Comparative Effects of Cynomel and Hypo Support Formula

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Abstract. In a previous study, two subjects on stable dosages of the synthetic T_3 product Cynomel found dosages of an organic dietary desiccated thyroid product (Hypo Support Formula or HSF) that maintained or improved clinical measurements provided by the previous dosages of Cynomel. The equivalence of HSF to Cynomel in maintaining the measurements was calculated to be 1 capsule of HSF to 15 mcg of Cynomel. In this study, another subject stable on Cynomel switched to the dosage of HSF previously calculated to effectively maintain the clinical and physiological measurements. **Methods:** A single-subject two-phase repeated-measures study design was used. The subject was a 24-year-old female. She had been stable for a year and a half on 100 mcg of Cynomel. She underwent 12 comprehensive metabolic evaluations on different days in the Cynomel phase. She then immediately switched from Cynomel to HSF and underwent 12 additional evaluations. The evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. **Result:** The subject's physiological and clinical measurements, stable for 1.5 years on 100 mcg of Cynomel, were not statistically different when she used 7 capsules of HSF each day. The only significant differences in the subject's measures were an increase in pain intensity and distribution during the HSF phase. **Conclusion:** For most measurements, including the BMR, BHR, and BAT, and hypothyroid symptoms intensity including depression, 7 capsules of HSF maintained the same values as 100 mcg of Cynomel. This outcome is consistent with that of the first study in which Cynomel and HSF were compared.

Key Words. Basal metabolic rate ● Basal temperature ● Cynomel ● Desiccated thyroid ● Hypo Support Formula ● RLC Labs ● Triiodothyronine

Introduction

Despite the widespread use of dietary desiccated thyroid products, only one product has thus far been tested in a systematic clinical trial.[1] In the study reported here, that product, Hypo Support Formula[2] (HSF), was again tested. The purpose was to determine whether the equivalence of HSF to Cynomel,[3] calculated from data in the first study, would enable a patient stable on Cynomel to maintain the same clinical and physiological status upon switching to HSF.

Methods

Subject. One female subject took part in the study. She was a 24-year-old female. Before starting thyroid hormone treatment with Cynomel in 2006, she was euthyroid according to her TSH and thyroid hormone levels. Despite her biochemically euthyroid status, ten days after beginning the use of Cynomel, she had complete relief of an eight-year history of almost constant profuse bleeding. Her bleeding had been misdiagnosed as Von Willebrand's bleeding disease with a factor VII platelet defect.

Since the age of 14, the subject had suffered from profuse bleeding that had required infusions and medications intended to reduce or stop the bleeding. She had copious, prolonged menstrual bleeding, nose bleeds, bleeding gums, easy bruising of the skin, and severe bleeding during dental procedures. None of the prescribed medications had been more than mildly and transiently effective at reducing her bleeding.

On June 18, 2006, the author measured the subject's basal metabolic rate with indirect calorimetry. Her measured BMR was 620 kcal/day. Using her sex, age, height, and weight in the Mifflin-St.Joer equation, her predicted BMR was calculated to be 1208.74 kcal/day. By this equation, then, her BMR was 48.74% below the predicted rate. By the Harris-Benedict equation, which also uses sex, age, height,

and weight, her BMR was 52.25% below the predicted rate. Using her lean body weight of 78.28 lbs (measured with 4-electrode bioelectrical impedance) in the Sterling-Pasmore equation, her BMR was 42.62% below her predicted BMR.

The only likely BMR-lowering factor affecting the subject was inadequate thyroid hormone regulation. This was obvious from a deductive differential diagnosis: she did not have low lean body weight or an androgen deficiency. She also was not restricting her calorie intake, which could severely lower the BMR.[22]

At the time, a substantial research literature existed showing that what was often diagnosed as Von Willebrand's bleeding disease was actually excessive bleeding secondary to hypothyroidism.[25] However, the young woman who is the subject of this study constitutes one of the untold tragedies resulting from the pseudoscientific and dogmatic belief that an elevated TSH is definitive and essential for the diagnosis of inadequate thyroid hormone regulation. Her many well-intending clinicians' harbored the false belief that her reference range TSH levels ruled out a need for thyroid hormone therapy. This false belief was the culprit that subjected the young woman to eight years of dreadful suffering, compromise, and debilitation from chronic, uncontrollable, massive bleeding.

Numerous hematologists, gynecologists, and other specialists included TSH levels in the patient's laboratory testing. But each of these clinicians dismissed the likelihood that inadequate thyroid hormone regulation could be the cause of her bleeding. Their reason was that her TSH levels were within the current reference range. This study subject is a sterling example of the *gross failure* of the TSH to well serve humanity. I reiterate, "Despite her biochemically euthyroid status, ten days after beginning the use of Cynomel, she had full and lasting relief from an eight-year history of almost constant copious bleeding."

On June 13, 2007, when the subject was 23-years-old, she underwent her second BMR. At the time, she was taking 75 mcg of Cynomel. Her BMR was 864 kcal/day. Her lean body weight of 78.6 lbs was high enough so that her predicted BMR (using the Sterling-Pasmore equation) was 1084.68 kcal/day. Her measured BMR, then, was 20.4% lower than her BMR predicted by her lean body weight. Before she had begun to use the 75 mcg of Cynomel, however, her BMR had been 42.62% below her predicted BMR. The 75 mcg of Cynomel, then, had increased her BMR by 22.22%. Because her BMR and other measures indicated that she was still underregulated by thyroid hormone, she increased her daily dose of Cynomel to 100 mcg.

The subject's third BMR measurement occurred on November 19, 2007. She was in her first trimester of pregnancy. Her measured BMR was 1550 kcal/day. Her predicted BMR based on her lean body weight was 1161.96 kcal/day (using the Sterling-Pasmore equation). This BMR was 33.4% above the BMR predicted by her lean body weight. Using the Harris-Benedict equation, the BMR of 1350.85 kcal/day was 14.74% above the predicted BMR; and using the Mifflin-St.Joer equation, her BMR of 1275.66 kcal/day was 21.51% above the predicted BMR for her sex, age, height, and weight.

Predictably, opponents of the use of any thyroid hormone preparation other than levothyroxine (T_4) will hastily attribute the patient's increased BMR to overstimulation by her use of Cytomel. However, her increased BMR is entirely consistent with the increased basal energy expenditure of pregnancy.[51,52] That 100 mcg of Cynomel did *not* account for her increased BMR is shown by her reference range BMRs after her pregnancy while still using 100 mcg of Cynomel.

For example, the author performed another comprehensive metabolic evaluation for the subject on May 24, 2008. The reader should bear in mind that in calculating a "normal" BMR for patients, a "reasonable" reference range is considered to be 10% below or above the calculated average. On May 24, 2008, the subject's BMR of 1200 kcal/day was 4.8% above the BMR calculated from her lean body weight, and, using two different equations for sex, age, height, and weight, her measured BMR was 1.5% and 8% below the calculated average. All three equations indicate that her Cynomel dose of 100 mcg per day provided her with a "normal" BMR.

Procedures. Upon waking from sleep and when comfortable with the temperature and bedding, the subject measured her basal metabolic rate with a hand-held indirect calorimeter (the Med Gem®, Healthetech, Golden, Colorado). She then measured her basal temperature of her left armpit with an electronic thermometer that gave a digital reading (Walgreens model VT-820W5T). In another study

by the author,[7] this type of electronic thermometer was compared to measurements with Galinstan-in-glass thermometers (Geratherm Medical AG, Fahrenheitstraße 1, D-98716 Geschwenda), which are equivalent to mercury thermometers. Measurements with the electronic and Galinstan thermometers strongly correlated and were highly consistent.[7] After taking her basal axillary temperature, the subject then took her basal pulse rate and blood pressure with an electronic sphygmomanometer (Omron Healthcare, Inc., Model HEM-711ACN, Bannockburn, IL).

After arising from bed, the subject drank two 8-ounce glasses of water, and, after urinating, measured her height and weight on a balance beam scale (Healthometer, Continental Scale Corp., Bridgeview, IL). She then measured her body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

Next the subject filled out three sets of evaluation forms: (1) a questionnaire with visual analog scales for 12 major symptoms characteristic of hypothyroidism;[6] (2) Zung's Self-rating Depression Scale (W.W.K. Zung © 1991); and (3) body drawings with 36 divisions for shading in the distribution of pain since the previous evaluation.[11]

After each evaluation, all measurements and scores were tabulated in an Excel spreadsheet in preparation for statistical analyses.

Study Design. An intrasubject replication study design (also termed a two-phase single-subject repeated measures design) was used.[8-16] Statistical comparisons were made of the data from the first, the Cynomel phase, and the second, the HSF phase.

In the Cynomel phase, the subject underwent 12 clinical evaluations. These occurred between October 10 and December 21, 2008. In the HSF phase, she underwent an additional 12 clinical evaluations. These occurred between December 26, 2008 and March 21, 2009. The mornings that the subject chose to undergo evaluations were selected on two bases: convenience, and the perception that she was, upon awakening, in a mental and physical basal state.

Before the study began, the subject had been stable on a daily dose of 100 mcg of Cynomel.[3] She continued Cynomel at that dosage until she had completed 12 clinical evaluations. The morning after she completed the 12th evaluation, she ceased taking Cynomel and began taking HSF. Her HSF dosage was calculated from the physiological equivalence derived from the first comparative study of Cynomel and HSF.[1] The equivalence was 1 capsule of HSF for each 15 mcg of Cynomel. She therefore immediately began taking a daily dose of 7 capsules of HSF. The 7 capsules were equivalent to 105 mcg of Cynomel, but based on experience in previous clinical trials by the author with synthetic T_3,[44,45,47,48,49] the additional 5 mcg were considered clinically insignificant.

During each of the phases, the subject underwent several electrocardiograms (ECGs). The tracings were compared with ECGs performed before the study began in case adverse cardiac effect began to develop.

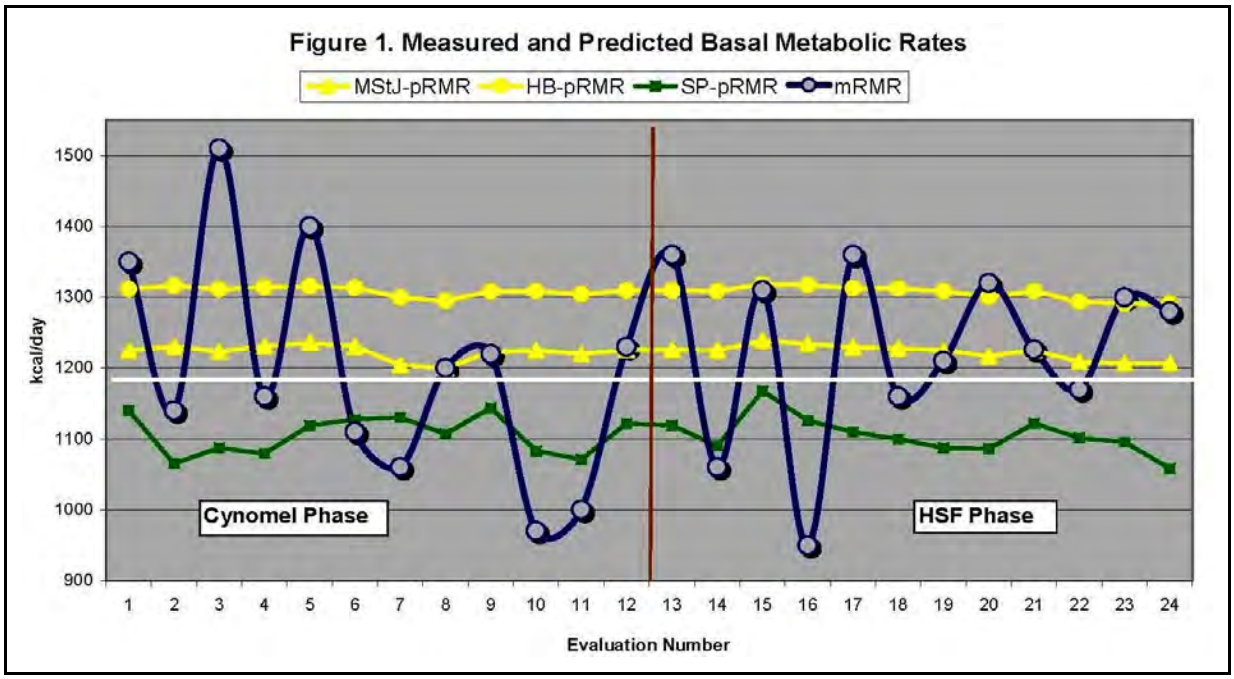
When the study began, the subject filled out a sheet of visual analog scales containing common symptoms of thyrotoxicosis. The scores on the sheets were compared to subsequent sheets during and after the study as indicators of possible symptoms of thyrotoxicosis.

Statistical Analyses. The *t*-test was used to test for differences between mean measurements. Levene's test for equality of variances was used to test for differences in the variance of measurements between the Cynomel and HSF phases. Bloom's probability table was used to statistically analyze any differences between Cynomel and HSF phases by the trend line method. The level of significance was set at $p \leq 0.05$. Statistical analyses were performed with SPSS for Windows® (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002.

Results

Basal Metabolic Rate. The subject's mean measured BMR during the Cynomel phase did not significantly differ statistically from that in the HSF phase (1195.83 ± 161.10 kcal/day vs 1225.50 ± 124.93, $p = 0.619$). Variances of the BMRs within each phase also did not differ ($F = 0.548$, $p = 0.467$).

Figure 1 contains the subject's measured BMRs. Each BMR along the blue trend line is represented by an empty circle. By Bloom's probability table,[5] with the baseline including 12 BMRs (left side of graph), and 6 below and 6 above the trend line (see the white horizontal line), 10 measured BMRs in the HSF phase (right half of graph) would have to be above or below the trend line for HSF-phase BMRs to be significantly different from those in the Cynomel phase. This criterion is not met. The lack of a significant difference using this method is consistent



with the lack of difference in the mean measured BMRs of the two phases determined through the use of the *t*-test.

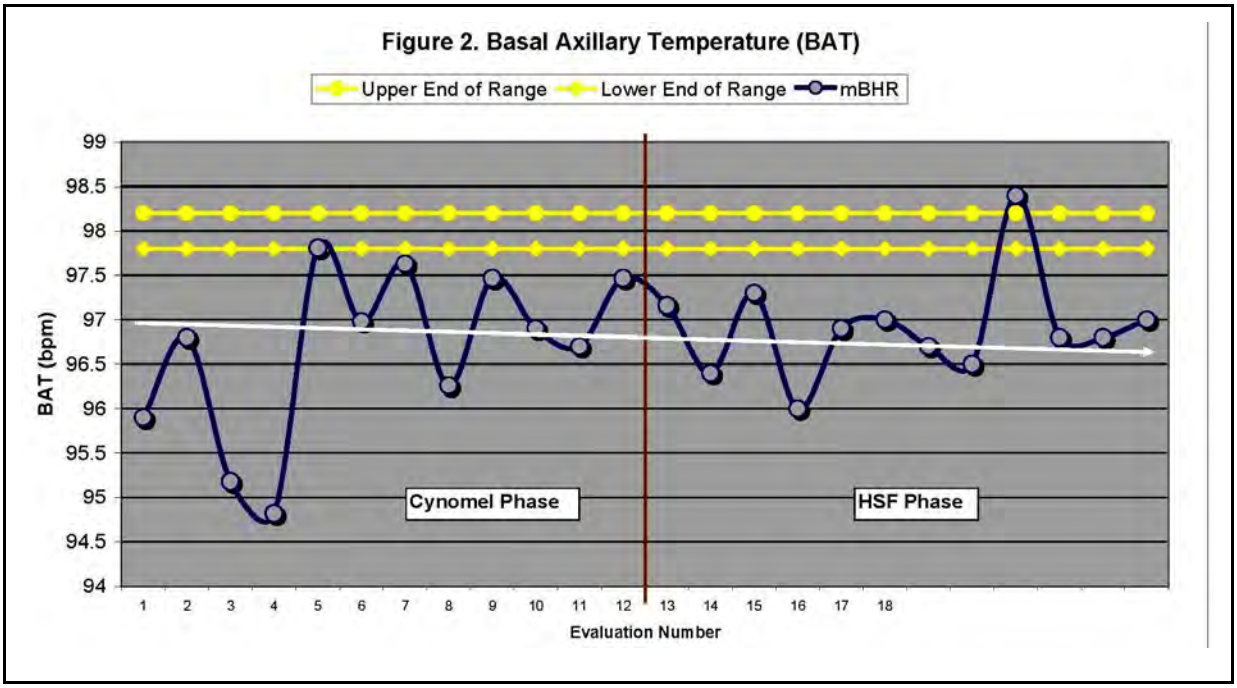
Basal Axillary Temperatures. In the Cynomel phase of this study, shown in the left side of the graph in Figure 2, two temperature measurements (the 3rd and 4th) appear very low compared to the other measurements. The two measurements were 95.18°F (35.10°C) and 94.82°F (34.90°C). However, these two measurements did not fall outside two 2 standard deviations from the mean. The mean was 96.66°F (35.92°C), and two standard deviations below the mean was 94.75°F (34.86°C). Because the two low measurements were within two standard deviations from the mean, they were included in the statistical calculations. The mean axillary temperature during the Cynomel phase (96.66°F [35.92°C]) did not significantly differ from that in the HSF phase (96.91°F [36.06°C]). The variances of the temperature readings in the two phases also did not differ.

The result of using the probability table of Bloom[5] is consistent with the results of use of the *t*-test for the means of the two groups of temperatures. Bloom's table also shows no significant difference. With 12 measurements in the Cynomel phase (left half of graph), with 6 data points above the trend line and 6 below (see the white line in Figure 2), 10 data points above or below the trend line in the HSF phase (right half of the graph) would be necessary for a significant difference between the two phases. This criterion is not met.

Basal Heart Rates. The subject's mean basal heart rate in the Cynomel phase did not significantly differ from that in the HSF phase (79.50 ± 9.15 vs 81.50 ± 4.78 bpm, $p = 0.51$). However, the variances of the two sets of heart rate measurements did differ ($F = 5.42$ $p = 0.03$). The *large* difference in the variability of the subject's heart rate is visibly obvious in the graph in Figure 3. Her heart rate varied far more in the Cynomel phase than in the HSF phase. The standard deviation of the rate in the Cynomel phase was 9.15 and in the HSF phase was 4.78.

Use of the probability table of Bloom[5] shows no significant difference in the heart rates between the two phases. With 12 heart rate measurements in the Cynomel phase (left half of graph), with 6 above and 6 below the trend line (see the white horizontal line in Figure 3), 10 data points would have to be above or below the trend line in the HSF phase (right half of the graph) for the subject's heart rate to have significantly changed during the HSF phase. This criterion is not met, so the subject's heart rates in the two phases did not significantly differ.

Blood Pressure. The subject's mean systolic pressure and diastolic pressure did not differ between the Cynomel and HSF phases. Variability in the pressures also did not significantly differ



between the phases.

Body Composition. No significant differences were found between the Cynomel and HSF phases for fat weight, percent body fat, lean body weight, nor any of three measures body water content.

Mean Symptoms Intensity. The subject's mean hypothyroid symptoms intensity did not significantly differ between the two phases. Variability of the symptom intensities in the two phase also did not significantly differ.

The subject's scores in the two phases on Zung's Self-rating Depression Scale did not significantly differ. The variability of the Zung's scores in the two phase also did not significantly differ.

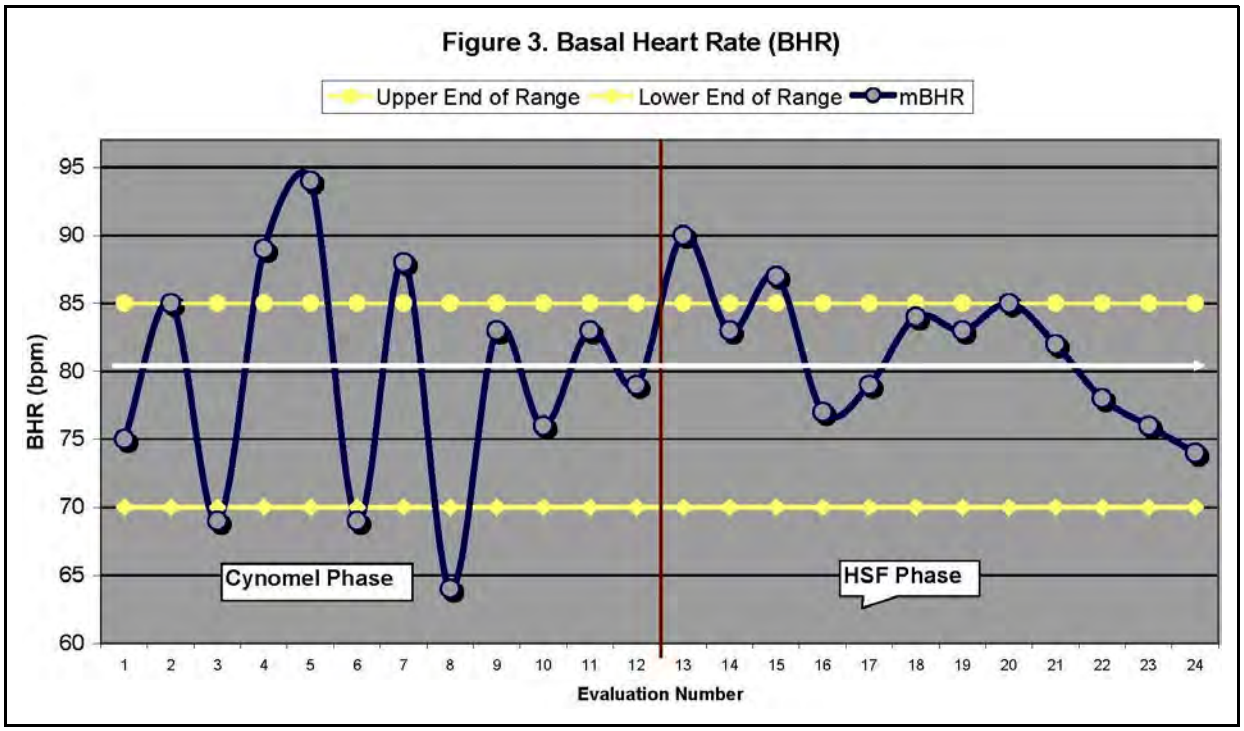
Pain Scores. The patient's estimated pain intensity (1-to-10 point severity scale) was significantly higher in the HSF phase than in the Cynomel phase (6.875 ± 0.99 vs 4.8892 ± 1.50, $p = 0.001$). Her pain distribution was also significantly higher in the HSF phase than in the Cynomel phase (29.62% ± 705 vs 15.25% ± 3.42, $p = 0.001$). The subject's pain distribution across 36 body divisions significantly and positively correlated with the intensity of her pain ($r = 0.68$, $p = 0.003$).

Discussion

The physiological and clinical measures used in this study indicate that HSF was as effective as Cynomel. No symptoms of thyroid hormone overstimulation nor ECG abnormalities occurred during the subject's use of Cynomel or HSF. The only exception is that the subject's pain intensity and distribution were significantly higher during the HSF phase. No significant changes in the subject's body body composition occurred during the study. Although her basal axillary temperatures were below the lower limit of the range established by Barnes, her temperatures did not significantly differ in the two study phases.

Comparative Effects of Cynomel and HSF. In this study, the subject used HSF, a dietary desiccated thyroid product, as a substitute for Cynomel, a synthetic T_3 product. Her use of HSF in a phase that included 12 comprehensive metabolic evaluations followed a phase in which she had also undergone 12 such evaluations while using Cynomel. During the phase in which she substituted 7 capsules of HSF for 100 mcg of Cynomel, her physiological measures did not significantly differ from those in the preceding Cynomel phase. Except for an increase in pain intensity and distribution, her symptoms did not significantly differ in the two phase. The results of this study are consistent with those of the first study of HSF and Cynomel[1] in that 1 capsule of HSF appears to be physiologically equivalent to 15 mcg of Cynomel.

Safety. In neither of the two phases of the study did the subject develop symptoms of thyrotoxicosis.



This was partly determined by comparing the intensity ratings of symptoms of thyrotoxicosis on visual analog scales that the subject filled out before the study and at intervals during the two phases.

The subject was not hyperreflexic. Her Achilles reflex speed was normal in both the contraction and relaxation phases.

Before the subject study began and during each phase, the subject underwent several electrocardiograms (ECGs). Tracings made during the study were compared with those before the study began. The tracings before and during each phase of the study were essentially the same, showing no indication of altered electrical rate or rhythm.

The lack of thyrotoxicity, normal Achilles reflexes, and unchanged normal ECGs indicate that neither Cynomel nor HSF in the dosages the subject used had adverse effects.

Pain. The subject's pain intensity and pain distribution were both significantly higher in the HSF phase than in the Cynomel phase. She has for extended times used each product alone. Her subjective impression is that when using Cynomel, she has less joint pain, which is a lifelong symptom of hers. She also believes she sleeps better when using Cynomel. Improved sleep could account for her lower pain scores during the Cynomel phase.[26,27,28]

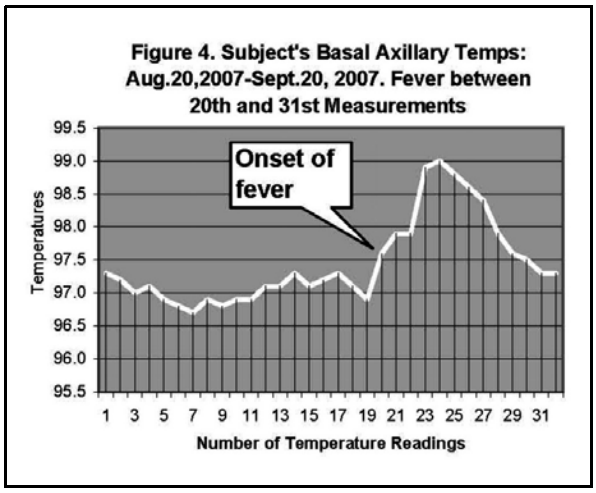
The subject's increased pain perception and pain scores on HSF is different from findings in the first study comparing HSF and Cynomel.[1] In that study, both the male and female subjects had subjective improvement in pain perception. Only the male subject, however, had statistically significant reductions of his scores for pain intensity and distribution. (For a discussion of possible factors involved in pain and thyroid hormone regulation, please see the discussion section of the previous study report.[1])

Body Composition. No significant differences were found in any measures of body composition between the Cynomel and HSF phases. No changes were found in fat weight, percent body fat, lean body weight, nor any measure of body water content. The subject's impression, however, is that she has retained less weight when using Cynomel than when using HSF. Lower weight when using Cynomel, however, was not objectively confirmed in this study. While her weight was lower in the Cynomel phase than in the HSF phase (107.29 ± 1.157 vs 106.39 ± 2.213 lbs), the difference was not statistically significant ($p = 0.229$).

Basal Axillary Temperatures. The subject was stable on 100 mcg of Cynomel before this study. She remained completely free from the chronic, profuse bleeding that had dominated her life for 8 years. She also had BMRs that were close to those predicted from her lean body weight and her sex,

age, height, and weight, and on one occasion, a BMR consistent with the increased energy expenditure of pregnancy.

Despite these benefits, the patient's basal axillary temperatures were typically below the lower end of the reference range reported by Barnes (97.8°F-to-98.2°F).[4] For example, the mean of 19 basal axillary temperatures that she took between August 20, 2007 and September 7, 2007 was 97.03°F (36.13°C). In the two phases of this study, however, her basal temperatures were, respectively, 96.66°F (35.92°C) and 96.91°F (36.06°C).



Regardless of these low temperatures, the subject was capable of increased temperatures during infections. Figure 4 shows her basal axillary temperatures between August 20 and September 20, 2007. During the later half of that span of time, she contracted an infection. She felt feverish, had malaise and swollen cervical lymph nodes, and she was bedridden for the better part of a week. Her 20th measurement, taken when her symptoms had begun, showed an increased basal temperature. Her temperature ascended and by the 31st measurement had declined considerably back toward her lower mean temperature.

Limitations. This study was unblinded and this raises the possibility of observer bias. The number of repeated measurements, however, and the objective nature of the methods of measurement make it highly unlikely that the outcome was influenced by subtle biases.

The single-subject two-phase repeated measures design used in this study has merits lacking in randomized studies. The subject in this type of study, for example, serves as his or her own control in the two different phases. This eliminates the need for randomization, as the subject in each phase is as perfectly matched as possible to the subject in the other phase. Moreover, repeated measures under systematically varied conditions provides data for both traditional group statistical analyses and clear visual inspection for functional relationships between independent and dependent variables.

Conclusion

The results of this study show equivalent effects of HSF and Cynomel on all physiological measurements used and on most clinical assessments tools. The results are therefore similar to those of the first study[1] that assessed the effects of the two products.

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