

AD _____

Award Number: DAMD17-01-1-0360

TITLE: Effects of Moderate Aerobic Exercise Combined with
Caloric Restriction on Circulating Estrogens and IGF-I in
Premenopausal Women

PRINCIPAL INVESTIGATOR: Nancy I. Williams, Sc.D.

CONTRACTING ORGANIZATION: The Pennsylvania State University
University Park, Pennsylvania 16802-7000

REPORT DATE: October 2003

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

Best Available Copy

20040511 025

PII Redacted

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY
(Leave blank)**2. REPORT DATE**
October 2003**3. REPORT TYPE AND DATES COVERED**
Annual Summary (17 Sep 2002 - 16 Sep 2003)**4. TITLE AND SUBTITLE**

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

5. FUNDING NUMBERS

DAMD17-01-1-0360

6. AUTHOR(S)

Nancy I. Williams, Sc.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)The Pennsylvania State University
University Park, Pennsylvania 16802-7000

E-Mail: niw1@psu.edu

8. PERFORMING ORGANIZATION REPORT NUMBER**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012**10. SPONSORING / MONITORING AGENCY REPORT NUMBER****11. SUPPLEMENTARY NOTES****12a. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE**13. ABSTRACT (Maximum 200 Words)**

The 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 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 reduce the levels of two hormonal biomarkers, circulating estrogens and insulin-like growth factor I (IGF-I). As expected caloric restriction combined with aerobic exercise training occurring 4 times per week has resulted in increases in aerobic capacity, weight loss ranging from 2.5-7.5 kg and loss of body fat ranging from 3% to 7% over four months. Results for T3, IGF-1, and estrone look promising, although the number of subjects who have completed the study thus far is too low to test these changes statistically. Compliance to our dietary and exercise protocols has been excellent, with subjects completed 3.8/4 workouts per week, and meeting or exceeding their caloric intake goals. In conclusion, we are making good progress toward completion of this study.

14. SUBJECT TERMS

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

15. NUMBER OF PAGES

46

16. PRICE CODE**17. SECURITY CLASSIFICATION OF REPORT**

Unclassified

18. SECURITY CLASSIFICATION OF THIS PAGE

Unclassified

19. SECURITY CLASSIFICATION OF ABSTRACT

Unclassified

20. LIMITATION OF ABSTRACT

Unlimited

Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	5
Key Research Accomplishments.....	8
Reportable Outcomes.....	8
Conclusions.....	11
References.....	11
Appendices.....	11

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 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 reduced 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 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 centers on the 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 control groups. Both normal weight (BMI 21-25 kg/m²) and overweight (BMI 26-30 kg/m²) will be assigned to either exercise or control (no exercise, 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.

Recruiting/ Screening	Control 1	Control 2	Exercise 1	Exercise 2	Exercise 3	Exercise 4	Post- Exercis Testing
Beck Depression EDI Medical History Menstrual History Physical Activity Food Frequency Questionnaire	Urine Collection → Menstrual Symptoms → Ovulation Detection Kit Mid-luteal Progesterone VO _{2max} (FP) Body Composition FP) Physical Exam (FP) Endocrine Screening (FP) Menses	3-Day Diet Record Ovulation Detection Kit Mid-luteal Progesterone Diet Counseling (LP) Serum E ₁ & E ₂ (Days 3, 6, 8, 10, 12, 14, 16, 19, 22, & 25): Serum & DBS (FP): IGF-I, IGFBP-1, Insulin, T ₃ , leptin Menses	3-Day Diet Record (FP & LP) Body Composition Serum (FP): IGF-I, IGFBP-1, Insulin, T ₃ , leptin Menses	3-Day Diet Record (FP) Body Composition Serum (FP): IGF-I, IGFBP-1, Insulin, T ₃ , leptin Strict Diet & Menses	3-Day Diet Record (FP) Body Composition Serum (FP): IGF-I, IGFBP-1, Insulin, T ₃ , leptin Exercise Control Menses	3-Day Diet Record (FP) Body Composition Serum E ₁ & E ₂ (Days 3, 6, 8, 10, 12, 14, 16, 19, 22, & 25): Serum (FP): IGF-I, IGFBP-1, Insulin, T ₃ , leptin Menses	VO _{2max} Body Comp Serum & DE (FP): IGF-I, IGFBP-1, In T ₃ , leptin Menses
	→ = Entire Study FP = Follicular Phase		EDI = Eating Disorder Inventory LP = Luteal Phase E ₁ = Estrone			E ₂ = Estradiol	

Figure 1. Study Design

Progress According to the Approved Statement of Work:

(See previous Annual Summary for 2001-2002)

Proposed Month 13-16

1. Repeat steps above for year 2 recruiting and beginning testing (n=15 in each of 4 groups)
2. Perform assays on metabolic hormones in serum
3. Send serum and blood spot samples from year 1 subjects to DSL
4. Perform urinary assays on LH, E3G, PdG

Actual Month 13, September, 2003- We continued aliquotting and processing urine samples and data entry.

Actual Month 14, October, 2002 -completed data entry and are beginning preliminary data analysis; began assaying urine for E1G and PDG; beginning to assay metabolic hormones, i.e., insulin, leptin, T3, and IGF-I; preparing data reports for subjects that completed the study, and getting ready to recruit for Year 2.

Actual Month 15, November, 2002-Finished sending out data reports for all nine subjects that completed; held off on recruiting until Spring due to upcoming holiday season; continued assaying urine, but encountered difficulties with performance of research technician assigned assay duties

Proposed Months 16-24

1. Continue year 2 recruitment efforts only if necessary

2. Continue year 2 subject screening/initial testing
3. Complete year 2 subject exercise training/experimental testing
4. Perform urinary assays on LH, E1G, PdG

Actual Month 16, December, 2002- Held off running urinary assays, re-assigned duties of research technician, planned for new recruitment strategy

Actual Month 17, January, 2003- Placed ad for volunteers in local newspaper, and began "rolling recruitment strategy", by continuing to place ads and posting weekly fliers on campus. This was due to low enrollment. We also increased the age of enrollment to 40 years, again to increase study numbers. This increase will not affect the scientific underpinnings of the study.

Actual Month 18, February, 2003- Enrollment continuing, several subjects began study

Actual Month 19, March, 2003- Enrollment continuing, several subjects began study

Actual Month 20, April, 2003 Enrollment continuing, several subjects began study; having enlisted new technical help, began urinary assays for subjects that had completed study

Actual Month 21, May, 2003 Enrollment continuing, several subjects began study; continued assaying urine for reproductive hormones, began assaying metabolic hormones and serum estradiol and estrone

Actual Month 22, June, 2003- Enrollment continuing, several subjects began study; completed urinary assays of E1G and PDG; began assays for T3

Actual Month 23, July, 2003- Enrollment continuing, several subjects began study; continued assays for T3

Actual Month 24, August, 2003; Enrollment continuing, several subjects began study; continued assays for T3; began assays for IGF-1

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.

Preliminary Results From Years 1 and 2:

Subject Recruitment: We have accumulated over 249 contacts since September of last year. We have recently stepped up recruitment efforts and plan to enroll 55-60 new subjects by January, 2004. This will allow us to reach our target initial enrollment of 60, but we may need to extend the time frame of the study if sign-ups slow down towards the holidays. Forty-six women started the study and 19 have dropped out for the following reasons: 3 for menstrual abnormality, 5 medical, 10 self (time, intervention, etc.), and 1 noncompliant. The forty-six women described their ethnicity as the following: 32 Caucasian, 8 Asian, 3 African-American and 2 other. Ten women have completed the study, fourteen women are more than half-way through the study at this point in time.

Table 1. Initial characteristics of subjects completed and currently enrolled

Group	Age (yrs)	Weight (kg)	Height (cm)	BMI (kg/m ²)	% Fat	VO ₂ max (ml/kg/min)
Light Conditioning/Low BMI	32 ± 4	63 ± 3	167 ± 6	23 ± 2	29 ± 1	31 ± 1
Light Conditioning/High BMI	33 ± 5	68 ± 2	156 ± 6	28 ± 2	35 ± 5	25 ± 3

Exercising/ Low BMI	31 ± 4	62 ± 6	165 ± 6	23 ± 2	27 ± 5	32 ± 5
Exercising/ High BMI	30 ± 6	77 ± 8	166 ± 6	28 ± 2	37 ± 3	29 ± 7

Values are mean +/- SD

Results From Subjects Completing the Study: Subjects met our initial targets for weight, age, BMI and fitness levels. Average menstrual cycle length was 29.7 ± 5 days, and did not change significantly in either Low or High BMI group. Aerobic exercise training was 4 times per week for four consecutive menstrual cycles at 76 ± 3 % of maximum heart rate for 40-60 minutes, resulting in an average of 24% increase in aerobic capacity as defined by VO_2 max (32.6 ± 4.7 to 42.0 ± 10 ml/kg/min; $P < 0.05$ pre vs post). Dietary intake was successfully reduced using the food exchange system (Low BMI = 1778 ± 234 to 1230 ± 139 kcals; High BMI = 2345 ± 187 to 1350 ± 284 kcals; $P < 0.05$ pre vs post in both groups). The combination of moderate exercise and diet produced significant weight loss in both groups (Low BMI -3.3 %; High BMI -7.6% $P < 0.05$, Figure 3). Significant changes in percent body fat occurred in both groups (Low BMI 32 ± 4 % to 25 ± 8 %; High BMI 39 ± 5 to 32 ± 6 %: $P < 0.05$).

Body Weight Changes of Subjects Currently Exercising: Figures 1-4 illustrate the changes we are seeing in body weight in our experimental groups that are currently exercising. These changes in body weight represent an estimated 30% increase in energy expenditure for the "exercising groups", combined with a 25% reduction in caloric intake. The exercise completed by the "light conditioning" group represents an estimated 10% increase in energy expenditure, and no changes in caloric intake. All subjects meet every other week with the nutritionist to go over dietary records and review educational modules for that week.

Urinary Assays: We have completed urinary E1G and PDG for 9 subjects thus far and are now confirming ovulation day in these cycles by assaying urinary LH. We expect to complete these assays within the next two months, and then continue running them in batches as subjects complete the study. Preliminary results suggest no changes in cycle length, follicular phase length, luteal phase length with exercise, but a trend toward a reduction in the magnitude of the pre-ovulatory estradiol peak. Figure 5 shows representative data for subject D-001, and illustrates this reduction in the estradiol peak.

Metabolic Hormone Assays: We have completed assays for subjects who have completed the study for T3, and are in the middle of IGF-1 and leptin. We plan to run insulin and IGF-1 in the next three months, and continue with all these assays as individuals finish the study. We will run them in batches of 3-4 subjects at a time. Preliminary results indicate that IGF-1 is reduced with weight loss. Figures 6-8 illustrate this decrease in during the Control 2 month, and then during Exercise 4, in two out of three subjects who lost 3.2 to 7.5 kg

Serum estradiol and estrone: We have completed these assays for 9 subjects, and have them up and running to complete as subjects finish the study. We will run them in batches of 3-4 subjects at a time. Figures 9-12 changes in serum estrone, estradiol, and urinary estrone-1-glucuronide.

Blood Spot Assays: We had technical/administrative problems with our contracted source for the development of the blood spot assays, Diagnostic Systems Laboratory (see information in Appendix). They discontinued the blood spot assays. ZRT Laboratory was recommended. The PI contacted ZRT Laboratory and was unsatisfied with their customer support and knowledge base regarding quality control of the assays. The PI then re-contacted Doug Granger of Salimetrics at Penn State, and we now have a contract with them to develop the assays for leptin, T3, and IGF-1. We chose these hormones because they will be the best indicators of energy

availability, and therefore correlate the best with changes in body weight and estradiol and estrone. We should get results from them in six months time from this point forward.

Personnel/Technical Issues: Our progress has been delayed somewhat due to personnel issues relating to poor performance on the part of a research technician who is no longer with us.

Additionally, our project coordinator is out on maternity leave but will return in four weeks.

Overall Results from Years 1 and 2: All aspects of the study are up and running. Preliminary analyses indicate support for the hypotheses that estrone and IGF-1 will decrease with our exercise and diet intervention. Assay development using the blood spot technique is progressing, and thus we will be able to test the validity of this method for two newly developed assays, i.e., T3 and IGF-1, both of which, in our hands, will be very useful for doing field work and for obtaining samples from subjects outside of our immediate geographical area. Future grant proposals, and follow-up studies will make use of these techniques.

KEY ACCOMPLISHMENTS

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

REPORTABLE OUTCOMES

The following outcomes have occurred since Dr. Williams received BCRP funding.

Published Manuscripts:

Williams, N.I., Caston-Balderrama, A.L. Helmreich, D.L., Parfitt, D.B., Nosbisch C, Cameron, J.L. Longitudinal changes in reproductive hormones and menstrual cyclicity in cynomolgus monkeys during strenuous exercise training: rapid transition to exercise-induced amenorrhea *Endocrinology* 142: 2381-2389, 2001

Williams N.I., DL Helmreich DL, DB Parfitt, Caston-Balderrama AL, JL Cameron. Evidence for a causal role of low energy availability in the induction of menstrual cycle disturbances during strenuous exercise training. *J Clin Endocrinol Metab* 86: 5184-5193, 2001

Miles MP, Mackinnon LT, Grove DS, **Williams NI,** Bush JA, Marx JO, Kraemer WJ, Mastro AM. The relationship of natural killer cell counts, perforin mRNA and CD2 expression to post-exercise natural killer cell activity in humans. *Acta Physiol Scand* 174: 1-9, 2002.

McConnell HJ, KA O'Connor, E Brindle, and **NI Williams.** Validity of methods for analyzing urinary steroid data to detect ovulation in athletes. *Med. Sci. Sports Exerc*, 34(11): 1836-1844, 2002

Whipple TJ, Petit Moira, Sharkey N, Demers L, **Williams NI.** Leptin and the skeleton. *Clin. Endocrinol.* 57: 701-711, 2002.

Williams, NI. Experimental disruptions of the menstrual cycle: Lessons from long-term prospective studies. *Med Sci Sports Exerc* 35 (8): 1564-1572, 2003.

Manuscripts in Review

Williams, NI, Flecker KL, McConnell. Weight and Diet Concerns in Female Athletes: Association with Menstrual Cycle Length (submitted to *Int J Sports Nut Exerc Metab*, September, 2002)

Whipple TJ, Le B, Demers LM, Petit M, Sharkey N, and **Williams NI.** Acute effects of moderate intensity resistance exercise on bone cell activity (submitted to the *International Journal of Sports Medicine*, 2003).

McConnell HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, and **Williams NI.** Basal Ghrelin is Sensitive to Changes in Body Composition and Metabolic Rate during a Diet and Exercise Program in Normal Weight Young Women. (Submitted to *J. Clin. Endocrinol. Metab.* as a Rapid Communication, 2003).

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. (submitted to *Nature Medicine*, October, 2003)

Abstracts

Mastro AM, **Williams NI**, Kraemer WJ, Orsega-Smith EM, Perry MD, Dixon RH, Bleznak AD, Underwood J. Exercise, quality of life, and the recovery of CD4 (+) lymphocytes following chemotherapy for breast cancer *Proceedings of the American Association for Cancer Research 92nd Annual Meeting*, New Orleans, LA, 42 : 331, March 24-28, 2001

Perry MD, Mastro AM, Orsega-Smith E, Miles MP, Kraemer WJ, **Williams NI.** Exercise training and immune function following chemotherapy for breast cancer. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

Orsega-Smith E, **Williams NI** (FACSM), Perry MD, Mastro AM, Kraemer WJ, Bleznak A, Dixon R, Underwood J. Fatigue, quality of life and physical function after chemotherapy for breast cancer. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

Galucci, AN, **Williams NI.** Physiological indicators of psychological stress prior to competitive exercise. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

McConnell HJ, O'Connor KA, Brindle E, **Williams, NI.** Assessing reproductive function in exercising women: validity of ovulation detection algorithms. *Proceedings of the Endocrine Society Annual Meeting*, Abstract #P2-408, 2001

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).

McConnell HJ, **Williams NI**, O'Connor KA, Clark KL, Putukian M. Menstrual irregularities and disordered eating in female athletes: survey vs follow-up clinical and physiological studies. (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).

Mastro AM, **Williams NI**, Ford J, Fuener K, Orsega-Smith E, Kraemer WJ, Bleznak AD, Dixon RH, Underwood J, Miles M, Wagner K. IL-6 and interferon-gamma levels following chemotherapy for breast cancer. *Proceedings of the American Association for Cancer Research Annual Meeting*, San Francisco, CA, April 6-10, 2002

Hertel J, **Williams NI**, Gribble PA, McConnell HJ, DiPasquale AA, Putukian M. Changes in risk factors of ACL injuries across the menstrual cycle: A pilot study. *Proceedings of the American College of Sports Medicine Annual Meeting*, St. Louis, MO, May 29-June 1, 2002

Williams NI, McConnell HM, Gardner JK, Albert AC, Cameron JL. Lifestyle factors such as exercise, caloric intake, and psychological stress: relationship to reproductive hormones and possibly the risk of breast cancer. *Era of Hope* meeting, Department of Defense Breast Cancer Research Program, Orlando, FL, September 25-28, 2002

Dougherty, K., Galucci AN, McConnell HJ, **Williams NI**. Cortisol and testosterone levels prior to competitive exercise. (Submitted for presentation at the 2003 American College of Sports Medicine Annual Meeting, San Francisco, CA, June, 2003).

Williams NI, McConnell HJ, Gardner JK, Cameron JL, Schuchert MK, Richard EL, Snook ML. Susceptibility of menstrual cycle to various stressors: correlation with baseline luteal progesterone levels. (Presented at the 2003 American College of Sports Medicine Annual Meeting, San Francisco, CA, June, 2003).

McConnell HJ, Schuchert MK, Gardner JK, Frye BR, **Williams NI**. Basal Ghrelin is sensitive to changes in body weight during a controlled diet and exercise program in normal weight young women. (Presented at the 2003 Endocrine Society Meeting, Philadelphia, PA, June 2003).

Whipple TJ, Le, B., Demers, L., Petit M.A., Sharkey N. **Williams, NI**. Acute Effects of Moderate Intensity Resistance Exercise on Bone Cell Activity. (Presented at Association for Bone and Mineral Research Meeting, 2003).

Grants Applied For:

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

Cancer Research and Prevention Foundation

Co-Investigator

1/04-12/05

0%

\$76,865

“Exercise and Estrogen Metabolism: Implications for
Breast Cancer Prevention”

CONCLUSIONS

We are making good progress toward the completion of this study. Preliminary examination of the data look interesting and supportive of the hypotheses put forth in the study, but statistical power is too low at this point to draw firm conclusions.

REFERENCES

NONE

APPENDICES

Figures 1-12

Letters to and from Salimetrics, Inc.

N. Williams Curriculum Vitae

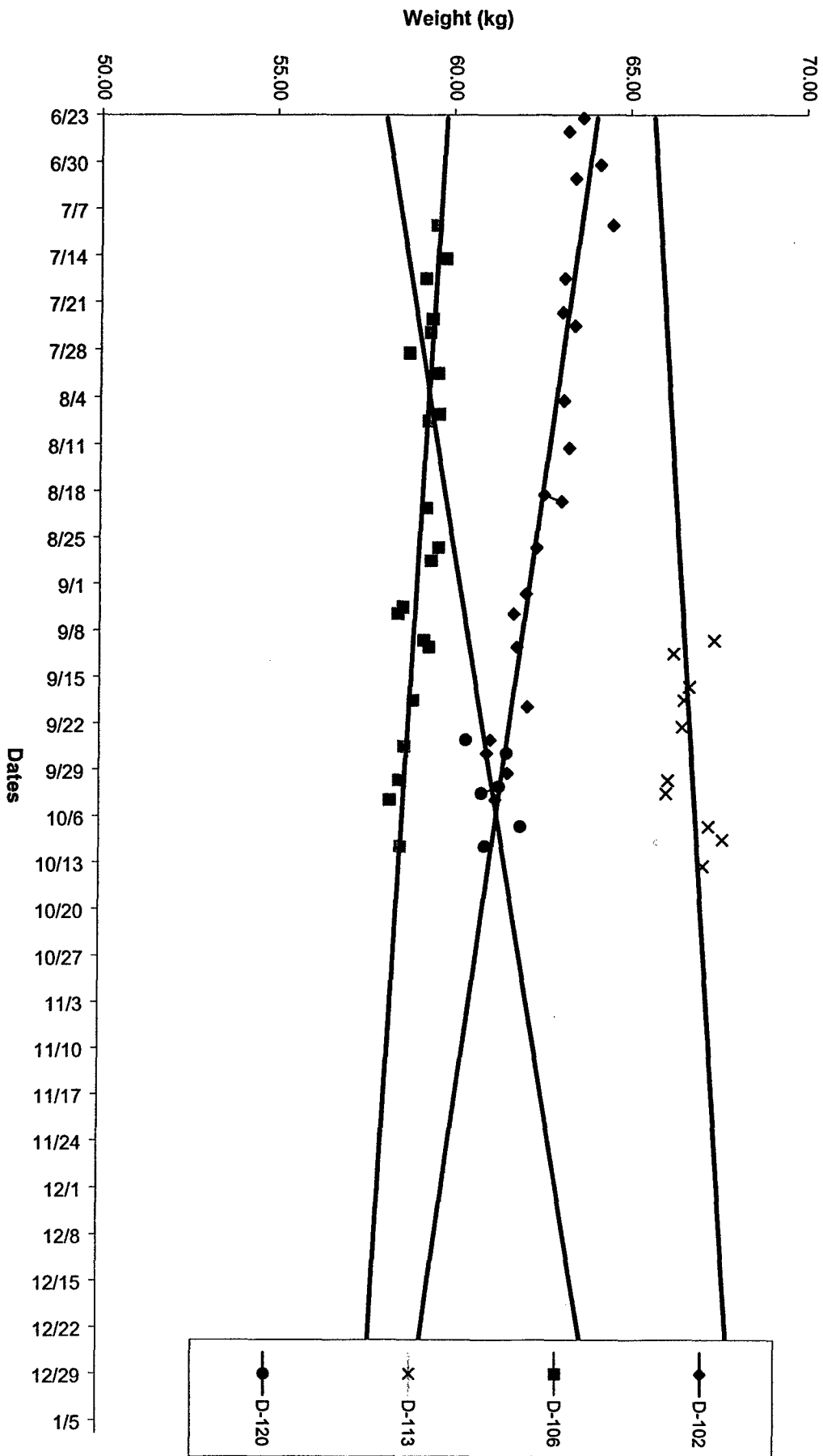
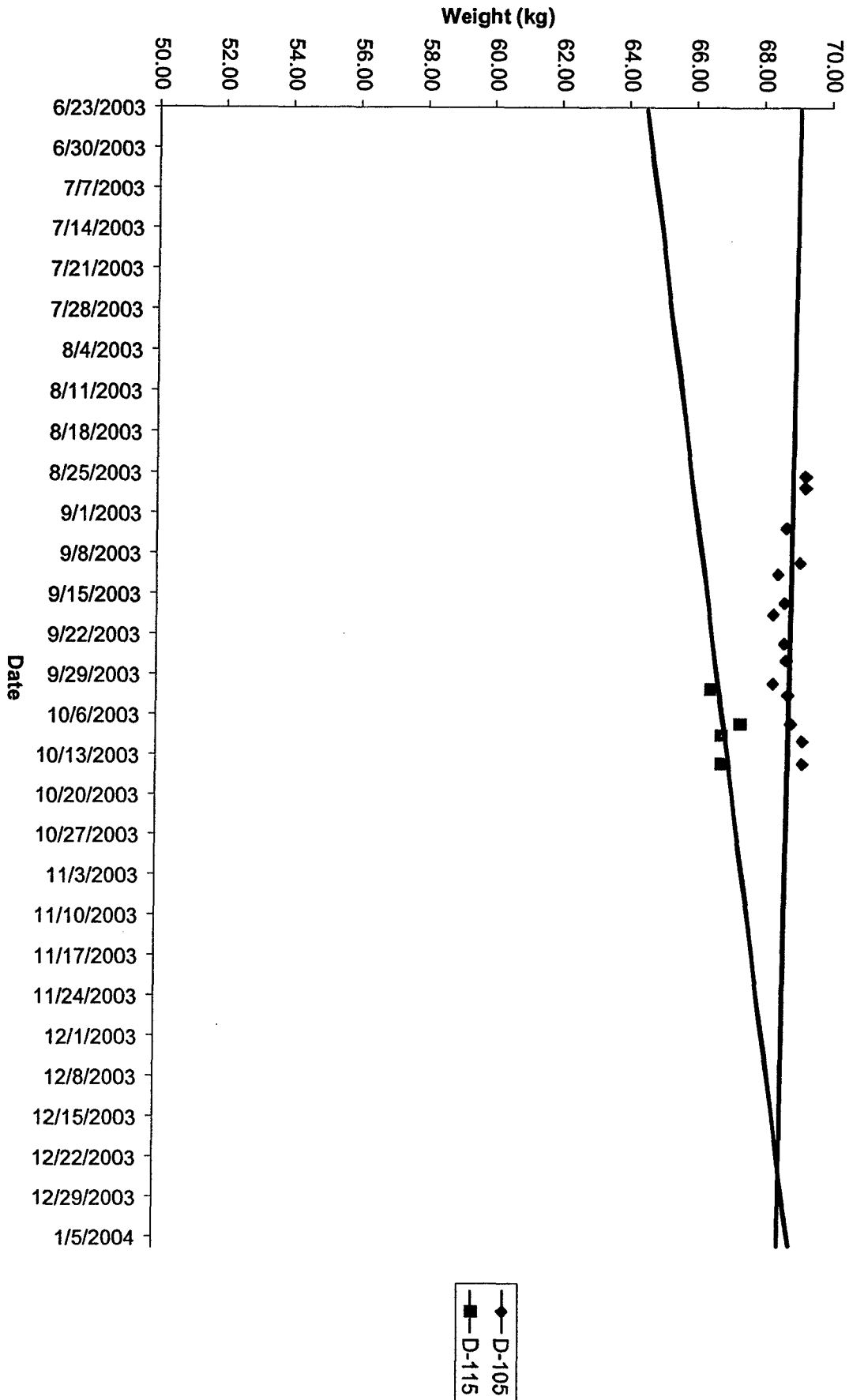


Figure 1
Light Conditioning/Low BMI

Figure 2

Light Conditioning/High BMI



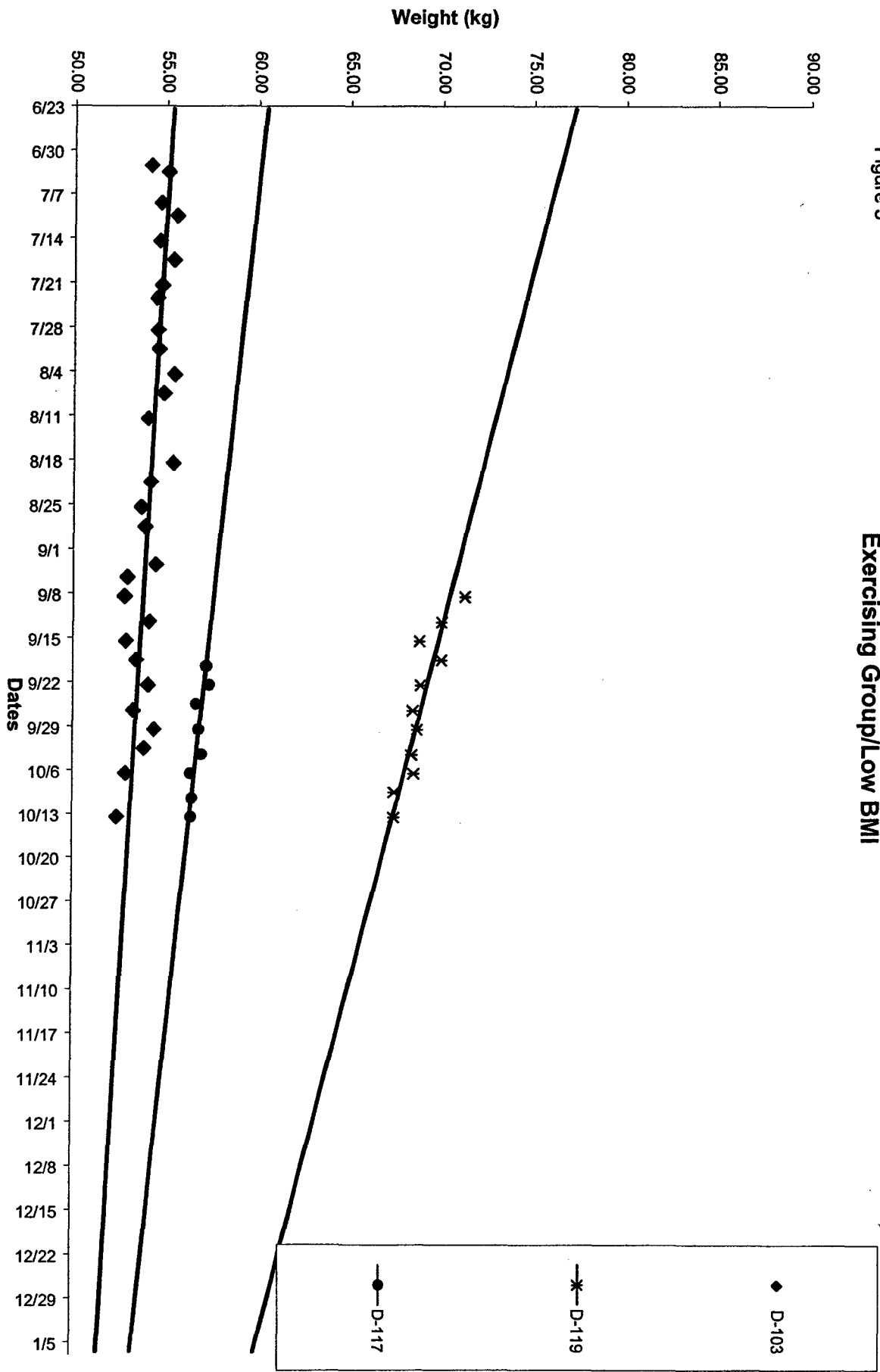


Figure 3

Exercising Group/Low BMI

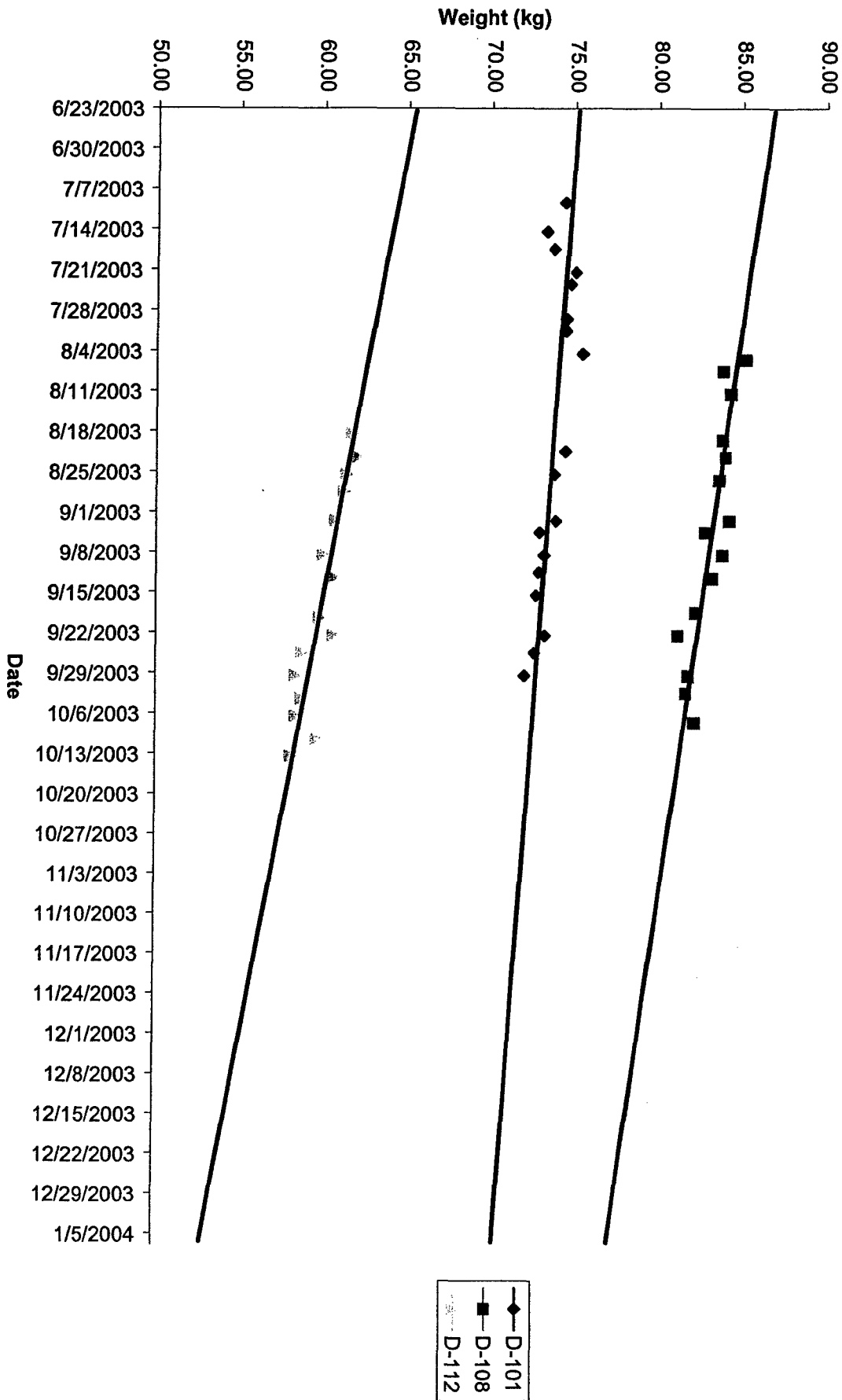
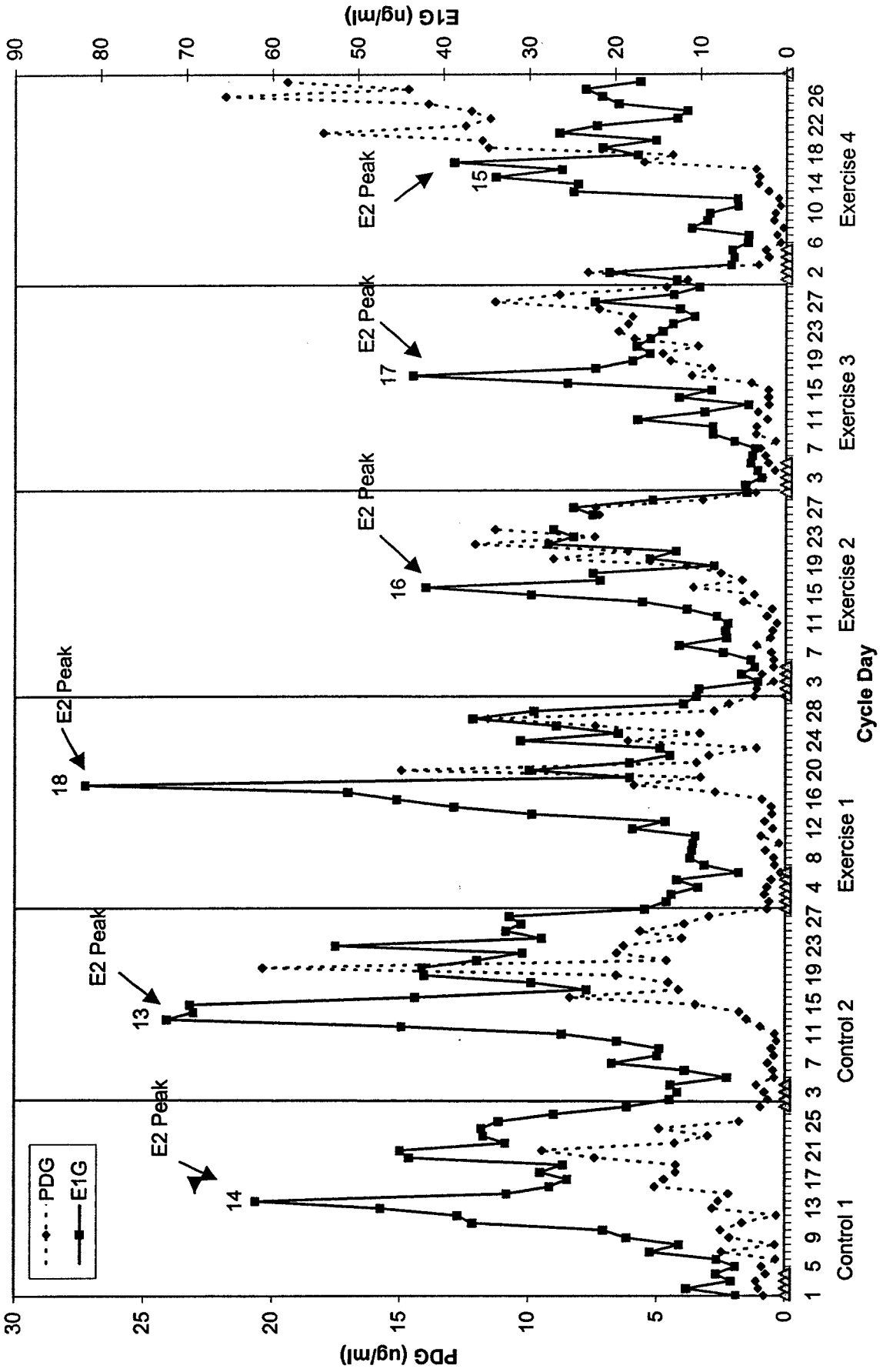


Figure 4

Exercisers High BMI

Figure 5

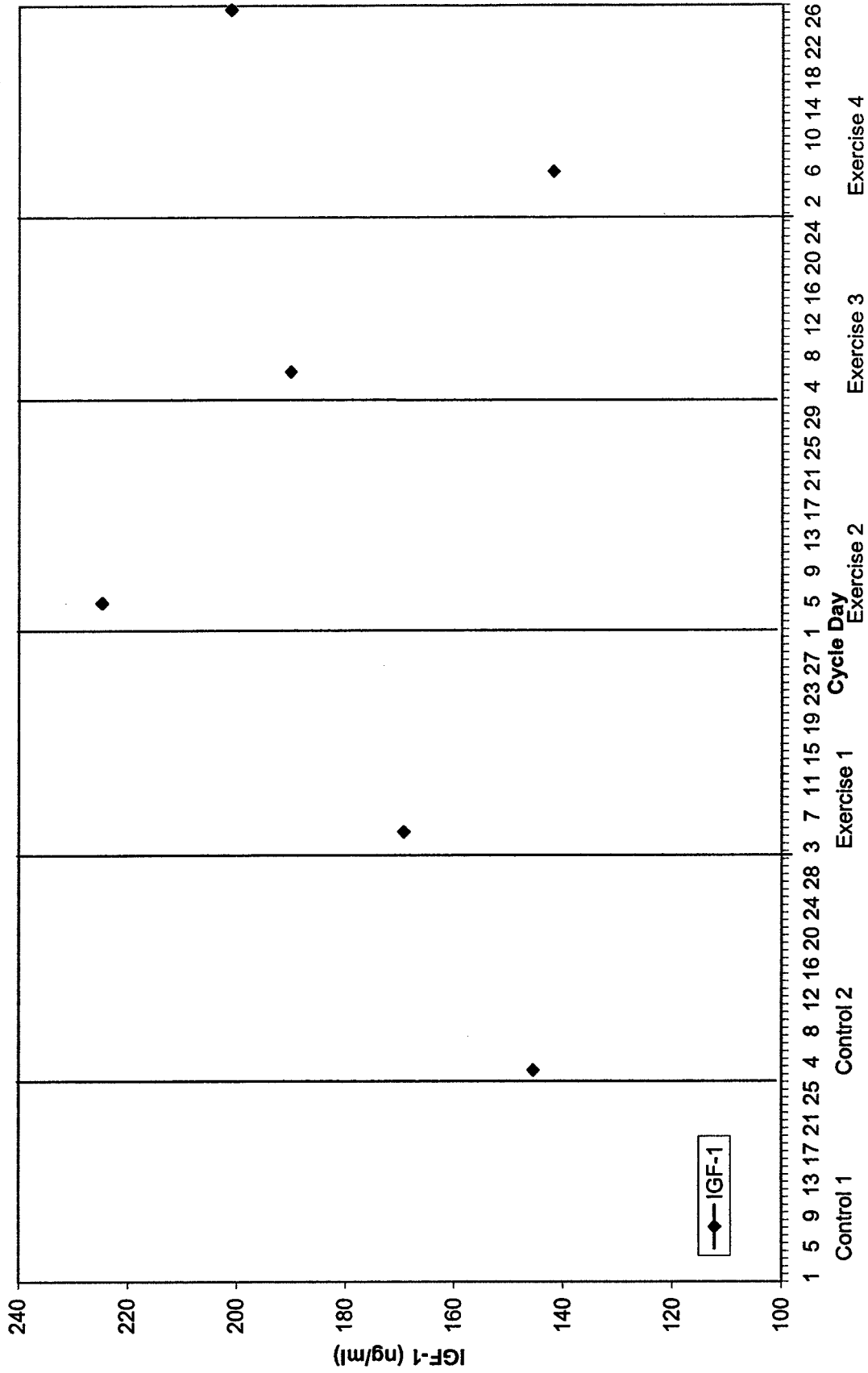
D-001



D-012 IGF-1

-7.5 Kg
-6.15 % body

Figure 6

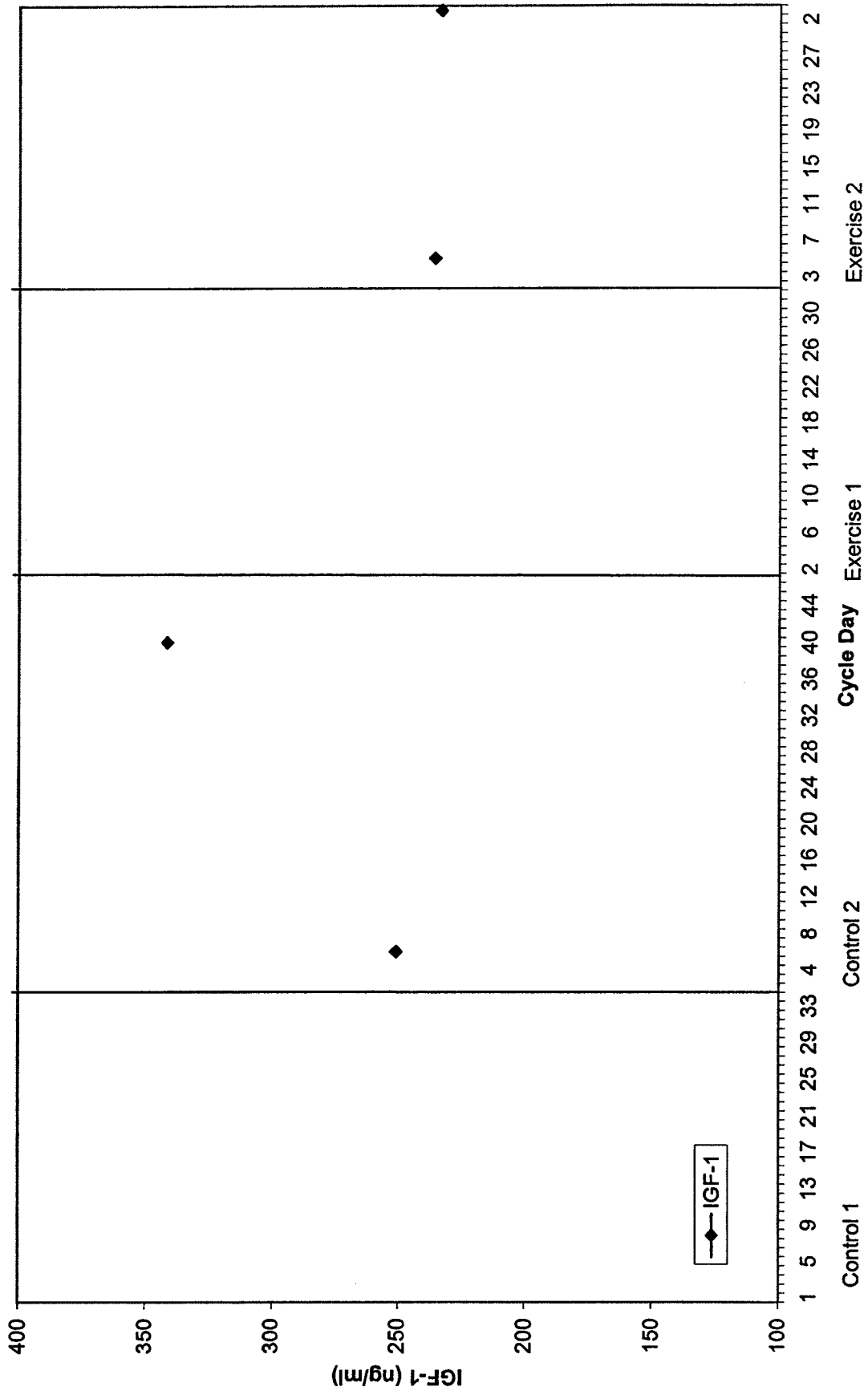


IGF-1

- 3, 2 4)
- 4, 6 ? fact

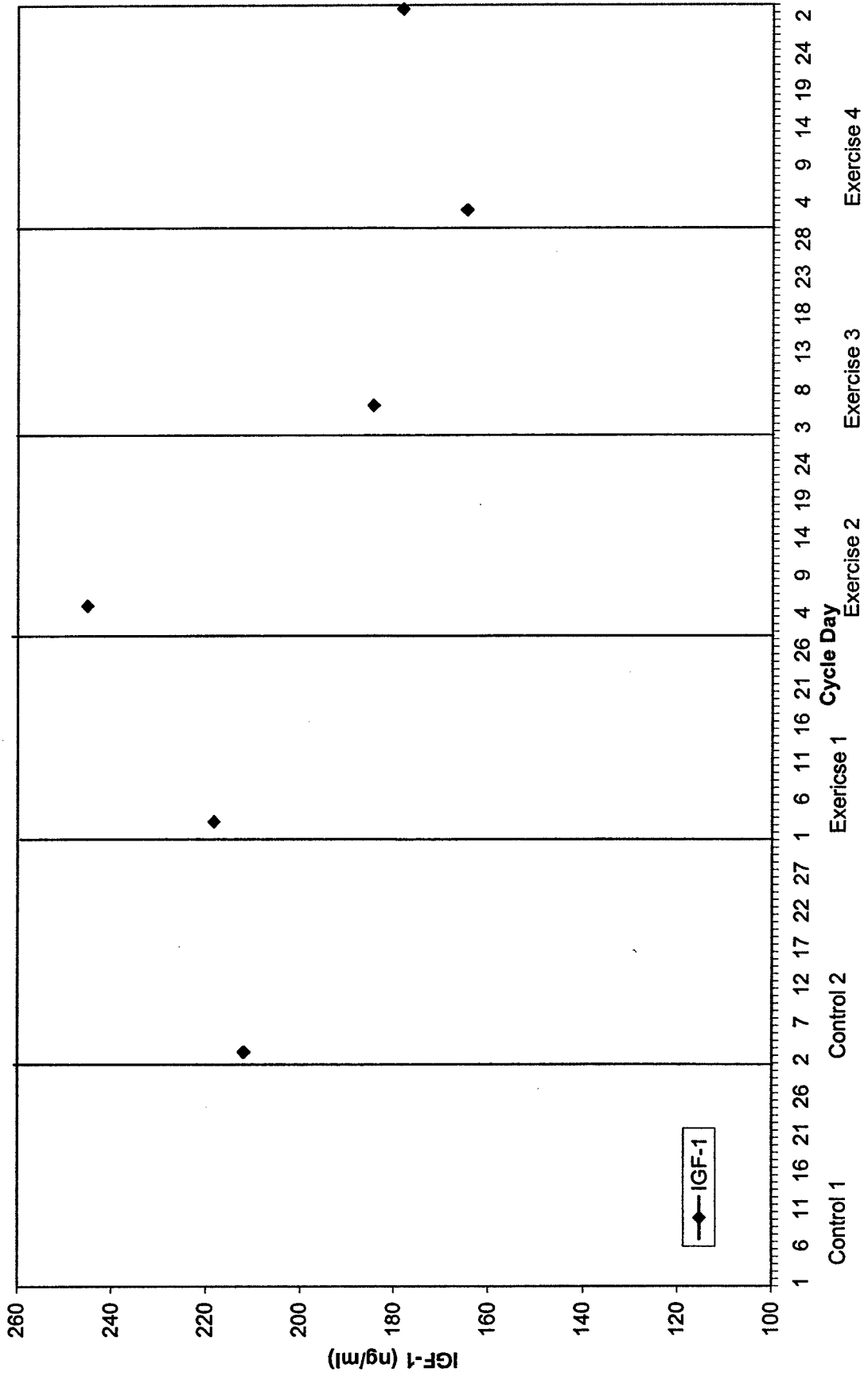
D-019 IGF-1

Figure 7



D-011 IGF-1

Figure 8



- 4.1 ug
- 5.2% fat

Figure 9

D-009

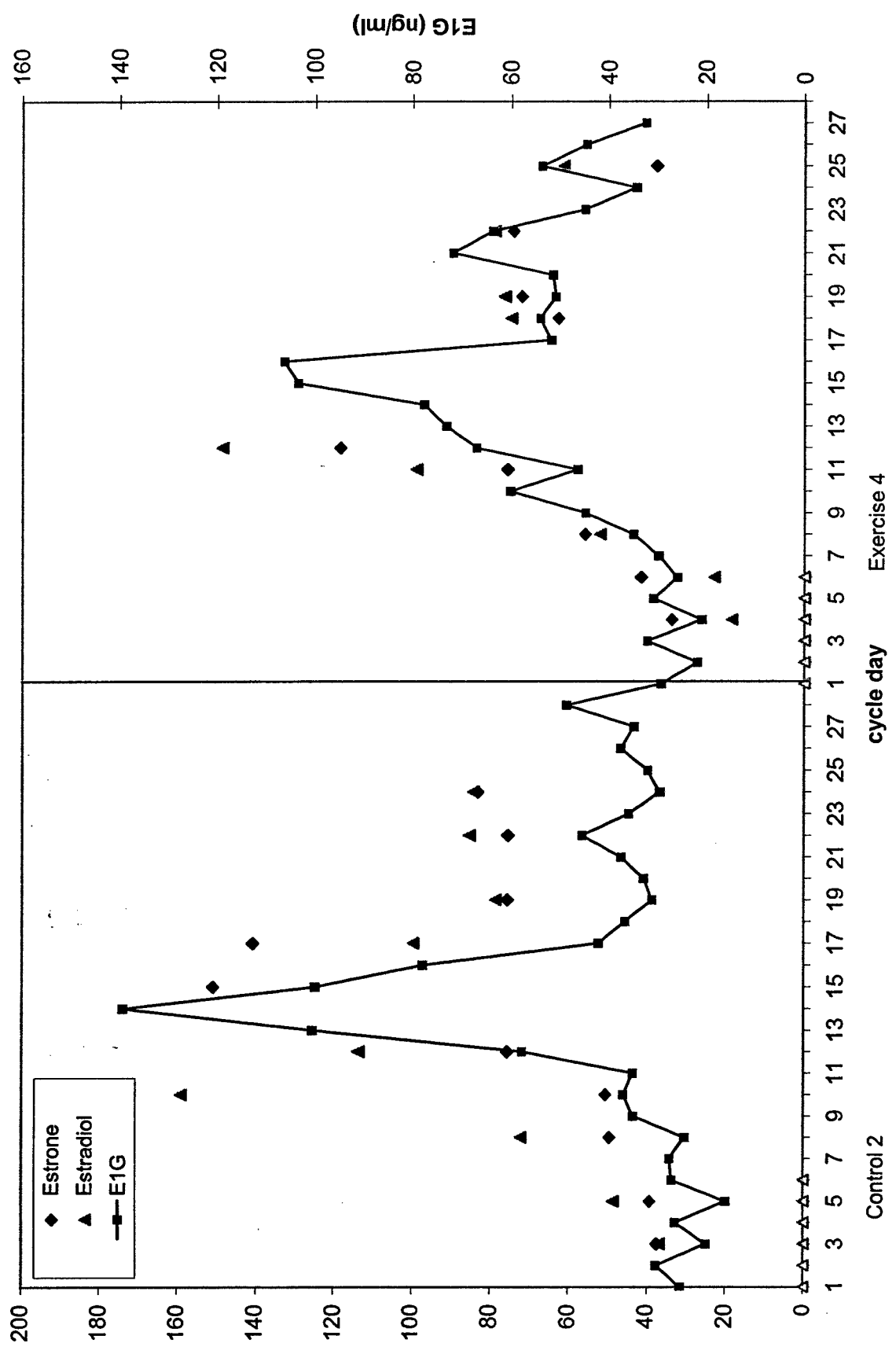


Figure 10

D-010

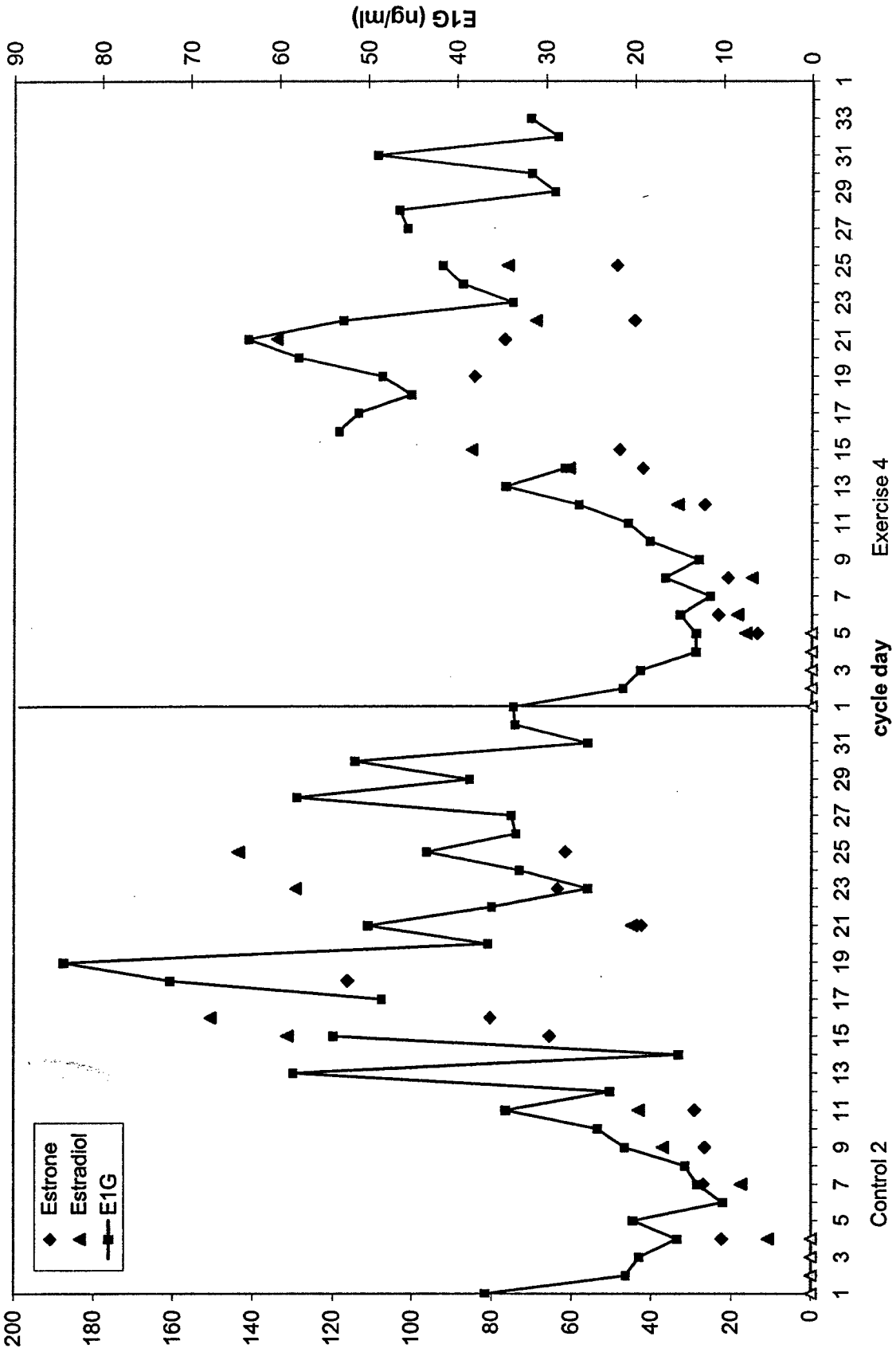


Figure 11

D-011

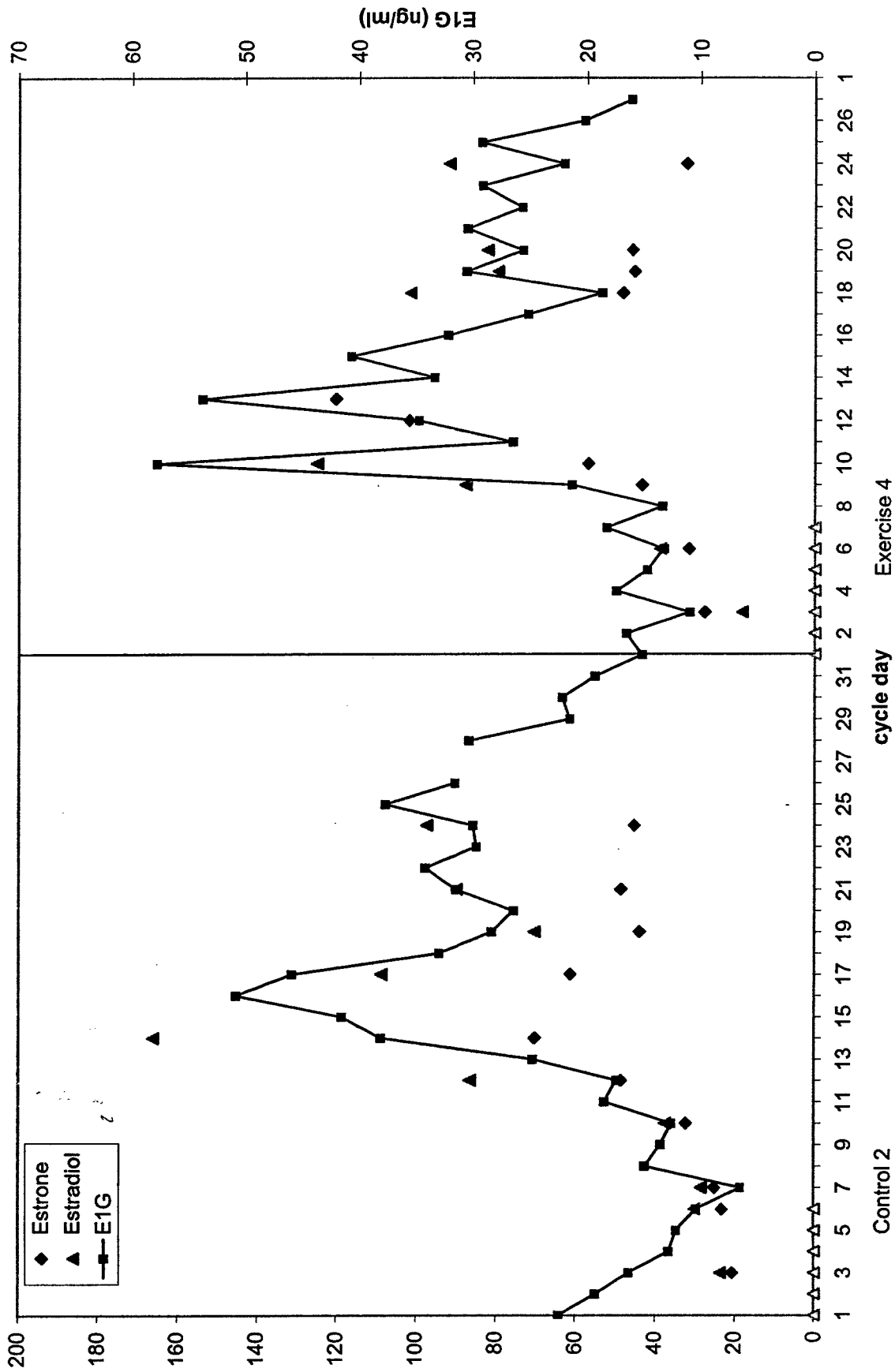
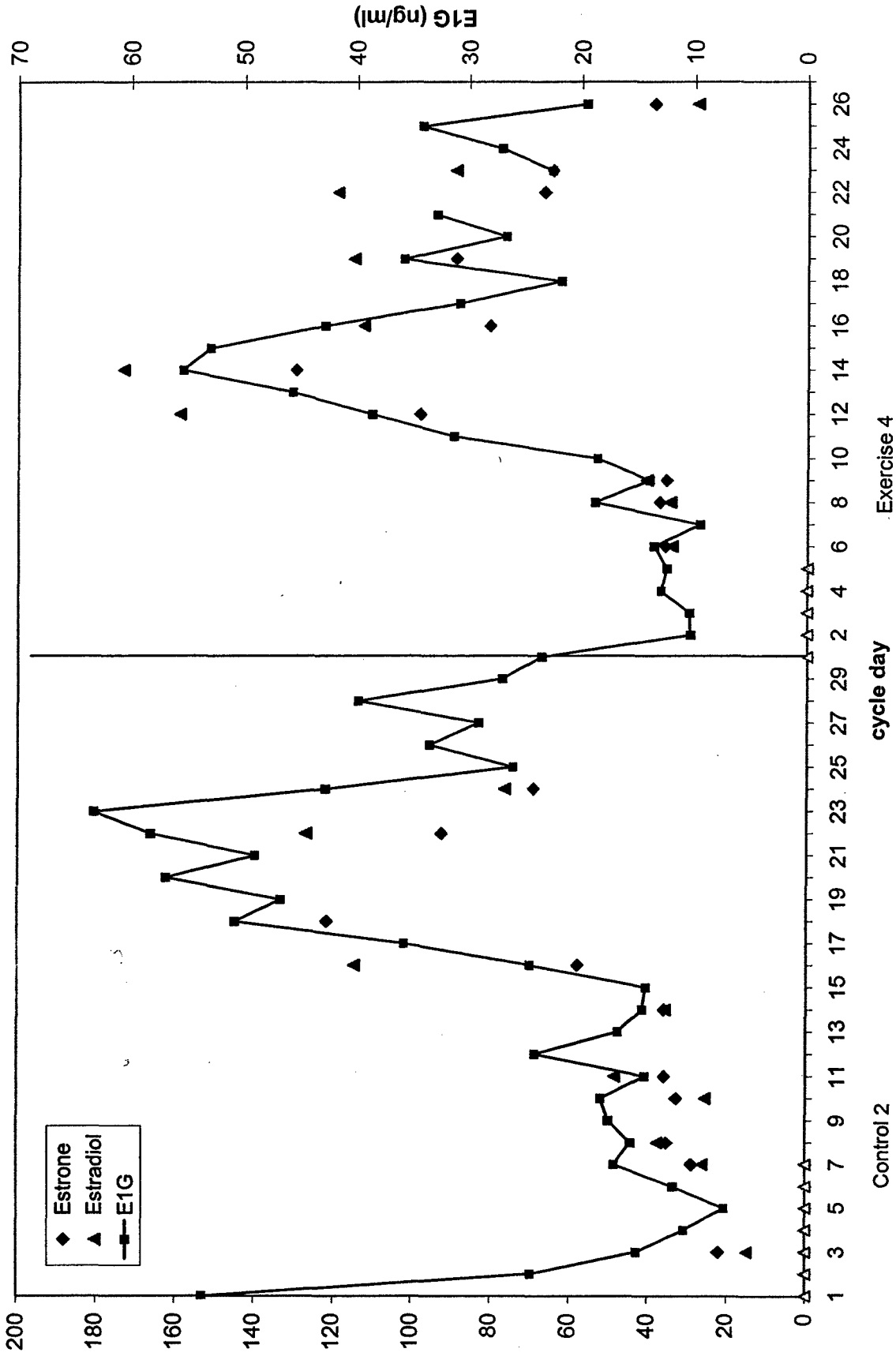


Figure 12

D-012



Blood Spot Collection Protocol

As a sample collection technique, blood spot collection can offer certain advantages over other methods such as venipuncture, urine or saliva collection. Blood spots are relatively easy to procure, minimally invasive, and can be stored longer at room temperature than samples from other methods. The following describes a collection protocol designed to optimize the sample volume and standardize the sampling procedure.

1. The subject should wash her hands in warm water.
2. Bathe the hand in warm water for two minutes, or longer if necessary, to accomplish a flush of the skin.
3. Dry, and wipe the finger with an alcohol wipe.
4. Prick the finger with a lancet.
5. When blood flow begins, wipe away the first bit with a tissue.
6. The next drops are absorbed onto the paper (Schleicher and Schuell, #903) by positioning the finger just above, but not touching, the paper so that the blood wicks onto, rather than drops onto, the paper until the spot is large enough.
7. The paper should be handled by the edges only to avoid introducing any contaminating substances and placed on a clean surface or rack to air-dry at room temperature – usually about 4 hours, depending upon the humidity levels.
8. After drying, place the card in a zip-lock bag, preferably with a dessicant, and store at -20 C until analysis.

Notes:

Do not smear the blood onto the paper

Do not apply one drop onto another

Do not expose the spots to direct sunlight or other source of heat

Dr. Nancy I. Williams
Associate Professor
Room 267Q
Recreation Building
Department of Kinesiology
& Noll Physiological Research Center
Penn State University
University Park, PA 16802

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
Director of Research and Development, Salimetrics LLC

August 20, 2003

Tech Support
Salimetrics, LLC
PO Box 395
State College, PA.
16804-0395

Re: Blood spot assays

Dear Technical Support Services:

We are currently running a study to test whether a program of moderate aerobic exercise that is combined with a moderate level of dietary restriction will result in significant decreases in two biomarkers of breast cancer. We also would like to validate a method of assessing energy status. We have been collecting dried blood spots from our volunteers. We wanted to know what blood spot assays you run. We would like to run some estrogen or progesterone assays. We would also like a cost estimate for supplies and running these assays on our blood spots. Currently, we have about 10 blood spots from our volunteers. We would appreciate any information that you could give us regarding your assays. We can be contacted through email at niw1@psu.edu or by calling our lab at 863-4488. Thank you in advance for your time and information.

Sincerely,

Nancy I. Williams
Primary Investigator

NANCY I. WILLIAMS
Curriculum Vitae

BIOGRAPHICAL

PII Redacted

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: niw1@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

- 1997-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
- 1996-1997 Visiting Assistant: Human Anatomy & Physiology
Professor Department of Biological Sciences
Ohio University
Athens, Ohio
- 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, York University, 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/AFFILIATIONS

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

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:

<u>Sem/Year</u>	<u>Course</u>	<u>Title</u>	<u>Credits</u>	<u>Enrollment</u>
-----------------	---------------	--------------	----------------	-------------------

Fall 1997	Kines 481W	Scientific basis of Exercise for Older Adults	3	50
	Kines 496C	Independent Study	3	1
Spring 1998	Kines 456	Fitness Appraisal	4	96
	Kines 496C	Independent Study	3	5
	Kines 395b	Practicum	3	2
Summer 1998	Kines 496C	Independent Study	1-3	3
Fall 1998	Kines 456	Fitness Appraisal	4	86
	Kines 456h	Fitness Appraisal (honors option)*	4	1
	Kines 496c	JumpStart to Health/Fitness	3	6
	Kines 496c	Independent Study	3	5
	Kines 496c	Independent Study (Schreyer Student)**	3	1
	Kines 596c	Supervised Teaching	3	1
	Kines 597i	Neuroendocrine- Immune Interactions	1	4
	Kines 395b	Practicum	3	1

COURSES TAUGHT ...cont.

Sem/Year	Course	Title	Credits	Enrollment
Spring 99	Kines 456	Fitness Appraisal	4	103
	Kines 424	Female in Exercise and Sport	3	36
	Kines 496c	Independent Study	3	16
Summer 99	Kines 456	Fitness Appraisal	4	14
Fall 99	Kines 424	Female in Exercise and Sport	3	16
	Kines 496c	Independent Study**	3	5
	Physio/Bio 572	Animal Physiology	3	12
Spring 00	Kines 456	Fitness Appraisal	4	78
	Kines 424	Female in Exercise and Sport	3	33
	Kines 496c	Independent Study**	3	5
Summer 00	Kines 456	Fitness Appraisal	4	12
Fall 00	Kines 424	Female in Exercise and Sport	3	35
	Physio/Bio 572	Animal Physiology	3	25
	Kines 496c	Independent Study**	3	5
Spring 01	Kines 424	Female in Exercise and Sport	3	35
	Kines 496c	Independent Study**	3	5
Fall 01	Kines 424	Female in Exercise and Sport	3	35
	Kines 496c	Independent Study**	3	5
Fall 02	Kines 424	Female in Exercise and Sport	3	35
Fall 03	Kines 424	Female in Exercise and Sport	3	40

*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

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

Mentor (Pending) Building Interdisciplinary Research Careers in Women's Health; Principal Investigator is Jay Moskowitz, MD, Penn State College of Medicine, Hershey, PA

Committee Chair- Undergraduate Honors Thesis

- 2000 Kathleen Flecker – Shreyer's Honor's College: "Weight and diet concerns among female athletes with menstrual cycle irregularities" (Winner 3rd place Undergraduate Research Exhibition)
- 2002 Chrissy Rezk – Shreyer's Honor's College: "Cognitive restraint and urinary cortisol in athletes with menstrual cycle disturbances"
- 2002 Meredith Snook- Shreyer's Honor's College: To be determined

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)
- 2002 Michael Perry (In progress) (Kinesiology)
- 2002 Kelly Dougherty (In progress) (Kinesiology)
- 2002 Brian Frye (In progress) (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)
- 2000 Heather McConnell, MS (In progress) (Physiology)
- 2001 Thomas Whipple, MS, PT, (In progress) (Kinesiology)

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 Brittney Salkeld "The effect of oral contraceptive use on measures of fatigue and energy metabolism" (Kinesiology)
- 2003 James Butler Media Studies (ongoing)
- 2003 Micheal Curren (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 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 present 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

Dudley Allen Sargent Research Fund (intramural): 1988, 1989, 1990
Sargent College of Allied Health Professions
Boston University, Boston, Massachusetts

Principal Investigator:

"Effects of exercise and caloric restriction upon luteinizing hormone secretion"

Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program , 1997-1998

Principal Investigator:

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

Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program , 1998-1999

Principal Investigator:

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

Penn State University
College of Health and Human Development
Interdisciplinary Seed Grant Program , 1999-2000

Co- Investigator: (PI Jay Hertel)

"Changes in risk factors of anterior cruciate ligament ruptures in female collegiate athletes across the menstrual cycle"

Pathology Initiation Grant
Hershey Medical Center, Dept. Pathology

January 2002-January 2003 5%

Co-Investigator (PI is Williams' Doctoral student, Thomas Whipple, MS, PT)

"The Role of Resistance Exercise and Energy Availability on Bone Metabolism"

Children's Youth and Family Consortium
Penn State University, CHHD

January 2002- January 2003 5%

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

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"

Pharmavite Corporation, Seattle, Washington

Research Grant-in-Aid, 1998-1999

Principal Investigator:

" Consumer Taste and Education of a Nutritional Sports Supplement"

US Army Medical Research and Materiel Command

1998-2001 5%

US Army Breast Cancer Program

Co-Investigator:

"Use of Exercise to Increase CD4 Lymphocytes following Chemotherapy Treatment for Breast Cancer "

NIH

1 RO1 HD39245-01 (Williams)

5/1/01 - 4/30/04 30%

PHS/NICHD

Principal Investigator:

"Bioenergetics of Exercise-induced Menstrual Disturbances"

US Army Medical Research and Materiel Command

9/17/01- 9/16/04 50%

US Army Breast Cancer Program (IDEA AWARD)

Principal-Investigator:

"Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (IDEA Award) "

US Army Medical Research and Materiel Command

9/17/01- 9/16/05

US Army Breast Cancer Program
(CAREER DEVELOPMENT AWARD)

Principal-Investigator:

"Effects of Moderate Aerobic Exercise Combined with Caloric Restriction on Circulating Estrogens and IGF-1 in Premenopausal Women (Salary Only)

Retirement Research Foundation 2000-2001 2%

Co-Investigator: (PI is J.L. Cameron, PhD)

"Physical Exercise and Brain Aging"

National Institutes of Health (NIH)

HD-02-012 Cooperative Reproductive Science Research Centers at Minority Institutions

Co-Investigator: 5%

"The efficacy and safety of metformin and lifestyle factors in the amelioration of hyperandrogenemia and its associated symptomology"

Pending Support

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

" Clinical Sequelae Exercise-Induced Hypoestrogenism"

National Institutes of Health (NIH)

Co-Investigator (PI is Terryl Hartman, PSU)

4/01/04-3/31/08 20%

"Female Cancer Survivors Weight and Activity Intervention"

NASA

Co-Investigator (PI is James Pawelczyk, PSU)

4/1/05-3/31/06 5%

"Improving Orthostatic Tolerance in Women: Control of Splanchnic and Cutaneous Vascular Capacitance"

Cancer Research and Prevention Foundation

Co-Investigator

1/04-12/05 0%

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

RESEARCH REPORTS

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

PUBLISHED MANUSCRIPTS

- Skrinar, G.S., **N.I. Williams**, B.A. Bullen, J.W. McArthur, and N.M. Mihok. Changes in body consciousness relate to regularity of exercise training. *Perceptual and Motor Skills*. 75: 696-698, 1992
- Bloomfield, S.A., **N.I. Williams**, D.R. Lamb, FACSM, and R.D. Jackson. Non-weight bearing exercise may increase lumbar spine bone mineral density in healthy post menopausal women. *Amer. J. Phys. Med. Rehabil.* 72: 204-209, 1993
- Williams, N.I.**, J. McArthur, B. Turnbull, B. Bullen, G. Skrinar, I.Z. Beitins, G.M. Besser, L.H. Rees, I. Gilbert, D. Cramer, L. Perry, D.S. Tunstall-Pedoe. Effects of follicular phase exercise on LH pulse characteristics in sedentary eumenorrheic women. *Clinical Endocrinology* 41: 787-794, 1994
- Williams, N.I.**, J. Young., J. McArthur, B. Bullen, G. Skrinar, and B. Turnbull. Strenuous exercise with caloric restriction: Effect on luteinizing hormone secretion. *Med. Sci. Sports Exerc.* 27 (10): 1390-1398, 1995
- Williams, N.I.**, M.J. Lancas, and J.L. Cameron. Stimulation of luteinizing hormone (LH) secretion in male rhesus monkeys by food intake: Evidence against a role for insulin. *Endocrinology* 137(6): 2565-2571, 1996
- Williams, N.I.** Low energy availability and reproductive disturbances: a review of clinical and hormonal effects. *Dance Medicine and Science* 2:(1) 19-31, 1998
- Williams, N.I.**, B.A. Bullen, J.W. MacArthur, G.S. Skrinar, and B.A. Turnbull. Effects of short-term strenuous endurance exercise upon corpus luteum function". *Med. Sci. Sports Exerc* 31(7): 949-958, 1999.
- Sharkey, N.A., **Williams, N.I.**, Guerin, J.B.: The role of exercise in the prevention and treatment of osteoporosis and osteoarthritis. *Nursing Clinics of North America*, 35 (1): 209-221, 2000
- Williams, N.I.**, Caston-Balderrama, A.L. Helmreich, D.L., Parfitt, D.B., Nosbisch C, Cameron, J.L. Longitudinal changes in reproductive hormones and menstrual cyclicity in cynomolgus monkeys during strenuous exercise training: rapid transition to exercise-induced amenorrhea *Endocrinology* 142: 2381-2389, 2001
- Williams N.I.**, DL Helmreich DL, DB Parfitt, Caston-Balderrama AL, JL Cameron. Evidence for a causal role of low energy availability in the induction of menstrual cycle disturbances during strenuous exercise training. *J Clin Endocrinol Metab* 86: 5184-5193, 2001
- Miles MP, Mackinnon LT, Grove DS, **Williams NI**, Bush JA, Marx JO, Kraemer WJ, Mastro AM. The relationship of natural killer cell counts, perforin mRNA and CD2 expression to post-exercise natural killer cell activity in humans. *Acta Physiol Scand* 174: 1-9, 2002.
- McConnell HJ, KA O'Connor, E Brindle, and **NI Williams**. Validity of methods for analyzing urinary steroid data to detect ovulation in athletes. *Med. Sci. Sports Exerc*, 34(11): 1836-1844, 2002

Whipple TJ, Petit Moira, Sharkey N, Demers L, **Williams NI**. Leptin and the skeleton. *Clin. Endocrinol.* 57: 701-711, 2002.

Williams, NI. Experimental disruptions of the menstrual cycle: Lessons from long-term prospective studies. *Med Sci Sports Exerc* 35 (8): 1564-1572, 2003.

MANUSCRIPTS IN REVIEW

Williams, NI, Flecker KL, McConnell. Weight and Diet Concerns in Female Athletes: Association with Menstrual Cycle Length (submitted to *Int J Sports Nut Exerc Metab*, September, 2002)

Whipple TJ, Le B, Demers LM, Petit M, Sharkey N, and **Williams NI**. Acute effects of moderate intensity resistance exercise on bone cell activity (submitted to the *International Journal of Sports Medicine*, 2003).

McConnell HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, and **Williams NI**. Basal Ghrelin is Sensitive to Changes in Body Composition and Metabolic Rate during a Diet and Exercise Program in Normal Weight Young Women. (Submitted to *J. Clin. Endocrinol. Metab.* as a Rapid Communication, 2003).

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. (submitted to *Nature Medicine*, October, 2003)

MANUSCRIPTS IN PROGRESS

Williams NI, Galucci AN, Dougherty K. Physiological indicators of psychological stress prior to competitive exercise.

Williams NI, McConnell HJ, Galucci AN, Clark KL. Menstrual irregularities and disordered eating in female athletes: survey vs follow-up physiological studies.

Hertel J, **Williams NI**, Olmsted LC, McConnell HJ, Gribble PA, Putukian, M. Neuromuscular performance and knee laxity do not change across the menstrual cycle of female athletes.

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, FACSM. "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, N.I.,** K.A. Greaves, T.E. Kirby and D.R. Lamb. Exercise training and cardiovascular function in the elderly. (presented at *Federation for the Society of Experimental Biology* meetings in Washington, DC, 1987) *FASEB Proceedings*, Vol. 46, p. 492, 1987
- Williams, N.I. ,** J. McArthur, B. Turnbull, B. Bullen, G. Skrinar, I. Gilbert, G.M. Besser, and L.H. Rees. Early effects of follicular phase exercise on LH pulse characteristics in sedentary eumenorrheic women. (presented at the *American College of Sports Medicine Annual Meeting, Orlando, FL, May 29-June 1, 1991*) *Med. Sci. Sports Exerc.* 23(4), p. S93, 1991
- Williams, N.I.,** J. McArthur, B. Bullen, G. Skrinar, B. Turnbull, and J. Young. Slowed LH pulse frequency in trained eumenorrheic women due to caloric restriction combined with heavy training. (presented at the *American College of Sports Medicine Annual Meeting, Dallas, TX, May 27-May 30, 1992*) *Med. Sci. Sports Exerc.* 24(5), p. S36, 1992
- Peachey, S., G. Skrinar, E. Kuligowska, B. Bullen, **N. Williams**, B. Turnbull, and J. McArthur. Effect of enhanced follicular phase endurance training on follicular maturation in women. (presented at the *American College of Sports Medicine Annual Meeting, Dallas, TX May 27-May 30, 1992*) *Med. Sci. Sports Exerc.* 24(5), p. S171, 1992
- Skrinar, G.S., D. Hutchinson, and **N. Williams**. Exercise: An adjunct therapy for persons with psychiatric disabilities. (presented at the *American College of Sports Medicine Annual Meeting, Dallas, TX, May 27-May 30, 1992*) *Med. Sci. Sports Exerc.* 24(5), p. S36, 1992
- Bullen, B., B. Turnbull, J. McArthur, G. Skrinar, **N. Williams**, and I. Beitins. Exercise and Diet: Correlates with the onset of menstrual disorders. *Proceedings of the Second IOC World Congress on Sport Sciences*, Barcelona, Spain. p. 155, 1992
- Williams, N.I.,** A.L. Caston, and J.L. Cameron. Induction and reversal of exercise-induced amenorrhea: Temporal correlation with plasma T₃ levels. (presented at the *76th Proceedings of the National Endocrine Society, Anaheim, CA, June, 1994*) *Endocrine Society Abstract*, #1775, 1994
- Williams, N.I.,** M.J. Lancas, and J.L. Cameron. Stimulation of luteinizing hormone (LH) secretion in male rhesus monkeys by food intake: Evidence against a role for insulin. (presented at the *77th Proceedings of the National Endocrine Society, Washington, DC, June, 1995*) *Abstract*, #OR22-3, 1995
- Williams, N.I.,** and J.L. Cameron. Stimulation of luteinizing hormone (LH) secretion in male rhesus monkeys by food intake: Role of circulating triiodothyronine (T₃) (presented at the *10th International Congress of Endocrinology/78th Proceedings of the National Endocrine Society, San Francisco, CA, June, 1996*) *International Congress of Endocrinology/Endocrine Society*, #P2-505, 1996.
- Williams, N.I.,** Berga, S.L., and J.L. Cameron. Mild metabolic stress potentiates the suppressive effect of psychological stress on reproductive function in female cynomolgus monkeys. (presented at the *79th Proceedings of the National Endocrine Society, Minneapolis, MN, June, 1997*) *Endocrine Society Abstract* #P1-367, 1997.

- Williams, N.I.**, Bullen B.A., McArthur J.W., Skrinar G.S., and Turnbull B.A. Effects of short-term strenuous exercise on corpus luteum function. (presented at the *American College of Sports Medicine Annual Meeting, Orlando, FL June 3-6, 1998*) *Med. Sci. Sports Exerc.* 30 (5), p. S324, 1998
- Williams, N.I.** Bullen B.A., McArthur J.W., Skrinar G.S., and Turnbull B.A. Effects of short-term strenuous exercise on corpus luteum function. (presented at the *American College of Sports Medicine Annual Meeting, Orlando, FL June 3-6, 1998*) *Med. Sci. Sports Exerc.* 30 (5), p. S324, 1998
- 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 College of Sports Medicine Annual Meeting, Seattle, WA June 3-6, 1999*) *Med Sci Sports Exerc* 31(5), S65, 1999
- 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, **Williams NI**, Bush JA, Mastro AM. Effects of prolonged exercise on natural killer (NK) cell cytotoxic activity and LFA-2 expression. Book of abstracts. *Fifth IOC World Congress, Sydney, Australia, Oct 31-Nov 5, 1999*, p. 51.
- 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*)
- Williams NI**, Clark KL, McConnell, Matuch A, O'Connor KA. Menstrual irregularities and disordered eating in female athletes: survey vs follow-up physiological studies (presented at the *American College of Sports Medicine Annual Meeting, Indianapolis, IN, June 3-6, 2000*) *Med Sci Sports Exerc* 32 (5), S64, 2000
- Mastro AM, **Williams NI**, et al. Exercise and Recovery of CD4 (+) cells after chemotherapy for breast cancer (presented at *Era of Hope Meeting of US Army Medical Research and Materiel Command, June 8-12, 2000, Atlanta, GA*)
- 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)
- Miles MP, MacKinnon LT, Grove DS, **Williams NI**, Bush JA, Marx JO, Kraemer WJ, Mastro AM. Potential mechanisms of post-exercise Suppression of NK cell activity: Cell number, Perforin mRNA and CD2. (research abstract presented at the 2000 American Physiological Society Meeting "The Integrative Biology of Exercise", Portland, ME, September 20-23, 2000.
- Mastro AM, **Williams NI**, Kraemer WJ, Orsega-Smith EM, Perry MD, Dixon RH, Bleznak AD, Underwood J. Exercise, quality of life, and the recovery of CD4 (+) lymphocytes following

chemotherapy for breast cancer *Proceedings of the American Association for Cancer Research 92nd Annual Meeting*, New Orleans, LA , 42 : 331, March 24-28, 2001

Perry MD, Mastro AM, Orsega-Smith E, Miles MP, Kraemer WJ, **Williams NI**. Exercise training and immune function following chemotherapy for breast cancer. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

Orsega-Smith E, **Williams NI** (FACSM), Perry MD, Mastro AM, Kraemer WJ, Bleznak A, Dixon R, Underwood J. Fatigue, quality of life and physical function after chemotherapy for breast cancer. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

Galucci, AN, **Williams NI**. Physiological indicators of psychological stress prior to competitive exercise. *Proceedings of the American College of Sports Medicine Annual Meeting*, Baltimore, MD, June 2-6, 2001

McConnell HJ, O'Connor KA, Brindle E, **Williams, NI**. Assessing reproductive function in exercising women: validity of ovulation detection algorithms. *Proceedings of the Endocrine Society Annual Meeting, Abstract #P2-408*, 2001

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*).

McConnell HJ, **Williams NI**, O'Connor KA, Clark KL, Putukian M. Menstrual irregularities and disordered eating in female athletes: survey vs follow-up clinical and physiological studies. (*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*).

Mastro AM, **Williams NI**, Ford J, Fuener K, Orsega-Smith E, Kraemer WJ, Bleznak AD, Dixon RH, Underwood J, Miles M, Wagner K. IL-6 and interferon-gamma levels following chemotherapy for breast cancer. *Proceedings of the American Association for Cancer Research Annual Meeting*, San Francisco, CA, April 6-10, 2002

Hertel J, **Williams NI**, Gribble PA, McConnell HJ, DiPasquale AA, Putukian M. Changes in risk factors of ACL injuries across the menstrual cycle: A pilot study. *Proceedings of the American College of Sports Medicine Annual Meeting*, St. Louis, MO, May 29-June 1, 2002

Williams NI, McConnell HM, Gardner JK, Albert AC, Cameron JL. Lifestyle factors such as exercise, caloris intake, and psychological stress: relationship to reproductive hormones and possibly the risk of breast cancer. *Era of Hope* meeting, Department of Defense Breast Cancer Research Program, Orlando, FL, September 25-28, 2002

Dougherty, K., Galucci AN, McConnell HJ, **Williams NI**. Cortisol and testosterone levels prior to competitive exercise. (Submitted for presentation at the 2003 American College of Sports Medicine Annual Meeting, San Francisco, CA, June, 2003).

Williams NI, McConnell HJ, Gardner JK, Cameron JL, Schuchert MK, Richard EL, Snook ML. Susceptibility of menstrual cycle to various stressors: correlation with baseline luteal progesterone levels. (Submitted for presentation at the 2003 American College of Sports Medicine Annual Meeting, San Francisco, CA, June, 2003).

McConnell HJ, Schuchert MK, Gardner JK, Frye BR, **Williams NI**. Basal Ghrelin is sensitive to changes in body weight during a controlled diet and exercise program in normal weight young women. (Submitted for presentation at the 2003 Endocrine Society Meeting, Philadelphia, PA, June 2003).

Whipple TJ, Le, B., Demers, L., Petit M.A., Sharkey N. **Williams, NI**. Acute Effects of Moderate Intensity Resistance Exercise on Bone Cell Activity. (Submitted for presentation at Association for Bone and Mineral Research Meeting, 2003).

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 Yassenoff Jewish Community Center*, Columbus, Ohio, June 6, 1987.

"ACSM Certification, Tracts Offered and Benefits Provided", *American College of Sports Medicine, New England Chapter Annual Meeting*, Worcester, Massachusetts, November 2-3, 1989.

"Special Topics for Students", *American College of Sports Medicine, New England Chapter Annual Meeting*, Worcester, Massachusetts, November 2-3, 1989.

"Exercise Testing and Prescription", *Harvard Medical School Department of Continuing Education Conference: "Current Advances in Nutritional Medicine and Disease Prevention: Medical Treatment Strategies"*, Boston, Massachusetts, April 25, 1991

"Eating Disorders and Body Image With Special Emphasis on the Female Athlete", *New York State Association of Physician's Assistants*, Calicoon, NY, April 18, 1998.

"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

"Low Energy Availability and the Menstrual Cycle: Clinical and Physiological Implications" *Society for the Study of the Menstrual Cycle, Bi-Annual meeting*, June, 2001, Hartford Connecticut

"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

SYMPOSIUM PRESENTATIONS

Chairperson, Symposium on "Special Topics of Interest to Students in ACSM", *American College of Sports Medicine, New England Chapter Annual Meeting*, Worcester, Massachusetts, November 2-3, 1989.

"Menstrual Disturbances in Athletes: Lessons from Prospective Experiments on Animals and Humans (Chairperson Anne B. Loucks, PhD) Lessons from Experimental Disruptions of the Menstrual Cycle in Primates and Humans, N. Williams (*American College of Sports Medicine Annual Meeting*, St. Louis, MO, May 30, 2002)

Chairperson, Symposium on "Current Practices for Screening and Prevention of the Female Athlete Triad" (*American College of Sports Medicine Annual Meeting*, San Fransisco, CA, May 31, 2003).

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 Collge of Sports Medicine, Credentials Committee, Spring 2003-

American College of Sporst Medicine, Position Stand Review Committee, "Female Athlete Triad," Spring 2002

REVIEWER

Journals *Journal of Applied Physiology, ACSM Health Fitness Journal
Medicine, Science, Sports and Exericse, Journal Clinical Endocrinology
and Metabolism*

Grants Dissertation Awards, Susan B. Komen Foundation for Breast Cancer
Research (2001-2003)

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-present)-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 2003)

Intercollege Program Committee (Physiology)

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

Department Committees (Department of Kinesiology)

Curriculum Committee Fall, 1998 to Spring 2002
Candidacy Committee Fall, 1998 to 2002

Search Committee (Noll Laboratory Exercise Physiology positions)	Fall, 1998
Search Committee (General Education Fitness Position)	Spring 99
Search Committee (Department of Kinesiology Chair)	Fall 01-Spring 02
Curriculum Revisions (ad hoc)	Spring 01-Spring 02
Advisory Committee for Fitness Assessment Program	Spring 02-present
Search Committee (Director, Noll Laboratory)	Fall 02-present
Advisory Committee	Fall 02-present
Search Committee (Pedagogy Positions)	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.