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# Hypermetabolic low triiodothyronine syndrome of burn injury

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**The free tetraiodothyronine index ($FT_4I$) and free triiodothyronine index ($FT_3I$) in burn patients represented the serum levels of free (dialyzable) $T_4$ and free $T_3$, respectively. $FT_4I$ and $FT_3I$ were lower with greater burn size and were lower in nonsurvivors than expected for the burn size. There was no compensatory elevation of basal or releasing hormone-stimulated thyrotrophin (TSH) concentrations. Reverse $T_3$ was higher with greater burn size. $T_3$ treatment restored $FT_3I$ but did not affect mortality or resting metabolic rate (MR) measured in survivors, compared with placebo therapy. Whereas the hypermetabolic response to burn injury appeared to be independent of thyroid hormones, MR was correlated positively with burn size and with elevated plasma norepinephrine and epinephrine concentrations for several weeks after injury. Lack of augmented TSH concentrations, absence of low plasma reverse $T_3$, and presence of hypermetabolism suggest that the reduced plasma free $T_3$ does not indicate functional hypothyroidism, but may represent an adaptation to the assumption of metabolic control by the sympathetic nervous system.**

Many nonthyroidal illnesses (NTI), such as starvation, infection, liver disease,[1, 2] kidney disease,[3] malignancy,[4] myocardial infarction,[5] diabetes mellitus,[6] and accidental burn injury[7, 8] are associated with a decrease in total and free $T_3$ concentration in plasma (low $T_3$ syndrome). Reduction in $T_4$ may signify a more critical severity of illness: among patients admitted to a medical intensive care facility, those with a low total $T_4$ had a subsequent mortality (63%) of more than 4-fold that of patients with normal $T_4$.[9] In the same[10] and in another[11] medical ICU, patients with a reduced $T_4$ level also had a dramatically reduced free (dialyzable) $T_4$ concentration and $FT_4I$ compared to patients with normal $T_4$[10] or to normal controls.[11]

A major unresolved issue is whether this chemical hypothyroidism of illness and trauma represents functional hypothyroidism requiring replacement therapy. Alternatively, it could represent an adaptive response. Such a response might serve to lower MR at a time when normal oxygen demand and catabolic activity could presumably be disadvantageous, or it might occur without lowering of MR if another system assumes the dominant role in stimulating MR. Previous studies of burns or other NTI have not examined concentrations of thyroid hormones and catecholamines in plasma with respect to the extent of illness or injury or to metabolic rate. However, patients with injury from burns[12] or other trauma[13] or with several kinds of febrile illnesses[14] have been hypermetabolic, an association unexpected with hypothyroidism. Accidental burn injury in which severity of insult to the patient can be quantitated as burn size provides a model in which the hormonal and metabolic variables can be explored in relationship to each other and to time after injury and extent of injury. We have assessed the pituitary-thyroid axis using thyrotrophin-releasing hormone (TRH) and have examined the interrelationship among thyroid hormones, catecholamines, and metabolic rate in patients recovering from burn injuries of varying extent, with or without $T_3$ replacement.

## PATIENTS AND METHODS

### *Study 1*

Five nonburned healthy controls (CONT) and 10 burn patients received a single 250 μg iv bolus of thyrotropin-releasing hormone (TRH) between postburn days (PBD) 10 and 20. Five burn patients survived (SURV) and 5 nonsurvivors (NSURV) expired later (Table 1). No patient received dopamine or corticosteroids before or during TRH stimulation. Serum samples were taken for TSH assay before and at intervals up to 90 min after TRH injection. The TSH-time curve integral (area under the curve) was computed. Analysis of variance and the Student-Newman-Keuls test were used to compare means.

### *Study 2*

Thirty-six men, aged 17–23 yr and burned in a single gasoline fire in a military camp, were entered into a prospective study of $T_3$ *versus* placebo administration on a protocol approved by the institutional committee monitoring ethical considerations of clinical studies. Eight of

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TABLE 1. Basal $FT_4I$ and $FT_3I$ and TRH-stimulated TSH response in normal and burned subjects

| Group | Age (yr) | N/Sex | TBS range (mean)[a] | Days before death | $FT_4I$ | $FT_3I$ | TSH Integral (U·min/ml) |
|---|---|---|---|---|---|---|---|
| CONT | 31–40 | 5/M | | | 7.9 ± 0.35 | 153 ± 9.5 | 1245 ± 208 |
| SURV | 19–54 | 5/M | 50–68 (58) | | 5.9 ± 0.7[b] | 95.0 ± 21.0[c] | 1326 ± 216 |
| NSURV | 18–63 | 4/M 1/F | 28–68 (47) | 4–7 | 2.9 ± 0.6[c] | 25.0 ± 6.0[c] | 579 ± 109[c] |

[a] TBS, total burn size as % body surface; for group designations, see Figure 2.
[b] $p < 0.05$; [c] $p < 0.01$; for SURV, comparison group is CONT; for NSURV, comparison group is SURV. Error terms are SEM.

these CONT patients had minimal injury. The remaining 28 had 2nd and 3rd degree total burn size (TBS) of 18–93% of body surface area and were randomly assigned in double blind fashion to treatment with either placebo or $T_3$ 200 μg/day orally or by nasogastric tube in 4 divided doses until their wounds were healed. This dose of $T_3$ was previously found to maintain normal $T_3$ levels in burn patients.[15] Because 4 deaths occurred during placebo (NSURV) and 4 during $T_3$ treatment (NSURV-TX), the patients were assessed according to the 5 groups characterized in Table 2. We sampled blood for determination of thyroid hormones (serum) and catecholamines (plasma) beginning on PBD 3–5, and then approximately thrice weekly, when the patients were under basal conditions in the supine position between 0500–0700 h, just before their next dose of placebo or $T_3$. At weekly intervals in the morning, after overnight recumbency and at least an 8-h period free of caloric intake, resting MR was measured in all surviving patients. Because of the large number of measurements to be made, priority was given to those who appeared the most stable clinically, and their MR was followed longitudinally. The others, whose MR was not measured, happened to be nonsurvivors. A record was kept of the total daily caloric intake and the separate intakes of carbohydrate, protein and fat.

In Study 2, the period of PBD 3–26 was chosen for analysis, because the major decrement in catecholamines and MR occurred by PBD 26, the CONT patients were available for varying periods up to this time, and all survivors received placebo or $T_3$ treatment during this time (Table 2). All values sampled within 24 h of dopamine or corticosteroid administration were discarded from analysis. In one analysis the variables were considered as the mean value for each patient. But, because major changes in most variables took place over time, the time factor was accounted in separate analyses using individual values of variables in a standard stepwise multiple linear regression program (BMDP, UCLA) performed on a PDP 1140 computer. For a given dependent variable, the program chose only those independent variables (from the ones entered) which significantly ($p < 0.05$) reduced the residual variance of the dependent variable about the values predicted from the other chosen independent variables. To test for possible dependent variation related to TBS and PBD, both of these and their respective squared values were entered as possible independent variables into most of the multiple regression analyses. Additional possible independent variables were also entered to determine whether they would account for dependent variation better than would TBS and PBD. In some analyses, death or $T_3$ treatment was entered as the additional independent variable. In other analyses involving several hormones as the additional possible independent variables, the relevant dependent and independent variables are identified under "Results" and in Table 3.

TABLE 2. Group characteristics of the $T_3$ treatment study[a]

| | N | %TBS (mean) | %TBS (range) | Begin placebo or $T_3$ (PBD) | End placebo or $T_3$ (PBD) |
|---|---|---|---|---|---|
| CONT | 8 | 4.5 | 2–7.5 | | |
| SURV | 10 | 44.3 | 18–82 | 3 | 31–104 |
| NSURV | 4 | 68.4 | 55–93 | 3 | 6–54 |
| SURV-TX | 10 | 45.3 | 28–75 | 3 | 26–83 |
| NSURV-TX | 4 | 72.9 | 62–85 | 3 | 12–22 |

[a] TBS, total burn size as % body surface; PBD, postburn day; CONT, controls with small burns; SURV, placebo-treated survivors; NSURV, placebo-treated nonsurvivors; SURV-TX, $T_3$-treated survivors; NSURV-TX, $T_3$-treated nonsurvivors.

In both of these studies (1 and 2), no patient received iodine or iodine-containing compounds topically or systemically. All patients received initial vigorous fluid resuscitation followed by administration of calories, mainly by the enteral route, to approach the estimated metabolic requirement. Wounds were treated with open topical applications of mafenide acetate or silver sulfadiazine and excision and grafting when appropriate. Systemic antibiotics were administered for sepsis or infection.

*Assays*

Determinations of $T_4$, $T_3$ (Ortho), reverse $T_3$ ($rT_3$, Serono) and TSH (Diagnostic Products) were made by radioimmunoassays with kits obtained from the manufacturer. Least detectable concentrations were 0.2 μg/dl for $T_4$, 10 ng/dl for $T_3$, 2 ng/dl for $rT_3$, and 0.5 μU/ml for TSH. Pooled hypothyroid, normal, and hyperthyroid sera yielded respective mean values (and interassay coefficients of variation) as follows: for $T_4$, 4.7 (7.4%), 9.5 (7.1%), and 17.1 μg/dl (7.6%); for $T_3$, 60 (8.3%), 124

TABLE 3. Regression analyses of hormonal variables and MR

| Analysis[a] | n | $r^2$ |
|---|---|---|
| $FT_4I^b = 7.34 - 0.0003\ TBS^2 - 0.002\ DA + 0.001\ PBD^2$ | 143 | 0.344 |
| $FT_3I^b = 98.6 - 0.568\ TBS + 0.046\ PBD^2 - 0.035\ DA$ | 143 | 0.417 |
| $rT_3^b = 44.2 - 3.75\ PBD + 0.094\ PBD^2 + 0.255\ TBS - 0.002\ TBS^2$ | 143 | 0.540 |
| $TSH = 1.69 + 0.085\ PBD$ | 141 | 0.129 |
| $NE^c = 1425 + 22.7\ TBS - 122\ PBD - 0.186\ TBS^2 + 2.92\ PBD^2 - 58.2\ FT_4I$ | 142 | 0.639 |
| $EPI^c = 143 + 3.0\ TBS - 8.75\ PBD$ | 142 | 0.397 |
| $DA^c = 208 + 0.026\ TBS^2 - 1.23\ FT_3I$ | 142 | 0.290 |
| $DBH/P^c = 90.1 - 0.306\ FT_3I$ | 141 | 0.037 |
| $MR = 35.1 + 0.243\ TBS + 0.017\ NE - 1.74\ TSH + 0.041\ DBH/P$ | 36 | 0.827 |
| $MR^d = 35.2 + 0.022\ NE + 0.036\ EPI$ | 37 | 0.576 |

[a] In each analysis, all variables (except MR) were entered, together with TBS and PBD and their squared values, as possible independent variables with the following exceptions:

[b] If a thyroid hormone ($FT_4I$, $FT_3I$ or $rT_3$) was the dependent variable, none of these was entered as an independent variable.

[c] If a catecholamine-related measurement was the dependent variable (NE, EPI, DA, or DBH/P), none of these was entered as an independent variable.

[d] In this analysis, only NE, EPI, and DA were entered as possible independent variables. The proportion of MR variability ($r^2$) associated with NE alone was 0.50, and the inclusion of EPI accounted for an additional 0.076.

(3.3%), and 298 ng/dl (4.48%); and for TSH, 36.4 (9.1%), 3.3 (10.7%), and 1.5 μU/ml (35%). For $rT_3$, pooled hypothyroid and normal sera yielded respective means (and interassay coefficients of variation) of 11.8 (8.3%) and 22.3 ng/dl (13.9%). Indices of free thyroid hormone concentration ($FT_4I$ and $FT_3I$) were calculated as the product of the total $T_4$ or $T_3$ and the resin $T_3$ uptake ($T_3U$) divided by the normal calibrator $T_3U$ provided in the kit (Ortho). The $FT_4I$ and $FT_3I$ in 100 representative samples from burn patients (Fig. 1) were validated as indices of free hormone levels by comparison with the respective free $T_4$ and free $T_3$ concentration based on the dialyzable fraction which was also determined (Nichols Institute, San Pedro, CA). These samples were taken from patients with various burn sizes, including some with nearly healed wounds and normal thyroid hormone levels. In a group of 49 normal adults, mean $FT_4I$ was 7.48 (range 5.1–11.1) and mean $FT_3I$ was 125 (range 69–273). These index values have no assigned units. Plasma norepinephrine (NE), epinephrine (EPI) and dopamine (DA) were determined by radioenzymatic assay[16] as was dopamine beta-hydroxylase (DBH).[17] Total plasma protein was determined according to the method of Lowry et al.[18] Resting MR was measured at ambient 31°C by indirect calorimetry based on $O_2$ consumption measured for successive 2-min intervals using a head canopy with continuous air flow.[19] The lowest value for a 30-min period, usually when the patient was asleep, was taken for the MR measurement.

## RESULTS

Figure 1 shows the comparison of $FT_4I$ and $FT_3I$ with the free hormone levels by dialysis ($FT_4$ and $FT_3$, respectively) in 100 representative samples from burn patients. The close correlations indicate that low $FT_4$ and $FT_3$ are associated with proportionately low $FT_4I$ and $FT_3I$, respectively.

In Study 1 (Table 1 and Fig. 2), TRH stimulation in SURV did not produce an exaggerated TSH response, though 4 out of 5 had basal $FT_3I$ below the lowest value for healthy controls. The response was blunted and delayed in NSURV, whose TSH concentration was higher at 60 than at 30 min after injection in every case. In contrast, TSH was lower at 60 than at 30 min after TRH injection in all CONT and SURV.

In Study 2, 4 of 14 $T_3$-treated and 4 of 14 placebo-treated patients died with sepsis or pneumonia. There were a total of 16 patients with TBS > 50% (to include

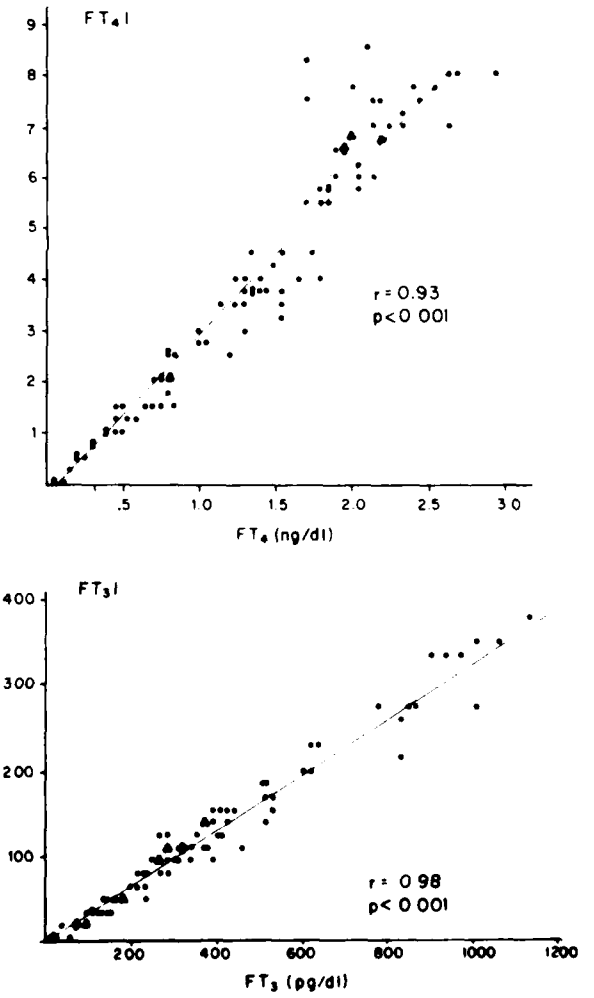


FIG. 1. Correlation of $FT_4I$ and $FT_3I$ with respective free hormone concentrations derived from the dialyzable fraction.

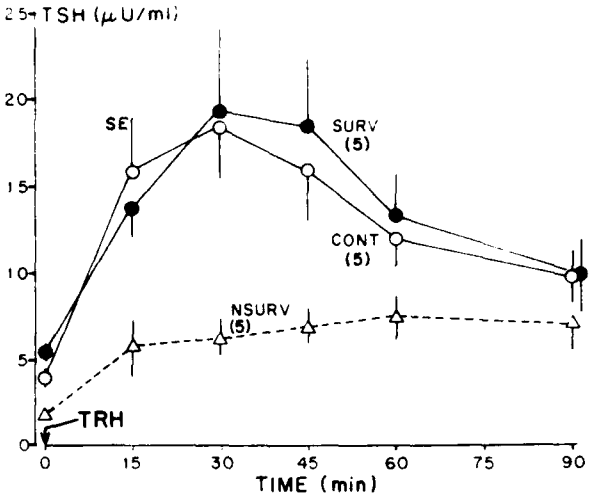


FIG. 2. TSH response to TRH in surviving (SURV) and nonsurviving (NSURV) burn patients and nonburned healthy controls (CONT). The number of patients is indicated in parentheses.

all nonsurvivors), in which 4 of 8 $T_3$-treated and 4 of 8 placebo-treated patients died. The CONT group with a very small injury (Table 2) known not to influence MR[12] consisted of particularly appropriate control subjects for this study. They were homogeneous with the other patients with respect to age, sex, physical training, and previous environment, and they were housed in the same general ward area. Therefore, hormonal values for the more extensively burned patients are better compared to values for these controls rather than to normal ranges in a heterogeneous population.

$FT_4I$ and $FT_3I$ in SURV were lowest initially (PBD 3–5) and generally returned to CONT levels over 3–4 weeks. In NSURV, the values were initially lower and did not rise before death which occurred on PBD 6–54. On PBD 5 (CONT samples not taken earlier), $FT_4I$ (mean ± SE) in SURV was slightly but not significantly lower (6.59 ± 0.46) than in CONT (7.62 ± 0.42), and $FT_3I$ in SURV (63.6 ± 3.9) was lower ($p < 0.001$, Student's *t*-test) than in CONT (99.8 ± 4.5). On PBD 3, $FT_4I$ in NSURV was 3.57 ± 0.63 compared to 7.11 ± 0.62 in SURV ($p < 0.01$) and $FT_3I$ in NSURV was 26.5 ± 7.38 compared to 69.8 ± 12.1 in SURV ($p < 0.001$). Because both time since burn and burn size were important variables, hormonal values in relation to burn size were first considered as the mean value for each patient over PBD 3–26. Subsequently, individual values were analyzed over this time period with PBD and TBS as independent variables in multiple regression analyses. Because of variation with time and less variation of $FT_4I$ than $FT_3I$ with burn size, only the multiple regression approach, accounting for time since burn, showed a significant burn size-related suppression of $FT_4I$ in SURV.

Based on mean values for each patient, the reduction in $FT_3I$ was proportional to burn size in patients not treated with $T_3$ (Fig. 3, *upper left*). Comparison of mean $FT_4I$ and TSH suggests that the thyroid axis was similarly suppressed in NSURV and in $T_3$-treated patients (Fig. 3, *upper right*). An inverse relationship between $rT_3$ and $FT_4I$ or $FT_3I$ can also be seen in patients not treated with $T_3$ (Fig. 3, *lower panels*). Multiple regression analyses showed that $T_4$, $T_3$, $FT_4I$, and $FT_3I$ ($p < 0.001$) were inversely proportional to TBS or $TBS^2$ in placebo-treated patients. In these patients, $T_4$, $T_3$, $FT_4I$, $FT_3I$, and TSH were excessively low ($p < 0.01$) for burn size in the NSURV group. $T_3$ treatment raised $T_3$ and $FT_3I$ in SURV-TX and NSURV-TX ($p < 0.001$) and suppressed $T_4$, $FT_4I$, and TSH ($p < 0.001$) in survivors but not in nonsurvivors. Figure 3 (*right panels*) shows the corresponding results based on mean values for each patient for $FT_4I$, TSH, and $FT_3I$. Multiple regression analysis showed that in placebo-treated patients, higher $rT_3$ was associated with greater TBS ($p < 0.01$). $T_3$ treatment reduced $rT_3$ in SURV-TX ($p < 0.001$) but not in NSURV-TX patients (Fig. 3, *lower panels*).

Patients with more extensive burns had higher NE levels and MR, particularly in the first 3 weeks postinjury, and MR was positively correlated with NE (Fig. 4). NE and MR were both inversely correlated with $FT_3I$ ($p < 0.001$, not shown) in placebo-treated patients. Multiple regression analysis showed that EPI ($p < 0.001$) and DA ($p < 0.01$) were also elevated in proportion to TBS and that NSURV had elevated plasma DA ($p < 0.01$) but not NE or EPI concentrations out of proportion

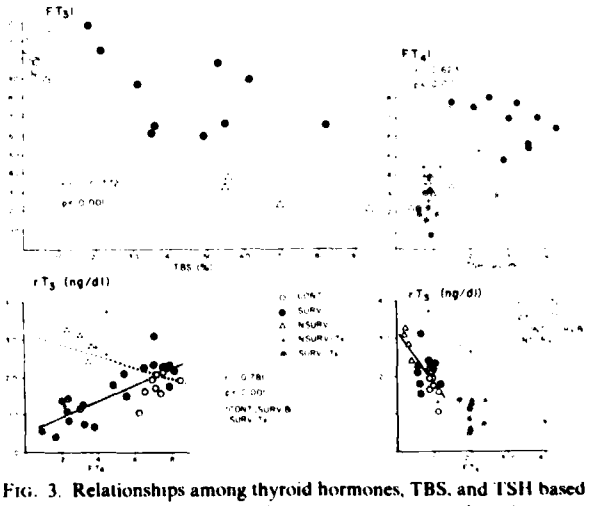


FIG. 3. Relationships among thyroid hormones, TBS, and TSH based on linear correlations of mean hormone values for each patient over PBD 3–26. In the *upper right panel*, location nearer the origin indicates suppression of the pituitary-thyroid axis, and the *dashed line* completely separates CONT and placebo-treated SURV from the others nearer the origin. The *shaded areas* (*lower panels*) include at least all points in the regressions for groups specified in the figure. In the *lower left panel*, the regression depicted (*solid line*) is positive, because nonsurvivors are excluded. If only $T_3$-treated patients are excluded, then the relationship between $rT_3$ and $FT_4I$ (*dotted line*) is negative ($r = -0.49$, $p < 0.05$).

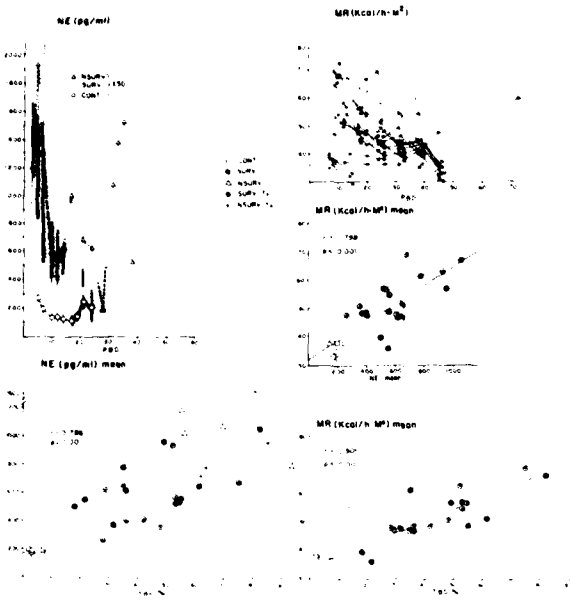

FIG. 4. Elevated NE and MR in burn patients related to PBD and TBS. Linear correlations are based on mean values over PBD 3–26. For group designations, see Table 2.

to TBS. Although SURV-TX had slightly lower NE values than did placebo-treated SURV for any given TBS and PBD ($p < 0.05$), NE levels were still markedly elevated in SURV-TX ($p < 0.001$). There was no detectable effect of $T_3$ treatment on EPI, DA, or MR.

Interrelationships among the measured values in untreated patients were defined by considering $FT_4I$, $FT_3I$, $rT_3$, TSH, NE, EPI, DA, DBH corrected for total serum protein (DBH/P), or MR as the dependent variable in separate multiple regression analyses. The remaining hormones (except those noted in Table 3) were entered together with TBS and PBD as possible independent variables. The resultant computer-chosen independent variables (Table 3) indicate that TSH has no correlation with thyroid hormones; thyroid hormones and catecholamines vary with burn size and time since the burn, and NE is inversely related to $FT_4I$. MR was more closely related to NE than to EPI, in that the latter was not chosen as a predictor for MR from among the other variables. When TBS, PBD, and thyroid measurements were excluded from analysis, NE accounted for 50% of total MR variability, and inclusion of EPI accounted for another 7.6%. In analyses not shown, $FT_4I$, $FT_3I$, NE, and MR were not correlated with total or fractionated caloric intake among SURV, indicating that differences in nutrition did not influence the metabolic variables estimated in these patients. However, the mean total caloric intake for individual nonsurvivors was lower (NSURV, 609–1354; NSURV-TX, 537–1522 kcal/$M^2$·day) than for survivors (SURV, 1526–2192; SURV-TX, 1630–2256 kcal/$M^2$·day).

## DISCUSSION

In agreement with previous findings,[7, 8, 15] we have confirmed that severe burns suppress free indices of thyroid hormone levels. Additionally, we now show that this is related to extent of injury and is without an augmentation of TRH-stimulated plasma TSH. An augmented TSH response is the expected normal result of even smaller decrements in thyroid hormones.[20] NSURV of burns had the lowest $FT_4I$ and $FT_3I$ and also exhibited a blunted and delayed TSH response to TRH. The altered regulation of TSH in burn patients resembles that found in other forms of NTI.[3, 4] These results are compatible with failure of brain centers controlling the thyroid axis[21] or with direct suppression of TSH release by elevated DA[22] or cortisol.[23, 24] Whether the excessively low $FT_4I$, $FT_3I$ and TSH values for NSURV burn patients are a result of sepsis, a deficient caloric intake, or other factors is yet to be determined. Though some unidentified factor also might interfere with hormone release from the thyroid, the thyroids from our patients at autopsy microscopically indicate lack of TSH stimulation.

Inhibited peripheral conversion of $T_4$ to $T_3$ and accumulation of the inactive $rT_3$ (the product of inner ring monodeiodination of $T_4$ in the periphery) are features of other forms of NTI.[1, 2, 6] Similarly, we found an inverse relationship of $rT_3$ to $FT_4I$ in burn patients not treated with $T_3$. The presence of normal or high $rT_3$ may be evidence for lack of hypothyroidism in burn injury, in that such levels of $rT_3$ have also been used to distinguish other forms of NTI from classical hypothyroidism.[25]

Burned patients are hypermetabolic, which again suggests the absence of functional hypothyroidism. Their hypermetabolism is blunted by propranolol,[12] a $\beta$-blocker. Their urinary catecholamines are elevated[12, 26, 27] in proportion to MR[12, 27] as are their plasma catecholamines as shown in the present study. MR was more closely correlated with NE than EPI, suggesting $\beta_1$ mediation of some of the hypermetabolism. Another study failed to find a correlation between plasma catecholamines and MR in children whose hypermetabolism and catecholamine levels were partially reduced by restricting heat loss with occlusive dressings.[28] Reduction in metabolic and sympathetic signals together with fewer measurements may have reduced the chance to observe a correlation in that study. Burn patients also exhibit other signs of elevated sympathetic activity,[12, 15, 27] such as elevation of heart rate, cardiac output and core temperature. In our placebo-treated patients, larger burn size and lower $FT_4I$ were closely correlated with higher plasma NE and higher MR, and MR was inversely related to plasma TSH. Thus, downward adjustment of TSH secretion appears not to indicate central hypothyroidism but perhaps is a response to the metabolic effect of catecholamines. $T_3$ treatment did not alter mortality in

this study. Failure of $T_3$ replacement to alter the MR further indicates that the hypermetabolic response to injury is independent of stimulation by the thyroid axis. The fall in thyroid hormones may be an adaptation to the assumption of metabolic control by the sympathetic nervous system after severe injury.

The hypermetabolic low $T_3$ syndrome may occur in a variety of settings. Other types of trauma[13] and several types of febrile illnesses[14] are associated with hypermetabolism, and febrile illnesses are associated with elevated catecholamine excretion[29] and decreased $T_3$ levels.[30] Patients with extensive burns and probably patients with other nonthyroidal illnesses develop a hypermetabolic low $T_3$ syndrome. Their hypermetabolism is due, at least in part, to elevated catecholamine secretion. The syndrome in burn patients would appear potentially harmful in terms of extremely high levels of catecholamines or low levels of free thyroid hormones, but an attempt to alter it with $T_3$ administration did not greatly affect catecholamines, hypermetabolism, or mortality.

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REFERENCES

1. Cavalieri RR, Rapoport B: Impaired peripheral conversion of thyroxine to triiodothyronine. *Ann Rev Med* 1977; 28:57
2. Gregerman RI, David PJ: Effects of intrinsic and extrinsic variables on thyroid hormone economy. In: The Thyroid. Werner SC, Ingbar SH (Eds). Hagerstown, NJ, Harper and Row Publishers, 1978, pp 223–246
3. Lim VA, Fang VS, Katz AI, et al: Thyroid dysfunction in chronic renal failure. *J Clin Invest* 1977; 60:522
4. Maturlo SJ, Rosenbaum RL, Pan C, et al: Variable thyrotropin response to thyrotropin-releasing hormone after small decreases in plasma free thyroid hormone concentrations in patients with nonthyroidal diseases. *J Clin Invest* 1980; 66:451
5. Faber J, Kirkegaard C, Lumholtz IB, et al: Variations in serum $T_3$, $rT_3$, 3, 3'-diiodothyronine and 3', 5'-diiodothyronine induced by acute myocardial infarction and propranolol. *Acta Endocrinol* (Copenh) 1980; 94:341
6. Pittman DS, Suda AK, Chambers JB Jr, et al: Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. *J Clin Endocrinol Metabol* 1979; 48:854
7. Becker RA, Wilmore DW, Goodwin DW Jr, et al: Free $T_4$, free $T_3$, and reverse $T_3$ in critically ill, thermally injured patients. *J Trauma* 1980; 20:713
8. Popp MD, Srivastava LS, Knowles HC Jr, et al: Anterior pituitary function in thermally injured male children and young adults. *Surg Gynecol Obstet* 1977; 145:517
9. Slag MF, Morley JE, Elson MK, et al: Hypothyroxinemia in critically ill patients as a predictor of high mortality. *JAMA* 1981; 245:43
10. Slag MF, Morley JE, Elson MK, et al: Free thyroxine levels in critically ill patients. *JAMA* 1982; 246:2702
11. Melmed S, Geola FL, Reed AW, et al: A comparison of methods for assessing thyroid function in nonthyroidal illness. *J Clin Endocrinol Metabol* 1982; 54:300
12. Wilmore DW, Long JM, Mason AD Jr, et al: Catecholamines: Mediator of the hypermetabolic response to thermal injury. *Ann Surg* 1974; 180:653
13. Cuthbertson DP: Surgical metabolism: Historical and evolutionary aspects. In: Metabolism and the Response to Injury. Wilkinson AW, Cuthbertson DP (Eds). Chicago, Year Book Medical Publishers, Inc., 1976, pp 1–34
14. Kinney JM: Surgical hypermetabolism and nitrogen metabolism. In: Metabolism and the Response to Injury. Wilkinson AW, Cuthbertson D (Eds). Chicago, Year Book Medical Publishers, Inc., 1976, pp 237–252
15. Becker RA, Vaughan GM, Goodwin CW Jr, et al: Plasma norepinephrine, epinephrine, and thyroid hormone interactions in severely burned patients. *Arch Surg* 1980; 115:439
16. Durrett LR, Ziegler MG: A sensitive radioenzymatic assay for catechol drugs. *J Neurosci Res* 1980; 5:587
17. Weinshilboum RM, Axelrod J: Serum dopamine-beta-hydroxylase activity. *Circ Res* 1971; 28:307
18. Lowry OH, Rosenborough NJ, Farr AL, et al: Protein measurement with the folin phenol reagent. *J Biol Chem* 1951; 193:265
19. Aulick LH, Hander EH, Wilmore DW, et al: The relative significance of thermal and metabolic demands on burn hypermetabolism. *J Trauma* 1979; 19:559
20. Vagenakis AG, Rapoport B, Azizi F, et al: Hyperresponse to thyrotropin-releasing hormone accompanying small decreases in serum thyroid hormone concentrations. *J Clin Invest* 1974; 54:913
21. Utiger RD: Tests of the hypothalamic-pituitary-thyroid axis. In: The Thyroid. Werner SC, Ingbar SH (Eds). Hagerstown, NJ, Harper and Row Publishers, 1978, pp 367–374
22. Scanlon MF, Lewis M, Weightman DR, et al: The neuroregulation of human thyrotropin secretion. *Front Neuroendocrinol* 1980; 6:333
23. McKenzie JM: Stress and thyroid function. In: Clinical Neuroendocrinology: A Pathophysiological Approach. Tolis G, Labrie F, Martin JB, et al (Eds). New York, Raven Press, 1979, pp 319–328
24. Vagenakis AG: Regulation of TSH secretion. In: Clinical Neuroendocrinology: A Pathophysiological Approach. Tolis G, Labrie F, Martin JB, et al (Eds). New York, Raven Press, 1979, pp 329–343
25. Chopra IJ, Solomon DH, Hepner GW, et al: Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illness. *Ann Intern Med* 1979; 90:905
26. Black JA, Harris F, Miller RWS, et al: Catecholamine excretion in burns in children. *Burns* 1977; 3:218
27. Harrison TS, Seaton JF, Feller I: Relationship of increased oxygen consumption to catecholamine excretion in thermal burns. *Ann Surg* 1967; 165:169
28. Caldwell FT, Bowser BH, Crabtree JH: The effect of occlusive dressings on the energy metabolism of severely burned children. *Ann Surg* 1981; 193:579
29. Mason JW, Buescher EL, Belfer ML, et al: A prospective study of corticosteroid and catecholamine levels in relation to viral respiratory illness. *J Human Stress* 1979; 5:18
30. Kallner G, Ljunggren J: The role of endogenous cortisol in patients with non-thyroidal illness and decreased $T_3$ levels. *Acta Med Scand* 1979; 206:459