

Pituitary and peripheral hormone responses  
to  $T_3$  administration during Antarctic residence

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REED, H. LESTER, JORGE A. FERREIRO, K. M. MOHAMED SHAKIR, KENNETH D. BURMAN, AND JOHN T. O'BRIAN. *Pituitary and peripheral hormone responses to  $T_3$  administration during Antarctic residence*. Am. J. Physiol. 254 (Endocrinol. Metab. 17): E733-E739, 1988. Very little is known regarding hormonal adaptation in human subjects who are exposed to the extremes of temperature and light that are found in polar latitudes. We have previously reported a 50% elevation in the serum thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH), a fall in serum total triiodothyronine ( $T_3$ ) and free  $T_3$  ( $fT_3$ ), and no change in serum total thyroxine ( $T_4$ ) or free  $T_4$  ( $fT_4$ ) after 42 wk of Antarctic cold exposure. To differentiate between central and peripheral mechanisms that may lead to these changes, we report the effect of sequentially increasing oral doses of  $T_3$  (Cytomel) on serum  $T_3$  and  $fT_3$  levels and on the resultant attenuation of the TSH response to TRH in nine men before, during, and after 42 wk residence in Antarctica. Serum  $T_3$  values basally and following the administration of 25, 50, and 75  $\mu\text{g/day}$  of  $T_3$  were lower after 42 wk of cold exposure ( $151 \pm 4$ ,  $160 \pm 8$ ,  $189 \pm 10$ , and  $222 \pm 14$  ng/dl, respectively, compared with control values of  $160 \pm 7$ ,  $178 \pm 7$ ,  $202 \pm 9$ , and  $251 \pm 19$  ng/dl, respectively,  $P < 0.05$ ). Likewise, the  $fT_3$  values measured after these three increasing  $T_3$  doses were also lower after 42 wk of cold exposure. The pituitary response to TRH was attenuated by each  $T_3$  regimen ( $48 \pm 6$ ,  $68 \pm 4$ , and  $77 \pm 4\%$  decreases in the control period), and this suppression was not different after 20 and 42 wk of Antarctic residence. Serum  $T_4$  and  $fT_4$  values were similar throughout the study. We conclude that the pituitary sensitivity to  $T_3$  was unchanged during the study and that changes in TSH responsiveness and serum  $T_3$  levels were likely due to changes in peripheral  $T_3$  metabolism.

thyrotropin; thyrotropin-releasing hormone; 3,5,3'-triiodothyronine; cold adaptation

EUTHERMIC MAMMALS are uniquely characterized by their ability to maintain a constant core temperature despite variations in climatic conditions. Among other factors, mammalian nonshivering thermogenesis is thought to be regulated by iodothyronines (11, 38), glucocorticoids (8), catecholamines (1, 19, 25), opioid peptides (29), glucagon (34), hypothalamic neuronal efferents (14), and brown adipose tissue (3, 13). Adaptive responses of serum iodothyronines to a decline in environmental temperature have received a great deal of attention, not only because they can be easily studied in

an in vivo model, but also because of their known importance in regulating thermogenesis.

Humans repeatedly exposed to a cold environment develop characteristic physiological changes, which some authors have called adaptive (21). However, earlier studies have not established consistent serum hormonal changes that correlate with these known physiological differences. One possible explanation for these conflicting results to date has been the application of widely disparate stimuli. Ambient temperature, altitude, duration, and interval between cold exposures, age, nutritional state, clothing, and physical activity all differ in these various reports.

We have previously reported a cohort of euthyroid human males exposed to an intermittent cold stimulus of known duration; an 11-mo sojourn (1980-1981) on the Antarctic continent. These subjects were studied before, during, and after 42 wk of continuous Antarctic residence. We described in this group, a 50% elevation in the plasma thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH), a fall in serum total 3,5,3'-triiodothyronine ( $T_3$ ) and free  $T_3$  ( $fT_3$ ), and no change in serum total thyroxine ( $T_4$ ) or free  $T_4$  ( $fT_4$ ) during the Antarctic cold exposure (27). We feel that this constellation of thyroid hormone values represents an environmentally associated and as yet poorly understood change in thyroid hormone economy. We believe this model is distinctly different than the changes observed during starvation (4, 12), overfeeding (6), depression (7, 20), or the euthyroid sick syndrome (40). Konno et al. (18) have described a group of hypothyroid patients maintained on fixed doses of thyroxine who demonstrated an augmentation of the TSH response to TRH during the Japanese winter. However, we know of no euthyroid human studies that have prospectively measured the serum dose-response curve to oral  $T_3$  or  $T_4$  administration and the pituitary sensitivity to these hormones before and after prolonged cold exposure. We now report a different cohort, age and sex matched with our original subject population and who lived at the same Antarctic base under similar environmental conditions in a later calendar year (1982-1983), to further define the mechanisms that may account for our earlier observations. Possible explanations of these previous findings might include either an increased clearance of  $T_3$ , a decreased produc-

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tion of  $T_3$ , or an altered sensitivity of the hypothalamic pituitary axis to endogenous  $T_3$ . We thus prospectively studied the responses to increasing doses of orally administered triiodothyronine (Cytomel, Smith Kline & French, Philadelphia, PA) of both serum  $T_3$  and  $fT_3$ , and the suppression of the TSH response to TRH before, during, and at the completion of 42 wk of continuous Antarctic residence.

#### MATERIALS AND METHODS

Nine healthy Caucasian males ( $25 \pm 1$  yr), members of the 1982–1983 annual winter-over party at McMurdo Sound, Antarctica, were studied under varying climatic conditions, with each subject serving as his own control. Informed consent was obtained from all participants. All volunteers were within the height and weight standards for US Navy personnel during the entire period of the study. The mean  $\pm$  SE body weights of the subjects before and after the study ( $81 \pm 4$  kg and  $82 \pm 4$  kg, respectively) were not different.

The basal diet consisted of 2,000–2,500 kcalories (kcal), with ~40% as carbohydrate, 35% as protein, and 25% as fat. During the Antarctic residence, the calories consumed per subject increased to 3,000–3,500 kcal/day, but the relative contributions from carbohydrate, protein, and fat remained the same.

Basal and dynamic thyroid function testing were performed in September, 1982, during mission training in Port Hueneme, CA (i.e., at sea level and with average temperature of  $20 \pm 5^\circ\text{C}$ ). The subjects were then transported to McMurdo Sound, Antarctica, for duty. Thyroid testing was repeated at the completion of the austral summer (March of 1983), after 20 wk of exposure, and again at the end of the austral winter (August of 1983), after a total of 42 continuous wk of exposure.

Each subject wore standard military polar clothing during outdoor activity; however, the face and hands were often exposed with this uniform. The subjects were similar with regard to the amount of out-of-door exposure each experienced throughout the study ( $2.8 \pm 0.7$  h/day). Because of the physical nature of the base, each subject was exposed not  $<0.25$  h/day on two separate occasions during each of 294 days of the study, thus serving as a model of multiple repeated environmental exposures. Ambient temperature was recorded during each evaluation period (Fig. 1). Each subject's cold exposure time per 24 h was also recorded and correlated to the observed hormonal changes. Indoor fluorescent lighting was used during the austral winter months, and all eight subjects maintained routine 8-h sleep/wake patterns, with an indoor temperature of  $15.5$ – $20.0^\circ\text{C}$ .

At each study period (warm control, 20 and 42 wk), subjects underwent basal measurements of serum  $T_4$ ,  $fT_4$ ,  $T_3$ ,  $T_3$  resin uptake ( $T_3\text{RU}$ ), TSH, and TSH response to TRH. At each study period, after obtaining basal samples, the subjects were administered sequentially increasing doses of  $T_3$  at levels of 25, 50, and 75  $\mu\text{g/day}$  respectively, on 3 successive days. The 25- $\mu\text{g/day}$  dose of  $T_3$  was divided into five doses of 5  $\mu\text{g}$ ; the 50- $\mu\text{g/day}$  dose was divided into five doses of 12.5, 12.5, 10, 10, and 5  $\mu\text{g}$ ; and the 75- $\mu\text{g/day}$  dose was divided into five doses of 25,

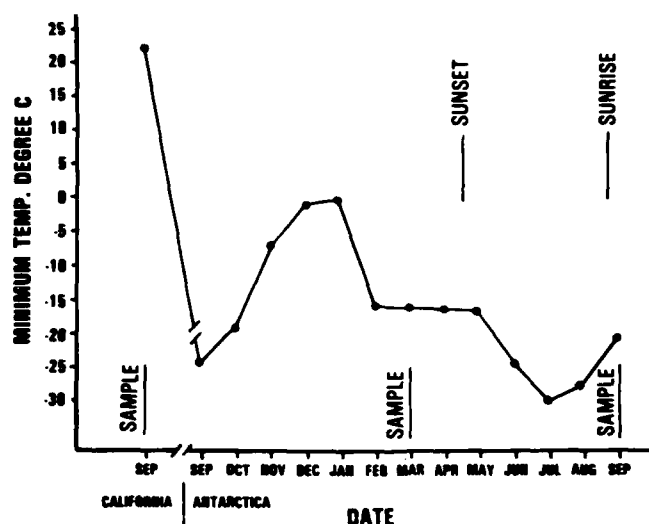


FIG. 1. Minimum ambient temperature ( $\bullet$ ) is shown for sampling periods in Port Hueneme, CA, and McMurdo, Antarctica.

12.5, 12.5, 12.5, and 12.5  $\mu\text{g}$ . Doses were administered at 1000, 1400, 1800, 2200, and 0200 during the 3-day period. Pill boxes were collected and pills were counted to assure compliance with the protocol. This dosing interval was used to optimize the balance between near steady-state  $T_3$  serum levels, a minimum of sleep deprivation (26), and maximal TSH suppression (41) as well as to allow comparison with similar dosing intervals previously published by our laboratory (4). Basally, before Cytomel, serum was collected for  $T_3$ , and a TSH stimulation test was carried out. At each dose level (25, 50, and 75  $\mu\text{g/day}$ ), serum was collected at 0800 for  $T_3$ ,  $fT_3$ , and TSH, and a TRH stimulation test was performed. The TSH response to TRH was carried out in nonfasted subjects at 0800 on each of the 3 days by measuring the initial serum TSH value and the value at 15, 30, 45, and 60 min after the bolus intravenous administration of 250  $\mu\text{g}$  of TRH (17, 31, 12). The integrated TSH response to TRH was expressed using Simpson's approximation for discrete intervals. All similar hormone samples were coassayed.

Serum  $T_4$  (normal 5.3–10.5  $\mu\text{g/dl}$ ) and  $T_3$  (normal 80–204 ng/dl) were measured commercially by radioimmunoassay (RIA) performed by Nichols Institute (Los Angeles, CA). Serum  $fT_4$  (normal 1.3–3.8 ng/dl) and  $fT_3$  (normal 260–480 pg/dl) levels, measured by dialysis technique, were also determined by Nichols Institute. Serum TSH was measured by RIA (normal 1.5–6  $\mu\text{IU/ml}$ ); Kallsted Laboratories, Austin, TX). The lower limit of the TSH assay was 1.5  $\mu\text{IU/ml}$ . The  $T_3$  resin uptake was measured by solid-phase  $^{125}\text{I}$  radioassay (Diagnostic Products, Los Angeles, CA). The "normalized" free  $T_4$  index was calculated as the  $T_3$  resin uptake value divided by a normal pool  $T_3$  resin uptake (0.35) and then multiplied by the total  $T_4$ .

Statistical analysis was performed by using analysis of variance with repeated measures and Duncan's multiple-range test for differences between means (Statpak version 4.1, Northwest Analytical, Portland, OR). Generation of three single variable regression curves (one con-

trol, one at 20 wk, and one at 42 wk) of the serum  $T_3$  response to incremental doses of  $T_3$  produced the family of  $T_3$  dose-response curves shown in Fig. 3. Comparisons between the curves were done by two-way analysis of variance with two repeated measures.

## RESULTS

### Serum $T_4$ and $fT_4$ (Table 1)

The mean  $\pm$  SE  $T_4$  value of  $6.0 \pm 0.4$   $\mu\text{g/dl}$  obtained after 20 wk of exposure and the  $T_4$  value of  $6.3 \pm 0.3$   $\mu\text{g/dl}$  after 42 wk of exposure were not different than the control  $T_4$  of  $6.4 \pm 0.4$   $\mu\text{g/dl}$  measured in a warm climate. The  $fT_4$  remained unchanged after 20 and 42 wk of exposure ( $1.7 \pm 0.1$  and  $1.9 \pm 0.1$   $\text{ng/dl}$ , respectively), when these were compared with a control value of  $2.0 \pm 0.1$   $\text{ng/dl}$ .

### $T_3$ RU and $fT_4$ Index (Table 1)

The  $T_3$ RU increased slightly throughout the observation period, from a control value of  $31.2 \pm 1.0\%$  to a value of  $33.9 \pm 0.8\%$  after 42 wk of cold exposure ( $P < 0.05$ ). There were no differences between the values obtained after 20 and 42 wk of polar living. The free  $T_4$  index ( $fT_4$ I) remained unchanged through the study period.

### Serum $T_3$ (Table 2, Figs. 2 and 3)

The serum  $T_3$  values, measured basally and after each incremental dose of oral  $T_3$ , were lower after 20 ( $P = 0.01$ ) and 42 ( $P = 0.05$ ) wk compared with control values by two-way analysis of variance with two repeated measures ( $P = 0.03$ ), when all doses and dates are combined.

### Serum $fT_3$ (Table 2, Fig. 4)

The serum  $fT_3$  after  $T_3$  administration tended to decline after 20 wk; however, this change was not statistically significant. The  $fT_3$  declining trend, which continued during the measurements at 42 wk, was significantly different with respect to date when analyzed by two-way

analysis of variance with two repeated measures ( $P = 0.009$ ).

### $T_3/T_4$ Ratio (Table 1)

The  $T_3/T_4$  ratio measured at each seasonal interval (control, 20 and 42 wk of exposure) before the administration of oral  $T_3$  was unchanged  $25.6 \pm 1.6 \times 10^{-3}$ ,  $25.6 \pm 2.0 \times 10^{-3}$ , and  $24.1 \pm 1.1 \times 10^{-3}$ , respectively.

### TSH Response to TRH (Fig. 5)

**Basal: without oral  $T_3$  administration.** Static TSH serum levels, after 20 and 42 wk of cold exposure, were  $2.9 \pm 0.4$  and  $2.2 \pm 0.3$   $\mu\text{IU/ml}$ , respectively, and these values were not statistically different than the warm control basal value of  $2.1 \pm 0.3$   $\mu\text{IU/ml}$ . However, the integrated TSH response to TRH markedly increased from a control value of  $502 \pm 77$  to  $699 \pm 70$   $\mu\text{IU} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$  after 20 wk, and this value remained elevated with a value of  $688 \pm 67$   $\mu\text{IU} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$  after 42 wk of Antarctic residence ( $P < 0.01$ ). The mean ( $\pm$ SE) paired increases of the TSH response over control non- $T_3$ -treated values were  $54 \pm 14$  and  $52 \pm 14\%$  after 20 and 42 wk, respectively.

**After oral  $T_3$  administration (Fig. 5).** The TSH response was equally attenuated by oral  $T_3$  both before and after cold exposure. The absolute integrated TSH response values during suppression with 25, 50, and 75  $\mu\text{g/day}$  of  $T_3$  remained higher when measured after 20 wk of exposure ( $386 \pm 33$ ,  $183 \pm 15$ ,  $121 \pm 10$   $\mu\text{IU} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$ ) compared with warm climate control values of  $134 \pm 24$ ,  $140 \pm 14$ ,  $96 \pm 4$   $\mu\text{IU} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$  (Fig. 5). The absolute TSH response values after 42 wk ( $373 \pm 50$ ,  $191 \pm 20$ ,  $117 \pm 8$   $\mu\text{IU} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$ , respectively) remained elevated above warm climate controls ( $P < 0.05$ ) but were not different than corresponding values obtained after 20 wk of exposure. However, the mean percentage suppression of the TSH response in our subjects at each dose level of  $T_3$  was not different either before or after cold exposure. Before deployment, the TSH response was suppressed by  $48 \pm 6$ ,  $68 \pm 4$ , and  $77 \pm 4\%$  after respective doses of 25, 50, and 75  $\mu\text{g/day}$ . These decrements did not change

TABLE 1. Serum total  $T_4$ ,  $fT_4$ ,  $T_3$ RU,  $fT_4$ I, and  $T_3/T_4$  without  $T_3$  during control and after 20 and 42 wk of Antarctic residence

| Subject No. | Control                  |                         |                              |             |             | 20 Wk                    |                         |                              |             |             | 42 Wk                    |                         |                              |             |             |
|-------------|--------------------------|-------------------------|------------------------------|-------------|-------------|--------------------------|-------------------------|------------------------------|-------------|-------------|--------------------------|-------------------------|------------------------------|-------------|-------------|
|             | $T_4$ , $\mu\text{g/dl}$ | $fT_4$ , $\text{ng/dl}$ | $T_3/T_4$ , $\times 10^{-3}$ | $T_3$ RU, % | $fT_4$ I, % | $T_4$ , $\mu\text{g/dl}$ | $fT_4$ , $\text{ng/dl}$ | $T_3/T_4$ , $\times 10^{-3}$ | $T_3$ RU, % | $fT_4$ I, % | $T_4$ , $\mu\text{g/dl}$ | $fT_4$ , $\text{ng/dl}$ | $T_3/T_4$ , $\times 10^{-3}$ | $T_3$ RU, % | $fT_4$ I, % |
| 1           | 7.7                      | 2.1                     | 21.5                         | 37.2        | 8.2         | 6.5                      | 1.5                     | 25.8                         | 37.9        | 7.0         | 7.2                      | 2.0                     | 21.5                         | 36.4        | 7.5         |
| 2           | 6.6                      | 1.7                     | 21.5                         | 29.7        | 5.6         | 6.3                      | 2.1                     | 22.7                         | 31.2        | 5.6         | 7.1                      | 1.6                     | 21.1                         | 30.8        | 6.3         |
| 3           | 5.5                      | 1.9                     | 25.1                         | 33.9        | 5.3         | 5.5                      | 1.9                     | 23.8                         | 36.1        | 5.7         | 5.9                      | 2.1                     | 21.9                         | 37.1        | 6.3         |
| 4           | 6.1                      | 2.0                     | 30.0                         | 28.9        | 5.0         | 6.9                      | 2.0                     | 22.5                         | 32.9        | 6.5         | 6.1                      | 1.8                     | 27.7                         | 33.2        | 5.8         |
| 5           | 7.9                      | 2.3                     | 21.6                         | 29.1        | 6.6         | 7.8                      | 2.2                     | 16.9                         | 34.3        | 7.6         | 7.9                      | 2.2                     | 20.8                         | 33.0        | 7.5         |
| 6           | IS                       | IS                      | IS                           | 33.2        | IS          | IS                       | IS                      | IS                           | IS          | IS          | 6.3                      | 2.1                     | 22.2                         | IS          | IS          |
| 7           | 6.9                      | 2.7                     | 23.4                         | 30.9        | 6.1         | 5.7                      | 1.5                     | 27.4                         | 33.4        | 5.4         | 5.6                      | 1.6                     | 24.1                         | 33.7        | 5.4         |
| 8           | 4.8                      | 1.6                     | 27.7                         | 29.1        | 4.0         | 5.0                      | 1.6                     | 30.2                         | 35.9        | 5.1         | 5.3                      | IS                      | 29.8                         | 32.8        | 5.0         |
| 9           | 5.7                      | 1.7                     | 34.0                         | 29.7        | 4.8         | 4.3                      | 1.1                     | 35.3                         | 37.6        | 4.6         | 5.6                      | 1.6                     | 27.9                         | IS          | IS          |
| Means       | 6.4                      | 2.0                     | 25.6                         | 31.2        | 5.7         | 6.0                      | 1.7                     | 25.6                         | 34.9*       | 5.9         | 6.3                      | 1.9                     | 24.1                         | 33.9*       | 6.3         |
| $\pm$ SE    | $\pm 0.4$                | $\pm 0.1$               | $\pm 1.6$                    | $\pm 1.0$   | $\pm 0.5$   | $\pm 0.4$                | $\pm 0.1$               | $\pm 2.0$                    | $\pm 0.8$   | $\pm 0.4$   | $\pm 0.3$                | $\pm 0.1$               | $\pm 1.1$                    | $\pm 0.8$   | $\pm 0.4$   |

$T_4$ , total thyroxine;  $fT_4$ , free thyroxine;  $T_3$ , total triiodothyronine;  $T_3$ RU,  $T_3$  resin uptake;  $fT_4$ I, normalized free  $T_4$  index;  $T_3/T_4$ , total  $T_3$ -to-total  $T_4$  ratio; IS, insufficient sample. \*  $P < 0.05$  compared with control.



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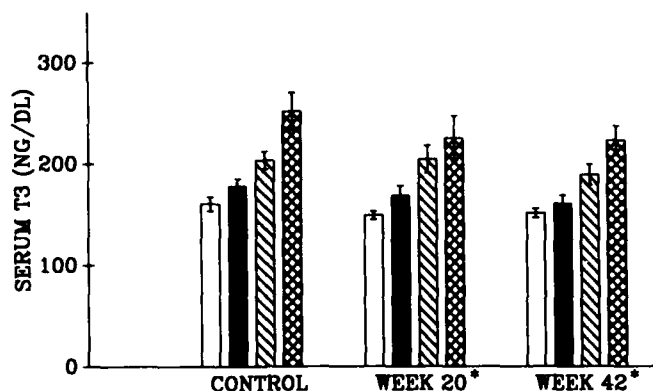


FIG. 2. Serum (mean  $\pm$  SE) levels of total  $T_3$  without  $T_3$   $\square$  and after 25 (■), 50 (▨), and 75  $\mu\text{g/day}$  (▩) of oral  $T_3$  measured as control in a warm climate and after 20 and 42 wk of cold exposure. \*  $P \leq 0.05$  compared with control by using 2-way analysis of variance with respect to treatments 1 (date) and 2 (dose).

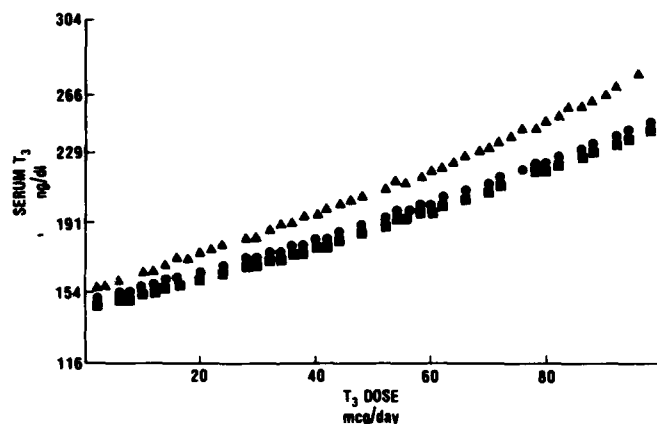


FIG. 3. This figure shows a computer-derived serum dose-response curve of serum  $T_3$  to oral  $T_3$ , calculated in a control climate (▲) and after 20 (●) and 42 wk of cold exposure (■). Dose response of  $T_3$  after 20 and 42 wk is different from basal ( $P < 0.05$ ).

with the same dose of  $T_3$  after 20 and 42 wk. The values were  $44 \pm 2$ ,  $73 \pm 2$ , and  $82 \pm 2\%$ , respectively after 20 wk, and  $47 \pm 3$ ,  $72 \pm 1$ , and  $82 \pm 2\%$ , respectively after 42 wk of Antarctic residence. The calculated dose needed to suppress the TSH response by 50% is  $29 \pm 4 \mu\text{g/day}$  and this dose was not different before or after 42 wk of cold exposure.

#### Exposure and Diet

Even though the amount of consumed calories increased, there was no significant increase in body weight throughout the observation period. Occupationally related activities were similar in both the control and cold environment. All members of the party were similarly exposed to the cold environment ( $2.8 \pm 0.7 \text{ h/day}$ ). There was no correlation between an individual's mean exposure time per day and any hormonal changes noted throughout the 42 wk of polar living.

#### DISCUSSION

The population residing in the polar latitudes has increased recently since the discovery of fossil fuel de-

posits in these regions. The environments near the geographic poles are marked by prolonged periods of darkness or sunlight and extended winters with severely cold temperatures. Adaptive responses of serum thyroid hormones in a cold environment have received considerable attention in the past, and in this paper we extend these observations by measurement of the serum  $T_3$  response to oral  $T_3$  and the pituitary response to this hormone before and after Antarctic residence.

Serum total and free  $T_4$  levels remained unchanged in our study group, consistent with our earlier findings (27). Unchanged serum levels of  $T_4$  during seasonal variation and during continuous cold exposure have been reported in most (17, 23) but not all (35) previous studies. However, in hypothyroid patients on  $T_4$  replacement, Konno (18) showed that serum  $T_4$  tended to be lower during the Japanese winter when compared with paired summer controls.

The serum total and free  $T_3$  values (after  $T_3$  administration) in the present study were lower when measured after 42 wk of cold exposure compared with basal warm climate controls, confirming our earlier description (27). Vining et al. (39) have published data consonant with our findings in an Australian Antarctic cohort. Their subjects had lower serum  $T_3$  values in winter compared with summer; however, they did not measure either  $fT_3$  or basal values before departing for Antarctica. Dessypris et al. (9) observed a lower serum total  $T_3$  in the inhabitants of the Arctic regions of Finland, compared with their matched southern counterparts. In contrast to these findings Nagata et al. (23) have reported increased levels of serum total  $T_3$  in the natives of Kijimadaira, Japan, in winter compared with values obtained during a warm summer. This group of natives, however, was poorly clothed and lived in inadequate housing that resulted in nearly continuous cold exposure during the group's 3-mo winter. Our subjects varied from this group in that they were well clothed and exposed intermittently to a cold environment for 11 continuous months.

The augmented TSH response to TRH observed in the present study confirms our earlier observations (27). This test of TSH reserve is reliably reproducible (6–12% cv) in the same subjects (17, 31). An elevated nonstimulated serum TSH in Antarctic residents and in the residents of northern Finland has been observed (9, 39). However, the insensitivity of our TSH assay in the low ranges may have precluded us from detecting basal nonstimulated differences. Others have not been able to detect a change in the seasonal TSH response to TRH in normal subjects residing in midlatitude temperate climates (17, 31). The differences between these studies and our own are most likely a result of the severity of cold environment in the polar latitudes compared with midlatitude temperate climates.

The possible mechanisms to account for decreased serum  $T_3$  and  $fT_3$  levels include decreased production of  $T_3$  (4, 40), increased metabolic clearance of  $T_3$  (2, 5, 33), and decreased absorption of oral  $T_3$  after chronic cold exposure and/or circadian variation (24). Any postulated mechanism must take into account a balanced  $T_4$  economy, because  $T_4$  was unchanged.

TABLE 2. Serum total and free  $T_3$  with  $T_3$  administration during control and after 20 and 42 wk of Antarctic residence

| Subject No.         | Control     |              |              |              | 20 Wk*      |              |              |              | 42 Wk*      |              |              |              |
|---------------------|-------------|--------------|--------------|--------------|-------------|--------------|--------------|--------------|-------------|--------------|--------------|--------------|
|                     | Dose No.    |              |              |              | Dose No.†   |              |              |              | Dose No.†   |              |              |              |
|                     | 0           | 25           | 50           | 75           | 0           | 25           | 50           | 75           | 0           | 25           | 50           | 75           |
| Total $T_3$ , ng/dl |             |              |              |              |             |              |              |              |             |              |              |              |
| 1                   | 166         | 218          | 187          | 228          | 168         | 201          | 186          | 237          | 155         | 161          | 209          | 206          |
| 2                   | 142         | 192          | 229          | 309          | 143         | 197          | 240          | 293          | 150         | 188          | 244          | 260          |
| 3                   | 138         | 156          | 183          | 217          | 131         | 150          | 176          | 179          | 129         | 139          | 166          | 184          |
| 4                   | 183         | 187          | 233          | 294          | 155         | 190          | 272          | 263          | 169         | 196          | 193          | 227          |
| 5                   | 171         | 173          | 241          | 341          | 132         | 175          | 253          | 318          | 164         | 184          | 211          | 312          |
| 6                   | 151         | 181          | 195          | 276          | 148         | 182          | 204          | 262          | 140         | 158          | 198          | 234          |
| 7                   | 161         | 167          | 210          | 219          | 156         | 162          | 171          | 197          | 135         | 148          | 160          | 200          |
| 8                   | 133         | 149          | 174          | 196          | 151         | 141          | 166          | 128          | 158         | 142          | 154          | 202          |
| 9                   | 194         | 176          | 170          | 180          | 152         | 116          | 165          | 144          | 156         | 125          | 162          | 174          |
| Means $\pm$ SE      | 160 $\pm$ 7 | 178 $\pm$ 7  | 202 $\pm$ 9  | 251 $\pm$ 19 | 148 $\pm$ 4 | 168 $\pm$ 9  | 204 $\pm$ 14 | 225 $\pm$ 22 | 151 $\pm$ 4 | 160 $\pm$ 8  | 189 $\pm$ 10 | 222 $\pm$ 14 |
| Free $T_3$ , pg/dl  |             |              |              |              |             |              |              |              |             |              |              |              |
| 1                   |             | 486          | 472          | 541          |             | 494          | 478          | 606          |             | 468          | 531          | 572          |
| 2                   |             | 455          | 494          | 581          |             | 376          | 502          | 701          |             | 422          | 561          | IS           |
| 3                   |             | 395          | 511          | 610          |             | 403          | 463          | 498          |             | 350          | 391          | 482          |
| 4                   |             | 449          | 533          | 659          |             | 460          | 647          | 636          |             | 418          | 418          | 525          |
| 5                   |             | IS           | 530          | 643          |             | IS           | 547          | 764          |             | IS           | 505          | 723          |
| 6                   |             | 444          | 382          | 579          |             | 397          | 398          | 515          |             | 288          | 375          | 432          |
| 7                   |             | 340          | 463          | 440          |             | IS           | 407          | 472          |             | IS           | 407          | 441          |
| 8                   |             | 382          | 402          | 492          |             | 374          | 415          | IS           |             | IS           | 367          | 483          |
| 9                   |             | 433          | 340          | IS           |             | 325          | 438          | 318          |             | 269          | 360          | 445          |
| Means $\pm$ SE      |             | 423 $\pm$ 17 | 459 $\pm$ 23 | 568 $\pm$ 26 |             | 404 $\pm$ 21 | 477 $\pm$ 27 | 564 $\pm$ 50 |             | 369 $\pm$ 33 | 435 $\pm$ 26 | 513 $\pm$ 34 |

Oral triiodothyronine ( $T_3$ ) doses were measured in  $\mu\text{g}/\text{day}$ . IS, insufficient sample. \*  $P < 0.05$  compared with control; †  $P < 0.05$  for each dose compared with control (analysis by 2-way ANOVA with 2 repeated measures).

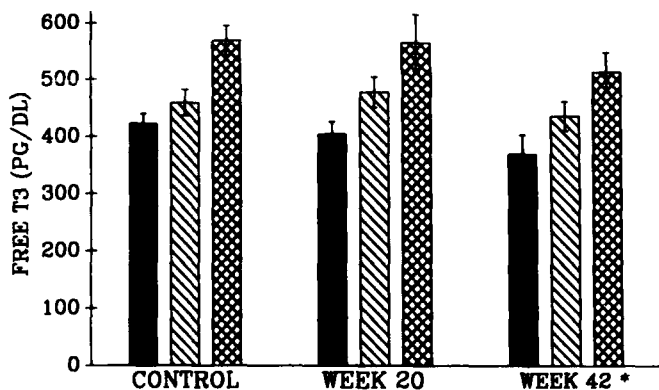


FIG. 4. Serum (mean  $\pm$  SE) free  $T_3$  was measured as in Fig. 2, after 25 (■), 50 (▨), and 75  $\mu\text{g}$  (▩) of oral  $T_3$ . \*  $P < 0.05$  compared with control by using 2-way analysis of variance with respect to date as a treatment.

We feel that decreased production of  $T_3$  as found in the sick euthyroid syndrome or during hypocaloric feeding cannot account for our findings because serum  $T_3$  in our subjects was not "normalized" after oral  $T_3$  administration (4, 16, 40). Additionally, if decreased peripheral production of  $T_3$  was a significant contributing factor in this setting, one should observe a lowering of the  $T_3/T_4$  ratio and an increase in reverse  $T_3$ , neither of which has been noticed in the previous group observed in this setting (27). Also, the increased caloric consumption seen in our subjects should lead to increased serum  $T_3$  levels as demonstrated by Danforth et al. (6). However, the present study documented lower serum  $T_3$  levels, leading us to implicate other factors to explain the changes

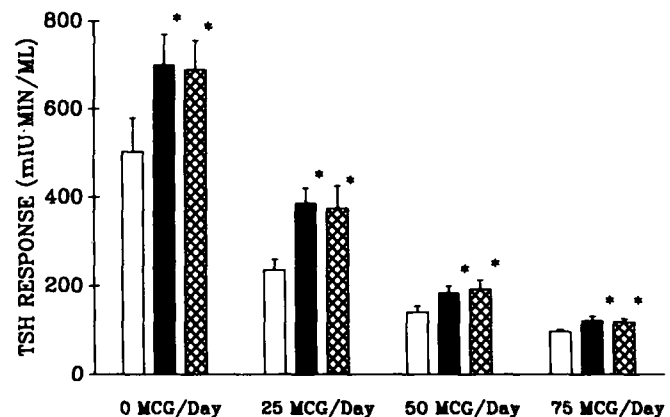


FIG. 5. Integrated thyrotropin (TSH) response to thyrotropin-releasing hormone (mean  $\pm$  SE) measured in 9 subjects before and after 25, 50, and 75  $\mu\text{g}/\text{day}$  of  $T_3$ . This response was measured in a warm control climate (□) and after 20 (▨) and 42 wk (▩) cold exposure. There was no difference between results obtained after 20 and 42 wk cold exposure. MCG, microgram. \*  $P < 0.05$  compared with warm control climate values.

described.

Increased degradation of  $T_3$  and  $T_4$  has been described in rodent models chronically exposed to cold (2, 33). Iodothyronine disposal may be increased by a number of mechanisms including nonspecific hepatic induction as occurs with phenytoin (Dilantin) (36) or catecholamines (22) or via increased enterohepatic circulation (5). It is interesting to note that elevated plasma catecholamine levels do occur during acute cold exposure (25). If increased disposal of  $T_3$  plays a significant role in our observations, we would expect to find lowered serum  $T_3$

after administered oral  $T_3$ , a finding we describe herein. Ingbar et al. (15) suggest such a mechanism during severe and prolonged human cold exposure by using iodine clearance studies, when they described increased thyroïdal iodide turnover in cold-exposed human subjects. Also, in support of a proposed clearance mechanism, Konno et al. (18) showed an augmented TSH response to TRH and somewhat lowered serum  $T_4$  in replaced hypothyroid subjects during the Japanese winter when compared with summer controls. Either increased peripheral disposal of  $T_4$  or decreased  $T_4$  absorption might have accounted for these observations. Similarly, Rastogi et al. (30) reported increased urinary  $fT_3$  and  $fT_4$  levels in paired subjects studied in winter compared with summer without changes in serum total  $T_3$  or total  $T_4$ , suggesting either a seasonal change in the binding of these thyroid hormones and/or a small decrease in the half-life of thyroid hormones in winter.

Although we cannot exclude decreased absorption of orally administered  $T_3$  as a possible mechanism, this explanation is unlikely in that  $T_3$  is consistently well absorbed by the normal gastrointestinal mucosa (10, 32, 41). Circadian nocturnal elevations in the  $T_3/T_4$  ratio have been described by Nimalasuriya et al. (24). However, we do not feel that the changes in light exposure affected our findings, in that we describe a decrease in  $T_3$  and no change in the  $T_3/T_4$  ratio during both the dark (42-wk) and light (20-wk) period without a significant difference between these measurements.

Mechanisms by which the augmented TSH response occurs may include a circadian or diurnal variation in human TSH or  $T_3$  (24, 30). Our data, however, were all obtained at the same clock time and show no difference between exposure to 24 h of daylight (after 20 wk of exposure) or 24 h of darkness (after 42 wk of exposure) on this response. The physical and social isolation found during Antarctic duty is a possible but somewhat unlikely contributing factor based on the known alterations in thyroid economy that occurs during depression. In this emotional setting the TSH response to TRH is decreased, not increased as we have found (7, 20). However, we can find no specific studies that have investigated thyroid function during confinement alone. Additionally, an increase in iodine in the diet may increase the TSH response to TRH, as Vagenakis et al. (37) describe, with an associated decrease in serum  $T_4$  and  $T_3$  as well as an elevation in unstimulated TSH. However, in our present study, no change in serum  $T_4$  or basal levels of TSH were observed, and iodine intake did not change to our knowledge.

Sawin et al. (32) have described a 50% decrease in the TSH response to TRH measured 2 h after a mean dose of 29  $\mu\text{g}/\text{day}$  of oral  $T_3$ . Our findings that  $29 \pm 4 \mu\text{g}/\text{day}$  suppress 50% of the TSH response both in a warm control climate and a polar setting are similar and in agreement with Sawin et al. (32). Thus there appears to be no change in the hypothalamic pituitary sensitivity to oral  $T_3$  after cold exposure when compared with either basal warm climate controls or previously published controls (32). The absence of a change in the sensitivity of the hypothalamic pituitary axis coupled with lower serum

$T_3$  and  $fT_3$  levels before and after oral  $T_3$  administration implies an increased metabolic clearance of  $T_3$  and a decreased negative feedback on TSH secretion by circulating  $T_3$ . The specific metabolic implications of these findings and how they may relate to human environmental adaptation require further study.

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