Commander	R+0	-0.003	-0.003	R+8	-0.020	-0.008			
	Scientist Pilot		0.000	-0.015		+0.004	-0.005			
	Pilot		-0.013	-0.011		-0.020	+0.004			
3	Commander	R+0	-0.040	-0.012	R+5	-0.014	+0.003	R+20	-0.001	+0.023
	Scientist Pilot		-0.040	-0.039		-0.043	-0.025		-0.007	-0.010
	Pilot		NA	NA		+0.012	+0.004		0.000	-0.004
4	Commander	R+0	-0.010	-0.011	R+5	-0.024	-0.015	R+11	-0.023	-0.007
	Scientist Pilot		-0.059	-0.020		-0.025	+0.002		-0.036	-0.006
	Pilot		+0.003	-0.004		-0.008	-0.019		+0.009	-0.017

*C/T_D = Diametral Ratio
†C/T_A = Areal Ratio
NA = Not available
R = Recovery

TABLE II. DIASTOLIC CARDIOTHORACIC RATIO DIFFERENCES
PREFLIGHT VERSUS POSTFLIGHT

Skylab Mission	Crewmembers	POSTFLIGHT ROENTGEN EXAMINATION FIRST Date (Days)	FIRST C/T_D*	FIRST C/T_A†	SECOND Date (Days)	SECOND C/T_D	SECOND C/T_A	THIRD Date (Days)	THIRD C/T_D	THIRD C/T_A
2	Commander	R+0	+0.012	+0.002	R+8	-0.006	+0.003			
	Scientist Pilot		+0.003	-0.012		0.000	-0.007			
	Pilot		-0.008	-0.025		-0.003	-0.003			
3	Commander	R+0	-0.005	-0.006	R+5	+0.009	+0.012	R+20	+0.035	+0.027
	Scientist Pilot		-0.034	-0.022		-0.029	-0.015		-0.011	+0.006
	Pilot		NA	NA		+0.002	+0.005		+0.012	-0.007
4	Commander	R+0	+0.014	-0.018	R+5	+0.026	-0.010	R+11	+0.018	-0.003
	Scientist Pilot		+0.013	-0.006		+0.034	+0.014		+0.022	+0.012
	Pilot		+0.015	-0.013		-0.001	-0.017		+0.003	-0.010

*C/T_D = Diametral ratio
†C/T_A = Areal ratio
NA = Not available
R = Recovery

TABLE III. DIFFERENCES IN SYSTOLIC CARDIAC AREAS PREFLIGHT COMPARED TO POSTFLIGHT

Skylab Missions	Crewmembers	POSTFLIGHT ROENTGEN EXAMINATION								
		FIRST			SECOND			THIRD		
		Date (Day)	D_1xD_2* (cm^2)	Plan.† (cm^2)	Date (Day)	D_1xD_2 (cm^2)	Plan. (cm^2)	Date (Day)	D_1xD_2 (cm^2)	Plan. (cm^2)
2	Commander	R+0	-16.10	- 2.40	R+8	-19.00	- 9.50			
	Scientist Pilot		-29.20	- 9.80		+10.70	- 2.10			
	Pilot		-15.50	- 9.80		+20.90	+ 6.00			
3	Commander	R+0	+19.76	- 1.90	R+5	+21.20	+ 6.30	R+20	-72.00	+24.80
	Scientist Pilot		-55.80	-26.70		-30.40	-15.50		-19.64	- 6.60
	Pilot		NA	NA		+ 7.35	+ 6.10		- 8.63	- 2.30
4	Commander	R+0	-16.30	- 7.60	R+5	- 7.70	+ 6.30	R+11	-11.00	- 5.60
	Scientist Pilot		-21.00	- 9.90		-10.50	- 5.60		-11.30	- 8.40
	Pilot		- 1.70	- 3.30		+ 1.30	- 7.70		- 0.30	- 6.90

*Cardiac area determined from the product of the major and minor diameters

†Cardiac area determined by planimetry

NA = Not available

R = Recovery

TABLE IV. DIFFERENCES IN DIASTOLIC CARDIAC AREAS PREFLIGHT COMPARED TO POSTFLIGHT

Skylab Missions	Crewman	POSTFLIGHT ROENTGEN EXAMINATION								
		FIRST			SECOND			THIRD		
		Date (Day)	D_1xD_2* (cm^2)	Plan.† (cm^2)	Date (Day)	D_1xD_2 (cm^2)	Plan. (cm^2)	Date (Day)	D_1xD_2 (cm^2)	Plan. (cm^2)
2	Commander	R+0	-14.20	- 2.70	R+8	- 4.80	- 5.10			
	Scientist Pilot		-33.80	-12.00		- 3.00	- 5.60			
	Pilot		-40.70	-14.70		- 4.00	+ 1.40			
3	Commander	R+0	- 2.10	+ 0.30	R+5	+18.00	+16.30	R+20	+46.90	+27.10
	Scientist Pilot		-25.40	-16.50		-10.80	- 8.50		+30.00	- 5.00
	Pilot		NA	NA		-12.80	+ 2.20		-28.20	- 7.70
4	Commander	R+0	-107.10	-17.30	R+5	-89.10	- 9.10	R+11	-78.30	- 6.90
	Scientist Pilot		-41.20	- 1.70		- 0.00	+11.30		- 7.50	+10.30
	Pilot		-24.60	-15.60		- 4.60	- 7.60		+ 5.00	- 2.00

*Cardiac area determined from the product of the major and minor diameters

†Cardiac area determined by planimetry

NA = Not available

R = Recovery

Table V summarizes the determinants of cardiac sizes, their preflight and postflight means and standard deviation as well as the statistical significances. The mean differences, preflight versus postflight, of the cardiac areas, measured by planimetry, and of the derived measurement (C/T_A), were statistically significant ($P<0.01$ or $P<0.05$). Return to preflight values was quite variable for all crewmen, but most showed this directional trend by 4 to 5 days after splashdown. There was a significant correlation ($r = -0.91$) between postflight decrement in systolic heart size as measured by C/T_D, and the corresponding augmentation in heart rate responses registered during lower body negative pressure stress. There was no apparent correlation between the duration of orbital stay and the postflight change in heart size.

TABLE V. DETERMINANTS OF CARDIAC SIZE FROM ROENTGENOGRAMS

Cardiac Phase	Measurement	PREFLIGHT Mean	PREFLIGHT Standard Deviation	POSTFLIGHT (R+0) Mean	POSTFLIGHT (R+0) Standard Deviation	Statistical Significance
Systole	C/T_D*	0.416	0.029	0.390	0.018	P <0.05
	C/T_A†	0.180	0.019	0.166	0.018	P <0.01
	$D_1 x D_2$‡	238.87(cm^2)	38.13(cm^2)	221.90(cm^2)	40.82(cm^2)	NS
	Plan.§	123.81(cm^2)	13.31(cm^2)	114.22(cm^2)	12.74(cm^2)	P <0.05
Diastole	C/T_D	0.403	0.018	0.399	0.021	NS
	C/T_A	0.177	0.015	0.164	0.020	P <0.01
	$D_1 x D_2$	248.41(cm^2)	28.28(cm^2)	212.27(cm^2)	34.09(cm^2)	P <0.05
	Plan.	121.71(cm^2)	7.74(cm^2)	111.67(cm^2)	12.20(cm^2)	P <0.01

N = 8 (R+0 Film of Skylab 3 Pilot unsatisfactory)
*Cardiothoracic ratio based on the respective diameters
†Cardiothoracic ratio based on the respective areas
‡Cardiac area determined from the product of the minor and major diameters
§Cardiac area determined by planimetry
P = Probability
N.S. = Not significant

DISCUSSION AND CONCLUSIONS

Radiographic techniques for evaluating the size of the heart have the advantages of technical simplicity and widespread availability of equipment. Although the conventional cardiothoracic ratio has for many years provided a useful clinical standard (7) it carries a rather large variability due to body position, phase of respiration and other uncontrollable elements of thoracic configuration. In our practice the C/T_A and the associated cardiac area were found to compare well with the C/T_D, were easily obtained and quite adequate for serial comparisons on the same subject (3). In addition, the areal measurements provide more comprehensive information concerning the heart size than transverse diameters. The observed postflight decrease in frontal plane cardiac silhouette size could be attributed to a decrease in myocardial tissue mass and/or intrachamber blood content, anatomical reorientation or a combination of all of the above mentioned factors. Previous studies have shown that significant among determinants of cardiac size is the amount of blood returned to the heart (8). It is quite conceivable that caudad displacement of blood and other fluids together with an absolute decrease in the circulating blood volume (9) could account for the observed decreases in the cardiac silhouette size. At the present time there is certainly no indication that the Skylab crewmen exhibited a greater decrease in their cardiac size than that observed in the Apollo astronauts following shorter duration space missions, nor that the decrease in diastole heart size was of greater magnitude than that of the systolic phase of the cardiac cycle. A small diastolic size might more clearly delineate a deficit in blood return and chamber filling rather than loss of myocardial mass.

Further studies during the Shuttle era should be directed toward a better understanding of the intracardiac chamber and myocardial tissue components possibly involved in the reported X-ray findings.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of M. M. Ward in the preparation of this paper.

REFERENCES

1. Berry, C. A. 1973. Chapter 8 In Bioastronautics Data Book, 2nd Ed., NASA SP-3006.

2. Hoffler, G. W., R. A. Wolthuis and R. L. Johnson. 1974. Apollo Space Crew Cardiovascular Evaluations. *Aero. Med.*, 45:807.

3. Nicogossian, A., G. W. Hoffler, R. L. Johnson and R. J. Gowen. Determination of Cardiac Size Following Space Missions: The Second Manned Skylab Mission. Presented at the Annual Aerospace Medical Meeting, Washington, D.C., May 1974.

4. Krasnykh, I. C. 1974. Roentgenological study of cardiac function and mineral saturation of bone tissue after thirty days of hypokinesia. *Kosm. Biol. Av. Med.* 8: 98. (Russian).

5. Barnhard, H. J., J. A. Pierce, J. W. Joyce and J. H. Bates. 1960. Roentgenographic Determination of Total Lung Capacity. *Amer. J. Med.*, 28:51.

6. Loyd, H. M., T. String and A. B. DuBois. 1972. Radiographic and Plethysmographic Determination of Total Lung Capacity. *Radiology* 56: 881.

7. Sutton, D. 1969. Textbook of Radiology. Ed. Livingstone, Edinburgh & London, England.

8. Larsson, H. and R. S. Kjellberg. 1948. Roentgenological heart volume determination with special regard to pulse rate and the position of the body. *Acta Rad.*, 29: 159.

9. Johnson, P. C. Blood Volume Changes. Presented at the Skylab Life Sciences Symposium, August 1974, NASA - JSC, Houston, Texas.

SYMPOSIUM SUMMARY

SKYLAB: A BEGINNING

Lawerence F. Dietlein, M. D.
Deputy Director of Life Sciences
National Aeronautics and Space Administration
Lyndon B. Johnson Space Center

"The Eagle has landed; Tranquillity Base here." This simple and now historic message of July 20, 1969, marked the attainment of perhaps the greatest peacetime goal in the history of man. It fulfilled President Kennedy's directive issued some 8 short, hectic years earlier, when he proclaimed on May 25, 1961: "I believe we should go to the moon . . . before this decade is out." It marked the culmination of a technically complex engineering accomplishment that began with Mercury and continued uninterrupted through Gemini and prelunar Apollo. The ultimate goal of these efforts was a manned lunar landing. None of these programs had as a major objective the detailed study of man's biomedical responses to the space environment, except in the broadest sense of survival and the ability to live and work effectively in that environment. Nevertheless, throughout each program, information concerning man and his new surroundings was obtained wherever possible and whenever practicable, ever mindful of the time constraints imposed by the lunar landing goal and the weight limitations of the launch vehicles.

In these few days, the preliminary biomedical results of NASA's Skylab effort have been presented to you. A major goal of Skylab was to learn more about man and his responses to the space environment for missions lasting up to 84 days. The results are necessarily preliminary, for in the short time which has elapsed since the end of the program, no in-depth cross-correlation of the voluminous multidisciplinary data has been possible. This will be done through successive future meetings of specialized working groups.

In this 1974 Skylab Life Sciences Symposium, you have been briefed on the results of measurements and experiments that were conceived some six to eight years ago, and which have added immeasurably to our understanding of man, his physiological responses and his capabilities in space.

In one sense Skylab is the *beginning* of an in-depth study of man in this unique environment, for Skylab has resolved some problems while inevitably raising new questions.

MERCURY 1961-1963

In order to view the Skylab data in their proper context, let us go back for a moment some 13 years to 1961. At that time both the United States and Soviet Union were placing animals, such as chimpanzees Ham and Enos, in orbital flight. The goal of these flights was to refute untested but plausible theories of catastrophic failures in various vital functions if such animals were suddenly thrust into weightless flight. There were, of course, additional stresses to be reckoned with in space, the most important of which are listed in table I and which are by now quite familiar to you.

TABLE I. PRINCIPAL ENVIRONMENTAL STRESSES IN MANNED SPACE FLIGHT

- Weightlessness
- Ionizing radiation
- Temperature and humidity
- Accelerations
- Circadian rhythm disruption
- Noise and vibration
- Atmospheric composition

But the factor of greatest concern to man with his many gravity-influenced body systems was and continues to be null gravity. Many dire effects - some of them diametrically opposed to each other - were postulated as direct consequences of exposing man to zero gravity. Some of these predictions are listed in table II and are well known from previous publications (1, 2).

TABLE II. PREDICTED WEIGHTLESS EFFECTS

Anorexia	Demineralization of bones
Nausea	Renal calculi
Disorientation	Motion sickness
Sleepiness	Pulmonary atelectasis
Sleeplessness	Tachycardia
Fatigue	Hypertension
Restlessness	Hypotension
Euphoria	Cardiac arrhythmias
Hallucinations	Postflight syncope
Decreased g tolerance	Decreased exercise capacity
Gastrointestinal disturbance	Reduced blood volume
Urinary retention	Reduced plasma volume
Diuresis	Dehydration
Muscular incoordination	Weight loss
Muscle atrophy	Infectious illnesses

A few of these predictions were later shown to be valid; happily, most of them were not substantiated by subsequent flight experience. During the Mercury Program, NASA scientists made some tentative realistic predictions of their own regarding the time course of certain symtoms should they develop during weightless flight. These are indicated in figure 1 and, except for sensory deprivation and sleep changes, have been generally proved quite realistic.

The first indication of cardiovascular or circulatory impairment related to space flight was the orthostatic intolerance exhibited by Schirra following his 9-hour MA-8 flight and Cooper after his 34-hour MA-9 flight. Cardiovascular data from the last and longest Mercury flight are indicated in table III, including orthostatic intolerance and dizziness on standing, weight loss (dehydration) and hemoconcentration.

TABLE III. FLIGHT MERCURY-ATLAS-9 (MA-9) CARDIOPULMONARY DATA SUMMARY

EVENT	PULSE (bpm)	PRESSURE (mm Hg)	RESPIRATION RATE (breaths/min)
Prelaunch	72	113/79	19
Orbital	89	119/81	15
Postflight	83 (supine)	89/64	--
(1 to 7 h)	123 (erect)	90/73	--
(18 h)	58 (supine)	98/61	--
	80 (erect)	94/68	--

Flight time: 34 h 20 min.
Weight Loss: 3.5 kg (7.75 lb)
Postflight temperature: 310.6° K (99.4° F) (Oral)
Hematocrit: 43 (Preflight); 49 (Postflight)
Subjective symptoms: Dizziness

GEMINI 1965-1966

The biomedical studies conducted during the Gemini Program were directed toward evaluating the magnitude of flight-related changes first noted following the Mercury flights, and other physiological changes that might occur in Earth-orbital flights of up to two weeks' duration. Heavy emphasis was placed upon evaluation of the cardiovascular system, since the principal changes observed during Mercury involved alterations

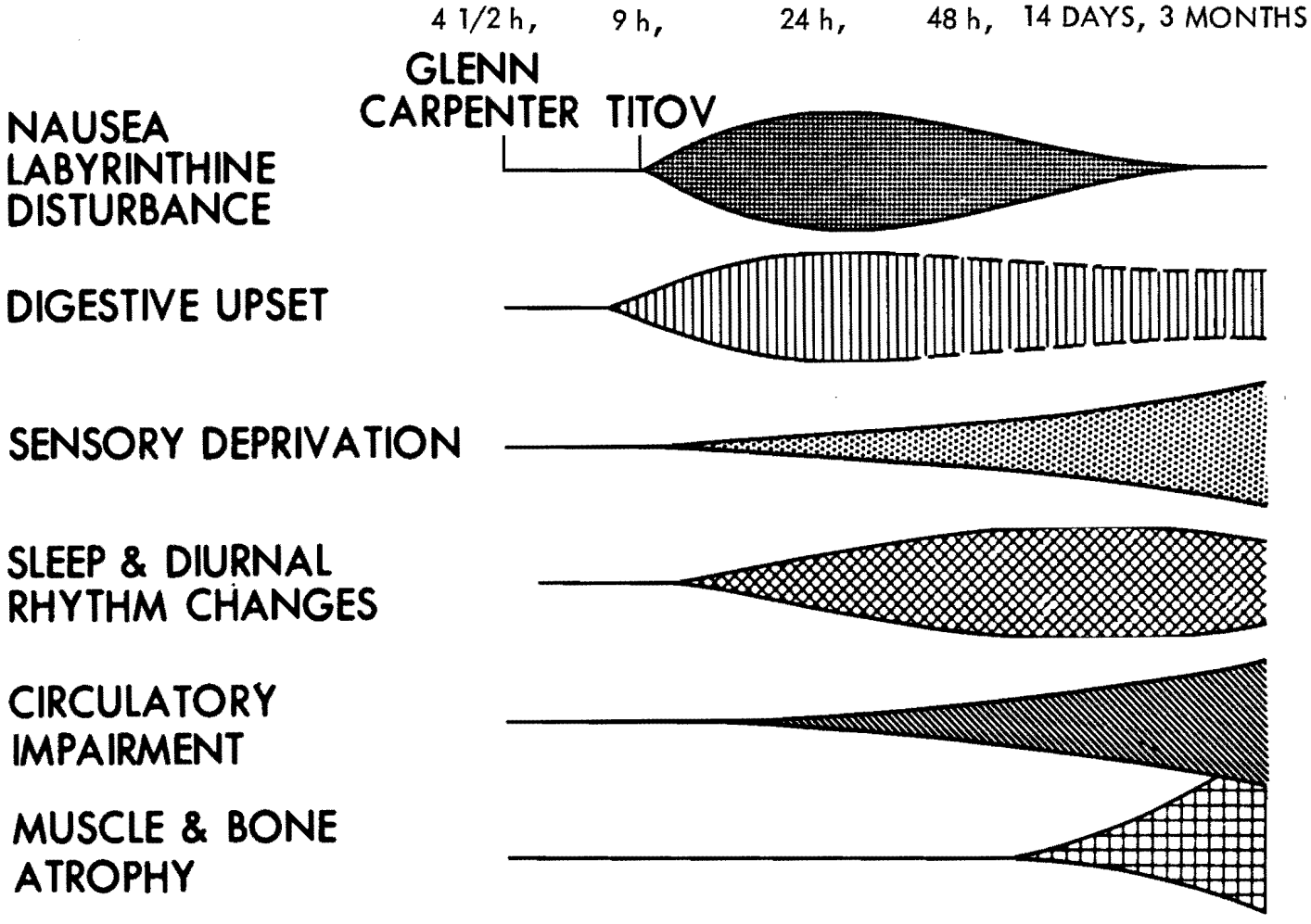


Figure 1. Expected time course of symptoms if they occurred in weightlessness.

in cardiovascular reflexes that regulate blood flow in the face of a continuous hydrostatic gradient in Earth's gravity field.

The preflight, in-flight, and postflight studies conducted during the Gemini Program were intended to detect alterations in the functional status of the principal human body systems with increased flight duration. The results of these studies indicated that some of the major human physiological systems undergo consistent and predictable alteration as a result of space flight. The significant biomedical findings in Gemini are listed in table IV.

TABLE IV. SIGNIFICANT BIOMEDICAL FINDINGS IN GEMINI PROGRAM

- Moderate loss of red cell mass
- Moderate postflight orthostatic intolerance
- Moderate postflight loss of exercise capacity
- Minimal loss of bone density
- Minimal loss of bone calcium and muscle nitrogen
- High metabolic cost of extravehicular activity

It should be emphasized that the principal objectives of the 10 Gemini flights were to perfect the techniques of rendezvous, station keeping, docking and extravehicular activity--all critical to the Apollo lunar landing mission, then only four and one-third years away from Gemini 3. Three flights of the Gemini series were of medical and physiological interest. Gemini 4, 5, and 7, lasting 4, 8, and 14 days respectively. Several in-flight measurements or experiments were accomplished on these missions, as well as preflight and postflight studies. There investigations confirmed the postflight orthostatic intolerance observed. in Mercury and extended the findings to include moderately decreased exercise capacity and red cell mass, minimal loss of bone calcium and muscle nitrogen, and the high metabolic cost of extravehicular activity. The medical findings of the Gemini Program have been reported in detail elsewhere (2, 3, 4).

APOLLO 1968-1973

Eleven manned missions were completed in the five year span of the Apollo program: four prelunar flights (Missions 7 through 10); the first lunar landing (Mission 11), and five subsequent lunar exploratory flights (Missions 12 through 17). Apollo 13 did not complete its

lunar landing mission because of the unfortunate pressure vessel explosion in the service module. Instead, it returned to Earth after a partial lunar orbit.

As stated previously, biomedical studies in Apollo were limited essentially to the preflight and postflight mission phases, along with in-flight monitoring and observations. Apollo witnessed the addition of vestibular disturbances to the list of significant biomedical findings incident to space flight.

Vestibular disturbances with nausea were noted by Soviet Cosmonaut Titov during his one-day, Vostok 2 flight on August 6, 1961, and by the crews of other later Soviet flights. No astronauts had experienced any motion sickness symptoms until the early Apollo experience. In retrospect, however, the anorexia and reduced caloric intake observed on certain Gemini and later Apollo flights, may have been, in fact, early symptoms of vestibular disturbance.

Apollo 8 and 9 especially were plagued with vestibular problems: five of the six crewmen developed stomach awareness, three of the six, nausea, and two of these six proceeded on to frank vomiting. In Apollo 15 and 17, three of six of the crewmen also experienced stomach awareness. The flight plans of Apollo 8 and 9 required that the certain crewmen leave their couches soon after orbital insertion. All three Apollo 8 crewmen noted some motion sickness symptoms (stomach uneasiness or awareness, nausea, or vomiting), confined generally to the first day of flight. There is some confusion concerning the etiology of the Apollo 8 crew's symptomatology, since the Commander felt that a viral gastroenteritis accounted for (or aggravated) his symptoms. In Apollo 9, the vestibular disturbance lasted for a considerably longer time, and in the case of the most severely affected crewman, necessitated a postponement of the flight plan. And thus an additional problem area was introduced into the American space experience. This disturbance, which had long plagued the Soviets and which had been predicted in the early 1960's as a probable effect of weightless flight, had made its belated American debut. Its late appearance was probably related to the relative immobility of the crews in their spacecraft during the Mercury and Gemini flights and the absence of any rotation of the vehicles themselves.

Other significant biomedical findings in Apollo are indicated in table V. Generally, they confirmed the Gemini findings of postflight dehydration and weight loss, postflight orthostatic tolerance decrease, and postflight reduction in exercise capacity (5).

TABLE V. SIGNIFICANT BIOMEDICAL FINDINGS IN APOLLO PROGRAM

- Vestibular disturbances
- Adequate diet; less than optimal food consumption
- Postflight dehydration and weight loss
- Decreased postflight orthostatic tolerances
- Reduced postflight exercise tolerance
- Apollo 15 cardiac arrhythmias
- Decreased red cell mass and plasma volume

In addition, the decreased red cell masses and plasma volumes noted in Gemini were confirmed, but were less pronounced in Apollo.

One final observation deserving mention was the cardiac arrhythmia episode of Apollo 15. Two of the crewmembers each experienced a single run of bigeminy during the mission - the first significant arrhythmia observed *during* any American space flight up to that time. Two short bursts (9 and 17 beats, respectively) of nodal tachycardia were observed on the postponed MA-6 launch attempt of John Glenn in 1962. At the time of the arrhythmia, he was lying in his couch preparing for the final countdown. No arrhythmias were subsequently observed on Glenn either during flight or following his historic five hour orbital flight. In the case of the two Apollo 15 astronauts, it was first thought that a dietary deficiency of potassium might have been a contributory factor. Subsequent careful analysis of their intake and mission simulation studies failed to bear this out. The etiology remains obscure. Fatigue, following vigorous lunar surface activities most certainly was a factor. Other contributory factors remain speculative and are likely to remain so. It should be noted that one of these two crewmen sustained a myocardial infarction in April 1973, some 21 months after his flight in July 1971. Thus coronary atherosclerosis was very likely a factor in one case at least.

For further details concerning the biomedical results of Apollo, the reader is referred to the final summary report which will be available shortly (6).

SKYLAB 1973-1974

The three principal objectives of the Skylab Program were the study of man, his Earth and his Sun. This symposium has reported on man's responses to long-duration space flight (7). Reports on the other two study objectives of the program will be forthcoming at a later date.

Before summarizing the salient biomedical findings of Skylab, I should like to stress the sometimes overlooked fact that, in assessing the effects of weightlessness on man during prolonged space flight, we are not examining *absolute* effects or responses. Clearly, man is not vegetating in space, but is actually doing his utmost to maintain a high level of physical fitness and performance. Thus the absolute detrimental effects of null gravity will, in most cases, have to be determined in subhuman surrogates. Other points worth emphasizing are the relative inflexibility of the principal studies or measurements made on space missions, including Skylab, once conceptual design has been finalized; and the fact that space flight investigations are essentially "field studies", fraught with many attendant difficulties, in which the investigator is even farther removed from the experiment and subject than in field studies on Earth. And finally, although the measuring equipment is highly reliable in performance and the astronaut a superbly trained, perceptive scientist/observer in his own right - yet the circumstances fall short of the classical picture of the experimenting scientist in his exceptionally well equipped laboratory, constantly fine-tuning his equipment and personally conducting experimental trials and collecting precious data.

All these factors, notwithstanding, the efforts of the Skylab investigative team have resulted in a major contribution toward understanding man in his new environment.

Cardiovascular

In the cardiovascular area we have learned that so-called cardiovascular deconditioning does occur during flight, that the change is adaptive in nature and stabilizes after a period of four to six weeks, that this change does not impair crew health or performance aloft and that it is triggered by factors tending to reduce circulating blood volume. These changes are summarized in table VI.

TABLE VI. SKYLAB CARDIOVASCULAR SUMMARY

- Cardiovascular deconditioning was observed during flight; changes appear adaptive in nature and tend to stabilize after 4 to 6 weeks.
- Cardiovascular changes do not impair crew health or ability to function effectively in weightless flight.
- Lower body negative pressure tests provide fairly reliable predictive index of postflight cardiovascular status.
- Cardiac electrical activity as measured by vectorcardiogram was not significantly altered and remained within physiological limits.
- Decreased cardiac output noted in crewmen postflight; thought to be related to reduced venous return.
- Single episode of significant cardiac arrhythmia in one Skylab 2 crewman during exercise early in mission.
- No significant in-flight decrement in work capacity or physiological responses to exercise.
- All crewmen have shown postflight decrease in exercise capacity and altered physiological responses.
- Skylab 3 and 4 crews returned to preflight cardiovascular status by the fourth and fifth day and the Skylab 2 crew on the twenty-first day postflight. Increased exercise by Skylab 3 and 4 crewmen thought to be a factor in improved recovery rate.

The provocative lower body negative pressure test has proved to be a fairly reliable predictive index of postflight cardiovascular status. Cardiac arrhythmias have been rare: only one episode noted early in Skylab 2 during intensive personal exercise interpreted as multiple, unifocal ventricular premature beats with no evidence of coupling.

Other arrhythmias observed have been limited to isolated rare to occasional premature beats. Cardiac electrical activity has been within physiological limits as judged from the vectorcardiographic data.

Exercise tolerance *during* flight was unaffected. It was only *after* return to Earth that a tolerance decrement was noted.

Finally, the rapid postflight recovery of orthostatic and exercise tolerance following two of the three Skylab missions appears to be directly related to total in-flight exercise as well as to a graded, regular program of exercise during the postflight debriefing period.

As indicated in table VII, the postflight orthostatic intolerance and diminished exercise capacity are both related etiologically to a decreased effective circulating blood volume at one-g, with consequent decreased venous return and cardiac output.

TABLE VII. CARDIOVASCULAR SYSTEM

Findings

- Postflight orthostatic intolerance
- Postflight diminished exercise capacity

Probable etiological factors

- Decreased effective circulating blood volume postflight
- Diminished venous return at one-g
- Muscular imbalance occasioned by functional disuse atrophy of antigravity muscles
- Altered internal milieu (fluid/electrolyte dynamic flux) during early postflight period
- ? altered venous reflexes/tone
- Fatigue

Other factors to be considered are muscle imbalance, altered electolyte flux, possible changes in venous tone or reflexes and, of course, fatigue. There is no convincing incidence of myocardial damage as an etiological factor; however, transient cellular changes during the period of homeostatic perturbation would not be surprising or unusual. In animal oxygen toxicity studies, we have observed such changes in lung, liver and kidney.

The thrust of future cardiovascular investigations is indicated in table VIII. Continued human studies, as well as critical invasive experiments on animals must be conducted to define the time course of pertinent mechanisms. The Gauer-Henry reflex has yet to be demonstrated. This will not be easy to demonstrate in man, since the critical time-period to be investigated is thought to coincide with the early operationally exacting first day of the mission.

TABLE VIII. CARDIOVASCULAR SYSTEM

Rule out

- Permanent myocardial damage (cellular level) - remote

Candidate future cardiovascular studies

- In-depth, noninvasive cardiovascular dynamics monitoring
- Invasive pressure/volume/flow changes in early flight (animal)
- Demonstrate presence or absence of Gauer-Henry reflex
- Total body exercise regimen to maintain integrity of antigravity as well as major muscle groups
- Assess role of venous (capacitance) vessels in observed deconditioning process
- Assess role of fatigue

Attention must also be given to devising an effective, practicable exercise regimen for all major muscle groups, including the anti-gravity muscles.

Finally, we must assess the roles of the capacitance vessels or veins and the elusive fatigue factor in the deconditioning phenomenon.

Mineral/Fluid Balance

Findings in this area are summarized in table IX. They include the moderate losses of calcium, phosphorus and nitrogen that have been observed in the first two Skylab missions. Preliminary evaluation of data from these flights as well as from the 84-day mission tends to support the general observation that these losses are comparable to those observed at bed rest or six grams of calcium per month or five tenths percent of total body calcium per month. Complementary mineral losses in the *os calcis* have been relatively low. It would appear from these data that missions of from 8 to 9 months' duration would be feasible without preventive or remedial measures.

The Skylab experience has provided evidence that the caloric requirements of space flight are identical with those for the individual on Earth - at least for high activity missions such as Skylab. From the Gemini and Apollo experience we were led to believe that the in-flight caloric requirements was some 300 calories/day less than Earth requirements. This judgment may have been colored by the relative low

activity profiles of these missions, and the fact that the food provided was often not consumed. In retrospect, as mentioned before, this anorexia may have been a manifestation of early motion sickness and not recognized as such at the time.

TABLE IX. SKYLAB MINERAL/CALORIC, FLUID/ELECTROLYTE SUMMARY

- Moderate losses of calcium, phosphorus, and nitrogen have been observed comparable to those seen in bedrested subjects: 6 grams/month calcium or 0.5 percent/month total body calcium.
- Rate of calcium loss would not preclude extended missions of 8 to 9 months' duration. Longer missions may require remedial measures.
- Significant *os calcis* mineral loss:
  Skylab 3: Scientist Pilot: 7.4 percent
  Skylab 4: Scientist Pilot: 4.5 percent; Pilot: 7.9 percent
- Caloric requirements during flight identical with individual requirements at one-g.
- Renal function unimpaired; however, apparently unique adaptive functional changes observed require further study.
- Skylab 4 anthropometric studies consistent with predicted shift of body fluids during weightless flight.

Renal function was unimpaired during flight through a complex interplay of humoral and possibly hemodynamic factors as we will consider shortly. In addition, anthropometric studies performed on Skylab 4 support a cephalad shift of body fluids at zero-g.

With regard to the musculoskeletal system, the negative balances observed are due primarily to the absence of gravity as shown in table X. However, the correct balance of weight bearing, muscular activity, hormonal influence and circulatory factors required to prevent or arrest mineral and nitrogen loss during bedrest simulations has to date defied definition. Elevated cortisol secretion during flight helps to confound the picture and doubtless contributes to nitrogen and potassium loss.

Continued studies must be pursued--and we are currently active in this area—to define absolute catabolic change in the musculoskeletal system of animals. We also continue to evaluate various countermeasures in bedrest studies in order to determine the most suitable for flight use. More attention must be given to the selection of individuals who are most refractory to catabolic influences of space flight. The prediction formula of Vogel, *et al.*, may be useful in this regard.

TABLE X. MUSCULOSKELETAL SYSTEM

Finding

- Moderate losses of calcium, nitrogen, and phosphorus

Possible etiological factors

- Primary - loss of gravity gradient
- Secondary

  Absence of weight bearing
  Absence of hydrostatic venous gradient
  ? hormonal imbalance (elevated cortisol secretion)
  Combinations of above

Candidate future studies

- Absolute catabolic in-flight changes (bone, muscles) in animals
- Countermeasure evaluation

  Dietary
  Physical
  ? Hormonal

- Selection criteria for prolonged missions (Prediction formula)

Fluid and Electrolytes

Following Apollo and before Skylab a working hypothesis was advanced (5) which provided a logical flow of events outlining the adaptive changes in the fluid, electrolyte and hormonal area. The essential steps in this adaptive process are outlined in figure 2. In brief, the relative hypervolemia (total circulating blood volume) experienced on orbital insertion resulted in decreases in antidiuretic hormone (Gauer-Henry reflex) and aldosterone resulting in a diuresis of water and solute (sodium and ?potassium). Such a diuresis may have occurred during mission day 1, but was not evident since fractional urine samples could not be obtained due to mission constraints. Thus, a diuresis could have occurred but was obscured by collection procedures or modified by increased insensible loss and sweating which were not measured.

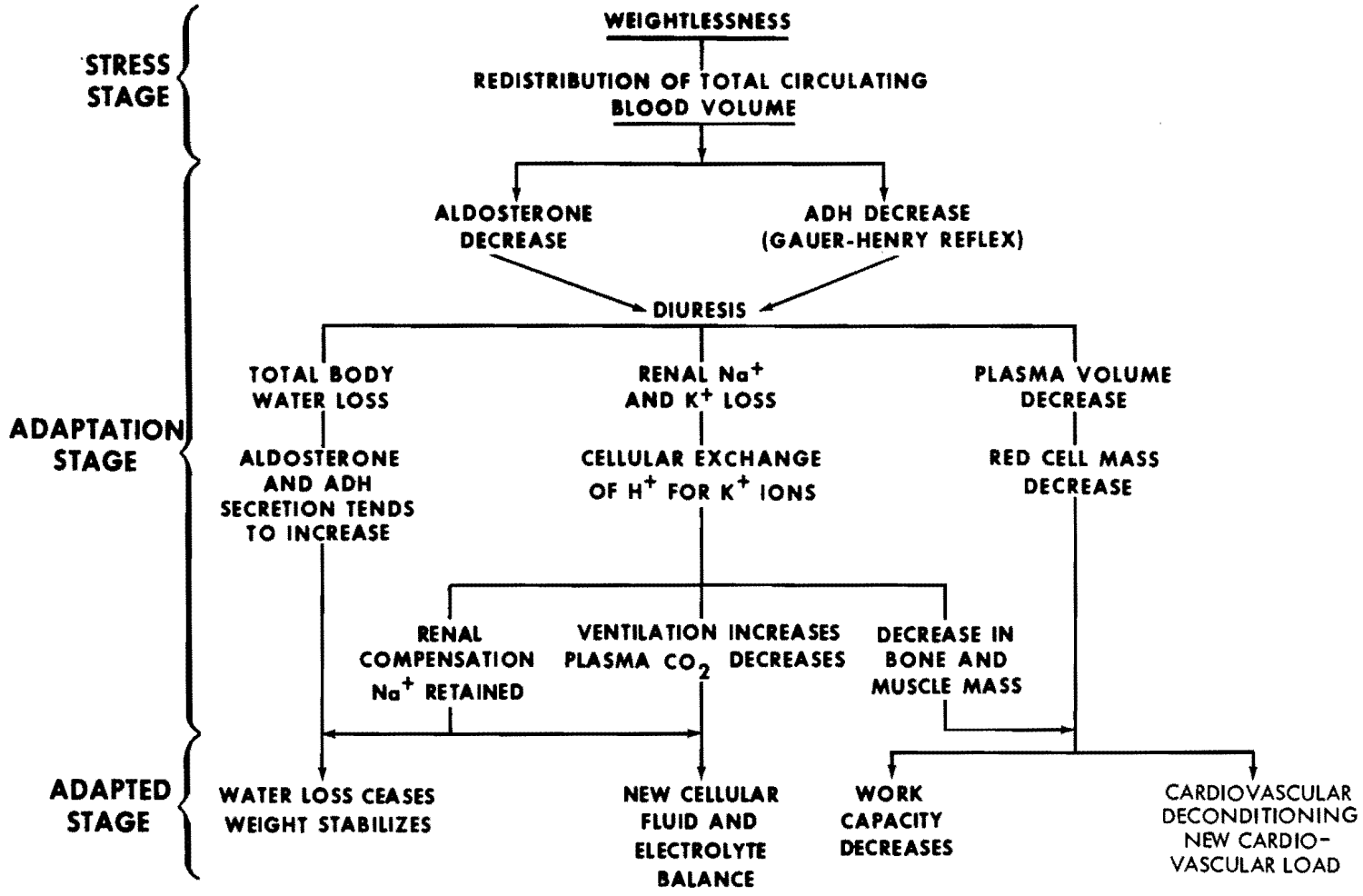


Figure 2. Adaptive responses to weightlessness pre-Skylab hypothesis.

Even assuming the occurrence of a diuresis during early mission, there are some consistently paradoxical findings which are difficult to reconcile with the working hypothesis. These findings are listed in table XI. Antidiuretic hormone secretion was uniformly decreased during all missions with the exception of Skylab 2 in which case it was elevated, especially in early mission following the overheating of the orbital workshop. Also, aldosterone secretion was consistently elevated throughout all missions, and particularly in the early part of Skylab 2 and 3. Despite this elevated aldosterone, solute (sodium and potassium) excretion was consistently elevated and was reflected in the increased urine osmolality. As stated earlier, the consistently elevated cortisol secretion doubtless contributed to muscle catabolism and increased nitrogen and postassium loss. Its overall effect on fluid and electrolyte homeostasis must remain conjectural at this point in time.

In general then, it is evident that internal homeostasis and satisfactory renal function are maintained through complex humoral and/or hemodynamic (physical) factors that await clarification.

Future studies currently being pursued at this Center include demonstration of the presence (or absence) of the Gauer-Henry reflex during early weightlessness, the changes in renal hemodynamics during zero-g; the renal response to provocative stresses such as water loading, salt loading and water deprivation during space flight; and the hormonal interplay involved in these processes.

TABLE XI. FLUID/ELECTROLYTE AREA

Pre-Skylab working hypothesis

Paradoxical Skylab urinary findings

- ↓ Antidiuretic hormone (↑ Skylab 2)
- ↑ Aldosterone secretion
- ↑ Na^+ K^+ excretion
- ↑ Osmolality
- ↑ Cortisol

Interpretation

- Internal homeostasis maintained
- Renal function maintained
- Interaction of complex humoral (and ? hemodynamic) factors required to maintain homeostasis during weightlessness

Future studies

- Demonstrate Gauer-Henry reflex
- Renal hemodynamics in zero-g
- Renal response to water/salt loads, dehydration in zero-g
- Humoral interactions involved in above

Hematology

Red cell mass loss was again observed following the Skylab missions. The mean loss in Gemini was about 17 percent; in Apollo, 10 percent; and in Skylab, 8 percent. Further, the mean loss in Skylab 2, 3, and 4 was 9.4 percent, 8.6 percent, and 5.9 percent respectively. Other findings in the areas of hematology, immunology and cellular biology were not consistently remarkable as indicated in table XII.

TABLE XII. SKYLAB HEMATOLOGY, IMMUNOLOGY AND CYTOLOGY SUMMARY

- Loss of red cell mass observed postflight appears to be suppression of red cell production rather than increased destruction.
- Red blood cell mass loss not related to mission duration.
- No significant changes consistently observed in humoral or cellular immune responses.
- Cellular proliferation (tissue culture) normal during space flight.

The red cell mass losses are apparently related to marrow suppression (table XIII), since there is little evidence to support increased cell destruction. The stimulus resulting in marrow suppression is not clear and requires further study. Toxic suppression appears remote; physical factors, such as a pulse of increased bone marrow venous pressure should be investigated. It is apparent that there is no increased red cell mass loss with increased mission duration. The apparent diminition in red cell mass losses from Gemini through Skylab may be a reflection of the distance of the first postflight sampling period from the initial in-flight suppressive stimulus (fig. 3).

TABLE XIII. HEMATOLOGIC SYSTEM

Finding

- Red cell mass loss

Etiological factor(s)

- Increased destruction - no evidence
- Marrow suppression
  - Toxic
  - Physical (increased blood volume. Bone marrow venous pressure)

Candidate future studies

- Ground-based marrow-suppression factors
- Validate Skylab results on longer Earth-orbital flights

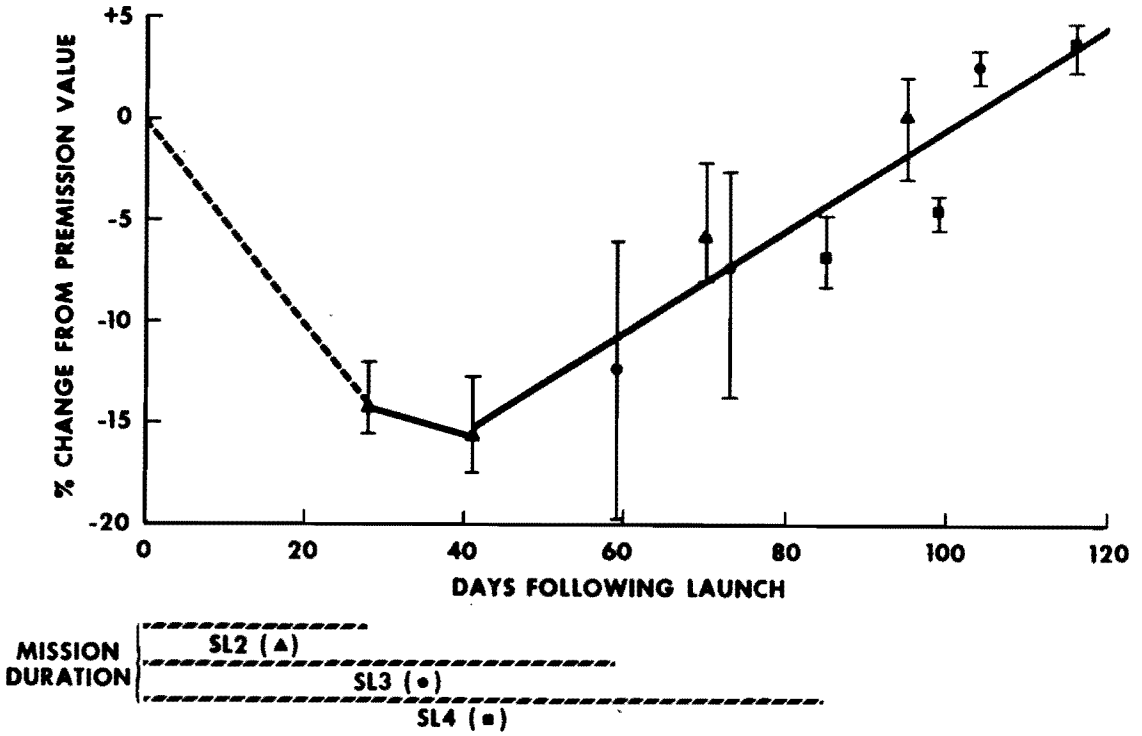


Figure 3. Red Cell Mass/Skylab.

Clearly, ground-based studies regarding the bone marrow suppression mechanism must be pursued. Further validation of the Skylab results should be pursued on orbital flights of longer than 4 months' duration, since the mean life span of the red blood corpuscle is 120 days.

Neurophysical and Performance Areas

The salient findings in the neurophysiological and performance areas of Skylab are indicated in table XIV.

TABLE XIV. SKYLAB NEUROPHYSIOLOGICAL AND PERFOMANCE SUMMARY

- After initial in-flight adaptive period, all crewmen show marked increased tolerance to motion sickness measured by rotation and head movements. Tolerance threshold gradually reverted to baseline post flight. Antimotion medications helpful in control of symptoms.
- No major disturbances noted in quantity or quality of sleep.
- Carefully regulated crew work/rest cycles essential for maintaining crew efficiency.
- Postflight hyperreflexia confirmed and quantitated.
- Improved in-flight performance efficiency exhibited by all crews.
- Overlearning recommended for critical tasks on short-duration missions.

Among these findings, the occurrence of motion (space) sickness symptoms during the first few days of space flight is of paramount operational importance for the forthcoming Shuttle flights. Some possible etiological factors are indicated in table XV, although at the present time true etiological factor or factors cannot be specified. It would appear that otolith function is profoundly influenced by null gravity and its modulating influence perturbed; sensory inputs are accordingly distorted and appropriate responses are not forthcoming, since these are based on a one-g environmental memory store. Presumably, a repatterning of this central memory network must perhaps occur, so that new and unfamiliar zero-g sensory inputs are correctly interpreted and appropriate motor responses elicited. This repatterning of the central memory core is, we believe, the end result of the process of habituation or adaptation. Other contributory factors should be considered such as hypervolemia or increased venous pressure effects on the vestibular system.

Future studies in this area should address the problem of space sickness susceptibility and the development of a reliable predictive test for this susceptibility in candidate crews and passengers. Basic studies should be pursued relative to etiological factors involved in the space sickness syndrome and the role of one-g training in its prevention or mitigation. Finally, improved medications should be sought for more effective prevention or control of the vagal manifestations of this vestibular disturbance in space.

TABLE XV. SKYLAB VESTIBULAR FINDINGS

Possible etiological factors

- **Otolith receptor physiological deafferentation**
  - **↓ Modulating influence on canals**
  - **Direct interaction with canals**

Rule out:

- **Influence of hypervolemia (Transient ↑ pressure) on vestibular system**

Candidate future studies

- **Role of altered cues: visual, kinesthetic other sensory**
- **Effect of overhydration, dehydration and increased venous pressure on motion sickness threshold**
- **Predictive test for zero-g space sickness susceptibility (? parabolic flights)**
- **Basic studies regarding etiology**
- **Role of one-g training in prevention**
- **Improved medications for prevention/control**

GENERAL SUMMATION

Table XVI lists the general conclusions reached as a result of the Skylab biomedical experience. In substance, the findings indicate that man adapts well to and functions effectively in the space environment for time periods approaching three months. Appropriate dietary intake coupled with adequate, programed exercise, sleep, work and recreation periods are essential to crew health and well being. No untoward physiological responses have been noted that would preclude longer duration space flights, but more research is required in order to understand the mechanisms involved in the observed responses.

Finally, remedial or preventive measures may be required for Mars-type missions, and further study of man in Earth orbit for an uninterrupted six-month period should ideally precede this Mars-type mission - truly the gateway to exploration of the Universe: a step which may bring man closer to answering the eternal questions of whence he came, why he is here, and whither he goes.

TABLE XVI. SKYLAB GENERAL SUMMATION

- Biomedical results show that man can adapt and function effectively in weightless environment for extended periods.
- Daily in-flight personal exercise regimens coupled with appropriate dietary intake and programed adequate sleep, work and recreation periods essential for maintaining crew health and well-being.
- No untoward physiological changes noted that would preclude longer duration manned space flights; however, research required to understand the mechanisms responsible for many observed changes.
- Remedial or preventive measures may be required for mission durations in excess of 9 to 12 months (*e.g.*, bone demineralization countermeasures)
- Ideally, further observations of man in Earth orbit for an uninterrupted period of 6 months should precede a Mars-type mission.

REFERENCES

1. Space Medicine in Project Mercury, NASA SP-4003, NASA Scientific and Technical Information Division, 1965.

2. Gemini Summary Conference, NASA SP-138, Manned Spacecraft Center, Houston, Texas, February 1-2, 1967.

3. Gemini Midprogram Conference, Including Experiment Results, NASA SP-121, Manned Spacecraft Center, Houston, Texas, February 23-25, 1968.

4. Hypogravic and Hypodynamic Environments, NASA SP-269, Proceedings of Symposium at French Lick, Indiana, June 16-18, 1969.

5. Berry, C. A. 1974. The Medical Legacy of Apollo. *Aero. Medicine* vol. 45 no. 9.

6. The Biomedical Results of Apollo. In press.

7. Presented at Skylab Life Sciences Symposium. Johnson Space Center, Houston, Texas, August 27-29, 1974.

SYMPOSIUM PANEL DISCUSSION

Charles A. Berry, M.D., M.P.H., Moderator
President, The University of Texas
Health Science Center at Houston
Houston, Texas

DR. BERRY: Could we ask the panelists to please come up and take a seat at the table?

Well, colleagues, ladies and gentlemen, we've reached that point that we've all been waiting for, to try and decide the total meaning of all the material which has been presented. That's an awesome task. I think Dr. Dietlein did a fantastic job of pulling his material together. I certainly think his summary was excellent and he did a very good job of telling us where we are.

There are a few remarks that I would like to make at the outset, and then I would like to note how we're going to work the remainder of this session. For this period, we have asked the panelists covering various areas, to be a part of this discussion and give their views of the data. They're not limited to their special area of discussion, but they should present their views concerning what they have heard of these results. These statements will be relatively brief so that we don't end up with a whole series of papers all over again. The objective is to have some interchange among those of us on the panel and with you in the audience. We particularly want those who have been investigators, those of you who have been carrying out some of these studies, to address questions you may have to the panelists. It would be interesting to determine if they view the data the same way you did.

Now I think it's very important that we all realize one of the things that Dr. Dietlein said and is well stated in the title of his paper. This point is still a beginning. It's a culmination, though, of many things, as you saw from the slides that he presented; and that there are many people in this room who have had a tremendous amount to do with reaching this point. There are some people whom I think have not been singled out — and this is always dangerous, once you start doing that. I want to say at the outset that there is no way possible that I could single out all the people in this room who have something to do with making today possible, and this day is possible only after roughly the last 15 years of activity in this field — a tremendous effort to get us to the point where we had data to review as has been done today.

I would like to congratulate the entire biomedical team for the development of this symposium. As you know, this team is composed of members from both inside NASA and from the scientific community. Within NASA we have people from the Johnson Space Center, from other Centers and Headquarters. My congratulations are directed to this entire group, and in particular, to the Johnson team who worked so earnestly in organizing the program in which we are participating this afternoon. Now some of the individuals who are in this audience are people who have formerly worked with this team in one form or another. They've had activities tied with the team -- trying to get data for one area or another or working with the operations teams. Many of you are here because of those particular interests and we're thankful to all of you. There are some people here, though, who have played a particular role in some of our activities over the years because they've taught many of us and led many of us down these productive paths. Dr. Strughold I see sitting over here. He's been with us for many, many years and really led us into space medicine. I think we owe a particular debt to him. We also have a couple of people in the audience who were quite active in leading the team of us who were involved at the very beginning of the program back in the Mercury days. They have since moved to other areas, one of them only recently, but they are still very tied to our area of interest. I'm referring to Stan White and Bill Douglas, who are here in the audience. We have Dr. Hitchcock down here in the very front of the room, and it's people such as he who have helped to teach us along the way and have made great imprints upon the capability to develop data such as you've seen here. Dr. Bjurstedt and Dr. Gauer from across the oceans are here with us in the room. You've heard Dr. Gauer's name mentioned so many times during the symposium. Drs. Luft and Sam White from Lovelace started very early in the program working with us, and they have continued with that activity. We could go on and on and on with people like these. There is another thing I would like to emphasize -- there are a number of panelists here who went through some very trying times with us.

I saw Herb Hultgren out in the audience during the last three days, and I'd like to say something about the role he and some other fine people played with us. You've heard many very fine comments about what great teamwork we had; what a great job everyone has done and how happily it's all ended. Today, everyone is bouncing and full of joy. I'd like to tell you that this last year has not always been bouncing and full of joy for the people who have been working on this program. At times, I tell you very personally, I considered it hell. And I'm not sure that some other people on the team didn't consider it that way also. So while it has all turned out great, I don't want anyone to go away from here with the idea that it's easy and that it all just sort of happens, because it doesn't just happen.

There were daily problems, and these were alluded to in some of the opening morning speeches when some of our key people in the Program Office mentioned that there had been some of these early problems. Some of the people who were talking about the program operations mentioned these, and there was daily some sort of difficulty in trying to work out the problems which were occurring on a minute-to-minute and hour-to-hour basis. These problems and their resolutions were important to the outcome of these data which you've heard discussed here. While some of them may have sounded not important at the time, they had great importance; and those decisions required were not always easy to reach, and they always weren't made to everyone's satisfaction, of course. There was severe management concern, and Dr. Dietlein, I think, led up to that very well in some of the things that he was telling you about past history.

I'd like to call to your attention the fact that the cardiovascular system, while it was the first system that was ever noted to show measurable changes and with which we had problems, certainly remained one of concern. This concern was augmented by our problems with Apollo 15 -- the arrhythmias which were mentioned -- and then a great deal of data which we obtained from our Russian cohorts. I would just make one parenthetical statement here; that we have come a long way in our dealing with our Russian colleagues over these years. A great deal has changed in the last 15 years. We've exchanged a significant amount of data directly. They're looking at many of the same problems and questions as we are. They're not always looking at them in the same way that we are, but they're searching for an understanding of the physiological mechanisms.

These concerns of top management surfaced to the point that we were required to get decisions weekly, for medical purposes, as to whether we would continue to extend the mission or not. I can tell you that those weekly meetings were deadly serious; that the Administrator was very, very serious about what he was going to do, or not do, and he required that he be reassured by evidence. It was fine to try and give that reassurance on a personal basis, backed by our NASA team such as we had conducting these missions, but we needed other assistance. We formed two particular consultant groups. One group was a cardiovascular group. And John Shepherd, who's here on the panel, spent a great deal of time with that. Scott Swisher, who is also a member of this panel, was on that group. This group met many times during the course of the program. They met with others and gave of their time unstintingly to help us convince management; I needed that support and I'm deeply grateful for it. We also had a group that was organized to try and look at the vestibular area, and one of those people is here on the panel, Melvill Jones. It's hard to find many vestibular experts once you get past Ash Graybiel. We went to great

lengths to try and find vestibular people to come. They did meet and we appreciate the guidance they provided.

I've reviewed the remarks that I had a chance to present in trying to sum up this program on two previous occasions; namely, the Fifth-Man-in-Space Symposium last December, and then again in May at the Aerospace Medical Association meeting. In December, we were still flying the last mission and in May, we were at the point where the missions were completed and we were sort of able to sum up, at least with data as they were revealed at that point in time. I don't think that I would change anything that I said in any of those remarks, and so I'm not going to repeat them here today. I think that Dr. Dietlein has summarized very well the status that we all believe exists and that man has shown adaptive changes to a unique environment. In some cases, these changes are definitely going to require some countermeasures. I think in the calcium balance area we're going to have to use countermeasures. I suspect even in the cardiovascular area we're going to continue to look for these procedures.

There is one observation that I would like to leave you with, and that is the fact that we are defining many new norms as we look at these findings. There's no question about that. We're looking at man, normal man, placed into this very unique environment. As we make our observations, we know we can't look at the absoluteness of weightlessness because man is going about his mission activities. Still I believe that we are conducting an unparalleled experiment in man's adaptation. As we derive these new norms, we are able to look at the hypothesis that we've developed. There are some gaps in this hypothesis and they lead to the future research that needs to be done. I hope that our panelists are going to identify a good deal of that needed research in their discussions.

I'm left with the feeling that while we have probably come up with more questions than answers, still we have gained a lot of answers. And certainly, if you look back at the time of the beginning of Mercury, we've come a long way in deciding what's really happening to man in this very unique environment. Now I'd like to begin our panel discussion. The cardiovascular system was mentioned first. To save time, I'll not introduce everybody on the panel until we come to them. First, although listed on your program, Neal Bricker is not with us. Nor is Ted Cooper. I'm going to call on Dr. Epstein in a moment, as he is replacing Dr. Cooper. I'd first like to call on John Shepherd, because of his interest in the cardiovascular system which we've mentioned so frequently and most recently in our elaborations of the last day and a half. And so, John, I'd like for you to take a few minutes and give us your views about how you sum this all up, as far as the cardiovascular system is concerned.

John T. Shepherd, M.D., D.Sc.
Director for Research
Mayo Clinic and Foundation
200 First Avenue S.W.
Rochester, Minnesota 55901

For those of us from the biomedical community who have followed the progress of the manned space program from its inception, this symposium has been a great occasion, and Mr. Richard Johnston and his colleagues at the Space Center deserve our congratulations. Over these years you, our colleagues in NASA, have been receptive to suggestions and tolerant of our lack of understanding of the lead time which is essential for the proper implementation of experiments to be conducted during manned space flight, and the constraints that are necessary to meet the overall objective of each mission. By the cooperation you have achieved between the astronauts, the in-house NASA scientists and the scientific community, we now have, as Dr. Larry Dietlein said in his excellent summary of the symposium, objective data of man's ability to adapt to the space environment, and hence of his potential for extended space missions. As Doctors Kerwin and Musgrave so aptly put it, "just feed us, house us and let us exercise".

Dr. Berry has reminded us that all this has not come about easily, but rather as a consequence of a logical progression of knowledge and appropriate adjustments as we moved through the missions from Mercury, Gemini, and Apollo to Skylab. Many of you will recall our long-past panel discussions at Woods Hole, Cape Cod, as we talked wisely of cardiovascular deconditioning, without much idea of what we were talking about in coining this term. We worried about potassium loss and cardiac arrythmias in the later Apollo missions. Today for those interested in the cardiovascular system, you have provided a clear picture of the physiological changes in space flight, which can fit into an accepted and logical pattern of normal cardiovascular adaptation.

With the achievement of the weightless state, fluid shifts quickly from the lower to the upper part of the body. Evidence for this has been given by the astronauts. Doctors Gibson and Kerwin have described to us the fullness of the head which they experienced, the distension of the head and neck veins, the congested sinuses and the facial puffiness. Leg measurements have demonstrated a rapid decrease in leg volume. With this transfer of blood and tissue fluid from the legs to the central circulation (one might estimate the amount to be around 700 milliliters) the volume of the heart and the cardiac filling pressure is increased. This results in a small increase in cardiac output, due mainly to an increase in stroke volume because of the greater end-diastolic volume of the ventricles (Frank-Starling mechanism). At the

same time the activity of the mechanoreceptors in the cardiopulmonary region is increased; this results in a greater inhibition of the vasomotor centers with a resultant reduction in sympathetic adrenergic outflow. Consequently the peripheral blood vessels dilate so that the total systemic vascular resistance is decreased. Evidence for this was provided by Dr. Johnson, who showed that during weightlessness there was a widening of the arterial pulse pressure and by Dr. Thornton who indicated from measurements made on the calf of the leg by venous occlusion plethysmography that the blood flow to the legs may be increased.

Even though the cardiopulmonary receptors are strongly activated by the increased volume of blood in the heart and lungs, the magnitude of the peripheral vasodilatation is limited by the counterbalancing effect of the carotid baroreceptors. In cats and dogs these latter receptors are more effective in opposing the increase in muscle blood flow and the glomerular filtration rate will be increased. Diuresis is facilitated by the reduced reabsorption from the renal tubules, since stimulation of the cardiac receptors results in a diuresis which is brought about by a blood-bone agent.

At the same time the amount of renin released from the kidney is reduced because these cardiopulmonary receptors act continuously to inhibit its release and the more so when they are strongly stimulated. As a consequence less angiotensin II is secreted. Thus there is a loss of fluid from the body as a consequence of this normal response to an increased central blood volume. Somehow, as I hope Dr. Scott Swisher will tell us, the red blood cells are reduced in proportion to the decrease in plasma volume. The astronauts have reported that exercise relieves the fullness of the head. With the severe exercise which they undertook the blood flow to the active muscles is increased as the arterioles dilate. This causes an increase in pressure in the capillary and post-capillary vessels in these muscles so that fluid passes from the capillaries into the interstitial spaces and more blood is accommodated in the post-capillary bed; as a consequence, the distension of the vessels in the thorax and head is lessened. With the application of a given set of negative pressures to the lower part of the astronaut's body during the Skylab missions, there was a greater increase in heart rate and in diastolic blood pressure (indicative of a greater reflex constriction of systemic resistance veesels) than when the same stimulus was applied on Earth. In the weightless state, with less blood and tissue fluid in the legs, and more in the central circulation, more blood is pulled into the lower body with application of the same negative pressure than in a gravity environment. The reduction of the stimulation of the cardiopulmonary mechanoreceptors is greater, the inhibition of the vasomotor centers is less, and hence the increase in sympathetic adrenergic outflow is more than that with the same test preflight.

If we could amputate the legs, which have little use and indeed may be an inconvenience in space flight, these shifts in blood volume would not occur. In fact, the major question for prolonged space flight is what to do about the legs. The bones in the legs lose calcium as they no longer perform their normal function of weight bearing. Exercise seems the best answer and the astronauts described an ingenious plastic platform they used that slips backwards with each step, so that as the subject walks he stays in the same position.

Immediately on return to Earth gravity these changes are reversed. There is more blood in the legs and less in the upper part of the body. Since both the plasma and the red cell volume are slightly reduced, the system as a whole must adjust to a smaller total blood volume. The filling pressure of the heart is decreased, the heart volume is less and as shown by the excellent echocardiographic studies of Doctors Henry and Epstein, the stroke volume and diastolic volume are reduced. With exercise under these conditions the increased cardiac output to meet the increased oxygen requirements is achieved by a faster heart rate and a smaller stroke volume. Also, the hemodynamic response to lower body negative pressure will continue to be exaggerated until blood volume which is customary for Earth's environment is restored. Again it is important to emphasize that these are the normal compensatory physiological responses to changes in blood volume and its distribution within the vascular system. At this time, immediately postflight the astronauts report that they are thirsty and drink freely.

As we turn from the studies of Skylab and look to the Shuttle era, the success of the former has provided the stimulus for gaining new understanding of man in the latter. There is much still to be learned from well-conceived animal experiments and complimentary studies on man, both on Earth and at zero-g.

For example, the presence of mechanoreceptors in the heart and lungs has long been known, and many investigators are active in studies designed to elucidate their function and morphology. Complex unencapsulated sensory endings are present around the junctions of the pulmonary veins and of the caval veins with the left and right atrium respectively. It has been postulated that there are two types of these receptors, one type having its bursts of activity coincident with the a-wave of the atrial pressure pulse, and the other with activity related to the v-wave. Others conclude that their characteristics are similar. They are connected to medullated vagal afferents and their stimulation causes an increase in heart rate, a decrease in activity in nerves to the kidney and a diuresis caused by a blood-bone agent. Discussion continues as to whether the diuresis is caused by a decrease in the concentration of antidiuretic hormone or an increase of an unknown diuretic substance. By contrast with these receptors

with medullated afferents, there exists in the left ventricle and in the atria a diffuse and large population of receptors connected to slowly-conducting non-medullated vagal afferent fibers. Activation of these receptors causes bradycardia, a generalized vasodilatation, and especially an augmentation of the vagal outflow to the heart receptors, probably located in the left ventricle and with unmyelinated afferents in the vagi. Thus it is possible that a similar mechanism in man contributes to the sickness experienced by the astronauts. The lung too, like the heart, is a source of reflexes which modify the cardiovascular system and which merit further study. The role of left ventricular receptors in the causation of the vasovagal reaction also needs elucidation; it has been suggested that the vigorous contraction of the ventricles when their volume is reduced might excite these receptors and induce a reflex bradycardia. Perhaps this might occur in susceptible subjects with the reduction in central blood volume that follows the application of negative pressure to the lower body. The Shuttle too with its increased facilities for observations in man will permit a more detailed analysis of the rapid adaptations in the body systems which occur within the first few hours of weightlessness and which provide the explanation for the subsequent responses to various stresses.

Thus the wealth of data which has been accumulated on the adjustments of man to space travel, and which have been so well described in this symposium, truly establish his future role in the exploration of our universe.

SELECTED REFERENCES

(The following list of selected references was furnished by Dr. Shepherd for the use of interested readers seeking further details of statements made by him here.)

REFERENCES

1. Abrahamsson, H. and P. Thorén. 1972. Reflex relaxation of the stomach elicited from receptors located in the heart. An analysis of the receptors and afferents involved. *Acta physiol. scand.* 84: 197.

2. Gauer, Otto H., James P. Henry, and Claus Behn. 1970. The regulation of extracellular fluid volume. *Ann. Review Physiol.* 39: 547.

3. Kappagoda, C. T., R. J. Linden, H. M. Snow and E. M. Whitaker. 1974. Left atrial receptors and the antidiuretic hormone. *J. Physiol.* (London) 237: 663.

4. Linden, R. J. 1973. Function of cardiac receptors. *Circulation*, 48(3): 463.

5. Öberg, Bengt and Peter Thorén. 1972. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat — A possible cause of the vasovagal reaction. *Acta physiol. scand.* 85: 164.

6. Paintal, A. S. 1973. Vagal sensory receptors and their reflex effects. *Physiol. Rev.* 53: 159.

7. Pelletier, Conrad L. and J. T. Shepherd. 1973. Brief Reviews: Circulatory reflexes from mechanoreceptors in the cardio-aortic area. *Circ. Research* 33: 131.

Professor: Dr. Otto H. Gauer

Director, Physiological Institute of the Free University
West Berlin, Germany

[Note: Although Dr. Otto Gauer was not a Panelist *per se* his comments together with illustrations and references fit most appropriately into the panel discussions at this point, and are therefore included.]

I was much impressed by Dr. Kerwin's vivid description of the severe engorgement of the cephalad circulation characterized by extended neck veins, a puffy face and nasal congestion. These findings are corroborated by Dr. Thornton's report of a dramatic loss of extracellular fluid and blood volume from the thighs and calves in the order of two (!) liters. This figure is based on foolproof anthropometric measurements. Although venous pressure was not recorded, we can safely assume, that the intrathoracic circulatory compartment, which has to accommodate the lion's share of this volume, was greatly distended. In the weightless condition the cephalad fluid displacement was in all likelihood greater than that induced by whole body immersion in a thermoneutral bath. It is therefore not surprising that similar effects on circulation and fluid balance in the weightless condition (1-6) and in whole body water immersion have been observed. Upon immersion, intrathoracic blood volume increases by 700 milliliters (1), and the heart volume by 320-120 (mean 180/milliliters) (5). (Figure 1, table I.)

This engorgement is reflected in an elevation of central venous pressure to 12-15 mm Hg (3) (fig. 2). The distension of the heart has a primary effect on cardiac dynamics and secondary reflex effects on the arterial and capacitance systems (table I). Thus an increase in cardiac output, a fall in total peripheral resistance (TPR) and a reduction in the tone of the capacitance system were well established during immersion and weightlessness. Furthermore the volume control reflex is activated for the relief of the central engorgement. This reflex is by no means adequately described by the sequence: left atrial distension, reduced antidiuretic hormone (ADH) secretion, diuresis. Numerous factors are involved (2,4) (fig. 3). Although the final results, namely, plasma volume loss, impaired orthostatic tolerance and reduced working capacity are the same after exposure to immersion or weightlessness there are considerable differences in the behavior of the effector mechanism. For example; during immersion a negative fluid balance is effected by excess urinary excretion, in weightlessness this effect is attained by deficit drinking. During immersion the attenuation of plasma volume

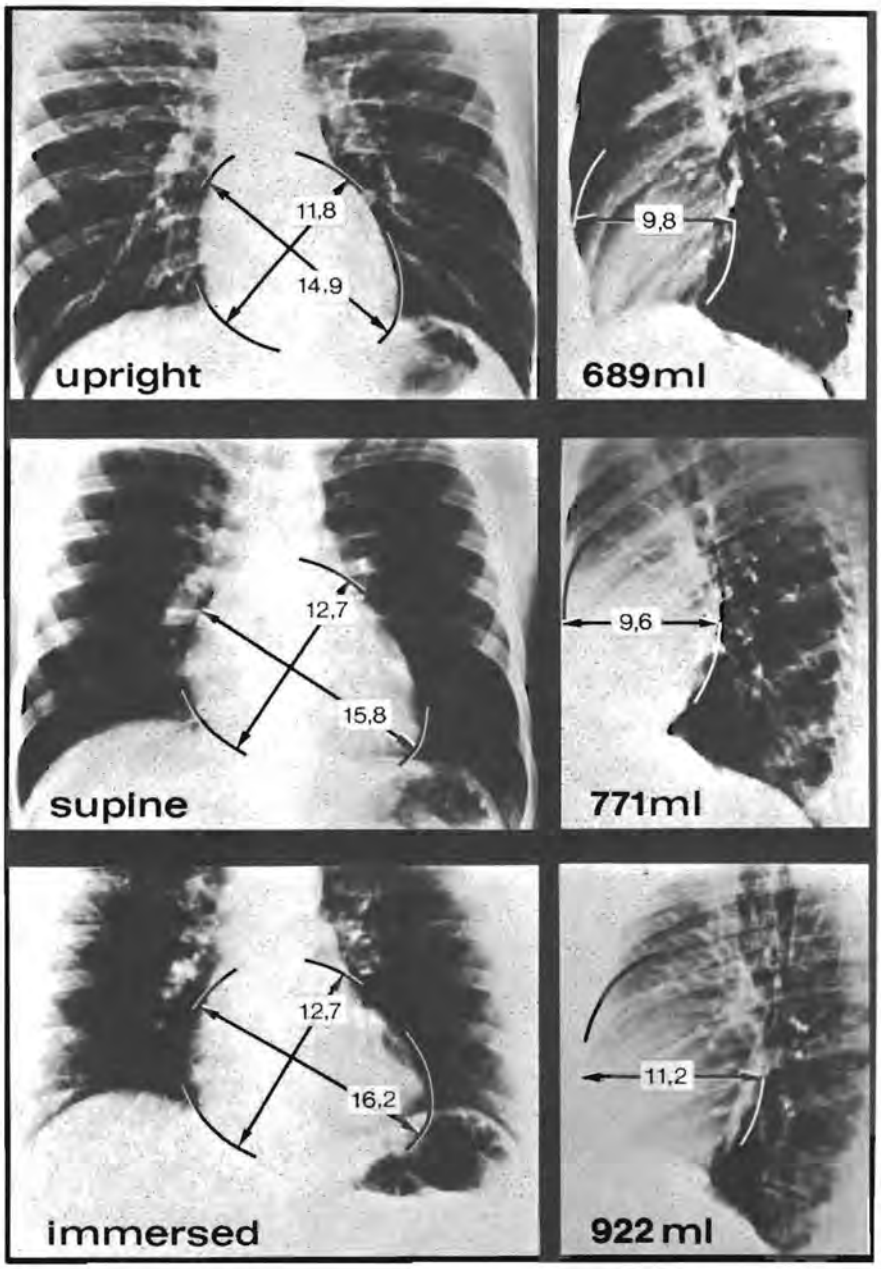


Figure 1. Roentgenometric demonstration of the change of heart size in relation to posture and immersion in a bath. The lines to calculate heart volume from the postero-anterior (left) and the lateral projection (right) have been drawn. With immersion of the subject standing in air heart volume rises by 233 ml. Considering the severe congestion of the cephalad circulation in the weightless condition a similar increase in heart volume can be expected. (Lange,L. *et al.*, 1974.)

TABLE I. CIRCULATORY CHANGES INDUCED BY WHOLE BODY IMMERSION*

Primary and secondary effects on the circulation induced by whole body immersion. (Data from Arborelius *et al.* 1972, Echt, Lange and Gauer 1974 and Lange *et al.* 1974)

	Primary Effects	
Δ	Central Blood Volume (L)†	+700 ml
Δ	Heart Volume (G)†	+180 ml
Δ	Central Venous Pressure (G,L)	+12 to +18 mm Hg
Δ	Intrathoracic Pressure (G,L)	+ 4 to + 5 mm Hg
Δ	Transmural Pressure (G,L)	+ 8 to +13 mm Hg

	Secondary Effects	
Δ	Stroke Volume (L)	+35%‡
Δ	Cardiac Output (L)	+32%‡
Δ	Total Peripheral Resistance (L)	-30%
Δ	Peripheral Venous Tone (G)	-30%
Δ	Arterial Pressure (L)	+10 mm Hg§

*Subject standing or sitting erect in air versus standing or sitting in water.

†(G) Gauer and co-workers; (L) Lungren and co-workers.

‡Heart rate was unchanged.

§The arteriovenous pressure gradient was not changed since CVP was increased by the same amount.

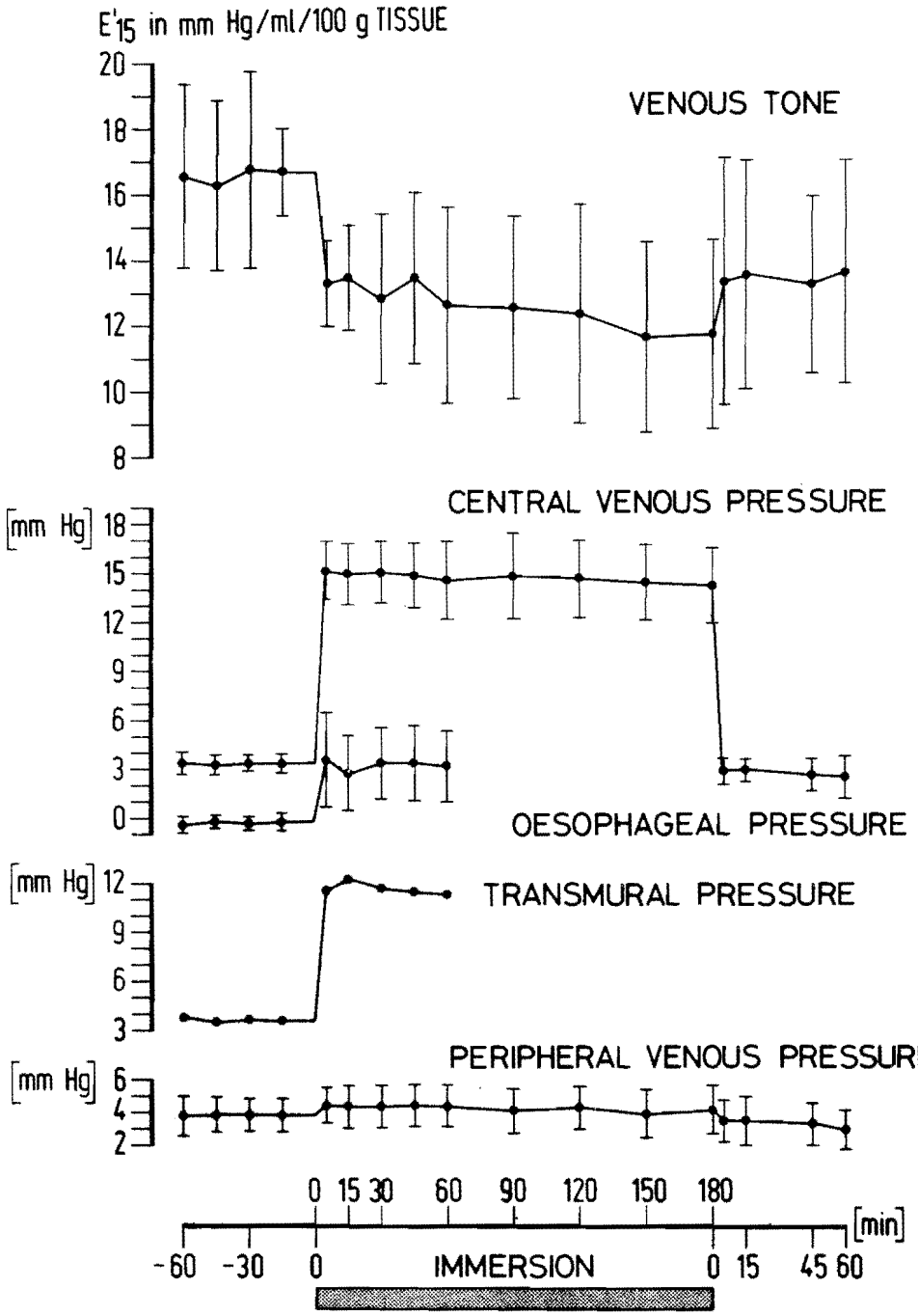


Figure 2. The effects of whole body immersion on various parameters. From above: peripheral venous tone; central venous pressure, oesophageal pressure, central venous transmural pressure, peripheral venous pressure. Recording of oesophageal pressure was discontinued after 1 hour immersion. N=5. (Echt, M. *et al.*, 1974,)

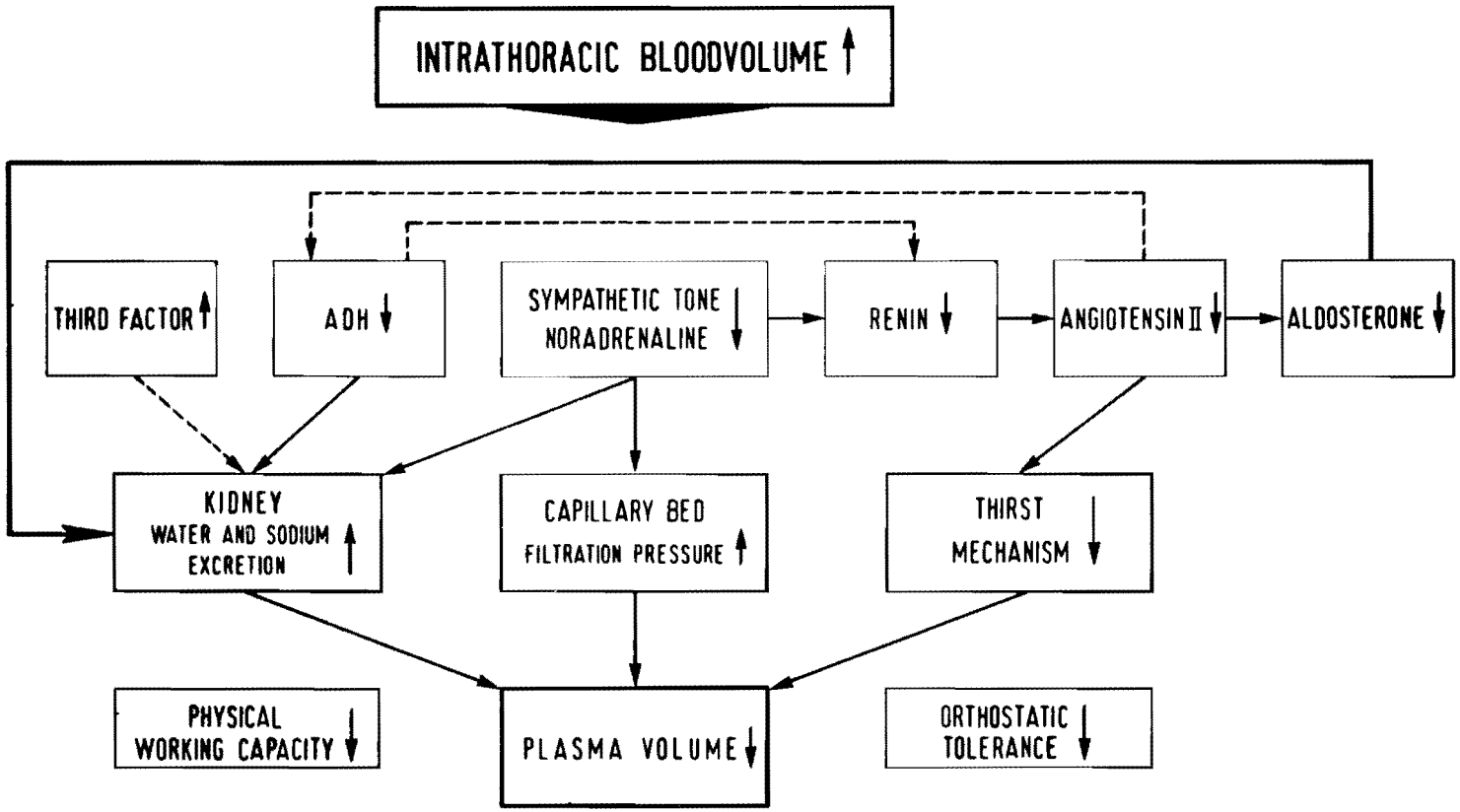


Figure 3. Intrathoracic vascular distension induced by whole body immersion and plasma volume control. With an increased intrathoracic volume the combined effect of several hormonal mechanisms leads to an increased renal excretion of water and sodium, a tendency towards outward filtration in the capillary bed and (probably an attenuation of the thirst mechanism. The three effects combined (or single) lead to a reduction in plasma volume. (Gauer, O.H.,1973.)

is supported by an increased outward filtration (6), which is probably distributed over the whole body (2). In the weightless condition this outward filtration is obviously confined to the cephalad regions. Not easily explained is the observation presented by Dr. Leach, that sodium loss in the weightless condition occurs in spite of an increased aldosterone activity. Of particular interest is the adaptation of the red cell mass to the reduced plasma volume. In summary, numerous problems have been presented by the Skylab results. If they can be solved, our knowledge of the overall regulation of circulation and fluid metabolism will be greatly augmented.

REFERENCES

1. Arborelius, M., Jr., U. I. Balldin, B. Lilja and C. E. G. Lundgren. 1972. Hemodynamic changes in man during immersion with the head above water. *Aerospace Med.* 43: 592-598.

2. Behn, C., O. H. Gauer, K. Kirsch and P. Eckert. 1969. Effects of sustained intrathoracic vascular distension on body fluid distribution and renal excretion in man. *Pflügers Arch.* 313: 123-135.

3. Echt, M., L. Lange and O. H. Gauer. 1974. Changes of peripheral venous tone and central transmural venous pressure during immersion in a thermo-neutral bath. *Pflügers Arch.* 352.

4. Gauer, O. H. Recent advances in the physiology of whole body immersion. Proceedings of the Fifth International Symposium on Basic Environmental Problems of Man in Space. Ed. by A. Graybiel. Washington, D. C., 1973.

5. Lange, L., S. Lange, M. Echt and O. H. Gauer. 1974. Heart volume in relation to body posture and immersion in a thermo-neutral bath. *Pflügers Arch.* 352.

6. Oberg, B. 1964. Effects of cardiovascular reflexes on net capillary fluid transfer. *Acta Physiol. Scand.* (Suppl. 229) 62: 1-98.

Stephen E. Epstein, M.D.
Chief, Cardiology Branch
National Heart and Lung Institute
Department of Health, Education and Welfare
Bethesda, Maryland 20014

Dr. Shepherd painted quite beautifully the broad strokes of what can be derived from the data you've heard over these past few days. What I'd like to do now is to focus on a few specific questions I believe still remain to be answered regarding the long-term effects on myocardial function of prolonged space flight.

The results of the excellent paper presented by Dr. Bergman on systolic time intervals led him to the conclusion that there seemed to be at least some depression of myocardial function following return from space. However, it is quite clear from the studies of Dr. Bergman and his associates that systolic time intervals are exquisitely sensitive to preload; that is, during lower-body negative pressure (when, as our echocardiographic data show, left ventricular end-diastolic volume decreases), measurements of the systolic time intervals change. Therefore, interpretation of the meaning of changes in systolic time intervals is complicated, and distinction between alterations in intrinsic myocardial function from changes in the loading conditions of the heart may be impossible. However, on the basis of the ventricular function curves we were able to perform with echocardiography, we found no evidence of deterioration in intrinsic myocardial function. Parenthetically, I'd like to suggest that it might be interesting to relate the changes in systolic time intervals to the existing left ventricular end-diastolic volume. We know what left ventricular end-diastolic volume was at the time Dr. Bergman was measuring the systolic time intervals. Thus, we might be able to conclusively demonstrate whether or not changes in these intervals are caused by changes in ventricular volume.

Although I would like to state that the echo studies unequivocally demonstrate that there is no impairment in myocardial function, I don't think we can be absolutely definitive. After all, we studied only three astronauts, and we studied them only under resting conditions. The exercise studies, presented by Mr. Ed Michel, *et al.*, indicate that there is depression in cardiac output and stroke volume during *submaximal* levels of upright exercise that returns to normal in a rather brief period of time after splashdown. It seems reasonable to ascribe these transient changes to the decreased left ventricular volume we measured by echocardiography. However, one of the limitations of the exercise studies is that post flight, only submaximal levels of exercise performance were studied. The crucial measurement that still

must be made is what the *maximal* performance of the heart is in late postflight, compared to preflight. For example, if an impairment of myocardial function exists, measurements made at submaximal levels of exercise may be entirely normal and not necessarily reflect an impairment of the maximal pumping capacity of the heart.

One other aspect of myocardial function that has not been touched on at all is whether there is any alteration in myocardial compliance. This possibility occurred to us when we found that during the echo studies, although there was a decreased left ventricular end-diastolic volume post flight, we were unable to increase end-diastolic volume back to preflight levels by subjecting the astronauts to lower-body positive pressure, or by elevating their legs. One of the explanations of such a finding is that the mission led to a decrease in cardiac compliance. If this were the case, it could be due to a change in the heart muscle itself, or to a change in the dimensions of the pericardial sac. For example, if fluid volume is diminished during space flights and the heart is functioning at smaller volumes, it is possible that the pericardium adapts to this change by shrinking and decreasing the volume of the pericardial sac. The pericardium may thereby act as a restricting membrane postflight so as to keep the heart from returning the preflight volume until increased intracardiac pressures generated by the normalization of intravascular volume slowly distend the pericardium. It would be relatively easy to measure compliance changes in the heart by combining echocardiographic studies with more invasive techniques.

In summary, I think it would be important during future space missions to obtain more echocardiographic studies with ventricular function curves. Perhaps such studies could be performed in-flight, in which case it would be interesting to test Dr. Shepherd's hypothesis that left ventricular volume is increased during flight and only in transition to one-g does volume decrease. I also believe that maximal exercise testing would be essential to perform and that compliance studies of the heart should be considered to ensure that no other deleterious change in myocardial function has occurred that we have neglected to look at.

As a final comment, I would like to say that this has been a very fruitful collaboration for all of us at the National Institutes of Health. We already have begun to employ some of the techniques we have used on the astronauts to study the patients we see in our clinics and wards, and I'm optimistic that new data and insights will be generated using in patients some of the techniques we've helped develop and learn about here at NASA. Thank you.

Christian Lambertsen, M.D.

Department of Pharmacology and
Experimental Therapeutics
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

It was worth restating that Dr. Berry said the program is the culmination of 15 years of effort. This is about half or a good portion of the lifetime of many members of this audience. This period of time has involved extensive work in many fields of physiology and "space medicine". After the very detailed and excellent review of only one kind of problem, namely, the cardiovascular responses to weightlessness we should move away from that and picture what was one of the very first physiological concerns and which has not even been mentioned yet during this symposium. This is the exchange of gas with the respirable environment that is transported from Earth for the astronauts to breathe. This evidently has become an entirely manageable aspect of manned space flight. However, I would like to restate one of our earlier concerns, namely, that if individuals became ill with diffuse pulmonary disease (such as viral pneumonia), that this might generate peculiar kinds of circumstances such as diffuse atelectasis in a weightless state in the handling of pulmonary debris and secretions. It will still be wise to keep alert to details of the respiratory gas exchange and pulmonary function as one moves on into longer and longer periods of time where illness may develop or consequences of physical changes such as fluid shifts may progressively modify pulmonary function.

Now going from the still important considerations of respiratory exchange, we could next look at the whole man. Something that has been established is that man himself is able to proceed through the whole pattern of flight and come back. The whole man, including his senses, his vision, his hearing, his ability to react to his environment performed very well. His mind worked all right, so that even if his cardiovascular system could not tolerate all of the specific gravitational stresses on return quite the way we wanted them to, he did quite well with his mentality, his fingers and thumbs and other important parts while he was out there. He could carry out exceptionally useful and intelligent work. This means that gas exchange and factors involved in circulation to his head, and his hands and some of the parts in between were functioning all right. Now if we take the whole individual and examine him a little more closely, his heart probably also got along well because it was exercising all of the time as it normally tends to do in us even when we are at rest. It is normally an

exercising organ and, therefore, probably its muscle was not likely to suffer quite as much from the weightless state as his legs were.

I also saw no sign that the actual skeletal motor mass, the voluntary muscles of the individuals themselves, if they were treated right by being given adequate doses of exercise or of strain, had to experience a decrement at all. Massive work loads and rates of oxygen consumption were accomplished by the whole individual in this space environment - probably larger degrees of oxygen consumption than most of us can even begin to think about performing here and now. Therefore the individuals were certainly not limited in terms of performing hard labor activity in the space environment. Their muscles, therefore, in terms of the exertion of force, were certainly not handicapped. The circulation to the muscles may have been handicapped on return, leading to some of the decrement in exercise capability at one-g. However, it is necessary to distinguish between the intrinsic capacity of skeletal muscle itself to contract and the factors involved in supply of nutrients and oxygen to the muscles during a period of work. Therefore one has to consider the muscle and the circulation separately. If in the circulatory system, the heart itself was not severely in jeopardy, then one would have to look towards the circulatory regulating mechanisms as the limiting system on return. And I think they have been elaborated upon quite enough for now.

The question I have been posing is, then: Can we divide the overall exposure and experience into stages and look at these stages separately? Surely we can. One of these parts is the stage of prolonged exposure to the weightless state. The composite of all the observations described has indicated that individuals can, in fact, go on for long periods and keep themselves in reasonably good shape, even with the fluid shifts and even with the central vascular congestion and calcium loss. In addition, there is clearly a reasonably prompt return to - or adaptation on return to sea level and one-g again, back to Earth's atmosphere. The stage of real problems is that of transition between that harmless exposure in space and the readaptation on Earth. It therefore seems to me that the concentration that those of you directly involved in this work must make is on the stage of transition from one more or less "normal" state in weightlessness to a second normal state after return to one-g again, because the failures really occurred at that point. Actually it is still true that present astronauts are active, working, laborers in space but passive on entry into the Earth's gravitational field. Some day one will require active, self-controlled entry, and it is at that particular point that these questions are going to be most important: Can the individual be fully active during the stress of return, including during the entry; not only can he readapt to life in this atmosphere and at one-g well enough.

It seems now that a good deal of the attention from here on is going to be required to take the excellent observations made in the program to date and modify the experiment procedures drastically in ways that are controllable. I would urge that from this point on more attention be given to long-term studies in which individuals in space are allowed to actually deteriorate naturally, without attempting to sustain their physiological systems so that they can function fully on return. In other words, we now need professional "subjects" in addition to the pilot-commander and other responsible individuals in the spacecraft system. Then, having generated natural failure and studied it, one should study use of low-mass materials, such as drugs as stressors, which may, in fact, be able to modify fluid volumes, modify cardiovascular tone, supplement or replace baroreceptor mechanisms, and modify calcium loss. I think we now have to set up the kind of long-term laboratory in space in which such professional subjects are, in fact, considered not as "astronauts" but as "subjects", with physically competent individuals serving as transport crew for other individuals who are being studied in detail along with other experimental animals. Out of such an approach can come the exact pattern of unmodified deteriorations and adaptations to be dealt with in planning toward the ultimate in manned space flight.

Scott N. Swisher, M. D.

Chairman, Department of Medicine
Michigan State University Medical School
Life Sciences Bldg., Room B220
East Lansing, Michigan 48823

I believe the crucial problem that this symposium has heard about is that related to red cell mass change. The material presented on the change in red cell morphology may be a fascinating insight into a whole new set of problems, but we are still a long way from even beginning to be able to make an interpretation of these observations. I want to spend most of my time on the first problem.

There's a rather interesting psychological set, if you will, that overlays many of the reported investigations which has had a great influence on the way the observations are now coming together and beginning to make a coherent picture. The NASA Manned Space Flight Program has had a very laudable, and I must say, enviable record of attention to crew safety issues. But one of the things this has done is that it has put many of us who have been either peripherally or directly interested in one or another of the investigative aspects of the program in what might be called a "pathophysiological frame of mind". We tended to look first at changes as possible expressions of pathological mechanisms and possibly rightly so; but, in so doing, I think we have from time to time lost sight of what we were really observing, *i.e.* evolving physiological adaptations. I am delighted to see that this conference had its principal focus on physiological adaptation, and the concerns about pathological processes have been put into second rank.

It seems there is no argument that there is a distinct downward shift in red cell mass. Again taking the view that this is not a pathological process, that it is not a process which thus has the potential of becoming continuously downward in its direction, but that it is the searching for a new adaptation, one can, of course, then take a fairly comfortable position about it, at least insofar as the safety of the astronaut functioning in space. Dr. Lambertsen has raised the question about the flight transitional states, which really are the important ones. Here we have some very interesting data that I think need to be reexamined. The data presented suggest that the red cell mass deficits in the shorter flights, the earlier ones we were able to study, were possibly greater than those encountered in missions of longer duration. There may be some technical explanations for this. This may not be a set of entirely comparable measurements. We must try in retrospect to reconstruct the exact circumstances of those, and see if it's possible

that we were overmeasuring the red cell mass decrement in the earlier flights and that our more recent flights and related observations are those which are closer to the truth. You will notice also that the variability in the measurements were much greater in the earlier flights. But it is also possible, and this would be of great interest, that there is a kind of overshoot in the downward readjustment of red cell mass and that this overshoot is gradually recovered over a longer period of time to a new steady state.

I feel that the formulations we have heard of the mechanisms of readjustment are both clear and reasonable. Dr. Thornton's formulation is that the change in central blood volume is the crucial factor that all other changes proceed essentially from it, in a passive or active kind of readjustment. Dr. Johnson's formulation, which you heard, is an interesting one. I would have to raise a question with his formulation which in sense says that there are metabolic changes which favorably shift the oxygen-carrying capacity of the red cell mass and that this in turn permits the downward red cell mass adjustment. That is one way of looking at it in contrast to the way which Dr. Thornton presented these changes in oxygen-carrying capacity. It would seem that a metabolic process which produced the shift rightward in the oxygen dissociation curve might be more likely the secondary event than the causative event in the red cell mass decrease.

It's interesting that the "pathophysiological view" still persists! I notice Dr. Dietlein's slides still had the concept of "marrow inhibition". Maybe we really ought to speak of the marrow that is just turned down or turned off because it's not necessary that its activity remain at the normal earthbound one-g level. With this concept, bone marrow is really just resting and not inhibited.

Before we can really get a picture of what happens in a situation like this and in comparable experiments in animals, (for example, the artificially polycythemic overtransfused animal), we have one very large black box in the canonical diagram of the regulation of erythropoiesis that must be opened up. This contains the sensor system, if you will, the sensor-set point physiology. We know a few things. We know erythropoiesis is a hormonally controlled apparatus. At least there is one stimulatory hormone. The apparatus responded to oxygen, possibly not only to oxygen tension but to oxygen transport, which has something to do with blood flow. The time constants of the system are long, and the rude canonical diagram would suggest that it is a system that is driven upward, then relaxes and passively adjusts itself downward in the absence of the stimulus. Many alternative models of this system are yet to be explored. Is it possible that it is a multihormonal system, that there is some type of driver-antagonist hormonal balance, that there are pro-hormones, and that hormone conversion rates are

important? What is the process of sensing, in biochemical, physical, chemical, or electrochemical terms? Are second messengers involved? Until we can answer these questions not only in the case of man but by fundamental experimental investigation, we will have to accept the rather general picture we now have of the mechanism of space flight induced red cell mass decrease. The best assumption to me seems to be that it reflects a new balance in the circulation and in the perceived blood volume. This formulation certainly is an adequate one to explain what we have so far seen.

On the other hand, we ought to exert every effort to try to develop other formulations of these mechanisms of change, and not accept those which seem reasonable and rational on the basis of our very limited present knowledge. For example, is there some direct mechanism by which erythorpoiesis is influenced that may bypass the hormonal system even, or at least bypass much of the regulation in control of the hormonal system, which is directly dependent upon some compartment of blood volume? Many of you can develop notions about how these kinds of hypotheses could be approached investigationally. There is a possibility of control of the red cell mass change. I wanted to consider this because I feel Dr. Lambertsen is quite correct when he says that the next generation of investigators in space physiology is going to have to put much of their effort into problems of control, compensation and adaptation of systems that get beyond physiological limits in less than ideal subject astronauts. What about phlebotomy? People entering zero-g seem to have about 700 milliliters too much central blood volume, maybe even more. What about just taking that volume from them, preserving it in any one of a number of tricky ways that are now available, and putting it right back when they have to come home?

MODERATOR: Dr. Berry.

Well, the suggestions are getting better and better. We really thought about that, Scott. I want you to know we have thought about the phlebotomy route; we discussed it, but we thought everybody gets scared of needles and scareder of blood, it appears.

SPEAKER: Dr. Swisher.

I would suggest you sell it and not put it back.

MODERATOR: Dr. Berry.

Yes, you'd make a lot more money these days. Anyway, I'd like to ask Dr. Bob Heaney if he'd give us his view of this mineral balance area. I know he's been brainwashed somewhat, I'm sure, by Don Whedon by now, but I know him to be an individualist, and he's not going to listen to all that input and so he's going to give you his own strict view here.

Robert P. Heaney, M.D.

Vice President for Health Sciences
Creighton University
Omaha, Nebraska 68131

Two major points stand out clearly from both the Skylab mineral studies and their supporting ground-based projects. These are:

- bone loss definitely occurs under zero-g conditions. It is certain that this loss continues for at least sixty days, and it is almost certain that it continues for as long as 84 days. There has been no evidence that this phenomenon shows the type of adaptation to zero-g which has been exhibited in the other systems which have been the subject of this symposium.

- bed rest, under one-g conditions is surprisingly suitable as a model for the bone loss of zero-g.

I shall expand, briefly, on both of these points, before going on to a discussion of what lies ahead.

Bone Loss. We now have calcium balance data on six of the nine astronauts, and urine calcium values for all nine. Calcium balance shifted negatively for five of the six (one of the Skylab 2 crewmen showed essentially no change). Urine calcium increased substantially in all nine. This latter change, while highly suggestive of negative balance, cannot be fully assessed without knowledge of calcium absorption, so we must wait for final balance data from Skylab 4. Nevertheless, the continued high values for urine calcium through the entire length of the Skylab 4 study gives us no reason to believe that any kind of adaptation occurred during the 84 days of that mission. Finally, both from bed rest and from in-flight studies, we have no evidence that the exercise program or the physical countermeasures which have been employed to date in any way alter this bone loss. This is not to say that more strenuous measures would not work; it is simply to stress that those which have been tested have not been effective.

Vogel has observed significant *os calcis* bone loss in one of the three Skylab 3 crewmen, and in two of the three Skylab 4 crewmen. He suggests that it may be possible to predict susceptibility to bone loss in advance, but data are still too few to reach a final conclusion about the usefulness of this approach in a zero-g situation.

Bed Rest Model. Despite many initial reservations, one-g bed rest appears to mimic zero-g weightlessness to a surprisingly good extent.

The two situations behave similarly for calcium balance, urine calcium, *os calcis* mineral loss, and hemodynamic effects. Hence this appears to be an entirely suitable, ground-based model.

* * * * * *

With respect to these data and their implications, there appears to me to be three big questions which we must try to answer. These are:

- how clinically significant is the bone loss?
- what, if anything, can be done about it? and
- where do we go from here?

Seriousness of Bone Loss. Here I think the major point is to focus briefly on the distinction between negative balance in-flight and the negative balance shift which occurs between preflight and in-flight conditions. Recall that four of the six crewmembers for whom we have balance data were in substantial positive balance preflight; hence the shift in a negative direction is substantially larger than the actual negative balance. Positive balance is unusual in this age group; for this reason we must ask ourselves why it occurred. I think immediately of two major possibilities: preflight conditioning, or systematic measurement error. If the effect is due to conditioning, then it is only the in-flight negative balance which reflects actual bone loss; if there is a measurement error, then the actual zero balance or equilibrium point may be closer to the preflight situation, and the shift is then a better indicator of actual bone loss.

Skylab 2 showed no really significant negative balances; however Skylab 3 did, with two of the three crewmen demonstrating actual negative balances of pathological severity. We eagerly await the Skylab 4 data. If the balance shift is the better indicator of actual bone loss then four of the six crewmembers had pathological balances. The average shift, for example, in the three Skylab 3 crewmembers, exceeded 200 milligrams Ca/day. This is a really worrisome figure. With respect to bone loss, therefore, I feel we must conclude that it is at least, potentially serious, that it remains a problem, and that it shows little evidence of demonstrating that adaptability which has characterized so many of the other systems studied in the Skylab projects.

What Can Be Done About the Bone Loss? Recall that the relation between bone mass and stress was articulated many years ago and is known as Wolff's Law. Paraphrased, this law states that the mass and configuration of bone change in response to changes in external stress. Loss of bone, particularly in the legs, is an entirely normal adaptation

to reduced gravitational forces. Our rationale in attempting to suspend the operation of this law is that zero-g is not the ultimate environment for our astronauts and we want them to be able to function well once again in a one-g environment. I do not believe we would have the same concern if we were contemplating interstellar voyages at sublight speeds. It is the one-to-three year trips about which we worry.

Basically, therefore, we have - it seems to me - only four ways to go:

- We can select people who are sluggish responders to Wolff's Law, *i.e.*, who have a long time constant in their response to altered mechanical stresses. We don't now know how to look for such individuals, but Vogel's prediction term may be a start. I suspect that the urinary hydroxyproline component of his term is its most important and promising feature. Clinical analogs of slow responders are seen in human hypothyroidism and hypoparathyroidism. Incidentally, both hypothyroid and hypoparathyroid individuals would have high prediction terms.

- We can develop pharmacological or other treatments which effectively lengthen the time constant of response, *i.e.*, which convert astronauts into sluggish responders. Agents of possible utility include the diphosphonate compounds and fluoride, both of which, used preflight, show considerable promise of retarding in-flight bone loss. They may be useful in-flight as well, but premedication seems especially promising. We also need to look at a whole cluster of factors which, though not primary, may nevertheless frustrate our attempts to lengthen the time constant of bone remodeling response. There are a great many factors which are known to enhance any bone resorptive stimulus. These include such agencies as acidosis (even mild), high tissue oxygen tension, high bone blood flow, as well as the level of hormones such as thyroxin. (We heard yesterday of a tantalizing increase in free plasma thyroxin. We need to know what this means.) I think it is probably safe also to conclude that the diets consumed by the astronauts had a high acid ash content. You may have noted that the protein intake was at least twice the recommended adult dietary allowance. Whereas this is typical of the adult American male, there is some question about whether it is good for him under even one-g circumstances, and I suggest that there is both less justification for its use in zero-g, and even some reason to believe that it may be harmful.

- We can select individuals already adapted to something closer to zero-g. Here I refer to sedentary, skinny, small individuals. Perhaps someone more like Dr. Whedon or myself would be better suited than these wiry athletes. I have found myself asking,

repeatedly, these past three days, why there is this quite extraordinary emphasis on physical fitness for function in a weightless environment? Great muscular strength and endurance have obvious survival value in the jungle, are of problematic importance in a civilized environment (except as a means of burning our excess caloric intake), and are all but redundant in a zero-g environment, where it is the human nervous system and cybernetic flexibility which are of crucial importance. Pushing this suggestion even further, I think one must seriously consider selecting individuals who have already developed lower extremity disuse osteoporosis, whose legs are already - as in space - nearly useless appendages. I refer to individuals who have a variety of lower extremity paralyses.

° Finally, and I suggest this quite seriously, I think sober consideration should be given to selection of amputees. The legs are the major source of our concern about bone loss. At very least, they deadhead with us on these missions. We have seen that they are nearly useless. Their tissue requires food and consumes oxygen, and if we exercise them, they consume even more. The ultimate fuel cost of legs on long missions must be really staggering. There are many double amputees around, and many of them must be veterans of our own wars. Instead of stigmatizing them as less than "whole men", I think we must seriously ask ourselves whether they do not have an important role to play in space.

There is one other theoretical option, namely the development and application of even more strenuous exercise and countermeasures than those employed to date. It is not known that these would work, but they might. I have neglected this option because its cost for long missions would appear to be prohibitive. Hardware weight would be the least of that cost. The food, oxygen, and waste management requirements, and the fuel necessary to orbit it all, would be uneconomical in the extreme. Sooner or later considerations of economy must emerge. When that happens, minimization of caloric intake and expenditure will be seen to be desirable. This may mean longer reconditioning back on Earth, but that is not a serious problem. Running the mile within three days of splashdown is nice, but it's almost certainly a luxury.

The final question is *where do we go from here*? Obviously, the answer is, "Back to space". But we need more answers, and happily the bed rest model appears able to provide them. I thus suggest a significant emphasis on bed rest studies, with particular attention paid to the development of effective pharmacologic countermeasures. I stress once again that, on long flights, the food and fuel costs of drug countermeasures are far less than the cost of maintaining physical conditioning.

Because of the long lag time between experimental design and results, very careful advance planning is vital so as to insure that we obtain the maximum useful information from a set of bedrest experiments. We badly need numbers in this game, and we will not get sufficient experience from actual space flights, particularly in view of the fact that the Space Shuttle Program, for at least the next several years, will be confined to flights of no more than 30 days duration. Ground-based experiments constitute our only reasonable hope. Luckily, as I have already said, bed rest has turned out to be better than we had any reason to hope.

Thank you.

G. Melvill Jones, M. D.

Professor, Psychology and Director of Aviation Medicine
Canadian D.R.B. Aviation Medical Research Unit, Department of Physiology
McGill University
Montreal, Quebec, Canada

ADAPTIVE NEUROBIOLOGY IN SPACE FLIGHT

Introduction

A characteristic feature of this symposium has been a general re-orientation of research effort away from the earlier "acute" problems of conventional flight, towards longer-term problems of "chronic" adaptive change incurred by exposure of Man to long durations of maintained space flight. In the neurobiological sphere this trend is well exemplified by a change of focus from problems of acute disorientation due to sensory illusions in flight, to long-term adaptive changes in our neuromuscular systems due to prolonged exposure to the zero-gravity environment.

Naturally, faced with the pressing need to meet new goals in a current space flight program, immediate research objectives must necessarily be guided by severely practical objectives. Nevertheless, before discussing more applied aspects it may be helpful to touch upon a few currently emerging basic mechanisms which probably contribute to the adaptive capability of our nervous sytem.

Sensory-Motor Interactions

There is good evidence that much of our normal motor control is organised not merely as an on-going interaction between continuously operating automatic Sherringtonian reflexes, but rather as centrally released preformed packages of programed neural information (1, 2). One might well guess that adaptation to new requirments could be relatively easily met by merely reprograming relevant patterns of the outgoing central neural discharge. However, there is a growing body of research findings which indicates that even cortically released patterns of motor drive are not devoid of early interaction with corresponding sensory mechanisms. For example we now know that such a central discharge of motor drive is not only destined to activate muscles through relatively direct connections with spinal motoneurones, but also, through collateral branches of central fibers, to act directly upon SENSORY neural relay stations in spinal cord pathways. Thus the corticospinal (Pyramidal) motor tract, not only descends to spinal cord

networks generating motoneurone activity to drive skeletal muscles, but also sends many collateral branches to synapse directly on second order afferent neurones in the sensory gracile and cuneate nuclei of the dorsal columns of the cord. (1,3).

A clue to the functional implication of this rather surprising fact is perhaps to be found in somewhat analogous mechanisms operating in the periphery. For example it is now well established that in many circumstances both alpha and gamma motoneurones, innervating the main (extrafusil) and muscle spindle (intrafusil) fibers of a skeletal muscle, can be coactivated at the same time. It has been proposed that when the combined alpha-gamma program operates "according to plan", the muscle spindles contract (or relax) in just such a way as to null out any change in their sensory discharge caused by mechanical shortening of the main muscle (4). This rather neat arrangement would ensure that it all went well (*i.e.*,according to plan), then the central nervous system (CNS) would not be bothered with unnecessary sensory information. By contrast, if the "intended" response was *not* achieved, then needed sensory information would indeed reach the CNS which, in turn, would presumably modify the next motor command.

What do we know of the ways in which such modification could be brought about? One such mechanism might well be associated with the recently postulated concept of "Cortical Servo-Assistance" in skeletal muscle control (4). Briefly, there is growing evidence pointing to the probability that many muscular and other related afferent neural discharge from peripheral sensors bypass the sensory cortex of the cerebrum and project more or less directly to associated areas in the cerebral MOTOR cortex. These in turn relay suitably time (5) motor signals to relevant muscle groups (6) in a highly localized quasi-reflex manner. However, passing through cortical levels in the CNS, presumably responses of this nature could be subject to conscious, or even subconscious, modification (7) in such a way as to reestablished an acceptable match between corresponding motor and sensory signals associated with a given action.

Similar properties may apply to other sensory-motor systems. For example it has been proposed on the basis of neurophysiological experimentation that the vestibular primary afferent neural response to an INTENDED head movement may tend to be nulled out by a suitable outgoing efferent discharge to the end organ (8). In this case involuntary vestibular stabilizing reflexes in the neck and/or body muscles would only arise when unintended or pertubing head movements occurred. Again, the normal exercise of voluntary control would include the generation of an appropriate combination of neural signals to both the relevant motoneurones and the associated sensory systems. Mismatch between these

two informational neuronal systems due to changes in the environment would then bring about appropriate changes in their relationship so as to reestablish acceptable conformity in the new environment.

At a lower, more automative, level in the CNS, other mechanisms have recently come to light in a series of experiments specifically designed to investigate habituative adaptation in the adult human brain (9). During normal head movements, autostabilization of the eyes relative to space is brought about by two complementary physiological processes namely, visual tracking and the vestibulo-ocular reflex. By the simple process of optically *reversing* the "seen" visual field, these two processes are forced into direct opposition: during head rotation to the right visual tracking then supplies a *right-going* oculomotor drive, whilst the vestibulo-ocular reflex continues to supply what is now an opposing left-going drive. Obviously, the residual vestibular drive then disturbs, rather than aids, visual fixation during head movement. The question now arises whether or not central habituative adaptation can reorganize the available sensory-motor mechanisms to restore complementary interactions serving the common goal of image stabilization on the retina during head movement.

Remarkably, through a rather complex sequence of detailed changes, radical reorganization of the vestibulo-ocular reflex occurs such that after about 10 to 14 days of continued vision-reversal, the adult human vestibulo-ocular reflex becomes effectively reversed, thus once again serving a complementary function with visual tracking (10). Recent and current findings in this field from several different laboratories point strongly to cerebellar involvement in these autoadaptive changes (11,12,13). Although in this case cerebellar involvement may be hard to equate with the cortical servo-assistance mechanisms outlined above, yet a common factor remains in the outcome of these latter experiments. Peripheral sensory retinal signals generated specifically by undesirable (*i.e.*, blurring) movement of the image on the retina tend eventually to be nulled out by consequent readjustment (*i.e.*, reversal in this case) of the automative vestibular drive to the extraocular muscles which control eye movement.

Astronaut Adaptation

Turning to the astronaut's problem of sensory-motor adaptation to the space environment, one may guess that on setting out to make a movement in his normal earthbound environment he formulates a motor program, as a result of which the EXPECTATION is:

- a particular magnitude, direction and speed of limb and/or body movement, and
- an anticipated set of afferent sensory signals which would be generated had that movement been successfully achieved as planned.

In zero-gravity space environment, not only is the actual movement for a given neuromuscular program going to be changed, but so also is the compatibility of the evoked sensory response, since the pattern of the sensory message itself will also be modified by absence of the gravitational acceleration vector, even had the movement occurred as intended. Presumably the CNS is then forced to work through a series of sucessive organization readjustments which might in their simplest form be conceived somewhat along the following lines: first there would be a mandatory call for changed associations between patterns of intended motor command and the actual patterns of efferent, or outgoing, neural discharge generated by that command. Then there would be a logical need for compatible readjustment in the meaningful interpretation of informational content in the resulting patterns of evoked sensory discharge. In turn there would presumably have to be habituative, or goal-directed, modification of requisite automotive "reflex" responses (*e.g.*, ocular stabilization) to those changed patterns of sensory discharge.

Seen from this viewpoint it is little wonder that on entering the space environment an astronaut is faced with a more or less traumatic experience of habituative adaptation. Indeed in this symposium such adaptation has been shown to carry a significant practical penalty sometimes manifest as a temporary reduction in acceptable work load, and even on several occasions overt "habituation" sickness, together with potentially serious accessory penalties of endogenous malaise with its subtle changes in motivation and the loss of appetite familiarly associated with ordinary "motion sickness".

Fortunately, after 7 to 10 days all Skylab personnel appear to have adapted well to the new environment, even to the point of becoming remarkably agile in the organization and management of their daily movements through the Skylab interior. Nevertheless, this very fact necessarily implies that some form of readaptation must occur on return to Earth.

Important questions then arise concerning the rate and nature of readaptation to the normal Earth environment. Certainly, immediately after return both postural equilibrium and locomotion are seriously impaired. At first it was felt that return to near normal was only a matter of a day or so. But quantitative tests of postural balance control showed that readaptation probably occurs along a similar time course to the initial adaptation after entering orbit, namely 7 to 10 days. It could be argued that the measured difficulty of balance was merely a manifestation of diminished strength in the leg muscles. However, although disuse atrophy of leg muscles was shown to occur, this could hardly have been the only source of disequilibrium, since with *eyes open* normal balance tended to be restored very quickly; it was only with eyes shut that prolonged postural inadequacy was revealed.

Numerous other observations, such as dizziness on shaking the head, occasional misjudgements of footing, difficulty in walking round corners *et cetera*, collectively seem to indicate that the CNS does not simply "click back" to its remembered regimen before takeoff. Rather the evidence, both objective and subjective, points to a progressive reorganization in the nervous system which has to "unravel" the adaptive changes incurred in space, probably by means of habituation mechanisms akin to those responsible for the original space adaptation. In the present author's view this conclusion is strongly supported by the very striking findings of Dr. Ashton Graybiel and his colleagues from the Human Vestibular Function tests of experiment M131. Controlled head movements performed on the earthbound rotating chair produces a characteristic onset of motion sickness even with eyes shut. This could be attributable to sensory conflict between the thoroughly misleading semicircular canal signals which then arise and other more normal non-visual sensory inputs such as activation of the vestibular otolith organs by the gravity vector and/or proprioception from the neck.

Of very great interest is the finding that on performing similar head movements with eyes shut during rotation on the orbiting Skylab turntable, subjects were essentially free of the expected signs and symptoms of motion sickness. Since the essential difference between the two conditions is absence of a fixed gravity vector in space, it could be argued from the above finding that the earthbound phenomenon with eyes shut is due specifically to internal conflict between canal and otolith components in the vestibular system, rather than other sensory sources such as neck proprioception.

From the data presented in this symposium an even more striking observation seems to have been temporary retention of immunity to head movements with eyes shut, performed on the turntable after return to Earth. Dr. Graybiel has cautiously reserved judgement on this apparent finding on account of changes in his planned schedules of tests imposed by such imperative factors as changed preflight schedules of the astronauts. Nonetheless, the evidence is sufficiently strong to persuade the present writer that the postflight immunity mentioned above will eventually prove to be real. In that case there would appear to be two alternative conclusions:

- the space environment generally reduced susceptibility to motion sickness, or
- central adaptive changes of the kind discussed above left the CNS temporarily unresponsive to otolith stimulation by the steady "g" vector.

The fact that some astronauts were made seasick shortly after splashdown into moderately rough sea would seem to contravene the first conclusion, leaving one with the view that the time course of return of normal motion sickness on the turntable represents some index of genuine habituative readaptation; in this case perhaps reacquisition of a meaningful sensory perception of the gravity vector through the otolith-mediated afferent neural signals.

The reader could reasonably detect an inconsistency in this argument, on the grounds that seasickness after splashdown would probably be attributable to periodic stimulation of the otolith organ (14). However, in this context, it is important to appreciate that *changing* linear accelerative stimulation of the otolith organ must continue to be experienced during head and body movements in the orbiting Skylab: but the *constant* gravitational field is nevertheless consistently absent in space. Perhaps in the context of these combined observations we may be seeing additional evidence in favour of an earlier suggestion of Mayne (15) that otolith neural responses to changing accelerations and the steady acceleration of gravity may be informationally separated by "high-pass and "low-pass" filtering respectively in the CNS; as indeed is the case in some forms of man-made inertial guidance. In this case it would be easy to reinforce the earlier conclusion (*i.e.*, CNS temporarily unresponsive to otolith stimulation by the steady "g"-vector) that one form of adaptive change in space would amount to a "learned" ability to disregard the presence of those neural signals carrying information about a constant "g" vector. Such a conclusion would not be out of line with the observed difficulties of postural control after return to Earth, recovery from which would appear to run an almost parallel time course with the return of normal motion sickness induction during eyes-closed head movements on the turntable.

Of course these views on basic mechanisms must be treated as highly speculative. Still, without speculation there would be little chance of progress in subsequent experimental designs having more applied objectives.

Applied Considerations

Bearing in mind the relative imminence of Space Shuttle we should perhaps consider first any relevant implications to that program from this symposium. In the context of the present article a prime question must surely be: Could adaptive phenomena of the kind discussed above prejudice "fly-home" of a Space-adapted Shuttle pilot? Of course it may well turn out that continued maintenance of a high standard of training in the use of instrument aids will suffice to offset any unexpected disorienting factors; as indeed has proved to be true in most circumstances encountered in conventional instrument flight. However,

although one may hope for this we have to face the fact that for reasons discussed above it seems that Skylab adaptation was uniformly associated with a new form of more or less profound reorganization of the body's orienting mechanisms. It would therefore seem negligent to disregard the problem. Unfortunately the paucity of intervening space flights leaves little opportunity for full interrogation of this question. Nevertheless the very serious consequences of an adverse outcome encourages the urgent design and development of a suitable battery of experimental tests for inclusion in the forthcoming Apollo-Soyuz mission, despite the potentially limited space-adaptation offered by its short duration and relatively small internal volume of the combined vehicle. Indeed perhaps the practical urgency of the matter warrants the additional inclusion of a "try and see" approach in which the returning Apollo astronaut is immediately exposed to dual-control real instrument flight in a familiar high-performance aircraft.

A second feature bearing directly on the Shuttle program is the protracted period of space sickness malaise and loss of appetite encountered by a sizeable proportion of Skylab astronauts. Bearing in mind the short duration of the average Shuttle mission, it seems inevitable that effectively novice personnel engaged in research or other activities will be penalised by reduced work potential unless some form of successful preconditioning regimen is discovered. The difficulty of doing so has been highlighted in this Skylab symposium by the notable lack of correlation between space sickness and both personal motion sickness histories and immediately preflight habituation measures. Even pharmacological therapeutic measures did not always suffice. Consequently there would seem to be an urgent need to search for effective means both of of selecting suitable personnel and for their preconditioning and/or therapeutic treatment.

Preconditioning

Presumably the major source of space sickness must be directly related to the sudden absence of gravity, with the somewhat uncertain implication that changed patterns of vestibular otolith stimulation may offer the most likely source of disturbing afferent signals concerned with generating space sickness. It is true that other afferent sources such as kinaesthesia and muscle proprioception will also be affected by zero-"g". But such evidence as has been discussed above in connection with experiment M-131 does not encourage the view that these alone can provoke space sickness. Furthermore the habituation associated with readjustment of motor-eye coordination due to simple angular displacement of the visual scene is not apparently associated with vegetative symptoms of "motion sickness" (16).

Perhaps a fruitful approach might be to explore the possibility of employing strictly linear oscillatory stimuli in a low frequency range known to be highly provocative of motion sickness (14, 17). Probably motion should be constrained in the vertical direction to avoid directional changes in the resultant acceleration due to vectorial summation with gravity.

A further point to bear in mind is the potential need for prehabituation to a high gravity environment after long periods in space, as for example when landing on Mars. It would seem advisable in any case to search for means by which an astronaut in space might not only maintain his leg muscle mass, but also exercise his postural equilibrium systems. One might for example envisage bodily control, perhaps even through the legs and feet, of a suitably unstable mechanical device simulating the normally standing man.

Otolith Dynamics

On a long-term basis, it would seem important to learn more about the basic dynamic response characteristics of the vestibular otolith organs. After many years of research, corresponding response characteristics of the semicircular canals have become well understood and this knowledge permits accurate prediction of boundries encompassing movement profiles beyond which they feed misleading information to the brain (18). However, much less is known about the mechanical and neural dynamic response of the otolith organs (19,20,21) and there is an obvious need to make good this deficiency by insightful combinations of human and neurophysiological animal experimentation.

Habituation

Although some of the adaptive phenomena referred to as habituation have been extensively studied (22,23,24) the nature of the processes involved are yet far from understood. For example it has been customary in the past to consider the habituation process as essentially an attenuating one, whereby repetitive stimuli progressively cause less effect in the CNS. However, it is now clear that this is too simple a concept. For example in animal experiments it has been shown that after unilateral labyrinthectomy the spontaneous activity of ipsilateral second order vestibular neurones falls drastically, probably causing the resulting persistent ocular nystagmus. But as the animal adapts (habituates) to the point of relatively normal behaviour (no spontaneous nystagmus), so the spontaneous activity of those neurones rises again to normal. The functional advantage of this is that they can then be adequately driven by inhibitory commisural connections from the normal, contralateral, vestibular system (25). Again, we have already seen that

optical reversal of vision in the adult human subject leads progressively to active reversal of the involuntary vestibulo-ocular reflex, rather than its mere passive attenuation to zero gain (9, 10). It now appears from a number of difficult sources that not only can visual afferent signals from the retina influence vestibular afferent activity in both excitatory and inhibitory ways (11,12,26,27) but furthermore vestibular afferents can similarly modify the activity of visually evoked responses in the tectum of the mid-brain. Evidently there are multitudinous ways in which intersensory, and sensory-motor interactions can bring about change in the adult central nervous system. One must presume that eventually the rational use of these powerful adaptive facilities for our own ends must depend upon basic knowledge of their mechanisms and functional capabilities. In particular, it would seem important to learn how to define the physiological goals towards which one may wish the habituative change to be driven, since as already emphasized it appears that the habituation mechanism characteristically acts in the manner of a goal-seeking process (9).

Postural Equilibrium

A clear-cut feature of return to Earth is the transient postural disequilibrium already discussed in other contexts above. Thus the combined outcome of experiment M-131 and the "rail" tests of postural equilibrium suggest to this author that more profound adaptive changes are at play than mere deconditioning of postural muscles. However, the detailed nature of such change is by no means clear and since the matter has both basic and applied implications further experimental investigation would seem to be called for.

First, with the background supplied by M-131, advisably carried out in Skylab without vision, it would be of great interest to employ the same methodology to further explore the role of vision. Even in space, the cross-coupling canal "errors" introduced by head movement in the rotating chair would presumably drive the oculomotor system according to those "erroneous" canal signal. Consequently with eyes open the retinal image of the workshop interior would then be destabilized, very much as on Earth. Would the added sensory conflict from vision restore the otherwise absence of motion sickness?

Next, one could envisage development of the postural equilibrium test, using a servo controlled "postural" platform to make quantitative assessment of both normal static control of equilibrium and the postural response to unexpected perturbations. Furthermore, following the example developed in Dr. L. R. Young's Man-Vehicle Laboratory, M.I.T., it should be possible to extend the use of such a system to interrogate the component part played by changes of proprioceptive muscle feedback in the post-return postural disequilibrium (28).

Indeed the versatility of this general approach has been further developed, using galvanic stimuli to generate artificial vestibular stimulation. Thus a particular galvanic stimulus causes a sensation of head yawing, say, to the left, due presumably to preferential stimulation of the horizontal semicircular canals. Moving the head onto the left shoulder carries this sensation with it, so that the subject now feels he is "tilting" forwards. A quickly acting backward tilting reflex response can then be demonstrated in postural muscles acting on the ankle joint. If the head is then moved onto the right shoulder, the *same* electrical stimulus to the vestibular system generates a *sensation* of tilting backwards, because the planes of the relevant canals have then been turned through 180 degrees. The corresponding reflex response in the limb muscles is then appropriately *reversed*, despite the *unchanged* nature of the peripheral vestibular stimulus (29). Evidently in the Earth-adapted subject, vestibulospinal responses are automatically adjusted for maintenance of postural equilibrium according to the instantaneous attitude of the head (*i.e.*, the vestibular system) relative to the body. Would this versatile flexibility of basic vestibulospinal postural reflexes disappear in the space-adapted subject? And if so what time course would be taken by their reappearance during readaptation on Earth?

Concluding Remarks

The extensive Life Sciences program in Skylab has revealed that the zero-gravity environment of space induces a wide range of adaptive changes extending throughout the biological systems of the body. The detailed physiology behind some of these changes has been clearly defined for the first time by experiments described in this symposium. Other ingenious experiments have demonstrated adaptive changes which raise more questions than they answer, leading to a continuing challenge for further research.

However, taking an overview of the program as a whole, two outstanding features have emerged. First, Man can adapt to, and live in, the zero-gravity space environment for extended periods of time. But second, and therefore above all, none of the measured changes so far seen in missions extending up to 84 days have proved irreversible after return to Earth.

Nevertheless, these two salient and rewarding conclusions leave no room for complacency since this symposium has raised a wide range of new and varied problems needing urgent solutions. If the high quality of research reported during these past three days has anything to say for the future, we may indeed hope that these new problems will be tackled with equal energy and imagination.

REFERENCES

1. Evarts, E. V., *et al.* January 1971. Central control of movement. *Neurosciences Res. Bul.*, Vol. 9, No. 1.

2. Melvill Jones, G. and D. G. D. Watt. 1971. Observations on the control of hopping and stepping movements in Man. *J. Physiol.*, 219: 709-727.

3. Adkins, R. J., R. W. Morse and A. L. Towe. 1966. Control of somatosensory input by cerebral cortex. *Science*, 153: 1020-1022.

4. Matthews, P. B. C. 1972. Mammalian muscle receptors and their central actions. Edward Arnold Ltd., London, England.

5. Evarts, E. V. 1973. Motor cortex reflexes associated with learned movements. *Science*, 179: 501-503.

6. Rosén, I. and M. Asanuma. 1972. Peripheral afferent inputs to the forelimb area of the monkey cortex: input-output relations. *Exp. Brain Res.*, 14: 257-273.

7. Evarts, E. V. and J. Tanji. 1974. Gating of motor cortex reflexes by prior instruction. *Brain Res.*, 71: 479-494.

8. Klinke, R. 1970. Efferent influence on the vestibular organ during active movements of the body. *Pflugers Arch. ges. Physiol.*, 318:325-332.

9. Melvill Jones, G. and A. Gonshor. Goal-directed flexibility in the vestibulo-ocular reflex arc. Proceedings of Symposium on Basic Mechanisms of Ocular Motility and Their Clinical Implications. Stockholm, June, 1974.

10. Gonshor, A. and G. Melvill Jones. Plasticity in the vestibulo-ocular reflex arc revealed by long-term prism-reversal of vision during natural head movement. Submitted to press, 1974.

11. Maekawa, K. and J. I. Simpson. 1973. Climbing fibre responses evoked in the vestibulo-cerebellum of rabbit from the visual system. *J. Neurophysiol.*, 36: 649-665.

12. Ito, M., T. Shiida, N. Yagi, and M. Yamamoto. 1974. Visual influence on rabbit horizontal vestibulo-ocular reflex presumably effected via the cerebellar flocculus. *Brain Res.* 65: 170-174.

13. Robinson, D. Physiology and control aspects of supranuclear oculomotor systems. Proceedings of Symposium on Basic Mechanisms of Ocular Motility and Their Clinical Implications. Stockholm, June, 1974.

14. Money, K. E. 1970. Motion sickness. *Physiol. Rev.*, 50:1-39.

15. Mayne, R. 1974. The vestibule as an inertial sensing system. In "Handbook of Sensory Physiology" Vol. VI. Ed. Kornhuber, H.H., Bergmann-Verlag, Munich, Germany.

16. Howard, I. P. and W. B. Templeton. 1966. Human Spatial Orientation. Chapter 15. Wiley, New York, N.Y.

17. Melvill Jones, G. Human subjective and reflex responses to sinusoidal vertical acceleration. Progress Report NASA Ames Research Center, September, 1973.

18. Melvill Jones, G. 1972. Transfer function of labyrinthine volleys through the vestibular nuclei. *Progress in Brain Res.*, 37: 139-156.

19. Young, L. R. 1969. The current status of vestibular system models. *Automatica*, 5: 369-383.

20. Melvill Jones, G. and J. H. Milsum. 1969. Neural response of the vestibular system to oscillatory translational acceleration. Systems analysis in neurophysiology. Brainerd pp 8-20.

21. Melvill Jones, G. and N. Daunton. Comparison of brainstem neural responses to vertical and horizontal linear accelerations. Progress Report NASA Ames Research Center, Septmeber, 1973.

22. Guedry, F. E. 1965. Psychophysiological studies of vestibular function. In "Contributions to sensory physiology" Vol. 1, 63-135. Ed. Neff, W.D. Academic Press, New York, and London, England.

23. Guedry, F. E. 1974. Psychophysics of vestibular sensation. In "Handbook of Sensory Physiology", Vol. VI. Ed. Kornhuber, H. H., Bergmann-Verlag, Munich, Germany.

24. Collins, W. E. 1974. Habituation of vestibular responses with and without vestibular stimulation. In "Handbook of Sensory Physiology", Vol. VI, Ed. Kornhuber, H.H., Bergmann-Verlag, Munich, Germany.

25. Precht, W., H. Shimazu and C. H. Markham. 1966. A mechanism of central compensation of vestibular function following hemilabyrinthectomy. *J. Neurophysiol.* 29: 996-1010.

26. Dichgans, J. and Th. Brandt. 1972. Visual-vestibular interactions and motor perception. In "Cerebral control of eye movements and motion perception". Bibl. Ophthal. 82: 327-338. S. Karger, Basel, Switzerland.

27. Henn, V., L. R. Young and C. Finley. 1974. Vestibular nucleus units in alert monkeys are also influenced by moving visual fields. *Brain Res.* 71: 144-149.

28. Nashner, L. M. Sensory feedback in human posture control. Sc.D. Thesis, Man-Vehicle Laboratory, Center for Space Research, M.I.T., Rep. MVT-70-3, 1970.

29. Nashner, L. M. and P. Wolfson. Influence of head position and proprioceptive cue on short latency postural reflexes evoked by galvanic stimulation of the human labyrinth. *Brain Res.* In press, 1974.

VOLUME I
AUTHORS INDEX

VOLUME II

AUTHORS/PANELISTS INDEX