

Endocrine markers of semistarvation in healthy lean men in a multistressor environment

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Friedl, Karl E., Robert J. Moore, Reed W. Hoyt, Louis J. Marchitelli, Lester E. Martinez-Lopez, and E. Wayne Askew. Endocrine markers of semistarvation in healthy lean men in a multistressor environment. *J Appl Physiol* 88: 1820–1830, 2000.—We tested the hypothesis that key endocrine responses to semistarvation would be attenuated by changing only the food intake in a multistressor environment that also included sustained workload, inadequate sleep, and thermal strain. Serum hormones were compared within and between two groups of healthy young male volunteers participating in the 8-wk US Army Ranger course, with four repeated cycles of restricted energy intakes and refeeding: *group 1* ($n = 49$) and *group 2* ($n = 48$); energy deficits averaged 1,200 and 1,000 kcal/day, respectively. After 8 wk, most of *group 1* achieved a minimum body fat, serum 3,5,3'-triiodothyronine (T_3) was below normal (78 ± 20 ng/dl), testosterone (T) approached castrate levels (4.5 ± 3.9 nmol/l), insulin-like growth factor I (IGF-I) declined by one-half (75 ± 25 μ g/l), and cholesterol rose from 158 ± 31 to 217 ± 39 mg/dl. Bioavailable T_3 and T were further reduced by increases in their specific binding proteins in response to declining insulin. Refeeding, even with continuation of the other stressors, produced prompt recovery of T_3 , T, and IGF-I. Higher energy intakes in *group 2* attenuated the subclinical hypothyroidism and hypercholesterolemia, whereas consistent luteinizing hormone suppression indicated centrally mediated threshold effects on gonadal hormone suppression. We conclude that low T, T_3 , and IGF-I remained reliable markers of acute energy deficits in the presence of other stressors; elevated cholesterol and cortisol provided information about chronic status, corresponding to diminishing body fat stores.

weight loss; sleep deprivation; body fat; insulin; testosterone; insulin-like growth factor I; 3,5,3'-triiodothyronine; cholesterol; cortisol; growth hormone; thyroid-stimulating hormone; binding globulins; luteinizing hormone

IN THE 1950 Minnesota starvation study, Keys and colleagues (23) demonstrated that normal lean men who each lost an astounding 25% of their body weight over 24 wk had little or no change in serum proteins, fatty acids, hematologic parameters, liver function tests, electrolytes, or vitamin and mineral status (23). Many of these men had little measureable fat remaining (i.e., <5% of body wt) and were catabolizing a

significant amount of their lean mass. In a recent inquiry into the stress levels associated with high-intensity military training, clinical biochemistries were similarly unremarkable (32, 33), even as a group of young men mobilized nearly all of their available fat stores and lost weight at a faster rate than did the volunteers in the Minnesota study. Endocrine responses to the semistarvation stressor reveal the true severity of this physiological challenge and provide insight to normal metabolic adaptations.

The endocrine stress responses to chronic semistarvation in normal healthy men have not been revisited using current endocrine assay techniques in the 50 yr since the Minnesota starvation study (23). Most of the research into extreme energy deficit has involved sedentary obese patients on very-low-calorie diets or hospitalized patients who are catabolic as a result of intercurrent illness. These responses may not be the same as responses in soldiers operating away from their supply lines; refugees in flight from their homes, perhaps receiving food in intermittent relief operations; or young wrestlers preparing for their competitive season. In all of these circumstances, there is an energy deficit produced by limited intake in combination with a high energy flux produced by continued work (56). In contrast to the reduced obese, serious health and performance concerns arise sooner because smaller fat stores of these lean individuals become substantially depleted and body protein becomes an increasingly important source of energy (7, 15, 36).

This study examined the influence of chronic energy deficit on the thyroid-, gonadal- and somatotrophic-pituitary axes, by using US Army Ranger training as a paradigm of extreme semistarvation in a multistressor setting. A key stressor in this course has been restricted food availability, which produces an "uncomplicated" energy deficiency with large weight losses (32). This is actually a very complicated model because of the likely interactions of energy deficit; sustained high-energy expenditure (20); sleep deprivation with average sleep at 3.6 h/day (46); illness and injuries (29); and, depending on the time of year, environmental exposures to heat or cold. We report here the endocrine metabolic responses to US Army Ranger training in two summer classes studied at the same time of year, 1 yr apart, compared on the basis of a small increase in energy intake (+400 kcal/day), part of which reduced the energy deficit, while other stressors were unchanged.

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METHODS

This study was approved by the Human Use Review Committee at the US Army Research Institute of Environmental Medicine (Natick, MA) and by the Human Subjects Research Review Board, which has oversight responsibility for all Army medical research (Fort Detrick, MD). The study volunteers understood that they could withdraw from the study without adverse consequences at any time. All volunteers gave their written informed consent before starting the study.

Study design. Subjects were studied over time during their participation in a training course with four repeated bouts of normal feeding followed by 7- to 10-day periods of energy restriction. Morning blood samples were obtained after overnight fast at the start of the training and then at the end of each of four periods of energy restriction, before any refeeding began (*group 1*). The timing of these five sampling points with respect to the schedule of daily provided food energy is shown in Fig. 1A.

One year later, a second group of subjects participating in the same training but provided with a higher energy intake were studied using identical methods (*group 2*). *Group 2* received 400 kcal/day more food in a mixed diet (caloric content was divided into ~50% carbohydrate, 35% fat, 15% protein), representing a planned feeding intervention. Because of the competitive evaluations of individuals within the course, this could not be compared in a side-by-side study within the same class. To gain information about short-term responses to refeeding (while other course stressors remained undiminished), one sampling point was moved from the end of the first bout of energy restriction to the end of a period of refeeding in the third phase. These sampling points for *group 2* are shown on the feeding schedule in Fig. 1B.

Six months after the end of the course, no significant problems were observed in a subset of the first group, but numerous complaints about weight-gain overshoot after the first month prompted a follow-on study in *group 2*. Ten subjects who completed the course in *group 2* were studied again 5 wk after the end of the course and after cessation of all course stressors; these studies included the same endocrine and body composition measurements made during the course.

Study subjects. The volunteer subjects were male soldiers attending the US Army Ranger course. Army Ranger training tests the endurance and leadership abilities of young male soldiers under stressful conditions for the purpose of training and selection of elite combat unit leaders. No surrogate test has been devised to predict who will succeed in the face of fundamental personal discomforts such as hunger and fatigue nor has any alternative training been devised that helps a soldier achieve the self-knowledge of his physiological strengths and weaknesses under such challenges.

The volunteers were drawn from two summer Ranger classes, 1 yr apart (Class 11-91, $n = 190$, "*group 1*"; Class 11-92, $n = 178$, "*group 2*"). Because of the rigors of Ranger training, less than one-third of these volunteers finished the course (*group 1*, $n = 55$; *group 2*, $n = 50$); blood samples were available for 49 (*group 1*) and 48 (*group 2*) men. Reasons for not completing the course with the class were primarily for subjective evaluations of patrolling leadership ability; ~25% of class dropouts withdrew for medical reasons (29).

Comparisons of physical characteristics between finishers and nonfinishers in each study group are shown in Table 1. There were no differences between finishers and nonfinishers in each group. Comparisons between the two finisher study groups, the subjects of this report, revealed no significant

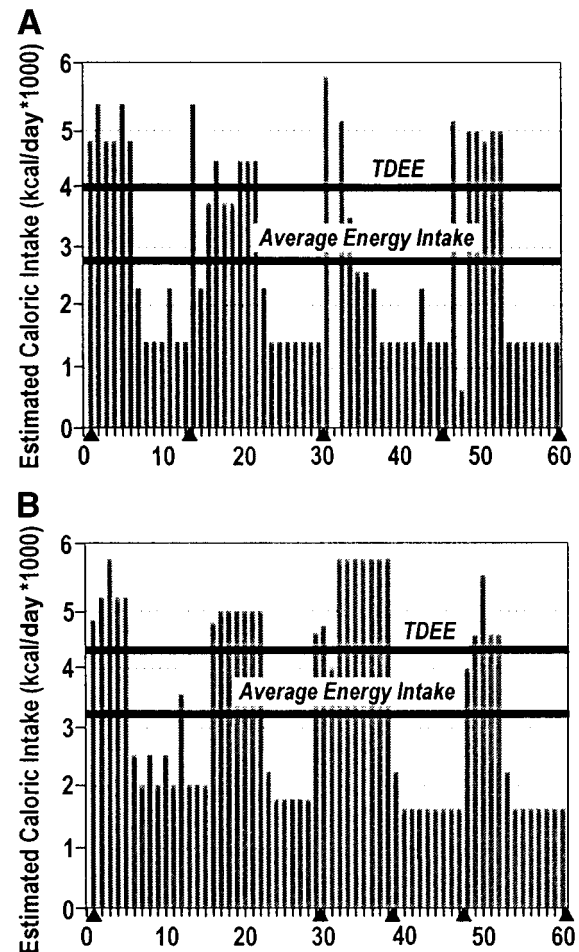


Fig. 1. Food energy provided to Ranger students on each training day (day is shown on x-axis) for *group 1* (A) and *group 2* (B). Morning blood samples were drawn (arrowheads) at the end of each of 4 phases of training in *group 1*; in *group 2*, a midphase sample was drawn after a period of refeeding (which occurred at start of each training phase). *Group 2* received an average of 400 kcal/day more than *group 1*. Additional samples were obtained posttraining (not shown); food intake in this postcourse period was ad libitum. Horizontal lines, mean daily energy intakes and mean total daily energy expenditure (TDEE).

differences at the start of training. Comparisons of immune function indexes between the two groups have been previously reported, including an apparent attenuation of immune deficits and infections with increased energy intake in *group 2* (24).

Study conditions. The Ranger course was divided into four phases of ~2 wk each, with training taking place in four different environments: temperate forest at Fort Benning, Georgia; the Chihuahuan Desert near El Paso, Texas; the Blue Ridge mountains in northern Georgia; and coastal swamp along tributaries of the Yellow River at Eglin Air Force Base, Florida. For administrative training reasons, the order of these phases was switched between *group 1* and *group 2*, with the desert phase moved from last to second place; the training plans remained unchanged. Each phase began with a few days of adequate feeding while soldiers were being taught new skills and was then followed by 7–10 days of one meal per day during realistic small-unit tactical operations typically involving 8- to 12-km patrols with loaded rucksacks in hostile terrain. At the end of the course, *group 1*

Table 1. Comparison of physical characteristics of dropouts and finishers from Ranger training and changes in body composition of finishers in two summer classes in successive years

Variable	Group 1			Group 2		
	Dropouts (n = 133), Baseline	Finishers (n = 55)		Dropouts (n = 117), Baseline	Finishers (n = 50)	
		Baseline*	8-wk Change†		Baseline*	8 wk Change†
Age, yrs	24.3 ± 3.8	23.6 ± 2.8		24.3 ± 4.2	23.0 ± 3.9	
Body mass index, kg/m ²	24.8 ± 2.2	24.3 ± 2.1	−3.9 ± 1.0	24.6 ± 2.3	24.5 ± 2.0	−3.1 ± 0.8‡
Body weight, kg	76.8 ± 9.3	75.9 ± 9.0	−12.1 ± 3.4	76.7 ± 9.1	78.4 ± 8.7	−10.0 ± 2.8‡
Fat mass, kg	11.7 ± 4.6	11.0 ± 4.0	−7.3 ± 3.2	11.7 ± 4.4	11.8 ± 3.9	−6.0 ± 2.2‡
Fat-free mass, kg	65.1 ± 6.2	65.0 ± 6.2	−4.8 ± 2.4	65.3 ± 6.8	66.7 ± 6.3	−4.0 ± 1.7‡
Bone mineral, kg	3.5 ± 0.5	3.5 ± 0.4	−0.1 ± 0.1	3.5 ± 0.4	3.6 ± 0.4	−0.1 ± 0.1

Values are means ± SD; n, no. of subjects. Fat and fat-free mass were determined from body weight, and dual-energy X-ray absorptiometry-assessed percent body fat; bone mineral mass was determined by dual-energy X-ray absorptiometry measurements of bone-containing pixels. *There were no significant differences for any variables compared between dropouts and finishers or between finishers in group 1 and group 2 ($P > 0.05$, *t*-test). †All variables demonstrated statistically significant reductions during the 8 wk course ($P < 0.01$, paired *t*-test). ‡Changes were significantly attenuated when more calories were offered during the course (group 2), except for similar small reductions in bone mineral ($P < 0.05$).

men were carrying an average weight of 32.5 ± 7.8 kg on patrolling exercises; this did not reflect starting loads, which would have also included water and ammunition expended during the patrol exercises (~2 to 5 kg additional weight).

Daily ambient temperatures averaged 30°C (high) and 18°C (low); relative humidity frequently exceeded 75%, with daily maximums averaging 92% during the 2 wk of the swamp phase. During patrolling exercises (approximately one-half of the time in the course), men slept at ambient temperatures without additional insulation (except for a rain poncho). This is reflected in a wide diurnal range of body core temperatures in Ranger students, including body temperature nadirs approaching 35°C measured in some individuals on cool nights (21). Students arrived at the course from all over the United States and had been encouraged to report 1 wk early for heat acclimation, particularly if coming from more temperate climates. Students with any history of environmental heat injury were specifically excluded from these summer courses.

Throughout the training, water consumption was strongly encouraged to prevent heat injury. Dehydration would have been readily detected by changes in measures such as hematocrit and hemoglobin (65) and was not a factor in this study (33).

The feeding schedule for both groups is shown in Fig. 1. There was virtually no food wastage during the Ranger course; thus food offered was assumed to closely reflect food intake. Intakes were estimated from the standard Army menus for the garrison feeding and from known content of Army field rations (the Meal, Ready to Eat, version XII, and the Long Life Ration Packet). Recipe specialists and trained observers examined preparation and portion sizes during the third phase of the group 2 study to confirm menu-based data for garrison intake estimations.

Sleep was monitored through the entire course by using wrist-worn activity monitors in subsets of the men in a class immediately after the group 1 class and in group 2. Average sleep for the duration of the course did not change between years (3.6 h/day) and was consistent with previously published measurements in Ranger students (46). In both years, there was a slight increase in average sleep (4.2 h/day) in the final training phase compared with the three previous phases (and irrespective of training environment), suggesting unplanned sleep resulting from cumulative fatigue.

Data collection. Nude body weight was measured at each sampling period. Abdominal circumferences were measured with a fiberglass tape measure held flat against the skin at

the level of the omphalion. Skinfold thicknesses were measured with Harpenden calipers at four sites on the right side of the body (13). Percent body fat was measured by dual-energy X-ray absorptiometry (DEXA; DPX-Plus, Lunar, Madison, WI) at the beginning and end of the study by using manufacturer-supplied algorithms (Total Body Analysis, version 3.6, Lunar). Radiation exposure from this procedure has been measured at 0.05 µGy/scan. Precision of the measurement is better than ±0.5% for percent body fat. Calibration between the two devices used at each site and after transport and recalibration at each site were performed by using manufacturer-supplied standards and by using the investigators as biostandards. Percent body fat remained <0.5% between devices, comparable to the repeat reliability of measurements on a single device. Because DEXA overestimates soft tissue fat-free mass (FFM) in semistarved individuals, FFM and fat weight were calculated from percent body fat obtained by DEXA and from body weight measurements, as previously described (13). Relative hydration of the lean mass increased over the course, on the basis of stable isotope dilution space and bioelectric impedance measurements; total body resistance did not decline with declining body mass (12).

Blood samples were collected between 0500 and 0800, after an overnight fast. One exception to fasted sampling occurred inadvertently in group 2 at the 4-wk sample, when most of the group gained access to a special meal of hot dogs and snack foods 2–4 h before the morning blood sampling occurred. This meal was clearly reflected in high serum triglyceride levels (mean >100 mg/dl) and restoration of growth hormone levels to the normal range (<1 IU/ml). Five weeks after the end of the course (the men had returned to their usual Army jobs, and food intake was unrestricted), 10 volunteers from group 2 were again tested to study recovery after cessation of all course stressors. Morning blood samples were collected after an overnight fast, and body composition measurements were repeated.

Endocrine assays. Multiple aliquots of each serum sample were stored frozen at −40°C until processed. Selected samples from group 1 and control samples drawn from investigators were retested with samples from group 2, serving as interassay quality control standards. Each volunteer's serum samples from the various time periods of the course were tested together in the same assay to remove interassay variations from the interpretation of changes within individuals.

All assays were performed by using commercially available test kits, without modifications of the manufacturers' recom-

mended procedures. Serum insulin-like growth factor I (IGF-I) was measured by RIA after acid-ethanol extraction of samples that had not been previously thawed (Allegro, Nichols Institute Diagnostics, San Juan Capistrano, CA) with intra- and interassay coefficients of variation (CVs) of <5 and 12%, respectively. Insulin was only measured in previously unthawed aliquots of *group 1* samples by RIA (Diagnostic Products, Los Angeles, CA). Growth hormone was measured by an avidin-coated bead RIA (Allegro HGH, Nichols) with intra- and interassay CV of <5 and <10%. 3,5,3'-Triiodothyronine (T₃) and thyroxine (T₄) were measured by RIA (ICN Biomedicals, Costa Mesa, CA). Thyroid-binding globulin (TBG) was measured by RIA (Nichols), and thyroid-stimulating hormone (TSH) was measured by using a third-generation immunoassay with a limit of detection of 0.04 mIU/l (Allegro HS-TSH, Nichols), both with intra- and interassay CVs of <5 and <10%. T₄/TBG ratio was calculated as T₄ (µg/dl)/TBG (µg/ml) × 10. Luteinizing hormone (LH) was measured by RIA (ICN Biomedicals) with intra- and interassay CVs of <5%. Sex hormone-binding globulin (SHBG) was measured by immunoradiometric assay (Farnos Diagnostica, Oulunsalo, Finland) with intra- and interassay CVs of <5%. Cortisol and testosterone were measured by RIA (Diagnostics Products) with intra- and interassay CVs <5%. Free testosterone and non-SHBG-bound testosterone were calculated from individual serum levels of testosterone, SHBG, and albumin (55).

Serum lipids were measured at the Pennington Biomedical Research Center (Baton Rouge, LA) by using enzymatic methods (Synchron CX5 automated chemistry analyzer, Beckman Instruments, Fullerton, CA). High-density lipoprotein (HDL) cholesterol was determined on EDTA-containing plasma after dextran sulfate precipitation of lower density lipoproteins. Low-density lipoprotein (LDL) cholesterol was calculated from LDL = cholesterol – HDL – (triglycerides/5) (in mg/dl).

Data analysis. Data were analyzed within groups by one-way analysis of variance. Post hoc tests were applied to variables with significant differences to define differences between means (Scheffé's test), and these were noted on Figs. 2–4 with letters denoting similar subsets (SPSS, version 8.0, Chicago, IL). Means at approximately the same time points in the course (baseline, 4 wk, 6 wk, 8 wk) were compared between *group 1* and *group 2* by unpaired *t*-test. Proportions were compared by χ^2 tests. All values are expressed as means ± SD. Statistical tests with *P* < 0.05 were accepted as significant.

RESULTS

Physical measurements. Physical characteristics of men in the two groups did not differ (Table 1). There were clear differences in the effect of the feeding intervention (i.e., *group 2*) on body composition changes during the course. Body weight loss was attenuated in *group 2* ($-12.6 \pm 2.8\%$ of initial weight) compared with *group 1* ($-15.5 \pm 3.1\%$; *t*-test, *P* < 0.01). Fat stores were markedly reduced by the end of the course for both groups. However, no reserves remained for most men at the end of the study in *group 1* (11 of 55 men had 4–5% body fat), whereas *group 2* was not pushed to this limit (1 of 50 men; χ^2 test; *P* < 0.05). The change in FFM in *group 2* was $6.1 \pm 2.4\%$ of initial FFM, or nearly 20% less than in *group 1* on the basis of change over initial FFM. The abdominal circumference declined by an average of 8.1 ± 3.0 cm in *group 2*, or 20% less than the average decline in *group 1* (Table 2). Body weight and abdominal circumferences increased at the end of the refeeding period (within the third phase of training; week 5) and then declined again to lower values by the end of the phase (week 6). This suggests a sawtoothed pattern of changes throughout the course, with similar temporary increments probably occurring in each of the four phases, even as end-of-phase weights and abdominal girth progressively decreased (Table 2).

Average energy deficits calculated from changes in energy stores (fat mass and FFM) were significantly different between the two groups: 5.0 ± 2.0 MJ/day (*group 1*) and 4.1 ± 1.6 MJ/day (*group 2*; *P* < 0.03). This difference is attributable to the increase in energy intake in *group 2* and not explained by a reduction in total energy expenditure. From previously reported data, energy expenditure was similar or slightly higher in *group 2*. This was based on comparison of doubly labeled water-based measurements in a small subsample of men in each group selected for a range of body sizes; these men were repeatedly dosed with ²H₂¹⁸O during the course (20).

Endocrine measurements during the course. Insulin levels declined from 35 ± 17 pmol/l (start) to 18 ± 9 pmol/l (2 wk) and remained significantly reduced at the

Table 2. Anthropometric measurements followed through Ranger training

Variable	Baseline	2 wk	4 wk	5 wk	6 wk	8 wk
Body weight, kg						
<i>Group 1</i>	75.9 ± 9.0*	71.0 ± 8.0*†	68.9 ± 7.6†		66.4 ± 7.2†‡	63.8 ± 6.7‡
<i>Group 2</i>	78.4 ± 8.7*		72.9 ± 7.7†‡	75.3 ± 7.5*†	70.8 ± 7.5†‡	68.4 ± 7.0‡
Abdominal circumference, cm						
<i>Group 1</i>	82.4 ± 5.9*	78.5 ± 5.9†	76.3 ± 5.1†‡		74.6 ± 4.3‡§	72.4 ± 3.9§
<i>Group 2</i>	84.2 ± 5.3*		79.4 ± 4.2†‡	81.3 ± 4.2†	78.0 ± 4.4‡§	76.0 ± 4.2§
Sum of skinfolds						
<i>Group 1</i>	45.0 ± 11.5*	32.7 ± 7.9†	27.9 ± 5.4‡		23.9 ± 4.5§	23.1 ± 4.4§
<i>Group 2</i>	47.1 ± 11.5*		ND	34.7 ± 7.0†	28.7 ± 5.5‡	26.0 ± 4.8‡

Values are means ± SD. ND, not done. Values with the same symbols are not significantly different (Scheffé's test, *P* < 0.05); there were no significant differences between group means at any time point. All values, except body weight for *group 2* at 5 wk, were significantly different from baseline value (Dunnett's test, *P* < 0.05). Note: for comparison to normal lean men, mean values in a group of healthy Kenyan runners in peak condition were 74.3 ± 3.8 cm (abdominal circumference) and 20.1 ± 2.2 mm (sum of skinfolds) (K. E. Friedl and J. S. Staab, US Army Research Institute of Environmental Medicine, unpublished observations, 1993).

end of each phase of training compared with baseline (insulin was measured only in *group 1*). Glucose was also significantly reduced from starting values by 10–20% at each phase, with mean values reaching the lower limits of the normal fasting range (3.9 mmol/l).

Circulating triglycerides were significantly reduced. Cholesterol levels, including HDL cholesterol (start: 1.2 ± 0.2 mmol/l, 8 wk: 2.0 ± 0.4 mmol/l), progressively increased through the course, and calculated LDL cholesterol (start: 2.4 ± 0.7 mmol/l, 8 wk: 3.4 ± 0.9 mmol/l) progressively increased through the course after an initial decline in the first 2 wk. A similar progressive rise in cholesterol and cholesterol subfractions was observed in *group 2* (Fig. 2).

T_3 declined significantly in the first month of the course and then leveled off with no further decline at 6

and 8 wk (Fig. 3). Refeeding within the course (*week 5*) temporarily restored T_3 levels. At each point in the *group 2* course, the decline in T_3 was attenuated compared with that of *group 1*, presumably due to the greater energy intake. The changes in T_4 and T_4 /TBG were smaller but demonstrated statistically significant declines that paralleled the changes in T_3 . TBG was significantly elevated in the second half of the course. TSH was elevated over baseline through most of the course, with significantly higher mean values by the middle of the course (Fig. 3). The proportion of individuals with TSH >6 mIU/l increased in both groups compared with baseline (χ^2 test, $P < 0.01$); 17–20% of individuals were in this category at the end of the two courses. Refeeding within the course temporarily corrected the rise in TSH (Fig. 3).

Serum IGF-I levels declined by approximately half of the baseline value by the middle of the course (Fig. 3). As with T_3 , IGF-I levels were temporarily restored to normal levels after 1 wk of refeeding *group 2* (wk 5); IGF-I and T_3 returned to their declining trajectory when food was again restricted. Although highly variable because of the pulsatile nature of growth hormone release, growth hormone levels were significantly elevated during the course, with means exceeding $4 \mu\text{g/l}$ at 8 wk; refeeding within the course temporarily reduced mean values to $<1 \mu\text{g/l}$. Highest levels were measured in the individual losing the greatest proportion of body weight, with progressive increases through the course from 0.5 to 3.5, 7, 12, and 37 $\mu\text{g/l}$ at 2, 4, 6, and 8 wk, respectively.

Cortisol levels increased significantly from initial values by 4 wk in *group 1* and by 6 wk in *group 2* (Fig. 3); the rise occurred as a similarly low body fat was achieved, indicated by mean sum of skinfold thicknesses ~ 28 mm (Table 2). The highest cortisol level (950 $\mu\text{mol/l}$) was measured in the individual who lost the greatest amount of body weight (23% of initial body wt) and began the course with minimal fat reserves (7% body fat).

Testosterone declined to levels well below the normal range for men, with parallel changes in both groups (Fig. 4). Refeeding produced a prompt recovery (*week 5*), even with other stressors continuing. The large rise in SHBG to outside of the normal male range (Fig. 4) paralleled changes also observed in TBG. This increase further reduced bioavailable testosterone, as indicated by the decline in calculated non-SHBG-bound testosterone levels to 10% of starting levels (nearly doubling the reduction observed for total testosterone). LH decreased significantly from 8.5 ± 3.1 IU/l (start) to 4.3 ± 2.2 IU/l (8 wk) in *group 1*, with similar changes in *group 2*; refeeding returned levels to baseline (Fig. 4).

Assessment of recovery (substudy). In a subsample of nine men, serum hormones were restored to normal levels within 1 wk after the end of the training except for T_3 , which was markedly elevated over normal (data not shown). These changes are comparable to the changes that were observed at the midmountain sampling period, which also represented ~ 1 wk of refeeding. All measurements had returned to normal within

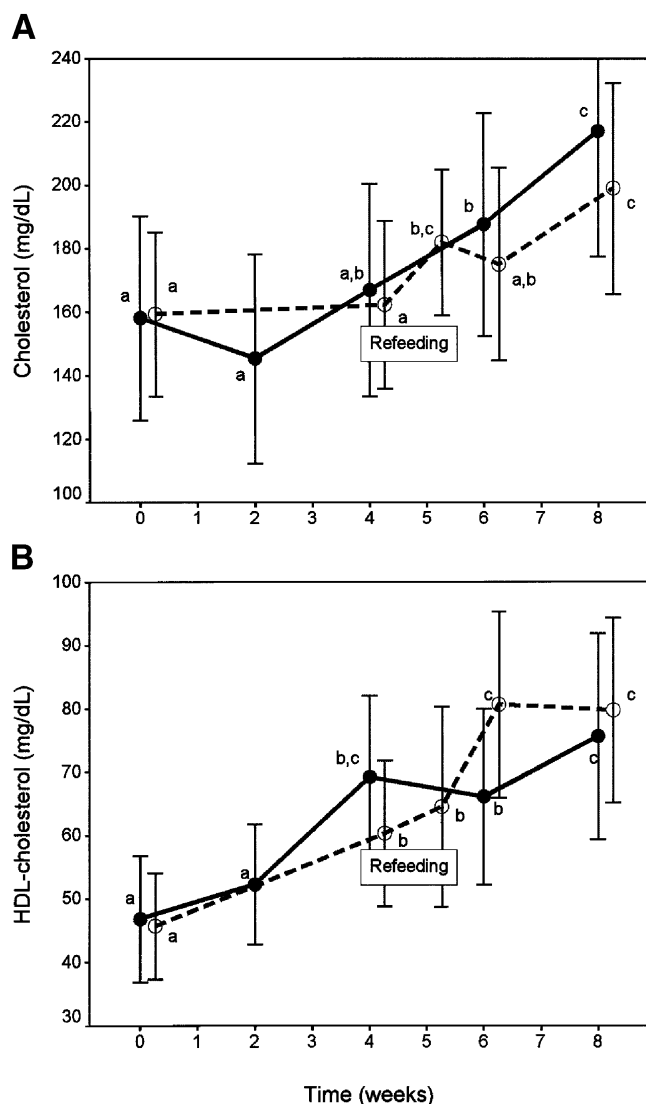


Fig. 2. Serum cholesterol (A) and high-density-lipoprotein (HDL) cholesterol (B) concentrations over 8-wk Ranger course for *group 1* (mean 1,200 kcal/day energy deficit; solid lines and ●) and *group 2* (mean 1,000 kcal/day energy deficit; dashed lines and ○). Values are means $\pm$ SD. Letters indicate means that are not significantly different (Scheffé's test). There were no differences between group means at any of the 4 common measurement points. To convert to SI units (mmol/l), multiply by 0.02586.

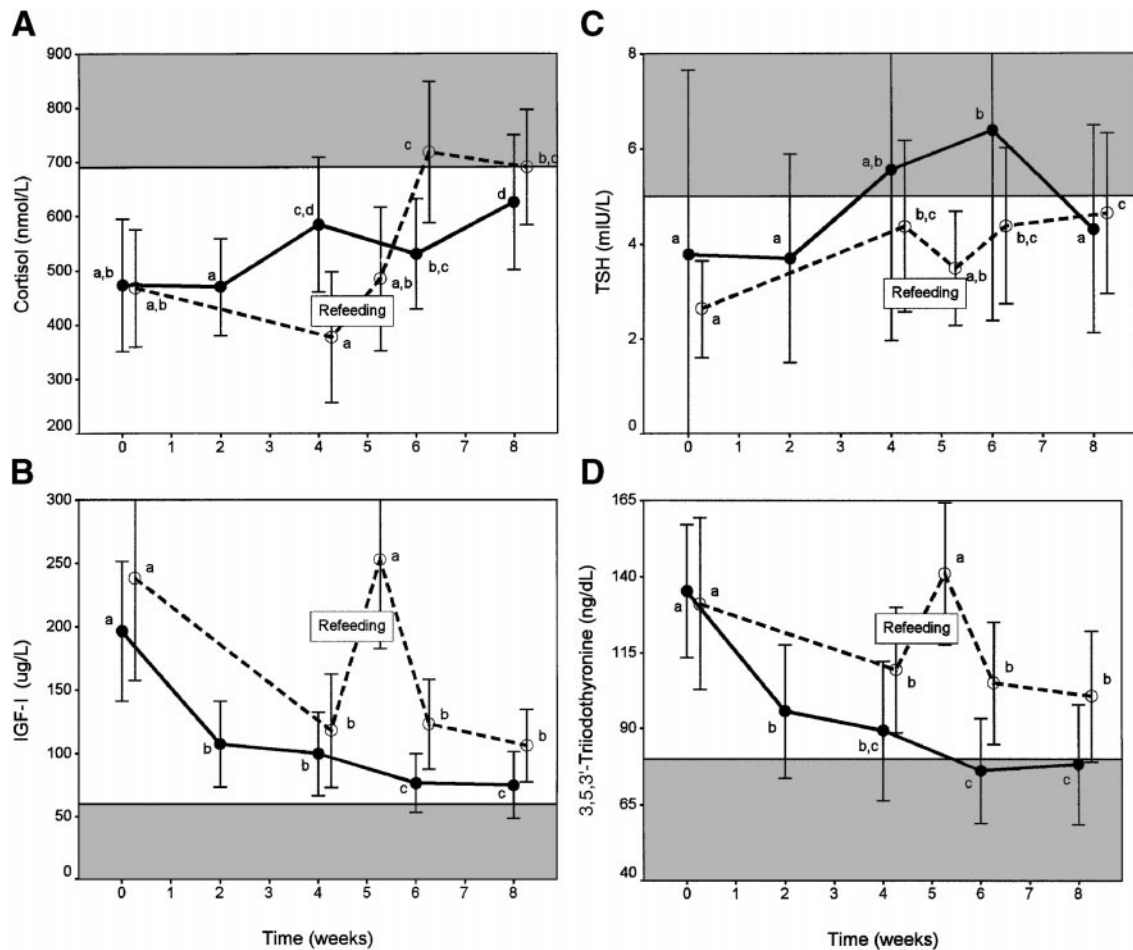


Fig. 3. Serum cortisol (A), insulin-like growth factor I (IGF I; B), thyroid-stimulating hormone (TSH; C), and 3,5,3'-triiodothyronine (D) for group 1 (solid lines and ●) and group 2 (dashed lines and ○) over 8-wk Ranger course. Values are means $\pm$ SD. Letters indicate means that are not significantly different (Scheffé's test); shaded regions represent areas outside of normal range for morning serum concentrations in normal young men. There were differences between group means at all of the common measurement points for cortisol, IGF-I, and T_3 ; 8-wk measurements of TSH were not different between group 1 and group 2. To convert T_3 to SI units (nmol/l), multiply by 0.01536.

~1 mo (5 wk) after the end of Ranger training, with the exception of rebound changes in body fat and several other metabolic markers (Table 3). In the 10 soldiers assessed, fat had increased by 40% above normal levels, and binding proteins (SHBG and TBG) were suppressed below baseline values in response to hypercaloric intakes. Data obtained in group 1 suggest that hyperphagia peaks at ~1 mo and that all parameters are normal by 6 mo posttraining (32).

Interactions between body composition changes and endocrine responses. Men with the highest rates of weight loss (highest quartile of weight loss: mean = $-18.7 \pm 1.7\%$ of initial weight; $n = 24$) had a lower final serum IGF-I and a higher HDL cholesterol but had no other distinguishing characteristic; IGF-I was inversely correlated with percent change in weight ($r = -0.38$; $P < 0.01$). Men with the lowest fat reserves at the end of the course were characterized by significantly higher total cholesterol and lower T_3 levels. There was a significant relationship between testosterone levels in the second half of the course (mean of

weeks 4, 6, and 8) and the proportion of weight loss contributed by fat ($n = 105$; $r = 0.31$; $P < 0.01$).

DISCUSSION

The results of this study reiterate the consistency of endocrine responses to energy deficiency, even in the face of competing stressors and with complications such as intermittent refeeding without full recovery of body energy stores. This highlights the importance of these mechanisms to sustain normal function and extend survival when energy balance is threatened. For example, observed declines in testosterone, T_3 , and IGF-I would be expected to reduce energy requirements, whereas increases in cortisol and growth hormone serve as counterregulatory hormones in glucose metabolism. The remarkably normal clinical chemistries previously reported in this study (32, 33) and in other very similar studies (23, 48) belie the severity of the physiological challenge that was reflected in the endocrine responses.

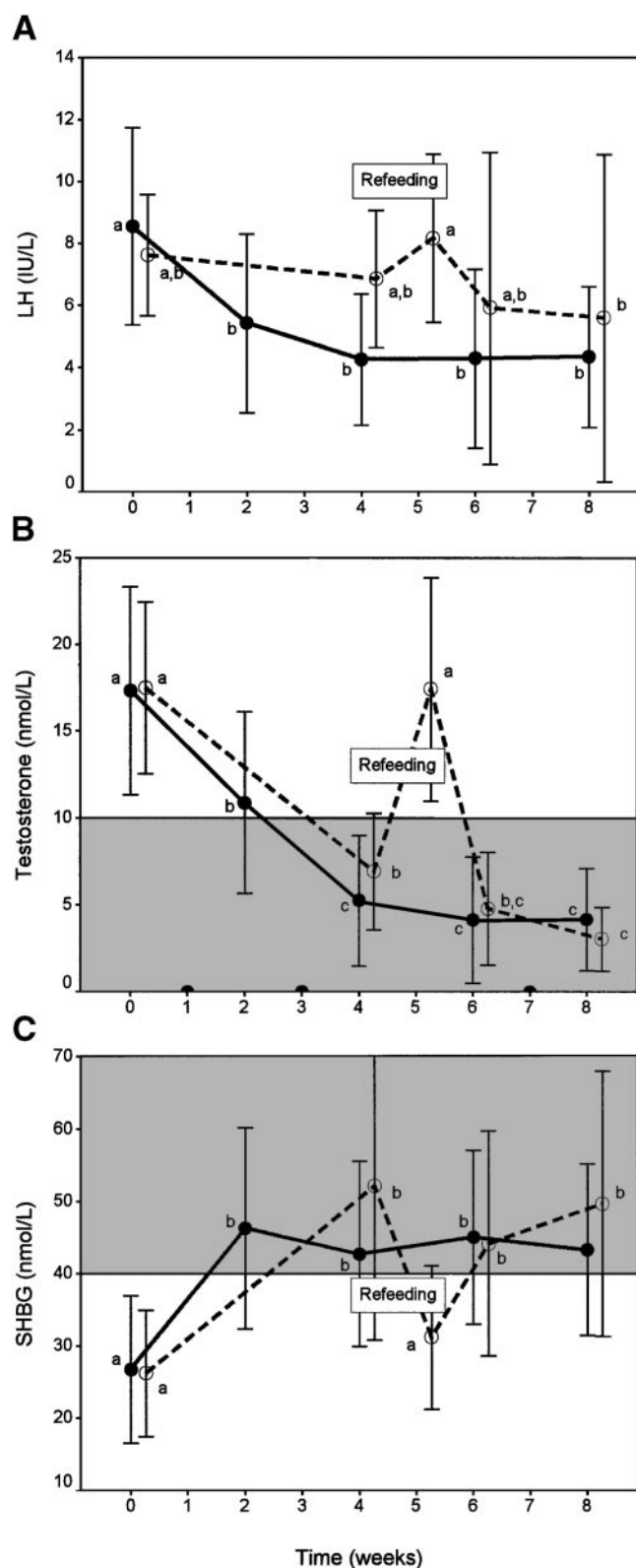


Fig. 4. Serum luteinizing hormone (LH; A), testosterone (B), and sex hormone-binding globulin (SHBG; C) concentrations for *group 1* (solid lines and ●) and *group 2* (dashed lines and ○) over 8-wk Ranger course. Values are means $\pm$ SD. Letters indicate means that are not significantly different (Scheffé's test); shaded regions represent areas outside of normal range for morning serum concentrations in normal young men. There were no differences between group means for LH or SHBG at any of the 4 common measurement points; testosterone differed between groups at 4- and 8-wk samples.

Comparisons between the two groups in this study indicate differences in the nature of the endocrine responses, with both graded responses to the severity of energy deficit (e.g., T_3 , IGF-I) and threshold effects (e.g., testosterone, SHBG). Mean T_3 slipped below the normal range when many of the men had reached a body fat nadir, but it remained within the normal range at the end of the course when the men still retained fat reserves in *group 2*. Thus, when the men were in a negative energy balance, reduced hormone concentrations appeared to correspond to the nature of the fuel sources from body energy stores, with lower hormone levels corresponding to a more extreme level of fat-store depletion and probably an increased rate of protein catabolism. This semiquantitative relationship was also apparent in the significant correlation between final IGF-I levels and rate of weight loss during the course; this has been previously reported with metabolic status and body composition changes (8, 31).

In contrast to T_3 and IGF-I, there was no difference in testosterone decline between *group 1* and *group 2*, suggesting a nonquantitative threshold effect. This is also evident in the model of Opstad and Aakvaag (40) in which a substantially increased feeding (compared with virtually no food for 1 wk) still did not prevent the testosterone decline. In a similarly demanding stress model involving French commandos, intakes ranging from 1,800 to 4,200 kcal/day in the face of an estimated 10,000 kcal/day requirement also produced significant declines in testosterone (17). These effects of energy deficit are centrally mediated as indicated by low LH levels. This may be secondary to the changes in T_3 (27). Reduced insulin levels associated with reduced food intake may be a key trigger for many of the hepatic and hypothalamic changes. For example, the binding proteins (TBG, SHBG) consistently increased, reflecting, at least in part, the insulin-induced alterations in both hepatic secretion rates and/or secretion of isoforms that were more resistant to clearance (44, 51). This was a threshold effect, with immediate increases occurring after the first 2 wk of the course and insensitivity to the graded increase in energy intake in *group 2*. SHBG also promptly increased with energy deficit in a 1-wk Norwegian Ranger course (1). In a sample 5 wk after the end of the course, SHBG levels were significantly below baseline, again implicating circulating insulin levels, which would have been substantially raised by the posttraining hyperphagia (32, 62).

The progressive rise in cholesterol may be related to one or both of the changes observed for thyroid hormones (3) and IGF-I (47). Subclinical hypothyroidism, signified by elevated TSH values, has been associated with hypercholesterolemia, and thyroid hormone treatment reduces cholesterol levels in some patients (4). The elevation of cholesterol has been reported for anorexic individuals and in obese individuals with very high rates of weight loss (45). Phinney et al. (45) hypothesized that the rise in cholesterol occurs with mobilization of cholesterol from fat depots at high rates of fat mobilization. However, in both the Minnesota study, in which the subjects achieved a greater relative weight loss, and the studies of Norwegian cadets who

Table 3. *Body composition and endocrine measures for a subsample of soldiers from group 2 studied again 5 wk after the end of the Ranger course*

Measurement	Start	4 wk	5 wk*	8 wk	+5 wk*
Body weight, kg	73.9 ± 2.9	68.1 ± 2.3	73.9 ± 1.5	65.5 ± 2.3	76.3 ± 3.0
Fat weight, kg	9.5 ± 1.5	ND	ND	5.3 ± 0.9	13.7 ± 1.2
Fat-free mass, kg	64.4 ± 1.6	ND	ND	60.2 ± 1.9	65.5 ± 2.2
HDL cholesterol, mmol/l	1.3 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	2.3 ± 0.2	1.2 ± 0.2
Cortisol, nmol/l	441 ± 22	417 ± 31	550 ± 50	706 ± 34	507 ± 51
IGF-I, µg/l	205 ± 16	101 ± 71	85 ± 21	88 ± 7	253 ± 11
3,5,3'-Triiodothyronine, nmol/l	1.84 ± 0.16	1.55 ± 0.11	1.96 ± 0.07	1.47 ± 0.08	2.46 ± 0.10
TSH, mU/l	2.4 ± 0.2	3.7 ± 0.5	3.0 ± 0.3	4.5 ± 0.5	2.7 ± 0.4
Thyroxine binding globulin, nmol/l	20.3 ± 1.0	22.9 ± 0.8	20.7 ± 1.1	24.0 ± 1.5	18.4 ± 0.9
Testosterone, nmol/l	16.3 ± 1.6	4.3 ± 0.5	14.6 ± 0.8	2.2 ± 0.9	19.3 ± 3.2
LH, U/l	8.0 ± 0.7	6.1 ± 0.6	6.3 ± 0.5	4.2 ± 0.9	8.6 ± 0.7
Sex hormone-binding globulin, nmol/l	24.6 ± 2.4	48.5 ± 3.9	28.0 ± 2.4	44.0 ± 4.0	19.7 ± 1.2

Values are means ± SE for 10 subjects. Fat weight and fat-free mass were calculated from body weight and percent body fat assessed by dual-energy X-ray absorptiometry. HDL, high-density lipoprotein; IGF-I, insulin-like growth factor I; TSH, thyroid-stimulating hormone; LH, leutinizing hormone. *Refeeding periods: at 5 wk, only the food restriction stressor was alleviated compared with 4 wk; at +5 wk, all stressors, including food and sleep restriction, were alleviated, compared with conditions at 8 wk. Samples taken after periods of refeeding (5 wk = within the course; +5 wk = after the course) were all significantly different ($P < 0.05$) from the previous sample, usually returning to baseline measures (start).

achieved higher rates of weight loss than individuals in our Ranger study, no changes in total cholesterol were observed. The hypercholesterolemic response was clearly a late phase of semistarvation. The more typical response to weight loss and exercise, involving an increase in HDLs and a decrease in LDLs (28, 54), was observed at the end of the first 2 wk of training in *group 1*, before the upturn in levels of all lipoproteins occurred.

The other stressors present in this training environment appeared to take a lower priority behind the energy deficit, in terms of the endocrine axes studied. The effects of the other principal stressor in this course, sleep deprivation, have been elegantly teased out from the effects of food restriction by Opstad et al. (37–42) in a shorter but more intensive military training model. Norwegian cadets engaged in 1 wk of military exercises with no organized sleep and little or no energy intake demonstrate a reduced adrenergic response (37) and demonstrate changes in the thyroid (42) and testicular (40) axes that were specifically associated with the energy-deficit component. These main effects of “pure” energy restriction are also consistent with a large body of literature on weight loss in obese patients, where circulating T_3 levels and sympathetic tone are reduced and cold sensitivity and gonadotropin abnormalities become more prevalent.

Even with the continued stress of inadequate sleep, T_3 and IGF-I specifically tracked nutritional status, as noted by their prompt recovery after refeeding during the course when sleep continued to be restricted. This is consistent with the studies of Opstad and Aakvaag (39, 41) in which the thyroid axis was sensitive to energy deficit and not responsive to sleep deprivation. In the converse model, in the absence of an energy deficit, Palmblad et al. (43) found that short-term sleep deprivation (48 h) increased T_3 ; thus the typically observed “low- T_3 ” anticatabolic adaptation to diminished energy availability (2, 64) appears to take precedence when both sleep and energy restriction occurs. The addition of acute bouts of exercise would be expected to have

little or no effect on the thyroid axis, other than what would be predicted from an equivalent period of energy deficit (35). On the other hand, the effect of a persistent cold stressor superimposed on this energy deficit in the winter Ranger courses may produce a very different thyroid response. Thermoregulation appeared to take priority over metabolic thrift in a study conducted by Stroud et al. (58) on himself and his expedition partner during an Antarctic crossing; despite very large weight losses and other endocrine changes, thyroid hormones were not suppressed.

Our observations of a rise in TSH during the course differ from typically observed responses to fasting and heat stress (5, 42, 61). This might be due to the prolonged reduction in testosterone, which has been shown to play a role in fasting-induced suppression of TSH (9). It may also be associated with the use of iodine-based water purification tablets. The iodine tablets used by soldiers in this course have been shown to produce modest decreases in T_4 and T_3 and an elevation of TSH within 1 wk of regular use (14). The addition of an iodine load to an already suppressed thyroid raises the possibility of a Wolff-Chaikoff effect, although this is unlikely in view of the rapid recovery of thyroid function after refeeding, both during and after the course.

Gonadal steroids are responsive to both psychological stress and energy deficit. This has been best documented in women in connection with amenorrhea (60), but the parallels to male reproductive hormones are strikingly similar. Testosterone is extraordinarily sensitive to psychological stress, with changes in either direction depending on how the stressor is perceived (25, 59). Unlike the adrenal response, testosterone remains suppressed with chronic anxiety (11) and is acutely sensitive to energy deficit (6). In Ranger students, psychological stress was a minor contributor to the stress burden that consisted primarily of overwhelming hunger and fatigue. The marked decline in testosterone was closely linked to energy balance, with prompt recovery during refeeding even with other stressors

unattenuated, including some of the highest energy expenditures in the course, averaging 6,000 kcal/day (32). Thus energy deficit, not exercise, was associated with the decline in testosterone. This has been reported for healthy young men in other settings such as weight restricting wrestlers, particularly those individuals achieving very low body fat (49, 57). Sleep deprivation, superimposed on the energy deficit, had minimal effects on LH secretion and circulating androgens (41). Exercise has no significant effect on LH secretion (50) and tends to produce only an acute increase in testosterone concentrations, probably through fluid shifts and temporary changes in hepatic clearance. Heat exposure and acclimatization do not appear to have an effect on testosterone levels; in an earlier study of 50 Special Forces soldiers deploying rapidly from a cool temperate climate into a hot humid tropical environment, no change in testosterone or LH occurred during a 30-day continuous outdoor exposure (K. E. Friedl and C. J. Hannan, Jr, unpublished observations, Madigan Army Medical Center, Tacoma, WA, 1988).

In the studies of Opstad and Aakvaag (38, 39, 41), adrenal activation is temporary, with recovery within a few days of continued stress. This same phenomenon was demonstrated in response to psychological stress, with an apparent adrenal supercompensation in soldiers under imminent threat of enemy attack in an isolated outpost in Vietnam (4). Cortisol concentration is clearly a sensitive indicator of acute novel stimuli but recovers with continued exposure (59). It may not be responsive to physiological challenges lacking either a psychologically noxious component or demanding a counterregulatory response for energy metabolism, including the early stages of fasting and heat exposure (30). A significant elevation in mean cortisol in Ranger students came only toward the end of the course, when fat reserves began to deplete. In *group 1*, many individuals were already at a minimum level of body fat when measured by DEXA three-fourths of the way through the course (13), corresponding to a substantial rise in cortisol, which was also reflected in the final sample. In *group 2*, only one individual reached a minimum of ~4% body fat at the end of the course, and mean cortisol levels for the group rose significantly only at the end of the course. Thus the cortisol response observed in this study may reflect the increased need to catabolize alternate body energy sources with the impending depletion of fat stores. Alternatively, cortisol may be elevated because of reduced clearance, as observed in severely malnourished individuals (53).

There are consequences to the metabolic hormone responses observed here. Previous studies in military field settings with energy deficits have noted declines in cellular metabolism, lower resting body temperature (18, 21), an increased sensitivity to ambient cold (18, 66), and a protective effect on catabolism of type I muscle fibers (52). In the Minnesota study, metabolic requirements declined by an estimated 25% over the decline expected simply from reduced levels of lean mass (10), implicating regulators of cellular metabolism. A similar decline was observed in a much shorter

term study of starvation of soldiers in a laboratory setting (16), highlighting the rapid metabolic suppression which occurs, even ahead of behavioral efficiencies observed in both the Minnesota study and in the later phases of the Ranger course.

Aside from effects related to overall reductions in metabolic rate, it is remarkable how well healthy young men are sustained by their energy reserves. In a similar study of intermittent feeding, Rai and colleagues (48) studied young soldiers on military patrols in a rugged mountainous jungle environment for three consecutive bouts of 7- to 10-day periods averaging 1,500 kcal/day energy deficits and 7 days of refeeding and recovery. Despite significant weight losses, there were no changes in a variety of clinical chemistries, in glucose tolerance, and in 48-h balance studies of vitamin status, and there was no marked change in physical or cognitive test parameters compared with patrols receiving full rations (48). Physical measurements such as grip strength and muscle cross-sectional areas are useful markers of nutritional status in hospitalized patients but provided little insight into the physiological status of the healthy men in our study. Grip strength did not decline during the Ranger course, and it did not decrease in the Minnesota study until FFM decreased by >10% (22). Upper arm muscle cross-sectional area declined from $68 \pm 9 \text{ cm}^2$ to $60 \pm 8 \text{ cm}^2$ with weight loss in the men in *group 2* (34); however, as a prognostic marker in cachectic patients, measurements of concern are typically <20 cm² (19). Even waist circumference, which declined by an average of 10 cm in *group 1*, did not distinguish starved Ranger students from healthy lean runners in peak physical condition. Like clinical chemistry values, physical characterization did not provide a useful index of metabolic status in the Ranger students.

Reduced circulating levels of hormones such as T₃ and testosterone, as observed in the present study, inevitably lead to suggestions that artificially restoring these to the normal range may offer some physiological or psychological advantage to the individuals. At least one experiment suggests a reason for caution in thyroid replacement. Rats with streptococcal pneumonia demonstrate a decline in circulating thyroid hormones and action, but, when normal thyroid levels are established with replacement hormone treatments, morbidity and mortality in the rats substantially increase (26). Streptococcal pneumonia has been a problem for Ranger students (29), making such an experiment a relevant concern. IGF-I may be more useful in preservation of some of the lean mass and whole body protein stores in catabolic patients (63). A useful intervention might include blocking maladaptive responses from catabolic factors that occur in a subset of men losing excessive amounts of FFM.

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