NASA/TM-2002-211860





Recovery After Prolonged Bed-Rest Deconditioning

John E. Greenleaf and David T. Quach

January 2003

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John E. Greenleaf Ames Research Center, Moffett Field, California

David T. Quach Ames Research Center, Moffett Field, California

National Aeronautics and Space Administration

Ames Research Center Moffett Field, California

Acknowledgments

The authors thank Esther Johnson and Beth Little of the Ames Life Sciences Library for reprint acquisition. This work was supported by NASA grant UPN 111-10-20 and the Ames Associate Fellow Fund for FY2000.

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RECOVERY AFTER PROLONGED BED-REST DECONDITIONING

John E. Greenleaf¹ and David T. Quach¹

Ames Research Center

SUMMARY

Recovery data were analyzed from normal, healthy test subjects maintained in the horizontal or head-down body position in well-controlled bed rest (BR) studies in which adherence to the well-designed protocol was monitored. Because recovery data were almost always of secondary importance to the data collected during the BR period, there was little consistency in the recovery experimental designs regarding control factors (e.g., diet or exercise), duration, or timing of data collection. Thus, only about half of the BR studies that provided appropriate data were analyzed here. These recovery data were sorted into two groups: those from BR protocols of less than 37 days, and those from protocols greater than 36 days. There was great disparity in the unchanged responses at the end of BR in these two groups. Likewise with the variables that required more than 40 days for recovery; for example, some immune variables required more than 180 days. Knowledge of the recovery process after BR in healthy people should assist rehabilitation workers in differentiating "healthy" BR recovery responses from those of the infirmity of sick or injured patients; this should result in more appropriate and efficient health care.

¹Laboratory for Human Environmental Physiology, Ames Research Center, Moffett Field, California.

INTRODUCTION

Prolonged bed rest (BR >24 hr) has been prescribed by physicians, at least from the time of Hippocrates (450 B.C.), to facilitate healing and rehabilitation of their patients. Hippocrates recognized some harmful effects of prolonged rest, especially loss of muscular strength and tooth (bone) demineralization (Chadwick and Mann, 1950). Prolonged assumption of the horizontal body position reduces musculo-skeletal and orthostatic stress, facilitates cerebral perfusion, and usually lowers total body energy utilization in the sick and injured so that metabolic reserves utilized for maintaining upright posture and muscular activity can be directed to those needed by the immune system for recovery.

However, neuroendocrine-immune homeostatic control mechanisms are reset during prolonged BR in response to stimuli from (1) virtual elimination of hydrostatic pressure within the cardiovascular-lymph system on vessels below the heart, and increased pressure on vessels above the heart, including the brain and vestibular organs; (2) reduced skeletal muscle force (torque) on bones from muscle atrophy associated with decreased body energy expenditure and body water volume; and (3) some adverse psychophysiological responses during the novel and sometimes stressful environment of partial confinement in bed and the accompanying hospital routine. The latter includes changes in the physical environment, and food and fluid selection associated with constipation and difficulty with bowel movements which may or may not alter taste sensitivity and attenuate appetite (Sorokin et al., 1969; Vickers et al., 2001). The integrated adaptive responses from these and other interactive stimuli constitute major factors contributing to the BR-deconditioning syndrome.

Deconditioning is defined as "1: to cause to lose fitness < prolonged inactivity deconditions a person physically >" (Gove, 1986). This "adaptive" homeostatic condition is optimal for survival during BR as long as the gravitational vector remains perpendicular to the long axis of the body (i.e., from the chest to the back). It is the rather abrupt change from the horizontal (or weightless) condition to the upright sitting or standing postures, where the gravitational vector is from head-to-foot, that activates the "adverse" adaptive physiological signs and symptoms of the deconditioning. It is clear this adaptive-homeostatic-deconditioning syndrome occurs simultaneously to some degree in patients bed-rested by physicians to facilitate healing and rehabilitation, and that it is induced in healthy subjects for study by scientists of this "undesirable" syndrome and to devise countermeasures. Hence, the practical question is whether prolonged BR is helpful or harmful for patient recovery and rehabilitation (Ehrlich et al., 1994; Heaman and Gupton, 1998; Siebens et al., 2000).

Until the ramifications of this treatment are fully elucidated, prolonged BR should be prescribed or modified judiciously (Bassey and Fentem, 1974). A classic definition of rehabilitation "b: the physical restoration of a sick or disabled person by therapeutic measures and of his physical disability.... d: the restoration of something damaged or deteriorated to a prior good condition...." (Gove, 1986). This definition could be expanded to encompass this reverse homeostatic-adaptive-reconditioning process during recovery.

Results from a symposium chaired by Harrison (1944) in Chicago on the abuse of rest in the treatment of disease, and Asher's (1947) aphorism—"Teach us to live that we may dread unnecessary time in bed, get people up and we may save our patients from an early grave"—set the stage for an upsurge of BR studies (Fortney et al., 1996). A few studies were conducted before 1940, but the primary interest was academic, not practical medical applications. The

number of studies concerned with medical applications of BR data increased during and immediately following World War II but, in published studies, there appeared to be only minor interest in the physiology and time course of the ambulatory recovery process. By 1979 there had been well over 1,000 European, Soviet, and United States BR studies (Sheehan et al., 1979). The physiological and psychological aspects of prolonged BR deconditioning have been studied intensively (Greenleaf et al., 1976; Greenleaf and Kozlowski, 1982; Luu et al., 1990; Sheehan et al., 1979) and a few of them have been reviewed in some depth (Fortney et al., 1996; Greenleaf 1989, 1997; Greenleaf and Kozlowski, 1982; Greenleaf and Norsk, 1996; Greenleaf et al., 1994; Gretebeck and Greenleaf, 2000). In essentially all BR studies, the recovery data were of secondary importance to the primary data obtained before BR (in the control period) and during recumbency.

Thus, most ambulatory recovery data had to be gleaned from its secondary status when control elements of the BR phase (e.g., diet, exercise) had usually been removed. Nonetheless, important findings were extracted and analyzed. A better understanding of the post-BR recovery process in healthy subjects could provide baseline data with which to compare recovery data from hospitalized patients. This report presents graphic displays of recovery times for the major physiological and psychological systems following shorter-term (<37 days) and longer-term (>36 days) BR deconditioning in order to serve as a basis for an in-depth review of the recovery process.

METHODS

Recovery data were analyzed only from normal, healthy test subjects in well-controlled studies in which adherence to the BR protocol was monitored. There was no differentiation between the horizontal or head-down body positions of the subjects. Bed-rest experimental designs utilized the horizontal (0°) body position prior to 1972 when Voskresenskiy et al. published data from a 30-day study comparing the 0° position with the -4° head-down position. The head-down position (usually by 6°) was employed in most BR studies after 1980 (Greenleaf et al., 1982; Luu et al., 1990; Sheehan et al., 1979). The experimental designs of the studies by Taylor et al. and Saltin et al.— which deviated from the usual design—consisted of an ambulatory control period with no countermeasures, sometimes countermeasures during BR, and no countermeasures during ambulatory recovery. Taylor et al. (1949) studied six men who underwent a 6-week period of physical fitness training before BR, then 21 days of 0° BR with no countermeasures followed by a 6-week physical conditioning regimen during normal, ambulatory recovery. In the second, Saltin et al. (1968) bed-rested five men (0°) for 20 days without countermeasures and then exercise-trained them for 55 days during ambulatory recovery.

Data collected during the recovery periods after BR were almost always of secondary importance to those obtained from the pre-control and BR periods. As a result, there was essentially no consistency in recovery experimental designs in regard to duration, control factors, or timing of data collection. Therefore, our guidelines utilized for rejecting data were (1) BR periods less than 5 days; (2) recovery periods less than 2 days; (3) test groups less than four subjects; (4) recovery period not specified; and (5) evidence of poor or inadequate experimental design. Thus about half of the available BR studies that had recovery data are analyzed here. The recovery data were separated into two major groups: those obtained from BR studies of less

than 37 days, and those greater than 36 days. Each group was divided further into "No Countermeasures" and "Countermeasures" sections that were utilized or not during the BR period. The BR day on which data were collected was indicated; it was usually near the end of the BR period, but not necessarily at the end of the BR period. Data were taken directly from report figures or tables, and not from authors comments in the text. Some data interpretation was qualitative when statistical analyses were not provided. Data for each variable were qualitatively averaged or adjusted to obtain one point, a range, or a direction for recovery.

In the figures, a small square indicates a single day and a rectangle (elongated square) indicates the range. The black dot with an arrow pointing to the left indicates recovery earlier than the dot and an arrow pointing to the right indicates recovery later than the dot. Data in the far left column are the raw recovery values used to establish the rectangles or arrows. Abbreviations used in the figures are defined in the figures.

RESULTS: BED REST LESS THAN 37 DAYS

Anthropometry

Many anthropometric responses were likely influenced by changes in body weight which often decreased (DEC) during BR because of negative caloric balance. This was a result mainly, of insufficient intake, especially if subjects were exercising during BR (fig. 1, p. 1). Limb circumferences and volumes (except leg and thigh) were generally unchanged during BR. Calf and thigh muscle volumes decreased and required more than 30 days to recover—perhaps up to 55 days; but lean body mass recovered in less than 30 days whereas recovery of body fat content may require 55 days. Body total bone content was unchanged during BR less than 36 days (fig. 1, p. 2). Thus, decreases in body weight and lower extremity muscle volume and thickness required the longer times for recovery after BR of less than 36 days.

Physiological Systems

Cardiovascular variables. Basal and resting heart rates were either unchanged (UNC) or increased (INC) during BR with recovery in fewer than 60 days (fig. 1, p. 4). The decrease in heart volume and stroke volume also recovered in 3-60 days. Cerebral vascular functions were unchanged (fig. 1, p. 5). The various blood pressures inhibited variable responses during BR, with resting SBP and end-diastolic volume recovering in less than 30 days; the decrease in left-ventricular diastolic volume recovered in 3-62 days (fig. 1, p. 6). Cardiac index (CO/BSA in m²) and right heart blood volume were unchanged, cardiac output increased and the decrease in stroke index, ejection fraction, femoral vascular resistance, central venous pressure, pulmonary arterial resistance, myocardial oxygen consumption, and coronary sinus blood flow and pressure required more than 2-10 days to recover. The decreased occlusive forearm and calf blood flows recovered by 30 days; limb venous compliance recovered beyond 2-7 days and limb pulse-wave velocities were generally unchanged (fig. 1, p. 7). Thus, many of the important cardiovascular variables that were disturbed during BR deconditioning do not recover promptly during reambulation.

Respiratory variables. All of the standard respiratory variables measured (except the increased oxygen and carbon dioxide alveolar-arterial gradients) required significant (>4 < 30 days) recovery periods (fig. 1, p. 9). Exercise training during BR shortened the 4-10 days recovery period of the decreased basal respiratory rate to about 1 day.

Blood-fluid hormonal variables. Because of its major importance in the totality of BRdeconditioning homeostasis, body fluid variables (and their recovery) have been studied extensively (fig. 1, p. 10). The characteristic decrease in plasma and blood volumes recovered between 2 and 30 days, and the hypervolemic effect of aerobic exercise training during BR can reduce recovery to 0-6 days. The decrease in red cell mass, volume, and total hemoglobin recovered in 6-30 days. The increased hematocrit and hemoglobin concentration recovered in 2-14 days (fig. 1, p. 11). The decrease in total body water content recovered by 7 days, but extracellular volume (plasma plus interstitial volumes) required more than 7 days, and intracellular volume was unchanged. It seems that cellular integrity (volume) follows the axiom that it is protected at the expense of the extracellular volume. Decreased glucose tolerance recovered within 7-14 days (fig. 1, p. 12). Plasma (and serum) sodium, potassium, calcium and osmotic concentrations remained unchanged with the decrease in plasma volume; the decrease in sodium and potassium balances recovered within 7 days (fig. 1, p. 13). Resting plasma vasoactive hormone concentrations were mostly unchanged or recovered beyond 3 days, whereas the decreased catecholamines recovered beyond 6 days (fig. 1, p. 14).

Cellular, enzyme variables. Many cells and cellular responses required more than 155 days to recover; the responsiveness of T and B lymphocyte; neutrophils, essinophils, suppressor/ cytotoxic cells (CD8⁺), and concanavalin A was essentially unchanged (fig. 1, p. 16). Some lymphocyte reactivities recovered in less than 3 days but others required more than 3 days.

Urinary-renal variables. When urinary volume increased or decreased during BR, the recovery—which was unaffected by exercise—required up to 18 days (fig. 1, p. 20). Increased urinary sodium, chloride, phosphorus, and calcium recovered in 7-10 days. Urinary pH, creatinine, urea nitrogen, atrial natriuretic peptide, aldosterone, cortisol, citrate, sulfate, oxalate, and glomerular filtration rate were all essentially unchanged after fewer than 36 days of BR. Increased urinary total nitrogen, phosphate, glucose, epinephrine, norepinephrine, and renal vascular resistance recovered beyond 7 days; urinary magnesium and 17-OH steroids recovered in fewer than 7 days (fig. 1, p. 22).

Physiological Tests

Only basal oral temperature, submaximal SBP, and low-level (+2.1 G_z) acceleration tolerance were unchanged after fewer than 14 days of BR (fig. 1, p. 24). The decreased resting metabolism (oxygen uptake) recovered beyond 2 days. Decreased treadmill and ergometer endurance had recovered before 35 days. Uniformly decreased maximal oxygen uptake recovered between 25 and 62 days. Decreased maximal anaerobic threshold recovered before 14 days, and increased maximal exercise heart rate recovered by 30 days. Decreased orthostatic and +G_z acceleration tolerances recovered between 3 days and beyond 20 days with no appreciable effect of exercise training during BR (fig. 1, p. 26). Most decreased maximal

voluntary muscular contractions recovered before 30 days; right knee and elbow flexion and plantar flexion recovered beyond 30 days (fig. 1, p. 27).

Psychological Tests

Contrary to the results of the physiological tests, many psychological tests including perceptive speed, slow nystagmus phase velocity, nystagmus frequency, perceptual speed, speed of closure, math, memory, fatigue scale, critical tracking, matrix and the Manikin test, were unchanged during BR (fig. 1, pp. 29, 30). The increase in aiming test and flexibility of closure and decrease in dual tracking required 6-16 days for recovery. Decreased taste sensitivity recovered before 7 days.

RESULTS: BED REST GREATER THAN 36 DAYS

Anthropometry

Changes (both increases and decreases) in most body segments recovered in fewer than 14 days. The exceptions were weights of the thigh and middle trunk, and circumferences of the middle trunk, lower trunk, and calf, which recovered beyond 11-14 days (fig. 2, p. 1). Essentially all increased skin folds (indicating increased fat and possibly water content) recovered by 14 days. Some soleus muscle fiber parameters, including the number of myonuclei, most fiber types, and cross-sectional area, were unchanged; decreases in total cytoplasmic volume and various fiber cross-sectional area recovered beyond 40 days. The decrease in total body bone mineral content was recovered between 70 and 180 days (fig. 2, p. 4). But the mineral content of some bones was unchanged: arms, proximal and distal radii, proximal and distal ulnae, ribs, and thoracic spine. Loss of mineral content that occurred in the trunk, pelvis, and calcaneous required more than 180 days for recovery; that in the tibia and fibula recovered beyond 30 days (fig. 2, p. 5).

Physiological Systems

Cardiovascular variables. The increased resting heart rate recovered in 14-30 days; most other heart variables were either unchanged or required 8-50 days for recovery (fig. 2, pp. 6, 7). While the ear-canal temperature was essentially unchanged, its decreased circadian amplitude recovered beyond 20 days (fig. 2, pp. 8, 9). General body thermoregulation recovered at about 30 days.

Respiratory variables. Unchanged respiratory variables were lung diffusion membrane and capillary capacity, peak expiratory flow, forced expiratory volume, and functional residual capacity; the increased alveolar pO_2 , alveolar-arterial O_2 gradient, and decreased forced expiratory volume, forced vital capacity, and CO diffusing capacity recovered beyond 7-15 days (fig. 2, pp. 10, 11).

Blood-fluid hormonal variables. Blood and plasma volumes and total body water recovered in fewer than 12-20 days; red cell mass recovered beyond 20 days (fig. 2, p. 12). Serum electrolytes (except magnesium and calcium) recovered in fewer than 14 days. Plasma insulin and glucose levels recovered within 10-20 days (fig. 2, p. 14).

Cellular, enzyme variables. Serum total protein and various globulins recovered in 7-30 days; alkaline phosphate and osteocalcin took more than 40 days (fig. 2, p. 15). Most dehydrogenases and phosphatases recovered beyond 7 days. Plasma amino acids are either unchanged (cystine, aspartic acid, glutamic acid, proline) or recovered after 14 days (fig. 2, p. 16, 17). Plasma triiodothyronine, thyroxine, and prolactin were unchanged; adreno-corticotrophic and growth hormones recovered after 20 days (fig. 2, p. 18). Most T-lymphocyte cells and natural killer cell activity and white cell lyphocytes and monocytes were unchanged (fig. 2, p. 19). The lipases recovered after 10 days.

Urinary-renal variables. Only urinary calcitonin, fecal phosphorus, and creatinine clearance were unchanged (fig. 2, pp. 21, 22). Urinary nitrogen, potassium, phosphorous, calcium, pyridinium cross-links, and deoxypyridinium and fecal calcium recovered beyond 28 days.

Physiological Tests

Maximal work parameters (O_2 uptake, endurance, heart rate) take longer than 2 days to recover; the step-test parameters and general body fatigue recovered in 30-70 days (fig. 2, p. 23). Orthostatic and acceleration tolerance generally required 17-50 days for recovery. The generally decreased muscular forces and strengths recovered between 10-20 days (fig. 2, p. 24).

Psychological Tests

Most body posture equilibrium and gait parameters (including foot sensitivity) recovered beyond 14 days (fig. 2, pp. 25, 26).

SUMMARY OF RESULTS

Figures 1 and 2 present relatively clean data from about half of the BR studies (those with well-controlled experimental designs) that contained recovery information. An a priori hypothesis would be that changes in variables after prolonged (>36 days) BR would be somewhat different from those with BR less than 37 days; and that recovery of variables after longer-term BR would be essentially similar (perhaps somewhat longer) to that of variables after the shorter-term BR. The general observation is that recovery is only somewhat longer with BR greater than 36 days. This would be expected if an equilibrium had not been reached in a variable before 36 days. However, many immune cell responses required more than 155 days for recovery during BR less than 37 days, and some bone parameters, as well as general body fatigue, recovered near and beyond 180 days during BR greater than 36 days.

A summary of responses at each end of the recovery spectrum, that is, those unchanged at the end of BR versus those with extended recovery (greater than 40 days), revealed unexpectedly heterogeneous responses. With BR less than 37 days, variables unchanged at the end of BR included the following:

- 1. Limb and body section circumferences and volumes
- 2. Many blood vessel pressures and cardiac parameters
- 3. Some plasma electrolytes
- 4. Some blood immune cells
- 5. Many cognitive and psychomotor responses

These can be compared with those unchanged variables during BR greater than 36 days, which included the following:

- 1. Some soleus fiber types
- 2. Bone mineral in arm bones, ribs, and thoracic spine
- 3. Heart rate and volume and some pulse wave velocities
- 4. Lung diffusion and flow
- 5. Serum calcium, phosphorus, albumin, and globulin concentrations
- 6. Some plasma amino acids
- 7. Some blood immune cells
- 8. Urinary calcitonin and creatinine clearance

Long-term recovery (>40 days) of variables following BR less than 37 days include the following:

- 1. Intervertebral disc size and area
- 2. Bone mineral in trunk, pelvis, and calcaneus
- 3. Serum alkaline phosphate, osteocalcin
- 4. Blood $CD4^+$, $CD8^+$, and $CD56^+$ cells
- 5. Urinary pyridinium crosslinks and deoxypyridinium
- 6. Step test recovery and general body fatigue
- 7. +Gx acceleration tolerance

These can be compared with recovery of those variables following BR greater than 36 days which include the following:

- 1. Body fat content
- 2. Hemoglobin concentration and white blood cells
- 3. Some blood cells including segmented neutrophils, basophils, CD3⁺, CD4⁺, CD19⁺, NK cells, and HLA-lymphocytes
- 4. Maximal oxygen uptake

5. Muscular strength of the hand grip, plantar flexion, knee flexion and extension, and elbow flexion

There is no regular pattern in the response of variables after shorter- and longer-term BR nor in long-term (>40 days) recovery with data from these selected studies. Some variables had not recovered by 180 days. Clearly, total body physiological equilibrium is reached sometime during continuous BR as exemplified by the case of a man, Jonnie Richardson, who went to bed in 1932 at age 16 in an isolated mountain cabin near Laurel Springs, North Carolina, and lived

for at least 50 more years. At age 66 he was described as "a ghost of a mountain man, a lilywhite frame with limbs as thin as the legs of a ladder-back chair" (San Jose Mercury).

Prolonged stay in recovery and rehabilitation facilities is very expensive, hence the stimulus for early ambulation. But how can the care-provider determine when recovery is sufficient? The extended recovery time of some immune cellular processes could increase the possibility of further disease or injury. Because most of the recovery data after prolonged BR are descriptive, solid, hypothesis-driven research into the mechanisms of the recovery process is urgently needed.

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INC = increase; DEC = decrease; UNC = unchange; LBNP = lower body negative pressure; RGS = reverse gradient suit; # = countermeasure done during Recovery period; HUT = head up tilt





BODY BONE (UNC)
> Suzuki et al. (1994)
> Suzuki et al. (1994)
INTERVERTEBRAL DISC
CROSS-SECTIONAL AREA (INC)
> Leblanc et al. (1994)



²³3











<14d

54d 54d <30d

>14d

>14d

B

B

<3d

ŝ






2-3d 2-3d >10d

88

9999

29G

-1d

7-14d

g

36

>10d

P2~

>1d

В

P2~







PLASMA ADRENOCORTICOTROPHIC HORMONE (UNC) od > Vernikos et al. (1993) PLASMA CORTISOL (DEC) >6d > Gmunder et al. (1992) PLASMA CORTISOL (UNC) 0d > Vernikos et al. (1993)

PLASMA NOREPINEPHRINE (DEC) > Gmunder et al. (1992)

~6d

PLASMA EPINEPHRINE (DEC)
> Gmunder et al. (1992)

>6d











URINARY POTASSIUM / INTAKE (INC) URINARY VOLUME / INTAKE (INC) > Noskov et al. (1985) URINARY SODIUM / INTAKE (DEC) > Noskov et al. (1985) 2E. Urinary-Renal Variables URINARY POTASSIUM (DEC) URINARY POTASSIUM (INC) URINARY VOLUME (INC)
> Greenleaf et al. (1977a)
> Greenleaf et al. (1977a)
> Hwang et al. (1988) URINARY VOLUME (DEC) URINARY VOLUME (UNC) > Guell et al. (1982) URINARY SODIUM (UNC) > Hwang et al. (1988) Sceenleaf et al. (1977a)
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TASTE SENSITIVITY FOR BITTER (DEC) > Budylina et al. (1976)

¢7d



Figure 2. Recovery data for bed-rest periods greater than 36 days.













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DIFFUSING CAPACITY FOR CO (DEC) >15d > Montmerte et al. (2002)

PULMONARY BLOOD FLOW (DEC) > Montmerte et al. (2002)

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P75

77

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188
Public reporting burden for this collection of informa gathering and maintaining the data needed, and cor collection of information, including suggestions for r Davis Highway, Suite 1204, Arlington, VA 22202-43	tion is estimated to average 1 hour per resp mpleting and reviewing the collection of infor educing this burden, to Washington Headqu 02, and to the Office of Management and Bu	onse, including the time for revi mation. Send comments regard arters Services, Directorate for i idget, Paperwork Reduction Pro	ewing instructions, searching existing data sources, ling this burden estimate or any other aspect of this nformation Operations and Reports, 1215 Jefferson ject (0704-0188), Washington, DC 20503.
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE Januar;y 2003	3. REPORT TYPE AND DATES COVERED Technical Memorandum	
4. TITLE AND SUBTITLE		i	5. FUNDING NUMBERS
Recovery After Prolonged Be	ed-Rest Deconditioning		
6. AUTHOR(S)			UPN 111-10-20
John E. Greenleaf and David	T. Quach		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)			8. PERFORMING ORGANIZATION REPORT NUMBER
Ames Research Center Moffett Field, CA 94035-1000			A-0207736
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)			10. SPONSORING/MONITORING AGENCY REPORT NUMBER
National Aeronautics and Space Administration Washington, DC 20546-0001			NASA/TM-2002-211860
11. SUPPLEMENTARY NOTES Point of Contact: Code SLR. (650) 604-3	, MS-239, Ames Research C 3234	Center, Moffett Field	, CA 94035-1000
12a. DISTRIBUTION/AVAILABILITY STA	TEMENT		12b. DISTRIBUTION CODE
Unclassified — Unlimited Subject Category 51 Availability: NASA CASI (2	Distribution: Nonstand 301) 621-0390	ard	
13. ABSTRACT (Maximum 200 words) Recovery data were analyze	ed from normal healthy test	subjects maintained	in the horizontal or head-down
body position in well-controll monitored. Because recovery	led bed rest (BR) studies in data were almost always of	which adherence to secondary importa	the well-designed protocol was
the DD mention the second strength	consistency in the recover		
ine BK period, inere was little		y experimental desig	gns regarding control factors
(e.g., diet or exercise), duration	on, or timing of data collect	y experimental designon. Thus, only abou	gns regarding control factors at half of the BR studies that
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