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Clinical Physiology of Bed Rest

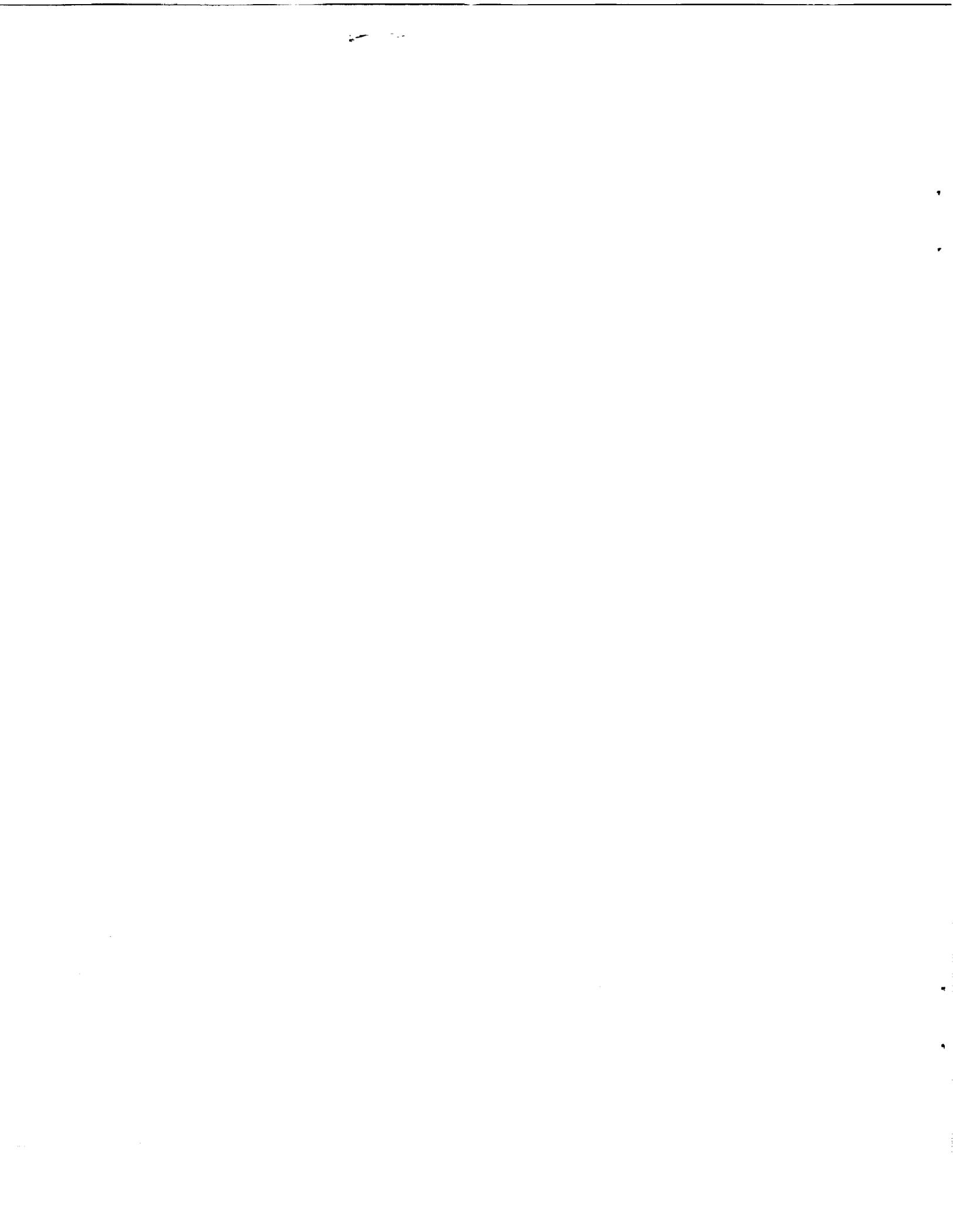## John E. Greenleaf

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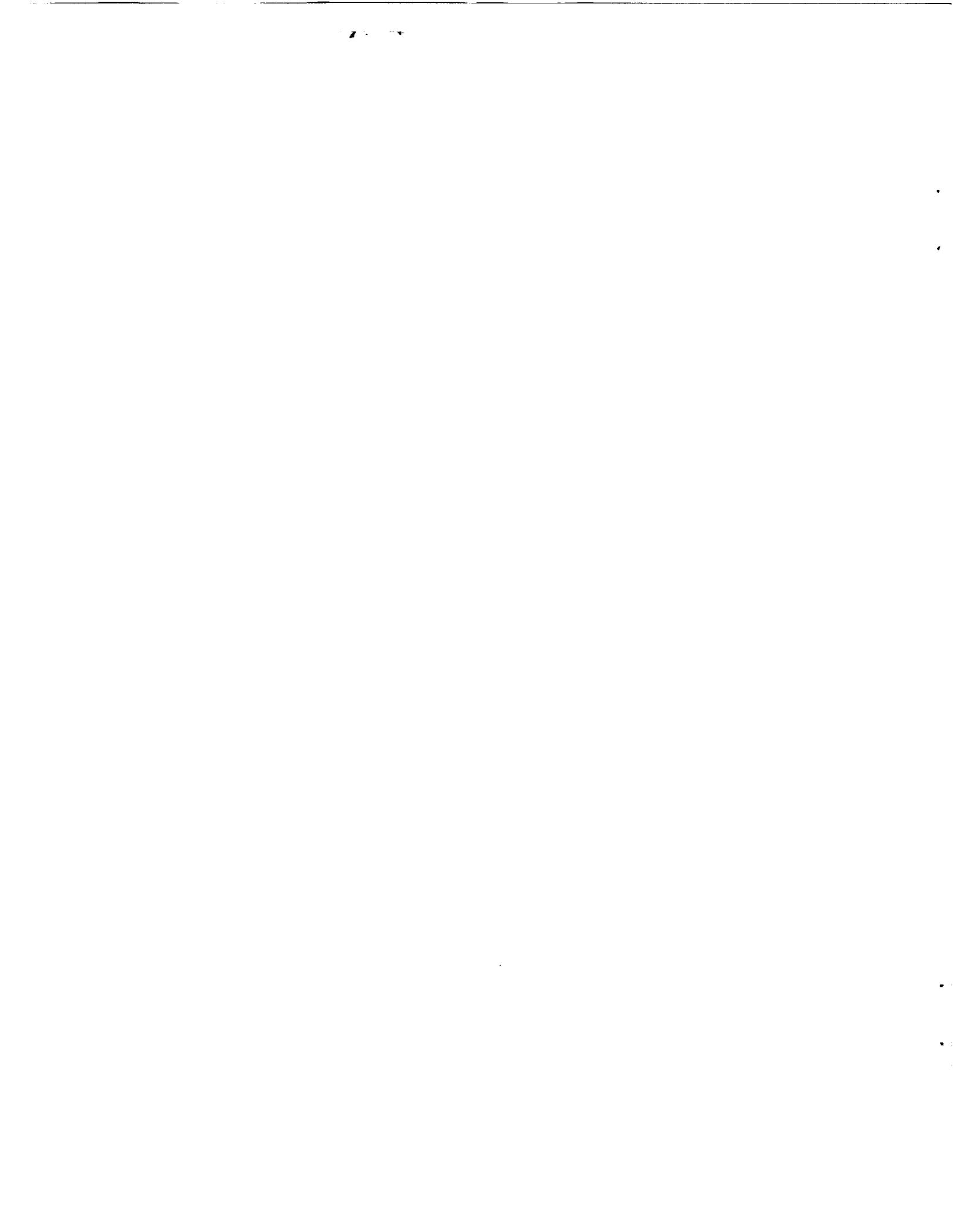
Clinical Physiology of Bed Rest

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Introduction

When a person assumes the upright posture, physiological responses counteract the effects of the footward shift of blood on the various systems of the body. Upper body elevation tends to "pool" blood in the dependent extremities, so the neuromuscular and cardiovascular systems must function in a coordinated manner to maintain adequate blood perfusion pressure in the brain and other vital organs. There is probably an optimal time requirement each day that the body should be maintained in the upright position for stimulation of the blood pressure control mechanism to insure its proper function, but this time period has not yet been determined scientifically.

Maintenance of optimal health in humans requires the proper balance between exercise, rest, and sleep as well as time in the upright position. About one-third of a lifetime is spent sleeping and it is no coincidence that sleeping is performed in the horizontal position, the position in which gravitational influence on the body is minimal. Although enforced bed rest is undoubtedly necessary for the treatment of some ailments, in some cases it has probably been used unwisely. In addition to the lower hydrostatic pressure within the normally dependent regions of the cardiovascular system and body fluid compartments during bed rest in the horizontal body position, and virtual elimination of compression on the long bones of the skeletal system during bed rest (hypogravia), there is often reduction in energy metabolism due to the relative confinement (hypodynamia) and alteration of ambulatory circadian variations in metabolism, body temperature, and many hormonal systems. If patients are also moved to unfamiliar surroundings, they probably experience some feelings of anxiety, and some sociopsychological problems may occur. Adaptive physiological responses during bed rest are normal for that environment; they are attempts by the body to reduce unnecessary energy expenditure, to optimize its function, and to enhance its survival potential.

Thus, the mechanisms and ramifications of these various deconditioning (adaptive physiological) responses, which probably occur in sick as well as in healthy persons subjected to prolonged bed rest, must be understood in order that they, and the signs and symptoms of the infirmity itself, can be properly differentiated. Otherwise, the accuracy of the diagnosis and the appropriateness of the treatment may be adversely affected. It should be emphasized that many of the deconditioning responses begin within the first day or two of bed rest (table 1). These early responses have prompted physicians to insist upon early resumption of the upright posture and ambulation of bedridden patients.

Much has been written on the dangers of prolonged bed rest, but none as succinct as that by Asher (ref. 1): "Look at a patient lying long in bed. What a pathetic picture he makes! The blood clotting in his veins, the lime draining from his bones, the scybala stacking up in his colon, the flesh rotting from his seat, the urine leaking from his distended bladder, and the spirit evaporating from his soul!"

In the sections that follow the (1) time-course of changes in the physiological responses during bed rest are outlined, (2) mechanisms of physiological responses to the hypodynamic factors (those related to reduced level of exercise) and to the hypogravic factors (those related to reduction in hydrostatic pressure within the cardiovascular system are discussed, and (3) practical aspects of bed rest as a treatment and problems and remedial procedures for patients emerging from prolonged bed rest are presented.

Time-Course of Physiological Changes During Bed Rest

The few data available indicate that the major early responses (0 to 3 days) involve changes in fluid-electrolytes and possibly venous compliance (table 1). Orthostatic intolerance, the tendency to faint (syncope) when moving from the horizontal to the upright (standing) body position, frequently occurs immediately following bed rest. There is usually a diuresis on the first day of bed rest resulting in reduction of plasma and interstitial fluid compartment volumes. By the end of the first week of bed rest, the increased urinary electrolyte (Na^+ and Ca^{2+}) and nitrogen losses are well established as is the change in the blood-clotting system with increased blood fibrinogen, fibrinolytic activity, and potential for clotting. Visual changes are also manifest. Eye hyperemia is probably due to the headward shift of fluids after assumption of the horizontal position. In the second week (8 to 14 days) reduction in red cell mass becomes apparent, and the heat dissipating mechanism becomes impaired due, in part, to changes in sweating, venous compliance, and skin blood flow. By the end of the first month, most adaptive changes have taken place; peak hypercalciuria is reached at about 42 days of bed rest (table 1).

Mechanisms of Responses to the Hypodynamic Factors

Although the term "cardiovascular deconditioning" is used frequently in conjunction with bed-rest deconditioning responses, the changes in the physiological mechanisms responsible for the total deconditioning process during bed rest certainly involve systems other than the cardiovascular system. In fact, the basic mechanisms that

Table 1. Time-course of physiological changes during bed rest

0-3 Days	4-7 Days	8-14 Days	Over 15 days
Urinary diuresis	Creatininuria	Pyrophosphaturia	Peak hypercalciuria
Urinary calcium loss	Hydroxyprolinuria	Decreased red cell mass	Changed sensitivity to thermal stimuli
Decreased plasma, interstitial, and extracellular fluid volumes	Phosphaturia	Decreased leucocyte phagocytosis ability	Decreased forearm blood flow
Decreased secretion of gastric juice	Negative N_2 balance	Increased sweating sensitivity	Secondary increase in auditory threshold acceleration
Decreased calf blood flow	Increased blood fibrinogen and clotting	Increased exercise hyperthermia	Decreased $+G_{x_x}$ tolerance
Increased venous compliance	Increased blood fibrinolytic activity	Decreased tissue heat conductance	
Increased neutrophil digestive function	Increased auditory thresholds		
Glucose intolerance	Decreased near-point of visual acuity		
Decreased $+G_z$ acceleration tolerance	Lengthened focal point		
Tilt-table orthostatic intolerance	Increased hyperemia of eye conjunctiva and dilation of retinal arteries and veins		
	Decreased neutrophil absorption		

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control the cardiovascular portion of the total deconditioning process probably reside in the neuro-endocrine systems, and the cardiovascular responses are secondary to these more fundamental mechanisms.

Reduced Physical Working Capacity

Peak or maximal oxygen uptake ($\dot{V}O_2$ max) is defined as the greatest utilization of oxygen by the body during exhaustive isotonic (dynamic) exercise with large muscle groups, usually the legs. Oxygen uptake is usually expressed in liters per minute or in milliliters per minute per kilogram of body weight. For each individual, the level of the $\dot{V}O_2$ max is directly proportional to the total active muscle mass and is dependent on the individual's hereditary capacity plus the level of physical training adaptation of the respiratory and circulatory systems and the intermediary metabolism to assimilate, transport, and metabolize oxygen from the ambient air into the body cells. The $\dot{V}O_2$ has been used frequently as a measure of the change in the functional capacity of the cardiovascular system during exercise training in normal subjects, and as a measure of the cardiovascular-respiratory system deconditioning response in bed-rested subjects.

To determine $\dot{V}O_2$ max properly in bed-rest studies, care must be taken to separate the pure exercise capacity from changes caused by imposition of additional orthostatic stress. An example is the increased vascular and fluid compartment hydrostatic pressure during exercise in the upright (standing or sitting) positions. Hence, all pre- and post-bed-rest maximal oxygen uptake tests should be performed with the subjects in the supine position. This requirement would preclude use of a treadmill or sitting cycle ergometer for these tests. Maximal oxygen uptake after bed rest is somewhat lower when measured in subjects in an upright position compared to subjects in the supine position, if care is taken to ensure use of equal muscle mass during the test in both positions (ref. 2). Also, application of lower-body negative pressure during seated and supine exercise in non-bed-rested ambulatory subjects imposes an additional hydrostatic stress, and the result is lower $\dot{V}O_2$ max in seated subjects (ref. 3). Thus, there seems to be competitive interaction between changes in hydrostatic pressure and exercise load when determining the maximal aerobic working capacity. Thus aerobic capacity decreases as circulatory hydrostatic pressure increases in the lower body and decreases in the upper body.

One contributing factor would appear to be the competing demands for the cardiac output, which is somewhat greater in the supine position (ref. 4), to simultaneously maintain systemic blood pressure and perfusion of exercising muscle. During exercise in the sitting position, there would be a greater active muscle mass (those used by the arms and trunk for body support and stabilization plus others used for moving the limbs), so the greater active muscle mass should result in greater $\dot{V}O_2$ max. If comparable muscle masses are used in the sitting and supine positions, $\dot{V}O_2$ max in the sitting position should be lower due to the added demands from orthostatic responses accompanying the increased hydrostatic pressure in the lower body.

A compilation of data on changes in maximal oxygen uptake measured on the treadmill (subjects standing) and cycle ergometer (subjects sitting or supine) from eight different studies during 4 to 10 days of chair-rest deconditioning and 10 to 20 days of bed-rest deconditioning (ref. 5) indicate that change of $\dot{V}O_2$ max with chair rest ($\overline{X}$ = -1.3%, range +9.7 to -7.7%) was less when compared with bed rest ($\overline{X}$ = -7.5%, range -0.3 to -26.4%). The greater protective effect on $\dot{V}O_2$ max during chair-rest deconditioning was probably due to the greater load on the cardiovascular system (from the increased hydrostatic pressure plus the greater muscular effort required to maintain the sitting position) rather than to the shorter chair-rest periods. Birkhead et al. (ref. 6) reported that quiet sitting for 8 hr/day during 30 days of bed rest virtually eliminated the reduction in $\dot{V}O_2$ max.

The major alterations in cardiovascular responses (for example, resting calf muscle blood flow (ref. 7), plasma volume (refs. 8 and 9), and orthostatic (ref. 10) and acceleration (ref. 11) tolerances) occur within the first four days of chair-rest and bed-rest deconditioning. When various remedial exercise-training procedures were utilized during 14 to 30 days of bed rest (ref. 5), the average reduction in VO_2 max was only 4.3%, indicating some remedial effect of exercise stimuli on amelioration of bed-rest deconditioning. Use of intermittent, isometric exercise training for 1 hr daily during 14 days of bed rest resulted in a smaller decrease in supine $\dot{V}O_2$ max (Δ = -4.8%) when compared with a similar period of continuous isotonic exercise training (at a load of 68% of the $\dot{V}O_2$ max) where the reduction in supine $\dot{V}O_2$ max was 9.2% (ref. 5). So, in some situations, isometric exercise training appears to exert a greater protective effect on aerobic capacity than isotonic exercise training. There is still an element of continuous (isometric) muscular contraction during so-called isotonic exercise on a cycle ergometer, however, and it is probably impossible to apply pure moderate- to high-intensity isotonic exercise. However, the fact that the isometric exercise training, with its greater incrase in systemic blood pressure, exerted a protective effect during deconditioning suggests the possible effect of a blood pressure component for maintenance of aerobic exercise capacity.

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From a more recent 30-day bed-rest study (ref. 12), it was found that performance of alternating, high-intensity isotonic lower-extremity cycle-ergometer exercise for 1 hr per day maintained $\dot{V}O_2$ max from ambulatory control levels (fig. 1). The exercise protocol started with a 5 minute warm-up period at 40% of $\dot{V}O_2$ max and then alternated at 2 minute intervals between 40%, 60%, 40%, 70%, etc. to 90% $\dot{V}O_2$ max. The average relative load for such a 30-minute session was only 50% $\dot{V}O_2$ max, as compared with the 68% $\dot{V}O_2$ max continuous exercise protocol mentioned above. Thus, higher-intensity rather than longer-duration exercise training appears to preserve $\dot{V}O_2$ max better during bed rest. In spite of maintenance of $\dot{V}O_2$ max, there was no effect of this isotonic regimen
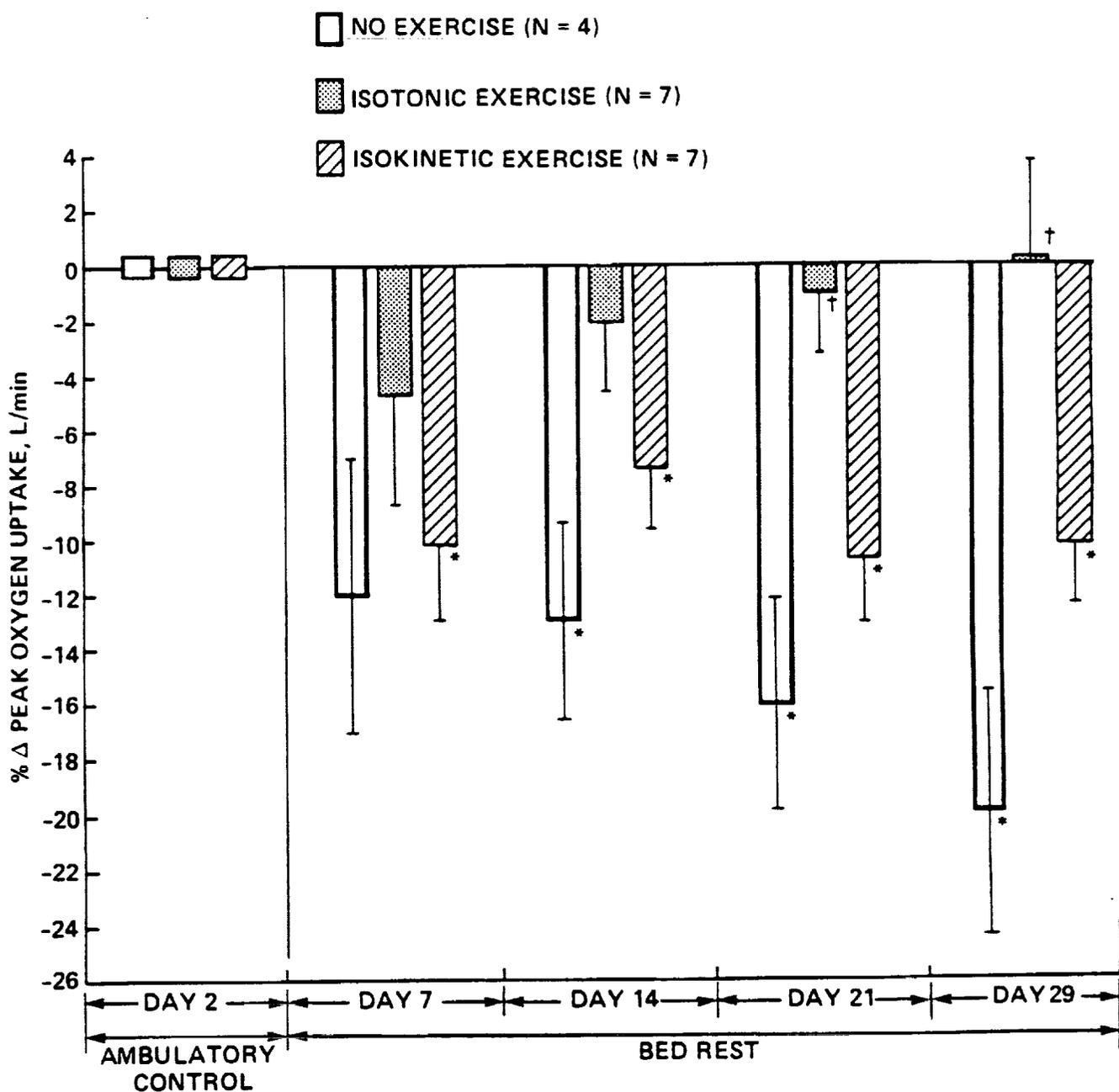
Figure 1. Mean (±SE) weekly change in peak oxygen uptakes (liters/min) in 3 groups during the ambulatory control and bed rest periods. *P < 0.05 from control (day zero); P < 0.05 from the corresponding no exercise value. (From ref. 35 with permission).

or of the isokinetic exercise training regimen on the typical reduction in tilt-table orthostatic tolerance during bed rest without exercise training (fig. 2 and ref. 13). Kakurin et al. (ref. 14) were also able to maintain $\dot{V}O_2$ max during 49 days of bed rest with a similar, but more complex, alternating exercise protocol. The reduced level of energy utilization (exercise) in subjects not performing exercise training during bed rest is accompanied by a concomitant reduction in blood pressure stimulation, since the level of systemic pressure is directly related to exercise load (ref. 15). Thus, the above findings imply that reduction of $\dot{V}O_2$ max during bed rest may be due to decreases in both exercise stimuli and hydrostatic and systemic pressures,

but demanding, alternating, high-intensity isotonic exercise training for 1 hr per day can maintain maximal oxygen uptake during prolonged bed rest.

There has been some discussion concerning the greater absolute reduction of maximal oxygen uptake during bed rest in well-trained athletes with relatively high working capacities compared with a lesser absolute reduction in $\dot{V}O_2$ max in essentially untrained men with lower working capacities. The hypothesis was that the greater the fall in $\dot{V}O_2$ max, the more deleterious the effect on the organism. The first data that could be intrepreted and applied to this hypothesis were available from a study by Taylor

ORTHOSTATIC TOLERANCE
Control day 1 vs. bed rest day 30
*p < 0.05 vs. day 1
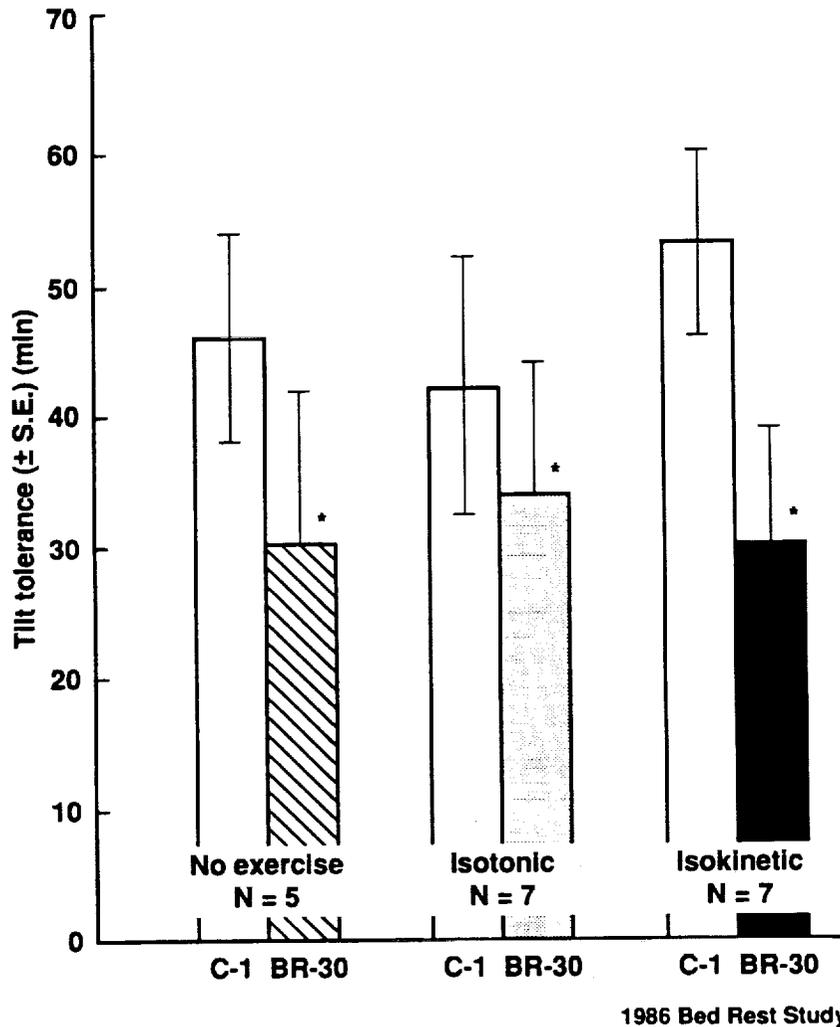

Figure 2. Mean (±SE) tilt-table tolerances in the 3 groups during ambulatory control (C-1) and at the end of 30 days of bed rest (BR-30). *P < 0.05 vs. C-1. (From ref. 44 with permission).

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et al. (ref. 16) of two normal but not exercise-trained men. The change in $\dot{V}O_2$ max during 28 days of bed rest for the more fit subject was from 4.15 to 3.24 1/min ($\Delta = 0.90$ 1/min, -22%); in the less fit man, the change was from 3.54 to 3.07 1/min ($\Delta = 0.47$ 1/min, -13%). Thus, the more fit man had the greatest absolute loss of $\dot{V}O_2$ max (0.90 1/min) and the largest relative loss of $\dot{V}O_2$ max (22%); moreover, his post-bed-rest level of $\dot{V}O_2$ max was only 0.18 1/min higher than that of his less fit companion. So the question remained whether the more fit man was in poorer condition after bed rest than the less fit man.

Subsequently, Saltin et al. (ref. 4) were able to compare changes in working capacity after 20 days of bed rest in two highly trained athletes ($\dot{V}O_2$ max 4.80 and 4.15 l/min) and in three essentially sedentary college students ($\dot{V}O_2$ max 2.64, 2.52, and 2.39 l/min). The average decrease in $\dot{V}O_2$ max for the trained men during bed rest was from 4.48 to 3.48 l/min ($\Delta = -1.00$ l/min, -22%), and from 2.51 to 1.74 l/min ($\Delta = -0.77$ l/min, -31%) in the sedentary men. Here the trained men had only a slightly greater loss in absolute $\dot{V}O_2$ max, by 0.23 l/min, but a much higher post-bed-rest level of $\dot{V}O_2$ max (3.48 l/min) than the sedentary group (1.74 l/min). These findings agree qualitatively with those of Taylor et al. (ref. 16). However, the relative loss of $\dot{V}O_2$ max in Saltin et al.'s (ref. 4) athletes was less (22%) than in their sedentary group (31%), in opposition to the results of Taylor et al. So the data of Saltin et al. still did not resolve the problem. Subsequently, a much larger compilation of data has become available from subsequent bed-rest studies (ref. 17) and indicates no direct relationship between the initial and post-bed rest levels of maximal oxygen uptake.

Many physiological functions are more closely related to the relative oxygen uptake ($\dot{V}O_2$ rel), a percentage of the $\dot{V}O_2$ max, than to the absolute $\dot{V}O_2$ max. Moreover, the use of $\dot{V}O_2$ rel greatly reduces interindividual variability (ref. 18). Thus, the pre-bed-rest level of $\dot{V}O_2$ max was compared with the percentage change in $\dot{V}O_2$ max ($\dot{V}O_2$ rel) during bed rest without remedial treatments using data from four studies (refs. 4, 16, 17, and 19). The results indicate essentially no significant relationship between those two variables (ref. 20). The correlation coefficient was -0.10. Although only two of Saltin et al.'s (ref. 4) subjects were highly trained athletes, most of Convertino et al.'s (ref. 17) men were active young college students, many of whom were athletes, but were not in active training. Since the range of $\dot{V}O_2$ max in normal hospitalized patients would probably fall between 1.5 and 4.0 l/min, these findings would be applicable for them. So it must be concluded that the resting level of maximal oxygen uptake

has no significant influence on the relative decrease in $\dot{V}O_2$ max during bed-rest deconditioning.

Comparatively few definitive findings have emerged that elucidate the mechanism of the reduced maximal oxygen uptake during bed-rest deconditioning. To reiterate, the oxygen transport system includes the respiratory, circulatory, and intermediary metabolic systems; the few data available suggest that the major deficiency resides within the circulatory system. Ventilatory parameters, such as total lung capacity, residual volume, forced vital capacity, pulmonary diffusing capacity, ventilation volume, or ventilation volume/O_2 uptake, were unchanged at rest or during submaximal exercise after three weeks of bed rest (refs. 4 and 21). However, mean ventilatory volume during maximal exercise decreased from a control level of 129 l/min to 99 l/min after bed rest; the corresponding respiratory rates were 43 and 56 breaths/min (ref. 4). So the changes in maximal ventilation followed the changes in $\dot{V}O_2$ max and maximal exercise load. That is, the decreased ventilation appeared to be a result of and not the cause of the lower maximal load and $\dot{V}O_2$ max after bed rest. Isometric or isotonic exercise training during bed rest have no effect on maximal exercise ventilatory volume measured after bed rest (ref. 4). The conclusion is that respiratory function is essentially unchanged during the first three weeks of bed rest.

The lower working capacity appears to be due to reduced delivery of oxygen by the cardiovascular system and also to reduced tissue exchange and utilization. After bed rest there is a decrease in heart volume by 11 to 18% (refs. 4, 16, and 22), unchanged peripheral resistance and arteriovenous oxygen difference, and decreased cardiac output due to reduced stroke volume (from 104 to 74 ml, $\Delta = -29\%$) that is not compensated by increased heart rate (ref. 4). Because of the uncompensated reduction in stroke volume, Saltin et al. (ref. 4) attributed the decrease in $\dot{V}O_2$ max to an unidentified myocardial effect that could be the result of myocardial muscular atrophy (diminished heart size), to altered central nervous system stimulation to the heart, or to diminished β-adrenergic responsivity. But potential adaptive responses of the intermediary metabolism have not been studied adequately during prolonged bed rest.

In the study of Saltin et al. (ref. 4), five men (19–21 yr) were subjected to 20 days of strict bed rest. The average change in their $\dot{V}O_2$ max was from 3.3 to 2.4 l/min ($\Delta = -26\%$). Data from a similar study by Georgievskiy et al. (ref. 23), in which four men (22–25 yr) also underwent 20 days of strict bed rest, show an average loss of $\dot{V}O_2$ max that was much less (3.2 to 2.9 l/min, $\Delta = -9\%$). Georgievskiy et al. also noted a smaller reduction in stroke volume (from 91 to 86 ml, $\Delta = -5\%$); moreover

they reported an increase in maximal heart rate that resulted in an unchanged cardiac output, a finding differing from that of Saltin et al.

Georgievskiy et al. (ref. 23) concluded that since there was adequate cardiac compensation, the mechanism for the reduction in $\dot{V}O_2$ max must reside in impaired delivery or impaired tissue uptake of oxygen, or both. There are data to support their conclusion. First, the decline in red cell mass, which became significant between 21 and 28 days of bed rest (refs. 9 and 24), could reduce the oxygen carrying capacity of the blood. Secondly, the well-established reduction in plasma volume (refs. 8 and 24), which occurs by the second day of bed rest (ref. 9), could compromise venous return and stroke volume. And finally, the lower venous return could be caused, in part, by reduced muscle function due to (1) reduction of thigh, calf, and ankle girths (refs. 25 and 26), (2) reduction of anterior tibial (−13%) and gastrocnemius-soleus (−21%) muscular strength (ref. 21), and (3) reduction of leg muscle tone (refs. 25 and 27). Partial loss of these three functions could be associated with atrophy of leg muscle fibers (ref. 28) and concomitant loss of lean body mass and muscle water content (refs. 4 and 26).

It is entirely possible, however, that the results of both studies (Saltin et al. and Georgievskiy et al.) are correct, because the reduction in $\dot{V}O_2$ max in Saltin's subjects was three times greater than that in Georgievskiy's subjects, and the former could not compensate for so great a change, while the latter could. That is, the mechanism that increases the heart rate can compensate for decreases in stroke volume at least to 9%. Somewhere between a 9% and 29% reduction in stroke volume the heart rate mechanism is no longer able to compensate. But the muscular impairment is present continuously. Obviously more research is needed to understand this mechanism.

Insulin-Glucose Intolerance and Hormonal Interactions

The exaggerated hyperinsulinemia and hyperglycemia following an oral glucose load after a period of extended bed rest suggests the presence of fundamental changes in the energy transformation (intermediary metabolism) system of the body. It appears that the reduced exercise level (hypodynamia), as opposed to reduced hydrostatic pressure (hypogravia), is the major cause of this glucose intolerance (ref. 29). Results from early experiments indicate that the longer the period of inactivity during bed rest, the greater the frequency and amplitude of the altered glucose tolerance responses (refs. 30–32).

The reduction in carbohydrate tolerance is directly proportional to the degree of immobilization (refs. 32 and 33).

Performance of moderately intensive daily isometric or isotonic exercise during bed rest reduces, but does not eliminate, the increment of imparied glucose utilization (refs. 29, 31, and 34). Restoration of normal carbohydrate tolerance after bed rest takes between 7 and 14 days if no remedial physical exercise is undertaken (ref. 35). But a program of intensive physical exercise training returns the glucose intolerance to normal or greater than normal by the seventh day of reambulation (ref. 33).

A comparison of insulin and glucose tolerance responses before and after 14 days of bed rest, when there was either no exercise or intensive isometric or isotonic exercise training for 1 hr/day, led to the conclusion that it was the total daily caloric expenditure (rest plus exercise intensity) and not the type or duration of exercise that affected the glucose and insulin responses (ref. 34).

The glucose intolerance was not directly related to the decreases in the maximal oxygen uptakes: −12.3% with no exercise, −4.8% with isometric exercise, but −9.2% with isotonic exercise (ref. 5). The magnitudes of the glucose and particularly of the insulin responses to the oral glucose load (area under 3-hr recovery curves) were inversely proportional to the total daily energy expenditure (fig. 3). The linear regression (r = 0.99) of the integrated area under the insulin response curves on the calculated 24-hr energy expenditures for the three bed-rest exercise regimens, assuming an average resting metabolism during bed rest of 90 kcal/hr, indicated that a 24-hr energy expenditure of about 3,000 kcal is needed to restore the "abnormal" insulin responses (fig. 4). If 90 kcal/hr were utilized for 22 hr of bed rest (1,980 kcal), then about 1,020 kcal must be supplied from exercise over the remaining 2 hr to bring the total daily caloric expenditure to 3,000 kcal. To attain the additional 1,020 kcal/day would require 4 hr of intensive, intermittent isometric leg exercise, or 1.5 hr of intensive (70% of the maximal oxygen uptake) isotonic leg exercise, or 1 hr each of the two exercise regimens. Few bed-rest studies have been performed where the daily remedial exercise intensity has approached 1,020 kcal. This exercise intensity would be inappropriate for most hospitalized patients. But it is still not certain that elimination of the excess hyperinsulinemia would return the elevated glucose response to normal. Although the descriptive and time-course changes in the glucose-tolerance responses during and after bed rest are reasonably well defined, the mechanism is not.

The lack of response of the increased glucose levels in the presence of high insulin concentrations during bed rest indicates that immuno-reactive insulin deficiency was not the cause of the glucose intolerance. Furthermore, exogenous insulin is no more effective than endogenous insulin in lowering the elevated plasma glucose (ref. 36). Glucose
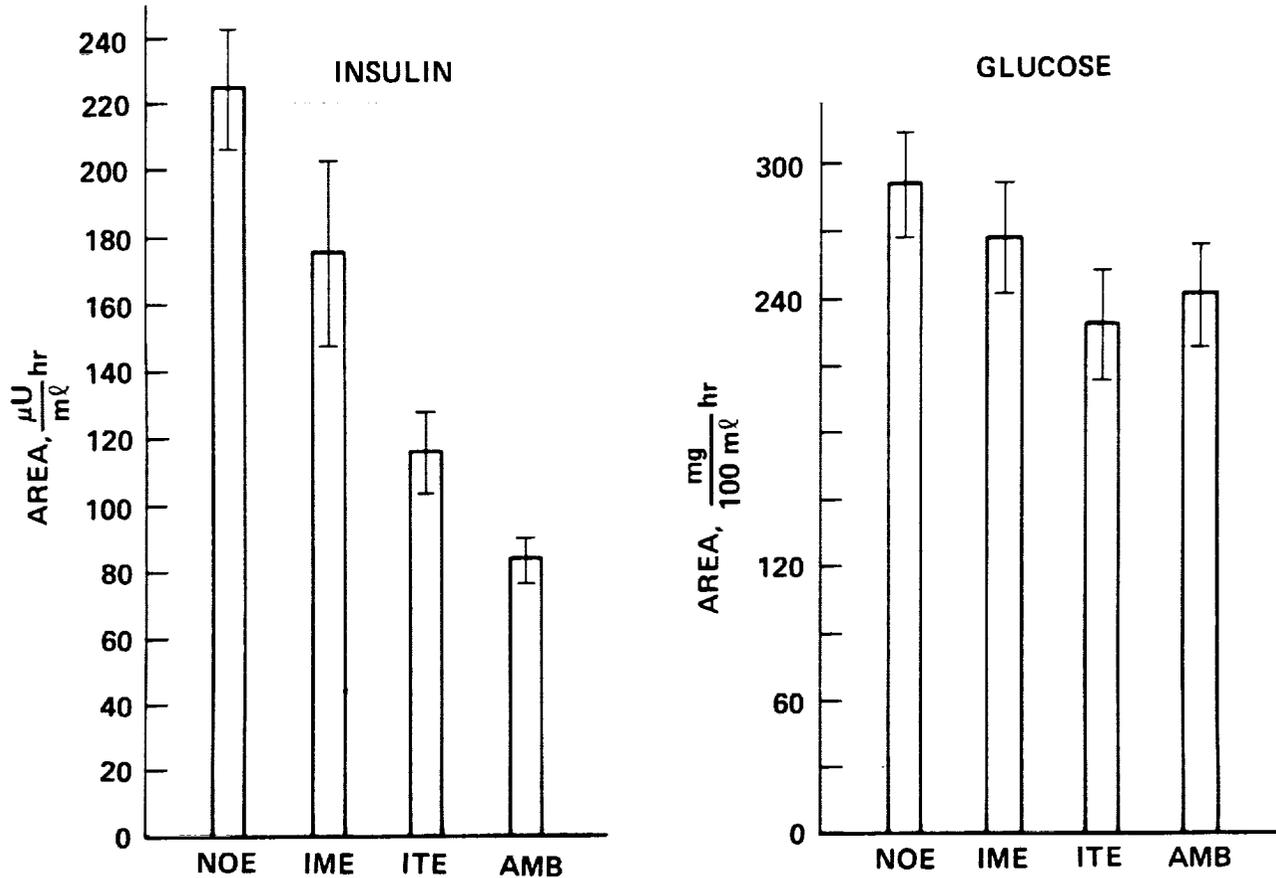
INSULIN

240
220
200
180
160
140
120
100
80
60
40
20
0

AREA, $\frac{\mu U}{m\ell}$ hr

NOE   IME   ITE   AMB

GLUCOSE

300

240

120

60

0

AREA, $\frac{mg}{100\ m\ell}$ hr

NOE   IME   ITE   AMB

Figure 3. Mean (±SE) integrated areas under the insulin and glucose curves during the 3-hr glucose tolerance test for the no-exercise (NOE), isometric-exercise (IME), isotonic-exercise (ITE), and ambulatory-control (AMB) regimens. (From ref. 27, with permission).

unresponsiveness to the hyperinsulinemia suggests one of the following: the insulin is modified by release of an insulin inhibitor, perhaps at the membrane binding sites; some other aspect of cellular-membrane function is changed; or there is a blockage of the function of a second factor with insulin-like activity. It is even possible that insulin is not involved at all. Lipman et al. (ref. 35) observed reduction in glucose uptake in the forearm and concluded that the impairment was due not to insulin deficiency or insulin antagonists, but to cellular alteration. The evidence discounts changes in resting plasma concentrations of the more important insulin antagonists during bed rest—plasma cortisol (refs. 37–39), free fatty acids (FFA) (ref. 37), growth hormone (refs. 37 and 38), or the catecholamines (ref. 40)—because, compared with ambulatory control levels, in most cases the concentrations of these hormones were either unchanged or lower during 2 weeks of bed rest.

Moderate exercise during bed rest has no effect on basal cortisol concentration (ref. 39). Infusion of 2-deoxy-d-glucose, a stimulant of pituitary and adrenal hormones, produced no significant differences between ambulatory control and bed-rest responses of plasma glucose, free-fatty acids, cortisol, or serum immunoreactive insulin concentrations, and the normally marked rise in growth hormone was blunted (ref. 37) in agreement with the findings of Pawlson et al. (ref. 38). The responsiveness of other glucose stimulating hormones such as glucagon, thyroxine, thyrotrophin, luteotrophin, and corticotrophin has not been evaluated in bed-rested subjects. But the general attenuation or lack of responsiveness of those hormones to 2-deoxy-d-glucose stimulation suggests some inhibition of pituitary and adrenal function during bed-rest deconditioning. This moderate inhibition of some gluco-regulatory hormones, however, cannot fully explain the glucose intolerance.
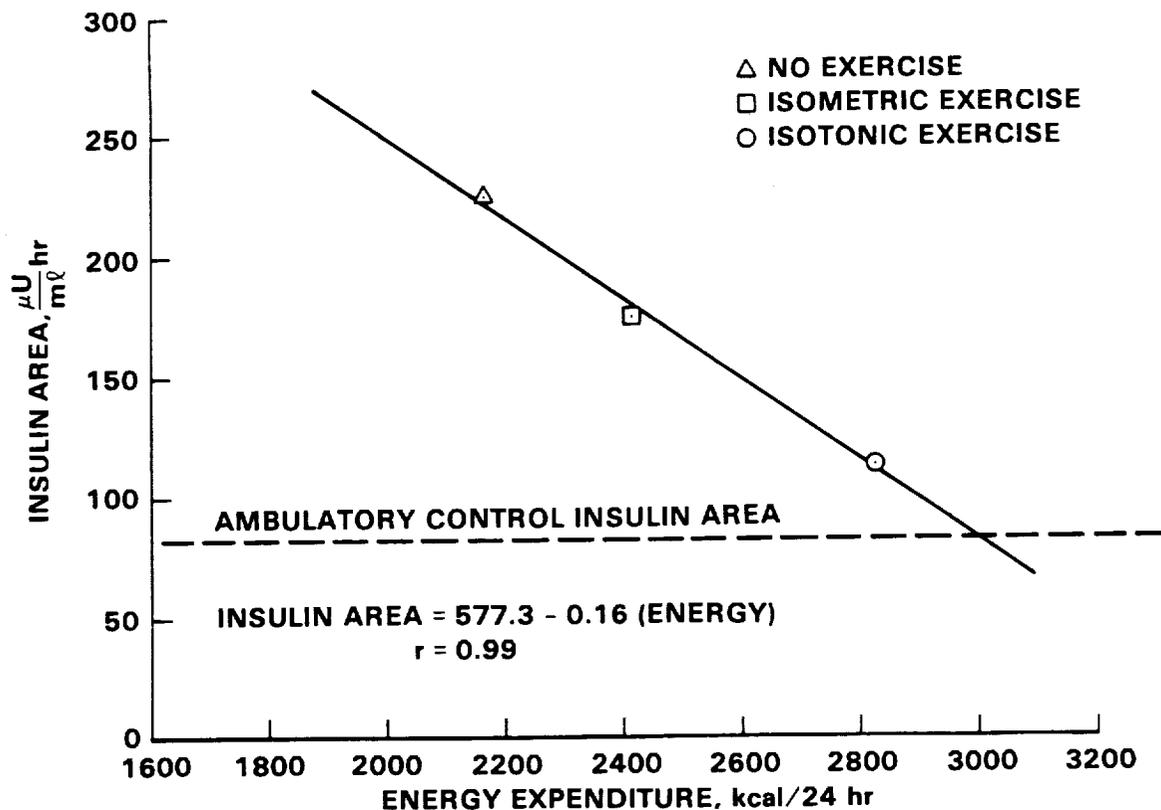
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Figure 4. Regression of the integrated areas under the insulin response curves during the glucose tolerance tests on the 24-hr energy expenditures for the three bed-rest regimens. (From ref. 27, with permission).

More recent work on the effect of physical exercise and exercise training on glucose metabolism in ambulatory subjects has emphasized the importance of changes in sensitivity and number of cellular membrane binding sites for insulin (ref. 41). Exercise training increases the sensitivity of existing insulin binding sites on monocytes, and it increases the concentration of insulin receptors in direct proportion to the increase in the subject's maximal oxygen uptake (ref. 41). But an increase in maximal oxygen uptake is also associated with an increase in blood flow to skeletal muscle. Dietze and his colleagues have presented clear evidence that the kallikrein-kinin system is involved with changes in muscle blood flow in normoxic (refs. 42 and 43) and hypoxic (ref. 44) conditions. Glucose uptake into working human forearm muscles is nearly inhibited in the presence of a kallikrein-trypsin inhibitor, and is restored with infusion of bradykinin, a vasodilator.

It is clear that the mechanism of glucose intolerance induced during bed-rest deconditioning is not simple. It appears to be associated with a number of functions, including daily energy expenditure, some inhibition of pituitary and adrenal function, changes in sensitivity and concentration of insulin membrane binding sites, alter-

ations in muscle blood flow modified by the kallikrein-kinin system, and, perhaps, with some yet-to-be-measured gluco-regulatory hormones.

It should be emphasized that essentially all bed-rested patients will exhibit abnormal glucose tolerance responses by the second day of bed rest and care should be taken to differentiate this "normal" response from similar responses resulting from pathological conditions.

Calcium Metabolism

The normal total plasma calcium concentration is about 5.0 ± 0.2 meq/liter and is composed of half ionized and half bound to protein. This variability in concentration is maintained very closely, particularly ionized calcium, because of the critical reactions even minor increases (nervous system depression) or decreases (tetany) can cause upon nervous system cellular membrane function. The skeleton can be nearly depleted of calcium before the plasma concentration changes appreciably. Calcium is lost from the adequately nourished body mainly in the feces (700 mg/day, 88%), in the urine (100 mg/day, 10%) and, under normal circumstances, a negligible amount

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(<20 mg/day, 2%) is lost in sweat and other body fluids. Urinary calcium loss greater than 250 mg/24 hr is considered pathological.

There are two general mechanisms for deterioration in the quantity and quality of bone: osteomalacia (adult rickets) and osteoporosis. Osteomalacia (reduced calcification) is caused by increased parathyroid hormone activity and subsequent increased osteoclastic absorption of bone resulting from insufficient calcium or phosphorous in the extracellular fluid, usually due to insufficient vitamin C. On the other hand, osteoporosis, a more common anomaly, results from abnormal formation of the collagen matrix due to depressed osteoblastic activity that reduces the rate of bone deposition. The causes of osteoporosis include insufficient vitamin C, D, or estrogen secretion, increased secretion of glucocorticoids and other adreno-cortical hormones, protein malnutrition, and depressed protein anabolism.

Immobilized men have significantly greater calcium losses than immobilized women (ref. 45). The skeleton of a 70-kg man contains between 1,200 and 1,500 g of calcium; the circulating plasma contains about 0.28 g. Ionized calcium does not exchange with the soft tissue (collagen) of bone because the soft tissue contains no calcium, but it does exchange with bone interstitial fluid (10 liters), which contains about 500 mg of ionized calcium. Nearly all plasma ionized calcium interchanges with interstitial ionized calcium each minute. About 0.05% of skeletal calcium is renewed each day.

There is an increased output of calcium and phosphorous in urine (fig. 5) and feces within the first two days of bed rest (refs. 21 and 26), but the plasma concentration of these ions remain constant (ref. 26). For unchanged plasma concentrations, a proportional reduction of the contents of these ions must accompany the decrease in plasma volume. During two weeks of bed rest, the following changes in plasma volume, calcium content, and phosphorous content were noted:

1. Plasma volume: decreased during bed rest by 12.6% with no exercise, by 11.3% with isometric exercise, and by 7.8% with isotonic exercise (ref. 8).

2. Plasma calcium content: decreased during bed rest by 11% with no exercise, by 7% with isometric exercise, and by 4% with isotonic exercise (ref. 8).

3. Plasma phosphorous content: decreased during bed rest by 9% with no exercise, by 7% with isometric exercise, and by 4% with isotonic exercise (ref. 8).

The rate of total calcium loss (1.54 g/week, 220 mg/day) was constant during 36 weeks of bed rest; the total loss was 4.2% of total body calcium (46), approximately the quantity of trabecular bone mass lost by males over 10 years of normal physiological aging (ref. 47). Urinary nitrogen excretion also increases by the second day of bed rest (ref. 21) reflecting the breakdown of collagen in bone.

It has been difficult to determine the relative influence of changes in hydrostatic pressure versus changes in energy metabolism in healthy subjects on the mechanism of bone calcium, phosphorous, and nitrogen losses during bed rest. Muscle atrophy could also result in similar molecular losses, particularly nitrogen and potassium. Isotonic physical-exercise training performed during bed rest appears to have little or no effect on calcium loss. Supine exercise for 1 hr/day at a work rate of 750 kcal (ref. 26) (fig. 6), or for 4 hr/day (1,760 kcal) does not change the rate of urine calcium loss (ref. 48). We discussed earlier that quiet standing provided some remedial effect on working capacity during leg exercise. But because of the time (weeks) required for full recovery of muscle girth and working capacity, we cannot conclude, as did Issekutz et al. (ref. 48), that all of the urine protein loss during bed rest comes from bone.

Longitudinal skeletal pressure applied intermittently through the legs against coiled springs or rubber bands with a force of 80% to 100% of the subject's body weight for 3–4 hr/day had little or no effect on urine calcium loss (refs. 49–51). But Whedon et al. (ref. 52) found that oscillation of the bed-rested subject from the horizontal to 20 deg foot-down and back (each oscillation was 1.75 min) for 8-21 hr/day resulted in a marked decrease in urine calcium loss (from 233 mg/day to 121 mg/day, $\Delta = -49\%$), and a 54% decrease in total urine and fecal calcium loss. There was essentially no muscular contraction and the compressional force on the skeleton during this oscillation was much less than with application of springs and bands, but it was applied for a much longer period of time. There were also oscillating blood volume shifts. So it would appear that if a remedial procedure for calcium loss is to be effective, it must approximate normal ambulatory conditions for more than 8 hr/day. Short-term high-intensity longitudinal compression or leg exercise is ineffective.

Cordonnier et al. (ref. 53) were among the first to report the reduction in urine calcium loss during bed rest following administration of supplementary sodium biphosphate. Goldsmith et al. (ref. 54) concluded that oral inorganic phosphate supplements (1–2 g/day) can ameliorate and sometimes prevent the hypercalciuria and negative calcium balance during immobilization. These results were supported by Hantman et al. (ref. 51) who also found that calcium supplements of 1.0–2.3 g/day and phosphate supplements of 1.7–3.0 g/day reduced the negative calcium and phosphate balances; however, administration of
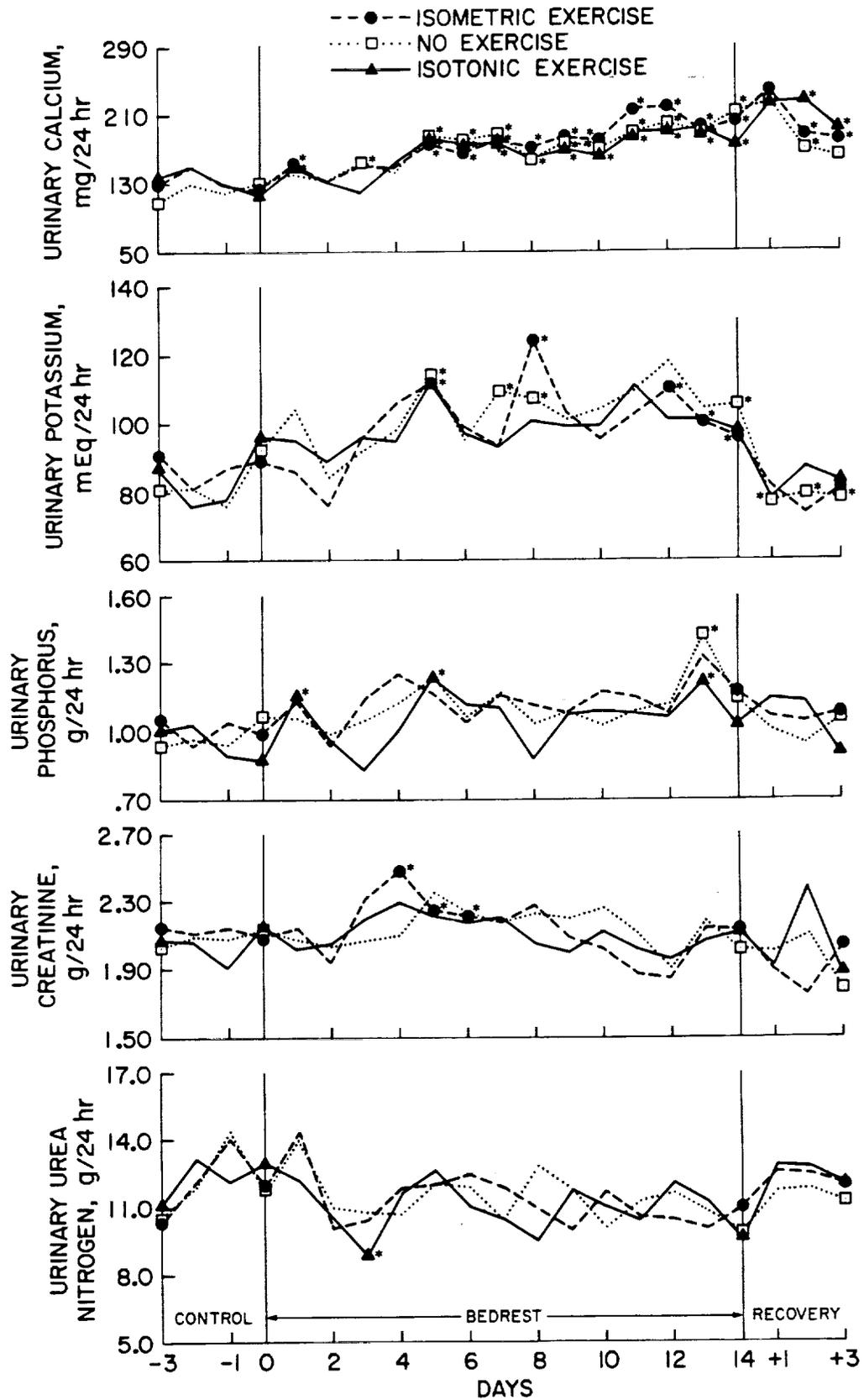
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Figure 5. Mean urine electrolyte and nitrogenous variables during control, bed rest, and recovery periods with no-exercise, isometric-exercise, and isotonic-exercise regimens. *P < 0.05 from day-1 control values. (From ref. 36, with permission).
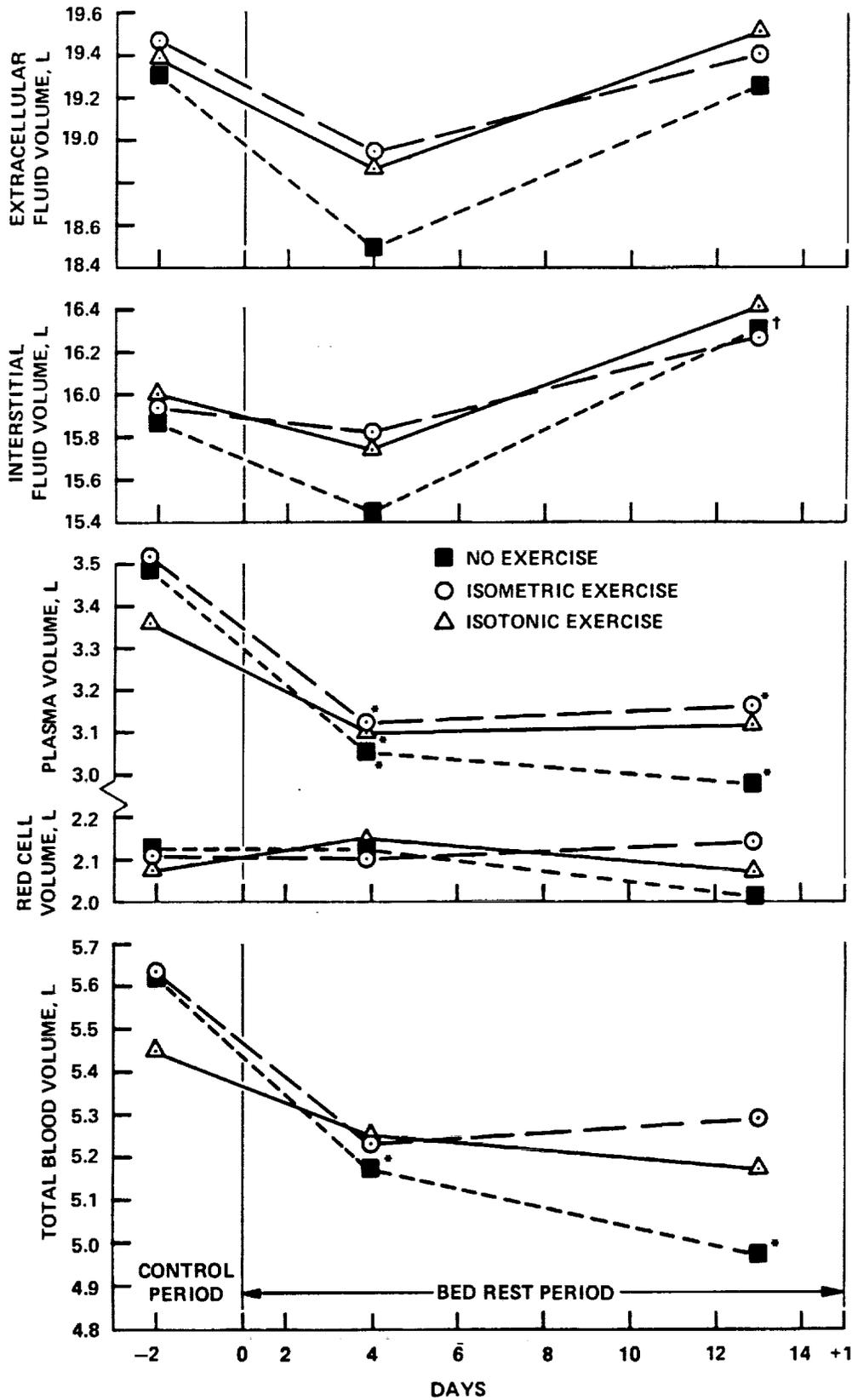
Figure 6. Mean fluid compartment values during the control period and bed-rest periods with no-exercise, isometric-exercise, and isotonic-exercise regimens. *P < 0.05 from control values. †P < 0.05 from day-4 control values. (From ref. 37, with permission).

synthetic calcitonin, which acts to increase plasma calcium, was without effect.

The reduction in urine calcium and phosphate losses with hypoxic exposure (ref. 55) suggests an effect on intermediary metabolism. Issekutz et al. (ref. 48) have argued that since there was a steady decline in urine calcium losses during 18 days of ambulatory recovery, the changes in blood flow were probably not a significant part of the recovery mechanism. Similar conclusions have been reached by Minaire et al. (ref. 47) based on observations that, after about 25 weeks of bed-rest, there is a steady state attained when bone mass ceases to decrease. But Donaldson et al. (ref. 46) did not observe attenuation in the rate of calcium loss during 36 weeks of bed rest. Obviously a steady state of bone resorption is reached sometime because long-term bed-ridden patients do not lose all of their boney substance.

Nonetheless this evidence does not prove that changes in blood flow during recovery are not important for restoration of bone. The large positive phosphate balance during recovery suggests it is assimilated into structures other than bone, perhaps into muscle. It would seem logical that increased nutrition via an increased blood flow would be necessary for recovery of both muscle and bone deterioration. Perhaps the more effective tension action of muscle upon bone would also aid in recovery of bone since muscular recovery occurs earlier.

Mechanisms of Responses to the Hypogravic Factors

Orthostatic Tolerance

Orthostatic tolerance can be defined as the time of useful consciousness when the patient is standing quietly or the body is suspended motionless in the head-up vertical position on a tilting table. The subject must be monitored closely because death can occur after the onset of unconsciousness if blood flow to the heart, and especially the brain, is not restored. Physiological (heart rate and blood pressure) responses during tilting, as well as the time to fainting, are used as general measures of the efficiency of the cardiovascular system in general and the blood pressure control system in particular.

Heart rate and systemic blood-pressure responses during changing body position (standing) were first used in an organized manner by Crampton (ref. 56) and Schneider (ref. 57) early in this century to estimate levels of physical fitness. Subsequently, tilting responses have been utilized as an index of efficiency of the cardiovascular system after various deconditioning procedures, such as space-

flight, water immersion, and bed rest. Orthostatic instability and the increased tendency to faint are well-established responses after prolonged bed-rest deconditioning (ref. 58), and the degree of orthostatic intolerance increases with increasing duration of bed rest (ref. 59). So an understanding of the mechanisms contributing to one consequence of bed-rest deconditioning (orthostasis) may help to understand the basic mechanisms of the deconditioning process itself.

The immediate response to a sudden change from a recumbent to an upright posture is a fall in systolic blood pressure above the heart. At the level of the brachial artery the decrease can be 40 mmHg with a slight rise in diastolic pressure. Within 30 seconds, the brachial systolic pressure returns to normal and usually rises by 5 to 10 mmHg in healthy people (ref. 60). The tendency for blood to "pool" (flow slowly) in the lower extremities impedes venous return, and is the probable cause of the precipitous fall in arterial systolic pressure. This fall is compensated by immediate arteriolar vasoconstriction and the precipitous decrease in arterial systolic pressure is accentuated by this impeded venous return. The decreased stroke volume is compensated by increased heart rate so cardiac output remains essentially unchanged. Movement of lower extremity skeletal muscles aids venous return. Orthostatic vasoconstriction is, in part, the result of decreased stimulation of vascular pressoreceptors located in the heart, aortic arch, carotid sinus, and the large arteries. The pressoreceptors normally act to depress increasing blood pressure by sending signals which act to depress the tonic activity of the vasoconstrictor center in the brain, thus causing vasodilation and a fall in blood pressure. Since the carotid sinuses are about 30 cm above the heart, the pressure in them must be below brachial pressure by the difference in hydrostatic pressure (about 25 mmHg). Thus, a continuous decrease in stimulation of the carotid sinus pressoreceptors must persist as long as an erect posture is maintained (ref. 60). Arteriolar vasoconstriction can retard blood pooling, but it cannot facilitate venous return. Resting skeletal muscle tone and active contractions facilitate venous return. Gastrocnemius intramuscular pressure (tone) in hereditary nonfainters is about 100 mmH$_2$O, whereas the pressure in fainters is about 50 mmH$_2$O. Leg exercise raises intramuscular pressure to prevent or retard fainting. The vasoconstrictive reflex causes peripheral vascular vasoconstriction, which also decreases heat dissipation; core temperature can rise by 1°C. Standing results in increased arteriolar blood pressure in the lower body that facilitates an isosmotic plasma-to-interstitial compartment fluid shift; plasma volume is reduced by 10–15%, which further aggravates the hypotension partly by reducing venous return. Standing also causes reduction in urinary output by a combined

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reduction in renal plasma flow and glomerular filtration rate, and increased water resorption from the action of increased plasma vasopressin.

Three general types of postural hypotension have been identified: sympathicotonic hypotension, asympathicotonic hypotension, and vasodepressor (vasovagal) hypotension (refs. 61 and 62). *Sympathicotonic hypotension* is characterized by responses to elevated levels of catecholamines, such as tachycardia, and decreases in systolic and diastolic blood pressures. The signs and symptoms just before fainting are heart palpitations, light headedness, non-thermal sweating, and, often, nausea. *Asympathicotonic hypotension* is characterized by serious neurogenic disorders with a profound fall in blood pressure without a rise in heart rate. The signs and symptoms are loss of sweating ability, disturbances of intestinal and bladder control, changes of pupillary reactions, and extrapyramidal defects. There appears to be decreased function (synthesis) of catecholamines. *Vasodepressor (vasovagal) hypotension* is characterized by reduction in blood pressure accompanied by tachycardia and followed by bradycardia, non-thermal sweating, and, perhaps, nausea.

Thulesius (ref. 62) has differentiated the types of orthostatic hypotension.

1. Sympathicotonic hypotension

   (a) Primary: functional disturbance; (b) secondary: oligemic (decreased blood or plasma volume), varicose veins, or thermo-vascular dilatation. Drug-induced: nitrates, neuroleptics, or pregnancy. Deconditioning: attenuated or loss of gravity forces, or bed rest, and postinfectious and hyperbradykinism.

2. Asympathicotonic

   (a) Primary neurogenic: (Bradbury–Eggleston, Shy-Drager); (b) secondary neurogenic: peripheral and central neuropathy. Diabetes, Wernicke's encephalopathy, syringomyelia, pernicious anemia, porphyruria, and amyloidosis. Iatrogenic due to thoracolumbar sympathectomy or ganglionic blockers.

3. Vasovagal

   (a) Acute syncope in standing (after initial period of high sympathicotonic drive); (b) traumatic reaction, fright and fear.

More recent information on asympathicotonic hypotension can be found in Onrot et al. (ref. 63), Robertson et al. (refs. 64 and 65), and Schatz (ref. 66). A summary of differential heart rate and blood pressure responses are: Type IA, hypertonic reaction—increased heart rate and

increased blood pressure; Type IB, sympathicotonic reaction—increased heart rate and decreased blood pressure; Type II, asympathicotonic reaction—unchanged heart rate and a profound decrease in blood pressure; Type III, vasodepressor (vasovagal) reaction—increase then a decrease in heart rate and a continuous decrease in blood pressure (ref. 62).

The normal physiological response to assumption of the upright posture is to move the body. The contracting muscles, particularly in the legs, push against the veins and help to move blood headward via the one-way valves within the large veins. But during the tilt-table test the body remains motionless and the muscle pumping action is stopped. Now the passive blood pressure control system is put under greater stress and must function decisively to forestall the onset of fainting. It is assumed that the longer the tolerance time the better the functioning of the passive blood pressure control system.

The level of the arterial pressure is a direct function of the cardiac output (stroke volume × heart rate) and the total peripheral resistance. A decrease in any of these parameters will tend to lower pressure. Changes in arterial pressure are detected immediately by baroreceptors in the carotid sinus and aortic arch. Increased pressure causes, by reflex action, these sensors to fire more rapidly, which inhibits the vasoconstrictor center in the medulla to cause peripheral vasodilatation, reduction in heart rate and strength of contraction, and lower pressure. A decrease in arterial pressure inhibits the vasodilatation center to cause vasoconstriction resulting in an increase in heart rate and strength of contraction and higher pressure. This baroreceptor reflex responds within seconds to changes in pressure; much more so to increasing than to the decreasing arterial pressures during tilting.

This high-pressure arterial reflex-control system is modulated by a low-pressure venous reflex system whose similar stretch receptors are located in the low-pressure pulmonary arteries and atria of the heart. The pulmonary receptors function much like those in the systemic arteries, although activation of the atrial receptors causes reflex vasodilatation of the peripheral arterioles. This vasodilatation reduces peripheral resistance and blood volume via two mechanisms: increased capillary flow and pressure causes greater filtration of fluid to the interstitial space, and inhibition of vasopressin, which causes increased urine flow (a much slower acting mechanism). Blood-volume reduction can also be elicited by sympathetic stimulation of the veins without significant change in peripheral resistance. The net result is lower arterial pressure. Thus, blood pressure regulation is influenced by changes in blood volume, an important mechanism during

tilting when blood volume is already decreased by bed rest.

In addition, brief mention will be made of the many hormones and ions that can influence blood pressure. The catecholamines are vasoconstrictors; they react within a few minutes to decreases in pressure. Angiotensin is the most powerful vasoconstrictor known. The renin-angiotensin system requires about 20 minutes to become fully active, but its effect can last for 1 hour. The other major vasoconstrictor is vasopressin. Serotonin (5-HT) and the prostaglandins can act to vasoconstrict or vasodilate, depending on their concentrations. Bradykinin and histamine vasodilate, as do increased plasma H^+, Na^+, K^+, Mg^{++}, CO_2, acetate, citrate, and osmotic concentrations. Vasoconstriction can also occur with increased Ca^{++} concentration and decreased osmolality.

Clearly, the mechanism of blood-pressure control during tilting, particularly after bed-rest deconditioning, is not a simple one. At the beginning of head-up tilting the increased hydrostatic pressure, due to the change of posture, causes blood to pool (flow slowly) in the lower extremities. There is a shift of at least 300 ml of blood from the thorax to the legs (ref. 67), which is accompanied by a shift (loss) of 14–18% of the plasma volume to the interstitial space; the result is a loss of at least 600 ml of fluid from the vascular system (ref. 68). As the venous return (cardiac input) begins to decrease, the cardiac output also begins to decrease. The result is an increase in heart rate of 20–30 beats/min to compensate for the decreases of 20–30% in stroke volume and cardiac output (refs. 67, 69, and 70).

Systolic blood pressure usually rises during tilting, but diastolic pressure remains relatively constant or rises slightly in response to the increase of 20–30% in peripheral vascular resistance (refs. 67 and 69). As tilting continues, the systolic pressure begins to fall and fainting occurs when the pulse pressure drops below about 10 mmHg, but this level varies among subjects.

Although some investigators (refs. 19 and 71) have found otherwise, others have reported a positive remedial effect from the performance of isometric- or isotonic-exercise training during bed rest upon post-bed-rest orthostatic intolerance (refs. 6, 59, and 72–76). The degree of orthostatic tolerance appears to be directly related to the amount of exercise performed during bed rest (refs. 74 and 75). That there is a significant positive effect upon orthostatic tolerance from the exercise training during bed rest is also suggested from the observations that significant intolerance results from prolonged confinement and from immobilization where the subjects spend a considerable portion of each day in an upright position (ref. 77). Orthostatic intolerance also results from prolonged chair

rest where the subjects are immobilized in the sitting position (ref. 78). In both studies (refs. 77 and 78) nearly normal hydrostatic pressure was acting, but significant orthostatic intolerance occurred.

In contrast to these findings, Birkhead et al. (ref. 6) reported that 8 hr/day of quiet sitting or 3 hr/day of quiet standing (ref. 49) performed during bed rest were the minimum daily times necessary in these body positions to virtually eliminate orthostatic intolerance. Also, the physiological responses to lower body negative pressure (LBNP)—applied by means of an air-tight cylinder over the lower half of the body and sealed about the waist at pressures of –35 to –45 mm Hg—correlated moderately well (r = 0.71) with similar responses during tilting (ref. 79). Use of both LBNP for 1–8 t hr during bed rest (refs. 72 and 80–83) and head-to-foot ($+G_z$) acceleration by centrifugation for up to 80 min/day (refs. 84 and 85) significantly improved and, with the longer exposures, virtually eliminated post-bed-rest orthostatic intolerance. Some remedial effects of LBNP are to effect chronic increases in venous tone (ref. 82) and plasma volume (ref. 83).

There is some evidence which indicates that endurance-trained athletes have significantly lower orthostatic tolerance than normal, untrained men. Korobkov et al. (ref. 86) reported that, after 40 days of bed rest, the physiological responses during a 70 deg head-up orthostatic tolerance test were much more stable in a group of highly trained weightlifters than in a group of highly trained distance runners; some of the latter fainted. The greater orthostatic stability among the weightlifters was attributed to the effect of the performance of the repeated Valsalva maneuver (increased blood pressure with greatly reduced blood flow) during weightlifting; this maneuver could have exerted a "conditioning" effect upon the venous circulation that acted in conjunction with a more efficient muscular pumping action. Since the legs are motionless during the orthostatic test, greater leg muscle mass and probably intramuscular pressures of the weightlifters could have exerted greater passive lateral pressure on the veins to inhibit pooling to a greater extent than in the runners. Stegemann et al. (ref. 87) observed, after 6 hr of water immersion deconditioning, a significantly shorter tilting tolerance (6.1 min) in endurance-trained athletes (they all fainted) while all the normal, untrained men tolerated 10 min of tilting without adverse effects.

Mangseth and Bernauer (ref. 88) also found a significantly lower tilt-tolerance (17 min) with syncope in four normal, ambulatory, trained distance runners compared with the tolerance (>30 min) of a control group of four untrained men. Although endurance exercise training induces a chronic increase in plasma volume of 12–15% (ref. 89),

which should tend to preserve or increase orthostatic tolerance (ref. 83), it also seems that some endurance-trained athletes have a more labile and less responsive blood pressure control system when positive and negative ambient pressures were applied externally near the carotid sinus (ref. 90). Decreased orthostatic tolerance was observed by Greenleaf et al. (ref. 91) in men after they were exercise-trained in a hot environment. They hypothesized that the lower orthostatic tolerance after training was due to a more compliant venous system caused by the increased blood flow requirements to transport oxygen to cells and the increased body heat content to the skin. However, six months of general physical training in ambulatory men, involving isotonic and isometric exercise, resulted in no change in tilt-table tolerance (ref. 92). Convertino has concluded that "aerobic fitness is generally not associated with orthostatic intolerance" (ref. 93).

During bed rest, however, there is an opposite effect of exercise or LBNP training on the functioning of the peripheral circulation. Without these remedial procedures vascular tone is either unchanged (refs. 82 and 94–96) or decreased, and peripheral blood flow is increased from ambulatory control levels (refs. 97 and 98). After intermittent isotonic exercise training (refs. 97 and 98) or LBNP training (ref. 82), however, resting venous tone increases and peripheral blood flow decreases. Compared with ambulatory control values, tissue heat conductance (which approximates changes in peripheral blood flow) also decreases by 16–23% during submaximal exercise in subjects given intensive isotonic or isometric exercise training during bed rest (ref. 99). Thus, the positive remedial effect of exercise training during bed rest on the orthostatic intolerance could be mediated, in part, by increased venous tone in the peripheral circulation, particularly in the lower extremities. But the presence of increased leg volume and fluid congestion during tilting with greater than normal venous tone after bed rest, is usually accompanied by increased leakage of plasma fluid through the vascular system via changes in capillary fluid dynamics, which would tend to decrease tolerance.

The mechanism of the decreased orthostatic tolerance following bed-rest deconditioning involves multiple factors. The accentuation of the intolerance by dehydration (ref. 100) and the attenuation or elimination of the intolerance by procedures that restore plasma volume, such as lower body negative pressure (refs. 81–83), oral hyperhydration with water and saline (refs. 101–103), and sitting and standing during bed rest (refs. 6 and 49), suggest that changes in vascular volume coupled with increased vascular pressure are important parts of the mechanism. That a combination of increased vascular volume following drinking and increased vascular pressure with LBNP results in more complete restoration of tolerance (ref. 67)

than when each was applied separately (refs. 101–104), suggests a significant interaction between the two treatments. Lower body negative pressure is a potent stimulus for sodium and water retention and appears to act by decreasing glomerular filtration (ref. 105). It is interesting that inflation of venous occlusive cuffs for 16 hr/day during the last 2 days of bed rest and oral ingestion of 9-alpha-fluorohydrocortisone for 2–4 days after 30 days of bed rest restored plasma volume to normal, but neither treatment had a significant effect on the post-bed rest orthostatic intolerance (ref. 106). However, Bohn et al. (ref. 107) reported that administration of 9-alpha-fluorohydrocortisone daily during 10 days of bed rest increased plasma volume and orthostatic intolerance was ameliorated.

These variable orthostatic responses associated with restoration of plasma volume indicate that the volume of blood is important, but not of prime importance, for maintaining tolerance. The importance of changes in tissue (intramuscular) pressure has been emphasized involving reduction in extracellular and interstitial fluid volumes during bed rest (refs. 108 and 109), and the postulated accompanying increase in capillary-to-tissue filtration caused by the increased hydrostatic pressure during tilting (refs. 21, 67, 110, and 111). Results from other studies have indicated reduction in plasma and extracellular fluid volumes by the fourth day of bed rest (ref. 8), and then subsequent restoration of extracellular volume followed by an even greater than normal increase in the interstitial volume (fig. 6), which compensated for the continued reduction in plasma volume during 10–14 days of bed rest (refs. 8 and 69). If tilt-tolerance was measured after 3–4 days of bed rest when the interstitial volume was reduced, perhaps there could be increased capillary filtration, but probably not after 10–14 days of bed rest when the interstitial volume was expanded. This expanded interstitial compartment could be an adaptive response during bed rest to prevent further capillary filtration from the plasma and also to prevent fluid shifts from the intracellular compartment. Further research is needed in this area because others have found no change in interstitial volume during bed rest (refs. 108 and 109).

Since changes in plasma volume and capillary filtration rate do not seem to be the prime mechanisms that account for orthostatic intolerance, the burden falls upon the vasomotor control system. Recall that norepinephrine excites mainly the alpha-adrenergic receptors (with moderate beta-receptor stimulation), that epinephrine excites both types of receptors about equally, and that alpha stimulation causes vasoconstriction and beta stimulation causes vasodilatation, cardioacceleration, and increased myocardial strength. Schmid et al. (ref. 96) observed that venous tone responses to infusion of tyramine (a

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norepinephrine stimulator) were attenuated after bed rest, but that infusions of norepinephrine after bed rest produced the normal increases in venous tone. Thus, bed-rest deconditioning did not affect responsiveness of vascular smooth muscle to constrictor stimulation (norepinephrine), but endogenous stores of norepinephrine, which could be released by tyramine causing vasoconstriction, were depeleted and failed to act during tilting. This mechanism would act mainly on alpha-receptors.

Function of the beta-receptor mechanism was investigated by Melada et al. (ref. 69) who found that intravenous administration of propranolol (0.15-0.20 mg/kg over 5 min followed by 0.04 mg/kg every 20 min), a beta-blocker, diminished the tachycardia and the incidence of syncope and hypotension during 60 deg head-up tilt. The increased level of plasma renin activity that occurred during tilt was accentuated by iso-proterenol (a beta stimulator) and essentially blocked by propranolol. So the renin-angiotensin system also appears to be implicated in the mechanism of the intolerance.

Thus, these findings suggest, in association with hypovolemia, that the more important aspect of post-bed-rest orthostatic intolerance is due to impaired vasomotor responses from a combination of decreased alpha-adrenergic stimulated vasoconstriction by norepinephrine, and by increased beta-adrenergic stimulated vasodilatation.

Practical Recommendations

Prolonged bed rest is a debilitating procedure for normal, healthy humans and should be prescribed conservatively for sick or debilitated patients. The healing responses progress simultaneously with the adaptive (deconditioning) physiological changes during the period of bed rest. For these reasons performance of properly designed and controlled physical exercise training regimens should be encouraged whenever possible. Even arm exercise training can confer total body training effects.

Trained athletes, highly endurance-trained athletes in particular, may not respond to bed-rest deconditioning like untrained patients. The athletes may exhibit exaggerated fainting responses when arising from the bed, especially when recovering from the effects of anesthetics after surgery. Inclusion of a patient's exercise-training status and physical fitness level would be a useful addition to their medical history.

Most bed-rested patients will exhibit "abnormal" responses to the standard glucose-tolerance test after seven days (perhaps sooner) of recumbency. They should not be diagnosed as having diabetic symptoms without further confirmatory tests.

There is some evidence that drug kinetics may be altered in patients during bed rest as a result of reduced plasma volume and reduced circulation time.

In preparation for reambulation after bed rest, patients should increase their hydrostatic pressure gradient by elevating their torso or by standing briefly whenever possible. They should also be encouraged to eat food and drink hyperosmotic fluids, for example citrus fruit juices, to aid in restoring bed-rest induced hypovolemia.

Conclusions

It is interesting to consider the philosophical implications concerning the degree and range of adaptive responses of subjects and patients to the horizontal position during bed rest—that is, to "deconditioning." The concept of deconditioning appears to be based on the hypothesis that man was designed or has evolved to function more or less in the upright position in the Earth's gravitational environment. That is, we have evolved from basically four-legged animals that usually moved in the horizontal body position on all fours, to essentially a four-limbed human creature that usually moves in the upright body position on two limbs. Thus, the deconditioning that occurs during bed-rest is a departure from the optimal posture of intermittent exposure to the upright position.

One could argue that most, if not all, of the major adaptive responses to prolonged bed rest—the general deterioration of the cardiovascular, fluid-electrolyte, and neuromuscular systems, as evidenced by decreased working capacity, impaired insulin-glucose tolerance, increased calcium loss and bone demineralization, and increased orthostatic intolerance—do nothing to increase the adaptive potential of the body. To state it another way, there are no positive benefits to the organism from prolonged maintenance of the horizontal body position, except that of reducing energy consumption. Since life requires movement, and movement, especially in the upright posture, requires energy, then optimal functioning requires a condition of negative entropy whereby energy must be generated continuously. In times of crisis and stress (illness), it is probably better for survival if nonessential energy consumption is reduced, hence the assumption of the horizontal position (the position and condition of minimal energy usage). But at the same time, the condition of minimal energy is also the condition of positive entropy where the system tends to seek a more random, less organized state that we call deconditioning.

So if the organism must spend some time each day in the sitting and standing positions, not only to facilitate movement, but also to provide the stimuli for adaptation to the upright anti-gravity position, then perhaps the upright position is more basic to the nature of man (ref. 112). On the other hand, if one considers the hypothesis that man evolved from creatures adapted to zero gravity (perhaps ancient space travelers), then what we now refer to as the deconditioned state is actually the more basic condition and the process of adaptation to the force of gravity via the upright posture is the deviant condition. That is, we are in the process of evolving from a condition of positive entropy (horizontal or weightless) to a condition of negative entropy (upright or gravitational) requiring ever increasing energy utilization.

The human body is formed in an essentially deconditioned state in the watery environment of the womb, and many physiological responses to aging are similar to those during deconditioning (phylogeny recapitulates itself in ontogeny). Hence, if we are to survive and adapt to the force of gravity we must continually transform energy to overcome the positive entropy of the more random or basic state—weightlessness.

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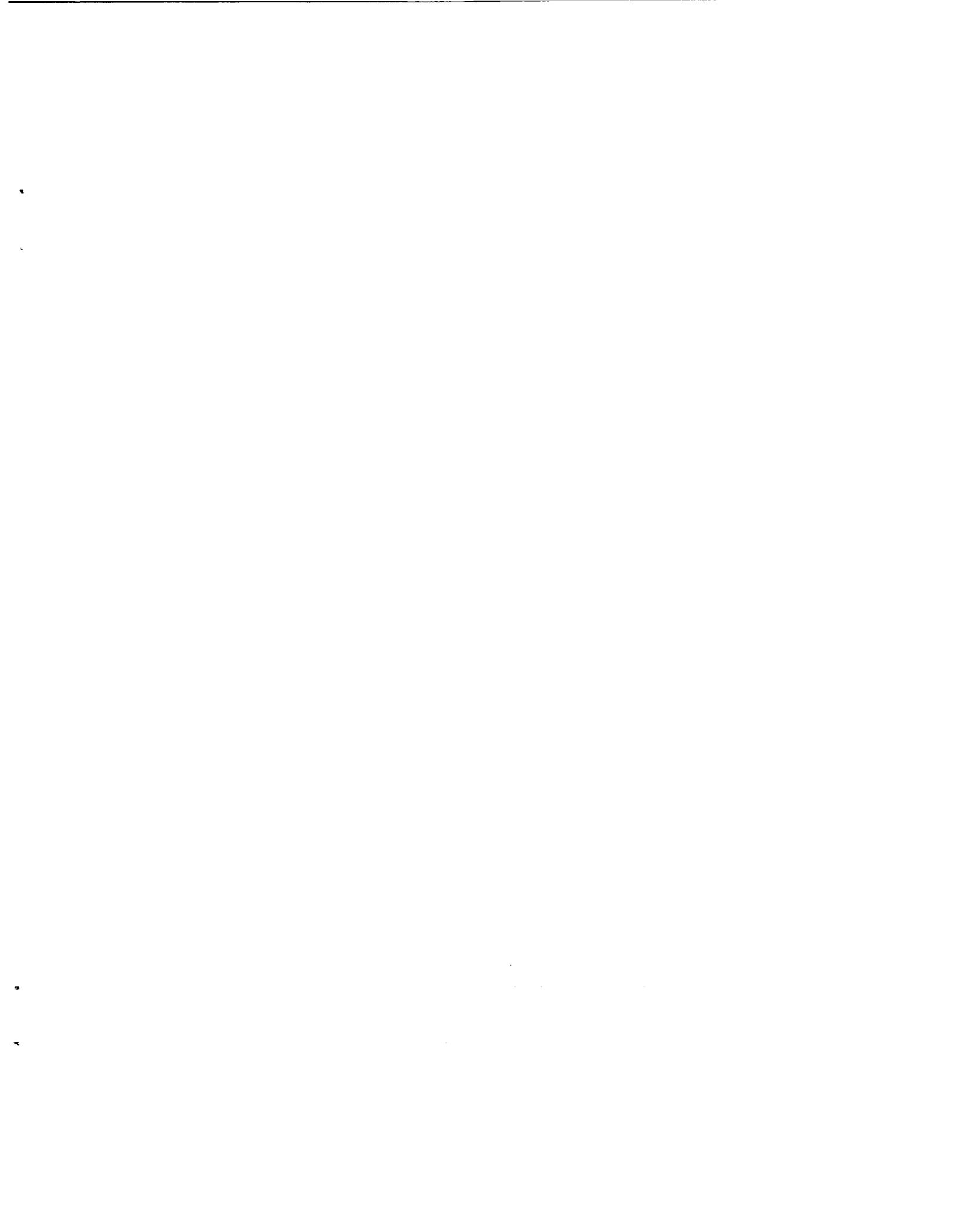
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13. ABSTRACT (Maximum 200 words)

Maintenance of optimal health in humans requires the proper balance between exercise, rest, and sleep as well as time in the upright position. About one-third of a lifetime is spent sleeping; and it is no coincidence that sleeping is performed in the horizontal position, the position in which gravitational influence on the body is minimal. Although enforced bed rest is necessary for the treatment of some ailments, in some cases it has probably been used unwisely. In addition to the lower hydrostatic pressure within the normally dependent regions of the cardiovascular system, body fluid compartments during bed rest in the horizontal body position, and virtual elimination of compression on the long bones of the skeletal system during bed rest (hypogravia), there is often reduction in energy metabolism due to the relative confinement (hypodynamia) and alteration of ambulatory circadian variations in metabolism, body temperature, and many hormonal systems. If patients are also moved to unfamiliar surroundings, they probably experience some feelings of anxiety and some sociopsychological problems. Adaptive physiological responses during bed rest are normal for that environment. They are attempts by the body to reduce unnecessary energy expenditure, to optimize its function, and to enhance its survival potential. Many of the deconditioning responses begin within the first day or two of bed rest; these early responses have prompted physicians to insist upon early resumption of the upright posture and ambulation of bedridden patients.

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