CHAPTER 2
CLINICAL BIOCHEMISTRY

by

W.C. Alexander, Ph.D.
Carolyn S. Leach, Ph.D.
Craig L. Fischer, M.D.*

Lyndon B. Johnson Space Center

Introduction

An extensive group of biochemical tests was instituted in support of the Apollo Program. These tests were conducted for each flight by the Clinical Laboratories of the Lyndon B. Johnson Space Center (JSC), and gave investigators their first documentation of the normal biochemistry of the astronauts who flew the Apollo missions. The results were especially meaningful since comparable data were not consistently available from the Mercury and Gemini Programs. The biochemical studies significantly increased the understanding of man's adaptation to the spaceflight environment and of the resultant physiological cost of spaceflight.

The biochemical evaluation of the Apollo crewmen was designed to document the physical qualification of the invididual for each mission and to detect problems which might require remedial or preventive action. Accordingly, the primary purpose of the laboratories during the Apollo missions was to support the crew by providing clinical biochemical and immuno-hematology data to the flight surgeon for evaluations of pre- and postflight health status. The chemical measurements of various blood and urine constituents were one portion of a comprehensive medical examination intended to disclose a state of well-being or the presence of occult disease processes. The biochemical studies furnished data which, when integrated with the facts obtained from a complete history and physical examination, permitted an objective assessment of crew physical status.

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*Now at Eisenhower Medical Center.

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The second objective of the biochemical studies was to elucidate and describe the physiological changes attributable to the spaceflight environment. Continued examination over extended periods of time established normal ranges for the astronaut population. The significance of subtle biochemical changes and the relationship of these changes to the influence of the spaceflight environment were thereby assessed.

Procedures

Blood Sample Collection

The preflight samples of blood were acquired depending on the location of the crew. Normally the serum, acquired at Johnson Space Center, or Kennedy Space Center was frozen immediately and transported to the JSC Clinical Laboratories for analysis. The immediate postflight samples were acquired on the Prime Recovery Ship, stabilized and returned to JSC for analysis. In both instances time critical analyses were performed prior to freezing in remote site laboratories.

The biochemical studies in Apollo varied somewhat between missions depending on overall mission objectives. In general, Apollo missions 7, 8, 9, and 10 were supported in the same manner, except that the number of 24-hour urine collections increased as the importance of these data became more evident. Apollo missions 11, 12, and 14 were characterized by a postflight quarantine and therefore received similar laboratory emphasis. Apollo missions 15, 16, and 17 were supported with an expanded protocol characterized by an increasing number of biochemical studies. The general methods included the withdrawal of 20 ml of venous whole blood at least three times, approximately thirty, fifteen, and five days before each mission. Similar amounts of blood were withdrawn within two hours after recovery, one day, six days, and thirteen days later. Fasting blood samples were obtained with the crewman recumbent and at approximately the same time each day except for the sample immediately after splashdown. The crews' intake of food and water prior to splashdown was varied, and operational considerations dictated the actual time and place of recovery.

Urine Sample Collection

Twenty-four hour urine samples were collected on each crewman beginning with Apollo 8 and coincident with each blood collection. The urine was aliquoted, stabilized, and frozen for transport to the JSC for subsequent analysis.

Overall Procedural Plan

The crews generally consumed a conventional diet during the pre- and postflight periods and Apollo flight food throughout the mission. Fluids were available *ad libitum* during all phases. In order to evaluate the data obtained, certain information from the clinical history of each crewman was required. This information included medication history one month prior to, during, and postflight; radiation; exposure to toxic products, if known; and description of the pertinent history and physical examination findings. Approximate dietary intake, and the amount and time of any alcohol consumption were also noted. The biochemistry program was judged successful based on the criteria that the

samples were obtained at the appropriate time and in the amount specified, and were processed and delivered to the laboratory in specified conditions.

Ground-based control subjects participated in the same procedural plan used for the flight crew evaluations. Before each mission, three men in good health and in approximately the same physical conditions as the crewmen were selected as control subjects. The goal of the ground-control program was to supply controls for the hematology evaluation and to predict any complex interactions with other phases of the preflight and postflight evaluation protocols. These individuals were utilized also for each mission to prevent misinterpretation of data due to sample preparation or artifacts resulting from sample manipulation and transport from remote site laboratories to the JSC facility for processing. The controls demonstrated that neither the blood sampling nor transport had any demonstrable effect on the measured parameters.

In addition, each crewman served as his own control, with the preflight period as baseline. The backup crew assigned to each flight participated in the biochemical evaluations to the same degree as the prime crew in the preflight interval. These data, provided no member of the backup crew actually flew, were used as adjunctive control data for comparative purposes.

The clinical biochemical methods were selected specifically for a given determination utilizing minimal sample volume. Standard biochemical laboratory techniques were used (table 1). Whenever possible, an aliquot of serum was frozen and stored for subsequent or retrospective analysis. The data were subjected to statistical analysis. The mean of preflight data (three crewmen, three sample dates) was obtained and the standard deviation of the mean calculated. The mean value of the postflight data (three crewmen, one sample date), the standard deviation, and the percent deviation from the preflight level were recorded. The results were submitted to student's paired t test (Snedecor, 1956). Annual comprehensive biochemical examinations were conducted also on the entire group of individuals selected for the astronaut program. The normative values for the astronaut population are defined in table 2.

Results

A summary of serum biochemical measurements from all Apollo crewmen is presented in table 3. There are no values which are out of normal range established for the astronaut population for the variables considered. However, when postflight values were compared with preflight levels, significant changes were found, as listed in table 4. This comparison described consistent and significant decreases in potassium, magnesium, lactic dehydrogenase (LDH), creatine phosphokinase (CPK), albumin, uric acid, triglycerides and cholesterol. Increases were described in creatinine, total protein, blood urea nitrogen (BUN), and glucose.

The 24-hour urine results are shown in table 5. Since the diet consumed in the pre- and postflight phases was not controlled, there was variation between means which resulted in large standard deviations; however, significant changes did occur, as shown in table 6. Significant postflight increases were measured in specific gravity and osmolality. Decreases were measured in the 24-hour urine volume, and in the 24-hour excretion of sodium, potassium, chloride, magnesium, and uric acid.

Table 1

Apollo Biochemical Laboratory Techniques

Serum Chemistries		
Constituent	Unitage	Method
Sodium	mEq/L	Flame photometry (Henry)
Osmolality	milliosmols	Freezing point depression (Gambino)
Cholesterol	mg%	AutoAnalyser (Lieberman-Burchard)
Triglycerides	mg%	AutoAnalyser (Kessler & Lederer)
Magnesium	mg%	Atomic absorption (Willis)
Glucose	mg%	AutoAnalyser (Ferrocyanide reduction)
Inorganic phosphate	mg%	AutoAnalyser (Fiske & Subbarow)
Potassium	mEq/L	Flame photometry (Willis)
Chloride	mEq/L	Titration (Buchler-Cotlove)
Total bilirubin	mg%	AutoAnalyser (Jendrassic)
Direct bilirubin	mg%	AutoAnalyser (Jendrassic)
Calcium	mg%	Atomic absorption (Willis)
Uric acid	mg%	AutoAnalyser (Hawk)
Urea nitrogen	mg%	AutoAnalyser (Diacetyl monoxime/Marsh et al.)
Creatinine	mg%	AutoAnalyser (Jaffe)
Alkaline phosphatase	International units	AutoAnalyser (Babson)
Creatine phosphokinase	milliunits/ml	Robot chemist (Oliver)
Creatine phosphokinase	International units	Rate reaction analysis (Boehringer-Mannheim)
Lactic dehydrogenase	milliunits/ml	Robot chemist (Wroblewski & LaDue)
Lactic dehydrogenase	International units	Rate reaction analysis (Boehringer-Mannheim)
Glutamic oxaloacetic transaminase	milliunits/ml	Robot chemist (Karmen, Wroblewski, & LaDue)
Glutamic oxaloacetic transaminase	International units	Rate reaction analysis (Boehringer-Mannheim)
Urine Chemistries		
Osmolality	milliosmols/24 hrs	Freezing Point Depression (Gambino)
Calicum	mEq/24 hrs	Atomic absorption (Willis)
Inorganic phosphate	mg/24 hrs (P)	AutoAnalyser (Fiske & Subbarow)
Specific gravity	None	Total solids
Chloride	mEq/24 hrs	Titration (Buchler-Cotlove)
Creatinine	mg/24 hrs	AutoAnalyser (Jaffe)
Volume	ml/24 hrs	Volumetric
Sodium	mEq/24 hrs	Flame photometry (Henry)
Magnesium	mEq/24 hrs	Atomic absorption (Willis)
Potassium	mEq/24 hrs	Flame photometry (Henry)
Uric acid	mg/24 hrs	AutoAnalyser (Hawk)

Table 2
Normal Biochemistry Values for Apollo Astronaut Population

Parameter	Number of Crewmen	Two Standard Deviation Range
A. Serum		
Osmolality	112	267.2-313.7
Sodium	127	115.8-164.9
Potassium	126	3.5-4.7
Chloride	127	98.4-111.2
Calcium	126	8.9-10.3
Magnesium	128	1.7-2.7
Inorganic phosphate	128	2.3-4.7
Blood urea nitrogen	126	11.3-25.7
Creatinine	125	0.9-1.5
Total protein	131	6.2-7.8
Albumin	131	3.7-5.3
Glucose	98	85.4-111.5
Triglycerides	86	26.9-195.9
Cholesterol	125	113.1-261.1
Uric acid	126	4.4-7.9
Total bilirubin	122	0.1.5
Alkaline phosphatase	128	7.8-37.1
Lactic acid dehydrogenase (RC)	59	29.8-65.4
(LKB)	66	134.1-263.0
Serum glutamic oxaloacetic transaminase (SGOT) (RC)	59	14.2-44.8
(LKB)	67	9.5-22.1
Creatine phosphokinase (RC)	59	0.68.4
(LKB)	62	2.6-110.7
B. Urine		
24-hr urine volume	87	102-2746
Specific gravity	85	1.007-1.031
Osmolality	73	282-1110
Sodium	88	20.1-306.9
Potassium	88	18.6-128.4
Chloride	88	20.8-278.9
Calcium	88	0.8-16.9
Magnesium	88	-30.5

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Table 3

Summary of Apollo Serum Biochemistry Results

Parameter	Unit	N*	Preflight Mean ± S. D.	Recovery							
				+2 hrs	Δ%***	+1 Day	Δ%***	+7 Days	Δ%***	+14 Days	Δ%***
Osmolality	Mosmo	32	291 ± 3	289 ± 6	− 0.7	290 ± 6	− 0.3	293 ± 6	+ 0.7	294 ± 6	+ 1
Na	mEq/l	33	141.5 ± 0.9	140 ± 2.3	− 0.4	140.9 ± 1.8	− 0.4	142.8 ± 1.6	+ 0.9	143.0 ± 2.8	+ 1.1
K	mEq/l	33	4.1 ± 0.3	3.8 ± 0.3	− 7.3	4.1 ± 0.3	0	4.1 ± 0.3	0	4.2 ± 0.2	+ 2.4
Cl	mEq/l	33	104.6 ± 2.2	104.0 ± 3.3	− 0.6	104.2 ± 1.8	− 0.4	105.7 ± 2.9	+ 1.1	106.6 ± 2.3	+ 1.9
Ca	mg/100 ml	33	9.6 ± 0.3	9.7 ± 0.4	+ 1.0	9.5 ± 0.3	− 1.0	9.5 ± 0.4	− 1.0	9.6 ± 0.3	0
Mg	mg/100 ml	33	2.2 ± 0.2	2.1 ± 0.2	− 5.0	2.2 ± 0.2	0	2.2 ± 0.1	0	2.3 ± 0.1	+ 5.0
PO_4	mg/100 ml	33	3.6 ± 0.4	3.6 ± 0.6	0	3.4 ± 0.5	− 6.0	3.8 ± 0.4	+ 6.0	3.7 ± 0.4	+ 2.8
BUN	mg/100 ml	33	18.5 ± 2.6	20.7 ± 3.8	+11.9	19.1 ± 3.4	+ 3.2	14.9 ± 2.4	−19.5	16.0 ± 2.9	−13.5
Creatinine	mg/100 ml	33	1.2 ± .1	1.3 ± 0.2	+ 8.3	1.2 ± 0.2	0	1.3 ± 0.2	+ 8.3	1.2 ± 0.2	0
Total protein	gm/100 ml	33	7.1 ± 0.3	7.3 ± 0.4	+ 2.8	6.9 ± 0.3	− 2.8	6.7 ± 0.3	− 5.6	6.8 ± 0.3	− 4.2
Albumin	gm/100 ml	33	4.6 ± 0.3	4.5 ± 0.4	− 2.2	4.3 ± 0.4	− 6.5	4.3 ± 0.2	− 6.5	4.2 ± 0.4	− 8.7
Glucose	mg/100 ml	33	95.7 ± 7.3	105.1 ± 13.6	+ 9.8	93.4 ± 13.8	− 2.4	99.1 ± 9.9	+ 3.6	94.2 ± 7.5	− 1.6
Triglycerides	mg/100 ml	28	119.7 ± 77.4	90.6 ± 23.5	−24.3	95.0 ± 37.9	−20.6	113.2 ± 37.7	− 5.4	157.9 ± 15.0	+31.9
Cholesterol	mg/100 ml	33	185.6 ± 36.3	174.4 ± 33.2	− 6.0	149.8 ± 26.2	−19.3	165.9 ± 27.1	−10.6	179.6 ± 33.8	− 3.2
Uric acid	mg/100 ml	33	6.1 ± 1.1	5.2 ± 0.9	−14.8	5.5 ± 1.0	− 9.8	5.6 ± 1.1	− 8.2	5.7 ± 0.9	− 6.6
Total bilirubin	mg/100 ml	33	0.8 ± 0.5	0.9 ± 0.9	+12.5	0.7 ± 0.5	−12.5	0.5 ± 0.3	−37.5	0.6 ± 0.3	−25.0
Alkaline phosphatase	Int. units	33	21.8 ± 4.0	22.4 ± 4.4	+ 2.8	21.8 ± 4.1	0	21.9 ± 4.8	+ 0.5	20.9 ± 5.1	− 4.1
**Lactic acid dehydrogenase	mμ/ml										
Missions 7 - 13		21	46.5 ± 7.7	46.0 ±	− 1.1	46.5 ± 8.5	0	46.5 ± 8.5	0	42.3 ± 5.4	− 9.0
Missions 14 -17		12	207.3 ± 24.2	186.4 ± 27.9	−10.1	196.7 ± 14.5	− 5.1	189.5 ± 27.7	− 8.6	180.0 ± 16.8	−13.2

Table 3 (Continued)

Summary of Apollo Serum Biochemistry Results

Parameter	Unit	N	Preflight Mean	Preflight S. D.	Recovery +2 hrs	Δ%***	+1 Day	Δ%***	+7 Days	Δ%***	+14 Days	Δ%***
**SGOT	mμ/ml											
Missions 7 - 13		21	29.5 ±	5.5	31.1 ± 6.6	+ 5.4	35.1 ± 9.9	+18.9	31.8 ± 5.9	+ 7.8	32.9 ± 6.9	+11.5
Missions 14 - 17		12	16.5 ±	3.7	15.8 ± 3.5	− 4.2	16.3 ± 3.0	− 1.2	13.3 ± 2.4	−19.4	14.0 ± 3.5	−15.2
**Creatine phosphokinase	mμ/ml											
Missions 7 - 13		21	25.3 ±	22.7	18.7 ± 7.5	−26.1	35.2 ± 19.2	+39.1	16.3 ± 11.3	−35.6	16.8 ± 16.6	−33.6
Missions 14 - 17		12	70.9 ±	24.1	62.9 ± 45.4	−11.3	81.0 ± 62.2	+14.3	43.1 ± 21.8	−39.2	38.3 ± 12.9	−45.9

*Number of crewmen.

**Procedural change.

***% means percent change when compared to preflight mean.

Table 4
Significant* Serum Biochemistry Changes
(Pre $\bar{x}$ vs. Recovery Day)

Parameter	Direction of Change
Potassium	Decreased
Magnesium	Decreased
Creatinine	Increased
Lactic acid dehydrogenase	Decreased
Creatine phosphokinase	Decreased
Total Protein	Increased
Albumin	Decreased
Blood urea nitrogen	Increased
Glucose	Increased
Triglycerides	Decreased
Cholesterol	Decreased
Uric acid	Decreased

*Significant change is defined as $p < .05$.

Discussion

The clinical biochemical investigations conducted on the Apollo crewmen showed no preflight or postflight abnormalities of clinical significance. Some transient changes, however, were observed postflight which occurred consistently and merit discussion.

Blood Constituent Measurements

Postflight decreases in serum potassium, although not significant clinically, were found in 24 of the 33 crewmen. This early finding was an important factor in the decision to conduct more extensive electrolyte studies on the later Apollo flights (Leach et al., 1970). Based on measurements in Apollo 16 and 17 the increase in aldosterone which occurred during flight was believed to be partly responsible for the decrease in serum potassium, and for the lack of change in serum sodium postflight. Decrease in serum magnesium was interpreted as evidence of a reestablishment of ionic equilibrium principally in muscle tissue occuring while in space.

Immediate postflight creatinine and blood urea nitrogen (BUN) levels were increased over preflight mean values with return toward preflight levels by one day after recovery. These increases often are associated with prerenal diversion of water, increased protein catabolism, and impaired renal function. Although no evidence of renal impairment was suggested in the associated chemistry data, it could not be ruled out. Increased protein catabolism or dietary factors probably influenced the creatinine and BUN levels, as well as the state of hydration of the returning crewmen.

Table 5

Apollo Twenty-four Hour Urine Results

Parameter	Units	N*	Preflight Mean ± S. D.	Recovery							
				+24 Hrs	Δ%**	+48 Hrs	Δ%**	+72 Hrs	Δ%**	+6 Days	Δ%**
Specific gravity	SpGr	30	1.019 ± .005	1.024 ± .006	+ .5	1.018 ± .007	− .1	1.016 ± .005	− .3	1.017 ± .004	− .2
Osmolality	Mosmo	30	789 ± 238	1017 ± 569	+28.9	1373 ± 163	+74.0	1170 ± 996	+48.3	750 ± 288	− 4.9
Urine volume	ml	30	1989 ± 494	1090 ± 599	−49.2	1541 ± 691	−22.5	1370 ± 674	−31.1	1805 ± 860	− 9.3
Sodium	mEq/24 hr	30	173 ± 61	90 ± 60	−48.0	106 ± 45	−38.7	156 ± 75	− 9.8	206 ± 57	+19.1
Potassium	mEq/24 hr	30	73 ± 19	43 ± 17	−41.1	54 ± 15	−26.0	50 ± 23	−31.5	68 ± 23	− 6.9
Chloride	mEq/24 hr	30	156 ± 53	60 ± 42	−61.5	97 ± 51	−37.8	137 ± 67	−12.2	181 ± 60	+16.0
Calcium	mEq/24 hr	30	9.3 ± 3	7.8 ± 4.4	−16.1	9.5 ± 4.7	+ 2.2	9.9 ± 4	+ 6.5	12.4 ± 5.8	+33.3
Magnesium	mEq/24 hr	30	8.6 ± 2.7	5.7 ± 2.7	−33.7	5.7 ± 2.4	−33.7	6.9 ± 3.4	−19.8	9.7 ± 4.5	+12.8
IPO_4	mg/24 hr	30	965 ± 267	956 ± 361	− .9	804 ± 340	−16.7	832 ± 381	−13.8	1107 ± 211	+14.72
Creatinine	mg/24 hr	30	1852 ± 468	1842 ± 660	− .5	1669 ± 703	− 9.9	1779 ± 565	− 3.9	1945 ± 641	+ 5.0
Uric acid	mg/24 hr	30	825 ± 303	638 ± 268	−22.7	688 ± 346	−16.6	675 ± 274	−18.2	761 ± 249	− 7.8

*Number of crewmen tested.

**Percent change from preflight mean.

Table 6
Significant* Twenty-four Hour Urine Biochemistry Changes
(Pre $\bar{x}$ vs. Recovery Day)

Parameter	Direction of Change
Specific gravity	Increased
Osmolality	Increased
Volume	Decreased
Sodium	Decreased
Potassium	Decreased
Chloride	Decreased
Magnesium	Decreased
Uric acid	Decreased

*Significant change is defined as $p < .05$.

The serum creatine phosphokinase (CPK) levels were reduced immediately postflight, and mild elevations were evident by 24 hours after recovery. This alteration was probably a result of muscle inactivity incident to weightlessness and to increased muscular activity during the first 24-hour postflight interval. The decrease in LDH could not be as readily explained, since this enzyme would be expected to increase with exercise (Halonen & Koltinen, 1962). However, it is likely that preflight LDH levels were atypically elevated due to rigorous physical conditioning by the crew, such that the postflight reduction in LDH may simply have been a return to normal enzyme balance.

The postflight elevation of blood glucose may have been related to stress associated with reentry. In support of this prediction the epinephrine and steroid increases correlated well with the hematologic findings of a transient postflight neutrophilia, eosinopenia, and lymphopenia. However, short-term bedrest is associated also with glucosemia (Lutwak & Whedon, 1959), which raises the possibility that the increased glucose seen after the Apollo missions was not entirely a result of stress. As in bedrest, the finding may be a result of diminished uptake of glucose by inactive muscle cells (Lipman, 1970).

The decrease in cholesterol, triglycerides and uric acid may have been a result of the low residue, high fat and carbohydrate diet consumed during the Apollo flights However, these values did not return to preflight levels in two weeks after the mission, even though the crewmen began eating a conventional diet immediately after recovery. This fact suggested possibly that other metabolic consequences were involved. Adrenal steroids have been shown to be elevated during flight which may have accounted for the decrease in the stores of precursor cholesterol, particularly if not replaced by the diet (see Section III, Chapter 1). The decreased cholesterol was in agreement with elevated thyroxine levels, and contributed to the evidence for increased thyroid function during flight (Sheinfeld et al., 1975); (see also Section III, Chapter 1 of this book).

The increase in total protein at recovery, and subsequent decrease in the days following, portrayed the immediate postflight state of hydration of the individual crewmen and the redistribution of fluid compartments which occurred throughout the postflight interval. The immunological proteins were elevated also in many of the crewmen, which perhaps contributed also to total protein elevation (Fischer et al., 1972); (see also Section III, Chapter 3).

Urine Constituent Measurements

The postflight 24-hour urine collections revealed significant retention of sodium, potassium, and chloride ions associated with a reduced total urine volume and hyperosmolality. These findings are consistent with the reestablishment of preflight fluid and electrolyte balance and with hormonal adjustments required for readaptation from the space flight environment. The decrease in urinary uric acid predictably reflects the anabolism which occurs during the postflight period. Although dietary factors cannot be ruled out in uric acid metabolism, by six days postflight the crewmen should have consumed diets sufficient to return those levels to the preflight mean. For a more detailed review of the urinary constituents, the reader is referred to Section III, Chapter 1 of this book.

Summary

The objectives of the biochemical studies conducted for the Apollo Program were (1) to provide routine laboratory data for assessment of preflight crew physical status and for postflight comparisons; (2) to detect clinical or pathological abnormalities which might have required remedial action preflight; (3) to discover as early as possible any infectious disease process during the postflight quarantine periods following certain missions; and (4) to obtain fundamental medical knowledge relative to man's adjustment to and return from the space flight environment. The accumulated data suggest that these requirements were met by the program described. All changes ascribed to the space flight environment were subtle, whereas clinically significant changes were consistent with infrequent illnesses unrelated to the space flight exposure.

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