Effects of 9-Alphafluorohydrocortisone on Dehydration Due to Prolonged Bed Rest

PAUL M. STEVENS, M.D., and CAPT. THEODORE N. LYNCH, USAF, MC

The effects of 9-alphafluorohydrocortisone on the metabolic changes which occur during six days of bed rest were studied in four healthy subjects.

During the first 24-hours of bed rest a loss of weight and an increase in urinary water and sodium excretion was noted in all subjects. By the end of the sixth day of bed rest the hematocrit had increased while the plasma volume had decreased by a mean of 560 cc.

The experimental protocol was then repeated but 9-alphafluorohydrocortisone, 2 mg./day, was given during the last two days of bed rest. During this time, the weight increased, water and sodium retention occurred, the hematocrit decreased and the plasma volume showed a significant increase of 239 cc. by the end of the sixth day of bed rest.

It is suggested that part of the "orthostatic deconditioning" described following prolonged bed rest is due to plasma volume loss and that treatment with two days of 9-alphafluorohydrocortisone is a simple and efficient way to replete plasma volume losses due to prolonged bed rest.

From the Internal Medicine Branch Aerospace Medical Sciences Division, USAF School of Aerospace Medicine, Brooks Air Force Base, Texas.

IT HAS BEEN KNOWN for some time that prolonged bed rest leads to a diminution in blood volume.[15] This has repeatedly been demonstrated and is generally thought to be partly related to the salt and water diuresis which occurs in the recumbent position. In recent orbital spaceflight, the decrease in extracellular fluid and more specifically plasma volume during prolonged weightlessness has become of paramount importance because of its relationship to orthostatic tolerance and general physical fitness. Bed rest and water immersion have both been used as experimental methods to simulate weightlessness. Loss of plasma volume and orthostatic tolerance have consistently occurred with both of these simulation methods.[4,8] Most countermeasures against orthostatic deconditioning have involved a redistribution of blood volume to more or less simulate what normally occurs in the erect posture. It is probable that this redistribution of blood volume significantly affects central volume receptors so that salt and water are retained. Since there seems to be an association between loss of plasma volume and orthostatic intolerance, a study was undertaken to determine if 9-alphafluorohydrocortisone (9-FF) could be used as a short-term simple therapeutic agent to replenish the salt and water loss due to the prolonged bed rest.

MATERIAL AND METHODS

Four healthy U.S.A.F. airmen, ages 18-21, were used as subjects for the study. All were in good physical condition and had been subjected to the Air Force Basic Training Course prior to entering the Metabolic-Cardiovascular Ward for the study. During their equilibration period all subjects were encouraged to maintain normal activity and forbidden to use the beds except during the normal 8-hour sleep period. The ward was air conditioned and environmental factors kept constant.

The subjects were placed on a metabolic balanced diet consisting of 2900 calories and a total of 235 mEq. of sodium. Fluid intake was maintained constant at a level of 2100-3300 cc's daily injested in 150-200 cc aliquots at hourly intervals over a 16-hour period.

The study was performed in two phases. Phase I consisted of a 6-day period of complete bed rest, never allowing the subject to assume the upright position except for sitting on a bedpan for bowel movements. Activity was kept at a minimum level. At the end of this phase, an ambulatory period of one week was maintained with exercises of the "5 BX" variety performed twice a day. Bed rest was not allowed during this ambulatory period except during the 8 hours of normal sleep. Following this period the subjects started Phase II by once again returning to bed for another 6-day period. During the 5th and 6th day of this bed rest period, 1 mg of 9-FF was given orally every 12 hours.

Post voiding weights were recorded daily using bed scales. The subjects were always weighed naked and recumbent at the same time of day. Complete intake and output measurements were kept. Water balance was calculated by subtracting the urinary output from the fluid intake. Daily balances were closed out at 6:00 a.m. thus reflecting the previous day's occurrence. Urinary sodium was measured by automated flame spectroscopy with an internal lithium standard and excretion calculated from the 24-hour urine values.

"Plasma volume" was measured by the RIHSA method. On the day prior to bed rest, baseline values were obtained. The measurement was then repeated on the morning of the 4th and 7th day of bed rest. The subjects resumed normal ambulatory activity immediately after the plasma volume determinations on the morning of the 7th day. During the ambulatory period, the plasma volume was measured in the recumbent position after allowing the subject to equilibrate in that position for at least 30 minutes. The measurements were taken at the same time of day throughout both phases of the experiment.

Hematocrits were measured by the microhematocrit method with duplicate measurements being made each time a sample was drawn for the blood volume determination. This meant that on any one day the hematocrit value recorded was the mean of at least 6 separate determinations. Urinary sodium excretion was calculated from the 24-hour urine values.

On the 7th day of each phase the subjects remained in bed only until they were weighed and plasma volumes and hematocrits were measured. The water balance and sodium excretion of that day depended on measurements which did not end until 6:00 a.m. the following morning and reflected the added influence of ambulation.

RESULTS

Clinical Observations—No deleterious side effects were noted in any of the subjects during the two days of 9-FF therapy. Blood presure and pulse rates taken 4 times a day revealed no consistent changes.

Weight—The four subjects showed a mean loss in body weight of 1.25 kg by the morning of the 7th day of pure bed rest (range 0.83–1.96 kg). Most of the change in weight occurred during the first two days of bed rest and thereafter the weight tended to remain more or less stable.

In the second phase of the experiment a mean weight loss of 0.8 kg was noted by the morning of the 5th day of bed rest (range 0.42–1.4 kg). On the morning of day 6, 24 hours after institution of 9-FF, the weight in all subjects had significantly increased. By 5:00 p.m. of that day after a total of 3 mg of 9-FF, all subjects had regained the weight they had lost over the previous 6 days and actually exceeded their pre-bed rest ambulatory values. On the morning of the 7th day, after a total of 5 mg of 9-FF, the mean weight of the four subjects was still 0.51 kg above ambulatory pre-bed rest value (Table I). This represents a mean increase in weight of 1.31 kg during the 2 days of 9-FF therapy.

Fluid Balance—During Phase I the water balance in all subjects decreased during the first 24 hours following the onset of bed rest. Since the intake was relatively constant, this was due to an increase in urinary output. In most individuals the urinary output remained relatively stable at a slightly higher level during the following 6 days of bed rest. In subject #4 the gradual increase in apparent positive water balance may have been due to a transient febrile illness which occurred during the 3rd and 4th day of bed rest producing an increased insensible water loss (Figure 1).

During Phase II of the experiment, all subjects again showed an immediate diuresis during the first 24 hours of bed rest. The output then remained relatively constant over the next 3 days. Following the first day of 9-FF therapy, a positive water balance was noted in all subjects. This reduced urinary output was maintained

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Fig. 1. Composite of results on four subjects showing relative changes in weight, apparent water balance, urinary sodium, hematocrit, and plasma volume during pure bed rest and bed rest with 9-FF. (See opposite page 1153.)

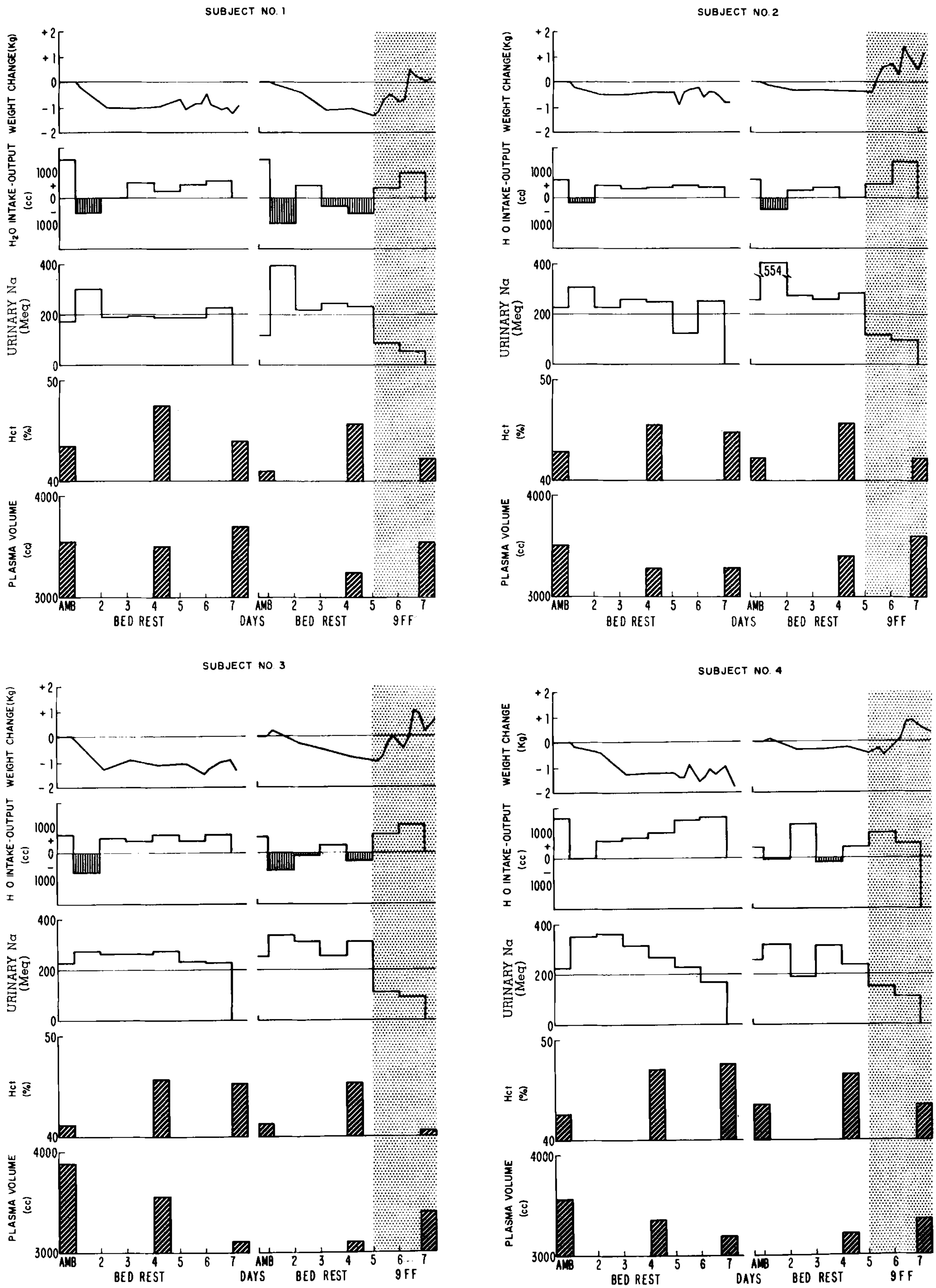
SUBJECT NO. 1
SUBJECT NO. 2
SUBJECT NO. 3
SUBJECT NO. 4
WEIGHT CHANGE (Kg)
H_2O INTAKE-OUTPUT (cc)
URINARY Na (Meq)
Hct (%)
PLASMA VOLUME (cc)
554
AMB 2 3 4 5 6 7
BED REST
DAYS
9FF

TABLE I. WEIGHT CHANGES (Kg) DURING 7 DAYS OF BED REST

Subject	1	2	3	4	1	2	3	4
Day of Bed Rest	Control	Control	Control	Control	9-FF	9-FF	9-FF	9-FF
1 — 10 AM	—0.22	—0.19	—0.01	—0.17	—0.09	+0.13	+0.20	+0.10
2 — 10 AM	—1.01	—0.46	—1.28	—0.37	—0.47	—0.26	—0.26	—0.31
3 — 10 AM	—1.04	—0.57	—0.98	—1.28	—1.11	—0.24	—0.54	—0.32
4 — 10 AM	—0.94	—0.54	—1.16	—1.23	—1.03	—0.22	—0.82	—0.15
5 — 8 AM	—0.66	—0.43	—0.96	—1.24	—1.40	—0.36	—1.00	—0.42
— 10 AM	—1.05	—0.93	—1.33	—1.37	—1.18	—0.28	—0.80	—0.40
— 5 PM	—0.84	—0.43	—1.48	—1.36	—0.73	—0.10	—0.34	—0.31
— 10 PM	—0.84	—0.27	—0.89	—0.85	—0.50	+0.56	+0.01	—0.50
6 — 6 AM	—0.59	—0.17	—1.54	—1.59	—0.81	+0.75	—0.47	—0.15
— 10 AM	—0.79	—0.61	—1.22	—1.40	—0.75	+0.29	—0.15	+0.15
— 5 PM	—1.24	—0.43	—1.0	—1.08	+0.51	+1.43	+1.02	+0.75
— 10 PM	—1.00	—0.43	—0.80	—1.34	+0.22	+1.14	+0.88	+0.65
7 — 6 AM	—1.25	—0.83	—0.78	—1.04	+0.02	+0.47	+0.20	+0.45
— 10 AM	—0.96	—0.83	—1.24	—1.96	+0.13	+1.04	+0.55	+0.31
Net Change	—0.96	—0.83	—1.24	—1.96	+0.13	+1.04	+0.55	+0.31
Mean Change		—1.25 kg				+0.51 kg		

during the second day of 9-FF therapy (Figure 1). It is interesting to note that on day 7, during which time the subjects were ambulatory after 10:00 a.m., the fluid balance became even more positive suggesting further water retention. This occurrence was more striking following the 6 day period of bed rest without 9-FF (Table II).

Urinary Sodium—Sodium excretion increased during the first day of bed rest in all subjects. During the subsequent six days of bed rest the sodium excretion remained steady at more or less baseline ambulatory levels in 3 of the 4 subjects. Subject #4, who, as previously mentioned, developed a short febrile illness, continued to show progressive decrease in urinary sodium excretion (Table III).

TABLE II. FLUID INTAKE MINUS OUTPUT (cc) DURING 6 DAYS OF BED REST

	Bed Rest				Bed Rest and 9-FF			
Subject	1	2	3	4	1	2	3	4
Days								
Ambulatory 1	1729	834	1049	1694	1314	749	679	709
Ambulatory 2	1254	504	364	1529	1774	234	729	150
Bed Rest 1	—571	—81	—701	—11	—1021	—441	—625	26
Bed Rest 2	19	479	569	739	529	234	—141	1269
Bed Rest 3	599	439	416	799	—351	384	324	—196
Bed Rest 4	269	429	639	1019	—601	19	—361	424
Bed Rest 5	549	476	451	1479	419	504	629	929
Bed Rest 6	749	434	704	1604	1024	1429	1074	529
Ambulatory 7	2144	1414	1574	1434	1764	1519	1739	1579

TABLE III. URINARY SODIUM OUTPUT

	Bed Rest				Bed Rest and 9-FF			
Subject	1	2	3	4	1	2	3	4
Ambulatory (Mean 2-5 days)	168	222	223	224	119	256	250	255
Bed Rest								
Day 1	300	309	274	352	420	554	338	319
Day 2	187	223	263	361	219	270	311	188
Day 3	191	259	264	317	243	258	256	315
Day 4	187	253	270	264	231	279	309	239
Day 5	187	121	233	213	81	114	112	152
Day 6	228	256	231	169	55	96	87	107
Ambulatory								
Day 1	55	135	105	271	72	108	82	90

During Phase II of the experiment, all individuals again showed a sodium loss during the first 24 hours of bed rest with a return to mean baseline level over the next 3 days. After 24 hours of 9-FF therapy all four subjects showed obvious sodium retention as manifested by a decrease in urinary sodium excretion. This sodium retention persisted throughout the 48 hours of 9-FF therapy (Figure 1).

Hematocrit—In Phase I all four subjects developed significant hemoconcentration by the beginning of the 4th day of bed rest. This hemoconcentration persisted to the beginning of the 7th day in similar magnitude in three of the four subjects. Subject #1 either reacted anomalously or a laboratory error accounts for his apparent hemodilution on continued bed rest (Figure 1).

During the second phase of the experiment, a similar hemoconcentration was noted at the beginning of the 4th day of bed rest in all four individuals. Following 48 hours of 9-FF therapy, hemodilution occurred in all four subjects (Figure 1) and their hematocrits returned to pre-bed rest baseline values (Table IV).

"Plasma Volume" Changes—The inherent difficulties in measuring "Plasma Volume" by the RIHSA method were further compounded by the increasing levels of background radioactivity resulting from repeated injections. Therefore, no great credence is placed on the actual quantitative values obtained, particularly during Phase II. A definite trend however is present.

During Phase I, three of the four subjects showed a progressive decrease in plasma volume after 3 and 6 days of bed rest (Figure 1). Their mean decrease after

TABLE IV. HEMATOCRIT (PER CENT) CHANGES DURING BED REST

	Bed Rest				Bed Rest and 9-FF			
Subject	1	2	3	4	1	2	3	4
Ambulatory	43.4	42.7	41.4	42.5	41	42.2	41.4	43.5
3 Days Bed Rest	46.6	45.3	46.4	46.3	45.6	45.7	45.1	46.4
6 Days Bed Rest	44	44.8	47.1	47.6	42.3	42.3	40.4	43.4
Net Change after 6 days	+0.6	+2.1	+5.7	+5.1	+1.3	+0.1	—1.0	—0.1
Mean Change		+3.37				0		

6 days amounted to 506 cc (Table V). Subject #1 who reacted anomalously in respect to hematocrit, showed a significant decrease in plasma volume at the beginning of the fourth day, but with 2 more days of bed rest it returned toward normal (Table V).

During Phase II, after 2 days of 9-FF therapy, all subjects showed an increase in plasma volume (Figure 1). This mean increase of 239 cc occuring during the 5th and 6th days of bed rest is strikingly different from the mean decrease of 128 cc which occurred during the same period of time when 9-FF was not used (Table V and VI).

DISCUSSION

Bed rest and recumbency are both associated with a diuresis of salt and water.[13] Marked decreases in blood volume as well as significant orthostatic intolerance are usually associated with prolonged bed rest.[8] The relationship between a chronic decrease in blood volume and orthostatic intolerance has not been clearly established; however, it is well known that acute depletion of as little as 500 cc of blood results in severe orthostatic intolerance.[18]

The exact mechanism of recumbency diuresis is not clear. During standing the force of gravity shifts blood into the lower extremities. This results in a decrease in "central blood volume," of approximately 500 cc.[12] During recumbency, the reverse occurs and the central blood volume is increased by the same amount. Furthermore the absence of a hydrostatic gradient in the lower extremities during recumbency promotes a shift of fluid from the interstitial to the intravascular compartment which further increases the blood volume. The redistribution of blood volume occurring during recumbency may be interpreted by intrathoracic volume receptors as an excess, thus promoting a diuresis.[13] Inhibition of anti-diuretic hormone by left atrial volume receptors as well as a decrease in aldosterone secretion have both been implicated.[3,16]

With the advent of manned spaceflight, much interest has been centered about the effects of prolonged weightlessness. It has been suggested that the circulatory changes during weightlessness are similar to those

TABLE V. PLASMA VOLUME (cc) DURING BED REST

Subject	1	2	3	4
Ambulatory	3561	3102	3692	3548
4th Day of Bed Rest	3493	2780	3077	3353
7th Day of Bed Rest	3694	2740	2902	3183
Net Change from Baseline	+133	—362	—790	—365
Mean Change*		—506cc		

*Subject #1 was omitted from the mean because of his atypical response.

TABLE VI. PLASMA VOLUME (cc) DURING 9-FF THERAPY

Subject	1	2	3	4
4th Day of Bed Rest	3243	2823	3031	3190
7th Day of Bed Rest	3529	3075	3231	3330
Net Change	+286	+252	+200	+140
Mean Change		+239cc		

occurring during prolonged bed rest and water immersion.[5] Profound loss in body weight of up to 8.5 pounds has been noted in relatively short term spaceflights. Blood volumes have also been shown to decrease. Orthostatic tolerance following weightlessness has been significantly diminished[9] and has been the cause of much concern.

Although no specific causal relationship has been shown between chronic contraction of blood volume and orthostatic intolerence, it seems logical to assume that one exists. Most of the presently investigated orthostatic intolerance countermeasures involve mechanical attempts at redistribution of blood volume during weightlessness so that it more closely resembles normal standing in a 1 gravity field. Venous occlusive cuffs on the extremities[6] and lower body negative pressure[14] both accomplish this purpose. Venous occlusive cuffs has been shown to have beneficial effect on the orthostatic deconditioning which occurs following immersion[6] as well as prevent some of the associated plasma volume loss.[17] Lower body negative pressure when used for 2 days at the end of a 6 day period of bed rest also promotes salt and water retention resulting in expansion of the plasma volume.[7]

Idiopathic orthostatic hypotension has been successfully treated with aldosterone[2] and 9-FF.[10] Postural hypotension secondary to salt wasting and decreased central blood volume has been reported and subnormal aldosterone excretion rates were thought to be responsible.[1] Excessive excretion of sodium in the recumbent position has also been shown to be associated with orthostatic hypotension.[11]

In view of these facts, it was of interest to study the effects of short-term 9-FF on the natriuresis and diuresis occurring during prolonged recumbency. That 9-FF promotes salt and water retention is certainly not a new concept. The fact that in 24 to 48 hours it is capable of counteracting the fluid and sodium changes produced by prolonged bed rest is of practical significance. The data show that a significantly beneficial effect occurs. The weight loss was promptly regained within 36 hours and associated with water and salt retention. After 48 hours the weight was above pre-bed rest value and sodium retention continued. By 48 hours the plasma volume had significantly increased and the hematocrit had decreased to pre-bed rest values reflecting this hemodilution (Figure 1). Maintenance of adequate salt and water intake was felt to be mandatory in achieving these results. No notable side effects were seen. No attempt has been made at this time to evaluate the effects of this measure on the orthostatic intolerance which results from bed rest. Other factors, such as changes in tissue tension, vascular reactivity, and catacholamines which play an important role in orthostatic tolerance, will probably not be affected by this measure. However, in view of the fact that expansion of blood volume by albumin infusions has been shown to either abort or prevent orthostatic hypotension,[19] a beneficial effect would be expected.

The rapidity of action of 9-FF suggests it need only be used for 24-48 hours prior to re-exposure to gravitational stress. The simplicity of this form of volume repletion in subjects depleted by prolonged bed rest, makes it very attractive as a reconditioning measure following prolonged spaceflight.

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