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SOME EVILS OF PROLONGED BED-REST DECONDITIONING*

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ABSTRACT

The adaptive physiological and psychological responses in humans as a result of their decreased physical fitness (deconditioning) during prolonged bed rest are appropriate for that new hypogravic (reduced hydrostatic pressure) and hypodynamic (reduced energy utilization) state. In healthy people, however, this new adaptive state follows the tenet that use promotes function and disuse results in disfunction and atrophy. Virtually all body systems are affected by this hypoactive deconditioning, and four are discussed: insulin-glucose intolerance because of potential diabetic effects and as an indicator of more far-reaching changes in intermediary metabolism; muscular atrophy because it impedes reambulation and may be associated with the glucose intolerance; immune function because of its critical role, in conjunction with the neuroendocrine system, for physiological control; and psychological perturbations which influence behavior and, with the immune system, the healing process in hospitalized patients. It is probable that these deconditioning responses could interfere with accurate differential diagnoses in early and especially later stages of bed rest.

Key words: atrophy, hypogravia, hypodynamia, physical fitness

Introduction

Assumption of the horizontal body posture for about 8 hr per day during sleep seems to be a fundamental requirement for maintaining optimal health. The necessity for sleep is clear, but that for the horizontal posture may not be. But these two factors are probably synergistic because the horizontal posture facilitates relaxation and sleeping. However, exposure for not much more than 8 hr per day to bed rest (BR) can be detrimental to those who, upon arising, must then function in the Earth's gravitational field.

Physiological mechanisms are activated continuously in response to various neuroendocrine-immune stimuli that readapt the body to alternating upright, sitting, and horizontal body postures and various energy states. Such stimuli activated in people during horizontal BR are: (a) virtual elimination of hydrostatic pressure on the vasculature below the heart; (b) reduced skeletal muscle force (torque) and longitudinal compression on bones (especially those of the spine and lower extremities) resulting in atrophy of both muscle and bone; (c) usually some reduction in energy expenditure;

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(d) altered stimuli to the vestibular organs; and (e) often adverse psychophysiological effects associated with a stressful environment. These stimuli are not mutually exclusive and do interact. The result is deconditioning, defined as: "1: to cause to lose fitness (prolonged inactivity deconditions a person physically) 2: to remove the effects of specialized training or unusual habits..." (26). The word evil refers to the undesirable consequences of over-prescribed and often unnecessary use of BR with people in the horizontal body position.

Extensive data are available from controlled laboratory studies with otherwise healthy subjects bed-rested for up to one year (22, 30, 33, 51), and observations from a man who had been self bed-rested at age 16 continuously since 1932 (4). However, the normal acclimative physiological and psychological responses induced in healthy bed-rested people are probably also induced in sick or injured hospitalized patients and may interfere with their differential diagnoses and subsequent recovery. Thus, the purpose for this review is to discuss some of the more egregious physiological and psychological responses to BR-deconditioning in both the clinic and laboratory with the suggestion that care should be taken in prescribing prolonged BR.

Clinical aspects of prolonged bed-rest deconditioning

History. The purposes for most early application of BR studies were clinically oriented. The evils of BR-deconditioning were well-known to Hippocrates (500 B.C.) who observed an obvious reduction in strength, as well as a general functional deterioration, in those who returned from a period of excessive rest and inactivity (10). From 1855 to 1929 there were a few investigators that had utilized short-term BR (<5 days) alone, and in conjunction with exercise, to study protein and calcium-phosphorus metabolism, circadian rhythms, and basal and respiratory metabolism (22). Prior to World War II the general prescription for BR was two weeks after childbirth, three weeks after herniorrhaphy, and four to six weeks after myocardial infarction (3, 13). World War II reactivated interest in these problems and in 1944 T.R. Harrison organized a symposium on "The Abuse of Rest in the Treatment of Disease" that included reports on cardiopulmonary lesions (16), obstetrics (18), orthopedic surgery (23), heart disease (37), psychiatry (56), and general surgery (68). Powers (68) observed post-operative complications incidental to early ambulation on the first day after the operation in 100 consecutive patients, and later ambulation (after 10-15 days of BR) in 100 other unselected patients, after similar major operations. The number of complications for the respective early and later post-operative activity were: local surgery 4, 8; pulmonary 3, 6; cardiac 0, 3; vascular 2, 5; genitourinary 8, 14; gastrointestinal 0, 5; for totals of only 17 complications with early ambulation and 46 with later ambulation. This was probably the beginning of the resurrection of early ambulation after operations and BR. The general finding from the symposium was that, while a period of time in the recumbent body position is necessary for amelioration of some injuries and illnesses, too much time in bed is often harmful; the earlier the ambulation the better – a conclusion still applicable.

Disabilities. Unnecessary clinically oriented problems due to prolonged BR include: joints – atrophy of articular structures, contractures, and attenuated range of motion; muscles – atrophy from disease and inactivity; bone – atrophy, osteoporosis, and pathologic fractures; urinary–tract infection and renal stones; heart – decreased cardiac reserve and stroke volume, and resting and post-exercise tachycardia; circulation – increased blood viscosity, orthostatic hypo-

tension, and thrombophlebitis; lung – pulmonary embolism, atelectasis, and hypostatic pneumonia; gastrointestinal – anorexia, hospital-acquired malnutrition, constipation, and impaction; skin – atrophy resulting in decubitus ulcer; and psyche – anxiety, internal aggression, irritability, depression, and disorientation (3, 13, 21, 37). Many of these disabilities exacerbated by the reduced activity, hypovolemia, and total body dehydration from BR, can be alleviated or eliminated by an understanding of their etiology and application of appropriate countermeasures (usually exercise/ambulation). While some infirmities require prolonged BR, the amelioration of many of the above problems falls on the nursing and support staff, and on the physicians. If these problems continue unchecked, a vicious cycle ensues requiring additional treatment and continuing BR.

Saga of Jonnie Richardson. In 1932, after returning home from a ball game in the mountains of northwest North Carolina where he had a little drink or two of whiskey, 16 year-old Jonnie Richardson, ordered to bed by his dominant mother, was never to arise again. In 1982, 50 years later at age 66, he said that he had not sat up since 1942 and had not rolled over since 1960. His older sister who visited him every day said, in 1982, that the family doctor had diagnosed heart trouble and a goiter but he couldn't endure an operation. Richardson, who managed on $159/mo, declined being moved to his sister's home for fear of losing his. His immediate needs were met by a tangle of wires and hoses that converged at his bed side; water came from a stream 700 ft away, and bodily functions were handled with plastic bags. His entertainment was viewing black cattle, brown rabbits, and deer in the woods and listening to news, weather and some gospel music on his radio or television. He used to read but couldn't hold a book, his eyes were failing, and his lily-white frame had "limbs as thin as the legs of a ladder-back chair" (4).

Clinical studies. Analysis of data from several recent clinical studies has emphasized the undesirable effects of prolonged BR. For treatment of premature labor or preterm rupture of membranes Kovacevich et al. (43) found, by retrospective analysis of data collected during 1997 and 1998, that the prevalence of thromboembolic events was 16/1000 among 192 women who underwent prescribed extended BR (>3 days). Conversely, this incidence ratio was significantly smaller (1/1000 women, $p < 0.002$) for 6164 deliveries in women who were not subjected to prolonged BR. Maloni (54) concluded, from a review of literature, that inappropriate prescription of BR in pregnancy causes unnecessary physiological and psychological stress on the mother that often continues into her recovery period.

From a literature search of more than 2000 abstracts dated 1996 to 1998, Allen et al. (1) selected data from 39 randomized-controlled trials and performed benefit/harm ratio analyses of the effect of BR (from 4 hr to 20 weeks) on 15 different disorders in 5777 patients. In the 15 trials where BR was a primary treatment; no condition was improved and nine were deleterious including labor, acute low back pain, proteinuric hypertension during pregnancy, myocardial infarction, and especially rheumatoid arthritis. In the remaining 24 trials where BR followed a medical procedure; no condition improved and eight proved deleterious including cardiac catherization, radiculography, spinal anaesthesis, and lumbar puncture. Routine BR for 24 hr appears to be unnecessary after cervical myelography (52) and after lumbar puncture (53). Thus, in some conditions BR was harmful but never helpful. Moseley (59) has concluded that the major challenge faced by those trying to avoid excessive clinical BR deconditioning is overcoming resistance to change.

Table 1. *Time-Course of Physiological and Biochemical Changes During Bed Rest*

0 - 3 days	4 - 7 days	8 - 14 days	Over 15 days
Urinary diuresis	Creatininuria	Pyrophosphaturia	Peak hypercalciuria
Increased urinary sodium and calcium loss	Hydroxyprolinuria	Decreased red cell mass	Changed sensitivity to thermal stimuli
Decreased plasma, interstitial, and extracellular fluid volumes	Phosphaturia	Decreased leukocyte phagocytosis	Secondary increase in auditory threshold
Decreased secretion of gastric juice	Negative N_2 balance	Excessive exercise hyperthermia	
Decreased calf blood flow	Increased blood fibrinogen and clotting	Decreased tissue heat conductance	
Increased venous compliance	Increased blood fibrinolytic activity	Increased blood viscosity	
Increased neutrophil phagocythosis	Increased auditory thresholds		
Glucose intolerance	Decreased near - point of visual acuity		
Decreased $+G_z$ acceleration tolerance	Lengthened focal point		
Decreased urinary PO_4	Increased hyperemia of eye conjunctiva and dilation of retinal arteries and veins		
Orthostatic intolerance	Decreased neutrophil absorption		
Increased blood viscosity	Reduced bone formation		
Muscle atrophy	Decreased serum parathyroid hormone and 1,25 – dihydroxyvitamin D		
	Increased blood viscosity		

So perceptive clinical observations and analysis of BR infirmities, coupled with proper understanding and application of the physiological mechanisms involved, could result in effective countermeasures that should ameliorate many of these iatrogenic and non-iatrogenic maladies.

Physiological aspects of prolonged bed-rest deconditioning

Many physiological and biochemical changes occur during BR deconditioning, and it is often difficult to determine their onset and duration. A time-interval estimation of some of these changes, extracted from various research reports, indicates that virtually every body system is affected (Table 1). But it is a certainty, without countermeasures, that progressive atrophy of muscle and bone continues throughout the period of BR (see Jonnie Richardson).

Muscular atrophy, strength, and training. Atrophy is defined as "1: decrease in size of a part or tissue after full development has been attained: a wasting away of tissue (as from disuse, old age, injury, or disease)" (26). Maximal static strength is measured with a fixed joint pressing against a fixed measuring device; and maximal isokinetic strength (peak torque) is measured at maximal effort with a moving joint at a specific limb speed (in degrees/sec).

In general, there is a proportionally greater loss at maximal static muscular strength than comparable muscular mass (atrophy) during prolonged BR. Mean loss of static strength in the upper body (hand, forearm, arm shoulder, back) of about 6% is the same as that in the lower body (abdomen, thigh, leg) muscles of 5% during the first 6 weeks (7 to 44 days) of BR (Fig. 1, upper panel). However, during the ensuing 7 weeks of BR (63 to 95 days), the additional loss of strength in the lower body (by 39%) was somewhat greater than that (by 25%) in the upper body. But these mean and differential strength losses were not proportional to the comparable muscle mass losses in the lower body (Fig. 1, middle panel) where, earlier (28 to 35 days) in BR, the mean mass decreased by 10% whereas strength decreased by only 5%. Later, at 119 days of BR, the 5% loss of mass can be compared with the much greater decrease in strength (by 39%) from 63 to 95 days of BR.

In contrast to static strength, the pattern and magnitude of changes in muscle mass resemble more those of maximal isokinetic strength with greater loss earlier (at 35 days of BR) rather than later at 112 days of BR (Fig. 1, lower panel). But similar to static strength responses, the decreases in peak torque were also greater in the lower than in the upper extremities. Thus, during BR deconditioning it seems clear that the magnitude of change in maximal static strength is different from that of maximal isokinetic strength probably because of different muscle activity and methods of measurement. Thus changes in muscle mass are more closely related to changes in maximal isokinetic strength, and maximal strength losses are about twice as great in the lower extremities than in the upper extremity muscles.

Muscular strength and endurance were studied during daily (2 x 30 min) isotonic (each 30 min of leg cycling from 40% to 90% of maximal oxygen uptake) exercise training (ITE, n = 7) and daily (2 x 30 min) isokinetic (each 15 min of 50 maximal knee flexion-extension repetitions for each leg at a velocity of 100°/sec through 90° to 100° arc) exercise training (IKE, n = 7) during 30 days of 6° head-down BR (27). Mean knee extension total work (torque x velocity x repetitions, in N-M) increased by 27% with IKE, was unchanged with ITE, and decreased by 16% in the no exercise (NOE, n = 5) group; whereas knee flexion total work was unchanged in all groups. Peak torque (strength) for right knee extension

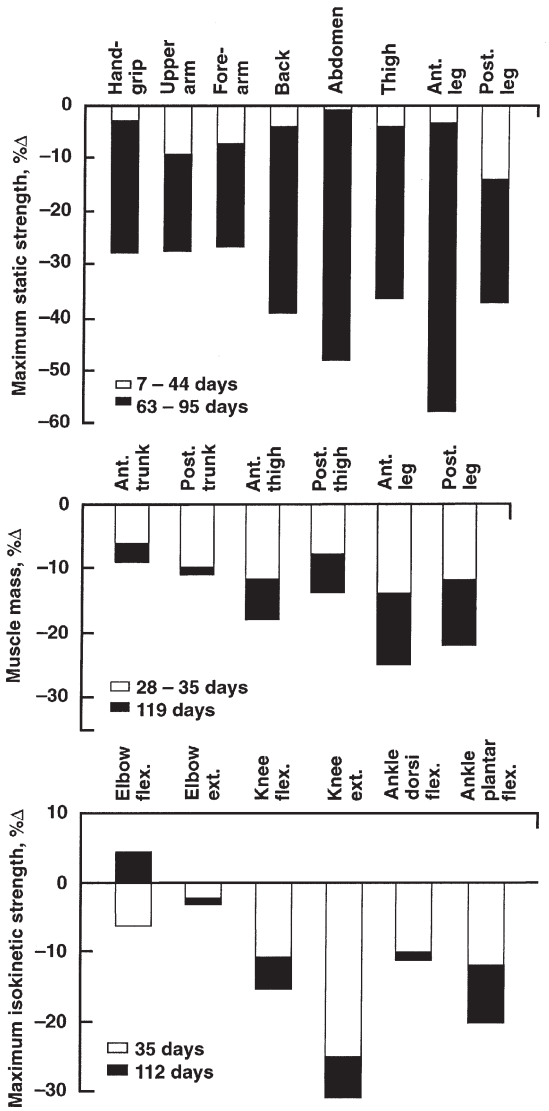

Fig. 1. *Upper panel - mean percent changes in maximal static strength in upper and lower body muscle groups earlier: 7 to 44 days, from Greenleaf et al. (35) and later 63 to 95 days, from Yeremin et al. (86) during BR. Middle panel - mean percent changes in muscle mass (limb circumferences) in the trunk and lower extremities. From LeBlanc et al. (45) and Ellis et al. (20). Lower panel - mean percent change in isokinetic (dynamic) muscular strength at 60°/sec after 35 and 112 days of BR. From LeBlanc et al. (45)*

increased with IKE, was unchanged with ITE, and decreased with NOE (Fig. 2, upper panel), but was more random with knee flexion (Fig. 2, lower panel). Shoulder abduction and adduction strength and endurance were measured on BR days 10 and 26: in all groups mean total work was unchanged but mean peak torque increased. Thus, in confirmation of results from previous studies, upper body muscular strength is maintained better than that in the lower body. While the muscle-specific isokinetic exercise training was usually able to overcome the deconditioning effect and actually increased strength above pre- BR levels, the non-specific isotonic exercise training was also able to overcome the deconditioning effect and at least maintain lower extremity strength near pre-BR levels.

The mechanism of muscular atrophy

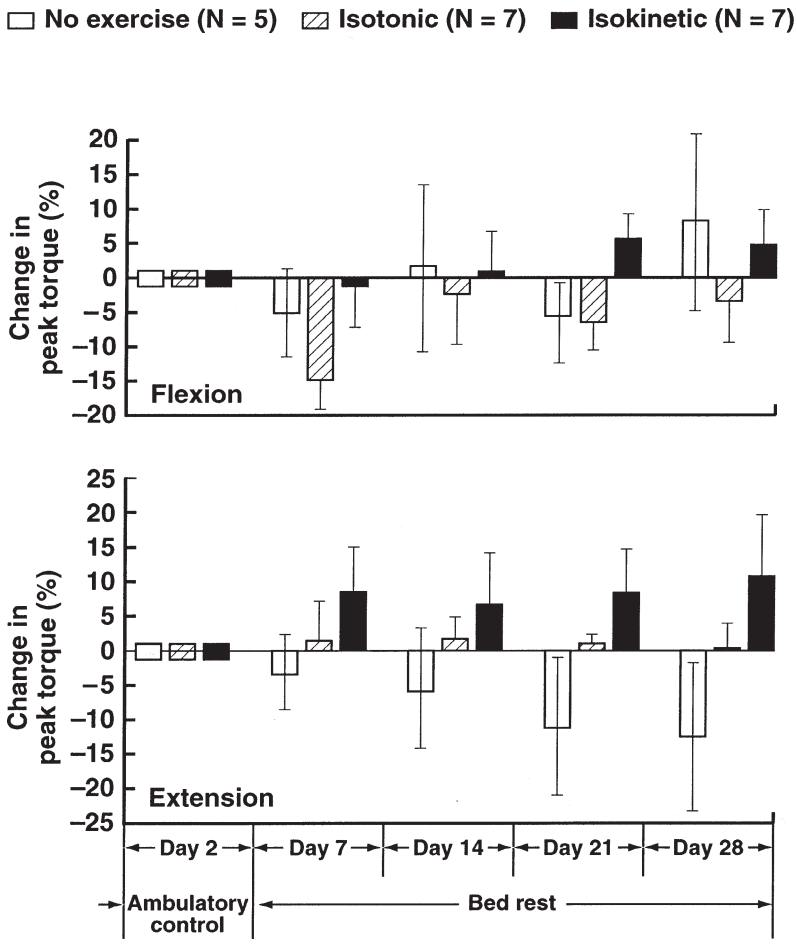

Fig. 2. *Mean (± SE) percent change in peak torque (strength) for right knee flexion (upper panel) and for right knee extension (lower panel) after 28 days of -6° head-down BR with isokinetic, and no exercise training. From Greenleaf et al. (28) with permission.*

involves gross anatomical changes in its water, fat, and connective tissue content resulting from various cellular responses. Because the lower extremity anti-gravity muscles that assist in maintaining the erect body posture are affected more during BR –deconditioning, the soleus (an ankle plantar flexor) and quadriceps (knee extensor) muscles are frequently studied. Gross structural anatomy of muscle after 30 days of BR in men (38) and 5 months of close confinement in dogs (62) indicates fiber disorganization, degeneration, and reduced mitochondrial density. These aberrations in the dogs were reversible and normalized after their release from confinement.

In men, after 17 days of 6° head-down BR–deconditioning without countermeasures, the peak isometric force of soleus muscle fibers (mainly slow Type 1, myosin heavy chain) decreased significantly by 11% to 13% while unloaded fiber shortening velocity at peak power increased by 13% to 34% (83, 84). Thus, as the atrophy reduces contractile force, the increased velocity maintains power; i.e., force x velocity (71). While the thick myofilament fiber packing density was unchanged with deconditioning, the thin filament (actin) density was decreased by 16% to 24%; and a 1% decrease in thin filament density increased unloaded shortening velocity by about 10%

(71, 84). Thus, changes in the geometry between thick and thin myofilaments; e.g., increased interfilament spacing (because of fewer filaments) inducing earlier cross-bridge detachment, would result in increased velocity. Larsson et al. (44) studied the vastus lateralis muscle from subjects after 37 to 42 days of BR and also found a reduced number of force-generating cross-bridges.

Insulin-glucose intolerance. Oral glucose (blood sugar) tolerance tests (OGTT) have been used for nearly 100 years to diagnose early stages of diabetes mellitus in people with otherwise normal fasting plasma glucose concentrations [pGlu]. Some hyperglucosemia data from the early 1900's were obtained from healthy elderly people, and later from patients hospitalized with arteriosclerosis and cardiac infarcts (56%, n=192), circulatory disturbances (>67%, n=72), arthritis (57%, n=222), and in patients with tuberculosis, carcinoma, pregnancy, spinal cord injury, and depressive psychomotor inhibitive psychoses (8). This variety of ailments, as well as the fact that the hyperglucosemia remained after health was restored, led researchers to question whether some aspects of prolonged BR itself – with attendant muscular atrophy – could be the cause. With this hypothesis in mind the earlier data indicated that a long period of physical exercise training reduces blood sugar (69), shorter more strenuous exercise increases blood sugar (70), and exercise lowers blood sugar in diabetics who had an adequate supply of insulin. Then Blotner (6) measured the dextrose (glucose) tolerance in 36 men and 34 women (18 to 92 yr, < 79 kg wt) and in 10 boys and 6 girls (4 to 13 yr) hospitalized from 1 mo to 13 yr for a variety of diseases and injuries. A family history of diabetes occurred in only 2 of the adults (3% of the 70 patients) - a normal incidence. The results indicated that dextrose tolerance was decreased in patients confined to BR for those extended periods; that tolerance returned to normal during reambulation after BR; and because the patients' muscles were capable of normal carbohydrate metabolism he concluded that reduced pancreatic function during BR was the more likely cause of the Glu intolerance. Blotner (6) also concluded that reduced muscular activity was the common denominator in those 86 patients, and that the "diminished sugar tolerance noted in old persons is not due to age but to the inactivity associated with age and that if these people were normally active their sugar tolerance would likely be normal." There was no mention of the change in body position in the BR patients as a possible contributing factor for their intolerance.

Basal [pGlu] is elevated significantly from an ambulatory control level of 83-84 mg/100ml to 86-89 mg/100ml by Day 2 of horizontal BR because of the concomitant reduction in plasma volume (PV, hypovolemia); thereafter the pGlu content decreases in proportion to the PV so that [pGlu] decreases to control (basal) levels by BR Day 13 (17).

Because insulin-glucose intolerance occurs within the first 3 days of BR (17, 47, 76, 85) and most likely after 24 hr of BR (65), it would seem that this short period would eliminate significant muscular atrophy as a major factor for the intolerance. Lipman et al. (47) found abnormal tolerance in monkeys after 2 to 16 weeks of vertical whole-body immobilization in full body casts, thus tending to negate the influence of the horizontal posture (reduced hydrostatic pressure) as a factor for the intolerance. They also performed OGTT on 8 subjects on day 40 of an ambulatory-control period, and on day 35 of horizontal BR during which 4 of the subjects performed ergometer exercise supine for 3 x 20 min periods/day at 70% of their maximal oxygen uptake (600 kcal/day), while the rema-

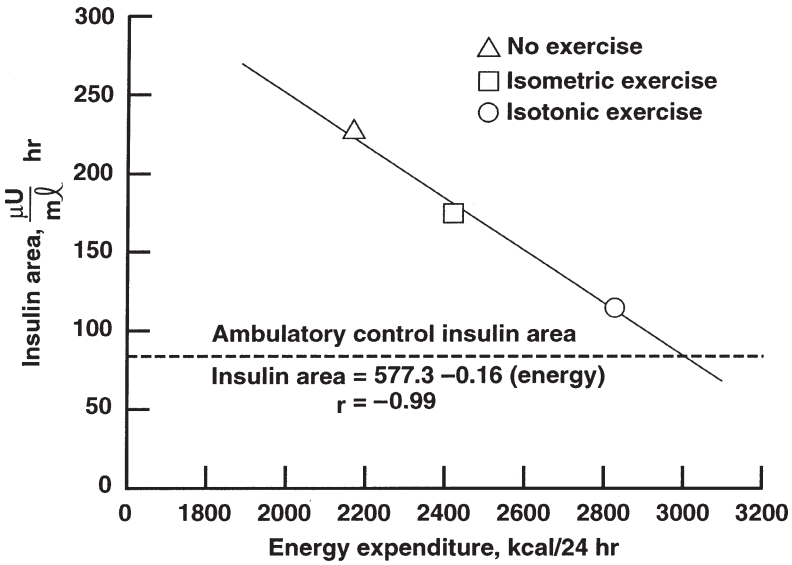

Fig. 3. *Regression of integrated area under insulin response curves during glucose tolerance tests on 24-hr estimated energy expenditure for 3 bed-rest regimens. From Dolkas and Greenleaf (17) with permission.*

ining 4 control subjects performed no additional exercise during BR. They found a hierarchy of areas (μU/ml/min) under the insulin OGTT curves: BR-no exercise (8743 ± SE 1818), BR-exercise (4633 ± 1002), Control-no exercise (3406 ± 217), and Control-exercise (1772 ± 1039). Thus, BR-exercise tended to normalize (reduce) the intolerance – area under the curves – (4633 vs. 8743), as did Control-exercise (1772 vs. 3406). But the greater BR-exercise area (4633) vs. Control-exercise area (1772), and the greater BR-no exercise area (8743) vs. the Control-no exercise area (3406) suggested an upright posture factor for the lower tolerance.

Those findings were extended by Dolkas and Greenleaf (17) who found a highly significant negative linear correlation coefficient (r = -0.99) between total daily energy expenditure (kcal/24 hr) and area under the insulin tolerance curve (μU/ml/hr) resulting from no exercise and daily isometric and isotonic exercise-training regimens during 14 days of horizontal BR (Fig. 3).

To determine the effect of prior strength and endurance training on Glu metabolism during 3-days of BR deconditioning, insulin sensitivity was measured in 10 strength-trained athletes and 8 long-distance runners who had trained daily for at least 3 yr (76). The two groups of athletes had greater hyperinsulemia (endurance group more so) than the 11 sedentary men. Areas under the immunoreactive insulin curves (IRIauc) were increased significantly after BR in all 3 groups; highest in the endurance group (by 100%) versus the lowest (by 40%) in the sedentary group. The ratio of IRIauc/GLUauc increased significantly only in the endurance group. Thus, intensive strength and endurance training before BR does not seem as effective for reducing BR-induced Glu intolerance as daily intensive exercise training during BR (17). It appears the exercise stimuli during BR must be reinforced at intervals less than 3 days.

A daily caloric expenditure of about 3000 kcal seems to be required to maintain normal Glu tolerance during BR (Fig. 3). Perhaps also during normal ambulation? This 3000 kcal/day threshold may explain

why some sedentary and some elderly people have abnormal OGTT responses because they have sub-threshold daily energy expenditure. The longer the period of BR with reduced activity the greater the frequency and amplitude of the OGTT curve (6, 8, 36) and 7 to 14 days of ambulatory recovery are required to normalize insulin-glucose intolerance after prolonged BR if no remedial exercise training is undertaken (48); but intensive exercise conditioning during recovery normalizes the intolerance by Day 7 (50).

Although the description and time-course changes of insulin-carbohydrate responses before, during, and after prolonged BR are essentially defined, the mechanism is not. The lack of response of the increased plasma glucose levels during an OGTT in the presence of high insulin concentrations during BR suggests that immunoreactive insulin deficiency is not the major cause of the Glu intolerance; and exogenous insulin is no more effective that endogenous insulin for lowering the increased [pGlu] (2). The unresponsiveness of the elevated [pGlu] to the hyperinsulinemia suggests that the insulin is modified by the presence of an insulin inhibitor perhaps at its membrane binding sites; that some other cellular membrane function is changed or blocked; or that there is functional inhibition of a second factor with insulin-like activity. Most evidence suggests no significant changes (or decreases) in the resting blood concentrations of some important insulin antagonists during BR such as cortisol, free fatty acids, and growth hormone (49), arterial (58) and urinary (67) catacholamines, or the many plasma amino acids (19) which have a similar relationship to insulin as does glucose.

Because suppression of hepatic Glu production by insulin was unchanged after 7 days of BR deconditioning without remedial exercise training, Stuart et al. (79) concluded that the substantial resistance of insulin on Glu metabolism occurs primarily in the skeletal muscle metabolism which accounts for about 90% of the clearance of an oral or intravenous Glu load (5), but the 24-hr onset of Glu intolerance suggests otherwise.

Another important hypodynamic situation inducing altered Glu metabolism occurs during the post-surgical catabolic state where the magnitude of the decrease in insulin sensitivity is quite consistent and related to the degree of surgical trauma (61, 80), and can persist for 2 to 3 weeks after spinal fracture (61) and elective abdominal surgery (81). Nygren et al. (65) determined insulin-Glu sensitivity in 7 patients (41 to 56 yr) who underwent elective uncomplicated surgery and found that this catabolic-induced insulin resistance was due mainly to a combination of increased endogenous Glu production (from liver and kidney) via glucagon, and decreased insulin sensitivity – in relation to whole-body Glu disposal – in peripheral tissues; i.e., muscle. Here, also, the counter-regulatory hormones such as cortisol, catecholamines, growth hormones, alanine and other glycogenic amino acids, as well as some cytokines, were not elevated after surgery. Data from a group of healthy volunteers who were subjected to the same surgical protocol but without the surgery (24 hr of BR with a low caloric diet) also showed significant reduction in insulin-stimulated whole body Glu disposal with no effect on endogenous Glu production (65). It appears that post-surgical insulin resistance can be induced by only 24-hr of BR, a duration seemingly too short to effect muscle metabolism significantly. This again raises the question of a possible effect of the change in posture!

Immune function. Body immune function in healthy ambulatory people is modulated by body position; i.e., upright versus supine posture (25, 41), by isolation and

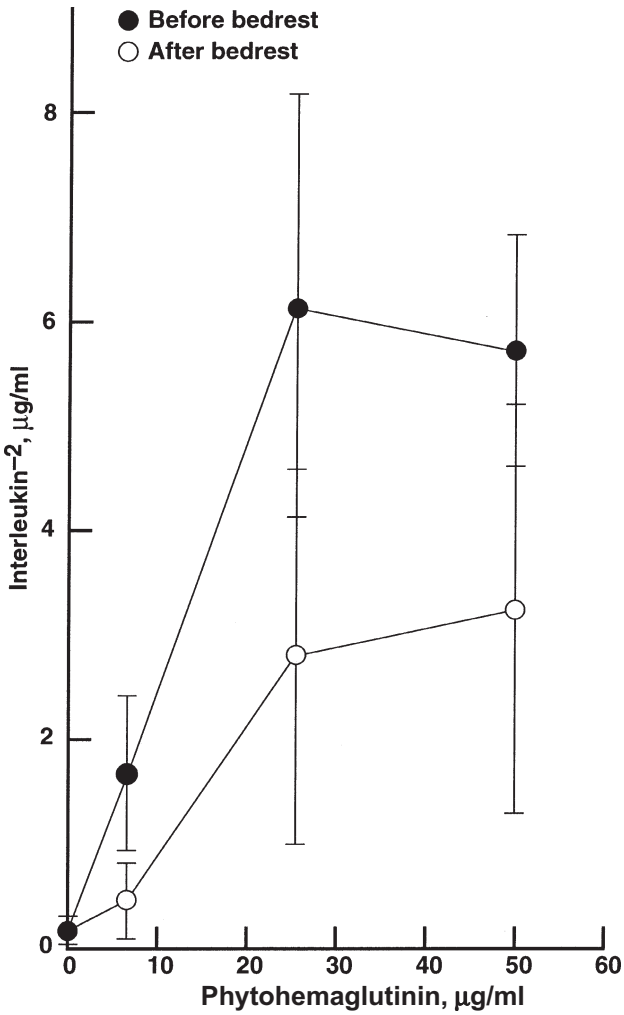

Fig. 4. *Mean (± SE) PHA-induced interleukin production by peripheral blood mononuclear cells from 6 men before and after 6 weeks of head-down bed rest. From Schmitt and Schaffer (74) with permission.*

confinement (74), and by their levels of physical exercise training where moderate exercise enhances immune function (9, 31, 40, 63, 64, 82) but prolonged exercise and intensive exercise training appear to depress immune function (24, 64). Immune modulation is not influenced by prior level of physical fitness; i.e., maximal aerobic oxygen uptake (40), but performance of regular moderate exercise will enhance immune function and offer protection from infections (66).

People undergoing prolonged BR usually assume the horizontal or, in some experimental protocols, a slight head-down (minus 6 degrees) posture when they experience significant loss in their level of physical fitness (deconditioning) that is induced partially by reduced exertion and total body energy utilization. The latter decrements would probably be exacerbated in sick or injured hospitalized patients because of their further reduced body movement. Thus, it is not surprising that immune function should also be attenuated in subjects or patients without engaging in additional exercise tra-

ining while in bed (11, 12, 39, 57); with two possible exceptions (14, 60) where immune function appeared to increase. And exercise training during BR has been reported to restore some immune functions (11, 25, 39).

There are few data concerning immune function from well-controlled BR studies; many of the BR findings published before 1990 have been summarized by Greenleaf et al. (31). Most immune responses were either unchanged [immunoglobulin, T-cells, $CD4^+$, and natural killer (NK) cell activity] or decreased [blood properdin, neutrophil phagocytic activity, NK cell activity, salivary lysozymes, brain immunoglobulins A and G, and liver B-lymphocytes and phytohemagglutinin activity (PHA)]. Konstantinova (42) reported decreases in PHA reactivity and NK cell activity after 120 to 180 days of BR. Schmitt and Schaffar (74) found an increase in interleukin-1 (IL-1) production in unstimulated lymphocytes, but not in PHA-stimulated lymphocytes; and a nearly significant decrease in PHA-induced IL-2 production by peripheral blood mononuclear cells (PBMC) in men after 6 weeks of head-down BR (Fig. 4).

These latter findings were confirmed and extended by Schmitt et al. (75) who measured absolute counts of T-lymphocyte subpopulations and immune function of leukocytes over 119 days of horizontal BR in 2 physically-fit females. Mean total white-cell counts were not different between BR Day 0 (5055) and BR Day 50 (5700), and they returned to baseline levels (5300) by recovery Day +15 (Fig. 5). Percentages of $CD3^-/CD16^+/$ $CD56^+$ and NK cells were relatively stable during BR and recovery, but there were reductions in $CD3^+$, $CD4^+$, and $CD8^+$ cells through BR Day 106 with little restoration by recovery Day +15. However, the $CD4^+/CD8^+$ ratio (T-helper/T-suppressor) remained unchanged (between 1.9 and 2.1) to BR Day 106 – slightly above the upper limit of normal of 1.5 (32). A decreased $CD4^+/CD8^+$ ratio indicates immunosurpression; however this ratio increased to 6.4 at BR Day 119 and was 5.3 on recovery Day +15 (Fig. 5) suggesting immuno-enhancement later in BR and recovery. Mean mitogenic responses which determined the ability to respond to PHA or to CD3 antigen stimulation were essentially stable during BR, but decreased precipitously during recovery (Fig. 6). Mean NK cell activity decreased progressively over BR and remained low at recovery Day +15. An important change during BR was an increase in net IL-1 by PBMC in both subjects; no net IL-1 was detectable before or after BR. The IL-2 production decreased somewhat at BR Day 50 in both subjects, but returned to baseline by BR Day 119 (Fig. 6). A subsequent 6^o head-down BR study of 28 days was conducted on 6 physically fit male deep-sea divers. Only three of the men underwent strenuous short-term resistance exercise plus lower body negative pressure countermeasure training during BR Days 7 to 28. Immune data from the 3 exercisers and 3 non-exercisers were combined. The IL-2 was determined from PBMC cultured in the presence of increasing concentrations of PHA before (Pre-Day 7) and after (Post +0 Day) BR (Fig. 7). There was no difference in IL-2 production in the unstimulated (0 μg/ml) or minimally stimulated (0.5 μg/ml) PBMC. However, at PHA concentrations of 2 and 4 μg/ml, IL-2 secretion was suppressed (not increased) significantly after BR in all subjects. It is interesting that there was no significant difference in IL-2 responses between the exercise and no-exercise groups in this study or in that by Lesniak et al. (46) because moderate exercise training tends to enhance immune function while intensive exercise of training tends to suppress immune function in ambulatory people. Whether these effects of exercise intensity and duration on

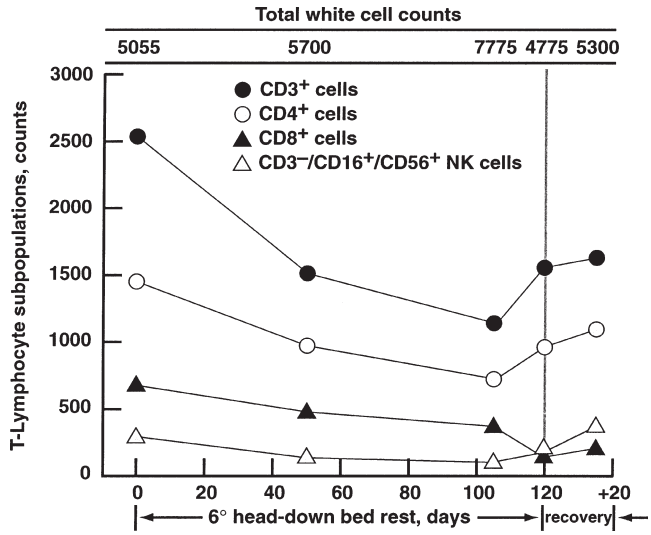

Fig. 5. *Mean absolute counts of total white blood cells and T-lymphocyte subpopulations from two physically-fit females during 119 days of horizontal bed rest, and after 15 days of ambulatory recovery. Redrawn from Schmitt et al. (75).*

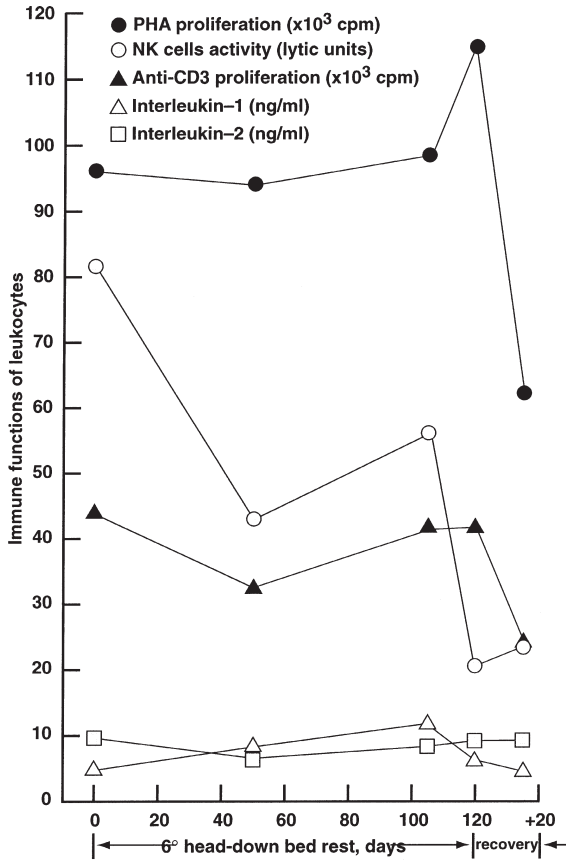

Fig. 6. *Mean immune functions of leukocytes from two physically-fit females during 119 days of horizontal bed rest, and after 15 days of ambulatory recovery. Redrawn from Schmitt et al. (75).*

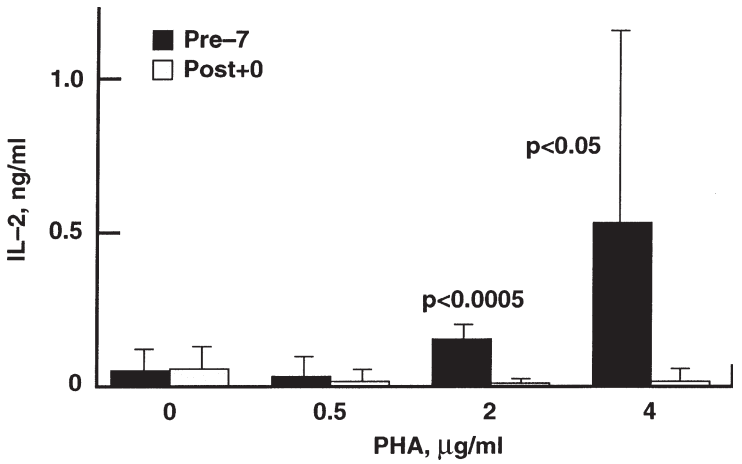

Fig. 7. *Mean (±SE) in-vitro interleukin-2 secretion before (Pre -7) and immediately after (Post + 0) 28 days of 6° head-down bed rest in six physically-fit male deep-sea divers. IL-2 was measured in supernatants from four concentrations of phytohemagglutinin (PHA) - stimulated T-lymphocytes. From Schmitt et al. (75) with permission.*

immune function occur during BR is unclear, particularly with IL-1 and IL-2.

Psychophysiological aspects of prolonged bed-rest deconditioning

Healthy people subjected to prolonged BR undergo not only physiological acclimation, but also additional psychological perturbations requiring the integration of various degrees of confinement and unfamiliar social interactions which may be exacerbated by symptoms of illness in hospitalized patients. Prescription of BR for treatment of psychiatric illness has been used and often misused. Before World War II one popular hypothesis was that essentially all nervous illnesses were the result of physical exhaustion, and that the pervasive treatment of the patient should be complete isolation and BR with "no visitors, no letters, no reading, no writing; the constant attendance of a nurse, some massage and electricity and, withal, high caloric feeding" (56). Menninger (56) counters this philosophy:.. "the abuse of rest as a treatment in psychiatric conditions represents a neglect or misunderstanding of the real pathologic condition of the neurotic patient under the guise of a treatment which is not only futile and expensive but very often definitely harmful." He recognized early that the proper treatment of many psychiatric patients – who often cannot work, cannot play, and cannot rest – is physical exertion via the directed use of muscles, and that enforced rest tends to exacerbate those problems. These considerations are also applicable for the conduct of controlled BR studies with healthy human test subjects.

There are few observations and fewer data concerning psychophysiological problems during prolonged BR (7, 15, 55, 72, 73, 77, 78). The following signs and symptoms pertain to naive male test subjects during prolonged BR without countermeasures. On days 1 to 2 the subjects are in good spirits but with an understandable underlying tendency of fear and uncertainty. On days 3 to 6 they begin to complain of unpleasant feelings, fullness in the head, and pain, especially in the lower back; some express general weakness and dizziness with side-to-side head movements. The novelty of the situation has disappeared and their attention is directed to their general discomfort. Days 7 to 35 is a period of acclimation to the experimental conditions where asthenic (feelings of weakness and debilitation) symptoms appear that are marked by irritability, a strong desire to get up,

and daily positive and negative mood swings. Sleep quality becomes shallow with more dreaming. One subject (on day 20) exhibited significant headache, dizziness, nausea, crying, general lassitude, depression, difficulty concentrating, fitful and little sleep, finger tremor, hyperhidrosis, and hyperkinesia; so his BR was terminated. But some subjects could lie quietly in one position for hours and be content for up to 70 days of BR (7). In days 36 to 70 the general signs and symptoms of asthenia increased when subjects often reacted more forcefully to every little infringement on their interests; everything bothered them. Some would pull the bed covers over their heads for hours at a time. Sleep disturbances were aggravated. But during the last few days of BR the subjects were elated and talkative, but sleep disorders increased.

Many of these signs and symptoms were attenuated when subjects, required to remain on their backs while in bed, were allowed to turn over and move about the bed; and when various exercise-training regimens were utilized as countermeasures (7, 15, 78).

To determine the effect of exercise training, 8 mood-state and 2 sleep-quality parameters were measured daily before, during 30 days of 6 ° head-down BR, and during 4 days of ambulatory recovery in a no-exercise training control group (n = 5), and in isotonic (n = 7) and isokinetic (n = 6) exercise-training groups (Fig. 8, [15]). There were improvements in physical discomfort, elation, and arousal state in the no-exercise group who had one maximal oxygen uptake test weekly; and no significant changes in mood parameters in the isokinetic

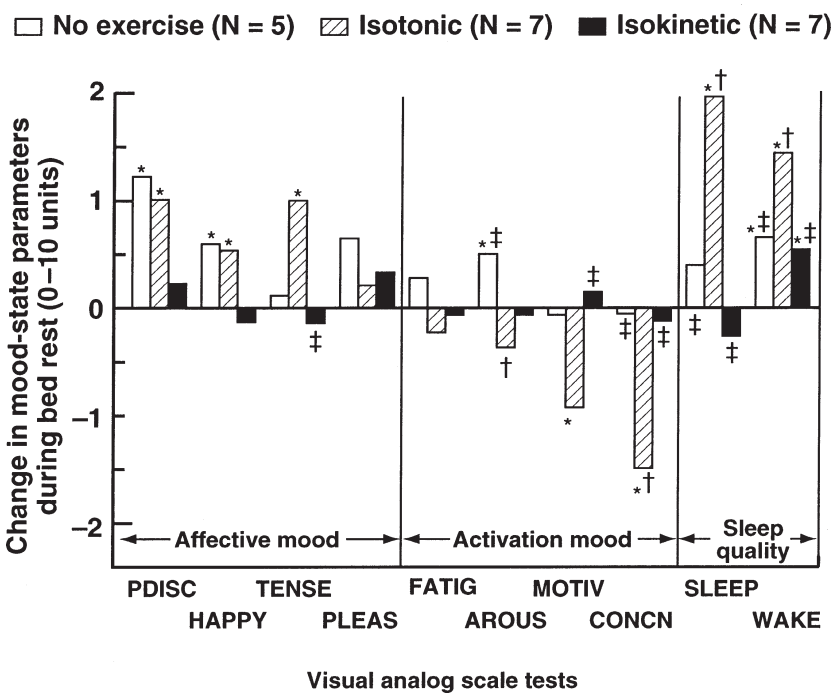

Fig. 8. *Mean change in daily affective and activation mood states and sleep quality measurements for the three groups of men during 30 days of 6° head - down BR. A positive change indicates improvement. PDISC (physical discomfort), HAPPY (elation), TENSE (psychological tension), PLEAS (contentedness), FATIG (energy level), AROUS (arousal state), MOTIV (motivation to perform), CONCN (ease of concentration), SLEEP (trouble falling asleep - higher score less trouble), and WAKE (number of waking episodes). *P<0.05 from zero; +P<0.05 from corresponding no exercise group, ‡ P<0.05 from isotonic exercise group. From DeRoshia and Greenleaf (15) with permission.*

group. In the isotonic group there were significant improvements in physical discomfort, elation, psychological tension; and significant decreases in motivation and concentration which probably indicated some degree of over-training. Isotonic exercise training attenuated trouble falling asleep but increased the number of waking episodes (Fig. 8). A concerted effort was made during this study to maintain a positive and upbeat emotional environment among the test subjects and between them and the staff. Fourteen of 18 subjects (4 declined to respond) rated their social interactions uniformly positive which probably mitigated many of the adverse asthenic responses reported in prior studies.

Upon reambulation after BR there is much talking and walking. Essentially all subjects complain of muscular pain in the lower extremities, especially on the bottom of the feet, immediately upon arising which undoubtedly contributes to the general physical weakness, poor exercise tolerance and reduced orthostatic stability.

Another interesting interpersonal situation, called migration of authority (77, 29, 34), is were the most outgoing, cheerful, and mobile subject acquires seniority of their group at the beginning of BR. Midway through BR this intragroup hierarchy is readjusted so that this subject migrates to near the bottom and seniority is transferred to a quieter and more-stable subject who retains this position throughout the remainder of the study. However, when this emerging leader of a previous study (34) found out that he would not retain that position in a second study (29), he withdrew during the control period.

Thus, the overall clinical picture is that of the typical neurasthenia syndrome with a predominance of hyperasthenic symptoms (aggression, irritability) associated with the somewhat milder asthenic symptoms of debility, hypokinesia, fatigue, and exhaustion that can be attenuated with positive effective leadership and isotonic-exercise training during BR.

Practical application

There is a potentially serious problem concerning differential diagnosis and treatment of longer-term BR patients; that is, separating the signs and symptoms of BR-deconditioning from those of the infirmity itself. They may or may not be independent. Most medical and hospital housekeeping problems of this type in BR facilities can be solved by elucidation (awareness) of the situation followed by application of appropriate preventive countermeasures or remedial procedures. A good place to enhance this educational process is in medical and nursing textbooks with appropriate sections on the physiology of BR-deconditioning as well as the functional physiology of physical exercise, the upright posture, and their use as countermeasures.

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