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Relationship Between Changes in Serum Thyrotropin and Total and Lipoprotein Cholesterol With Prolonged Antarctic Residence

Robert R. Harford, H. Lester Reed, Michael T. Morris, Ismael E. Sapien, Robert Warden, and Michele M. D'Alesandro

Antarctic residence (AR) is associated with a 50% increase in the thyrotropin (TSH) response to TSH-releasing hormone (TRH) and an expanded triiodothyronine (T_3) distribution volume and extravascular hormone pool, collectively called the polar T_3 syndrome. To investigate the possible biologic significance of this syndrome, we studied the relationship between nonstimulated TSH and serum lipid profiles in nine subjects, once while in California and monthly during 9 months of AR. We measured serum levels of TSH, total thyroxine (TT_4), free T_4 (FT_4), total T_3 (TT_3), free T_3 (FT_3), thyroid-binding globulin (TBG), total cholesterol (T-CHOL), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), dietary cholesterol (D-CHOL), dietary fat (D-FAT), and dietary kilocalories at each month. The paired mean monthly change from baseline was used to determine significance. The group's mean levels of TSH ($\sim 30\%$), TBG ($\sim 16\%$), T-CHOL ($\sim 4\%$), HDL-C ($\sim 10\%$), and D-CHOL ($\sim 19\%$) increased with AR ($P < .05$). Small but significant decreases ($P < .05$) were observed in the mean changes of TT_4 ($\sim 8\%$), FT_4 ($\sim 6\%$), and TT_3 ($\sim 6\%$). FT_3 , D-FAT, dietary kilocalories, body weight, TG, and the calculated low-density lipoprotein (LDL-C) were unchanged with AR. A significant rate of change ($P < .05$) during AR was also calculated from the slope of a fitted logarithmic function for TSH ($0.96 \pm 0.31 \text{ mU} \cdot \text{L}^{-1} \cdot \text{mo}^{-1}$), TBG ($61.19 \pm 12.29 \text{ nmol} \cdot \text{L}^{-1} \cdot \text{mo}^{-1}$), TT_3 ($0.09 \pm 0.04 \text{ nmol} \cdot \text{L}^{-1} \cdot \text{mo}^{-1}$), TT_4/TBG ($-0.06 \pm 0.01/\text{mo}$), TT_3/TBG ($-8.49 \pm 1.98 \times 10^{-4}/\text{mo}$), and TG ($-0.33 \pm 0.15 \text{ mmol} \cdot \text{L}^{-1} \cdot \text{mo}^{-1}$). Individual TSH changes with AR for the nine subjects varied and were highly correlated with paired changes in T-CHOL ($r = .628$, $n = 81$, $P < .001$) and similar changes in LDL-C ($r = .658$, $n = 81$, $P < .001$). No correlation was found between D-CHOL and serum lipid levels. Our study suggests that AR is associated with asymptomatic environmentally related thyroid alterations that correlate with metabolic markers (T-CHOL and LDL-C) of thyroid hormone activity on hepatic and adipose tissues.

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SEASONAL EPIDEMIOLOGIC studies suggest that both serum cholesterol concentration and coronary heart disease mortalities are higher in winter than in corresponding summer months.^{1,2} In a cohort of 1,446 hypercholesterolemic 35- to 59-year-old men on a standard diet, higher serum cholesterol levels were repeatedly seen near December compared with June over a period of 7 to 10 years.³ Statistics from death certificates in England and Wales have also indicated that coronary and cerebrovascular disease mortalities, which accounted for approximately half of the annual excess deaths, occurred during the winter months.^{4,5} Although this environmentally related cyclic seasonal variation in serum cholesterol levels and cardiovascular mortality has been observed for many years, the etiologic mechanisms responsible for this phenomenon are still largely unknown. More studies under various environmental conditions are needed to better understand this intriguing observation.

Environmental factors associated with extended Antarctic residence (AR) may mimic those found in a prolonged Temperate Zone winter. For example, circannual cycling of thyroid hormone kinetics in midlatitude residents⁶ may compare with the recently described polar T_3 syndrome,⁷ although the metabolic significance of both these reports is uncertain. After 5 months' AR, triiodothyronine T_3 production and distribution double and the thyrotropin (TSH) response to TSH-releasing hormone (TRH) increases by 50%, whereas the pituitary sensitivity to T_3 remains unchanged.^{7,8} Since serum cholesterol level is known to reflect adipose and hepatic effects of thyroid hormone imbalance,⁹ we chose to study the relationship between environmentally associated changes in thyroid hormone status and lipid profiles during AR. To investigate this association, we measured the monthly changes from predeployment values for serum total and lipoprotein cholesterol for 9 months in

nine subjects residing in McMurdo, Antarctica, and correlated these changes with a sensitive assay of serum TSH, which is considered a reliable index of pituitary thyroid hormone status.¹⁰ Dietary intake of cholesterol (D-CHOL) and fat (D-FAT) and changes in body weight were also measured. We predict that if the previously described environmentally induced thyroid hormone changes are metabolically significant, both TSH and lipid homeostasis should covary with AR, as they often do in subclinical hypothyroidism.¹¹

SUBJECTS AND METHODS

Nine healthy members (seven men, two women; seven white, one black, and one Hispanic) of the U.S. Navy 1989-90 annual winter-over contingent at McMurdo, Antarctica, were studied, with each individual serving as his or her own control. Before deployment, subjects were studied once in Port Hueneme, CA

From the Thermal Stress/Adaptation Program, Naval Medical Research Institute, Bethesda, MD; and the Endocrine Service, Madigan Army Medical Center, Tacoma, WA.

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Address reprint requests to Robert R. Harford, MD, Thermal Stress Program, Code 427, Naval Medical Research Institute, 8901 Wisconsin Ave, Bethesda, MD 20889-5607.

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(latitude 34°03' N, longitude 118°14' W) in August 1989 to obtain basal values for comparison with data collected during the AR. After arrival at McMurdo, Antarctica (77°51' S, 166°37' E), in October 1989, subjects were studied each month from December 1989 (2 months after arrival) through August 1990. The protocol was approved by our institution's committee for the protection of human subjects, and each volunteer gave written informed consent.

All participants were within the weight and body fat standards for the U.S. Navy (male $\leq 22\%$, female $\leq 32\%$ body fat) during the entire study period. The age range of the group was 21 to 35 years with a median of 31 years, and the average height was 175 ± 2.41 cm. Weight measurements were obtained monthly on the morning of the study, and subjects were weighed in cotton shirts, pants, underwear, and socks, without shoes. An internationally used U.S. Navy diet with a minimum of 150 $\mu\text{g/d}$ iodine was consumed during the entire study period. A 3-day dietary diary was completed before each monthly blood collection, and the dietary intakes of cholesterol and fat were analyzed from these diaries (N Squared Nutritionist III, Salem, OR). No subject was chronically medicated (oral contraceptives included), and the women maintained regular menstrual patterns by history. Subjects experienced 24 hours of total daylight for 5 months in the summer and 24 hours of total darkness for 4 months in the winter. The mean daily temperatures ranged from a high of $-2.93^\circ \pm 0.46^\circ\text{C}$ in January 1990 to a nadir of $-28.06^\circ \pm 1.38^\circ\text{C}$ in August 1990. Subjects moved between buildings for work, meals, and recreation; consequently, the average outdoor exposure was 0.83 ± 0.07 h/d. Fluorescent lighting was used throughout the study period indoors, and the ambient indoor temperature ranged between 5° and 22°C near the floor to between 12° and 25°C at the level of the head.

Serum lipid, thyroid hormone, and binding protein concentrations were analyzed from postabsorptive (10 to 12 hours after last food intake) blood samples collected in conjunction with a study of T_3 kinetics¹² involving the monthly ingestion of 50 μg (76.8 nmol) Cytomel (T_3 ; Smith Kline & French Lab, Philadelphia, PA); this technique has been described elsewhere.⁶ Levels of TSH, total thyroxine (TT_4), free T_4 (FT_4), total T_3 (TT_3), free T_3 (FT_3), and thyroid-binding globulin (TBG) were measured from blood samples collected before the ingestion of Cytomel. Total (T-CHOL) and high-density lipoprotein (HDL-C) cholesterol and triglyceride (TG), on the other hand, were analyzed from blood samples drawn 60 minutes after Cytomel intake because of insufficient serum from the initial blood samples. To determine whether a single oral Cytomel dose may acutely alter T-CHOL concentrations, serum obtained before and every 30 minutes up to 2 hours after Cytomel ingestion was assayed for T-CHOL in three normal subjects (two men, one woman). There were no differences in T-CHOL concentrations between the samples [$F_{(2,15)} = 0.915$, $P = .471$], and thus we report the values as postabsorptive measures. The likelihood of monthly oral doses of this quantity of Cytomel increasing the next month's TSH values is also remote. In an analogous coexistent kinetic study lasting 1.5 years at our institution, serum TSH values were not progressively elevated when evaluated monthly, 30 days after the last oral Cytomel (76.8 nmol) ingestion.⁶ Additionally, we have reported that serum TSH level is unchanged 2 weeks after this same dose of T_3 even when repeating these biweekly intervals three times over 2 months.¹³

Levels of TSH (normal, 0.6 to 6 mU/L), TT_4 (normal, 58 to 161 nmol/L), FT_4 by analog method (normal, 10 to 26 pmol/L), TT_3 (normal, 1.3 to 2.8 nmol/L), FT_3 by analog method (normal, 2.2 to 6.8 pmol/L), and TBG (normal, 167 to 386 nmol/L) for any given subject were measured on the same day and in the same assay using commercially available kits (Diagnostic Products, Los Angeles, CA). The kits had a within-day percent coefficient of variation

(%CV) of less than 5.0% and a between-day %CV of less than 6.0%.

Serum levels of T-CHOL, TG, and HDL-C were determined with a Kodak Ektachem DT 60 analyzer (serial no. 9839, Eastman Kodak, Rochester, NY) capable of achieving precisions (within-assay and between-day %CV) better than the ideal precision goals ($\leq \pm 3\%$ CV) established by the National Cholesterol Education Program.¹⁴ Mean within-assay %CVs for T-CHOL (2.7%), TG (2.3%), and HDL-C (5.6%) and mean between-day %CVs for T-CHOL (2.6%), TG (1.9%), and HDL-C (7.3%) were in agreement with the manufacturer's reported guideline values. Very-low-density lipoprotein (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were calculated by the accepted formulas ($\text{VLDL-C} = \text{TG}/5$; $\text{LDL-C} = \text{CHOL} - \text{HDL} - \text{VLDL}$)¹⁵ and then converted to international units.

Statistical analysis was performed by one-way ANOVA for repeated measures with a randomized block design (ANOVA1R), paired t statistic, and, where indicated, by linear and logarithmic regression. When subjects' paired monthly mean change did not vary significantly with AR, the 9 months' changes were pooled into a single mean change for the AR period. However, if there were variations between monthly mean changes, significance was tested by least-squares linear and logarithmic regression for structure to the change. To further test the group's mean changes, individual regression was computed and supported the group's findings. Data are expressed as means $\pm$ standard error with significance set at $P < .05$ unless otherwise indicated.

RESULTS

Thyroid Hormones

TSH and TBG means increased by $\sim 30\%$ ($P < .01$) and $\sim 16\%$ ($P < .05$), respectively, whereas TT_4 , FT_4 , TT_3 , TT_4/TBG , and TT_3/TBG decreased by $\sim 8\%$ ($P < .001$), $\sim 6\%$ ($P < .001$), $\sim 6\%$ ($P < .01$), $\sim 14\%$ ($P < .01$), and $\sim 14\%$ ($P < .001$), respectively (Table 1). Least-squares regression analysis using a natural logarithmic function (equation: $Y = [\text{slope} \cdot \ln(\text{month})] + Y\text{-intercept}$) also revealed significant regressive structure (Table 1) to the changes in TSH ($P < .05$), TBG ($P < .01$), TT_3 ($P < .05$), TT_4/TBG ($P < .001$), and TT_3/TBG ($P < .01$). Although there were considerable individual variations, these regressions were confirmed when individual slopes and means were computed. TSH level increased at a rate of 0.96 ± 0.31 mU $\cdot$ L⁻¹ $\cdot$ mo⁻¹ ($n = 9$, $r = .7572$) and TBG level at a rate of 61.19 ± 12.29 nmol $\cdot$ L⁻¹ $\cdot$ mo⁻¹ ($n = 9$, $r = .8830$). TT_4/TBG decreased at a rate of $-0.06 \pm 0.01/\text{mo}$ ($n = 9$, $r = -.9199$) and TT_3/TBG at a rate of $-8.49 \pm 1.98 \times 10^{-4}/\text{mo}$ ($n = 9$, $r = -.8507$). Interestingly, although TT_3 concentration decreased with AR, its rate of change was positive (0.09 ± 0.04 nmol $\cdot$ L⁻¹ $\cdot$ mo⁻¹; $n = 9$, $r = .6824$). This suggests that the decrease in TT_3 levels was not progressive and most likely occurred within the initial months of AR and then returned to basal values with time.

Serum Lipids

The group's mean T-CHOL level increased by $\sim 4\%$ ($P < .001$) and HDL-C level by $\sim 10\%$ ($P < .001$). Although LDL-C, TG, and VLDL-C values tended to increase, their differences from basal values were not statistically significant (Table 2).

Table 1. Thyroid Hormone and Carrier Protein Changes With AR

Parameter	Basal	Mean Monthly Change From Basal (n = 9)	Rate of Change From Basal (n = 9)
TSH (mU/L)	2.62 ± 0.45	0.79 ± 0.21†	0.96 ± 0.31 mU · L ⁻¹ · mo ⁻¹ *
TT ₄ (nmol/L)	81.32 ± 6.92	-6.41 ± 1.03‡	-0.77 ± 2.29 nmol · L ⁻¹ · mo ⁻¹
FT ₄ (pmol/L)	14.49 ± 1.31	-0.92 ± 0.16‡	0.52 ± 0.30 pmol · L ⁻¹ · mo ⁻¹
TT ₃ (nmol/L)	1.70 ± 0.07	-0.10 ± 0.02†	0.09 ± 0.04 nmol · L ⁻¹ · mo ⁻¹ *
FT ₃ (pmol/L)	4.26 ± 0.23	0.25 ± 0.19	0.63 ± 0.36 pmol · L ⁻¹ · mo ⁻¹
TBG (nmol/L)	236.2 ± 16.0	36.98 ± 11.68*	61.19 ± 12.29 nmol · L ⁻¹ · mo ⁻¹ †
TT ₄ /TBG (nmol/nmol)	0.34 ± 0.03	-0.05 ± 0.01†	-0.06 ± 0.01/mo‡
TT ₃ /TBG (nmol/nmol)	7.29 ± 4.78 × 10 ⁻³	-9.90 ± 1.68 × 10 ⁻⁴ ‡	-8.49 ± 1.98 × 10 ⁻⁴ /mo‡

NOTE. Data represent the basal value ± SE obtained in California and the mean and rate of change from basal for thyroid hormone and binding protein levels of nine subjects during 9 months of AR. The rate constant is determined by the natural logarithmic function of a single dependent variable regression where month is the independent variable (equation: $Y = \text{slope} \cdot \ln(X) + Y\text{-intercept}$).

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

Dietary and Weight Analysis

D-CHOL mean monthly change from basal value with AR was significantly different from the control value ($P < .05$). D-CHOL basal mean intake was 342.44 ± 42.94 mg, and the mean change with AR was 64.37 ± 18.37 mg (~19% increase). Body weight and caloric and D-FAT intake remained unchanged throughout the study. The basal mean body weight was 78.22 ± 2.16 kg, and the mean change with AR was 0.51 ± 0.31 kg. Caloric and D-FAT intake mean changes with AR were -55 ± 71.77 kcal and 1.69 ± 0.79 g, and the basal means were $2,442.67 \pm 208.66$ kcal and 35.33 ± 2.33 g.

Correlation of Variables

The group's monthly TSH level mean changes from basal with AR were directly related to similar changes in serum levels of LDL-C ($n = 9$, $r = .7652$, $P = .0069$) but not T-CHOL ($n = 9$, $r = -.3293$, $P = .1916$). However, further investigation of the individuals' monthly changes (Figs 1 and 2) revealed direct correlations between TSH and LDL-C (0.27 ± 0.03 mmol LDL-C/mU TSH; $n = 81$, $r = .6583$, $P < .001$) and TSH and T-CHOL (0.27 ± 0.04 mmol T-CHOL/mU TSH; $n = 81$, $r = .6279$, $P < .001$). This observation suggests that the pooled monthly means minimize the individuals' T-CHOL changes. Thus to better appreciate the TSH and lipid correlations we chose to present the relationships in terms of individuals' monthly

changes. No associations were found among TSH and the other serum lipids. Although D-CHOL intake increased with AR, no correlations were observed between D-CHOL and serum T-CHOL ($n = 81$, $r = .0885$), LDL-C ($n = 81$, $r = .0110$), or the rest of the serum lipids.

DISCUSSION

Correlations between serum lipid levels and variables with seasonal environmental variations such as physical activity, diet, hemostasis, and blood pressure have been investigated in humans residing in Antarctica.^{16,17} The accepted link between thyroid hormone status and lipid metabolism is also well known.¹⁸ Since thyroid hormone alterations with extended AR have only recently been clarified,⁷ no study, to the best of our knowledge, examining the relationship between thyroid status and lipid homeostasis with AR has been reported.

In this study, we have demonstrated that AR is associated with thyroid status alterations that covary with serum lipid changes. Subjects in this study experienced a significant increase in serum levels of TSH, TBG, T-CHOL, and HDL-C, with meaningful decreases in serum TT₄, FT₄, TT₃, TT₄/TBG, and TT₃/TBG (Tables 1 and 2). The TSH changes were also strongly correlated with T-CHOL and LDL-C changes (Figs 1 and 2). Although both HDL-C and D-CHOL levels increased with AR, no correlation was observed between those changes and TSH. Furthermore,

Table 2. Serum Lipid Changes With AR

Parameter	Basal	Mean Monthly Change From Basal (n = 9)	Rate of Change From Basal (n = 9)
T-CHOL (mmol/L)	4.79 ± 0.30	0.17 ± 0.02‡	-0.07 ± 0.05 mmol · L ⁻¹ · mo ⁻¹
LDL-C (mmol/L)	2.91 ± 0.28	0.02 ± 0.03	0.08 ± 0.07 mmol · L ⁻¹ · mo ⁻¹
HDL-C (mmol/L)	1.24 ± 0.09	0.12 ± 0.02‡	1.39 ± 0.04 × 10 ⁻³ mmol · L ⁻¹ · mo ⁻¹
TG (mmol/L)	1.41 ± 0.25	0.08 ± 0.09	-0.33 ± 0.15 mmol · L ⁻¹ · mo ⁻¹ *
VLDL-C (mmol/L)	0.28 ± 0.05	0.02 ± 0.02	-0.07 ± 0.03 mmol · L ⁻¹ · mo ⁻¹ *

NOTE. Data represent the basal value ± SE obtained in California and the mean and rate of change from basal for TG, T-CHOL, LDL-C, HDL-C, and VLDL-C of nine subjects during 9 months of AR. The rate constant is determined by the natural logarithmic function of a single dependent variable regression where month is the independent variable (equation: $Y = \text{slope} \cdot \ln(X) + Y\text{-intercept}$).

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

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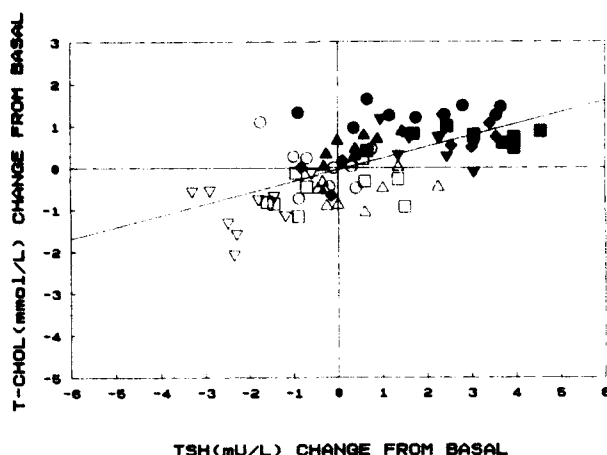


Fig 1. Correlation between the nine-monthly changes from basal values in TSH and T-CHOL with AR for nine subjects. Each subject is represented by a separate symbol; 0.27 ± 0.04 mmol T-CHOL/mU TSH, $n = 81$, $r = .6279$, $P < .001$.

no relationship was detected between the D-CHOL changes and serum lipid changes.

The serum lipid data that we report are in concordance with serum lipid findings of earlier Antarctic studies. Serum T-CHOL level has been reported to increase with AR in one Australian expeditionary cohort.¹⁶ In another Australian study, Antonis et al¹⁷ also failed to demonstrate an overall significant change in LDL-C, HDL-C, and TG with AR. Unlike Antonis et al,¹⁷ we report an overall increase in HDL-C level, but this may be due to differences in analysis technique or the population sample used (both men and women served as subjects in our study).

Some of the thyroid changes that we present are also consistent with the findings of our earlier Antarctic studies. Reed et al^{7,19} have reported increases in the TSH response to TRH, decreases in TT₃, and unchanged FT₃. Unlike those earlier studies where no change in TT₄, FT₄, TBG, and nonstimulated TSH were found, we now report small

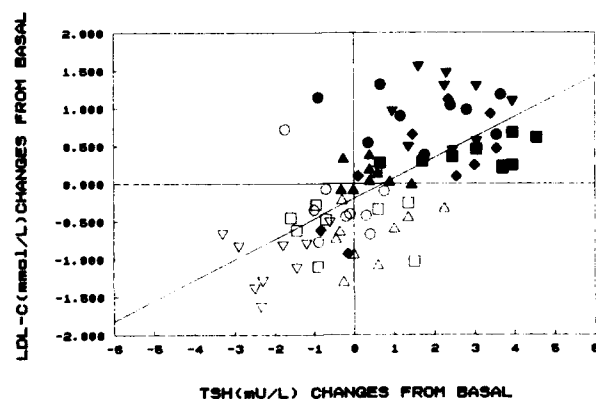


Fig 2. Correlation between the nine-monthly changes from basal values in TSH and LDL-C with AR for nine subjects. Each subject is represented by a separate symbol; 0.27 ± 0.03 mmol LDL-C/mU TSH, $n = 81$, $r = .6583$, $P < .001$.

decreases in TT₄ and FT₄ and increases in nonstimulated TSH and TBG. These variations may be attributed to methodologic differences such as our increased testing frequency (monthly instead of semiannually), utilization of analog radioimmunoassays instead of dialysis assays for FT₄ and FT₃ testing, and improved assay sensitivities. The thyroid hormone and carrier protein rate of change from basal (Table 1) further suggests that the changes with AR are variable (some are progressive while others are not) and explains why there may be data differences depending on the methodology used (eg, monthly instead of sporadic testing). Vining et al²⁰ also reported increasing TSH concentrations in an Australian cohort with AR. However, unlike this study, they did not have predeployment basal values for comparison. Nevertheless, when compared with basal values obtained after arrival in Antarctica, serum TSH levels increased with AR.²⁰

Of the factors reported to influence serum T-CHOL level that were considered in this study (age, diet, body weight, and thyroid status),^{21,22} only thyroid status alterations offer a likely explanation for the T-CHOL change that we now present. Despite our earlier reports of increased energy intake without body weight changes with AR,^{7,8,19} the young healthy adults in our present study displayed no change in body weight or dietary intake of calories and fat throughout the study period. This discrepancy may be due to differences in the dietary history-taking techniques; the dietary interviews were more detailed in our previous studies.⁷ Although dietary cholesterol intake was increased, no correlation between the D-CHOL change and serum lipid changes were observed. In addition, an increase in the D-CHOL intake seemed unlikely to account for the striking relationship between serum TSH and T-CHOL and LDL-C levels.

Since the serum thyroid hormone and lipid findings are not pathologically abnormal, they do not fit the classic presentation of subclinical hypothyroidism. However, the asymptomatic compensatory increase in TSH level with an associated elevation in T-CHOL level is suggestive of a partially corrected subclinical hypothyroidism condition and offers a likely explanation for the correlation between TSH and T-CHOL and LDL-C levels. This is further supported by the small but significant decrease in TT₄ and FT₄ levels (Table 1). Because this study was not designed to identify the mechanism responsible for the thyroid and lipid association that we present, we cannot give a definite explanation about the involved mechanism. However, since thyroid status is known to influence hepatic and adipose tissue metabolism of lipids,^{9,22} we can only hypothesize that the increase in serum T-CHOL level is due to a decreased thyroid hormone activity within these tissues.

Although presently undefined, our current data and earlier reports suggest a possible environmental explanation for the TSH increases with AR that we present. Adult males exposed to extreme arctic cold for 7 days have been reported to have elevations in serum levels of TSH.²³ Furthermore, either living in cold environments²⁴ or being repeatedly exposed for as little as 2 weeks in experimental

cold-chamber studies¹³ will increase T₃ requirements and change thyroid hormone homeostasis. Nutritional, pharmacologic, and pathologic explanations for the thyroid status alterations in this study are unlikely. The subjects were healthy euthyroid-appearing men and women and were not chronically medicated or malnourished. Sampling protocol is also an unlikely cause since similar procedures with a comparable group in an analogous 18-month study in Bethesda, MD, failed to demonstrate any protocol-related TSH changes.⁶

In most species, an important synchronizer of daily and seasonal physiologic rhythms is the change in the light-dark cycle.²⁵ Since we did not measure the effect of Antarctic photoperiod variations on a photosensitive marker such as melatonin, we can only speculate about its influences on our results. Nevertheless, a thyroid circadian rhythm alteration to photoperiod variations is unlikely because daily cortisol circadian rhythm is unchanged with AR, and TSH response to TRH is equally elevated regardless of summer or winter light-dark differences.^{8,19}

In conclusion, humans appear to have an asymptomatic pituitary, thyroidal, and serum cholesterol response to extended AR. Lipid responses covary with changes in serum TSH level, suggesting a common hormonal mediator. Since increased blood cholesterol levels are causally related to an increased risk of coronary heart disease,¹⁵ further investigations are warranted to at least identify the individual sensitivity and possible mechanisms responsible for these environmentally induced thyroidal and associated lipid alterations.

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