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 (T₃) 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 (31 to 217 µg/dl), and cholesterol rose from 158 ± 31 to 217 ± 39 mg/dl. Bioavailable T₃ 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 T₃, 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, T₃, 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.

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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, hemato logic parameters, liver function tests, electrolytes, or vitamin and mineral status (23). Many of these men had little measurable 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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METABOLIC MARKERS OF ENERGY DEFICIT

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 (carbohydrate 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 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

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).

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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 tempera-
ture 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 envi-
ronmental 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 hema-
tocrit 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 pub-
lished 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 un-
planned 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 mea-
sured 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 (DXA; DPX-Plus, Lunar, Madi-
son, WI) at the beginning and end of the study by using
manufacturer-supplied algorithms (Total Body Analysis, ver-
sion 3.6, Lunar). Radiation exposure from this procedure has
been measured at 0.05 µGy/scan. Precision of the measure-
ment 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 investi-
gators as biostandards. Percent body fat remained <0.5% be-
tween devices, comparable to the repeat reliability of
measurements on a single device. Because DXA overesti-
mates soft tissue fat-free mass (FFM) in semistarved individu-
als, FFM and fat weight were calculated from percent body
fat obtained by DXA 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 1
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 interas-
say 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-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 113)</th>
<th>Group 2 (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>5-wk Change</td>
<td>5-wk Change</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>24.3 ± 3.8</td>
<td>24.3 ± 2.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8 ± 2.2</td>
<td>24.3 ± 2.1</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>76.8 ± 9.3</td>
<td>75.9 ± 9.0</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>11.7 ± 4.6</td>
<td>11.0 ± 4.0</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>65.1 ± 6.2</td>
<td>65.0 ± 6.2</td>
</tr>
<tr>
<td>Bone mineral, kg</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.4</td>
</tr>
</tbody>
</table>

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).
Table 2. Anthropometric measurements followed through Ranger training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2 wk</th>
<th>4 wk</th>
<th>5 wk</th>
<th>6 wk</th>
<th>8 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>75.9 ± 9.0†</td>
<td>71.0 ± 8.0†</td>
<td>68.9 ± 7.6‡</td>
<td>66.4 ± 7.2‡</td>
<td>63.8 ± 6.7‡</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>78.4 ± 8.7*</td>
<td>72.9 ± 7.7†</td>
<td>75.3 ± 7.5†</td>
<td>70.8 ± 7.5†</td>
<td>68.4 ± 7.0†</td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>82.4 ± 5.9*</td>
<td>78.5 ± 5.9†</td>
<td>76.3 ± 5.1‡</td>
<td>74.6 ± 4.3§</td>
<td>72.4 ± 3.9§</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>84.2 ± 5.3*</td>
<td>79.4 ± 4.2‡</td>
<td>81.3 ± 4.2†</td>
<td>78.0 ± 4.4§</td>
<td>76.0 ± 4.2§</td>
<td></td>
</tr>
<tr>
<td>Sum of skinfolds</td>
<td>45.0 ± 11.5*</td>
<td>32.7 ± 7.9†</td>
<td>27.9 ± 5.4†</td>
<td>23.9 ± 4.5§</td>
<td>23.1 ± 4.4§</td>
<td></td>
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<tr>
<td>Group 1</td>
<td>47.1 ± 11.5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
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Values are means ± SD. ND, not done. Values with the same symbols are not significantly different (Scheffe'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: $1.2 \pm 0.2$ mmol/l, 8 wk: $2.0 \pm 0.4$ mmol/l), progressively increased through the course, and calculated LDL cholesterol (start: $2.4 \pm 0.7$ mmol/l, 8 wk: $3.4 \pm 0.9$ 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).

T₃ 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 T₃ levels. At each point in the group 2 course, the decline in T₃ was attenuated compared with that of group 1, presumably due to the greater energy intake. The changes in T₃ and T₃/TBG were smaller but demonstrated statistically significant declines that paralleled the changes in T₃. 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 ($\chi^2$ 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 T₃, IGF-I levels were temporarily restored to normal levels after 1 wk of refeeding group 2 (wk 5); IGF-I and T₃ 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 µg/l at 8 wk; refeeding within the course temporarily reduced mean values to <1 µg/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 µg/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 µmol/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 $8.5 \pm 3.1$ IU/l (start) to $4.3 \pm 2.2$ 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 T₃, 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
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 ± 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 T3 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, T3, 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) belies the severity of the physiological challenge that was reflected in the endocrine responses.
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., T₃, IGF-I) and threshold effects (e.g., testosterone, SHBG). Mean T₃ 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 T₃ 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 T₃ (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 postraining 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...
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 not observed. The hypercholesterolemic response was clearly a late phase of semistarvation.

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 T₃ and T₄ 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 7–10-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 ± 9 cm² to 60 ± 8 cm² 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). Strep-tococcal 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.

We gratefully acknowledge the assistance of Elaine Christensen, whose logistical planning was vital to the success of these studies; the technical assistance of Staff Sergeant Glenn Thomas, Sergeant Mike Johnson, and Specialist Sherryl Kubel in the group 1 study; and Specialist Jay Paulman, Sergeant Brad Nindl, Major Ronald Shippee, and Major Barry Fairbrother (Royal Logistics Corps, British Army) in the group 2 study. Serum lipids were analyzed by Dr. Richard Tulley...
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