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BIOCHEMICAL RESPONSES OF THE SKYLAB CREWMEN

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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

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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*	Potassium	Chloride	Creatinine	Glucose	Osmolality	Calcium	Phosphate
		meq/liter	meq/liter	meq/liter	mg pct	mg pct	mOsmoles	mg pct	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 stimutating 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 1-28	IN-FLIGHT DAYS 29-59	IN-FLIGHT DAYS 60-85	POSTFLIGHT DAYS 1-6	POSTFLIGHT DAYS 7-13	POSTFLIGHT DAYS 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

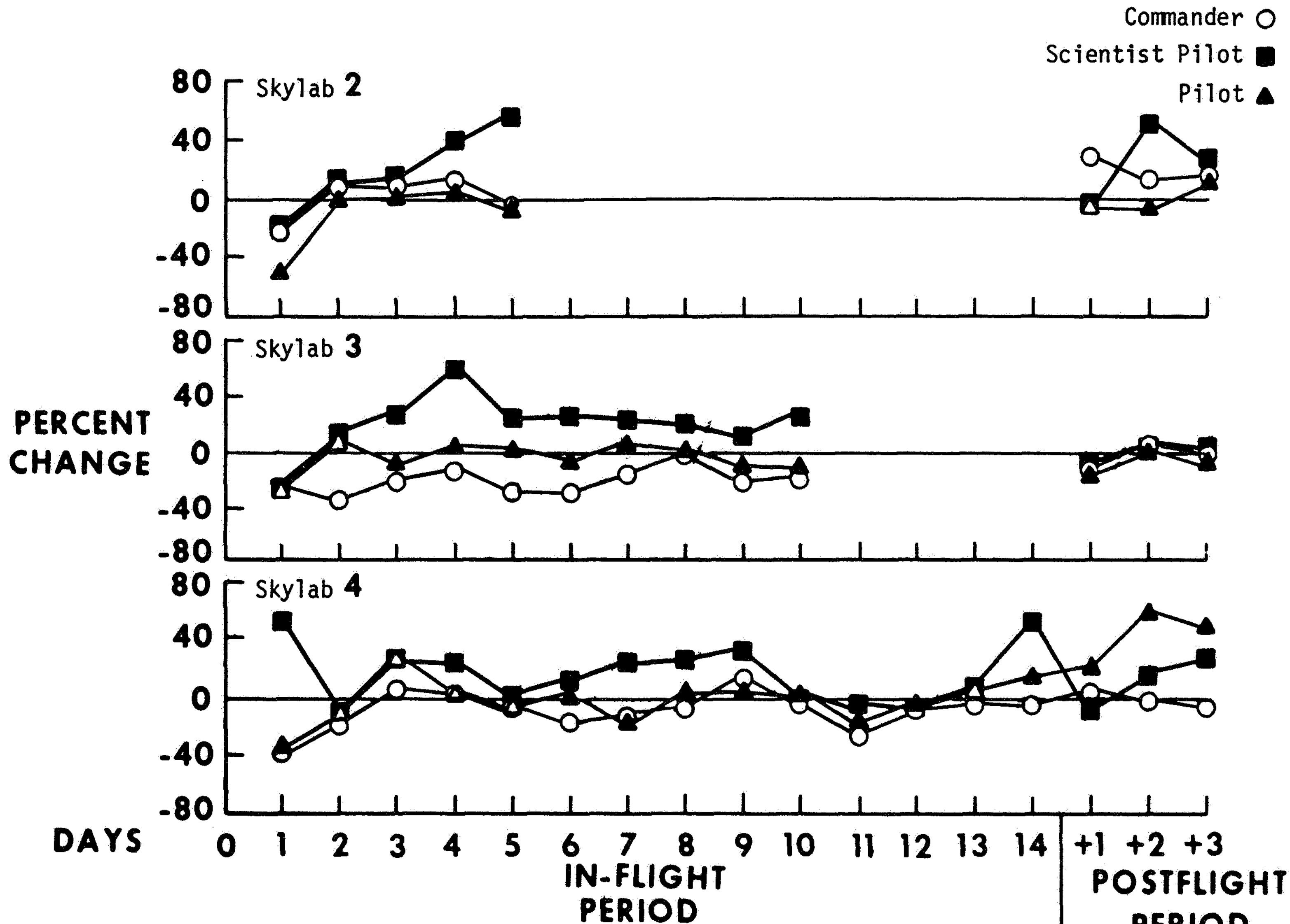

Figure 1. Urine volume excretion.

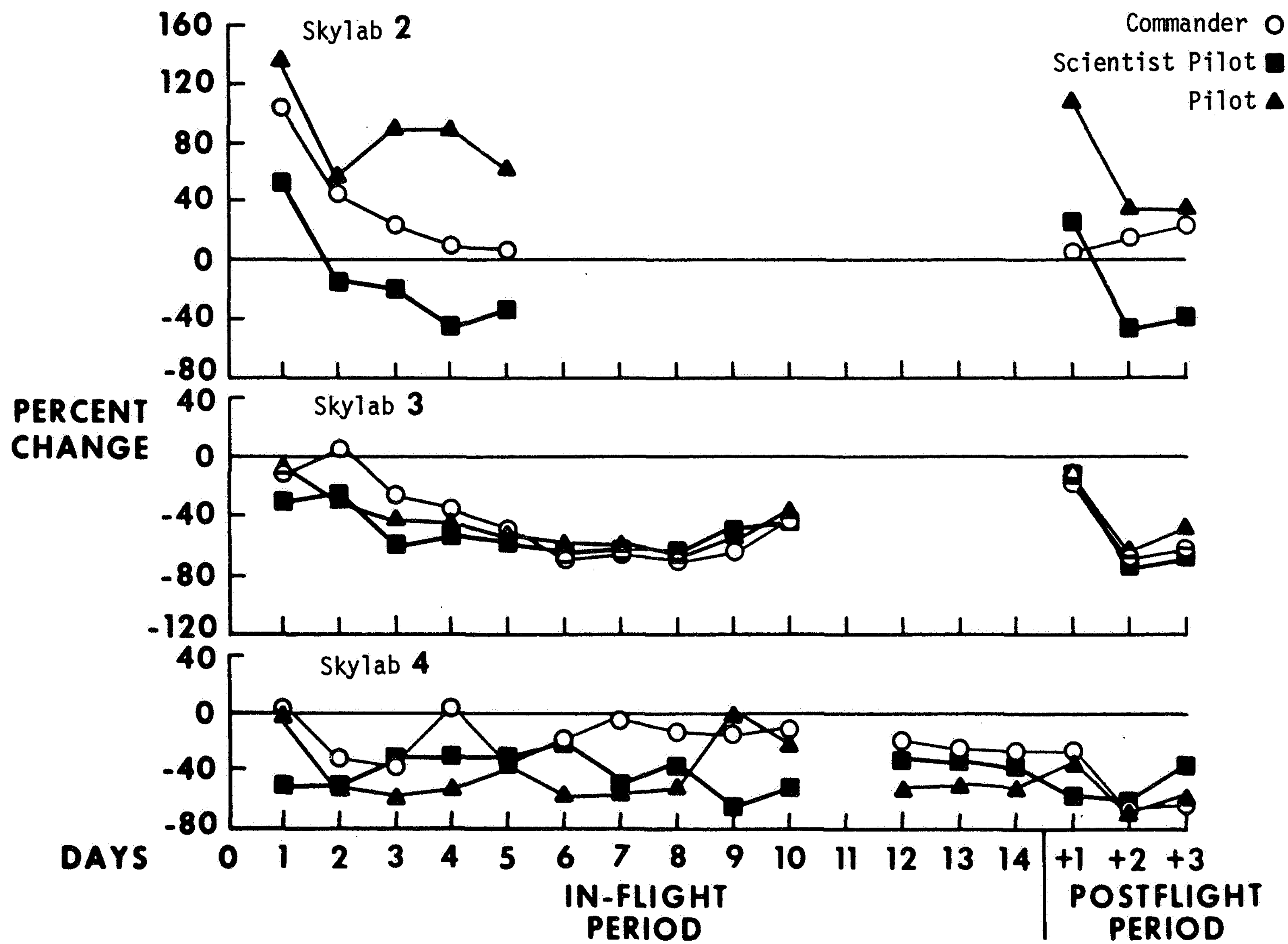

Figure 2. Urinary antidiuretic hormone excretion.

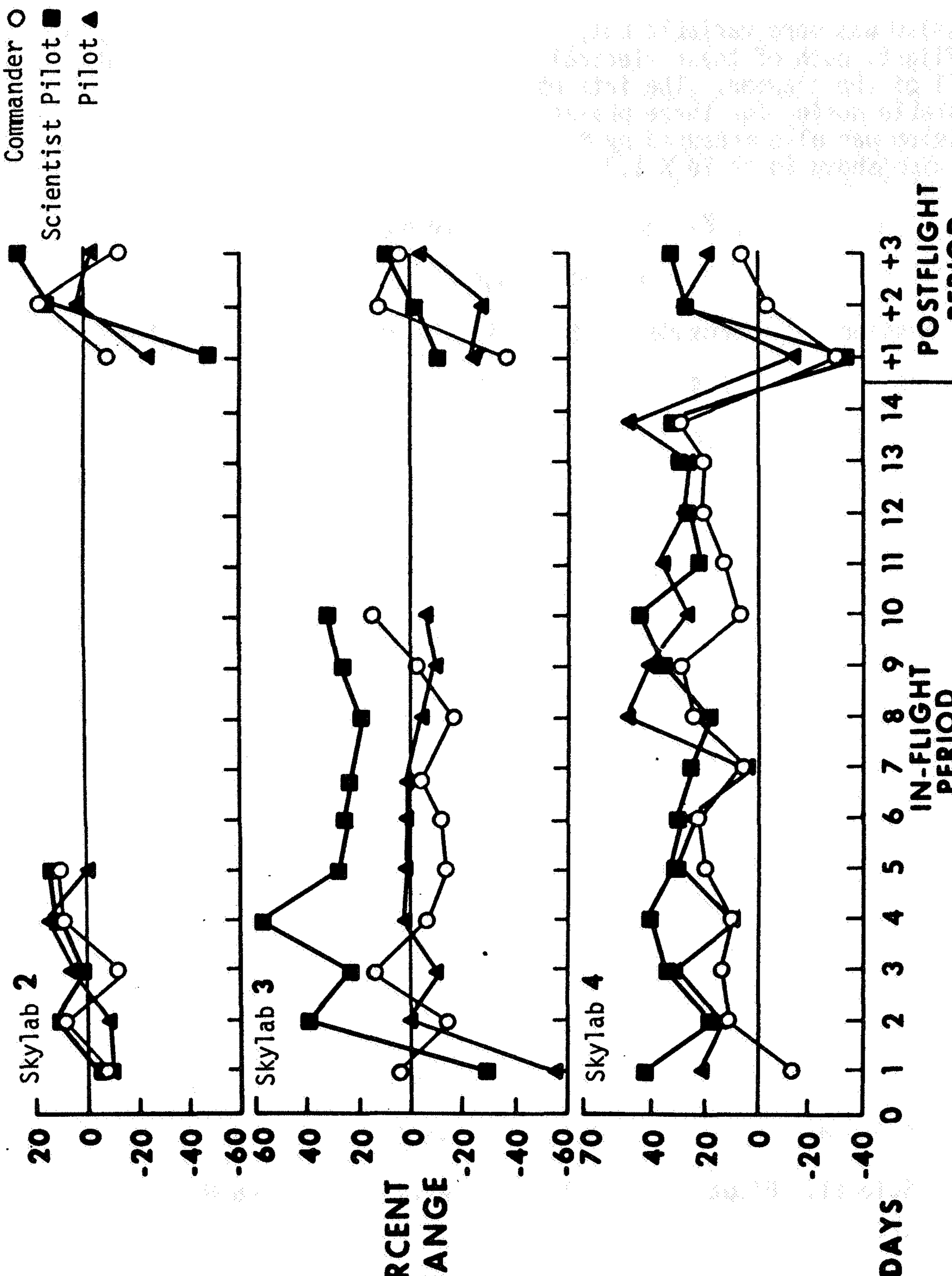

Figure 3. Urinary sodium excretion.

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

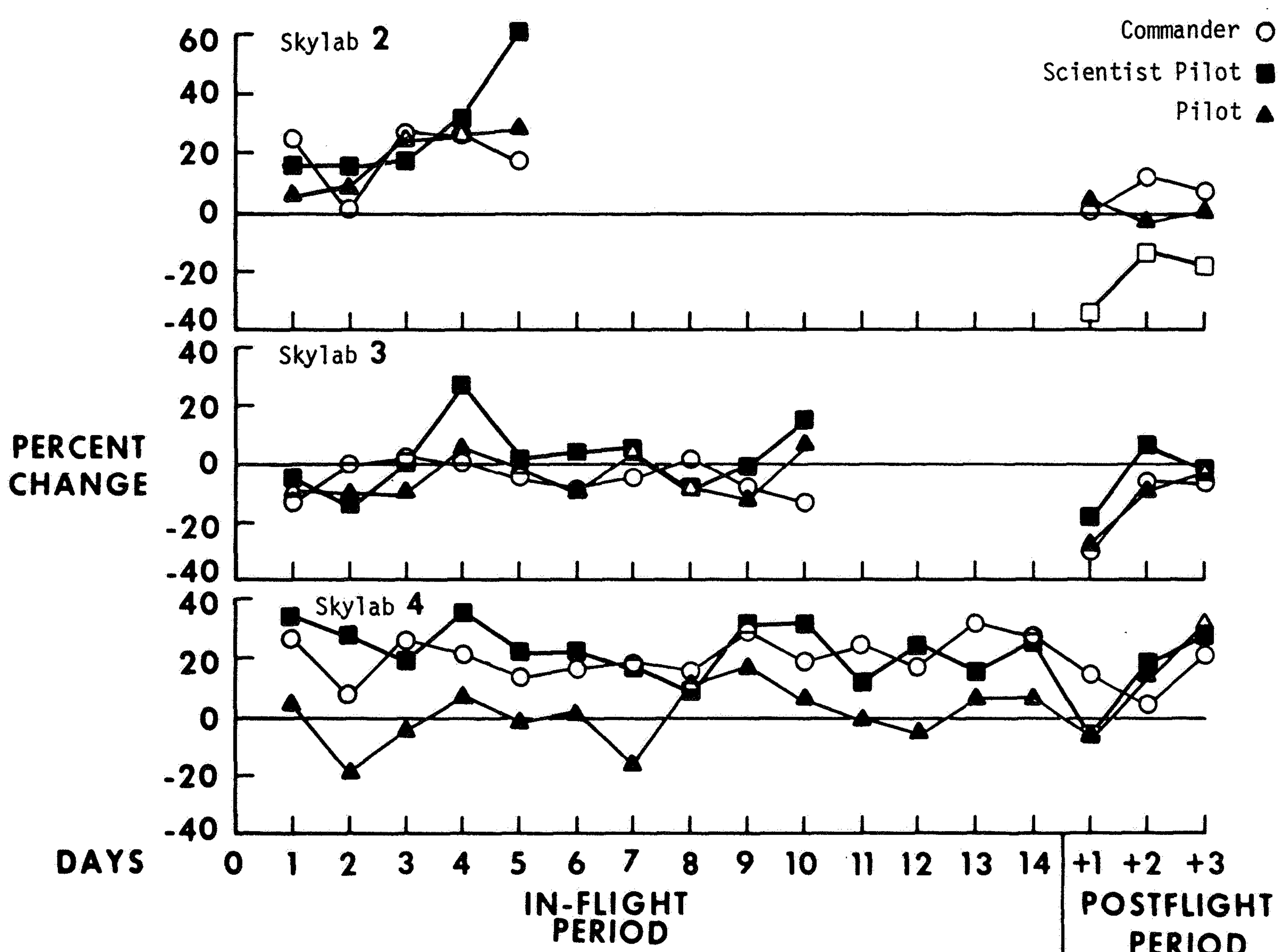

Figure 4. Urinary potassium excretion.

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

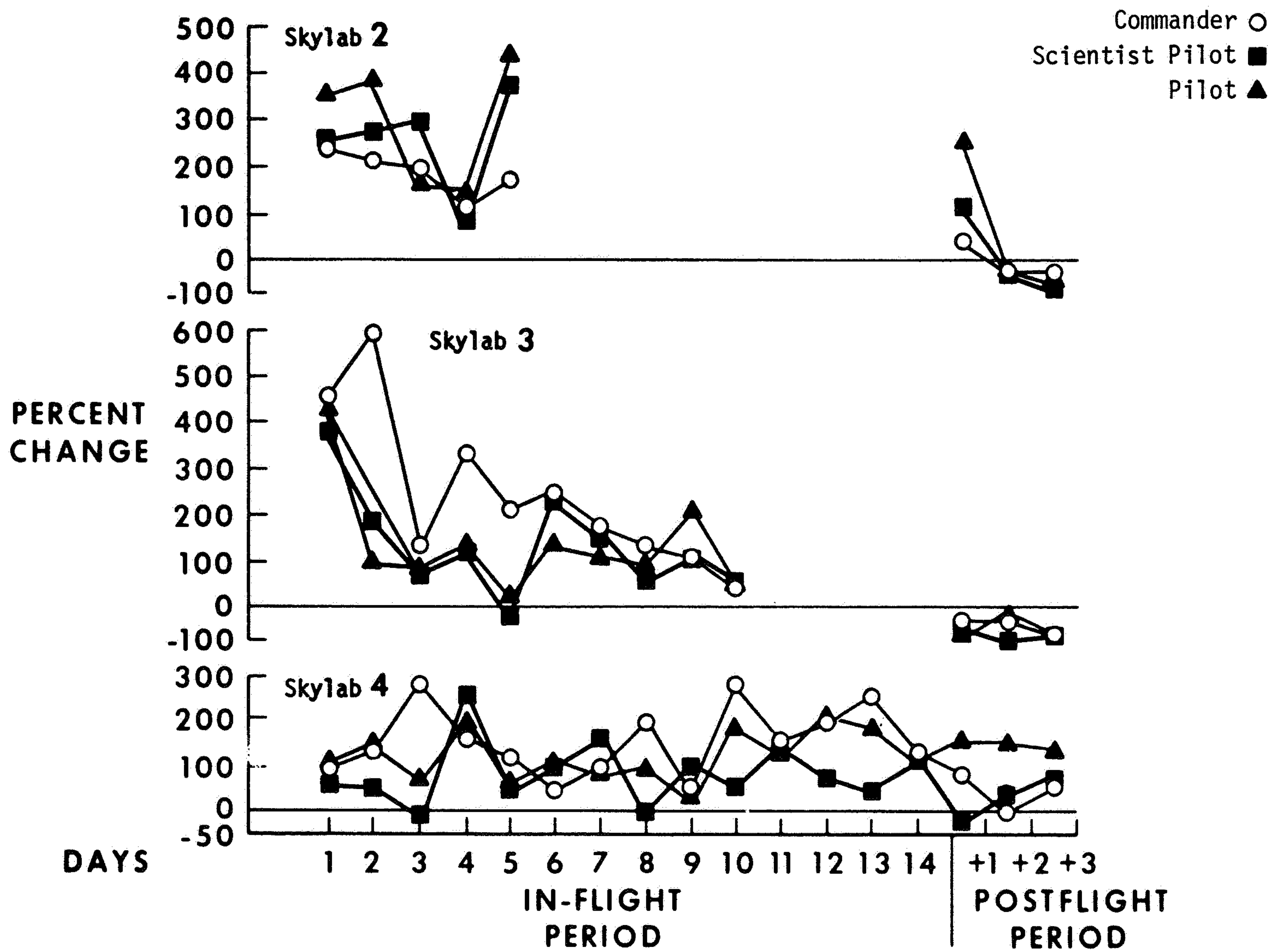

Figure 5. Urinary aldosterone.

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 pre-flight 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

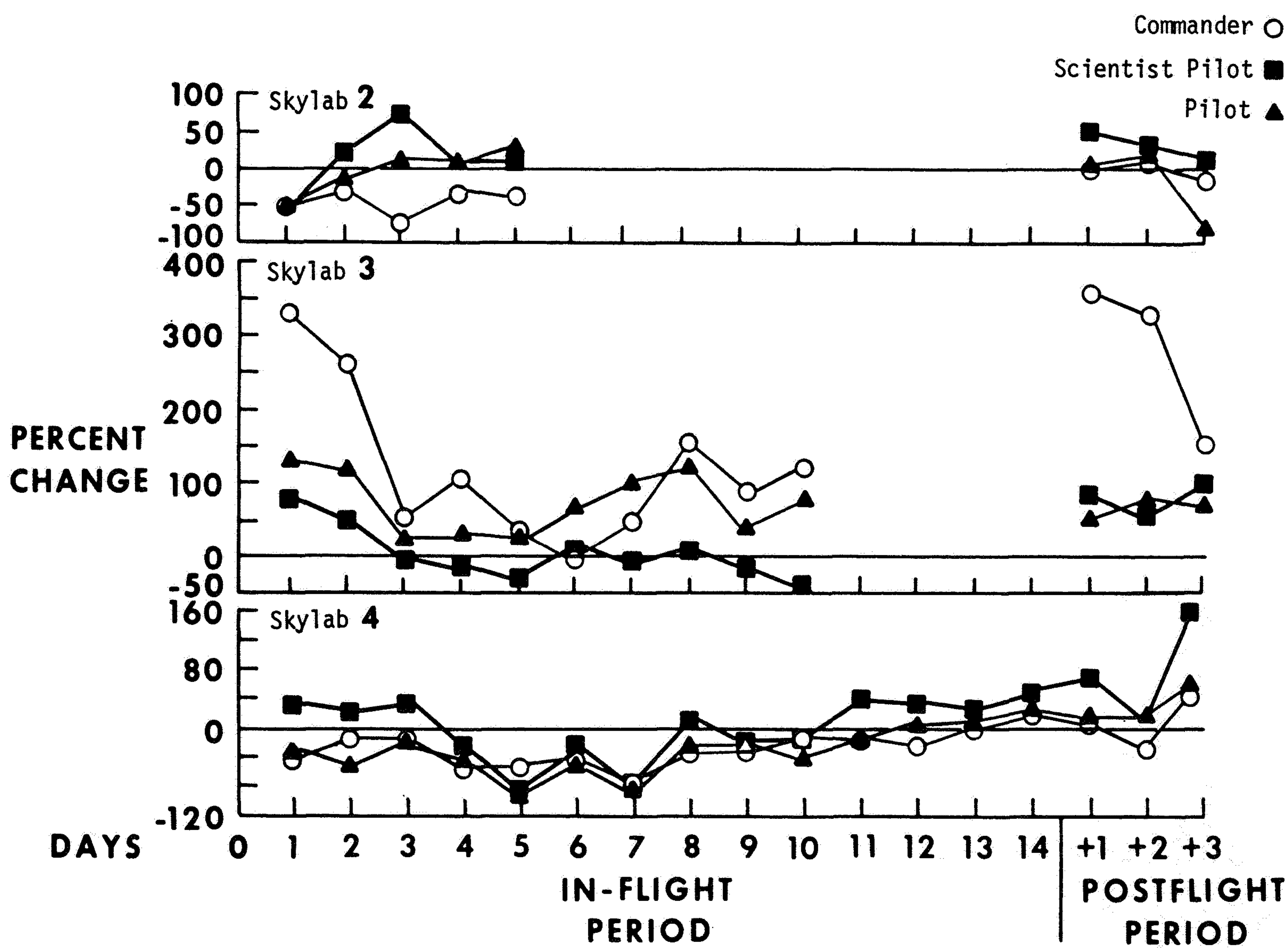

Figure 6. Urinary epinephrine.

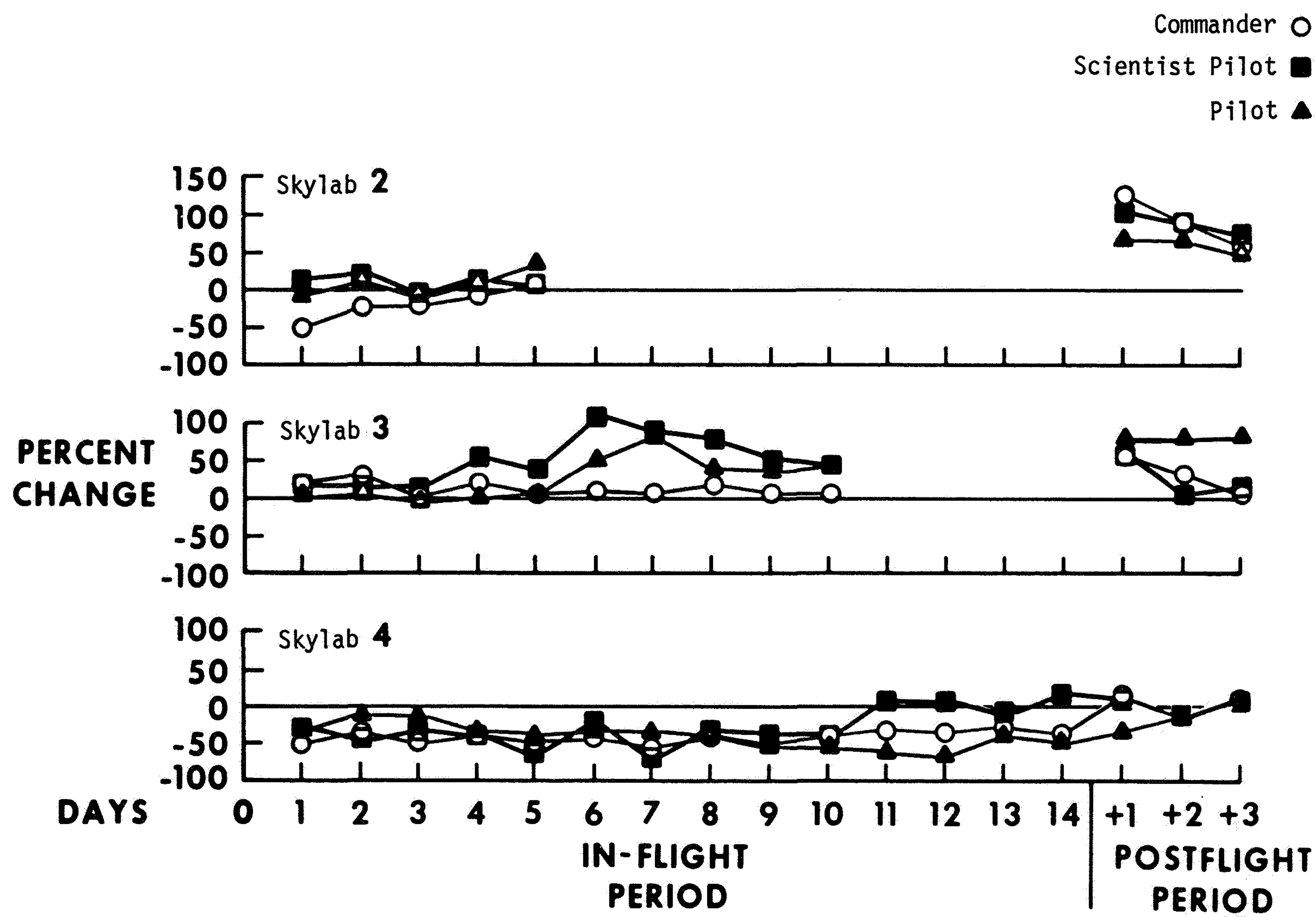

Figure 7. Urinary norepinephrine.

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-hydroxycorticosteroids 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 tetrahydrocortisone 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).

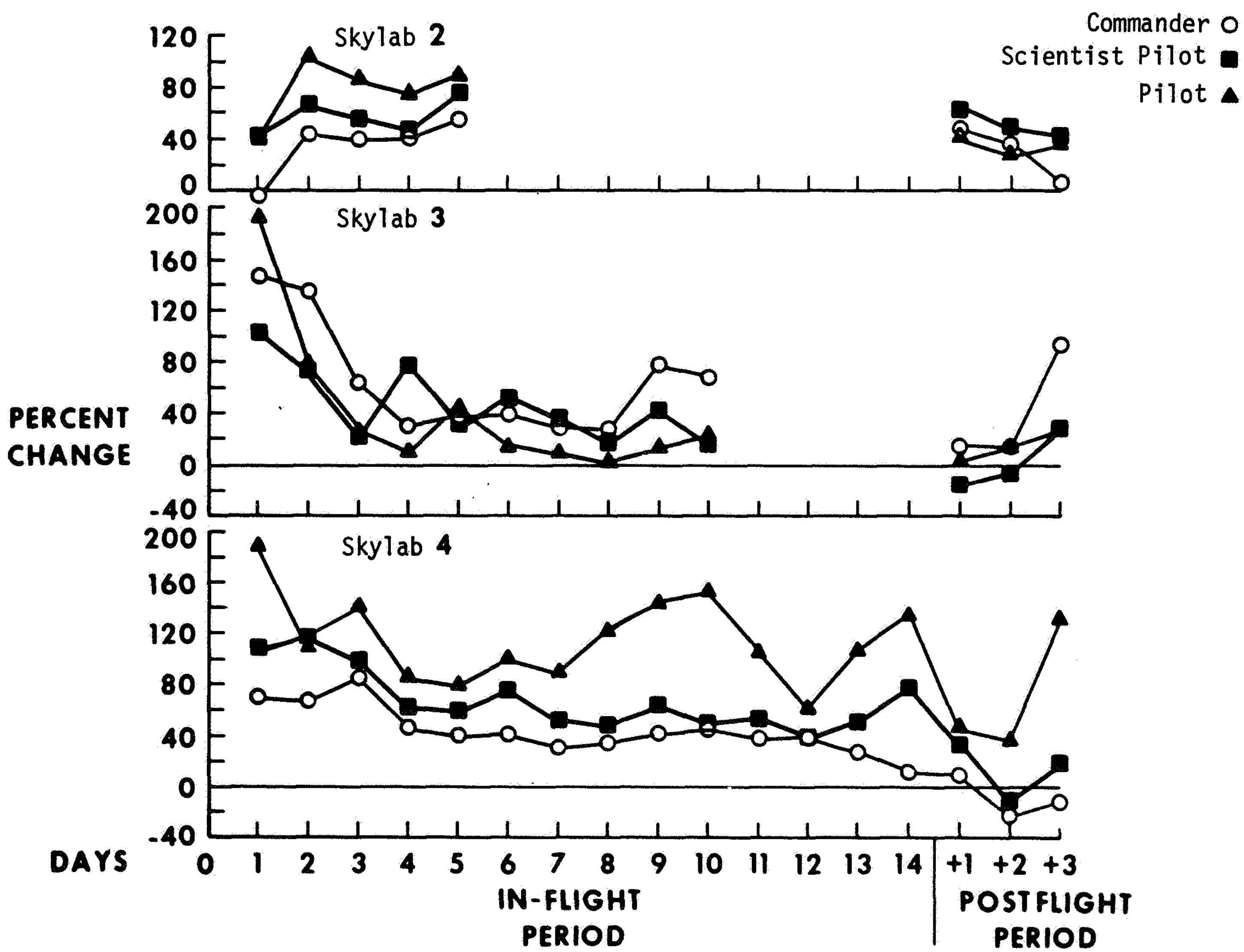

Figure 8. Urinary cortisol.

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).

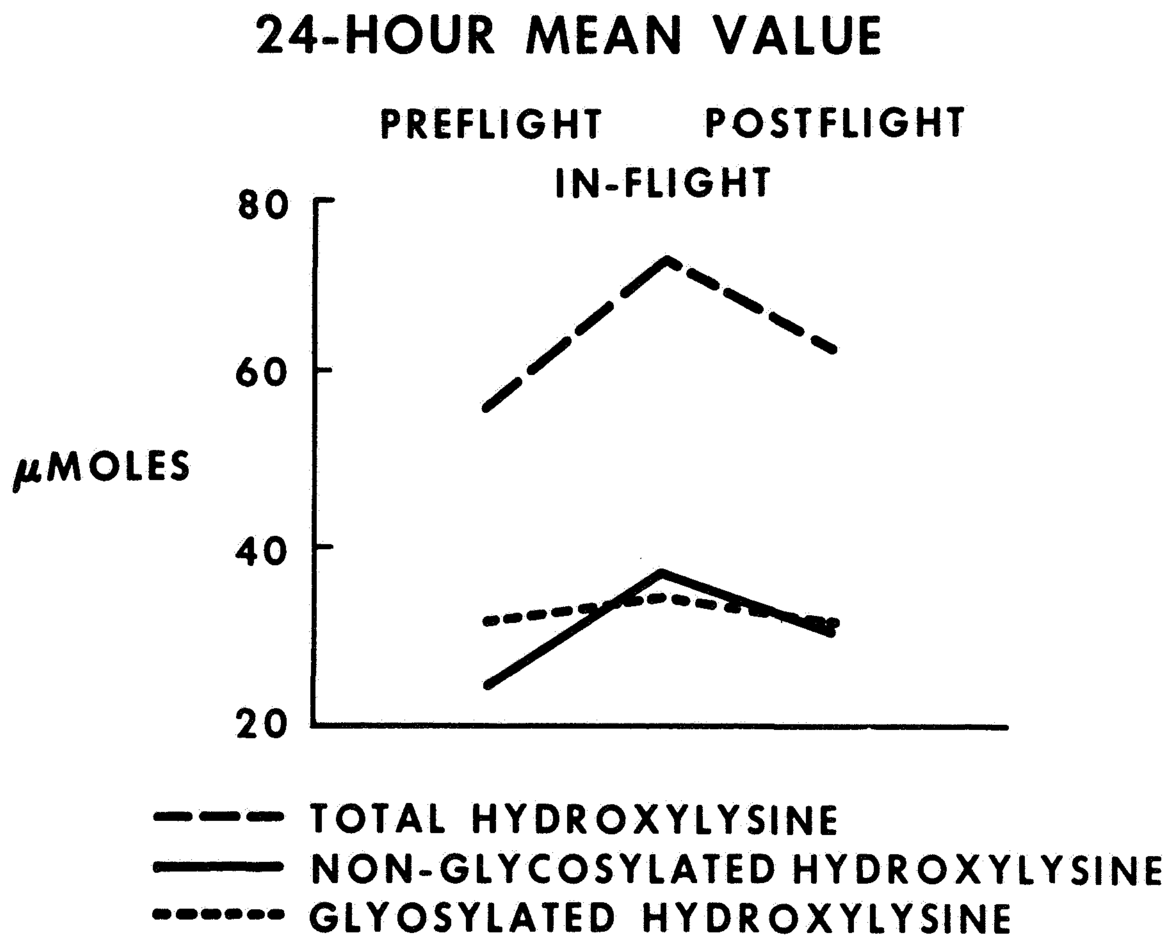

Figure 9. Urinary excretion of hydroxylysine and its glycosides (Skylab 4).

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.

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