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Free T_4, Free T_3, and Reverse T_3 in Critically Ill, Thermally Injured Patients

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A prospective study of thyroid function was performed in 25 thermally injured patients. These patients are divided into two groups. The first group contains five patients with greater than 50% burn size studied longitudinally during the first 15 days following thermal injury. Significant suppression of serum concentrations of 3,5,3′-triiodothyronine (T_3) and elevation of serum concentrations of 3,3′,5′-triiodothyronine (rT_3) were seen. The free thyroxine index and serum TSH concentrations remained within the normal range. To assess the clinical significance of these alterations in peripheral thyroid hormone concentrations, a second group of 20 patients was studied. We measured the free serum levels of T_4 (FT_4) and T_3 (FT_3) in ten patients, mean age 34 years, mean burn size 56%, studied during a period of clinical deterioration, and in ten patients of comparable age and burn size who were clinically stable. Both FT_4 and T_3 values were significantly lower in the unstable patients ($p < 0.01$). All FT_3 values for the unstable patients (M ± SE), 193 ± 14 pg/dl, were below the normal range for FT_3 of 230 to 669 pg/dl, and significantly lower than those observed in the stable patients (M ± SE), 430 ± 59 pg/dl ($p < 0.001$). This correlation of biochemical hypothyroidism with clinical deterioration may have functional significance for the critically ill trauma patient.

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The recovery course of the severely burned patient is characterized by hypermetabolism. Although severely burned patients demonstrate many of the clinical features associated with hyperthyroidism, such as elevated basal metabolic rate, tachycardia, hyperventilation, hyperpyrexia, hyperkinesia, and weight loss, studies of thyroid function by Cope and Stanbury and their colleagues in 1953 disclosed normal ^{131}I uptake and normal concentrations of serum protein bound iodine in thermally injured man (14). In 1970, Caldwell showed no increase in thyroid activity during periods of increased oxygen consumption associated with full-thickness burn in an animal model (11). In 1974, Wilmore and his colleagues in our laboratory related the hypermetabolism following thermal injury to increased sympathetic nervous system activity (38). Metabolic rate correlated closely with the urinary catecholamine excretion rate, and post-traumatic hypermetabolism could be attenuated by administration of beta but not alpha adrenergic blocking agents.

Alterations in peripheral thyroid economy occur following a wide variety of stress and disease states. The changes which generally occur are characterized by a decrease in serum concentrations of 3,5,3′-triiodothyronine (T_3) and a rise in 3,3′,5′-triiodothyronine (rT_3). It has been proposed that these reciprocal alterations in serum concentration of T_3 and rT_3 reflect a shift in the metabolism of thyroxine (T_4) from pathways which lead to generation of T_3 to pathways which lead to the generation of rT_3, a compound with diminished physiologic effect. It has also been proposed that a decrease in metabolic clearance rate of rT_3 without an increase in production rate accounts for the increase in serum concentrations of rT_3 in situations characterized by this alteration (18, 31). Decreased serum concentrations of T_3 and increased levels of rT_3 have been observed during starvation (33), anorexia nervosa (8, 31), severe trauma and hemorrhagic shock (34), hepatic dysfunction (12, 13), surgery (9), and severe infection (6, 12, 25, 37).

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Because of both the known alterations in hypothalamic function and the hypermetabolism which accompany thermal injury, this study was designed to assess thyroid function following thermal injury. In addition, we present data relating clinical deterioration of burn patients to significant depression of serum concentrations of free thyroxine (FT_4) and free triiodothyronine (FT_3).

MATERIALS AND METHODS

PATIENTS—GROUP I

Longitudinal measurements of T_3, rT_3, and TSH were made in five males, mean age 29 years, mean burn size 66.5% (range, 53 to 78%) who were injured simultaneously in a gasoline explosion. T_3 uptake (T_3U) and thyroxine (T_4) were also measured and expressed as the free thyroxine index (FTI). Venous blood specimens were obtained at 7 AM, at 2- to 3-day intervals beginning on the third postburn day and continuing for the first 15 days following thermal injury. Serum was immediately separated by centrifugation and the samples frozen until analysis. All but one of these patients developed bacteremia within the first week of admission, but all cleared their sepsis with appropriate antibiotic treatment and were free of systemic infection in the second week of observation.

PATIENTS—GROUP II

Serum concentrations of T_4, T_3, FT_4, FT_3, and TSH were measured in ten patients, mean age 34 years, mean burn size 56%, who were clinically stable and with sterile blood stream cultures. In addition ten patients, mean age 24 years, mean burn size 59%, were studied at a time of clinical deterioration, as indicated by either positive blood stream cultures, ileus, hypothermia, or altered mental status. None of the patients received dopamine, exogenous steroids, or any other medications known to influence thyroid metabolism.

ASSAYS

All samples from each group were measured in a single assay. Serum T_4 was measured by competitive protein binding (27), and T_3U by silica gel uptake. Previously described radioimmunoassays were employed for the measurement of TSH, T_3, and rT_3 (7). Free hormone concentrations were determined by equilibrium dialysis at the Nichols Institute, San Pedro, California. Measure-

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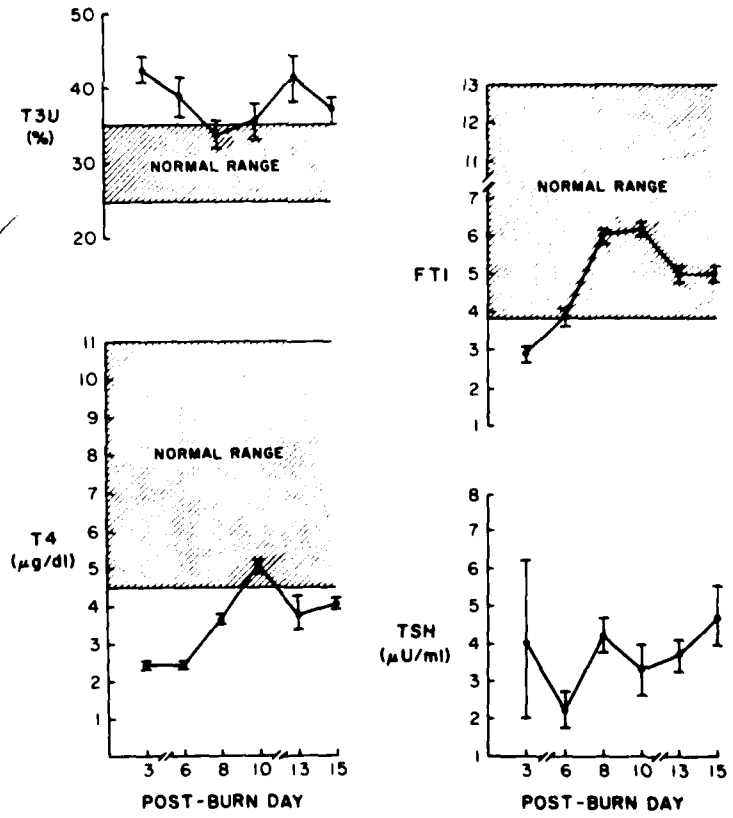

FIG. 1. Serum values (mean ± S.E.) for T_3U %, T_4 μg/dl, FTI, and TSH μU/ml in Group I patients during the first 15 days following thermal injury. Shaded areas indicate the normal range. Normal values for TSH are less than 85μU/ml.

ments obtained during the different study periods were compared by *t*-test analysis.

RESULTS

GROUP I (Figure 1)

T_3U. Values for T_3U ranged between 42 ± 2% and 35 ± 2% (mean ± S.E.) during the 15-day recovery period. Most values were at or above the upper limit of normal, probably reflecting the known fall in thyroid binding globulin capacity associated with severe trauma or illness.

T_4. Mean (± S.E.) serum T_4 ranged from 2.5 ± 0.5 to 5.0 ± 0.8 μg/dl. Seven of eight values were below the normal range.

FTI. The FTI is the product of the T_3U and T_4 and its level is correlated with measured free thyroxine levels. Values for FTI ranged from 3.0 ± 0.7 to 6.3 ± 1.1 (mean ± S.E.). With the exception of the third postburn day, all were within the normal range.

TSH. Serum TSH values ranged between 2.2 ± 0.6 and 4.7 ± 0.8 μU/ml (mean ± S.E.). One patient had an elevated TSH value of 11 μU/ml on the third postburn day.

GROUP I (Figure 2)

T_3. Serum T_3 ranged from 16 ± 4 to 52 ± 12 ng/dl (mean ± S.E.). All values were below the normal range.

rT_3. Serum rT_3 levels ranged from 104 ± 10 to 56 ± 9 ng/dl (mean ± S.E.). With the exception of day 13, all values were above the normal range.

GROUP II

Clinical and hormonal data from 10 clinically stable patients are presented in Table I. These patients were stable during the hypermetabolic phase of convalescence from burn injury, with sterile blood cultures and without clinical evidence of sepsis. All patients were febrile, with a mean body temperature 101.4° F, consistent with previous measurements in the uncomplicated burn patient (38). Serum concentrations of T_4 and T_3 were within the normal range, or slightly below it, consistent with the decreased plasma concentration of thyroid binding globulin which accompanies severe injury. Accordingly, the FT_4 and FT_3 values were within the normal range, except in Patient 5, whose TSH value was elevated as well. TSH elevations were noted in Patients 5 and 8. The mean TSH value for all ten patients (6.5 μU/ml) was within the normal range.

Table II presents clinical and hormonal data from ten Group II patients studied at a time of clinical deterioration (as judged independently by their attending physicians). Most patients had positive blood or urine cultures. All ten patients were receiving appropriate antibiotic therapy at the time of study. Although the mean body temperature of all patients was 100.4° F, Patients 12, 14, 16, 19, and 20 exhibited relative hypothermia, a clinical sign of sepsis in the burn patient. All patients demonstrated a change in their clinical course, consistent with clinical sepsis, either ileus or altered mental status. Blood cultures, from samples drawn once each day at 0600, showed positive growth in five patients. Urine cultures were positive for Gram-negative organisms in four patients. Serum T_4 concentrations were slightly below the normal range. As in the control patients, serum FT_4 values were, with the exception of Patient 15, within the normal range. However, all of the serum concentrations of T_3 and FT_3 were below the normal range. In addition, Patients 12, 15, and 20 exhibited elevated TSH values.

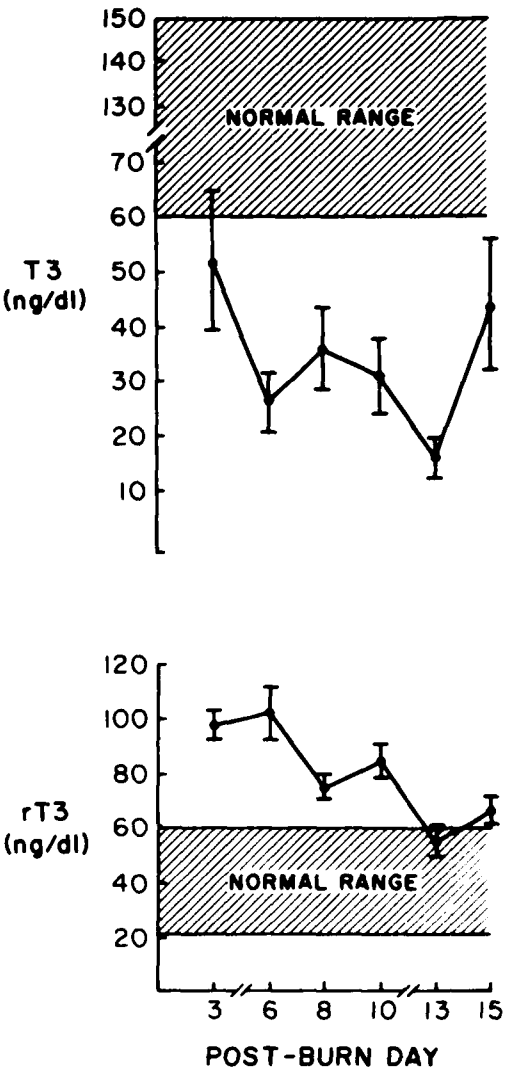

FIG. 2. Serum values (mean ± S.E.) for T_3 ng/dl and rT_3 ng/dl in Group I patients during the first 15 days following thermal injury. Shaded areas indicate the normal range.

Table III presents a comparison of clinical and hormonal data for control and septic patients. Clinical indi-

TABLE I
Characteristics of Group II burned patients—Clinically stable

Pt. No.	Age (Yrs)	Postburn Day Studied	% Total Body Surface Burn	Temp. (°F)	Clinical Evidence of Sepsis	Culture Results	T_4 μg/dl (nl, 5–11.5)	FT_4 ng/dl (nl,1.3–3.8)	T_3 ng/dl (nl,100–200)	FT_3 pg/dl (nl,230–669)	TSH μU/ml (nl,<8.5)
1	16	22	60	101.2	None	No growth	5.1	2.5	143	770	5.2
2	23	19	56	100.0	None	No growth	5.3	2.65	58	280	6.6
3	33	27	49	101.8	None	No growth	4.2	1.3	65	296	6.6
4	31	15	60	102.0	None	No growth	4.6	2.25	77	434	4.9
5	31	10	46	102.6	None	No growth	4.2	1.76	51	207	11.2
6	30	6	65	101.4	None	No growth	6.4	2.69	179	701	5.4
7	56	9	55	100.6	None	No growth	4.8	2.35	85	404	3.9
8	62	9	53	100.6	None	No growth	5.3	2.76	53	270	10.8
9	23	40	56	101.0	None	No growth	8.7	2.96	132	466	6.7
10	31	36	60	102.8	None	No growth	5.9	2.48	99	474	3.3

TABLE II
Characteristics of Group II burned patients—Clinically unstable

Pt. No.	Age (Yrs)	Postburn Day Studied	% Total Body Surface Burn	Temp. (°F)	Clinical Evidence of Sepsis	Culture Results	T_4 μg/dl (nl, 5–11.5)	FT_4 ng/dl (nl,1.3–3.8)	T_3 ng/dl (nl,100–200)	FT_3 pg/dl (nl,230–669)	TSH μU/ml (nl,<8.5)
11	32	40	57	101.4	Obtundation	*S. aureus**	5.3	1.48	78	225	5.3
12	26	19	68	98.6	Ileus	*Ps. aeruginosa*†	3.8	1.86	35	205	11.4
13	17	19	80	102.0	Obtundation	*S. aureus**	5.1	1.33	49	184	5.2
14	30	48	57	99.2	Ileus	*E. coli*†	5.0	2.05	55	205	5.5
15	19	42	61	102.0	Obtundation	*S. aureus**	4.0	1.00	53	225	9.7
16	19	20	57	99.2	Ileus	No growth	4.9	1.86	60	224	8.4
17	42	21	51	101.8	Obtundation	*Ps. aeruginosa**	5.9	1.71	72	223	4.2
18	24	10	51	101.6	Obtundation	*Ps. aeruginosa**	7.0	1.89	40	118	4.3
19	18	20	53	99.8	Ileus	*Ps. aeruginosa*†	5.0	2.60	47	213	6.3
20	19	8	60	99.0	Ileus	*Ps. aeruginosa*†	4.1	1.93	24	111	12.7

* Blood culture.
† Urine culture.

TABLE III
Comparison of data (Mean ± SE) between clinically stable and unstable patients

	Age (Yrs)	Postburn Day Studied	% Total Body Surface Burn	Temp. (°F)	T_4 μg/dl (nl, 5–11.5)	FT_4 ng/dl (nl,1.3–3.8)	T_3 ng/dl (nl,100–200)	FT_3 pg/dl (nl,230–669)	TSH μU/ml (nl,<8.5)
Stable patients	33 ± 5	19 ± 4	56 ± 2	101.4 ± .3	5.5 ± .4	2.37 ± .15	94 ± 14	430 ± 59	6.5 ± .8
Unstable patients	25 ± 3	24 ± 5	60 ± 3	100.4 ± .5	5.0 ± .3	1.77 ± .13	51 ± 5	193 ± 14	7.3 ± .1
p	N.S.	N.S.	N.S.	N.S.	N.S.	<.01	<.01	<.001	N.S.

ces of age, postburn day studied, per cent total body surface burn, and temperature were not different between groups. Significant differences between control and septic patient groups were found for FT_4 ($p < 0.01$), T_3 ($p < 0.05$), and FT_3 ($p < 0.001$). T_4 and TSH levels did not significantly differ between groups.

Tables IV and V present the daily caloric assessment and net energy balance available in most patients. All food items were prepared and individually weighed in the metabolic kitchen. Beverages and parenteral solutions were reconstituted according to desired nitrogen and calorie content. Each item was classified by its total calories and by the proportional content of carbohydrate, fat, and protein, and these data were stored in each patient's dietary profile. Daily nitrogen loss was estimated by 24-hour urea production corrected for stool and wound losses. Metabolic expenditure was usually determined by computer-stored nomograms which assess degrees of prior weight loss, changes in metabolic expenditure, preferred nitrogen to calorie ratio, as well as body weight and burn size. With difficult-to-manage patients whose caloric requirements changed with time or with the onset of septic complications, energy expenditure was measured by indirect calorimetry in an environmental chamber (38). To achieve positive energy balance, the estimated metabolic requirement was predicted by the sum of 1,000 plus the resting metabolic expenditure. Daily computer-generated profiles tabulated predicted caloric requirements, actual intake, and nutritional surpluses or deficits. The estimated energy balance was taken as the difference between total caloric intake and estimated metabolic requirement. These values were not significantly different between the clinically stable and clinically unstable patient groups.

DISCUSSION

During the hypermetabolic recovery phase of thermal injury (38), longitudinal measurements (Group I patients) of serum concentrations of T_3 and T_4 disclose low to low-normal values. FTI and basal serum TSH levels generally fall within the normal range, and serum levels of rT_3 are markedly elevated. These alterations in peripheral thyroid hormonal concentrations are similar to previous observations in patients with other catabolic disorders (6, 8, 9, 12, 15, 33, 34, 37). Because these changes may occur with fasting or reduced food intake (8, 33), the effect of diminished energy intake on these hormonal changes should be separated from the effect of increased sympathetic nervous system activity. During the first 48 hours following burn injury, fluid resuscitation of burn shock patients is a major priority. With restoration of blood volume, nutritional intake increases, and high protein-high calorie feedings are instituted. In the Group I patients studied longitudinally for the first 2 weeks, weight loss below preinjury body weight was minimal, although decreased dietary intake did occur in the early

TABLE IV
Caloric assessment* and energy balance* in Group II burned patients—Clinically stable

Pt. No.	Carbohydrate Gm/day	Protein Gm/day	Enteral KCal/day	Parenteral KCal/day	Total Caloric Intake KCal/day	Estimated Metabolic Requirement KCal/day	Estimated Energy Balance KCal/day
1	959	197	0	4,014	4,014	4,000	−14
2†							
3	655	228	3,341	1,200	4,542	4,735	−193
4	220	191	288	1,577	1,865	4,615	−2,750
5	909	323	13	4,301	4,314	4,570	−256
6†							
7	613	340	1,630	2,460	4,090	3,850	+240
8	433	327	1,463	1,811	3,274	4,050	−776
9	534	68	3,200	0	3,200	4,750	−1,550
10	428	491	0	4,133	4,133	4,750	−617

* All values represent the mean of the 3 days preceding the day of study.
† Caloric information not available. Patients eating regular diet and maintaining body weight.

TABLE V
Caloric assessment* and energy balance* in Group II burned patients—Clinically unstable

Pt. No.	Carbohydrate Gm/day	Protein Gm/day	Enteral KCal/day	Parenteral KCal/day	Total Caloric Intake KCal/day	Requirement KCal/day	Energy Balance KCal/day
11†							
12	616	161	4,377	0	4,377	4,155	+222
13	447	250	3,883	0	3,883	3,990	−115
14	506	232	3,225	874	4,097	3,500	+597
15	645	86	3,530	0	3,530	4,700	−1,170
16†							
17	309	97	237	1,247	1,483	2,850	−1,367
18	334	169	3,414	0	3,414	3,400	+14
19†							
20†							

* All values represent the mean of the 3 days preceding the day of study.
† Caloric information not available. Patients eating regular diet and maintaining body weight.

resuscitative phase. In the Group II patients, vigorous nutritional support was achieved, and alterations in thyroid hormone concentrations were observed with the onset of post-traumatic complications. This would suggest that the dietary influences in these patients are minimal in initiating the hormonal alterations observed.

The changes in peripheral thyroid hormone concentrations associated with the stress of illness may be a reflection of altered peripheral hormone turnover, changes in pool size, or altered production or release of these hormones. It has been suggested that the degradative mechanism for T_4 is reduced in infectious disease (36, 37). Others have reported that increased turnover of T_3 occurs with certain bacterial infections (21, 41), although serum concentrations of this hormone may not be altered. However, recent studies by Eisenstein et al. and Suda et al. suggest that elevations in serum rT_3 associated with catabolic states are due to a decreased metabolic clearance rate of rT_3 (18, 31), perhaps reflecting the concomitant fall in both serum T_3 and metabolic rate. It is unlikely that this mechanism can be applied to the severely hypermetabolic burned patient. Thyroid hormone kinetic studies are needed to address this question in the burned patient. Finally, it has been proposed by Dratman that the T_3 distribution space may be related to the function of the sympathetic nervous system or the functional mass of tissue innervated by the autonomic nervous system (17). T_3, like its precursors, phenylalanine and tyrosine, which also exhibit increased turnover following severe thermal injury (22), may be taken up by the adrenergic nerve for further metabolism and storage or may itself serve as a neurotransmitter. Interactions of this type would explain in part the apparent reciprocal relationship between thyroid hormone and catecholamine activity in various states of thyroid dysfunction (23), as well as in thermal injury.

An intact hypothalamo-pituitary axis is required for normal thyroid function, and T_3 and T_4 are thought to affect TSH elaboration through feedback mechanisms. Recent studies suggest that glucocorticoids, or T_4 alone, may effectively suppress TSH (24, 30). Thus a normal serum TSH level may not exclude hypothyroidism. Rather, it may reflect a normal serum-free T_4 in the presence of significantly suppressed serum T_3 and FT_3

values or suppression of the pituitary thyrotroph by the high levels of cortisol observed in burn patients. Although five of our patients had elevations of TSH, thyrotropin releasing hormone (TRH) stimulation tests were within normal limits (data not shown) in similar burn patients whose basal levels of TSH were within the normal range. Accordingly, intact pituitary responses have been reported in other patients with infective febrile illnesses (32, 37).

The clinical significance of the alterations of peripheral thyroid metabolism which accompany severe injury or illness is unknown. In ten patients studied during a period of clinical deterioration, we observed significant depression of serum concentrations of FT_4 and FT_3 compared with the levels observed in a matched control group. All of these unstable patients exhibited FT_3 levels below the normal range, but only one patient had a FT_4 level beneath the normal range. Accordingly, three of these patients had only slight elevations of TSH, suggesting that T_4, and especially FT_4, may have a significant role in feedback inhibition of the hypothalamo-pituitary axis. Further, the disparity between FT_4 and FT_3 levels in these patients suggests either a significant block in hepatic conversion of T_4 to T_3, or altered clearance, again pointing to the need for kinetic studies in the burned patient.

In summary, in the uncomplicated burned patient, serum concentrations of free thryoid hormones are generally within normal limits. This finding is consistent with the observation of euthyroidism in burned patients made by Cope and Stanbury in 1953 (14). However, in the clinically deteriorating burned patient, as determined by clinical evidence of sepsis and positive blood and urine cultures, serum concentrations of both total and free T_3 and free T_4 are significantly suppressed. This association of clinical deterioration with chemical hypothyroidism may have functional significance for the critically ill trauma patient.

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DISCUSSION

DR. JOHN KINNEY (Department of Surgery, Columbia—Presbyterian Medical Center, New York, NY 10032): I think one occasionally comes across a paper that can truly be said to have exciting promise, and I think this paper represents that kind of contribution.

It is extremely interesting that thyroid function has been making rapid progress among our medical confreres over the last 25 years. But when Cope and his coworkers found that hypermetabolism in burn patients was very marked, and then found that the I^{131} uptake and the PBI levels seemed to be normal, it went a long way toward telling all of us that the thyroid was perhaps not nearly as important as corticosteroids, catecholamines, and of course more recently glucagon. And thus thyroid has remained in the shadow when explaining the metabolic response to injury.

Over the past 15 years there has been a lot of attention to carrier proteins for the thyroid hormones. After all, more than 99% of the circulating thyroid hormone is bound to carrier proteins. The authors in this report have helped us by going to the effort of studying free T_4 and free T_3 and discussing the function of these free hormones.

Also there has been the rising interest in reverse T_3. As was mentioned by Doctor Becker, there are two ways of deiodinating T_4, and many papers have simply put the emphasis on the ratio between T_3-reverse T_3. Here we have a paper in which we are having our attention focused on the apparent importance of progressive decrease in T_3 per se.

I think for many of us this is a challenge to redefine for ourselves what hyperthyroidism and hypothyroidism really are. We all tended to learn that they were fundamentally related to oxygen consumption and heat production, and of course that may still be true. On the other hand, we are now being asked to expand our definitions and think of the thyroid in terms of cellular function, host defense, white cell function, and perhaps connective tissue integrity and what it means to wound healing.

This paper has not only the promise of helping us improve our understanding of the metabolic response, but also has some exciting possibilities for therapy.

Thank you.

DR. DONALD GANN (Rhode Island Hospital, Providence 02902): Like Doctor Kinney, I was also very impressed by this paper, and would like to compliment the authors.

Chopra and his colleagues have pointed out that after the degradation from T_4 to reverse T_3 there are further progressive deiodinations and that, unlike reverse T_3, the di-iodo and monoiodo products may actually act to inhibit the conversion of T_4 to T_3. What this means is that once the process gets shifted in favor of the generation of reverse T_3, there is sort of a built-in feedback mechanism to perpetuate the degradation in favor of reverse T_3 and therefore to produce an excess of inactive product.

I can understand that part of it, but something is missing for me. I would like to ask the authors first of all if they have any measurements that might indicate what factor initiates the process. For example, I know pharmacologic levels of corticosteroids can produce this shift. I am not clear that physiologic levels might be present in the septic patient can do so.

Second, I am intrigued by the question of the clinical significance, and I wonder if the authors feel it is simply a limited thermogenesis which is the important byproduct of the relative hypothyroidism or whether they have any clue to what else may be going on.

DR. RICHARD A. BECKER (Closing): Thank you very much, Doctor Kinney and Doctor Gann, for your comments.

With respect to what factors may induce a block in conversion of T_4 to T_3, I should point out that such a block has been observed in association with severe caloric restriction, hepatic disease, and in numerous systemic disorders, and as a side effect of several drugs, including propylthiouracil, propranolol, and iopanoic acid. It is the feeling of some investigators in this field that the common denominator of a block in conversion of T_4 to T_3 is catabolism. As Doctor Vagenakis and his colleagues and other investigators have shown, caloric deprivation, especially carbohydrate deprivation, may result in a diversion in T_4 metabolism away from the calorigenically active product, T_3. Subsequent studies have shown that the threshold for this effect is approximately 800 calories. That is, fasted patients who are refed 800 calories of fat and protein will continue to exhibit a block in T_4 to T_3 conversion. However, if they are refed 800 calories of carbohydrate, the block is released. This would suggest that substrate flow for gluconeogenesis, as well as other factors which may influence gluconeogenesis during periods of catabolism, are intimately linked to monodeiodination of T_4 to T_3 by the liver.

In reviewing deaths from thermal injury in our burn unit over the past 6 months, we have found eight patients who died during the first 7 to 10 days following thermal injury, that is, during the early hypermetabolic or flow phase of convalescence. We have been able to recover serum specimens taken as part of routine chemical analysis in these patients, and have looked at serum concentrations of thyroid hormone in these patients. We have found that on the third postburn day, both total T_4 and

total T_3 were significantly suppressed. We further found that in six of these eight patients the serum concentrations fell dramatically during the last 6 to 7 days that they lived, in many instances reaching concentrations consistent with myxedema coma, that is, T_4 concentrations in a range of 0.25 mcg per deciliter.

Similar observations were made concerning the free thyroxine index in these patients, as well as serum T_3 concentrations. In addition, several of these patients had elevated TSH levels. However, TSH did not become elevated until very late in the course, that is, within 1 to 2 days preceding death. This would suggest that the pituitary was either suppressed by steroids or other factors or did not recognize primary hypothyroidism until it had been exposed to low serum concentrations of thyroid hormone for a sufficient period of time.

Thank you.