Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery


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Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery. Am J Physiol Endocrinol Metab 293: E310–E315, 2007. First published April 10, 2007; doi:10.1152/ajpendo.00687.2006.—In a prospective randomized placebo-controlled study, we assessed potential physiological effects of nonthyroidal illness syndrome (NTIS) in acute illness. Coronary artery bypass graft surgery was employed as a prospective model of acute illness and NTIS. Triiodothyronine (T3) or placebo was infused for 24 h after surgery, with a T3 dose selected to maintain postoperative serum T3 concentrations at preoperative levels. Patients were evaluated before coronary artery bypass graft and during the postoperative period. Cardiovascular function was monitored with Swan-Ganz catheter measurements and ECG. Urinary nitrogen excretion and L-[1-13C]leucine flux were used to evaluate protein metabolism. Serum measurements of relevant hormones, iron, and total iron-binding capacity were used to assess effects on sex steroid, growth hormone axis, and iron responses to illness. Cardiovascular function was not affected by T3 infusion, except for a transient higher cardiac index in the T3 group 6 h after surgery (3.04 ± 0.12 for T3 and 2.53 ± 0.08 for placebo, P = 0.0016). Protein metabolism was not affected; changes in urinary nitrogen excretion and L-[1-13C]leucine flux were equivalent in the two groups (P = 0.35 and P = 0.95, respectively). No differences were observed in changes in testosterone, estrogens, growth hormone, insulin-like growth hormone I, iron, or total iron-binding capacity between T3 and placebo groups. We conclude that, in the early stages of major illness, the decrease in circulating T3 concentrations in NTIS has only a minimal transient physiological impact on cardiac function and plays no significant role in protecting against protein catabolism or modulating other endocrine responses or iron responses to illness.

EUTHYROID SICK SYNDROME was first described nearly three decades ago. Its most prominent feature is a marked decrease in circulating triiodothyronine (T3) levels with the onset of illness or fasting (19). Recently, a change in terminology from euthyroid sick syndrome to “nonthyroidal illness syndrome” (NTIS) has been adopted by many (8). This change in nomenclature reflects an underlying controversy as to whether NTIS is truly a euthyroid state or deserves therapy with thyroid hormone (8, 10, 11, 35, 37). Previous data addressing this question are scant. In some studies, T3 was administered to nonthyroidal illness or fasting (19). Recently, a change in terminology from euthyroid sick syndrome to “nonthyroidal illness syndrome” (NTIS) before surgery. We did not intend to answer clinical questions regarding the use of T3 in patients with NTIS. These observations can help further determine whether NTIS is indeed a euthyroid state in acute illness. They can provide additional information regarding questions of benefit (enhanced cardiovascular function) or harm (worsened catabolism) of administering T3 to patients with NTIS. These questions remain relevant as trials of T3 in cardiac surgery continue (2, 3).

METHODS

Patient Population

Fifty-nine patients (7 women and 52 men) undergoing elective CABG were included in the study. Because the primary aim of this study was to evaluate physiological effects of NTIS, volunteers were selected to provide a relatively healthy baseline (with no evidence of NTIS before surgery). We did not intend to answer clinical questions regarding the use of T3 in patients with markedly compromised preoperative cardiac function. Inclusion criteria were as follows: ≤80 yr of age, ambulatory before surgery with New York Heart Association classification I or II, preoperative ejection fraction ≥40%, no active endocrine illness as assessed by history and by serum levels of thyroxine (T4), T3, thyroid-stimulating hormone (TSH), testosterone (T), GH, and IGF-I within the normal range before surgery, no major illness other than cardiac disease, and no therapy with thyroid hormone, amiodarone, glucocorticoids, or sex steroids within the past year. Body mass index of patients ranged from 22 to 42. Baseline characteristics of patients are displayed in Table 1. A single group of five cardiovascular surgeons was involved with similar strategies for postoperative management of patients. The study was approved by the

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collections were initiated for determination of UN. UN was determined as excretion (UN) and L-[1-13C\]leucine flux. Evaluation was accomplished by measurement of urinary nitrogen. Inclusion criteria were as stated above. These patients were randomized in double-blind fashion to treatment or placebo groups. Patients in the T3 group received a bolus dose of 0.2 $\mu$g/kg at the time of cross-clamp (CC) removal followed by an infusion of 0.8 $\mu$g/kg over the subsequent 24 h. Placebo was administered in identical infusions. Dosing was selected to maintain serum T3 levels within the normal range on the basis of an unpublished previous multicenter trial (SmithKline) in which serum levels of T3 were assessed using bolus doses of 0.1, 0.4, and 0.8 $\mu$g/kg matched with infusion doses of 0.1, 0.4, and 0.8 $\mu$g/kg over 6 h after CABG.

Monitoring of Hemodynamics, ECGs, Cardiac Rhythms, and Cardiac Drugs

Cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP), and mixed venous O2 saturation were measured via an indwelling Swan-Ganz catheter upon insertion of the catheter and 1, 6, 12, and 18 h after CC removal. Derivative measurements were cardiac index (CI; calculated as CO divided by body surface area) and systemic vascular resistance (calculated as (MAP - CVP) / CO).

ECGs were performed just before admission and 36 h after CC removal to monitor heart rate (HR) and evidence of ischemia or myocardial damage. Arrhythmias as recorded by telemetry were monitored for 24 h after CC removal. In addition, in the first 20 patients, cardiac activity was recorded by Holter monitor for the 6 h before CABG and for 24 h after CABG. Administration of the following classes of drugs was monitored for the 24 h after CC removal: 1) vasodilators (primarily nitrates), 2) inotropes (primarily dopamine), 3) cardiac glycosides, 4) anti hypertensives (primarily nitropusside), 5) $\beta$-blockers, 6) calcium channel blockers, 7) angiotensin-converting enzyme inhibitors, 8) antiarrhythmics, and 9) diuretics.

Evaluation of Protein Catabolism

Protein metabolism was evaluated in a subset of 20 patients (10 each in placebo and T3-treated groups). These 20 patients were entered consecutively into the protein protocol during routine recruitment for the larger study. Inclusion criteria were as stated above. Evaluation was accomplished by measurement of urinary nitrogen excretion (UN) and L-[1-13C\]leucine flux. UN. At 9 h before the start of each leucine infusion, 12-h urine collections were initiated for determination of UN. UN was determined by a macro-Kjeldahl method, but copper sulfate was used as the catalyst.

L-[1-13C\]leucine flux. Leucine tracer kinetics were determined in each patient within 14 days before surgery after a 10-h overnight fast and again 20–24 h after surgery. At the time of postoperative testing, patients had been without oral intake for 36 h. Any solutions containing dextrose (with the exception of nutrisource) were discontinued 3 h before the leucine infusion. L-[1-13C\]leucine (99% 13C) was prepared as previously described (24, 25) and infused in a bolus of 2 $\mu$mol/kg followed by infusion of 2.4 $\mu$mol $\cdot$ kg$^{-1} \cdot$ h$^{-1}$ for 3 h. Blood samples drawn at 0, 135, 150, 165, and 180 min after administration of the L-[1-13C\]leucine bolus were placed in iced tubes, and an equal volume of 10% sulfoSalicylic acid was added. Plasma was analyzed for $\alpha$-ketoisocaproate (KIC) by gas chromatography-mass spectrometry (24, 25). Rate of appearance (R\textsubscript{A}) or “flux” of leucine into plasma was defined as

$$R_A = I_0(E_p/E_p - 1)$$

where I\textsubscript{0} is the infusion rate of L-[1-13C\] leucine, E\textsubscript{0} is the enrichment of the leucine infused, and E\textsubscript{p} is the enrichment of plasma leucine.

Monitoring of Serum Hormone Levels and Iron-Handling Parameters

Concentrations of T3, TSH, total T, GH, IGF-I, and iron, as well as total iron-binding capacity (TIBC), were measured on serum samples obtained from patients within the week before surgery and then following CC removal after surgery (Table 2). We did not monitor serum levels of T4, because we and other groups previously reported that serum levels of T4 declined in parallel with T3 (but to a lesser degree) after CABG (7, 14, 33). We also did not measure serum concentrations of free T or sex hormone-binding globulin, because we and others previously reported that serum levels of free T decreased in parallel with total T after CABG (22, 33).

Serum levels of T were measured using DPC Coat-a-Count T\textsubscript{125I} kit with all intra- and interassay coefficients of variation (CV) $<10\%$, except interassay CV of 11% at 2.64 nmol/l and intra-assay CV of 18% at 0.69 nmol/l. T3 was measured using the Ciba-Corning Magic T\textsubscript{3} 125I kit, with intra- and interassay CVs at $\sim$20, 50, and 80% binding $<10\%$. Serum concentrations of estrone (E\textsubscript{1}) and estradiol (E\textsubscript{2}) were determined by radioimmunoassay after extraction with cyclohexane and ethyl acetate and purification over a Cellel column with CVs as previously described (20, 21). Serum GH and IGF-I levels were measured using a commercial enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX). Intra-assay CVs for GH were 4.3% (0.70 ng/ml), 4.3% (3.68 ng/ml), and 3.3% (18.76 ng/ml), and interassay CVs were 6.5% (3.34 ng/ml), 6.6% (7.83 ng/ml), and 6.3% (15.24 ng/ml). IGF-I was assayed after extraction. Intra-assay CVs were 7.1% (26.5 ng/ml), 4.5% (48.4 ng/ml), and 6.5% (16.7 ng/ml), and interassay CVs were 8.8% (42.9 ng/ml), 4.8% (132.6 ng/ml), and 6.4% (379.1 ng/ml). Serum iron and TIBC were measured using standard methodology.

Statistics

Repeated-measures ANOVA was used to assess treatment and time effects and the time-treatment interaction. We used the time-treatment interaction as the major test of our hypothesis. Mean TSH values from T3 and placebo groups were compared using a two-tailed unpaired t-test. In addition, because a post hoc examination of confidence intervals suggested a difference between values in the placebo and

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age, yr</th>
<th>BMI, kg/m\textsuperscript{2}</th>
<th>Women/Men</th>
<th>EF, %</th>
<th>CI, l/min $\cdot$ m$^{-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>59.4±2.4</td>
<td>29.3±0.9</td>
<td>3/30</td>
<td>55.7±2.7</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>T3</td>
<td>63.7±1.7</td>
<td>27.8±0.6</td>
<td>4/28</td>
<td>55.0±2.7</td>
<td>2.6±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; EF, ejection fraction; CI, cardiac index; T3, triiodothyronine.

Maine Medical Center Institutional Review Board, and all patients provided written informed consent.

Administration of T3 or Placebo

Iron-Handling Parameters

Monitoring of Serum Hormone Levels and

Table 2. Scheme for measurement of hemodynamic and serum parameters

<table>
<thead>
<tr>
<th></th>
<th>PreOp</th>
<th>1 h</th>
<th>6 h</th>
<th>12 h</th>
<th>18 h</th>
<th>24 h</th>
<th>36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>59</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T3</td>
<td>59</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TSH</td>
<td>59</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>T</td>
<td>50</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>E\textsubscript{1}, E\textsubscript{2}</td>
<td>30</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GH, IGF-I</td>
<td>30</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Iron, TIBC</td>
<td>20</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

CC, cross clamp; HD, hemodynamic measurement; PreOp, preoperatively; TSH, thyroid-stimulating hormone; T, testosterone; E\textsubscript{1}, estrone; E\textsubscript{2}, estradiol; IGF-I, insulin-like growth factor I; GH, growth hormone; TIBC, total iron-binding capacity. Urinary nitrogen excretion and L-[1-13C\]leucine flux were measured before and 12–24 h after coronary artery bypass graft.

* AJP-Endocrinol Metab • VOL 293 • JULY 2007 • www.ajpendo.org
treatment groups at 6 h after CC removal, these values were compared using a two-tailed paired t-test.

RESULTS

Serum T₃ and TSH Concentrations

Figure 1 displays serum T₃ concentrations throughout the study in the placebo and T₃ groups. As anticipated, serum T₃ levels decreased markedly in the placebo group but remained at baseline levels in the T₃ group until discontinuation of the infusion at 24 h. TSH remained within the normal range in all patients in the placebo group at 24 h after surgery [1.81 ± 0.22 (0.43–3.84) μU/ml]. TSH in the T₃ group was 0.57 ± 0.07 (0.19–1.18) μU/ml, with values slightly below the lower limit of normal (0.4 μU/ml) in seven patients. TSH was significantly lower in the T₃ than in the placebo group (P < 0.0001).

Hemodynamic Parameters

CI was increased over baseline values by 1 h after CC removal in the placebo and T₃ groups (Fig. 2; P < 0.001). No significant difference in mean CI values was observed between the two groups, except at 6 h after CC removal, when CI in the placebo group fell below CI in the T₃ group (2.53 ± 0.08 vs. 3.04 ± 0.12 l·min⁻¹·m⁻², P = 0.0016). Values for systemic vascular resistance and mixed venous O₂ saturation were also equivalent in the placebo and T₃ groups (Table 3). ECG data demonstrated similar increases in HR after CABG in the placebo (19.2 ± 2.9 beats/min) and T₃ (22.4 ± 2.1 beats/min) groups. Holter monitor data confirmed this finding, with increases in HR of 24.8 ± 2.3 and 27.6 ± 2.5 beats/min in the placebo and T₃ groups (P = 0.43). ECG data also demonstrated no ischemic damage in either group.

Arrhythmias and Drug Administration

No differences in the incidence of arrhythmias were noted postoperatively between the placebo and T₃ groups. Particularly, no decrease in the incidence of atrial fibrillation was observed in the T₃ group.

Very few patients in these populations received dopamine. T₃ and placebo patients were equally likely to receive dopamine, and only small “renal” doses (≤5 μg·kg⁻¹·h⁻¹) were administered. Placebo and T₃ patients were also equally likely to receive 1) vasodilators, 2) inotropes, 3) cardiac glycosides, 4) antihypertensives (primarily nitrates), 5) β-blockers, 6) calcium channel blockers, 7) angiotensin-converting enzyme inhibitors, 8) antiarrhythmics, and 9) diuretics.

Protein Catabolism

Uₙ values were not significantly increased postoperatively in the placebo or the T₃ group. Pre-and postoperative Uₙ values were 6.27 ± 0.19 g/24 h (P = 0.19) in the placebo group and 5.36 ± 0.58 and 5.46 ± 0.50 g/24 h (P = 0.86) in the T₃ group. No significant difference was observed in the pre-to-postoperative change in Uₙ excre-

Table 3. SVR and \( \text{SV}_{\text{O}_2} \), in placebo and T₃ groups

<table>
<thead>
<tr>
<th></th>
<th>PreOp</th>
<th>1 h</th>
<th>6 h</th>
<th>12 h</th>
<th>18 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR, dyn·s·cm⁻²</td>
<td>Placebo 1.116±0.66</td>
<td>981±0.76</td>
<td>995±0.51</td>
<td>931±0.51</td>
<td>962±0.52</td>
</tr>
<tr>
<td></td>
<td>T₃ 1.115±0.77</td>
<td>810±0.57</td>
<td>949±0.53</td>
<td>966±0.49</td>
<td>942±0.426</td>
</tr>
<tr>
<td>( \text{SV}_{\text{O}_2}, % )</td>
<td>Placebo 0.81±0.1</td>
<td>0.75±0.1</td>
<td>0.64±0.1</td>
<td>0.65±0.1</td>
<td>0.63±0.2</td>
</tr>
<tr>
<td></td>
<td>T₃ 0.82±0.1</td>
<td>0.77±0.1</td>
<td>0.66±0.2</td>
<td>0.68±0.1</td>
<td>0.64±0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. SVR, systemic vascular resistance; \( \text{SV}_{\text{O}_2} \), mixed venous \( \text{O}_2 \) saturation.
Table 5. GH and IGF-I in placebo and T3 groups

<table>
<thead>
<tr>
<th></th>
<th>PreOp</th>
<th>1 h</th>
<th>24 h</th>
<th>36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.6±0.4</td>
<td>4.1±0.9</td>
<td>1.4±0.3</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>T3</td>
<td>2.0±0.4</td>
<td>4.6±1.0</td>
<td>2.3±0.6</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>IGF-I, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>121.7±16.2</td>
<td>60.6±13.1</td>
<td>67.7±6.4</td>
<td>62.7±2.7</td>
</tr>
<tr>
<td>T3</td>
<td>127.8±17.0</td>
<td>66.7±11.3</td>
<td>80.1±7.8</td>
<td>75.2±3.1</td>
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<tr>
<td>IGF-I/IGF ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>102.6±16.7</td>
<td>28.5±7.5</td>
<td>83.7±26.2</td>
<td>62.2±21.8</td>
</tr>
<tr>
<td>T3</td>
<td>97.8±19.5</td>
<td>28.0±7.6</td>
<td>86.7±39.9</td>
<td>74.8±9.4</td>
</tr>
</tbody>
</table>

Values are means ± SE.

measures ANOVA showed no difference between time points within each group.

\[
L-[1^{13}C]{\text{leucine flux}} \, (\text{µmol\cdot kg}^{-1}\cdot \text{min}^{-1}) \text{ increased slightly postoperatively in the placebo group: from 121±4 to 139±8 (} P < 0.05; \text{ Fig. 3). In the T3 group, the difference between pre- and postoperative values (126±9 and 145±8, respectively) was not significant (} P = 0.13). Postoperative changes in \L-[1^{13}C]{\text{leucine flux}} \text{ in the placebo group were not significantly different from those in the T3 group (18.2±17.7 and 19.0±31.1, respectively, } P = 0.95). \]

Sex Steroids

T decreased profoundly in the placebo and T3 groups to similar nadir levels within the range of prepubertal values (Fig. 4A). In the placebo group, serum T decreased from a preoperative value of 3.5±0.9 ng/ml to a nadir postoperative value of 0.9±0.4 ng/ml (} P < 0.0001) and in the T3 group from 4.0±1.4 to 0.8±0.3 ng/ml (} P < 0.0001). These decreases were statistically the same for both groups (} P = 0.11).

In contrast to T, serum E1 levels rose in the placebo and T3 groups (Fig. 4B). The increase in the T3 group (from 34.7±2.6 to 90.9±9.0 pg/ml) was not significantly greater than the increase in the placebo group (from 35.3±3.0 to 70.2±9.1 pg/ml, } P = 0.31). Serum levels of E2 did not rise significantly in either group, with similar values observed in both groups (Table 4).

GH Axis and Serum Iron and TIBC

Serum GH levels increased and IGF-I levels decreased in placebo and T3 patients (Table 5). No significant differences between these changes were observed between the two groups.
(P = 0.49 and P = 0.40 for GH and IGF-I, respectively). The decrease in the GH/IGF-I ratio was also equivalent in both populations (P = 0.30).

Decreases in serum iron concentrations and TIBC were observed after CABG (Table 6). No statistical difference was observed in changes in iron (P = 0.49) or TIBC (P = 0.40) between the placebo and the T3 group.

**DISCUSSION**

These data demonstrate that preventing the decrease in T3 during the early stages of NTIS in acute illness has minimal effects on the physiological processes evaluated in our study; there was only a slight transient enhancement in cardiac function. No effect on protein metabolism was evident. Similarly, we observed no evidence of NTIS modulation of the sex steroid, GH-IGF-I axis, or ion responses to acute illness. Thus, although NTIS does not appear to be an entirely euthyroid state, in at least this circumstance (early stages of major illness of moderate severity), physiological effects appear to be minimal. Whether this is true for less healthy patients or for more extended illnesses has yet to be determined.

With respect to cardiac function, one previous study in which a T3 dose similar to that in this study was used also reported a mild inotropic effect reflected by increased CI and decreased use of dopaminergic agents (28). Other studies in which much higher doses were used for 6 h still reported only minimal increases in CI (4, 17). Thus it is reasonable to assume that any hypothyroid effect of NTIS on cardiovascular function is minimal. The therapeutic effects of T3 supplementation appear to be clinically inconsequential, particularly compared with standard inotropic agents such as dopaminergic drugs.

With respect to protein metabolism, we did not confirm the previous study suggesting that NTIS is protective against catabolism (12). That study employed a model of fasting in seven healthy subjects, rather than acute illness. The dose of T3 resulted in T3 levels slightly above baseline and suppressed TSH values, indicating that a mildly hyperthyroid state may have been induced. Only urinary urea nitrogen excretion was monitored, rather than the more sophisticated parameters of UN and L-[1-13C]leucine flux that are now available. In our study, we were able to maintain serum T3 concentrations at preoperative levels. TSH remained within the normal range or minimally suppressed, with a lower mean TSH value in the T3 than in the placebo group. No trend in increased protein catabolism (measured by UN or L-[1-13C]leucine flux) was evident in our T3 patients compared with placebo patients. Therefore, it is unlikely that a larger study of similar patients would reveal a protective effect of NTIS on protein catabolism in the early stages of illness. Whether results with illness of greater severity or longer duration would differ was not addressed by the present study.

The lack of any discernable effect of T3 administration on other endocrine responses to acute illness rules against a role of NTIS in modulating those responses. The decrease in serum T and rise in E1 were not different between the T3 and placebo groups. Thus the hypogonadotropism and decreased testicular responsiveness to luteinizing hormone (6, 22, 33) seem to occur independently from NTIS. Nor does the increased aromatase activity that results in rising estrogen production with acute illness (34) appear to be blunted by NTIS. Similarly, we found no evidence that increased pituitary GH secretion, decreased hepatic responsiveness to GH, or iron handling is affected by NTIS.

Our data indicate that T3 supplementation is safe with respect to protein catabolism, cardiac arrhythmias, and myocardial ischemia after successful CABG. However, they also argue against continued trials of T3 therapy in CABG patients because of the lack of discernable benefits. A similar lack of benefit has been observed in children undergoing cardiac surgery (5). It is possible that a trial including only CABG patients with clearly compromised cardiac function postoperatively may demonstrate a clinical benefit. Until such results are available, T3 therapy should not be used in CABG patients. Results in transplant donors remain unresolved (15, 27, 30).

In summary, our data indicate that NTIS with marked decreases of serum T3 in the early stages of illness is accompanied only by minimal effects of hypothryoidism limited to a transient mild suppression of CI. No effects on protein catabolism, other endocrine responses to acute illness, or iron parameters were observed. The consistent onset of NTIS with illness is suggestive of an adaptive advantage at some point in evolution. Possibly NTIS was of greater importance in settings of marginal nutrition where humans lived (or live) on the edge of a catabolic state. Thus future studies of patients who are more nutritionally compromised before and during their illnesses may be of interest. The present data do not clearly indicate that NTIS is accompanied by significant physiological hypothyroid effects.

**ACKNOWLEDGMENTS**

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**REFERENCES**


