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**Effects of Moderate Aerobic Exercise Combined with Calorie Restriction on Circulating Estrogens and IGF-I in Premenopausal Women**

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**13. ABSTRACT (Maximum 200 Words)**

This proposal entitled "Effects of moderate aerobic exercise combined with caloric restriction on circulating estrogens and IGF-I in premenopausal women" will provide important contributions regarding the primary prevention of breast cancer in women. This study has examined the effects of exercise training combined with caloric restriction, resulting in weight loss, on two hormonal biomarkers for breast cancer i.e., circulating estrogens and insulin-like growth factor I (IGF-I). As expected, exercise training 4 times per week combined with a 20-30% decrease in caloric intake over four menstrual cycles has produced significant increases in aerobic capacity (28-33%); weight loss ranging from 1.0 to 9 kg, and loss of body fat ranging from 5 to 12% of initial percent fat. Light conditioning resulted in significant gains in aerobic capacity (33%), but only produced a trend toward a decrease in body fat percent (-3.1%), and no changes in body weight. Despite the highly significant changes in body composition and body weight in the exercising group, preliminary results indicate no significant changes in serum estradiol or serum estrone. IGF-I did not change significantly either, indicating that chronic exercise and dieting do not result in favorable changes in two hormonal biomarkers for breast cancer.

**14. SUBJECT TERMS**

Breast cancer, menstrual cycle, IGF-1, estradiol, exercise

**15. NUMBER OF PAGES**

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**16. PRICE CODE**

Unlimited

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INTRODUCTION

This proposal entitled "Effects of moderate aerobic exercise combined with caloric restriction on circulating estrogens and IGF-I in premenopausal women" will provide important scientific contributions with respect to the primary prevention of breast cancer in women. Specifically, this ongoing study will examine potential mechanisms relating to the role of physical activity in the reduction of the risk of breast cancer by testing whether moderate aerobic exercise can reduced the levels of two hormonal biomarkers, circulating estrogens and insulin-like growth factor I (IGF-I). Since elevated levels of both of these hormones have been associated with an increased risk of breast cancer, and because exercise may modulate circulating levels, we wish to extend previous findings from epidemiological and cross-sectional studies by performing a tightly controlled, prospective clinical study that addresses previously unanswered questions related to the role of exercise in the modulation of estrogen and IGF-I. Although previous studies have shown that negative energy balance, and not other stressful aspects of physical exercise, can modulate reproductive function and therefore circulating estrogen levels, no studies to date have determined the magnitude of energy deficit required for these changes during long-term training, and no studies have attempted to differentiate between the exercise-induced changes in ovarian versus adipose sources of circulating estrogens. Since both estradiol (ovarian) and estrone (adipose tissue) are biologically active, and because the importance of estrone as a risk factor increases with age and adiposity, it is important to consider the degree to which exercise which creates a negative energy balance affects both of these sources of circulating estrogens.

Circulating levels of IGF-I correlate with breast cancer risk, yet studies examining the responses of this hormone and its binding proteins to chronic exercise are lacking. Since IGF-I levels are very sensitive to nutritional status, previously reported stimulatory effects of exercise on IGF-I can be overridden if exercise is performed in the face of negative energy balance. In this regard, exercise that promotes weight loss can be viewed as a way to reduce levels of IGF-I, and therefore potentially reduce the risk of breast cancers. To date, no studies have addressed whether a program of moderate aerobic exercise and dietary restriction producing a negative energy balance that is carried out over a long duration will significantly alter IGF-I levels. Further, the degree to which these levels might be altered in individuals of differing initial energy stores has not been addressed.

Metabolic energy availability is an important contributing factor in the development of reproductive cancers. However, current methods for assessing energy availability, which include anthropometric measures, calculations of energy balance, evaluation of various serum and urinary biomarkers are prone to measurement error, not sensitive to alterations in energy availability, and are sometimes affected by disease states. The current project includes an introduction of a novel approach to estimating energy status by measuring metabolic hormones in plasma, insulin, IGF-I, IGFBP-1 and leptin. Recently, dried blood spot (DBS) sample collection techniques have allowed for endocrine based population studies examining a wide variety of ecological factors that contribute to variation in human reproduction. In order to use the proposed method of energy status assessment in large population-based applications, such as those addressing the role of physical activity and or diet in the risk of breast cancer, the battery of metabolic hormones that comprise the proposed method must be amenable to collection and assays. Although the DBS technique has been partially validated for some hormonal assays, it has not yet been properly validated for insulin, IGF-I, IGFBP-1 and leptin, and it is unclear whether the technique is responsive to physiological changes of these compounds. Therefore, the current work calls for the validation of the DBS sampling technique for these assays under physiological conditions.

The proposed studies will yield new and important information regarding the degree to which an exercise and diet program that results in an energy deficit will reduce the risk of breast cancer.

BODY

Study Design: The study utilizes a prospective, randomized design that tests the effects of a moderate exercise program (4X/wk; 4 months) combined with moderate dietary restriction that results in an average daily energy
deficit of -20%-30% kcals (Figure 1). Previously sedentary, eumenorrheic women aged 25-40 years will be
assigned to exercise or light conditioning groups. Both normal weight (BMI 21-25 kg/m²) and overweight
(BMI 26-30 kg/m²) will be assigned to either exercise or light conditioning group (exercise 2X/wk; no dietary
restriction) groups; 4 groups, n=15 each group. Subjects will be studied for a total of six menstrual cycles, i.e.,
2 control followed by 4 cycles with training and dietary restriction.

**Figure 1. Study Design**

**Progress According to the Approved Statement of Work:**

*(See previous Annual Summary for 2002-2003)*

Proposed Months 25-28:
1. Repeat Steps above for year 3 recruiting and beginning testing (n=5 in each of 4 groups)
2. Perform assays on metabolic hormones in serum
3. Send serum and blood spot samples from year 2 subjects to DSL

*Actual Month 25, September, 2003:* Enrollment increased dramatically, fourfold increase in enrollment; assays
completed, T3, and continued for IGF-1; arrangements made with Salimetrics Laboratory, University Park, PA
to develop blood spot assays for Leptin, T3, and IGF-I (See Appendix); begun assays on urinary LH to
document LH surges.

*Actual Month 26, October, 2003:* Continued with rolling recruitment, began screening procedures on recently
enrolled subjects, completed IGF-I assays on completed subjects, continued with urinary LH assays to
document LH surges

*Actual Month 27, November, 2003:* Continued with recruitment and testing, continued LH urinary assays

*Actual Month 28, December, 2003:* Continued with recruitment and testing, completed urinary LH assays on
first cohort of completed subjects

Proposed Months 29-36:
1. Continue year 3 recruitment efforts only if necessary
2. Continue year 3 subject screening/initial testing
3. Complete year 3 subject exercise training/experimental testing
4. Perform urinary assays on LH, E3G, PdG urinary
5. Send serum and blood spot samples from year 3 subjects to DSL.
5. Perform data analysis and statistics

Actual Month 29, January, 2004: Continued testing and recruiting
Actual Month 30, February, 2004: Continued testing and recruiting
Actual Month 31, March, 2004: Continued testing and recruiting
Actual Month 32, April, 2004: Continued testing and recruiting
Actual Month 33, May, 2004: Continued testing and recruiting
Actual Month 34, June, 2004: Performed assays on next cohort of completed subjects for T3, leptin, and IGF-I; continued testing and recruiting.
Actual Month 35, July, 2004: Continued to perform assays for T3, leptin, and IGF-I. continued testing and recruiting; began database checking and data reduction; preliminary data analysis
Actual Month 36, August, 2004: Stopped recruitment of subjects, continued with testing of currently enrolled subjects; Finished assays for T3, leptin, and IGF-I for most recently finished cohort. Performed assays for estradiol for most recently completed cohort.
Actual Month 37, September, 2004: Continued with testing, preliminary data analysis and database management; perform preliminary statistics for annual report; examine results from Salimetrics thus far

Newly Proposed Months 38-42, October, 2004-February, 2005:
Request extension for final report for this study (IDEA Award) from DAMD; perform urinary LH, E1G, and PDG assays, and serum metabolic assays when final cohort is finished; perform insulin, IGFBP-2, estradiol, and estrone on remaining completed subjects; send completed DBS samples from completed subjects to Salimetrics; perform data analysis; obtain results of DBS samples from Salimetrics, submit abstract for ERA of HOPE Meeting in December, 2004

Newly Proposed Months 43-48, March 2005- May 2005:
Write and submit manuscripts

Preliminary Results From Years 1, 2, and 3:

Subject Recruitment:

We have accumulated approximately 269 phone and e-mail contacts since September 03, bringing our 3 year total number of contacts up to 571. In the last 3 years seventy-eight women have begun the study and 52 have dropped out or been excluded for the following reasons: 14 with menstrual abnormality detected in the control months, 10 for medical reasons, 21 self-drop-out (time, intervention), 2 non-compliance, 2 with pregnancies during the study, and 3 because of weight/body composition measures outside inclusion criteria during screening. Although this represents a high drop-out rate (66%) prior to screening, our drop-out rate after screening procedures have been performed (including two control menstrual cycles to determine normal menstrual cyclicity) is 52%. That is, 52% of the women that made it through out screening procedures have dropped out of the study. This rate is much higher than predicted (20%).

Our recruitment efforts were stepped up beginning September 2003. Although we generally see do well with inquiries about the study, we had an especially disheartening recruitment effort this year, as our dropout rate...
was double what it has been in the past two years. Therefore, our current subject numbers are reflected in Table 1. Descriptive characteristics of these subjects are shown in Table 2.

### Table 1. Current Enrollment and Completed Subjects

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Initially Began Study After Screening (N)</th>
<th>Currently Enrolled (N)</th>
<th>Finished Study (N)</th>
<th>Potential Final (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Conditioning-low BMI</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Light Conditioning-high BMI</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Exercisers-low BMI</td>
<td>20</td>
<td>3</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Exercisers-high BMI</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 2. Initial Characteristics of Subjects Completed or Currently Enrolled in the Study

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33.63 ± 3.34</td>
<td>34.83 ± 4.26</td>
<td>32.00 ± 4.75</td>
<td>31.73 ± 2.90</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.43 ± 3.70</td>
<td>68.88 ± 3.73</td>
<td>60.05 ± 6.12*</td>
<td>73.56 ± 9.04*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.46 ± 5.27</td>
<td>160.97 ± 6.88</td>
<td>163.64 ± 5.90</td>
<td>163.08 ± 6.73</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.21 ± 1.93</td>
<td>27.35 ± 2.16*</td>
<td>22.77 ± 1.75*</td>
<td>27.95 ± 2.09*</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>31.10 ± 4.03</td>
<td>39.20 ± 4.07*</td>
<td>29.96 ± 3.50*</td>
<td>37.78 ± 4.62*</td>
</tr>
<tr>
<td>VO₂ Max (mg/kg/ml)</td>
<td>30.36 ± 1.99</td>
<td>26.43 ± 4.14</td>
<td>33.88 ± 5.19*</td>
<td>27.63 ± 6.43*</td>
</tr>
</tbody>
</table>

One-way ANOVA; Post-hoc: LSD; P<0.05
*LCLB vs LCHB
*ELB vs EHB

**Preliminary Results:**

**Aerobic Capacity, Body Weight and Body Composition:** Our light conditioning group exhibited a trend toward a decrease in percent body fat of -3.1% (P< 0.072), but no significant changes in body weight or BMI. The exercising group experienced significant declines in both body weight (-6.2%)) and percent body fat (-15.7% of initial percent fat), fat mass (-20.6%) and in BMI (-6.8%). Both groups significantly increased their aerobic capacity, i.e., Light conditioning increased by 33% and exercising group increased by 28% (Tables 3 and 4).

**Estradiol and Estrone:** When serum measurements of these hormones across Control Cycle 2 (n=10), and Exercise 4 cycles (n=10) are averaged, and then compared with paired samples T-tests, no differences are observed in either the light conditioning or exercising groups, despite the loss of body fat (Tables 3 and 4).
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- composite graph of these changes, depicted according to cycle day is illustrated in Figure 2. A representative depiction of the changes in both serum estrone and estradiol and urinary E1G is depicted in Figure 3.

### Table 3. Paired-Samples T-Tests Comparing Pre to Post Intervention in Light Conditioning Group

<table>
<thead>
<tr>
<th>Pair</th>
<th>Description</th>
<th>Mean</th>
<th>N</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td>Pre VO2 Max (ml/kg/min) Post VO2 Max (ml/kg/min) (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>28.3500</td>
<td>6</td>
<td>3.56693</td>
<td>1.45619</td>
<td></td>
</tr>
<tr>
<td>Pair 2</td>
<td>Pre UWW Weight (kg) (control month BIOEY 1-3) Post UWW Weight (kg) (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>63.1429</td>
<td>7</td>
<td>4.37516</td>
<td>1.65365</td>
<td>.001</td>
</tr>
<tr>
<td>Pair 3</td>
<td>Pre UWW % Body Fat (control month BIOEY 1-3) Post UWW % Body Fat (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>33.4514</td>
<td>7</td>
<td>4.71277</td>
<td>1.78126</td>
<td></td>
</tr>
<tr>
<td>Pair 4</td>
<td>Pre UWW BMI (control month BIOEY 1-3) Post UWW BMI (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>23.4186</td>
<td>7</td>
<td>3.52394</td>
<td>1.33193</td>
<td></td>
</tr>
<tr>
<td>Pair 5</td>
<td>Pre Month RMR (kcal/min) Post Exercise Month RMR (kcal/min)</td>
<td>.90045</td>
<td>6</td>
<td>.06965</td>
<td>.02844</td>
<td></td>
</tr>
<tr>
<td>Pair 6</td>
<td>Estradiol Ave PRE Estradiol AVERAGE POST</td>
<td>70.3756</td>
<td>5</td>
<td>13.53968</td>
<td>6.05513</td>
<td></td>
</tr>
<tr>
<td>Pair 7</td>
<td>Pre UWW Ave FFmass (kg) (control month BIOEY 1-3) Post UWW Ave FFmass (kg) (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>41.8900</td>
<td>7</td>
<td>2.10473</td>
<td>.79551</td>
<td></td>
</tr>
<tr>
<td>Pair 8</td>
<td>Pre UWW Ave Fatmass (kg) (control month BIOEY 1-3) Post UWW Ave Fatmass (kg) (Ex 3 BIOEY1; Post BIOEY2&amp;3)</td>
<td>21.1643</td>
<td>7</td>
<td>4.29164</td>
<td>1.62209</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.2343</td>
<td>7</td>
<td>4.82436</td>
<td>1.82344</td>
<td>.107</td>
</tr>
</tbody>
</table>
Table 4. Paired-Samples T-Tests Comparing Pre to Post Intervention in Exercising Group

<table>
<thead>
<tr>
<th>Pair</th>
<th>Description</th>
<th>Mean</th>
<th>N</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td>Pre VO2 Max (ml/kg/min) Post VO2 Max (ml/kg/min) (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>32.99</td>
<td>16</td>
<td>5.36675</td>
<td>1.34169</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>42.19</td>
<td>16</td>
<td>9.80064</td>
<td>2.45016</td>
<td>.001</td>
</tr>
<tr>
<td>Pair 2</td>
<td>Pre UWW Weight (kg) (control month BIOEY 1-3) Post UWW Weight (kg) (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>63.76</td>
<td>20</td>
<td>9.50026</td>
<td>2.12432</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>59.76</td>
<td>20</td>
<td>9.03649</td>
<td>2.02062</td>
<td>.000</td>
</tr>
<tr>
<td>Pair 3</td>
<td>Pre UWW % Body Fat (control month BIOEY 1-3) Post UWW % Body Fat (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>31.60</td>
<td>20</td>
<td>5.20520</td>
<td>1.16392</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.65</td>
<td>20</td>
<td>6.28069</td>
<td>1.40440</td>
<td>.000</td>
</tr>
<tr>
<td>Pair 4</td>
<td>Pre UWW BMI (control month BIOEY 1-3) Post UWW BMI (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>23.50</td>
<td>20</td>
<td>3.09325</td>
<td>.69167</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.94</td>
<td>20</td>
<td>2.66114</td>
<td>.59505</td>
<td>.000</td>
</tr>
<tr>
<td>Pair 5</td>
<td>Pre Month RMR (kcal/min) Post Exercise Month RMR (kcal/min)</td>
<td>.9231</td>
<td>20</td>
<td>.09858</td>
<td>.02204</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>.8964</td>
<td>20</td>
<td>.11824</td>
<td>.02644</td>
<td>.146</td>
</tr>
<tr>
<td>Pair 6</td>
<td>EstradiolAvePRE EstradiolAVERAGEPOST</td>
<td>95.05</td>
<td>12</td>
<td>21.46584</td>
<td>6.19665</td>
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<tr>
<td></td>
<td></td>
<td>93.34</td>
<td>12</td>
<td>28.63159</td>
<td>8.26523</td>
<td>.828</td>
</tr>
<tr>
<td>Pair 7</td>
<td>Pre UWW Ave FFmass (kg) (control month BIOEY 1-3) Post UWW Ave FFmass (kg) (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>43.33</td>
<td>20</td>
<td>5.13945</td>
<td>1.14922</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43.54</td>
<td>20</td>
<td>5.48725</td>
<td>1.22699</td>
<td>.460</td>
</tr>
<tr>
<td>Pair 8</td>
<td>Pre UWW Ave Fatmass (kg) (control month BIOEY 1-3) Post UWW Ave Fatmass (kg) (Ex 3 BIOEY 1; Post BIOEY 2&amp;3)</td>
<td>20.41</td>
<td>20</td>
<td>5.92869</td>
<td>1.32570</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>16.22</td>
<td>20</td>
<td>5.47167</td>
<td>1.22350</td>
<td>.000</td>
</tr>
<tr>
<td>Pair 9</td>
<td>EstroneAVERAGEPRE EstroneAVERAGEPOST</td>
<td>56.77</td>
<td>7</td>
<td>13.95731</td>
<td>5.27537</td>
<td>.785</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56.77</td>
<td>7</td>
<td>13.95731</td>
<td>5.27537</td>
<td>.785</td>
</tr>
</tbody>
</table>
Figure 2. Composite graph of estradiol measurements from Control Cycle 2 (Pre) and Exercise 4 (Post) cycles.
Figure 3. Representative example of a single subject’s urinary (E1G) and serum estrogens (estrone and estradiol) before (Control 2) and after (Exercise 4) exercise training combined with caloric restriction.

Serum Leptin, T3, and IGF-I: A significant decrease (P< 0.05) was observed in measurements for leptin (Table 5), primarily accounted for by the changes in the exercising group (P <0.05 group X time interaction). Serum T3 decreased significantly overall (P<0.05) (Table 6). No significant differences were observed in either group for IGF-I (Table 7).

Table 5. Serum Leptin for Light Conditioning (0) and Exercisers (1) Pre and Post study

<table>
<thead>
<tr>
<th>Group based on exercise</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Leptin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.00</td>
<td>13.0750</td>
<td>6.40459</td>
<td>6</td>
</tr>
<tr>
<td>1.00</td>
<td>15.9233</td>
<td>11.82781</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>15.2113</td>
<td>10.67270</td>
<td>24</td>
</tr>
<tr>
<td>Post Leptin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.00</td>
<td>15.0050</td>
<td>9.24739</td>
<td>6</td>
</tr>
<tr>
<td>1.00</td>
<td>7.4656</td>
<td>7.21061</td>
<td>18</td>
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<tr>
<td>Total</td>
<td>9.3504</td>
<td>8.25476</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 6. Serum T3 for Light Conditioning (0) and Exercisers (1) Pre and Post study

<table>
<thead>
<tr>
<th>Group based on exercise</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T3 Pre (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.00</td>
<td>107.0380</td>
<td>24.17636</td>
<td>5</td>
</tr>
<tr>
<td>1.00</td>
<td>104.0635</td>
<td>14.02287</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>104.7395</td>
<td>16.21055</td>
<td>22</td>
</tr>
<tr>
<td>Total T3 Post (ng/dl)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>.00</td>
<td>96.1460</td>
<td>22.05372</td>
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<tr>
<td>1.00</td>
<td>95.1106</td>
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<tr>
<td>Total</td>
<td>95.3459</td>
<td>16.99823</td>
<td>22</td>
</tr>
</tbody>
</table>
Table 7. Serum IGF-I for Light Conditioning (0) and Exercisers (1) Pre and Post study

<table>
<thead>
<tr>
<th>Groupsbasedonexercise</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1Pre (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.00</td>
<td>238.370</td>
<td>56.80587</td>
<td>5</td>
</tr>
<tr>
<td>1.00</td>
<td>211.485</td>
<td>50.48205</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>217.596</td>
<td>51.85874</td>
<td>22</td>
</tr>
<tr>
<td>IGF-1 Post (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.00</td>
<td>230.608</td>
<td>26.58635</td>
<td>5</td>
</tr>
<tr>
<td>1.00</td>
<td>203.638</td>
<td>58.94881</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>209.767</td>
<td>54.00045</td>
<td>22</td>
</tr>
</tbody>
</table>

Results for Dried Blood Spot Samples: Thus far, Salimetrics has provided us with results for leptin DBS samples. In comparison to the simultaneous venipuncture measurement of leptin as assayed in our laboratory, a significant correlation exists (P<0.05; Pearson Correlation) (Table 8, and Figure 4)

Table 8. Correlation between serum and DBS sample for leptin

<table>
<thead>
<tr>
<th></th>
<th>Av Control Month Leptin (ng/ml)</th>
<th>PreLeptinBlood Spot(ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Av Control Month</td>
<td>Pearson Correlation</td>
<td>.677(*)</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>Sig. (2-tailed)</td>
<td>.011</td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>PreLeptinBloodSpot (ng/ml)</td>
<td>Pearson Correlation</td>
<td>.677(*)</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>13</td>
</tr>
</tbody>
</table>

* Correlation is significant at the 0.05 level (2-tailed).
Figure 4. Scatterplot of leptin DBS vs venipuncture results

Overall Results from Years 1-3: Although our data set is not yet complete, it appears as though there are no dramatic changes in circulating estradiol, estrone, or in urinary E1G in our subjects, despite significant loss of weight and decrease in body fat. Preliminary results comparing DBS technique to venipuncture as assayed by RIA are very promising.

KEY ACCOMPLISHMENTS

This is an ongoing study, so preliminary publication of the data is not feasible.

REPORTABLE OUTCOMES

Training:
The following individuals have been supported by DAMD17-01-1-0360:
Faculty:
  Nancy Williams, Sc.D.
Undergraduate Kinesiology Students:
  Carmon Communale 3/04-5/04
  Kristin Gross 2/04-9/04

The following students received degrees in the past year under the direction of Dr. Williams. These students all assisted with the current project.

Kelly Dougherty, MS Kinesiology
Brian Frye, MS Kinesiology
Publications:
To date, no publications have resulted from the project supported by these funds because the data set is not yet complete. However, Dr. Williams has produced the following publications while being supported by this Career Award:

**Published Manuscripts:**


**Manuscripts in Review:**

De Souza MJ, and **Williams NI.** Beyond Hypoestrogenism in Amenorrheic Athletes: Energy Deficiency as a Contributing Factor for Bone Loss (Submitted to *Current Sports Medicine Reports*)

Mastro AM, Williams NI, Kraemer WJ et al. Exercise Intervention and Plasma Levels of IFN-α, and IL-6 following Chemotherapy for Breast Cancer. (submitted to the *Journal of Clinical Oncology*).

**Manuscripts in Progress:**

Williams NI, Perry MD, Kraemer WJ, and Mastro AM. “Effects of chemotherapy followed by exercise training on reproductive status and stress hormones in breast cancer patients”

**Williams, N.I. Williams, N.I.**, Berga S.L., and Cameron, J.L. Synergism of multiple sub-threshold stressors: effects of diet, exercise, and psychosocial stress on menstrual cyclicity

Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, **Williams NI.** Changes in ghrelin are concomitant with changes in body weight, leptin, and IGF-1 during an energy deficit-imposing diet and exercise program in normal weight, healthy young women

Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, **Williams NI.** Meal Calorie Content and Meal Timing Affect Specific Meal Response Characteristics of Total Ghrelin in Normal Weight Healthy Young Women
Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, Williams NI. The Meal Related Pattern and Diurnal Rhythm of Ghrelin are Elevated Following an Energy Deficit-imposing Diet and Exercise Intervention

Cancer Grants:
Active: The following grant was awarded for additional studies to be undertaken in collaboration with Dr. Kimberly Westerlind at the AMC Cancer Research Center in Denver, Colorado. This work will examine the effects of exercise on the ratios of urinary estrogen metabolites.

AMC Cancer Research Center
Co-Investigator (Williams)
PI (Westerlind) 1/04-12/05
$76,865

"Exercise and Estrogen Metabolism: Implications for Breast Cancer Prevention"

Pending: The principal investigator plans to submit an NIH R01 grant to secure funding to perform additional analyses on serum samples collected from the current project. This grant will be in response to PA-04-124 (Studies of Energy Balance and Cancer in Humans) July 7, 2004-Sept 2, 2006.

"Effects of energy deficiency on hormonal and immunological biomarkers for cancer"

Other Grants:

(Active Support)

1. NIH
   1 R01 HD39245-01 (Williams) 5/1/01 - 4/30/04
   (currently in 1 yr no cost extension) 30%
   PHS/NICHD
   Principal Investigator:
   "Bioenergetics of Exercise-induced Menstrual Disturbances"
   $1,538,361

2. US Army Medical Research and Materiel Command
   US Army Breast Cancer Program (IDEA AWARD) 9/17/01-9/16/05 15%
   $408,878
   Principal-Investigator:
   "Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (IDEA Award)"

3. US Army Medical Research and Materiel Command
   US Army Breast Cancer Program (CAREER DEVELOPMENT AWARD) 9/17/01-9/16/05 50%
   $312,081
   Principal-Investigator:
   "Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (Salary Only)"

15
4. Retirement Research Foundation 2000-2004 2% $56,832
Co-Investigator: (PI is J.L. Cameron, PhD) "Physical Exercise and Brain Aging"

HD-02-012 Cooperative Reproductive Science Research Centers at Minority Institutions
Co-Investigator: $1,160,204 5%
"The efficacy and safety of metformin and lifestyle factors in the amelioration of hyperandrogenemia and its associated symptomology"

6. Cancer Research and Prevention Foundation
Co-Investigator (PI is Kim Westerlind, AMC Cancer Research Center, Denver, CO) 1/04-12/05 0% $76,865
"Exercise and Estrogen Metabolism: Implications for Breast Cancer Prevention"

7. NASA
Co-Investigator (PI is James Pawelczyk, PSU) 4/1/05-3/31/06 5% $1,144,613
"Improving Orthostatic Tolerance in Women: Control of Splanchnic and Cutaneous Vascular Capacitance"

(Pending)

1. National Institutes of Health (NIH) 4/1/05-3/31/09 28.8%
Co-Principal Investigator (PI is Susan Bloomfield, Texas A&M) $2,000,000
"Impact of Food Restriction on Bone Health in Active Females"

(Not funded)

1. National Institutes of Health (NIH)
1 RO1 (Co-Principal Investigator with Mary Jane De Souza, Univ. Toronto) 7/01/02 - 6/30/07 15% PHS/NICHD $2,433,044 "Clinical Sequelae Exercise-Induced Hypoestrogenism"

2. National Institutes of Health (NIH)
Co-Investigator (PI is Terryl Hartman, PSU) 4/01/04-3/31/08 20% $2,085,448 "Female Cancer Survivors Weight and Activity Intervention"

3. Dairy Farmers of Canada 1/1/05-12/31/06 10%
Co-Principal Investigator (PI is Mary Jane De Souza, University of Toronto)
"Can Increased Dietary Calcium Improve Recovery of Bone Health in Exercising Women Undergoing a Lifestyle Intervention for Severe Menstrual Disturbances?"

4. National Institutes of Health (NIH)  4/1/05- 3/31/09  15%
Co-Investigator (PI is Terryl Hartmen, Dept. Nutrition, Penn State)  $856,295

"Antioxidant Status, Diet and Early Pregnancy"

Presentations:


CONCLUSIONS:

We are making good progress toward the completion of this study. Preliminary examination of the data look interesting but thus far analyses do not support the hypothesis that circulating biomarkers of breast cancer are altered by diet and exercise. The DBS technique looks promising as a potential field marker for energy availability, based on a favorable correlation between serum and DBS samples.
REFERENCES:
NONE

APPENDIX

1. Letter from Salimetrics
2. T3 performance and quality control characteristics
3. IGF-I performance and quality control characteristics
Dear Dr. Williams,

At Dr. Granger's request, I am writing to outline the basic objectives for our development of blood spot assays for Total T3 and IGF-1 for your project. You should have received quotes for these projects from Martha Orland last weekend. As you are aware, we have already developed similar assays for testosterone, leptin, estradiol, and progesterone. Based on our previous experience I don't expect protocol development for these markers will be problematic. Nevertheless, as with any research project a specific timeline is difficult to predict. We hope the development work will take no longer than 3 months time.

As in the past, our approach will be to begin by modifying commercially available enzyme immunoassay protocols. The assay development will include determination of assay range, lower limit of sensitivity, linearity and spike recovery, and confirmation that intra- and inter-assay coefficients of variation are within acceptable limits outlined by Chard (1990). We will also provide recommendations regarding sample collection, preparation, and the amount of sample needed to perform each assay.

In a previous note to Dr. Granger, you mentioned having matched serum/plasma samples. Once the assay is internally validated we highly recommend comparing values from the blood spot assay protocols with results you obtain from the serum tests. We can arrange those serum tests for you if you don't already have a source for those assays.

Once completed, we can provide testing services for your project at a cost of $25.00 per sample for T3 and >$30.00 per sample for IGF-1.

If you have any questions or are just interested in a progress report, please don't hesitate to call (800-790-2258 ext. 207) or email me (Ebs@salimetrics.com).

Best Regards,

Eve Schwartz
T3 BLOOD SPOT PERFORMANCE CHARACTERISTICS

LINEARITY OF DILUTION:
A plasma sample was diluted linearly and each dilution was mixed with equal parts of RBCs. 50 ul of each mixture was pipetted onto blood spot papers, frozen, thawed, and then assayed.

<table>
<thead>
<tr>
<th>DILUTION FACTOR</th>
<th>EXPECTED ng/dL</th>
<th>OBSERVED ng/dL</th>
<th>RECOVERY %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>287.75</td>
<td>287.75</td>
<td>100%</td>
</tr>
<tr>
<td>x2</td>
<td>143.88</td>
<td>135.20</td>
<td>94.0%</td>
</tr>
<tr>
<td>x4</td>
<td>71.94</td>
<td>77.84</td>
<td>108.2%</td>
</tr>
</tbody>
</table>

PRECISION:
The intra-assay precision was determined from the mean of 10 replicates each.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>N</th>
<th>MEAN ng/dL</th>
<th>STANDARD DEVIATION ng/dL</th>
<th>COEFFICIENT OF VARIATION %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C I</td>
<td>10</td>
<td>140.32</td>
<td>12.45</td>
<td>8.9</td>
</tr>
<tr>
<td>C II</td>
<td>10</td>
<td>70.07</td>
<td>4.43</td>
<td>6.3</td>
</tr>
</tbody>
</table>

The inter-assay precision was determined from the mean of average duplicates for 4 separate runs.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>N</th>
<th>MEAN ng/dL</th>
<th>STANDARD DEVIATION ng/dL</th>
<th>COEFFICIENT OF VARIATION %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C I</td>
<td>4</td>
<td>146.65</td>
<td>8.71</td>
<td>5.9</td>
</tr>
<tr>
<td>C II</td>
<td>4</td>
<td>64.73</td>
<td>6.42</td>
<td>9.9</td>
</tr>
</tbody>
</table>
SPIKE AND RECOVERY:

The zero calibrator was spiked with three different levels of T3 and mixed with equal parts of RBCs. 50 ul of each mixture was pipetted onto blood spot papers, frozen, thawed, and then assayed.

<table>
<thead>
<tr>
<th>Endogenous (ng/dL)</th>
<th>Added (ng/dL)</th>
<th>Expected (ng/dL)</th>
<th>Observed (ng/dL)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37.5</td>
<td>37.5</td>
<td>34.7</td>
<td>92.5</td>
</tr>
<tr>
<td>0</td>
<td>112.5</td>
<td>112.5</td>
<td>94.9</td>
<td>84.3</td>
</tr>
<tr>
<td>0</td>
<td>187.5</td>
<td>187.5</td>
<td>157.5</td>
<td>84.0</td>
</tr>
</tbody>
</table>

SENSITIVITY:

The low limit of sensitivity of the assay was determined by mixing equal parts of the zero calibrator and red blood cells and spotting 50 uL onto blood spot papers. The spots were frozen and thawed before assay. The lower limit of sensitivity was determined by interpolating the mean minus 2 SD for eleven zeros. The minimal concentration of T3 that can be distinguished from 0 is 30 ng/dL.
IGF-1 BLOOD SPOT PERFORMANCE CHARACTERISTICS

LINEARITY OF DILUTION:

A plasma sample was diluted linearly and each dilution was mixed with equal parts of RBCs. 50 ul of each mixture was pipetted onto blood spot papers, frozen, thawed, and then assayed.

<table>
<thead>
<tr>
<th>DILUTION FACTOR</th>
<th>EXPECTED ng/mL</th>
<th>OBSERVED ng/mL</th>
<th>RECOVERY %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>270.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>x2</td>
<td>135.09</td>
<td>133.04</td>
<td>98.5</td>
</tr>
<tr>
<td>x4</td>
<td>67.54</td>
<td>57.27</td>
<td>84.8</td>
</tr>
</tbody>
</table>

PRECISION:

The intra-assay precision was determined from the mean of 10 replicates of low, mid and high concentrations of IGF-1.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>N</th>
<th>MEAN ng/mL</th>
<th>STANDARD DEVIATION ng/mL</th>
<th>COEFFICIENT OF VARIATION %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10</td>
<td>25.0</td>
<td>1.75</td>
<td>7.0</td>
</tr>
<tr>
<td>Mid</td>
<td>10</td>
<td>59.14</td>
<td>3.19</td>
<td>5.4</td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>129.96</td>
<td>8.87</td>
<td>6.8</td>
</tr>
</tbody>
</table>

The inter-assay precision was determined from the mean of average duplicates for 4 separate runs.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>N</th>
<th>MEAN ng/mL</th>
<th>STANDARD DEVIATION ng/mL</th>
<th>COEFFICIENT OF VARIATION %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>4</td>
<td>93.13</td>
<td>4.44</td>
<td>4.8</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>166.85</td>
<td>7.55</td>
<td>4.5</td>
</tr>
</tbody>
</table>
• SPIKE AND RECOVERY:

The zero calibrator was spiked with three different levels of IGF-1 and mixed with equal parts of RBCs. 50 ul of each mixture was pipetted onto blood spot papers, frozen, thawed, and then assayed.

<table>
<thead>
<tr>
<th>Endogenous (ng/mL)</th>
<th>Added (ng/mL)</th>
<th>Expected (ng/mL)</th>
<th>Observed (ng/mL)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>55.0</td>
<td>55.0</td>
<td>64.3</td>
<td>116.9</td>
</tr>
<tr>
<td>0</td>
<td>110.0</td>
<td>110.0</td>
<td>117.1</td>
<td>106.5</td>
</tr>
<tr>
<td>0</td>
<td>165</td>
<td>165</td>
<td>158.7</td>
<td>96.2</td>
</tr>
</tbody>
</table>

SENSITIVITY:

The low limit of sensitivity of the assay was determined by mixing equal parts of the zero calibrator and red blood cells and spotting 50 uL onto blood spot papers. The spots were frozen and thawed before assay. The lower limit of sensitivity was determined by interpolating the mean minus 2 SD for 10 zeros. The minimal concentration of IGF-1 that can be distinguished from 0 is < 20 ng/mL.
BIOGRAPHICAL

University Address
Department of Kinesiology
Room 267Q Recreation Building
Penn State University
University Park, PA 16802

Phone: 814-865-1346
Fax: 814-865-1275
Email: niwl@psu.edu

EDUCATION

1984 B.S. Biology, Bucknell University, Lewisburg, PA
1986 M.S. Exercise Physiology, The Ohio State University, Columbus, OH
1992 Sc.D. Applied Anatomy & Physiology, Boston University, Boston, MA
1992-1996 Postdoctoral fellowship, University of Pittsburgh School of Medicine, Center for the Study of Reproductive Physiology (Judy L. Cameron PhD, mentor)

PROFESSIONAL EXPERIENCE

2003-present Associate Professor Department of Kinesiology and Noll Physiological Research Center
Joint Appointments:
   Intercollege Program in Physiology, Department of Nutrition, Life Science Consortium (Nutrition Science Option);
   Penn State University
   University Park, PA

1997-2003 Assistant Professor Department of Kinesiology and Noll Physiological Research Center
Joint Appointments:
   Intercollege Program in Physiology, Department of Nutrition, Life Science Consortium (Nutrition Science Option);
   Penn State University
   University Park, PA

1996-1997 Visiting Assistant Professor Human Anatomy & Physiology
   Department of Biological Sciences
   Ohio University
1992-1996 Postdoctoral Fellow: Center for the Study of Reproductive Physiology
School of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

1987-1992 Graduate Fellow: Department of Health Sciences
Sargent College
Boston University
Boston, Massachusetts

Research Projects: NIH grant: "Effects of exercise on pituitary hormone secretion"
NIH grant: "Exercise as an adjunct therapy for persons with mental illness"

Health/Fitness Center Coordinator: Faculty/Staff Fitness Program
Department of Health Sciences
Sargent College
Boston University
Boston, Massachusetts

1986-1987 Project Director: Exercise Physiology Laboratory
Department of Exercise Science
The Ohio State University
Columbus, Ohio

NIH Grant: "Effects of chronic exercise training on aging"

1984-1986 Research Assistant: Exercise Physiology Laboratory
Department of Exercise Science
The Ohio State University, Columbus, Ohio

NIH Grant: "Effects of chronic exercise training on aging"

HONORS AND AWARDS

Canada Research Chair Nomination (declined), York University, Toronto, Ontario, Canada 2003

Department of Defense Breast Cancer Research Program, Career Development Award, 2001
Fellowship Status: American College of Sports Medicine, 1998

NIH Individual National Research Service Award (NRSA), 1994-1996

Endocrine Society; Women in Endocrinology Travel Award, 1995

Association of Women in Science Education Foundation Award, 1990

American Association of University Women Predoctoral Fellowship, 1990

American College of Sports Medicine, New England Chapter Scholarship Award; 1989

Phi Sigma Biological Honor Society; 1984

Scholar/Athlete of the Year, Southern New Jersey Courier Post, 1980

PROFESSIONAL MEMBERSHIPS/AFPILIATIONS

Collaborative Scientist, Oregon National Primate Research Center  2003-present
American College of Sports Medicine  1984-present
Endocrine Society  1996-present
New England Chapter ACSM  1987-1992
Association for Women in Science  1987-1992
Mid-Atlantic Chapter ACSM  1997-present
Female Athlete Triad Coalition  2004-present

TEACHING

COURSES TAUGHT AT BOSTON UNIVERSITY:

HS 276 Physiology of Exercise Laboratory
HS 302 Exercise Physiology(Lecture)
HS 535 Clinical Fitness Evaluation
HS 573 Physiology of Activity (Lecture)
HS 573 Physiology of Activity (Laboratory)

COURSES TAUGHT AT OHIO UNIVERSITY:

BIOS 450/550 Principles of Endocrinology (section on neuroendocrinology)
BIOS 446/546 Exercise Physiology Laboratory
BIOS 345 Human Physiology
BIOS 346 Human Physiology Laboratory

COURSES TAUGHT AT PENN STATE UNIVERSITY:
<table>
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<tr>
<td>Fall 1997</td>
<td>Kines 481W</td>
<td>Scientific basis of Exercise for Older Adults</td>
<td>3</td>
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<td>Spring 1998</td>
<td>Kines 456</td>
<td>Fitness Appraisal</td>
<td>4</td>
<td>96</td>
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<td></td>
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<td>Independent Study</td>
<td>3</td>
<td>5</td>
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<td></td>
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<td>Practicum</td>
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<tr>
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<td>Kines 496C</td>
<td>Independent Study</td>
<td>1-3</td>
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<tr>
<td>Fall 1998</td>
<td>Kines 456</td>
<td>Fitness Appraisal</td>
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<td></td>
<td>Kines 456h</td>
<td>Fitness Appraisal (honors option)*</td>
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<td></td>
<td>Kines 496c</td>
<td>JumpStart to Health/Fitness</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Kines 496c</td>
<td>Independent Study</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Kines 496c</td>
<td>Independent Study (Schreyer Student)**</td>
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<tr>
<td></td>
<td>Kines 596c</td>
<td>Supervised Teaching</td>
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<td>Kines 597i</td>
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## COURSES TAUGHT ...cont.

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<th>Title</th>
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<th>Enrollment</th>
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<td></td>
<td>Kines 424</td>
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<td>Independent Study</td>
<td>3</td>
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</tr>
<tr>
<td>Summer 99</td>
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<td>Fitness Appraisal</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Fall 99</td>
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<td>Female in Exercise and Sport</td>
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*Supervised the writing of new laboratory experiment and handout for Kines 456
** Supervise students who work in my laboratory on research project examining the interactions between reproductive function disturbances, eating habits, and body image

### STUDENT TRAINING

28
Preceptor

NIH GM08619-07 Research Training in Physiological Adaptations to Stress. National Institute of General Medical Sciences, 1996-2005. Director is PA. Farrell, PhD, Noll Physiological Research Center, Penn State University

Committee Chair- Undergraduate Honors Thesis Students
2000  Kathleen Flecker – Shreyer’s Honors College: "Weight and diet concerns among female athletes with menstrual cycle irregularities" (Winner 3rd place Undergraduate Research Exhibition; attended medical school)

2003  Meredith Snook- Shreyer’s Honors College: “Effects of a diet and exercise on interactions between thyroid hormone, resting metabolic rate, and anthropometric measurements in normal weight healthy young women” (Earned full scholarship to University of Pittsburgh Medical School in a special clinical program designed to train clinicians to conduct clinical research)

Committee Chair- Masters Students
1999  Paula Wilkins "Body Image, Social Physique Anxiety, and Menstrual Dysfunction in the Female Athlete" (Physiology)

2000  Heather McConnell "Determining the validity of ovulation detection methods in an athletic population" (Physiology)

2000  Angelique Matuch "Quantifying physiological responses prior to competitive exercise" (Kinesiology)

2002  Megan Senior "Screening for Subclinical Eating Disorders in Female Athletes: The Use of an Indirect Interview Technique " (Nutrition)

2004  Michael Perry “Effects of chemotherapy followed by exercise training on reproductive status and stress hormones in breast cancer patients” (Kinesiology)

2004  Kelly Dougherty “No relation between leptin and exercise-associated reproductive disturbances in healthy normal weight young women” (Kinesiology)

2004  Brian Frye “Predictors of weight loss in a diet and exercise intervention in young women” (Kinesiology)

Committee Chair - Doctoral Students
1999  *Jill Bush "Proenkephalin peptide F concentrations in different blood bio-compartments: The effect of an acute resistance exercise protocol" (Kinesiology)

2004  Heather Leidy “Role of ghrelin in energy homeostasis” (Physiology)

* = co-chaired this committee in lieu of the early departure of her major advisor, William Kraemer

Committee Member- Masters Students
1997  Scott Mazetti "The influence of direct supervision of heavy resistance training on muscular performance and hormonal responses" (Kinesiology)

1998  Sang Kyung Kim "The effects of menstrual function on plasma peptide F immunoreactivity in response to high intensity cycle exercise" (Kinesiology)

1998  Jennifer DeSanto "Body Composition and energy balance: Comparison between eumenorrheic and amenorrheic athletes" (Kinesiology)

1998  Wallace Baker "Characterization of leukocyte infiltration after muscle damage" (Kinesiology)
1998  Steve Tokeshi "Maximal isokinetic force generation in upper body musculature during concentric and eccentric actions: a gender comparison" (Kinesiology)

1999  Jannell MacAulay "Submaximal cycle ergometry as a predictor of maximal aerobic capacity in women on oral contraceptives" (Kinesiology)

2000  Britney Salkeld "The effect of oral contraceptive use on measures of fatigue and energy metabolism" (Kinesiology)

2003  James Butler (Media Studies)

2003  Micheal Curren “Octreotide improves orthostatic tolerance in women” (Physiology)

Committee Member- Doctoral Students
1998  Jeff Volek "Fasting and postprandial serum lipoprotein responses to a hypocaloric low carbohydrate diet rich in monounsaturated fat and supplemented with n-3 fatty acids" (Kinesiology)

2002  Greg Daniels "Walking and running: Information and energetics" (Kinesiology)

2002-present  Nancy Johnston “Bio-markers of pre-term labor” (Nursing, Physiology minor)

Undergraduate Research Advising:
Summer 1998 Minority High School Student Research Apprentice Program at Penn State University
* Mentored student who helped with research projects in laboratory

Fall 98 to 2001 WISE program; Women in Science in Engineering
* Have averaged two female students per year who have worked in laboratory

Summer 2001 Minority Access to Research Careers (MARC)
* Mentored student who helped with research projects in laboratory

Summer 2002 McNair Scholars Programs
* Mentored first generation college student who performed research project

RESEARCH

INTRAMURALLY FUNDED GRANTS

(Completed)

Sargent College of Allied Health Professions
Boston University, Boston, Massachusetts
Principal Investigator:
"Effects of exercise and caloric restriction upon luteinizing hormone secretion"

2. Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program, 1997-1998; $5000

Principal Investigator:
"Prevalence of Female Athlete Triad Disorders: Estimation by Questionnaires and Subsequent Follow-up with Clinical and Laboratory Assessments of Physiological Status"

3. Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program, 1998-1999; $6000

Principal Investigator:
"Disturbances in Reproductive Function caused by Metabolic Stress: Possible Increased Susceptibility in Individuals with Elevated Levels of Perceived Psychological Stress"

4. Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program, 1999-2000; $6000

Co-Investigator: (PI Jay Hertel)
"Changes in risk factors of anterior cruciate ligament ruptures in female collegiate athletes across the menstrual cycle"

5. Penn State University
Pathology Initiation Grant
Hershey Medical Center, Dept. Pathology
January 2002-January 2003 5%
$15,170

Co-Investigator (PI is Williams' Doctoral student, Thomas Whipple, MS, PT)
"The Role of Resistance Exercise and Energy Availability on Bone Metabolism"

6. Penn State University
Children's Youth and Family Consortium
Penn State University, CHHD
January 2002- January 2003 5%
$13,925

Co-Principal Investigator (with Moira Petit, PhD (PSU-Hershey))
"Designing Intervention Programs to Optimize Bone Development: Application of Bone Markers to Monitor the Short-term Response to Exercise"
EXTRAMURALLY FUNDED GRANTS

(Completed)

1. NIH National Research Service Award (NRSA), 1994-1996
   Center for the Study of Reproductive Physiology
   School of Medicine
   University of Pittsburgh
   Pittsburgh, Pennsylvania

   Principal Investigator:
   "Metabolic cues governing reproductive hormone secretion"

2. Pharmavite Corporation, Seattle, Washington
   Research Grant-in-Aid, 1998-1999; $20,000

   Principal Investigator:
   "Consumer Taste and Education of a Nutritional Sports Supplement"

3. US Army Medical Research and Materiel Command
   US Army Breast Cancer Program
   1998-2001 5%
   $292,539

   Co-Investigator:
   "Use of Exercise to Increase CD4 Lymphocytes following Chemotherapy Treatment for Breast Cancer"

******************************************************************************

(Active Support)

1. NIH
   1 RO1 HD39245-01 (Williams)
   5/1/01 - 4/30/04
   (currently in 1 yr no cost extension) 30%
   PHS/NICHD

   Principal Investigator:
   "Bioenergetics of Exercise-induced Menstrual Disturbances"

2. US Army Medical Research and Materiel Command
   US Army Breast Cancer Program (IDEA AWARD)
   9/17/01- 9/16/05 15%
   $408,878

   Principal-Investigator:
   "Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (IDEA Award)"
3. US Army Medical Research and Materiel Command  
US Army Breast Cancer Program  
(CAREER DEVELOPMENT AWARD)  
9/17/01- 9/16/05  50%  
$312,081  
Principal-Investigator:  
"Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (Salary Only)"

4. Retirement Research Foundation  
2000-2004  2%  
$56,832  
Co-Investigator: (PI is J.L. Cameron, PhD)  
"Physical Exercise and Brain Aging"

5. National Institutes of Health (NIH)  
HD-02-012 Cooperative Reproductive Science Research Centers at Minority Institutions  
2003-2008  
Co-Investigator:  
$1,160,204  5%  
"The efficacy and safety of metformin and lifestyle factors in the amelioration of hyperandrogenemia and its associated symptomology"

6. Cancer Research and Prevention Foundation  
Co-Investigator (PI is Kim Westerlind, AMC Cancer Research Center, Denver, CO)  
1/04-12/05  0%  
$76,865  
"Exercise and Estrogen Metabolism: Implications for Breast Cancer Prevention"

7. NASA  
Co-Investigator (PI is James Pawelczyk, PSU)  
4/1/05-3/31/06  5%  
$1,144,613  
"Improving Orthostatic Tolerance in Women: Control of Splanchnic and Cutaneous Vascular Capacitance"

(Pending)

1. National Institutes of Health (NIH)  
Co-Principal Investigator (PI is Susan Bloomfield, Texas A&M)  
4/1/05-3/31/09  28.8%  
$2,000,000  
"Impact of Food Restriction on Bone Health in Active Females"

(Not funded)

1. National Institutes of Health (NIH)  
1 RO1 (Co-Principal Investigator with Mary Jane De Souza, Univ. Toronto)  
7/01/02 - 6/30/07  15%  
PHS/NICHD  
$2,433,044  
"Clinical Sequelae Exercise-Induced Hypoestrogenism"
2. National Instiutes of Health (NIH)
Co-Investigator (PI is Terryl Hartman, PSU)  4/01/04-3/31/08  20%
                                          $2,085,448
   “Female Cancer Survivors Weight and Activity Intervention”

3. Dairy Farmers of Canada
Co-Principal Investigator (PI is Mary Jane De Souza, University of Toronto)
   1/1/05-12/31/06  10%
   “Can Increased Dietary Calcium Improve Recovery of Bone Health in Exercising Women Undergoing a Lifestyle Intervention for Severe Menstrual Disturbances?”

4. National Institutes of Health (NIH)
Co-Investigator (PI is Terryl Hartmen, Dept. Nutrition, Penn State)  4/1/05-3/31/09  15%
                                          $856,295
   “Antioxidant Status, Diet and Early Pregnancy”

RESEARCH REPORTS
Williams NI, Christante DH, Swavely K, Laufer E, McBrearty C, and Clark KC. Penn State Univeristy JogMate Study: Product Effectiveness and Consumer Appeal
Submitted to Pharmavite Corp, Seattle, WA, July 15, 1999

PUBLISHED MANUSCRIPTS


**BOOK CHAPTERS**

35

MANUSCRIPTS IN REVIEW

De Souza MJ, and Williams NI. Beyond Hypoestrogenism in Amenorrheic Athletes: Energy Deficiency as a Contributing Factor for Bone Loss (Submitted to Current Sports Medicine Reports)

MANUSCRIPTS IN PROGRESS

Williams, N.I. Williams, N.I., Berga S.L., and Cameron, J.L. Synergism of multiple sub-threshold stressors: effects of diet, exercise, and psychosocial stress on menstrual cyclicity

Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, Williams NI. Changes in ghrelin are concomitant with changes in body weight, leptin, and IGF-1 during an energy deficit-imposing diet and exercise program in normal weight, healthy young women

Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, Williams NI. Meal Calorie Content and Meal Timing Affect Specific Meal Response Characteristics of Total Ghrelin in Normal Weight Healthy Young Women

Leidy HJ, Frye BR, Duke KM, Albert AE, Snook ML, Williams NI. The Meal Related Pattern and Diurnal Rhythm of Ghrelin are Elevated Following an Energy Deficit-imposing Diet and Exercise Intervention

ABSTRACTS

N.I. Williams, K.A. Greaves, G.R. Brodowicz, T.E. Kirby, and D.R. Lamb, FASCM. Cardiovascular effects of endurance training during submaximal exercise in elders. Exercise Physiology Laboratory, The Ohio State University, Columbus, Ohio, 43210. (research abstract presented at the Midwest American College of Sports Medicine Winter Meeting, Boyne Mountain, Michigan, February, 1986)

N.I. Williams, K.A. Greaves, and D.R. Lamb, FASCM. “Cardiovascular function in lean and obese children during acute submaximal exercise”. Exercise Physiology Laboratory, The Ohio State University, Columbus, Ohio, 43210. (research abstract presented at the Midwest American College of Sports Medicine Winter Meeting, Boyne Mountain, Michigan, February, 1987)


Williams NI, Clark KL, Mihalko SL, Matuch AN, McConnell HJ. Body image, disordered eating, exercise, and depression in athletes and non-athletes: association with menstrual status. (presented at the American
Miles MP, Mackinnon LT, Williams NI, Bush JA, Marx JO, Mastro AM, Kraemer WJ. NK cell activity and LFA-2 expression after running (presented at the American College of Sports Medicine Annual Meeting, Seattle, WA June 3-6, 1999)


Mackinnon LT, Miles MP, Grove DS, Williams NI, Bush JA, Marx JO, Kraemer WJ. Effects of prolonged exercise on expression of perforin mRNA in peripheral blood natural killer (NK) cells (presented at Sports Medicine Australia, 1999)


Flecker KA, Williams NI. Body Image, disordered eating and menstrual status in collegiate athletes. (presented at the National Conference for Undergraduate Research (NCUR), University of Montana, Missoula, Montana, April 27-29, 2000)


Senior MK, Williams NI, McConnell HJ, Clark KC. Screening for subclinical eating disorders in female athletes: validation of an indirect interview technique. (Presented at the 24th Annual meeting of the Mid-Atlantic Regional Chapter of the American College of Sports Medicine, Bushkill, PA, November 2-3, 2001).


INVITED PRESENTATIONS

"Cardiovascular/Medical Applications for Aerobic Exercise", Aerobics and Fitness Association of America (AFAA), National Primary Certification Workshop, Boston, Massachusetts, October 3, 1987.

"Principles and Benefits of Exercise Training for Seniors", Annual Health Program, Leo Yasenoff Jewish Community Center, Columbus, Ohio, June 6, 1987.


"Exercise and Female Hormones: What are the Health Risks and Benefits?" American College of Sports Medicine Health Fitness Summit, April 14-18, 1999, New Orleans, LA

"Women's Health and Fitness Issues" Panel Discussion at American College of Sports Medicine Health Fitness Summit, April 14-18, 1999, New Orleans, LA

"Modulation of Reproductive Function by Metabolic Cues", invited speaker for Bucknell University Biology Department Seminar Series, March 3, 2000. Bucknell University, Lewisburg, PA

"Career Development for Women" Women and Sciences and Engineering (WISE) program for potential college students from surrounding area and other states, June 19, 2000, Penn State University


"Physiological Connections Between Factors of the Female Athlete Triad" Penn State Athletic Training Conference", April 12, 2002, Penn State University, University Park, PA

"Exercise and Women's Health: Lessons from the Female Athlete Triad", Department of Health and Exercise Science, April 25, 2002, Wake Forest University, Winston-Salem, NC

"Subclinical Eating Disorders and Menstrual Cycle Irregularities in Female Athletes" Eating Disorders on Campus, The Institutional Response, June 7, 2002, Eighth Annual Conference, Penn Stater Conference Center Hotel, Penn State University, University Park, PA

"Effects of Exercise on the Menstrual Cycle: Physiological mechanisms and practical considerations" February, 2003, School of Kinesiology and Health Science, York University, Ontario, Canada.

"Effects of Estrogen on Vascular Function", February, 2003, School of Kinesiology and Health Science, York University, Ontario, Canada.


"Exercise-associated menstrual disturbances: Physiological mechanisms and role of caloric restriction", November 24, 2003, Department of Health and Kinesiology, Texas A and M University, College Station, TX

"Exercise-associated menstrual disturbances: Physiological mechanisms and role of caloric restriction", November 25, 2003, Department of Nutrition, Texas A and M University, College Station, TX

"Exercise-associated menstrual disturbances: Physiological mechanisms and role of caloric restriction", December 4, 2003, Department of Endocrinology, Endocrine Research Conference, Hershey Medical Center, Penn State University, Hershey, PA

"Exercise-associated menstrual disturbances: Physiological mechanisms and clinical sequelae", March 2, 2004, Department of Exercise Science, University of Massachusetts, Amherst, MA)
SYMPOSIUM PRESENTATIONS


WORKSHOPS ATTENDED

The X and Y: Current Topics in Gender – Specific Medicine, April 6-7, 2001
Harvard Medical School, Department of Continuing Education, Boston, Massachusetts

SERVICE

PROFESSIONAL SERVICE

COMMITTEES

American College of Sports Medicine Student Affairs Committee, Student Representative for New England Chapter, 1988-1990

American College of Sports Medicine Executive Committee, Member at Large, New England Chapter, 1990-1991

American College of Sports Medicine, Strategic Health Initiative Committee: Women, Sports and Physical Activity, June 2000-2002

American College of Sports Medicine, Credentials Committee, Spring 2003-present

American College of Sports Medicine, Position Stand Review Committee, “Female Athlete Triad,” Spring 2002-present

REVIEWER
Journals

Journal of Applied Physiology, ACSM Health Fitness Journal Medicine, Science, Sports and Exercise, Journal Clinical Endocrinology and Metabolism

Grants


Editorial Board

American College of Sports Medicine Health and Fitness Journal (2002-present)

Fellow

American College of Sports Medicine, June, 1998

Participant

"Biopsychology of Infertility Workshop"
Sponsored by National Institutes of Health (National Institute of Child Health and Human Development); September 21-22, 1995; NIH Campus, Bethesda, Maryland

UNIVERSITY SERVICE

Advisory Board: The Tremin Trust Research Program on Women's Health, Penn State University, University Park, PA, 2001-present

University Committees

Faculty Senate (Spring 2002)-Senate Committee on Intra-University Relations

College Committees (College of Health and Human Development)

College of Health and Human Development Seed Grant Review Committee (Fall 00)
Faculty Council (Fall 00- Spring 2001)

Intercollege Program Committee (Physiology)

Candidacy Exam Committee (Intercollege Program in Physiology) (Spring 01-present)

Department Committees (Department of Kinesiology)

Curriculum Committee
Candidacy Committee
Search Committee
(Noll Laboratory Exercise Physiology positions)
Search Committee
(General Education Fitness Position)
Search Committee
(Department of Kinesiology Chair)
Curriculum Revisions (ad hoc)
Advisory Committee for Fitness Assessment Program
Search Committee
(Director, Noll Laboratory)
Advisory Committee
Search Committee

Fall, 1998 to Spring 2002
Fall, 1998 to 2002
Fall, 1998
Spring 99
Fall 01-Spring 02
Spring 01-Spring 02
Spring 02-present
Fall 02-Spring 04)
Fall 02-present
Spring 2003-present
University Presentations

Fall 1997  Kinesiology Proseminar  “Professional Development”
Fall 1998  Kinesiology Proseminar  “Professional Development”
Fall 1997  Nutrition Ingestive Behavior Journal Club  “Reproductive disturbances and low energy availability: aberrant eating habits”
Fall 1997  Kinesiology Colloquium  “Low energy availability and the female athlete: Clinical and Hormonal Effects”
Fall 1997  Population Research Institute  “Modulation of Reproductive Function by Metabolic Cues”
Spring 1998  Nutrition Dept. Colloquium  “Modulation of Reproductive Function by Metabolic Cues”
Spring 1998  Biobehavioral Health Dept. Colloquium  “Reproductive disturbances caused by low energy availability: Interaction with psychological stressors”

OTHER SERVICE

News article, Kinesiology Today, Spring 1999 issue, “Study links Body Image to Athletes’ Fertility”

Interview/article, The Penn Stater, September/October 1999 issue “Research and Discovery Section” by Nick McCarthy

Interview/article, The Penn Stater, 2000 issue of undergraduate research, “Research and Discovery”

Interview/article, Intercom, July, 1999. featured in “Focus on Research” article, by Barbara Hale.

2000 Undergraduate Exhibition
Served as Judge for the 2000 Undergraduate Exhibition in April, 2000.