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I am submitting herewith a dissertation written by Pamela Diane Swan entitled "The Effects of Body Fat Distribution on Metabolism at Rest and During Exercise in Women". I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy with a major in Education.

Edward T. Howley

Edward T. Howley, Major Professor

We have read this dissertation
and recommend its acceptance:

Patricia A. Beitel

Jean Levin

Roland Bass

David R. Bassett, Jr.

Accepted for the Council:

Cowminkel

Associate Vice Chancellor
and Dean of the Graduate School

THE EFFECTS OF BODY FAT DISTRIBUTION ON METABOLISM
AT REST AND DURING EXERCISE IN WOMEN

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Pamela Diane Swan

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DEDICATION

If you understand,
things are just as they are.
If you do not understand,
things are just as they are.

Zen Verse

Dedicated to
my mother, Ruth
and
my father, Larry

And to the spirit of inquiry I have learned
from them both.

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ABSTRACT

Many of the metabolic complications of obesity have been strongly associated with the pattern of distribution of adipose tissue on the body. Fat metabolism has been shown to vary between various sites on the body. Abdominal adipose tissue is much more labile and sensitive to hormonal (catecholamine) stimulation than adipocytes from the gluteal-femoral region. Thus, it has been speculated that abdominally obese people have a higher potential for lipolysis and as a corollary, weight loss, than lower body obese individuals. Also, differences in energy balance regulation between individuals with different body fat distribution patterns have been suggested as a basis for the inconsistent success rates of exercise-based weight loss programs in obese women. The purpose of this investigation was to examine metabolic differences at rest and in response to exercise between two groups of obese women distinctly characterized by their body fat locations. Twenty-one overfat (% fat $\geq 30\%$) women volunteers between 18-40 years of age with normal health and blood lipid profiles were selected. The waist to hip circumference ratio (WHR) was used to categorize an upper body (UB) group (N = 10) with a WHR ≥ 0.85 and a lower body (LB) group (N = 11) with a WHR ≤ 0.75 . Subjects participated in a resting metabolic rate (RMR) test, two exercise tests (weight supported and weight bearing) to examine mechanical efficiency, and a prolonged walking test to assess fuel utilization. In addition, differences in the adrenergic regulation of metabolic rate and fuel mobilization were studied by pharmacologically blocking the beta-adrenergic receptors with propranolol at rest and during a bout of prolonged walking. The two

groups of women in this study were essentially similar in all basic characteristics (i.e., age, body size, body composition, and maximal aerobic power). The results of this study indicated no differences between the groups in resting metabolic rate (i.e., UB = 1730 ± 110 vs. LB = 1640 ± 81 kcals·day⁻¹). The mechanical efficiency values indicated that gross, net and delta efficiencies were not different between groups for either weight carrying or weight bearing exercise modes. The net efficiency for both groups for cycle exercise ranged between 17-20% and 10-19% for the treadmill. Prolonged walking induced a significant ($p < 0.0001$) decline in RQ with time in both groups. However, no difference in the amount or rate of fuel utilized as fat (estimated by the steady-state RQ values) during 60 minutes of walking was noted between the two groups (i.e., range 35-65% fat). Finally, the effect of beta-blockade did not selectively alter the metabolic responses between the groups. Propranolol administration decreased heart rate but did not significantly depress RMR in either group. A significant ($p < 0.006$) depression of lipid utilization by propranolol during prolonged walking was noted after 30 minutes in both groups. In conclusion, the results from this study can be interpreted to mean that obese women with distinctly different body fat distribution patterns have similar physiological potentials for energy expenditure at rest and during exercise. There was no indication from the current findings that one group was more energy thrifty than the other. Both groups of women showed equal capabilities for performing prolonged exercise with the typical metabolic shift in fuel utilization. Thus, there was no indication that the obese women volunteers in this study had an impaired or differing ability for substrate mobilization or fuel utilization during exercise. The implications of this study are that despite the well-defined

differences in metabolic activity shown *in vitro* between various adipose tissue sites, the manifestation of energy regulation mechanisms *in vivo* is much more obscure.

TABLE OF CONTENTS

CHAPTER	PAGE
I. Introduction	1
A. Statement of the Problem	4
C. Rationale	4
D. Hypotheses	7
E. Delimitations of the Study	9
F. Limitations of the Study	10
II. Review of Literature	11
A. Energy Metabolism and Metabolic Rate	11
1. Energy Balance and Thermodynamics	12
2. Fuel Utilization	21
3. Mechanical Efficiency	26
4. Adrenergic Control of Metabolism	30
5. Lipid Metabolism	39
6. Lipid Metabolism and Exercise	41
7. Summary	43
B. Body Fat Distribution	44
1. History and Definition	44
2. Cell Characteristics and Metabolism	49
3. Treatment	53
4. Summary	56

III. Methods	57
A. General Procedures	57
1. Subject Screening and Selection	58
2. Anthropometric Measures	60
3. Body Composition	61
B. Metabolic Tests	62
1. Resting Metabolic Rate	62
2. Exercise Tests	63
3. Lactate Analysis	67
C. Statistical Analysis	67
IV. Results	69
A. Basic Characteristics	69
B. Resting Metabolic Rate	71
C. Mechanical Efficiency	73
1. Cycle	73
2. Treadmill	76
D. Beta-Adrenergic Blockade	78
1. RMR	78
2. Fuel Utilization	78
3. Lactate	80
V. Discussion and Implications	85
A. Introduction	85
B. Basic Characteristics	85
C. Resting Metabolic Rate	87

D. Mechanical Efficiency	90
1. Cycle	90
2. Treadmill	94
E. Fuel Utilization	96
F. Adrenergic Regulation of Metabolism	99
1. Beta Blockade and RMR	99
2. Beta Blockade and Fuel Utilization	102
G. Summary and Implications	106
REFERENCES	108
APPENDIXES	124
A. Flyers and Advertisements	124
B. Information to Participants	127
C. Subject Informed Consent	134
D. Health History Questionnaire	136
E. Menstrual History Questionnaire	140
F. Diet Recall Form	142
G. Measurement of Waist to Hip Ratio	144
H. ANOVA F-Tables For Repeated Measures	146
VITA	154

LIST OF TABLES

TABLE	PAGE
1. Ranges of Mechanical Efficiency Values for Normal Weight and Obese Population Reported in the Literature	29
2. Subject Characteristics	70
3. Blood Lipid Profile Characteristics	72
4. Resting Metabolic Rate	72
H-1. Repeated Measures ANOVA for Cycle Gross Mechanical Efficiency	147
H-2. Repeated Measures ANOVA for Cycle Net Mechanical Efficiency	147
H-3. Repeated Measures ANOVA for Cycle Delta Mechanical Efficiency	148
H-4. Repeated Measures ANOVA for Treadmill Gross Mechanical Efficiency	148
H-5. Repeated Measures ANOVA for Treadmill Net Mechanical Efficiency	149
H-6. Repeated Measures ANOVA for Treadmill Delta Mechanical Efficiency	149
H-7. Repeated Measures ANOVA for Resting Metabolic Rate (kcal.day ⁻¹)	150
H-8. Repeated Measures ANOVA for Resting Metabolic Rate (kcal.kg ⁻¹ .hr ⁻¹)	150
H-9. Repeated Measures ANOVA for Resting Metabolic Rate (kcal.kg FFM ⁻¹ .hr ⁻¹)	151
H-10. Repeated Measures ANOVA for Respiratory Quotient	152

LIST OF FIGURES

FIGURE	PAGE
1. Mechanism of Regulation of the Blood Glucose Level Via the Glucose-Fatty Acid Cycle	24
2. The Process of Interaction for Each Type of Catecholamine Receptor	36
3. Values for WHR Associated with Risk for Coronary Heart Disease .	48
4. Mechanisms Associating Body Fat Distribution and Obesity to Abnormalities in Glucose Homeostasis	54
5. Relationship of Energy Expenditure to Work Rate on the Cycle Ergometer	74
6. Cycle Gross and Net Mechanical Efficiency	74
7. Cycle Delta Mechanical Efficiency	75
8. Treadmill Gross and Net Mechanical Efficiency	77
9. Treadmill Delta Mechanical Efficiency	77
10. Effect of Body Fat Distribution on RMR During Control and Propranolol Treatments	79
11. Heart Rate Response During Prolonged Walking With and Without Treatment With Propranolol	81
12. Relationship of RQ With Time During Prolonged Submaximal Walking With and Without Treatment With Propranolol	82
13. Percentage of Estimated Calories Utilized From Fat During Prolonged Walking With and Without Treatment With Propranolol .	83

CHAPTER I

INTRODUCTION

Studies have documented the association of excess body fat with an increased susceptibility to a variety of clinical disorders and a high mortality rate [6,146,151]. The high prevalence of obesity (i.e., excess body fat) in the United States [80] has made it a significant public health problem and an important topic for research [25]. Obesity is known as a heterogeneous disorder [69,85]. A prime explanation for this may be the recognition that not only the amount of excess fat must be considered when assessing the risks associated with obesity, but also the topography of the adipose tissue, per se, [24]. Abdominal or upper body obesity is progressively being accepted as a sub-type of obesity that carries a greater risk for various metabolic disorders than excess body fat by itself [24,30,82]. Individuals with upper body (UB) type obesity patterns are people characterized by a preponderance of abdominal fat and a high waist circumference to hip circumference ratio (WHR). This type of obesity has been implicated in many metabolic aberrations such as hyper-triglyceridemia, diabetes mellitus, hyperinsulinemia and hypertension [80,117]. Lower body (LB) obesity is characterized by a low WHR, with most fat being deposited on the buttocks, hips, and thighs. Interestingly, the same negative health problems and metabolic aberrations as listed above, have not been associated with this type of obesity.

The health risks of the different patterns of fat distribution are well established, but the differences in the success of therapy to treat the obesity is

much less well understood. Persons with LB obesity have been shown to be particularly "resistant to slimming" using either diet [170] or exercise protocols in comparison to the response of UB type fat groups [84,165]. A striking example of this heterogeneous metabolic response to exercise in those with different fat patterns has been shown by Krotkiewski and Bjorntorp [84]. They studied the effects of physical training on muscle tissue and adipose tissue in women and men with different patterns of fat distribution. Those with UB fat distribution lost fat and gained muscle mass demonstrating a "typical" adaptation to the negative energy balance imposed by exercise training. The LB group of women (no men fit this category) did not show this same fat loss adaptation with increased exercise. In fact the authors reported a significant body weight and fat gain and only a minimal amount of lean body mass increase in response to exercise training in the LB group. The authors suggested that possible differences in energy expenditure or metabolism between the two groups may help explain the unexpected response to exercise training [84].

It is conceivable that it would be more efficient (i.e., less of a caloric cost) to carry excess weight on the legs, hips, buttocks, than on the chest or stomach when performing various activities [56]. Thus, different modes of exercise (i.e., weight supported or weight bearing) could elicit different effects on the energy cost of exercise (i.e., mechanical efficiency) depending upon the location of the body-fat distribution. Any difference in metabolic efficiency at rest or in response to physical activity associated with body-fat distribution would be of importance for obesity therapy and preventive medicine.

The foundation for the models which attempt to explain the mechanisms responsible for the metabolic complications in individuals with UB fat pattern has been primarily based on results of *in vitro* studies. These studies have shown the abdominal fat deposits to be much more labile and more sensitive to the lipolytic action of catecholamines (norepinephrine and epinephrine) than adipose tissue from gluteal-femoral deposits [7,48]. There has been a consistent association between fat location, adrenoreceptor type and lipolytic activity [7,48]. Research has demonstrated an increased fat mobilization from abdominal tissue and an increased triglyceride storage (anti-lipolytic activity) in the gluteal/femoral sites [7,48,132]. In addition, there has been evidence of an association between an enhanced sympathetic nervous system activity (i.e., higher catecholamine levels) and an upper body fat pattern in men [31]. Thus, *in vitro* measures of adipose tissue show distinctive differences in metabolic function related to anatomic site. According to Campaigne [30] the prevention of obesity-related chronic disease is related to two questions pertaining to adipose tissue *in vivo*: a) can the regional distribution of adipose tissue be altered by diet and/or exercise, and b) are these interventions affected by the existing distribution of body fat?

Exercise is known to induce characteristic and predictable increases in catecholamine levels which are closely linked to increases in metabolic activity [172]. The influence of body fat distribution on the mobilization of fat as a fuel during exercise has not been previously studied. It is unknown what effect these metabolically discrete adipose tissue stores would have on energy usage in the intact human at rest or during activity. The intent of this research was to elucidate

the effects of body fat distribution on various metabolic parameters at rest and in response to exercise.

Statement of the Problem

The purpose of this investigation was to examine the metabolic differences between women characterized by upper body obesity and women with lower body obesity at rest and in response to exercise. More specifically, answers to the following questions were sought.

1. What is the effect of body fat distribution on resting metabolic rate?
2. What is the effect of body fat distribution on gross, net and delta mechanical efficiency in response to different modes and intensities of exercise?
3. What is the effect of body fat distribution on fuel utilization during prolonged submaximal exercise?
4. What is the effect of body fat distribution on adrenergic regulation of resting metabolic rate and fuel utilization during prolonged walking?

Rationale

Obesity is considered a consequence of a prolonged imbalance between energy intake and expenditure [32]. Traditionally, therapeutic interventions for treatment of obese individuals contain at minimum two components considered essential for successful weight loss, diet, and exercise. One conclusion that can be made from the studies reviewed is that body fat distribution needs to be taken into consideration when assessing the effects of these treatments. Theoretically, it

could be speculated that in conditions of negative energy balance, such as diet and or exercise, lipid mobilization would be highest in the abdominal region [24]. Indeed, some studies have shown that the abdominal circumference was reduced to a greater extent than the femoral diameter following dietary intervention, thus reducing the waist to hip ratio (WHR) [8,16,65,78,82,170,173]. However, exercise studies have shown much more varied results in terms of body fat reduction with physical training. There seems to be a sex-linked component in the determination of the efficacy of fat loss by exercise intervention [18,42,84,166]. In men, the loss of adipose tissue was found to be central, potentially reducing the risk of cardiovascular disease, whereas a relative "resistance" to fat loss was reported in women compared to men [42]. This association may, in fact, originate from the pattern of body fat distribution [18,42,84,166]. Those women with a high WHR, similar to what is found in most males, [45] were found to be able to benefit from an exercise training program to a much greater extent than those women with a low WHR [42]. In addition, Krotkiewski and Bjorntorp [84] actually observed an increase in body fat with an increase in physical training in lower body fat women. These results suggest a relationship between body-fat distribution and energy expenditure.

In both training studies cited [84,166], the authors stated that caloric intake was not modified or controlled, thus, energy intake must have increased disproportionately to energy expenditure, resulting in a positive energy balance and excess energy storage. It is likely that the investigators assumed that the caloric cost of the exercise was the same for all the individuals. However, if the LB women were more energy efficient than the UB group, then the energy expenditure

of a given activity for the LB group would be less. Consequently, fewer calories would be burned for the same amount of work done and more calories would be conserved, resulting in less overall fat loss in the LB group. Weststrate and co-workers [179] found a significant reduction in resting metabolic rate (RMR) in LB obese women as compared with UB obese women after correcting for age, fat free mass, and percent body fat. Their findings suggest that the LB obese may have lower energy requirements. It is unknown what influence a lower RMR would have on energy metabolism during exercise.

Adipocytes possess primarily β_1 - and α_2 - adrenoreceptors which are involved in the control of the lipolytic activity of the fat cell [48,90]. Catecholamines activate both kinds of receptors and promote stimulation of lipolysis with β_1 -receptor activation or inhibition of lipolysis with α_2 -receptor activation. Thus, the net lipolytic effect is a result of the difference between the simultaneously stimulated opposing actions of these receptor-hormone interactions. Modifications of adrenoreceptor number or affinity would affect this net response. Lafontan et al. [89] reported that the adipose tissue of the thigh exhibited resistance to epinephrine stimulated lipolysis compared with a much greater lipolytic action of abdominal adipose tissue. They suggested that there may be an imbalance in the activities between the alpha-adrenergic and beta-adrenergic receptors according to the anatomical localization of the fat deposits. Jensen et al. [69] reported increased free fatty acid (FFA) release relative to lean body mass in UB obese women compared to those with LB fat distribution. Increased FFA availability is necessary for optimal metabolic function in situations such as fasting and prolonged exercise [69]. Prolonged exercise of moderate intensity elicits an

increased demand for the utilization of fat as an energy source. Also, it is thought that increased FFA mobilization and concentration in the blood (increased FFA availability) leads to increased rate of fat utilization [33]. However, it is unknown if energy requirements of prolonged exercise in UB obese individuals would be met differently than those with LB fat.

Elucidation of potential differences in energy balance regulation between sub-groups of obese individuals would be of great importance for obesity therapy and prevention. Differences in response to exercise training suggest that metabolically distinct mechanisms may be functioning within these sub-groups. The current investigation sought to examine metabolic differences between two groups of obese women distinctly characterized by their body fat locations. Three basic areas of inquiry were conducted. The first included the assessment of resting metabolic rate. Second, an examination of mechanical efficiency (i.e., the relative caloric cost of exercise) in the two groups during weight supported and weight bearing exercise was made. And third, fuel mobilization/utilization during prolonged exercise was evaluated. In addition, an appraisal of the adrenergic regulation of resting metabolism and fuel utilization was made by pharmacologically blocking the beta-adrenoreceptors during rest and throughout a bout of prolonged walking.

Hypotheses

In order to fulfill the purposes of this study several hypotheses were formulated. These hypotheses were expressed directionally where results from past experiments suggested directionality. When direction was unpredictable, they were written in the null form.

- Hypothesis 1: Resting metabolic rate (RMR) for women with LB type fat distribution is lower than those with UB type.
- Hypothesis 2: In LB obese women RMR is lower following treatment with propranolol than during control (placebo) treatment.
- Hypothesis 3: In UB obese women the RMR following treatment with propranolol is not different from control values.
- Hypothesis 4: There is no difference in gross or net mechanical efficiency between body type groups (LB or UB) during three levels of weight-supported (cycle) exercise.
- Hypothesis 5: There is no difference in gross or net mechanical efficiency between LB and UB groups during three levels of weight-bearing (treadmill) exercise.
- Hypothesis 6: There is no difference in delta mechanical efficiency between body type groups (LB or UB) during three levels of weight supported (cycle) exercise.
- Hypothesis 7: There is no difference in delta mechanical efficiency between LB and UB groups during three levels of weight bearing (treadmill) exercise.
- Hypothesis 8: There is no difference in the respiratory quotient (RQ) at any time period during 60 minutes of prolonged walking between LB and UB body type groups.
- Hypothesis 9: In the LB group, there is no difference in RQ at any time period during 60 minutes of prolonged walking following propranolol treatment compared with placebo treatment.

Hypothesis 10: In the UB group, the RQ values are reduced to a greater extent following propranolol treatment compared with placebo treatment during 60 minutes of prolonged walking.

Delimitations of the Study

This study was delimited to:

- 1) Premenopausal, normally menstruating women, 18 to 40 years of age, who have a body fat composition percentage consisting of greater than 30%.
- 2) Women on birth control pills were considered to be normally menstruating.
- 3) Women who were in the follicular phase of their menstrual cycle (i.e., within 7 to 12 days after the 1st day of menstrual bleeding).
- 4) Women with a waist to hip ratio (WHR) of equal to or greater than 0.85 (UB group) and those with a WHR of equal to or less than 0.75 (LB group).
- 5) Women with no history of cardiovascular disease, lung disease, bronchial asthma or metabolic abnormalities including diabetes mellitus, Cushing's syndrome, or hypothyroidism.
- 6) Women with no orthopedic impairments and who were physically able to walk continuously for 60 minutes and who were able to pedal a cycle ergometer.
- 7) Women who did not smoke.

Limitations of the Study

This study was limited by the following factors:

- 1) The subjects for this study were not randomly selected but recruited from volunteers meeting specified criteria.
- 2) Differences in resting metabolic rate, mechanical efficiency, and fuel utilization between the two body type groups may have been influenced by factors other than those specifically controlled in the study such as undiagnosed disease or pathology.

CHAPTER II

REVIEW OF LITERATURE

In order to provide a conceptual framework and background for the purposes and hypotheses associated with this investigation, the literature review will be divided into two parts. Part one of this chapter will consist of a review of the processes and mechanisms involved in the regulation of metabolism in obesity. Specifically, the review will examine the research literature on the factors influencing energy metabolism and efficiency both at rest and in response to exercise. Part two will incorporate a discussion of the nature of body fat distribution in terms of specific metabolic characteristics and its influence on the development of metabolic disorders.

Energy Metabolism and Metabolic Rate

The association of obesity with disease relates, in part, to the propensity of obese individuals to metabolic aberrations such as glucose intolerance, hyperinsulinemia, and hyperlipidemia which may result from variations in their energy regulation mechanisms. In addition, the application/efficacy of therapy, management and/or prevention of weight gain, for obese, post-obese or potentially obese individuals depends directly upon an evaluation of their energy requirements [11].

Energy Balance and Thermodynamics

Although it is clear that one cannot become overfat without an adequate food supply, the idea of attributing the etiology of obesity entirely to overeating is a gross misunderstanding of the complexity of interactions involved in energy regulation and metabolism of the body. Not all big eaters become fat and some people who sincerely minimize their energy intake still have difficulty losing weight.

The elements affecting energy turnover involve determinants of food intake and determinants of energy expenditure. The common western diet affords compact, high-energy dense foods, rich in fat and refined carbohydrates, which enable those in the "modernized" world to easily consume high caloric intakes without excess bulk. In addition, humans do not show evidence that the regulation of appetite is achieved by an internal (calorie set point) control of food intake [44]. Thus, neither food bulk nor caloric content is limiting food intake for those in an affluent society. Therefore, without conscious cognitive control of food intake, weight gain is limited by control systems influencing energy expenditure rather than factors influencing food intake.

The first law of thermodynamics, which states that energy cannot be created or destroyed, may oversimplify the interrelationships between energy intake and energy expenditure in a biological system. In biological terms, the second law of thermodynamics makes possible a subtle distinction between the potential energy from food, the actual work accomplished and the inevitable "loss" of energy as heat from metabolic processes [44]. In other words, some energy is degraded, (i.e., lost as heat) depending upon the specific metabolic processes taking place. Results from studies on metabolic rate (i.e., the total amount of heat produced per

unit of time) have shown significant variability among people even after correcting for age, sex, and body size. The origin of the inter-individual variability in energy expenditure is unclear. It implies that people with similar physical characteristics can require more or less energy to maintain their body weight and can therefore be more or less "energy efficient" [129]. It is possible that fundamental differences between the energetics of gaining versus losing fat exist among people. The remainder of this review will concentrate on factors which could be implicated in differences in metabolic efficiency among individuals.

Energy expenditure

Daily energy expenditure is a summation of three ingredients; the basal metabolic rate, plus the work done (energy cost of physical activity), plus the heat produced (thermogenesis). The largest component involves the basal metabolic rate (BMR). It is assumed that BMR is a constant part of all energy expenditure and for most people it may be calculated to amount for more than half of the total EE [44]. The BMR is measured using a specific set of conditions during the early morning hours of deep sleep [128] and is considered a transient state [114]. To achieve precise BMR values a consistent control of environmental temperature, time of day/week/month/year, diet, emotional state, and physical activity patterns over several repeated measures is required [108,160]. In contrast, the resting metabolic rate (RMR) is a more useful (in clinical practice) estimate of caloric requirements [114]. RMR is defined as the sum of the oxygen consumption of the active cell mass of the body when the individual is sitting or lying quietly several hours after a meal or physical activity [36]. RMR is considered the best predictor of one's overall

energy requirements and usually can account for up to 65-70% of an individual's energy expenditure [114,115,128].

According to Mole [108] there are two basic factors which determine the metabolic rate of an individual at any moment in time: a) the number and size of the respiring cells in the tissues, and b) the intensity of the metabolic process in these cells. This intensity is directly linked to the work being performed and the efficiency of the chemical energy transformations.

Measurement Techniques of RMR

The metabolic process can be described as a dynamic flux of energy between the active cells utilizing nutrients and the energy released as heat in the procedure. Two common methodologies are employed to evaluate this process. The technique of direct calorimetry is a method of measuring the actual heat released from the living body. It, however, requires an elaborate (and expensive) chamber where the subject must remain for a prolonged time. The practical (convenient and less expensive) method of measuring resting metabolic rate is indirect calorimetry [160]. Indirect calorimetry has been shown to be a valid and reliable method of assessing cell metabolism [53,115]. Through an analysis of the oxygen consumed and carbon dioxide produced, a calculation of the kilocalories used [177]¹, as well as the types of fuels oxidized, can be made.

Obesity and energy expenditure

The possibility that inadequate energy expenditure and/or a defect in energy metabolism may underlie the onset and/or persistence of some types of human

¹ The Weir [177] equation to convert the respiratory quotient (VCO_2/VO_2) to kilocalories:

$$\text{kcal} = [(1.1 \times RQ) + 3.9] \times VO_2.$$

obesity has been a major research topic [59,144]. An impaired ability to utilize or dissipate energy suggests that ingested calories would tend to be conserved or stored as excess fat. Reduced energy expenditure in obesity could be a consequence of: a) a lower RMR, b) a blunted capacity for thermogenesis, c) a reduced energy expenditure in physical activity (i.e., related to a lower energy cost of exercise [increased mechanical efficiency]) or a reduced volitional participation in physical activity) or d) a combination of these factors [144].

RMR. Many studies have centered attention on basal and resting metabolic rate in order to investigate the role a low energy expenditure may play in the development of obesity [128,160]. The RMR is considered to be the best predictor of total daily caloric requirements in both lean and obese individuals, [115,128]. The absolute RMR and 24-hour energy expenditure have been found to be increased in obese subjects compared to normal weight subjects [66,68,128,160]. Further, body weight was found to be the variable having the highest correlation with RMR for healthy, non-athletic women, 18-65 years old [115]. The regression equations Owen's [115] group developed to predict RMR from body weight resulted in wide 95%-confidence limits which they suggested indicated the heterogeneous nature of RMR for lean and obese women. Thus, for purposes of comparing caloric requirements between obese and nonobese subjects, the authors suggest that it is important to directly measure metabolic rate [115] and adjust the RMR for the amount of fat-free mass (kg FFM) or amount of body weight (kg BW) for each individual [121,160].

When expressed per unit of fat free mass the RMR and BMR values of obese individuals have been shown to be generally the same as the range of values of

normal weight subjects [15,126,128,140,160]. One exception was a study by Hoffmans et al. [66] who described the obese to be more efficient (i.e., lower rates of calorogenesis) when RMR was expressed per kg BW or kg FFM. Consequently, although it is possible that the obese "suffer" from a higher metabolic efficiency, the majority of the evidence thus far have indicated that there is no impairment in resting energy expenditure in obesity.

The nature of the investigations previously described limit the interpretation of the initial question in this section (i.e., what role a low RMR plays in the development of obesity) because the values may only represent a symptom or a consequence of the fat already accumulated rather than a source of its etiology. Since it is difficult to gather and study a group of people "likely" or predisposed to get fat and evaluate their metabolism, RMR in groups of formally obese subjects have been assessed and compared with normal weight controls [97]. Formally obese subjects (of "normal" weight) have exhibited reduced energy requirements (between 35-70% less than normal) when compared to similar, normal-weight groups [60,97,152]. In addition, Ravussin and colleagues [129] have reported results from a prospective study that indicated reduced energy expenditure was a significant predictor of gains in body weight in a large group of ethnically similar men and women. Their longitudinal data were able to show a clear association between low resting metabolic rate and the propensity to gain body weight/fat.

Therefore, in contrast to the results from the cross sectional studies first described, these studies suggest that abnormalities in energy expenditure may indeed precede obesity. The source of the defect in energy metabolism in obesity remains controversial. Prevailing investigations have been devoted to ascertaining

the source of this defect. Currently the focus has been on the likelihood of an impaired thermogenesis (i.e., a blunted increase in energy expenditure in response to a caloric load or norepinephrine stimuli) [141].

Thermogenesis. Thermogenesis is defined as the heat production that is unassociated with or in excess of the heat from basal metabolic rate or work [44]. Several types of thermogenesis have been described: psychological thermogenesis (stress induced), dynamic thermogenesis (work induced), drug-induced, cold-induced (shivering and non-shivering), and diet-induced thermogenesis. All of these types of heat liberating mechanisms form a complex intertwined system that could lead to variations in caloric needs and heat output between people. The thermogenic responses to norepinephrine infusion, diet (overfeeding and underfeeding) and exercise have all been suggested as possible sources of thermogenic defects in obesity. Both diet and exercise acutely alter cellular respiration and they have the potential to also chronically produce adaptations in cellular function which influence RMR and thermogenesis [108].

Diet and overfeeding. In "normal" individuals food intake directly increases energy expenditure in two ways. The thermic effect of food also known as dietary induced thermogenesis (DIT), causes an immediate rise in resting metabolism and is related to the "obligatory" energy cost of digestion, transport, and storage of the ingested foods [108,121]. In addition, a long-term or "facultative" effect of overfeeding on energy expenditure has been noted [70,121]. The long-term effects can last for several days and correspond to an increased energy cost in excess of the cost of digesting, absorbing and storing nutrients. The factors involved in "facultative" thermogenesis include the costs of resynthesizing ATP and recycling

three carbon compounds (used in the breakdown and conversion of substrates), and the stimulation of sympathetic activity in response to the increased nutrient intake [70,108,121]. Basically, the long term increase in metabolic rate with overfeeding represents an increased stimulation from the sympathetic nervous system (norepinephrine) in response to a gain in tissue and an augmented metabolic intensity resulting from the need to maintain this added tissue [108].

Defects. The possibility that an impaired thermogenic response to food or adrenergic stimulation is associated with the development of obesity has been a popular premise [141]. Many studies have shown that indeed, the postprandial thermogenesis (i.e., the increase in RMR after a meal) is significantly lower in obese than in lean humans [15,72,76,141,142]. This finding supports the concept that a defective thermogenic response which can favor energy gain is responsible for the excess fat storage in obese individuals. However, other studies have failed to demonstrate a difference in DIT between obese and lean subjects [22,50,140]. Methodological differences such as meal size and composition may explain some of the discrepant findings. Yet, still other conflicting reports have shown no reduced thermic response to infused norepinephrine in obese subjects [32,52,77]. In general, these results further emphasize the characteristic heterogeneity in the metabolism of obese humans.

Diet and underfeeding. The metabolic rate has been shown to be depressed between 15% - 30% with starvation [14,78,104]. This appropriate adaptation functions to reduce the energy use of the tissues and to conserve calories during a time of low caloric intake. In contrast to overfeeding, several days of underfeeding are required to produce significant decreases in metabolism [108]. The initial

reduction in BMR following caloric restriction is considered a result of a decrease in the intrinsic metabolic intensity of the active tissues [108]. Thus, a chronically low caloric intake could cause an increase in cellular efficiency sufficient to slow or minimize weight/fat loss in the semistarved individual. With continued nutrient deprivation, reductions in metabolic rate have been shown to parallel the decrease in fat free mass because of the gradual loss in metabolically active tissue [78]. Thus, the drop in RMR which accompanies severe caloric restriction involves both a reduction of intrinsic metabolic activity (i.e., lower RMR/ kg FFM) as well as an overall loss of the metabolically active fat free mass.

This gradually lowered metabolic rate, which is an adaptation to a chronic restriction in energy intake may be a major factor in the poor prognosis for long-term weight maintenance programs. In the sedentary state, the body seems to gradually adjust its resting energy needs to meet the lowered energy supply thereby reestablishing energy balance at a lower level. Consequently, dietary restriction has been shown to have some success for short-term weight loss but continued reductions disrupt the functioning of the body's metabolic processes in variable ways and limit further body weight reductions.

Exercise. Programs which include an exercise regime are presently the choice strategy for weight management. The current concept is that physical training may minimize or counteract the dietary-induced fall in RMR in two ways: a) by increasing the amount of fat free mass and b) by prolonging an increase in oxygen consumption following exercise. In cases where caloric restriction is severe enough to cause a substantial loss in fat free mass, then exercise training has been found to be appropriate for maintaining FFM in most individuals [144]. However,

the common suggestion that acute or chronic exercise may also induce a post-activity elevation in metabolic rate (i.e., post-exercise thermogenesis) which could further promote weight loss is questionable. After providing an extensive review of the literature on the topic, Brehm [26] and Mole [108] each concluded that there is mixed evidence that exercise can cause a sustained elevation in metabolic rate or an increase in resting metabolic rate in obese individuals. In fact, most studies that reported this post-exercise increase have been done on lean, fit, young men and have employed very intense exercise levels [26]. Unless the exercise is of substantial intensity or duration (which may not be possible for obese populations to achieve) there is little indication that exercise can greatly influence post-exercise metabolism and promote added calorie burning [26,144].

The overall amount of physical activity one does is under voluntary control. A reduced quantity of energy expended by volitional exercise may be an etiological factor in the development of some obesity. Indeed, many investigations have found that the obese are less physically active than normal-weight counterparts [164]. An obvious advantage in prescribing exercise in a weight management program is the elevation in caloric expenditure which occurs during each exercise session. By increasing the amount of energy expended (assuming that caloric intake remains the same), the energy balance equation may be upset enough to facilitate gradual weight loss.

Physical exercise clearly creates a great demand for energy. The body's ability to meet overall energy needs during exercise depends upon the intensity and duration and mode of the exercise. These components have been shown to influence the composition of the fuel mobilized/ metabolized during the exercise

[105,124,163]. For example, high intensity, short duration exercise is predominately associated with glycogen usage, whereas lower intensity, prolonged exercise relies primarily on an increased employment of fat as the major energy source. Thus, the proportion of glucose-to-fatty acid utilized as fuel during exercise may determine the demands on (and therefore expenditure and reduction of) the glycogen and fat stores in the body [158].

Fuel Utilization During Exercise

During exercise, following the immediate use of ATP in the muscle, further energy needs are supplied via a substrate pool which operates as a continuum with fat on one extreme and carbohydrate on the other. Active cells can produce ATP from carbohydrate by utilizing two basic metabolic pathways: a) by an anaerobic pathway, and b) by an oxidative or aerobic pathway [124]. The anaerobic systems are considered the source of immediate energy and so the relative contribution of this pathway is gradually reduced as the duration of activity is increased. However, during intense or fatiguing exercise the percentage of energy provided through anaerobic metabolism remains high. In anaerobic metabolism the options for available substrate are limited to creatine phosphate (for very short duration of time) and stored glycogen.

Aerobic metabolism, on the other hand, operates in an inverse manner. Aerobic pathways gradually become more predominant as exercise time is extended and if the intensity remains low. Both fat and glucose can be utilized aerobically and the potential availability of these substrates is virtually unlimited. The

important point is that both systems operate simultaneously and energy needs, and thus fuel sources, are related to the duration and intensity of the event.

Respiratory quotient

The calculation of the respiratory quotient (RQ) is used to estimate the relative contribution of carbohydrate or fat to energy metabolism. It represents the ratio of the metabolic gas exchanged (i.e., amount of carbon dioxide expired to the volume of oxygen consumed; VCO_2/VO_2) [105]. The chemical differences, inherent in the various substrates (fats, carbohydrates, and proteins), dictate the amount of oxygen required and the amount of carbon dioxide produced specifically for each molecule's full oxidation [105]. Thus, depending upon the substrate metabolized, the quantity of CO_2 produced in relation to O_2 consumed will vary. The RQ for carbohydrate is 1.00. The RQ for fats differs slightly depending upon the type of fat but generally the most common fatty acid metabolized gives an RQ value of 0.70 [105]. Normally, the contribution of protein as an energy source is regarded as almost negligible during exercise, thus fat and carbohydrate are considered the primary fuels [105].

Each RQ value corresponds to an energy (kcal) equivalent based on the oxygen consumed. Thus, during an exercise bout the amount of calories from fat and carbohydrate can be calculated and then the percent contribution of each substrate to the overall energy cost can be estimated.

Prolonged exercise

In prolonged exercise (i.e., greater than 10 minutes) energy needs are met primarily from aerobic metabolism [124]. The factors that govern fuel selection (i.e., RQ values) and mobilization during extended exercise are determined by the

availability of the fuel, and the multitude of regulatory enzymes that control the functioning of the aerobic pathway [124].

Glycogen is considered the major store of fuel within muscle and it can be utilized under both aerobic and anaerobic conditions. In addition to the glycogen, working muscles utilize energy from the oxidation of fatty acids (FFA), which are mobilized from the adipose tissue and transported through the blood to the working tissues [111]. In the early stages of sustained exercise, liver glycogen may also be degraded, usually more readily than adipose tissue triglyceride, so that glucose will be a more important fuel than fatty acids [111]. As the exercise time is extended (approximately 20-30 minutes) the FFA level in the blood and the oxidation of fat by the muscle is increased and becomes the major "blood-born" fuel for the working muscle [111,124]. The oxidation of free fatty acids by the muscle during prolonged exercise does not merely supplement carbohydrate oxidation, it also tends to regulate the preferential use of fat which serves to conserve the carbohydrate stores for use in tissues that are dependent on glucose (i.e., brain, blood cells) [111]. Thus, fatty acid oxidation in muscle actually decreases glucose utilization in the tissue with prolonged exercise [51,111]. Figure 1 presents the mechanism of blood glucose regulation via the glucose-fatty acid cycle.

The biochemical regulation of glucose by fatty acid oxidation is achieved, in part, by the inhibition of the enzyme phosphofructokinase (PFK) by elevated levels of citrate [111,124]. However, the regulatory mechanisms are extensive in that there are several "de-inhibitors" of phosphofructokinase which, when concentrations of these increase, will reduce the citrate inhibition on PFK and hence increase the rate of glycolysis and glucose utilization in the cell [111,124]. Thus,

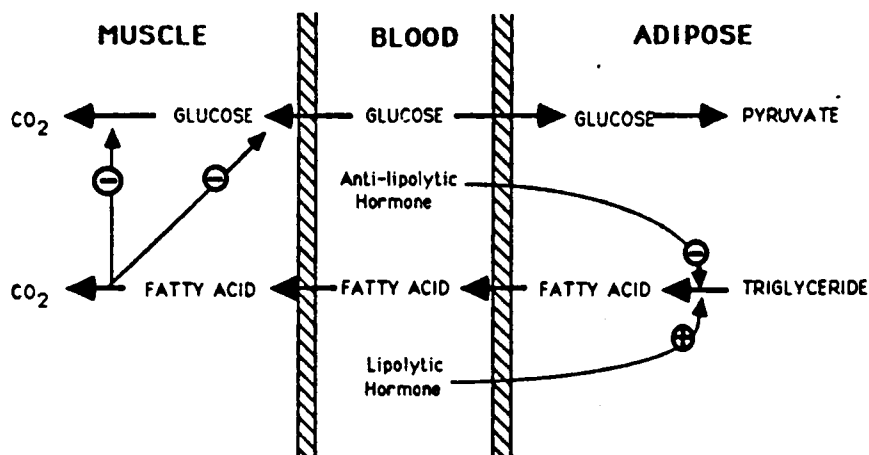


Figure 1. Mechanism of regulation of the blood glucose level via the glucose-fatty acid cycle. Adapted from: Newsholme, E.A. (1977). The regulation of intracellular and extracellular fuel supply during sustained exercise. Annals of the New York Academy of Sciences, 301, pg. 89.

although fatty acid oxidation can inhibit glucose utilization, this inhibitory effect is eliminated if the energy demand by the muscle exceeds that which can be provided by fatty acid oxidation.

It is clear that endurance training enhances muscle's ability to use fat as an energy substrate during exercise. Several studies of the effect of prolonged exercise on substrate utilization have shown that training increases the sensitivity of adipose tissue to lipolytic stimuli [42], as well as enhances the oxygen transport system and the ability of skeletal muscle to oxidize fat [10,33,57]. Also, untrained women (mean body fat = 29.9%) subjected to low intensity prolonged walking were fully able to rapidly adjust fat metabolism to meet the caloric needs of the work [21]. Thus, even in untrained individuals, a shift toward the mobilization and utilization of FFA with prolonged exercise has been documented. The implication for obese individuals is that engaging in prolonged periods of low intensity, "aerobic" type exercise will tend to burn more fat.

The actual energy cost of an exercise bout is determined by intrinsic physiological factors affecting energy metabolism. If these metabolic mechanisms are especially efficient, then the exercise is economical and energy conserving. The following section discusses the literature on the energy cost of exercise (i.e., mechanical efficiency) and its relationship to body composition and obesity.

Mechanical Efficiency

During steady-rate exercise, the oxygen consumption of an activity can be calculated² to equal the energy expended (i.e., calorie cost) during that activity. This cost is obviously related to the amount of work (i.e., the product of force x distance) performed during the activity. Mechanical efficiency or economy of movement is a concept derived from the relationship between the energy input and the resulting work output [105,180]. The examination of mechanical efficiency in obesity is important for assessing the efficacy of physical exercise as a calorogenic agent [122]. It serves for estimating both the metabolic parameters involved with the physiology of the muscle contractile process [136] and the caloric (oxygen) cost of exercise needed for nutritional evaluation [43].

Definition of mechanical efficiency

Efficiency measures are typically defined and calculated in four basic ways using various baseline correction factors. The basic equations for gross efficiency, net efficiency, work efficiency and delta efficiency follow [58].

$$\% \text{ GROSS EFFICIENCY} = \frac{\text{WORK ACCOMPLISHED}}{\text{ENERGY EXPENDED}} \times 100$$

² Oxygen consumption is converted into energy units based on the respiratory quotient (RQ) measured during steady-rate exercise. Then, the work output (usually expressed in kg.m) and the calories consumed must be converted into common units.

Example: $\text{VO}_2 = 1.59$ liters; $(\text{RQ} = 0.88)$ kcals at this $\text{RQ} = 4.899$ per liter of oxygen; thus $\text{CALORIES EXPENDED} = 1.59 \times 4.899 = 7.79$ kcals; Work done = 600 kg.m (1 kcal = 426.8 kg.m); work converted to kcals = $600 / 426.8 = 1.406$ kcals; thus $\text{PERCENT EFFICIENCY} = \text{work} [1.406] / \text{energy} [7.79] \times 100 = 18.05\%$.

$$\% \text{ NET EFFICIENCY} = \frac{\text{WORK ACCOMPLISHED}}{\text{ENERGY EXPENDED ABOVE THAT AT REST}} \times 100$$

$$\% \text{ WORK EFFICIENCY} = \frac{\text{WORK ACCOMPLISHED}}{\text{ENERGY EXPENDED ABOVE THAT OF 0 WORK}} \times 100$$

$$\% \Delta \text{ EFFICIENCY} = \frac{\Delta \text{ WORK ACCOMPLISHED}}{\Delta \text{ ENERGY EXPENDED}} \times 100$$

Gross efficiency (GE) is usually considered the measure of economy (i.e., the ratio of overall cost to the performance achieved) [124]. Net efficiency (NET) is frequently used interchangeably with the term movement or mechanical efficiency [58] as it corrects for the energy cost of resting metabolism. Work efficiency (WE) is useful in evaluating the change in energy expenditure to be expected when encountering a wind or climbing a hill [156]. The delta efficiency (DE) calculation measures the efficiency with which each additional increment of work is performed [159]. DE is considered valuable for determining and comparing the relative energy cost of performing each additional increment of work [156].

Values of ME measures

There is great variety in the literature as to the type of efficiency reported (i.e., GE, NET, WE, DE), the mode of exercise (treadmill, cycle ergometer), the

workloads/speeds employed, as well as the sex, age, body composition and training status of subjects. Some studies report gross and net efficiency while others only report work and delta efficiencies. The type of efficiency reported has been based upon the purposes of the investigation and the assumptions made by the researchers about what the measurement means. For example, the assumption by some researchers [43,58,180] is that work efficiency is a measure of the energy expended by the muscles (i.e., phosphorylative and contraction coupling) specific to the performance of external work. According to Stainsby et al. [156] this assumption is invalid. Stainsby et al. [156] made an excellent argument against the assumptions and validity of using base-line subtractions (e.g., unloaded pedaling) to determine the efficiency of muscle in performing external work (i.e., muscular efficiency). They emphasized that for a base-line to be valid it must continue unchanged under all the conditions in which it is applied. However, they demonstrated that the baselines usually used in the calculations of work efficiency do change with exercise. In summary they suggested that the definitions of the various efficiencies calculated during exercise can be considered useful as long as they are used for comparative purposes and are not considered representative of "muscular efficiency" [156].

A synthesis of the efficiency data reported in the literature on "normal weight" and "overweight" individuals is reported in Table 1. There is no way of specifically comparing values between these studies as they were not done with similar conditions. However, the purpose of listing these values is to achieve an overall picture of the representative range of values commonly reported for each of the efficiency measures.

Table 1. Ranges of Mechanical Efficiency Values for Normal Weight and Obese Populations Reported in the Literature

Type Efficiency	Type Subject	Value Ranges	Reference
GROSS	normal	10.0 - 21.0%	58, 136, 159
	obese	9.0 - 24.0%	122
NET	normal	12.4 - 24.0%	39, 58, 136
	obese	17.0 - 21.7%	39, 175
WORK	normal	24.8 - 39.0%	43, 58
	obese	35.4%	122
DELTA	normal	18.0 -33.0	43, 159
	obese	-none-	

Only Segal et al. [142 & 143] have reported a comparison of lean and obese in terms of the efficacy of physical activity as a calorogenic agent in obese populations. They concluded that there were no differences in net or work efficiency between the two groups. In sum, the vast majority of the studies which have reported efficiency values for various populations have shown ranges which are comparable between groups. However, it is clear that variability between the groups exist and more systematic comparisons are needed to help elucidate the source or meaning (if any) of this variability.

In conclusion, the concept that body composition is a regulated characteristic that responds in a "lawful" fashion to external and endogenous metabolic stimuli is a commonly held view [98]. The nature of the relevant control mechanisms and their interactions however are poorly understood. The sympathetic nervous system is one system known for its influence and control of energy storage, as well as the mobilization and utilization of fuel [44]. In the next section the adrenergic regulation of metabolism will be discussed.

Adrenergic Control of Metabolism

An extensive body of literature has accumulated on the metabolic effects of the catecholamines (i.e., epinephrine, [E]; and norepinephrine, [NE]) [46]. The sympathetic, or adrenergic division of the autonomic nervous system is distinguished by its quick response and then almost immediate inactivation or re-uptake of its mediators, once released. Also the catecholamine "alert signal" is received all over the body [161]. The vast involvement of adrenergic influence on all the tissues and systems of the body (i.e. CNS, heart and circulation, skeletal

muscle, respiration, energy metabolism, and other hormonal regulation) is beyond the scope of this review. Thus, only those effects that are directly involved with energy regulation will be discussed.

Synthesis of catecholamines

The regulation of catecholamine synthesis is dependent upon the time frame of the stimulation (i.e., acute or chronic). With an acute stimulation there is an immediate secretion by exocytosis, and new catecholamine synthesis proceeds from already existing precursors with no increase in enzyme biosynthesis. This result is considered the characteristic catecholamine effect because the catecholamines are so quickly removed or inactivated at the local nerve endings or tissues.

In contrast, chronic stimulation results in measurable increases in the biosynthetic enzymes which lead to an overall higher catecholamine level in the blood [161]. Hyper-secretion or chronic secretion increases concentrations at nerve ends or at peripheral receptors because the secretion rate is higher than the inactivating mechanisms. Inactivation of catecholamines following prolonged stimulation consists of gradual reuptake into the nerve endings, other tissues and/or by metabolism in the postsynaptic cell or liver. The reuptake of catecholamines is energy dependent [119] and the inhibition of uptake can occur by agents that uncouple oxidative phosphorylation. Compounds that are chemically related to catecholamines such as amphetamines, cocaine or tricyclic antidepressant drugs cause an inhibition of NE uptake, thus increasing circulating catecholamine concentrations and eliciting numerous side effects. Norepinephrine uptake is primarily neuronal but has also been observed in nonneuronal tissue (e.g., vascular

smooth muscle, heart, lung, liver) [119]. Nonneuronal uptake has a much lower affinity for NE and is thought to play its role at only very high NE concentrations [119]. Thus, in hypersecretion, when the local reuptake mechanisms are overwhelmed, systemic reuptake and metabolism can serve as a protective mechanism from high levels of circulating catecholamines.

Receptors

The catecholamines are hydrophilic substances that do not traverse the plasma membranes easily. They interact with membrane limited receptors, and do not have to be taken inside the cell to elicit their effects [161]. The interaction of a receptor with an appropriate agonist results in a specific cellular response. Originally, epinephrine's effects were noted as being both stimulatory and inhibitory [161]. Thus, it was thought that there must be two different subtypes of epinephrine. However, later it was discovered that there was only one type of epinephrine but the different effects were a result of two types of adrenoreceptors sensitive to one hormone, E [120,161].

The concept of alpha and beta receptor subtypes was based on the potencies of a series of adrenergic agonists in stimulating various physiological responses. When beta receptor antagonists and radio-labelled agonists and antagonists became available, new information accumulated concerning certain patterns in the biological effects of the receptors, and more receptors were described. It became apparent that certain receptors initiated processes by recruiting a different set of intracellular processes (second messengers) than did those of others. Tepperman and Tepperman [161] outline three criteria used to sort the catecholamine receptors: 1) rank order by response to different agonists; 2)

determine what effects are blocked by specific antagonists; and 3) determine the mechanism of action (i.e., stimulation or inhibition of adenylate cyclase) or by stimulation of phosphatidyl inositol turnover. Thus, these criteria have been used to describe four types of catecholamine receptors: α_1 , α_2 , β_1 , β_2 . Each of these are different glycoproteins with specific preference for one or more distinctive agonists or antagonists and a specific mechanism of action.

Alpha adrenoreceptors. Alpha adrenoreceptors have been recently investigated for their role in control of systemic blood pressure and other physiologic processes such as lipolysis. Alpha receptors are divided into α_1 and α_2 types. The α_1 effects involve turnover of phosphatidyl inositol and elevation of cytosol Ca^{2+} [48]. However, α_2 activation involves the inhibition of adenylate cyclase. The cells innervated by alpha adrenergic receptors are considered to be under antagonistic control because Ca^{2+} and cAMP have opposite effects [48].

Characteristic responses of each of the α adrenoreceptors are described as follows. α_1 -adrenoreceptors are considered excitatory. They involve the elevation of cytosol Ca^{2+} and increase phosphatidyl-inositol turnover. In general they induce vasoconstriction of vascular smooth muscle. α_1 selective agonists are methoxamine, phenylephrine, and oxymetazoline. α_1 selective antagonists/blocking agents are phenoxybenzamine, labetalol, prazosin, and chlorpromazine. α_2 -adrenoreceptors are involved in lowering cyclic AMP levels. They tend to generate inhibitory effects in many systems. In relation to energy metabolism, α_2 -adrenoreceptors inhibit hypothalamic heat conserving mechanisms and are inhibitory to glucose oxidation and lipolysis in adipocytes.

Alpha₂ selective agonists include dopamine, tramazoline, and clonidine. Alpha₂ selective antagonists are yohimbine, piperoxan, tolazoline, and thioridazine. Both norepinephrine (a bit more selective to alpha₁) and epinephrine (a bit more selective to alpha₂) are considered non-selective "natural" agonists. Phentolamine is a nonselective alpha blocker [46,48,120].

Beta-adrenoreceptors. The beta receptors are subclassed as β_1 and β_2 depending upon the relative potencies of agonists for mediating lipolysis and/or cardiac acceleration, considered β_1 , or for mediating bronchiodilation and vasodilation, defined as beta₂ [120]. Beta₁ effects are thought to be primarily due to norepinephrine released by sympathetic nerves [48]. Energy regulation responses that have been found to be activated by the β_1 -receptors are cardiac glucogenesis, adipose tissue lipolysis, and non-shivering thermogenesis of brown adipose tissue. Beta₂ effects are believed to be due to hormonal influence of epinephrine released by the adrenal medulla [48]. Metabolic responses that have been determined to be β_2 -receptor mediated are skeletal muscle contraction, skeletal muscle glycogenesis, and pancreatic insulin release [46,48,120].

According to Wolfe and Molinoff [182], in contrast to the high affinity and very specific nature of the alpha adrenoreceptors, the selective drugs available for distinguishing between β_1 - and β_2 -adrenoreceptors generally show only a limited difference in affinity. Epinephrine and norepinephrine are equipotent activators of β_1 -adrenoreceptors, whereas norepinephrine is less potent than epinephrine in activation β_2 -receptors. Preferential inhibition of β_1 -adrenoreceptors can be accomplished by practolol, metoprolol, and atenolol [182]. Blockers of β_2 -receptors

include butoxamine and H35/25. Many antagonists, including propranolol, alprenolol and pindolol, do not distinguish between β_1 and β_2 receptors [182].

Mechanism of receptor action

Hormone-receptor interaction results in a highly coordinated intercellular cascade of biological responses. The hormone-receptor-complex is considered the "first messenger" giving rise to the intracellular production of a "second messenger" capable of stimulating further biological responses [161]. The basic process of receptor interaction and response is outlined in Figure 2 for each type of adrenergic receptor [161].

Cyclic AMP (3', 5'-adenosine monophosphate) acts as a second messenger mediating the response of the catecholamine at the beta receptors [48,161,182]. Adenylate cyclase activity is considered a good biochemical measure of β -adrenoreceptor function (Wolfe and Molinoff, 1988). However, it was found that alpha receptors in the peripheral tissues did not act through increases in cyclic AMP levels [182]. Indeed, Rodbell [135] found that catecholamines could also cause an inhibitory effect on adenylate cyclase and thus reduce the cAMP concentration [161]. Thus, catecholamines can either stimulate (via β -receptors) or inhibit (via α_2 receptors) adenylate cyclase and influence cAMP levels [161].

In addition to cyclic AMP, other molecules have been proposed as second messengers which may mediate the effects of catecholamines. Wolfe and Molinoff [182] stated that the influx of calcium also has been considered as a second messenger in response to catecholamines. In the presence of calcium, an activator protein called Calmodulin (CaM), creates a Ca-CaM complex which acts like cAMP

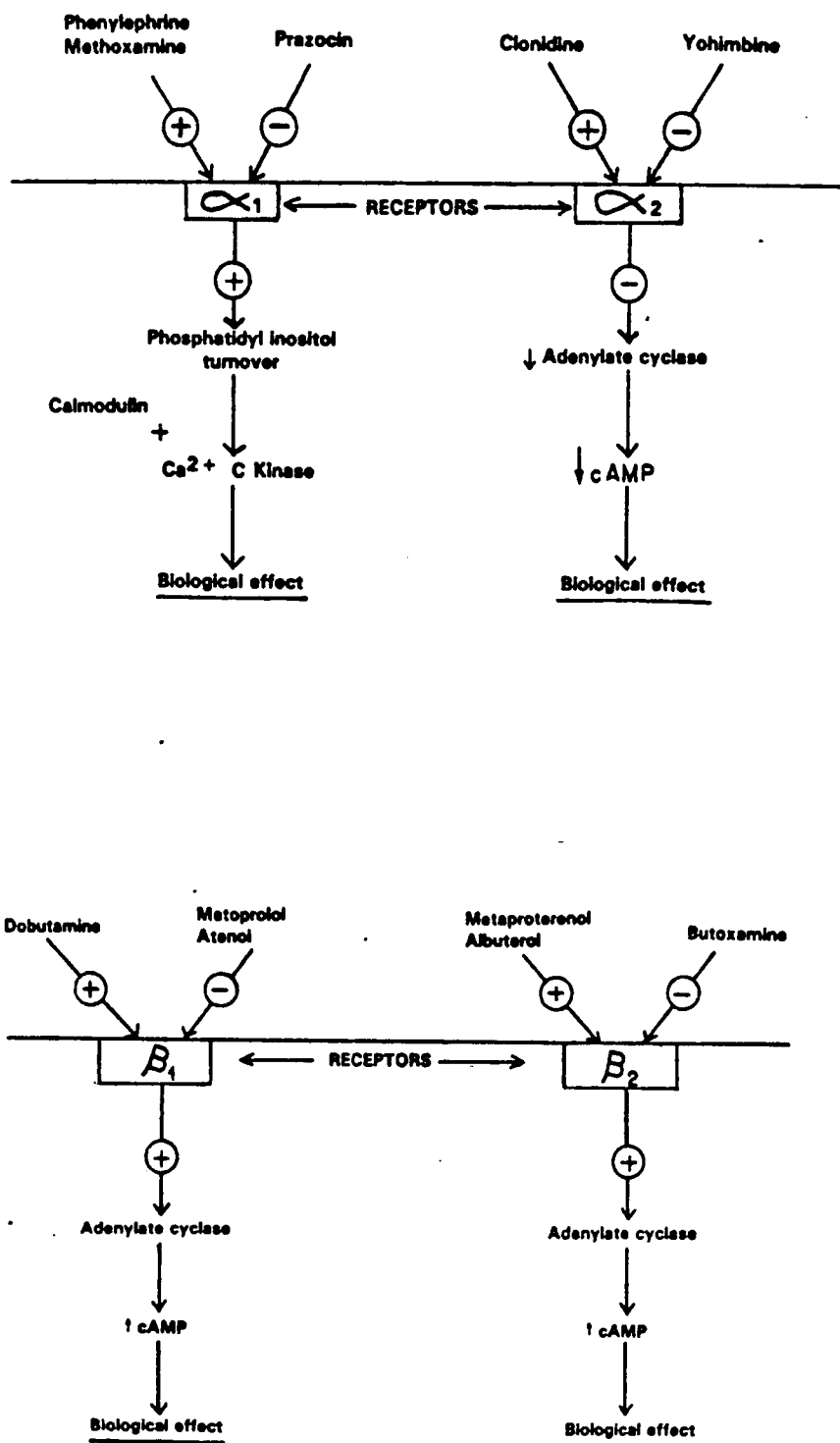


Figure 2. The process of interaction for each type of catecholamine receptor. Adapted from: Tepperman, J. and Tepperman, H.M. (1987). Metabolic and Endocrine Physiology, 5th Edition. Chicago: Year Book Medical Publishers, Inc. pg. 237.

in that it is involved in regulating a cascade of enzymatic reactions either by: a) a direct interaction between the Ca-CaM complex and the target enzyme or b) by activation of a Ca-CaM sensitive protein kinase [161]. The α_1 adrenoreceptor is characterized by its use of Ca-CaM rather than cAMP as a second messenger.

Effects of receptor blocking agents

Pharmacologic blockade of specific adrenergic receptors have been used to study the influence of sympathetic nervous activity on various metabolic responses [73,138]. For example, abnormal sympathetic nervous system activity has been suggested as a possible influence in metabolic aberrations associated with energy regulation in obese humans [31,44]. Sympathetic innervation has been demonstrated in adipose tissue, and adrenergic stimulation is known as one of the mediators of fatty acid mobilization [48,109,161]. It is possible to study the role of the SNS in the mobilization of FFA by using beta-blocking drugs. The magnitude of the decrease in FFA turnover following beta-blockade is considered a reflection of the role played by the SNS in fat mobilization [31].

A considerable amount of research has been done on the effects of beta-blockade on metabolism during exercise [73]. Beta-blockade is known to reduce oxygen consumption during maximal exercise [162]. Also, it is well established that lipolysis and fat utilization are impaired by β -adrenergic blockade [103]. Tesch and Kaiser [162] have suggested that the decrease in O_2 consumption with β -blockade could be a result of a reduced need for O_2 in the exercising muscle due to the utilization of carbohydrate as the preferred (and available) substrate. Indeed, even with low intensity, steady-rate exercise, the RQ is known to increase

following beta-blockade [73]. This implies an enhanced energy contribution from carbohydrate sources [162].

The decrease in FFA production in response to propranolol has been interpreted as the result of both the direct inhibition of beta-stimulated lipolysis as well as the persistence of an "unbalanced" alpha-mediated antilipolytic effect on the adipocyte [31]. In other words, the beta effect is reduced which enables the alpha response (which is anti-lipolytic) to predominate. In addition, β -adrenergic receptors have been found to be influenced by the concentration of circulating catecholamine levels [95]. Indeed, selective β_1 -blockers were found to be less effective than non-selective (i.e., propranolol) blockers under conditions of high sympathetic tone such as during exercise [95]. The authors attributed this finding to a gradual gain in sensitivity (and thus importance) of β_2 -receptors in adipose tissue when sympathetic outflow is high (e.g., during exercise).

During rest a greater absolute response to beta-blockade has been reported in obese versus lean men [31]. The authors suggest that the obese may be more sensitive to the blocking action of propranolol by either its direct effects inhibiting lipolysis or possibly by an indirect effect of the increased circulating catecholamines acting on the unopposed α_2 -receptors.

The metabolic effects of alpha-blockade and possible mechanisms involved with α_2 -antagonists stimulating lipolysis is currently under investigation [138]. There may be a potential for alpha-blockers to become a chemotherapeutic approach for the treatment of obesity in the future.

Lipid Metabolism

The mobilization of fatty acids (lipolysis) from adipose tissue triglyceride stores occurs simultaneously with the uptake and resynthesis of triglyceride (esterification). Thus, triglyceride is broken down to fatty acids, which are then re-activated and re-esterified to form triglyceride [111]. This "substrate cycle" between triglyceride and fatty acid in the adipose cell acts as a regulatory control for fatty acid mobilization. For example, any small change in the levels of lipolytic and/or antilipolytic stimulators (i.e., norepinephrine, epinephrine, insulin) will exert immediate changes in the rate of fatty acid mobilization from adipose tissue. Consequently, any circumstance which could alter the capacity, sensitivity or the cycling/flux ratio of the triglyceride-fatty acid substrate cycle would alter the mobilization of fat.

Adipose tissue deposits are considered one of the major target tissues of adrenergic influence [161]. The pharmacologic effects of adrenoreceptor agonists and antagonists on lipid metabolism relate to changes in plasma levels of FFA and glycerol [46]. Lipolysis in adipose tissue is a key process in the regulation of the circulating free fatty acid (FFA) levels. The release of free fatty acids into the blood from adipose tissue triglyceride stores, represent virtually the only route by which fat stores can be transferred to non-fat tissue for oxidation and net loss [69]. In human adipose tissue (in contrast to rat adipose tissue) only catecholamines and insulin have a pronounced effect on lipolysis [23].

Pharmacologic studies have shown that adipocytes contain all four types of adrenergic receptors [109]. Beta- (primarily β_1 -) that mediate stimulation of adenylate cyclase and increased lipolysis, and alpha- (primarily α_2 -) that mediate an

inhibition of adenylate cyclase and have an anti-lipolytic effect [48,109,161].

Alpha₂ and beta₁ receptors both stimulate glucose uptake by adipocytes but they have opposite effects on lipolysis [161]. In isolated human subcutaneous adipocytes the potencies of the catecholamines for activating lipolysis were found to be: isoprenaline > epinephrine > norepinephrine [46]. Phentolamine (an alpha antagonist) in combination with epinephrine, was found to augment the lipolytic response of epinephrine to equal the maximal response of isoprenaline [46]. Thus, it was concluded that the epinephrine activated lipolysis consisted of an integrated, mixed response which included both an inhibition of lipolysis by the alpha₂ receptors (insulin miminic) as well as the lipolytic response of the beta receptors [46].

In an extensive review of the adrenergic regulation of adipocyte metabolism, Fain and Garcia-Sainz [48] reported that beta-adrenergic activated adipocyte lipolysis was found to correlate with the phosphorylation of the hormone-sensitive lipase (HSL). It was shown that the triacylglycerol lipase in adipose tissue was directly activated by phosphorylation via a cAMP-dependent protein kinase and inactivated via dephosphorylation by a protein phosphatase [13]. However, Fain and Garcia-Sainz [48] also reported, that although the data suggested that increases in cyclic AMP related to lipolysis, it was difficult to always detect an elevation in cAMP for small increases in lipolysis. They stated that it was "very difficult to accurately measure the small increases (in cAMP) that regulate lipolysis" [48, pg. 950].

Perhaps difficulties in measuring minute levels of cAMP elevations are the result of simultaneous alpha₂ adrenergic stimulation of adipocytes. Catecholamine

activation of α_2 receptors results in a decrease of cAMP levels, a reduction of lipase activity and an antilipolytic effect which may mask or offset overall cAMP elevation. If both types of receptors are being simultaneously stimulated the resulting (measurable) cAMP levels and net lipolytic effect may be dependent upon different activities, number, or affinities of the two types of receptors on the adipocyte. Indeed, human adipocytes are richly invested with adrenergic receptors and the control and regulation of the hormone sensitive lipase activity could be affected by modification of adrenoreceptor number, affinity and or any subreceptor (second messenger) processes.

Lipid Metabolism and Exercise

The lipolytic activity in adipose tissue is known to be higher in both endurance trained male and female subjects [34]. Crampes et al. [34], studied the mechanism of this increase. For example, they found that epinephrine induced lipolysis of abdominal adipose tissue was enhanced in the trained subjects. This enhancement was found to be from an overall increased efficiency of the β -adrenergic pathway. However, sex differences were noted. In trained men, the beta adrenergic pathway was enhanced without change in the α_2 adrenergic pathway, whereas in trained women, the lipolysis increase was due to both an increased beta efficiency as well as a significant decrease in the α_2 -adrenergic pathway. Despite the decrease in α_2 efficiency in women, the overall α_2 -adrenergic pathway efficiency remained higher in women (both trained and untrained) compared to men. The authors concluded that endurance training led to greater potential of lipid mobilization and that the effect was more pronounced in

women. However, they did not comment on the fact that the antilipolytic effect in women was greater overall compared with men. In addition, only fat from the abdominal region was analyzed. Perhaps different results would have emerged had the gluteal/femoral sites been studied as well.

When gluteal sites were studied on normal untrained men and women by Richelsen [133], women were found to have a much higher α_2 -adrenergic antilipolytic effect than men. He concluded that the difference could be due to an increase in receptor number without modification of hormone affinity although appropriate experiments were not carried out to test this hypothesis.

The influence of adrenergic control on lipid metabolism is associated with many complex interactions such as the amount and distribution of adipose tissue, physical training status, hormonal status, and sex. An intriguing question remains about the influence anatomically distinct fat stores play in overall metabolism in the intact human.

Differences in catecholamine induced lipolysis have been found between species as well as between the anatomic site of the adipose tissue biopsied within species [46,81,161]. Further, discrepancies have been found between the α_2 -binding data that may be linked to differences in age, degree of obesity, hormonal status or sample site [48,131]. Lafontan et al. [89] published results indicating that the subcutaneous adipose tissue (AT) of the human thigh exhibited resistance to adrenaline stimulated lipolysis compared with the much greater lipolytic action of abdominal AT. They found that the adipose tissue beta receptors were not defective in the thigh but they concluded that there may be a different balance in the activities between the α -adrenergic and β -adrenergic receptors according to the

anatomical localization of the fat deposits. Rebuffe-Scrive et al. [132] also indicated a significantly lower lipolytic effect of norepinephrine in femoral versus abdominal adipose tissue in women. Interestingly, the femoral lipolytic activity in femoral AT increased during late pregnancy and lactation giving rise to the suggestion that hormonal status influences the affinity of the receptors. These results suggest that consideration of species as well as anatomic site and hormonal status are important when describing the metabolic effects of catecholamines on adipose tissue. The significance of these metabolically distinct regions will be discussed in the second part of this chapter.

Summary

The overall influence of epinephrine and norepinephrine on energy regulation in humans is vastly complex. There is little question that those who are somehow predisposed to obesity are more efficient in accumulating and maintaining fat than the habitually lean. However, the metabolic mechanisms which underlie the variability in fat levels between individuals who consume similar amounts and types of food and the ability of some individuals to maintain weight despite an extreme range of energy intakes and expenditures remains to be explained [44]. The inconsistent findings of low metabolic rates, defective thermogenesis, and the reported variability in success of weight loss therapies among certain obese groups suggest that there may be a sub-population of obese individuals with differing metabolic efficiencies. In this respect, subdividing obesity according to type or location of body fat distribution has been suggested as an important classification [179].

The variability in the energetic efficiencies among different people may involve genetic differences in sympathetic outflow [44] or differences in the thermogenically active tissue itself. Any element that affects the adrenoreceptor, in terms of number, affinity, or type/distribution, (e.g., physical training, hormone status, body fat distribution, sex, or age) could also regulate the storage and/or mobilization of energy and therefore influence the predisposition toward obesity.

Body Fat Distribution

One consistency found in the research literature on the relationship between obesity and disease is "that obesity is a heterogeneous disorder" [69, pg. 1168]. This heterogeneous nature of human obesity has inspired attempts to identify subgroups within the obese population. It remains inconclusive whether risk of disease is related to obesity per se or to certain concomitants of obesity such as body fat pattern distribution. This section will review the history and research on the relationship of adipose distribution with various metabolic disorders. Perhaps the strength of this association could help reconcile the inconsistent connection found between obesity and disease.

History and Definition

The three components Sheldon et al. [149] used to describe body shapes: endomorphy (round, fat), mesomorphy (muscular), and ectomorphy (linear, thin), and the systematic assessment of bodybuild by somatotype, gave the first clues concerning the connection of body fat distribution with disease. McCloy and Young [106] reported that thin people had a higher tendency to die from tuberculosis,

pneumonia, or infections (i.e., wasting type disease) than did mesomorphs or endomorphs. In contrast, the data showed a much greater death rate from circulatory disturbances in endomorphs when compared with the thin or medium build people. These characteristics were also used in predicting coronary heart disease in males in the Framingham study [35]. Localization of body fat by area was used in describing subcutaneous fat changes with age and body form [153]. These and other fat patterning methods have been used to categorize the amount of adipose tissue at a specific site relative to the overall level of obesity. Generally the observation has been made that women carry proportionately more fat on their buttocks and legs than do men [45]. In addition men generally carry the majority of their fat in the nape of the neck and abdominal region. This obvious sexual dimorphism probably resulted in questions about what (physiologically) may be involved in this unique distribution.

Terminology

Vague, in the 1940's, appears to have been the first to suggest that adipose tissue at different (sex-linked) locations could have different physiological functions [150]. Vague [169] utilized skinfold ratios and fat-to-muscle areas to postulate the importance of "male type" (upper) "android" fat distribution versus "female type" (lower) "gynoid" obesity in the increased risk of diabetes, gout and atherosclerosis. Since then, Vague's findings have been confirmed by Kissebah et al. [81]. They reported that android obesity, defined by Vague's brachial-to-femoral adipose/muscular ratio, was an important marker for glucose intolerance, hyperinsulinemia and hypertriglyceridemia.

The distribution of adipose tissue has been referred to with various descriptive terms: upper/ lower body fat, central/ peripheral, abdominal/ gluteal-femoral, visceral/ extremity, internal/ subcutaneous and "apple" verses "pear" shapes. Recently, anthropometric measurements used to characterize fat distribution have included various skinfold sites, circumference ratios and combinations thereof, including computed tomography [9,19,74,80,85]. The most frequently used circumference ratios have been the waist-to-hip ratio (WHR) and the waist-to-thigh ratios (WTR) [80,110,134]. Computed axial tomography (CAT) is considered the best method of precisely measuring the amount of total, subcutaneous, and deep (visceral) fat at different regions of the body [123]. The ability to separate the influence of the intra-abdominal fat from subcutaneous depots is important when analyzing the possible mechanisms involved in the metabolic abnormalities found in upper body obesity.

The WHR has been used as the most effective index for evaluating body fat differences. It has been found to be significantly correlated with the amount of intra-abdominal to subcutaneous fat levels measured with computed tomography [9]. Circumference measurements require less expertise and result in less observer variability (especially with obese individuals) than do skinfold thickness measurements, and therefore are more reliable [9,64]. Also the WHR measurement is preferred for assessing the distribution of body fat because it takes into consideration the underlying intra-abdominal fat which skinfold measures cannot. The circumference of the waist is usually obtained at the narrowest "natural waist" area above the umbilicus [25,101]. The hip circumference is at the maximal gluteal protrusion of the buttocks [25,101]. According to Bray [25], women with a WHR

of over 0.80 are at "high risk" for adverse health consequences, whereas men reach "high risk" if they have a WHR greater than 0.85 (see Figure 3). Further, the WHR is more predictive of disease risk than the standard obesity index, body mass index ($BMI = wt/ht^2$) or sum of skinfolds [80].

Association with disease

Several prospective studies have reported that body fat deposition, measured by circumferences and/or skinfolds, is predictive of diabetes [55,112]. Non-insulin dependent diabetes mellitus (NIDDM) patients have: a) a relative excess of fat on the trunk, b) more subscapular fat and less calf fat than non-diabetics and c) thicker subscapular skinfold thicknesses than non-diabetics. These characteristics also correlate highly with fasting plasma glucose levels [49,71,80].

Also, the WHR is associated with cardiovascular disease in both men [93] and women [94] and has the strongest relationship of any anthropometric variable to ischemic heart disease [94]. Several investigators have found that persons with upper body obesity have significantly higher fasting plasma triglyceride levels and higher glucose and insulin levels after a glucose load than those with lower body obesity [5,54,85,158]. Subscapular or trunk skinfold thickness has been shown to be independently related to hypertension and other coronary heart disease (CHD) risk factors [19,20,147,148]. In general, body fat distribution measured by either WHR or skinfolds has been found to be a significant risk factor for mortality and morbidity with a relative risk ratio of two or more [25].

Thus, interest in Vague's original findings have recently resurfaced as more research methods have been developed to increase our knowledge of the importance of the heterogeneous nature of adipose tissue.

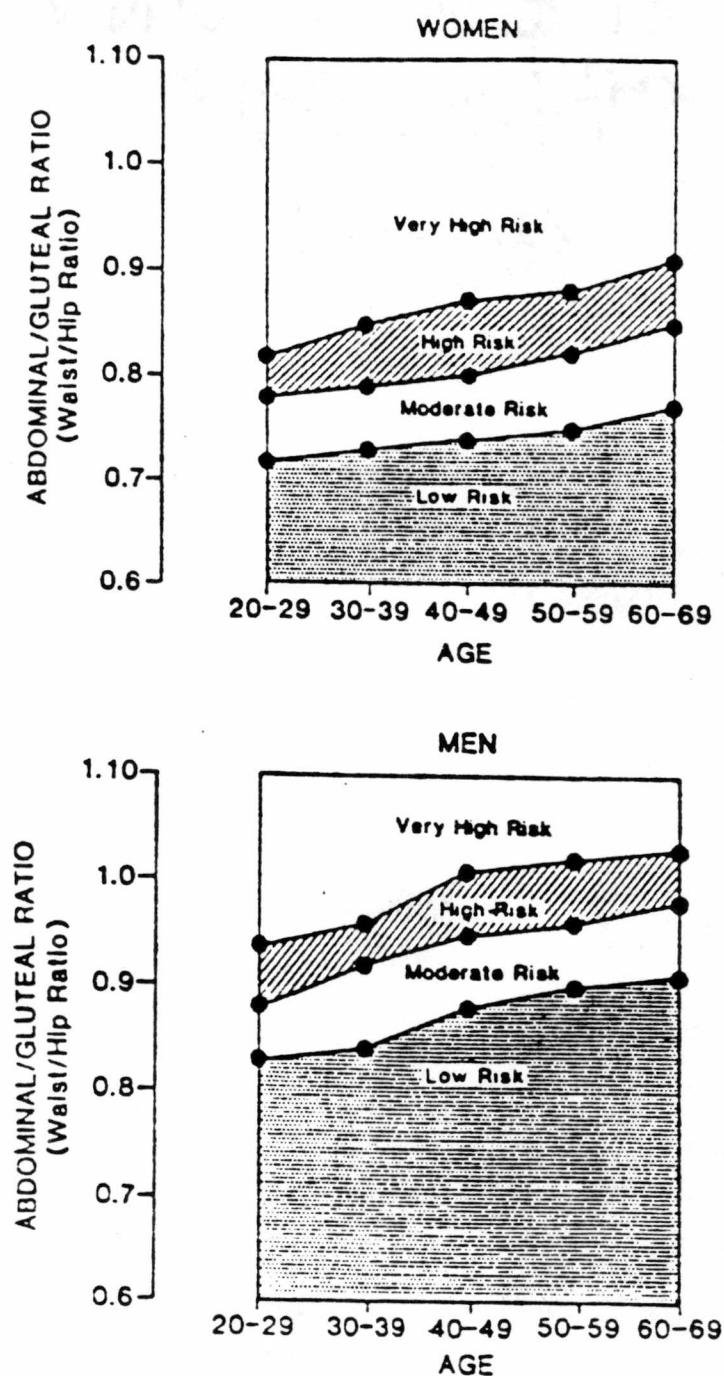


Figure 3. Values for WHR associated with risk for Coronary Heart Disease. Adapted from: Bray, G.A. (1989). Obesity: Basic considerations and clinical approaches. *Disease-A-Month*, 18(7), pg. 466.

Cell Characteristics and Metabolism

Techniques for measuring the cellular characteristics of adipose tissue (size and metabolism) have further demonstrated that human adipose tissue is not a homogeneous tissue. These characteristics have been subgrouped into three classifications of obesity based on anatomic features (cell size), etiologic cause (i.e., CNS lesions or hormonal imbalances) and the age of onset (i.e., childhood or adult) [25]. Importantly, all three classes seem to be linked with the location of the body fat.

Cell size

The size of the adipocyte is related to its metabolic function and to its location. Abdominal obesity is associated with increased fat cell size or hypertrophic adipocytes (enlarged fat cells), whereas gluteal-femoral fat cell deposits are considered more hyperplastic (increased number of fat cells) in nature [85]. Hypertrophic obesity is more closely associated with metabolic disorders and thus more a risk factor for disease than is hyperplastic obesity [85]. Adipocyte hypertrophy has been directly related to glucose intolerance, hyperinsulinemia, and hypertriglyceridemia [81,88].

Insulin insensitivity

Diminished insulin sensitivity has been suggested as one of the underlying abnormalities associated with upper body obesity [118]. Upper body fat localization is characterized by greater decreases in hepatic and peripheral insulin sensitivity, as well as a reduction in peripheral glucose utilization. Lower body obesity is associated with a mild decline in peripheral insulin sensitivity which is compensated for by an increase in pancreatic insulin production. Upper body

obesity is accompanied by a much more severe degree of insulin resistance, a higher amount of hyperinsulinemia, and a decline in hepatic insulin removal [80].

Lipoprotein metabolism

Individuals with upper body obesity have been shown to demonstrate metabolic and structural abnormalities in their plasma lipoproteins that are associated with increased risk for CHD [117]. Basal lipolytic activity varies between adipocytes from abdominal and gluteal-thigh depots [62,69]. In addition, differences in the ability of insulin to suppress lipolysis [62], and for catecholamines to stimulate lipolysis [18,69] have been reported between the fat sites. Adipocytes from the abdominal region are more responsive than gluteal adipocytes to norepinephrine stimulation of lipoprotein lipase's promotion of higher FFA (free fatty acid) turnover [17]. Thus, theoretically, lipolytically dissimilar adipocytes could influence the metabolic manifestations of obesity usually associated with increased risk of disease. For example, an increased FFA flux is associated with hypertriglyceridemia. This increase in lipolysis could result in glucose intolerance via the glucose-fatty acid cycle whereby elevated FFA levels compete with glucose uptake by tissues [51,69]. Jensen and colleagues [69] reported a greater basal FFA flux in upper body vs. lower body obese women.

Upper body obesity has also been associated with increased plasma levels of LDL, IDL, and VLDL levels (low-, intermediate-, and very low- density lipoproteins respectively). The increased concentration of these lipoprotein subspecies is consistent with an increased plasma flux of apo-B containing lipoproteins [12] and is a primary risk factor for CHD.

Intra-abdominal fat accumulation

Observed metabolic aberrations in fat deposition might arise from the increased accumulation of visceral or intra-abdominal fat cells that have a unique access to the liver and portal circulation. The liver is directly exposed to the lipolytic products of visceral adipocytes by its immediate proximity to the portal circulation [85]. Constant exposure to increased levels of FFA in the liver has been suggested as a source of hypertriglyceridemia [85].

Endocrine influences

Androgenic/estrogenic activity has been suggested as the major mechanism associated with metabolic abnormalities associated with fat distribution [80]. In healthy premenopausal women no significant relationship between body fat distribution and plasma total testosterone, androstenedione, or estradiol was found [80]. However, with increasing WHR there was a highly significant trend toward a decrease in steroid hormone binding globulin (SHBG) and an increase in free testosterone levels [61]. Plasma SHBG levels in women are determined by the balance between androgen and estrogen [80]. Thus, the decrease in SHBG and the increase in free testosterone is indicative of a relative increase in androgenic activity in upper body obese women. Differences in body fat distribution might therefore be a manifestation of the increased exposure to androgens.

The degree of androgenic activity correlates with abdominal adipocyte volume but does not relate to the adiposity in the thigh [61]. According to Rebuffe-Scrive [130], femoral-gluteal deposits function primarily as a storage organ whereas visceral deposits serve as rapidly mobilizable energy reserves. This specialization in adipocyte function is supported by biochemical evidence reviewed by Bjorntorp

[17]. For example, the storage capacity of an adipocyte is known to be considerable. However, this capacity is regulated at several steps along the way. One of the primary steps is where the adipocyte precursor cell is differentiated. This differentiation seems to be stimulated by progesterone and inhibited by androgens in vitro [17]. The growth potential of adipose tissue is contingent upon the number of cells capable of accumulating fat. In the obese female rat model there is an initial increase in differentiated (mature) adipocytes throughout the body. However, there is also an unlimited supply of undifferentiated precursor cells located in the femoral region capable of rapid differentiation and transformation into mature adipocytes in response to endocrine stimulation [80]. Progesterone is known to play a dual role both to induce lipoprotein lipase activity to facilitate lipid accumulation in adipocytes, as well as to stimulate the formation of new fat cells [17]. In women, this occurs primarily in the gluteal-femoral subcutaneous region. Gluteal-femoral fat tends to be hyperplastic and is more sensitive to certain steroid hormones such as corticosteroids, estrogen and progesterone than hypertrophic obesity [86].

Lipoprotein lipase activity is increased in the femoral-gluteal region in response to progesterone/estrogen. This increased activity is one regulatory factor which could determine where circulating triglycerides would be primarily taken up and stored. Interestingly, the gluteal-femoral adipocytes have been shown to have a low sensitivity to the lipolytic response of norepinephrine in both males and females [17]. Thus, there is a reduced capacity for mobilizing FFA from these stores. However, in women, during late pregnancy and lactation, femoral lipolysis has been shown to increase. It has been suggested that femoral adipocytes become as

sensitive to norepinephrine stimulation as abdominal adipocytes during this time in order to supply added energy for the fetus and newborn child [17].

Killinger and associates [79] have shown that the biochemical conversion of androgens to estrogens in adipose stromal cells is dependent on their site of origin. This extraglandular conversion is the major source of estrogens in males and post-menopausal females. This feature could have important implications as to the mechanism of the so called "protective" influence of estrogen in the development of CHD.

Androgenic activity can disrupt glucose-insulin homeostasis which can then create other systemic disorders leading to disease. Figure 4 describes the mechanism of androgenic activity on glucose-insulin homeostasis.

Treatment

If fat/weight reduction is desirable to control the ill effects of obesity, it is appropriate upper body obesity must be reduced. Three primary methods of weight reduction are usually employed: reducing caloric intake (diet), increasing caloric expenditure (exercise) or a combination of both. Wadden et al. [173] found that weight loss by dieting alone produced a significant reduction in the WHR in upper body obese women (pre = 0.905 vs. post = 0.881). Subjects with initial WHR levels above 0.85 resulted in greater reduction in this index than those with a lower body obesity pattern. Upper body obese women primarily lost fat from the upper body. The lower body obese women lost more fat overall than the upper body obese women (12.7 kg vs. 10.3 kg), but did not change in WHR, indicating a more uniform loss of fat. Pasquali et al. [116] responded to the Wadden group's findings

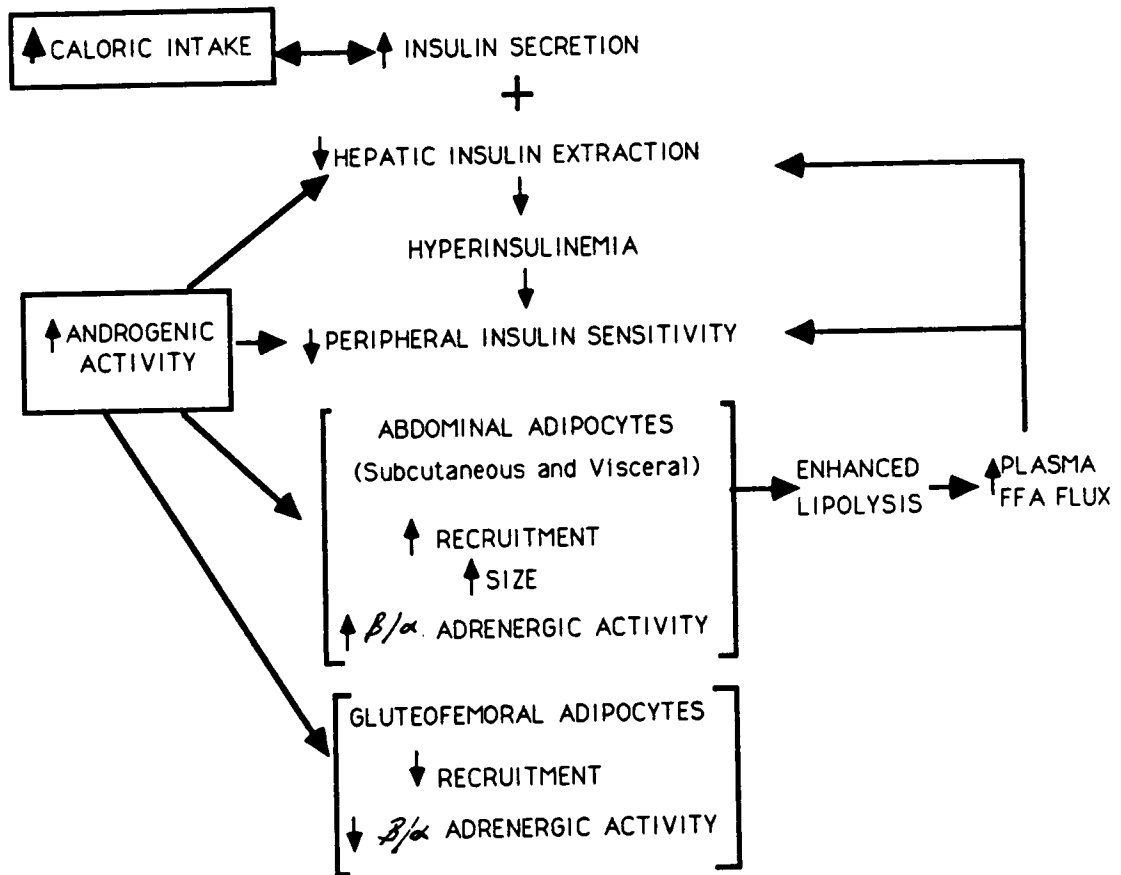


Figure 4. Mechanisms associating body fat distribution and obesity to abnormalities in glucose homeostasis. Source: Kissebah, A.H., Freedman, D.S., and Peiris, A.N. (1989). Health risks of obesity. *Medical Clinics of North America*, 73(1), pg. 130.

with results from their own (unpublished) evaluation of the effects of equivalent hypocaloric diets on central (WHR = 0.89) vs. peripheral (WHR = 0.78) obese women. In contrast to Wadden's findings their summary reported that the central type obese (CTO) lost significantly ($p < 0.05$) more weight than the peripheral type obese (PTO) (13.0 ± 5.3 kg vs. 8.6 ± 3.5 kg) even though energy intake was identical in the groups. As in the Wadden study, the WHR was reduced in the CTO but not in the PTO which again suggested a possible preferential fat loss from the abdominal region. Although these results are intriguing, both studies are suspect because they do not report the influence of behavioral or exercise therapies employed.

Krotkiewski and Bjorntorp [83,84] found that gynoid shaped women (WHR < 0.82) tended to gain fat weight with an exercise training program that did not restrict diet. However, the android shaped men and women (WHR > 0.82) tended to increase muscle mass and decrease body fat consistent with the "expected" training response. Although both groups exhibited the characteristic adaptations in circulatory efficiency and increased maximal oxygen consumption usually associated with 12 weeks of physical training, the authors concluded that "in pear-type obese women physical training induces an increase in body fat" [84, pg. 263].

Krotkiewski [82] reviewed results from short and long term weight reduction programs as to their efficacy for reducing the WHR among gynoid and android obese women. WHR reductions were significantly related to overall decreases in body weight. In general, android women demonstrated the greater decrease in body weight and in WHR after a 12 month, 1000 kcal/day diet program. In another study, physical training (6 months) without caloric restriction reduced body weight

and WHR in the android group but not in the gynoid group. The author concluded that fat patterning could be changed by manipulation of environmental factors such as caloric intake and exercise. However, the prognosis for weight reduction and reduction of WHR seems to be dependent upon the location of the fat stores.

Summary

The major conclusion to be drawn from the studies reviewed is that the metabolic status of adipose tissue is very heterogenous and seems strongly related to body site location. The clinical treatment of obesity should reflect these heterogeneous metabolic manifestations of obesity. The clinically important group are those women and men who are prone to develop upper body type adipose tissue distribution and not necessarily all "fat" people. Women with extreme levels of lower body fat are rarely affected by the adverse metabolic conditions typically associated with obesity. Thus, gynoid obesity has been called a "benign condition" from the viewpoint of risk of disease [17]. However, lower body fat depots may introduce specific site-related metabolic complications which may potentially inhibit or reduce the influence of weight-reduction treatments for those wanting to lose weight. The interesting association between site-specific metabolic regulation of fuels and the implications for weight loss and the potential development of disease requires further study.

CHAPTER III

METHODS

This investigation consisted of three basic areas of inquiry: a) the assessment of differences in resting metabolic rate between groups, b) the assessment of differences in mechanical efficiency (gross, net and delta) between groups, and c) the relationships and/or differences between groups in fuel utilization in response to treatment with and without beta adrenergic blockade during sixty minutes of prolonged walking.

General Procedures

The procedures included gathering data in eight parts. Parts one and two consisted of the initial recruiting and screening of subjects, and then the identification and selection of subjects by body composition and body fat distribution from a large sample of volunteers. Part three incorporated the resting metabolic rate measures. Parts four and five involved the employment of two mechanical efficiency tests (cycle ergometer and treadmill) at four different exercise intensities. The assessment of maximal oxygen consumption followed as part six. And finally, parts seven and eight consisted of two prolonged walking tests to evaluate fuel utilization and test the sympathetic nervous system's influence on fuel utilization during exercise by using the drug propranolol.

This study was reviewed and approved by the Human Subjects Review Board of the University of Tennessee Committee on Research Proposals.

Subject Screening and Selection

Overfat women between 18-40 years of age were recruited from throughout the university and local community population by the use of advertisement "flyers" and articles in the local newspapers (see Appendix A). Over 100 women volunteers responded to the initial orientation/information sessions. From this pool, two unambiguous groups of upper body (UB) and lower body (LB) obese women (obese = body composition $\geq$ 30% fat) were identified. All volunteers received complete verbal, written and videotaped information about the project, the measurements to be made, the risks involved and the time commitments required for the data collection (See Appendix B). Written informed consent was received from each volunteer prior to further participation in the study (see Appendix C). A health history questionnaire (see Appendix D), examined by a consulting physician, was used to screen subjects for any previous or existing health problems. Also, subjects evaluated their menstrual history by means of a 3 month recall questionnaire (see Appendix E). All subjects judged themselves to be physically able to perform the exercise requirements involved in the study (e.g., able to walk for 60 minutes at a moderate pace). In addition, a blood test³ was required prior

³ All blood samples were collected after a 12-hour fast by a Registered Nurse. Samples were put on ice and analyzed in a Hospital Laboratory within 3 hours of the blood draw.

to inclusion in the study to assess each subject's glycohemoglobin (Hb A₁)⁴ percentage and evaluate their blood lipid profiles.

Finally, subjects filled out a 24-hour dietary recall (see Appendix F) which was analyzed by means of a computer program (Nutritionist III, N-Squared Computing, Silverton, OR) for daily caloric intake. Subjects whose self-reported dietary intake was estimated as less than 1200 kcals per day were not accepted into the project. Thus, only subjects with blood lipid profiles and glycohemoglobin percentages within acceptable parameters (evaluated by the consulting physician), and normal histories for health, menstrual status, and diet were finally selected for inclusion in the study. Women on contraceptive pills were considered "normally menstruating" and were accepted into the study.

Following all the screening and selection procedures, a total of 11 LB and 10 UB subjects were finally chosen for participation in the study. One LB subject dropped out of the study before completing parts seven and eight. Two subjects, one LB and one UB, were physically unable (i.e., foot pain and a leg cramp, respectively) to finish all 60 minutes of the "treatment" bout of prolonged exercise and had to cease walking. All other subjects were able to successfully complete the exercise requirements of the study. After completion of the data collection, each subject was given a personal report which evaluated and explained her results.

⁴ The glycohemoglobin percentage was done as a possible indicator of "latent" diabetes. Glycohemoglobin is a normal fraction of the hemoglobin content of the blood, 3-6%. Increased levels (i.e., > 6%) are noted in diabetics. The measurement of Hb A₁ can reflect the average blood glucose levels during the previous 2-4 weeks [107].

Each was given a personalized exercise program/prescription based on her fitness level and weight reduction goals.

Anthropometric Measures

Body height and weight were determined by a Health-o-Meter, Physician Balance Beam Scale, Series 400, (Continental Scale Corp, Bridgeview, IL) measured to the nearest .25 inch and .25 pounds and converted to metric units, respectively. Body Mass Index (BMI) was then calculated as weight/height^2 (kg/m^2).

Standardized, [101] waist and hip circumference measures were made with the subject standing erect and wearing undergarments (see Appendix G). The waist was measured as the narrowest circumference at the "natural waist" as judged from the back of the subject. The measurement was taken in duplicate with a specially developed measuring tape (Figure Finder, Novel Products, Addison, IL) designed with a plastic "strain gauge" type device which enabled repeatable, standardized tension to be applied each time the tape was pulled. If no "narrow area" was perceived, a standard waist measure at the level of the umbilicus was utilized [101]. The hip measure was identified as the largest circumference of the hip/buttocks as judged from the side of the subject. On two occasions the hip circumference was larger than the maximum length of the measuring tape (> 152 cm). In these cases marks were made on the skin and the additional distance added to the tape length. The waist to hip ratio (WHR) was calculated as waist (cm) / hip (cm). Subject groups, UB ($\text{WHR} \geq 0.85$) and LB ($\text{WHR} \leq 0.75$) were determined by the waist/hip ratio.

Body Composition

Measurement of body density was made by standard hydrostatic weighing technique [2] using a submersion tank fitted with a submerged electronic "scale" placed upon force cell transducers coupled to an integrated amplifier (Precision Biomedical Systems, Inc., University Park, PA). The electronic output fed into a chart recorder for a continuous record of the subject's underwater weight. Body composition was determined from no less than five hydrostatic weighing trials with the subject bent forward while she fully exhaled. Body density was determined by the equation of Buskirk [29]:

$$D_b = \frac{M}{V} = \frac{\frac{M_a}{D_w} - M_w}{D_w} - V_r - V_{gi}$$

D_b = Density body

M = Mass

V = Volume

M_a = Mass air

M_w = Mass water

D_w = Density water

V_r = Volume residual

V_{gi} = Volume gastrointestinal tract (constant = .1 L)

Mass in water was determined as an average of the 3 heaviest weight trials. The percentage of body fat was calculated using an equation from Lohman [102], appropriate for this population.

$$\% \text{ FAT} = \left(\frac{509}{D_b} \right) - 465$$

D_b = Body Density

Lung residual volume was determined by the oxygen dilution technique [181] (Nitalyzer, Nitrogen Gas Meter, Model 505, MedScience, St. Louis, MO) immediately prior to hydrostatic weighing with the subject assuming the same posture as required in the underwater tank.

Metabolic Tests

Scheduling and assessment of all metabolic measures, both resting and exercise, were controlled by time of day and phase of menstrual cycle for all subjects. All measures were accomplished while the subject was in the follicular phase (i.e., day 1-12 after bleeding began) of her menstrual cycle and tests for each subject were conducted at essentially the same time of day for each testing period. Metabolic tests in parts 3-6 were done a month previous to the tests in parts 7-8.

Resting Metabolic Rate

Subjects reported to the laboratory fasted and previously inactive for at least four hours prior to the resting metabolic rate (RMR) tests. Metabolic measurements were determined by conventional open circuit spirometry techniques which are described as follows. The subject rested quietly (without sleeping and without reading) in a reclining chair for a total of 40 minutes while inspiring through a mouthpiece and two-way respiratory valve with her nose occluded by a noseclip. The room temperature was kept between 25-27 °C to facilitate a comfortable resting environment. Expired air was collected for a twenty minute period in a 200 L meteorological balloon/bag. The oxygen and carbon dioxide concentrations in the

expired gases were then determined by O_2 (Applied Electro-chemistry, Model S-3A, Sunnyvale, CA) and CO_2 gas analyzers (Model LB-2, Sensormedics Corp., Anaheim, CA). The flow rate of the gas through the gas analyzers was set at 0.6 L/min (i.e., 0.1 L/min, O_2 and 0.5 L/min, CO_2). The volume of gas expired was then determined by pushing the air in the bag through a 120 L, chain-compensated, "Tissot" spirometer (Warren Collins, Braintree, MA). Volume data were then converted to standard, temperature, pressure, dry (STPD) conditions before entering in metabolic equations. Prior to each testing session the gas analyzers were calibrated using known gas mixtures determined by the micro-Scholander technique [139].

Exercise Tests

All exercise testing procedures complied with the guidelines for exercise test administration as recommended by the American College of Sports Medicine [4]. A minimum of one day separated all exercise tests. The subject reported to the laboratory fasted and previously inactive for at least four hours before all of the exercise tests.

Heart rate and blood pressure

Heart rate responses were measured with a Uniq CIC, Model 8799, Heart Watch Computer (Computer Instruments Corp., Hempstead, NY) heart rate monitor. This device sensed electrical signals from the heart, in a manner similar to an electrocardiograph, and electronically computed and digitally displayed the heart rate. Arterial blood pressure was measured by mercury sphygmomanometry,

utilizing the 1st and 5th Korotokoff sounds as criteria for systolic and diastolic blood pressure responses.

Mechanical efficiency

The order of the mode of exercise utilized in determining mechanical efficiency (i.e., cycle or treadmill) was randomly assigned.

Cycle. The same mechanically braked Monark cycle ergometer (Quinton-Monark, Model 850, Seattle, WA) was used for all mechanical efficiency tests with calibration checked prior to each test. After the subject was fitted to the cycle (seat height, toe clips, and mouthpiece height) a two minute pre-exercise resting gas sample was taken in a meteorological balloon. Inspired ventilation was measured with a dry-test gas meter (Parkinson-Cowan, Type CD 4) fitted with a rotary potentiometer. The output from the meter was fed into a physiograph recorder providing a continuous ventilation record. The protocol for the submaximal cycle ergometer test for mechanical efficiency began with a three minute warmup at 0 kp with the subject maintaining a set pedal cadence of 50 rpm. Once the subject had practiced this cadence, (approximately 3 minutes), the first six-minute work bout, using 0.5 kp resistance, was initiated. Metabolic measures were made by standard open circuit spirometry with expired volumes of air collected in a meteorological balloon in the last two minutes of each work bout (i.e., two minute collection period). Expired gases were then analyzed as previously described. Gas analyzers were calibrated between each set of analyses using known gas concentrations. A ten minute recovery/rest period was given between each exercise bout. A total of four work bouts (0.5, 1.0, 1.5, 2.0 kp) were attempted by all the subjects. The pedal cadence (set by metronome) and cycle workload

were closely monitored during each exercise bout to insure that the work rate was as accurate and consistent as possible. Six subjects developed local muscular fatigue and were not able maintain the designated pedal cadence to finish the 2.0 kp work level.

Heart rate was taken each minute during exercise and during minutes 1, 5 and 10 of each recovery session. Blood pressure measures were taken during a 30 second period following each six minute exercise stage and during minute 10 of each recovery session prior to the next exercise bout.

Treadmill. The protocol for the submaximal treadmill test for mechanical efficiency was very similar to the submaximal cycle ergometer test. The subject warmed-up by practicing walking on the treadmill at a set walking speed of 80 m/min. Next, a series of four, 6-minute walk/ 10-minute rest bouts at intensities of 0%, 3%, 6%, & 9% grade were attempted by each subject. As before, all metabolic measures were made by standard open circuit spirometry with expired volumes of air collected in a meteorological balloon in the last two minutes of each work bout. Heart rate and blood pressure measures were made in an identical fashion as the cycle ergometer test. In this test six subjects were unable to achieve a steady-state (i.e., heart rate did not level off and was above 85% of the subject's age predicted maximum) at the highest work rate (9% grade). When a subject was no longer able to remain at a steady state they were urged on to continue walking until they achieved their maximal oxygen consumption.

Mechanical efficiency values were based on the ratio of work accomplished to energy expended. The definitions of each type of mechanical efficiency calculation (i.e., gross, net and delta) were taken from Gaesser and Brooks [58].

Maximal oxygen uptake test

The walking test for measuring maximal oxygen uptake immediately followed the last bout of submaximal treadmill walking. The subject was asked to continue walking at the same 80 m/min while the percent grade increased 2% every 2 minutes until there was no longer a rise in oxygen consumption as work load increased or until they reached volitional exhaustion. Values were considered maximal if the respiratory quotient was over 1.00. Treadmill speed and grade were reduced immediately following maximal exertion to facilitate a gradual walking cooldown and recovery.

Prolonged walking tests

As before, subjects reported to the lab fasted, previously inactive, and during the follicular phase of their menstrual cycle. Immediately upon arrival the subject ingested either a placebo "pill" or an 80 mg dose of propranolol (Inderal Hydrochloride). She was fitted with a heart watch and was instructed to sit quietly and/or read for 60 minutes while the effect of the drug was allowed to develop. After 60 minutes of seated rest, reading material was removed and a 40 minute RMR test, described previously, was administered.

The order of the prolonged walking tests (propranolol treatment vs. placebo) was randomized. Subjects were fasted but well hydrated before the test and allowed to drink water as desired during the walk. Both tests were performed at approximately the same time of day with at least one day separating each bout.

Prior to walking, the subject was encouraged to stretch and warmup her legs. The prolonged walking test for evaluation of fuel utilization required the subject to walk continuously for 60 minutes at 55 - 60% of her maximal oxygen

uptake. Analysis of a two-minute sample of expired gas employing standard open circuit spirometry at 10 minute intervals was used to evaluate the subject's VO_2 . Adjustments in the speed and/or grade of the treadmill were made periodically to facilitate the subject maintaining 55-60% of her maximal VO_2 . Evaluation of the respiratory quotient (i.e., the ratio of carbon dioxide produced to oxygen consumed) was determined at each gas collection interval. Heart rate was also monitored during each gas collection period throughout the test.

The development of high levels of lactate may act to inhibit free fatty acid mobilization and thus inhibit fat utilization. Thus, care was taken to ensure that the work intensity during the prolonged walking was sufficiently low to reduce the chance of stimulating a high production rate of lactic acid.

Lactate Analysis

The information on lactate levels was valuable for an estimate of the intensity of the anaerobic stress on the subject. Immediately following each prolonged walking test a finger tip sample of blood was taken. Fifty microliters of each sample was deproteinized in 2 ml of cold perchloric acid and centrifuged. The supernatant was decanted into a cold test-tube and frozen. The samples were later analyzed for lactate by the enzymatic lactic acid analysis [63] using a Turner 450 Fluorometer. Each was analyzed in duplicate.

Statistical Analysis

Descriptive statistics (mean, standard error of the mean, and range) were computed on all the anthropometric and descriptive variables used in the study. A

one-way analysis of variance was utilized to test for significant differences in these variables between the body fat groups. Also ANOVA procedures were used to test hypothesis 1 regarding group differences in resting metabolic rate.

A two-way factorial ANOVA with repeated measures (subjects nested in group) was used to test hypotheses 2-3 concerning differences in resting metabolic rate between groups (UB or LB) and within treatments (placebo or propranolol).

Two separate 2×4 factorial ANOVA's with repeated measures (subjects nested in group) were utilized to test hypotheses 4-7 pertaining to differences in gross and net mechanical efficiency between groups at four work intensities, for each separate mode of exercise (cycle/treadmill). For delta efficiency, a 2×3 factorial ANOVA with repeated measures was used to test for significant group differences at three intensities for each separate mode of exercise.

A $2 \times 2 \times 7$ ANOVA with repeated measures on time blocks and treatments, was used to test for significant differences in respiratory quotient between groups during the exercise time periods (i.e, hypothesis 8). Planned contrasts for each exercise time period were done to test hypotheses 9-10 concerning significant differences between groups and within treatments.

All statistical procedures were done with the Statistical Analysis System (SAS) [137]. Differences were deemed significant at $p < 0.05$; however, results approaching this level were evaluated for physiologic significance.

CHAPTER IV

RESULTS

This research sought to evaluate the differences in various metabolic parameters at rest and in response to exercise between two groups of obese women with dissimilar body fat distribution patterns. The effects of body fat distribution on resting metabolic rate, mechanical efficiency and on fuel utilization/mobilization during prolonged walking were considered in this investigation. Differences in the adrenergic regulation of metabolic rate and fuel mobilization were studied by pharmacologically blocking the beta-adrenergic receptors with the drug propranolol at rest and during a bout of prolonged walking.

Basic Characteristics

Twenty-one women volunteers with no known health problems were selected as subjects in this study. In general, the participants in this investigation were obese women of similar age, body size and similar body fat composition with significantly different areas of body fat accumulation. Table 2 shows the basic characteristics of the two groups. Only the circumference variables (i.e., waist and hip) were significantly different between the two groups. The mean waist to hip ratio (WHR) of the upper body obese group (UB) was significantly ($p < 0.0001$) higher than the WHR of the lower body obese group ($UB = 0.882 \pm SEM 0.01$ vs. $LB = 0.731 \pm SEM 0.001$). In addition, the subjects selected in this study were

Table 2. Subject Characteristics

	UB (N = 10)			LB (N = 11)		
AGE(yrs)	30.6	$\pm$	1.7	25.9	$\pm$	2.1
HT(cm)	166.5	$\pm$	2.1	163.4	$\pm$	1.1
WT(kg)	90.88	$\pm$	5.5	91.75	$\pm$	6.5
BMI(kg/m ²)	32.77	$\pm$	1.9	34.37	$\pm$	2.2
WST(cm)	101.3	$\pm$	3.5	91.2	$\pm$	3.2 *
HIP(cm)	114.6	$\pm$	3.2	125.1	$\pm$	4.5 *
WHR	0.882	$\pm$	0.01	0.731	$\pm$	0.001**
% FAT	39.43	$\pm$	1.5	42.38	$\pm$	2.2
FFM(kg)	53.84	$\pm$	2.4	50.93	$\pm$	1.8
RHR(bpm)	79.6	$\pm$	1.4	76.2	$\pm$	3.5
RSBP(mmHg)	117.0	$\pm$	1.7	119.4	$\pm$	2.9
RDBP(mmHg)	72.4	$\pm$	2.7	74.0	$\pm$	1.7
MHR(bpm)	186.5	$\pm$	3.2	187.4	$\pm$	3.4
MSBP(mmHg)	162.9	$\pm$	7.8	161.9	$\pm$	3.5
MDBP(mmHg)	63.3	$\pm$	4.8	69.6	$\pm$	5.5
VO _{2MAX} (l.min ⁻¹)	2.35	$\pm$	0.1	2.45	$\pm$	0.1
VO _{2MAX} (ml.kg ⁻¹ .min ⁻¹)	26.33	$\pm$	1.1	27.62	$\pm$	1.4

* p < 0.05

** p < 0.0001

Values are Means $\pm$ Standard Error of Mean

HT = Height; WT = Weight; BMI = Body Mass Index; WST = Waist Circ.; HIP = Hip Circ.; WHR = Waist/Hip Ratio; FFM = Fat Free Mass; RHR = Rest Heart Rate; RSBP = Rest Systolic Blood Pressure; RDBP = Rest Diastolic Blood Pressure; MHR = Max Heart Rate; MSBP = Max Systolic Blood Pressure; MDBP = Max Diastolic Blood Pressure

all comparable in both resting and exercise cardiovascular parameters (i.e., heartrate and blood pressure) as well as overall maximal aerobic capacity (i.e., VO_{2MAX}).

Table 3 reports the mean blood lipid characteristics of the subjects. The blood lipid profile was used in the screening and selection of the subjects. Values from the blood lipid tests were within normal acceptable limits and indicated relatively similar amounts of blood triglyceride and total cholesterol for both groups. However, in comparison to the UB group, the LB group had a significantly lower ($p < 0.0001$) ratio of total cholesterol to the fraction of high density lipoprotein cholesterol ($TCHOL/HDL = 3.18 \pm 0.6 \text{ mg}\cdot\text{dl}^{-1}$ vs. $4.11 \pm 1.0 \text{ mg}\cdot\text{dl}^{-1}$). The percentage of glycohemoglobin in the blood was not different between the groups. An average Hb A₁ percent of 5.07 ± 0.2 vs. $5.11 \pm 0.15\%$ was established for the UB and the LB groups respectively. These values are considered to be within the normal "non-diabetic" levels of 3-6% [107].

Resting Metabolic Rate

Table 4 shows the calculated RMR values for the different obese sub-groups. Resting metabolic rate was not statistically different between the groups regardless of how it was expressed (i.e., $\text{kcal}\cdot\text{day}^{-1}$, $\text{kcal}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$, or $\text{kcal}\cdot\text{kg FFM}^{-1}\cdot\text{hr}^{-1}$). In addition, the number of kcals estimated from the self-reported, 24-hr diet recall was also essentially the same between the groups. However, the LB group showed a much wider variability in dietary intake.

Table 3. Blood Lipid Profile Characteristics

	UB (N=10)	LB (N=11)
TCHOL(mg/dl)	196.6 ± 9.7	178.5 ± 9.8
HDLC(mg/dl)	49.7 ± 3.4	56.7 ± 2.5
TCHOL/HDL(mg/dl)	4.11 ± 0.3	3.18 * ± 0.2
LDLC(mg/dl)	119.4 ± 9.0	99.0 ± 7.9
TRIGLY(mg/dl)	137.4 ± 28.7	114.4 ± 22.7

* $p < 0.0001$ (Values are Mean $\pm$ Standard Error of Mean)

TCHOL = Total Cholesterol; HDLC = High Density Lipoprotein Cholesterol;
TCHOL/HDL = Total Cholesterol/HDLC Ratio; LDLC = Low Density Lipoprotein Cholesterol;
TRIGLY = Blood Triglyceride

Table 4. Resting Metabolic Rate

	UB (N=10)	LB (N=11)
RMR (kcal.s.day ⁻¹)	1730.0 ± 110.4	1640.0 ± 81.3
RMR (kcal.s.kg ⁻¹ .hr ⁻¹)	0.81 ± 0.03	0.76 ± 0.03
RMR (kcal.s.kg FFM ⁻¹ .hr ⁻¹)	1.34 ± 0.05	1.34 ± 0.04
DIETARY INTAKE (kcal.s.day ⁻¹)	2073.4 ± 158.3	2288.0 ± 337.8

Values are Means $\pm$ Standard Error of Mean

RMR = Resting Metabolic Rate; DIETARY INTAKE = 24-HR Diet Recall

Mechanical Efficiency

The mechanical efficiency values calculated were gross, net and delta efficiencies. Each of these were estimated during two modes of exercise (i.e., cycle ergometer and treadmill) at various work rates.

Cycle

Figure 5 indicates the positive relationship between the increase in energy expenditure with work rate for each group. In general, gross and net efficiency showed a corresponding increase as the work rate increased (see Figure 6). No differences in gross or net efficiency were noted between the two body fat groups at any work rate (see Appendixes H-1 & H-2). The mean gross efficiency values ranged between about 10% during very low intensity pedaling up to approximately 15% for both LB and UB groups. Net efficiency values showed initially a similar trend with increasing work rate, although during work rates of 50, 75, and 100 W, a plateau in percent efficiency of about 19% was seen in both groups. It is important to note that the UB group was much less able to tolerate the final work rate (100 Watts) than the LB group. Only 5 UB subjects compared to 10 LB subjects were able to maintain the pedal cadence and achieve a metabolic steady-rate (i.e., no change in heart rate and VO_2). Net efficiency showed an initial rise when the work rate was increased from 25 Watts to 50 Watts, but then essentially leveled off during subsequent work rates to remain at about 19.5% in both groups.

Delta efficiency on the cycle (see Figure 7) showed a decrease with increasing work rate. The work rates for delta efficiency were calculated as half-way between each progressive level (i.e., 37.5 W, 62.5 W, 87.5 W). The

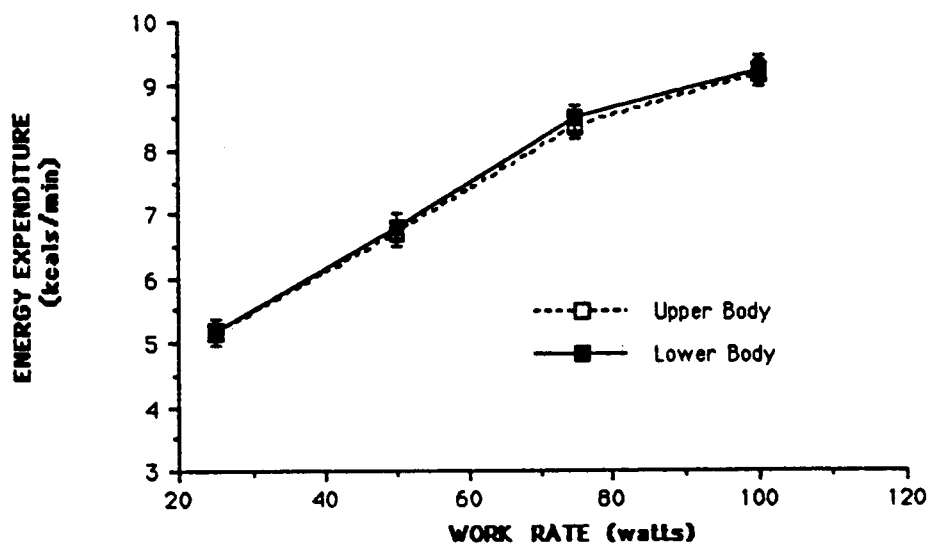


Figure 5. Relationship of energy expenditure to work rate on the cycle ergometer. Values are Mean $\pm$ SEM.

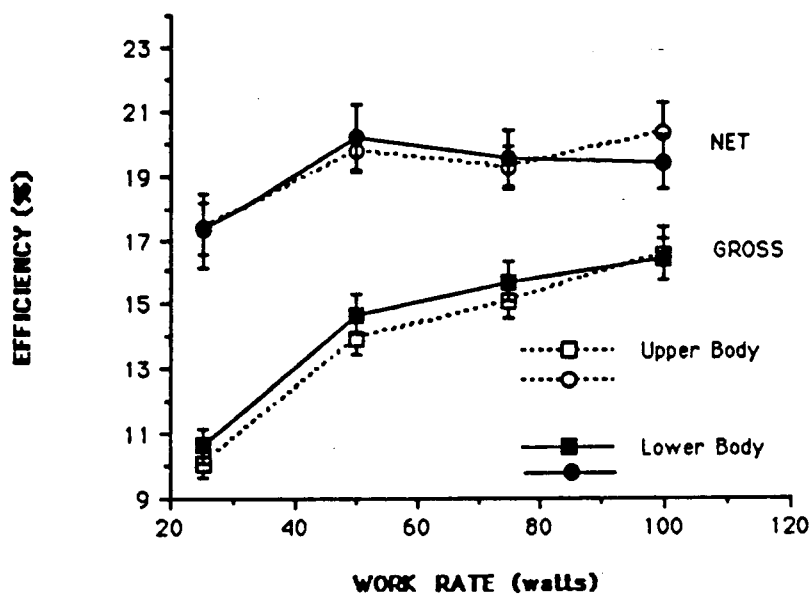


Figure 6. Cycle gross and net mechanical efficiency. Values are Mean $\pm$ SEM.

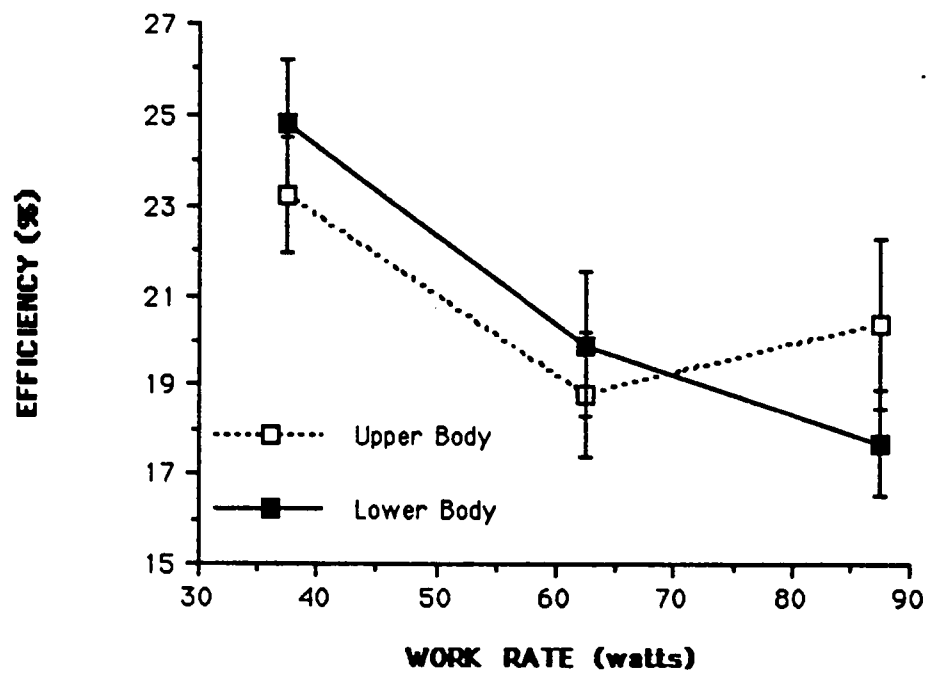


Figure 7. Cycle delta mechanical efficiency. Values are Mean $\pm$ SEM.

cycle delta efficiency values were not statistically different (see Appendix H-3) between the two body fat groups. However, there was a considerable amount of variability in the delta efficiency values for both groups. The mean delta efficiency at the final work rate for the UB group showed an unexpected rise that was not statistically different from the LB group. A key point to recall is that only 5 subjects made up the UB group in this last work load.

Treadmill

The same patterns in gross and net efficiency (see Figure 8) were shown for both groups during treadmill walking. There was a fairly linear increase in both gross and net efficiency with the increase in work rate. However, no differences in efficiency were noted between the groups (see Appendixes H-4 & H-5). The rise in net efficiency (e.g., range 10 - 18%) essentially paralleled the rise in gross efficiency with the absolute difference being between 2 - 3% for each work rate. A more equivalent number of UB subjects (N = 6) compared to LB subjects (N = 8) were able to sustain the highest intensity work rate with walking compared to the cycle test.

Delta efficiency values (see Figure 9) were only calculated at two work rates. As with the cycle data, there was great variability within groups in delta efficiency. Again no statistically significant differences were noted between groups in treadmill delta efficiency (see Appendix H-6). However, there was an obvious trend toward decreasing efficiency with increasing work rate.

Overall, the efficiency values between modes of exercise cannot be precisely compared as each was calculated from different work rates and each required a

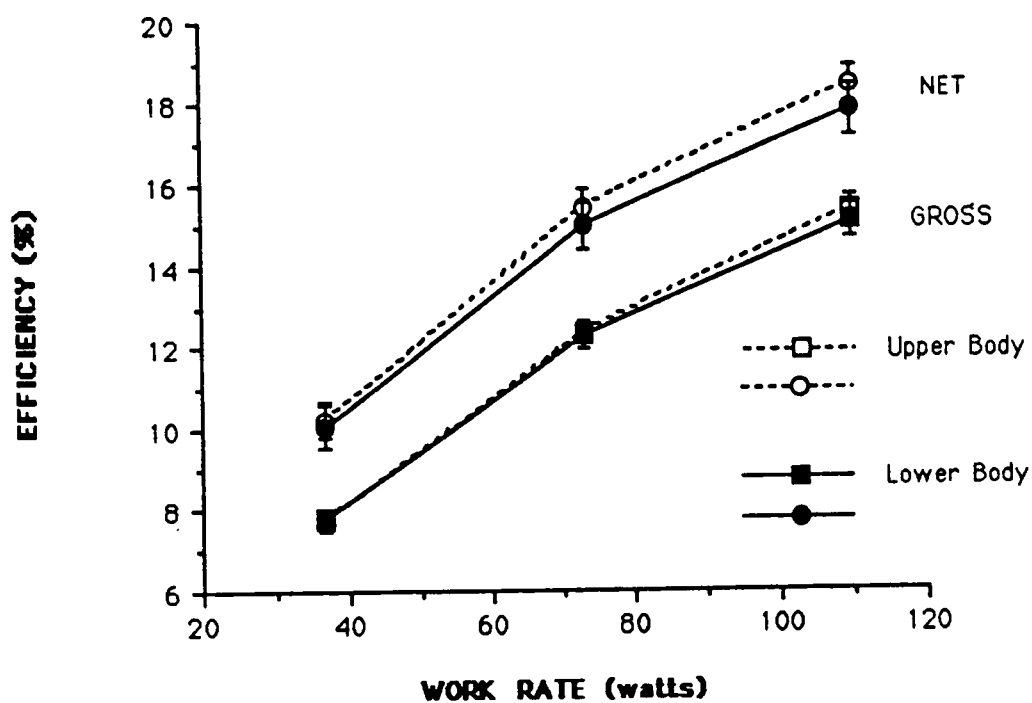


Figure 8. Treadmill gross and net mechanical efficiency. Values are Mean $\pm$ SEM.

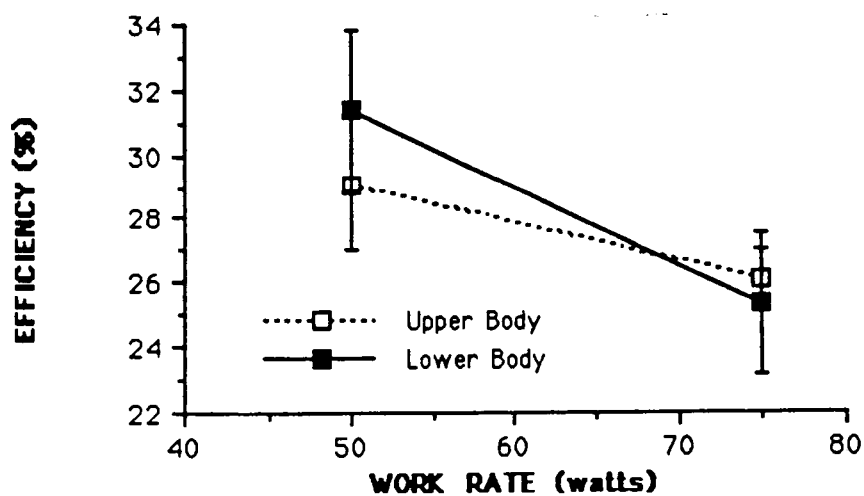


Figure 9. Treadmill delta mechanical efficiency. Values are Mean $\pm$ SEM.

much different muscular output. In general, efficiency, when expressed as delta efficiency, showed that for both groups treadmill walking was more efficient than cycling.

Beta-Adrenergic Blockade

RMR

Figure 10 shows the relationship of body fat distribution with resting metabolic rate for both treatments. There was no statistical difference in resting metabolic rate between groups either in the control condition or following the administration of propranolol regardless of how it was expressed (see Appendixes H-7, H-8 & H-9). The mean RMR in the UB group was somewhat higher than that recorded for the LB group but the trend was not significant. In addition, the values of RMR in the control condition were comparable to those reported previously (see Table 3).

Treatment with propranolol did not significantly lower RMR in either group although a trend was noted. There seemed to be a slightly lower RMR in response to beta-blockade in the UB group than the LB group however it was not a significant tendency.

Fuel Utilization

The intensity of the exercise was kept between 55-60% of the subjects VO_{2MAX} for each exercise bout. The consistency of the average heart rate responses during prolonged walking of both groups for each treatment (i.e., control &

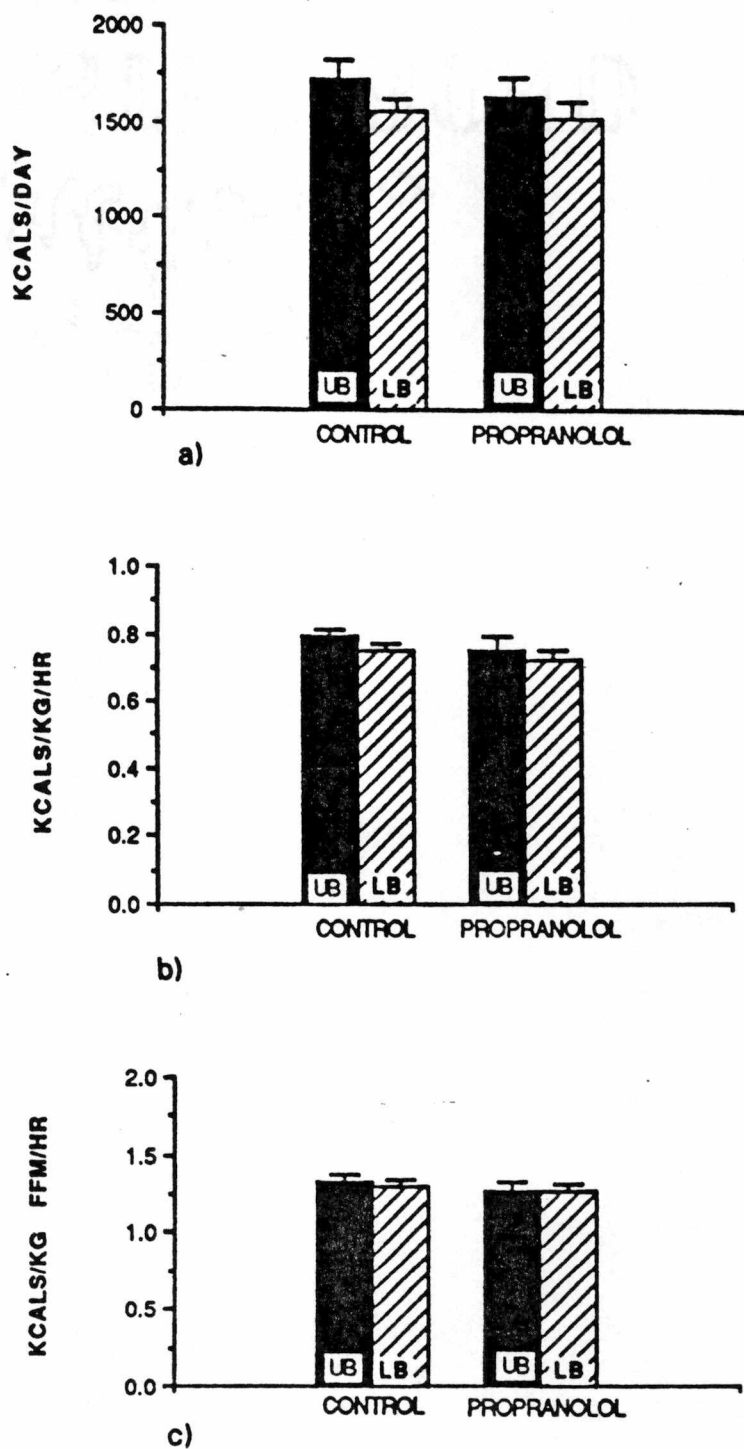


Figure 10. Effect of body fat distribution on RMR during control and propranolol treatments. RMR is expressed as: a) kcal.day⁻¹; b) kcal.kg⁻¹.hr⁻¹; c) kcal.kg FFM⁻¹.hr⁻¹. Values are Means $\pm$ SEM.

propranolol) is shown in Figure 11. The standard error is contained within the symbols for each heart rate data point.

Figure 12 shows a graph of the effects of prolonged walking on the RQ, with and without treatment with propranolol. The significant ($p < 0.0001$) decline in RQ with time was evident in both trials (see Appendix H-10). The propranolol bout induced a higher RQ compared to the control from minute 30 to 60 in both groups. The effect of propranolol treatment on exercise-induced fat utilization was noted earlier ($p = .006$) in the LB group than in the UB group (i.e., by minute 20 in the LB group vs. minute 30 in the UB group) (see Appendix H-10). There were no between group differences in the RQ values at any time period within either the control or the propranolol treatments.

The graph of the percentage of calories utilized as fat, which were calculated from the RQ, is shown in Figure 13. The distinct shift toward fat utilization was blunted with beta-blockade in both groups.

Lactate

The blood samples for lactic acid analyses were taken less than one minute after completion of the one hour walk. The analyses indicated that lactate levels for both groups during both treatments were well below the levels known to inhibit fat mobilization. There were no group differences in lactate values for either exercise treatment. The group mean lactate values for the control treatment were UB = 2.48 mM vs. LB = 2.54 mM and for the propranolol treatment were UB = 2.67 mM vs. LB = 2.52 mM. The range of lactate values for both groups during

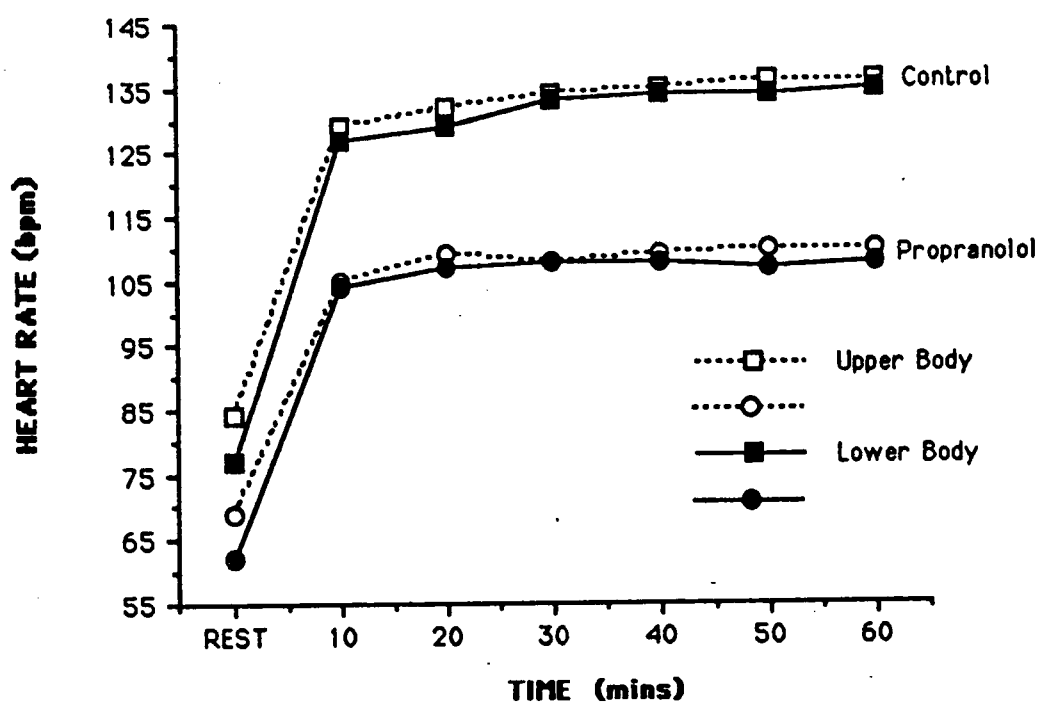


Figure 11. Heart rate response during prolonged walking with and without treatment with propranolol. SEM are contained within the size of the symbol.

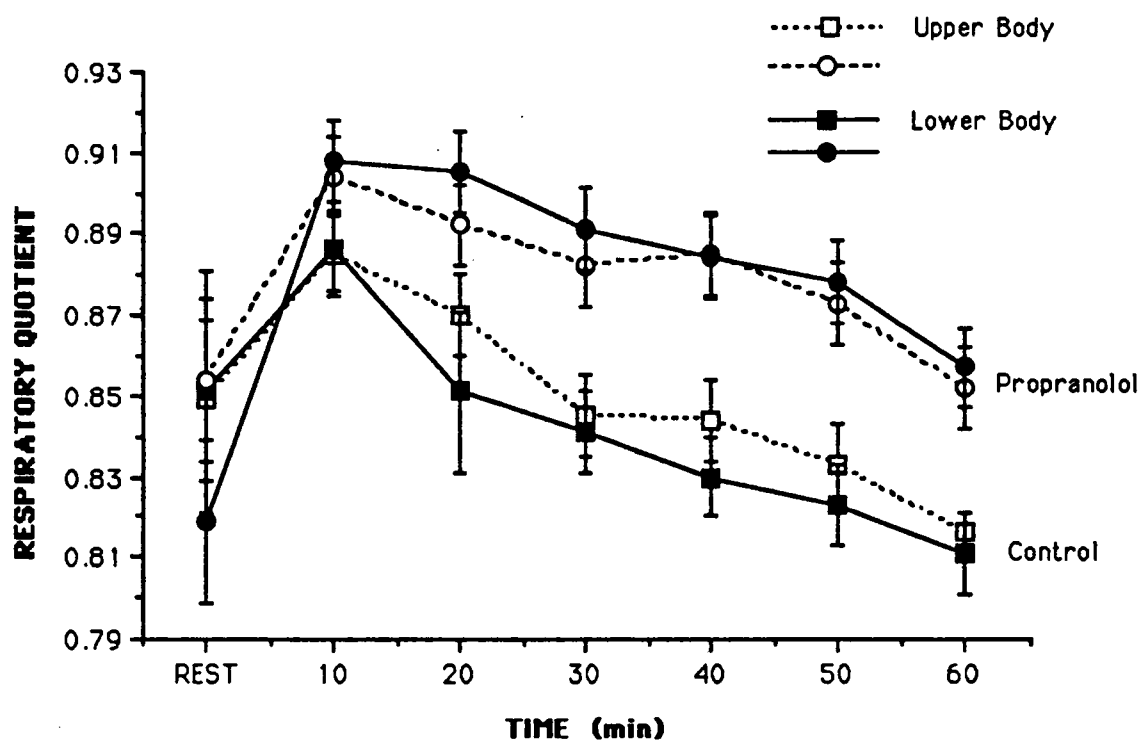


Figure 12. Relationship of RQ with time during prolonged submaximal walking with and without treatment with propranolol. Values are Means $\pm$ SEM.

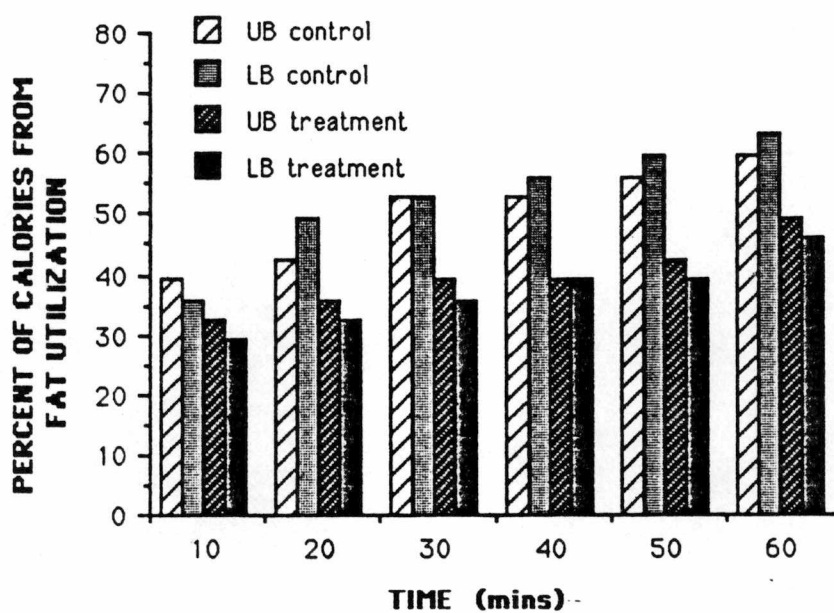


Figure 13. Percentage of estimated calories utilized from fat during prolonged walking with and without treatment with propranolol. SEM are contained within size of symbol.

the control condition were between 1.6 - 4.2 mM, and during the propranolol treatment were between 1.1 - 4.0 mM.

CHAPTER V

DISCUSSION AND IMPLICATIONS

Introduction

The first connection between body fat distribution and disease was qualitatively assessed about 40 years ago [169]. Within the last 15 years researchers have reported significant metabolic differences between adipocytes from various regions of the body which have been strongly implicated in the development of obesity-related disorders. The characterization of obesity by body fat distribution has been based on differences in adipocyte morphology and function [16,81,92,155].

Differences in energy balance regulation between sub-groups of obese individuals has been suggested as one possible source for the unpredictable success rate of weight loss and weight maintenance programs (i.e., diet and/or exercise) for some obese individuals [18]. Measured differences in response to exercise training suggest that metabolically distinct mechanisms may be functioning within these sub-groups. The current investigation sought to examine metabolic differences between two groups of obese women distinctly characterized by their body fat locations.

Basic Characteristics

The results confirmed that the sub-groups of obese women selected in this study had distinctly different body fat patterns. According to data reported by

Lanska, et al. [92], the average WHR for 15,925 obese women between 20-40 years of age was 0.766 (s.d. = 0.064). In the current study, the LB group had an average waist-to-hip ratio of 0.731 (with a range of 0.693 - 0.754), which was about the same as the mean reported by Lanska's [92] group, and the WHR of the UB group, 0.882, was almost two standard deviations greater than the reported mean. However, despite the dissimilar body shapes, age, body size (expressed by height, weight or BMI), body fat composition, cardiovascular characteristics, and maximal aerobic power were similar for the two groups. In other words, the two body fat distribution sub-groups were well matched.

The blood lipid profile showed cholesterol levels which were consistent with those reported in the literature for an obese, sedentary, population of women [41,54,74]. In addition, this study joins others [40,44,74] in demonstrating a trend for the LB group to have a "more favorable" lipid profile in terms of risk for coronary heart disease. There was a higher total cholesterol to HDL ratio in the UB group which was similar to what has been typically described in upper body fat obese women [41]. However, the higher risk profile of the UB women does not mean that they had some sort of undetected cardiovascular pathology. On the contrary, although the levels were higher than the LB group, they were within the "normal" ranges for "acceptable" risk [4]. Triglyceride levels were also typical of those from an obese population [3,41,54]. Again, the physiological trend, although not statistically significant, was for the LB group to have lower serum triglyceride levels than the UB group. Finally, neither group showed a greater tendency toward latent diabetes as both groups had essentially identical Hb A₁ values.

Resting Metabolic Rate

The mean RMR noted in this study, whether expressed as an absolute value (i.e., $\text{kcal}\cdot\text{day}^{-1}$) or expressed per kilogram of body weight or fat-free mass (i.e., $\text{kcal}\cdot\text{kg}^{-1}$; $\text{kcal}\cdot\text{kg FFM}^{-1}$), were found to be similar to those of obese women reported by other investigators [15,100,128,140]. Three of the studies that measured RMR [40,171,179] utilized analogous groups of subjects and methods as those in the present investigation. The RMR results from the current investigation corresponded best to those reported by Vansant et al., [171]. Vansant's [171] group reported that body fat distribution did not effect RMR values differentially (i.e., $\text{RMR UB} = 1521 \pm 306$ vs. $\text{LB} = 1544 \pm 220 \text{ kcal}\cdot\text{day}^{-1}$)⁵. In the current investigation, mean RMR values were only about 5% different between the groups.

However, den Besten's [40] group observed a slight trend toward higher RMR values in the upper body obese in comparison with the lower body obese group (i.e., about a 12% difference). Although the authors reported that this trend did not reach statistical significance (and no p value was reported), Weststrate et al. [179], presented RMR data which were found to be significantly different ($p < 0.04$) between the two body fat sub-groups. Weststrate and colleagues [179] suggested that the results of their study supported the hypothesis that body fat distribution affects energy expenditure in obesity. The subjects in the Weststrate [179] study had body fat distribution patterns similar to those in the present investigation (i.e., $\text{WHR} > 0.85$ and $\text{WHR} < 0.79$). Also, their subjects were of similar ages and had essentially similar body size (i.e., UB, $\text{BMI} = 35.4 \pm 1.4$ and

⁵ The values presented by den Besten, et al., [40], Vansant et al. [171], Weststrate, et al., [179] were converted to $\text{kcal}\cdot\text{day}^{-1}$ for ease of comparison with data from Table 3.

LB, BMI = 32.2 ± 1.4), and fat composition (i.e., UB %FAT = 48.1 ± 1.4 ; LB %FAT = 46.2 ± 3.7) as those selected in the present study. However, the RMR values reported in the earlier studies [40,171,179] were lower overall than the values recorded in the present investigation. For example, in the present investigation RMR was 1730 ± 110 kcal $\cdot$ day $^{-1}$ versus 1640.0 ± 81.3 kcal $\cdot$ day $^{-1}$ for the UB and LB groups respectively, whereas in Weststrate's [179] study, RMR values were 1453 ± 47.8 for the UB group versus 1316 ± 49 kcal $\cdot$ day $^{-1}$ in the LB group. The reason for this discrepancy in RMR values is unclear considering the similarity of the subjects in body size and amount of FFM. One explanation for these differences could be methodological. In the previous studies [40,171,179], RMR was measured in the early morning after an overnight fast which would almost function as an estimate of basal metabolic rate rather than RMR, as was measured in the present study. In the current investigation, subjects came into the lab previously inactive and fasted (4 hours minimum) to avoid the acute influence of the thermic effect of food or physical activity. This is a standard RMR measurement protocol [36]. However, the tests were performed at various times of the day which may have led to higher overall metabolic rates than those taken first thing in the morning as were done in the prior studies [40,179].

The literature on the effect of the menstrual cycle on differences in daily energy expenditure are equivocal [157,174,176]. Some investigators have shown no differences in energy expenditure between the two menstrual phases [157,178]. Whereas, others have reported a distinct increase in RMR during the luteal phase [67,174,176]. Indeed, Webb [176] concluded that there was a 9% elevation in 24-hr energy expenditure in the post-ovulatory (luteal) phase of the menstrual cycle.

All women in the present investigation, were studied during the same menstrual phase (i.e., follicular phase) to avoid the potential influence of hormonal status confounding metabolic variables. It is unlikely that the higher (in comparison to the previously cited studies) RMR values noted in the current investigation were a result of hormone status variability.

Finally, Weststrate et al. [179] reported no significant differences in age, body fat composition or fat free mass between the two body fat sub-groups in their study. However, they used an analysis of co-variance (adjusting for age, body fat %, and FFM) to compare RMR between the groups. Usually when age is used as a covariate in comparing RMR data it is done to adjust for differences in FFM between diverse age groups [168]. It is unknown why these type of analyses were performed when no significant differences were found initially between the groups on these variables. Therefore, even though they found that the UB group had a 10% higher RMR than the LB group after adjusting for these covariates, it is unclear if these values represent actual differences in daily caloric expenditure or simply differences that came out of statistical adjustment or corrections.

In conclusion, the data from the present investigation do not support the hypothesis that RMR is lower in the lower body fat obese group. No association between resting energy expenditure and body fat distribution was indicated. However, it is well known from *in vitro* cellularity studies that abdominal fat cell size is relatively larger and has a higher metabolic activity than that from the gluteal-femoral region [7,113,154]. In addition, gluteal/femoral adipose tissue is characterized as being more hypercellular and having a higher total amount of fat cell weight (FCW) [87] than abdominal fat [7,154]. Krotkiewsky et al. [87 & 88]

concluded that hypercellular obese women may be more resistant to weight loss than hypertrophic obese women. They suggested that energy balance may be regulated by or associated with fat cell weight [87]. The authors admitted that no "messenger" or regulatory control mechanism for a "lipostatic set point" had been found [87]. However, they continued that if there were a lipostatic set point, the individuals with hyperplastic obesity would have an increased drive for relapse during period of weight loss because of the greater total signal from the increased number of cells. This would suggest a relationship between body fat distribution and energy expenditure during times of negative energy balance. Further research on long-term weight loss and the mechanisms involved needs to be done to address this issue.

Mechanical Efficiency

The caloric cost of exercise in two groups of obese women was studied in this part of the investigation. It was hypothesized that body fat distribution patterns would influence the mechanical efficiency of the "mover" in differential ways depending upon the type or mode of activity being performed (i.e., weight carrying or weight bearing).

Cycle

Four studies were found in the literature concerning cycle mechanical efficiency (ME) and obesity [39,56,122,175]. Wang et al. [175] conducted a study on the metabolism of obesity with special reference to mechanical efficiency. On a group of 41 obese women they measured cycle ME and reported a range of between 17.7% for the most obese sub-group to 24.5% for the least obese group.

Freyschuss & Melcher, [56] reported a significantly ($p < 0.05$) lower cycle net efficiency (i.e., 17.8% vs. 20.8%) in 30 obese subjects (7 male and 23 female) before a weight loss program in comparison to after a 58% drop in body weight. And Dempsey et al., [39], found obese men to be particularly inefficient (i.e., 19.9%) compared to control subjects performing weight supported exercise. The cycle net efficiency values in the present investigation (i.e., range 17.3 - 20.2%) were very similar to the values previously reported for obese subjects [39,56,175]. However, the obese were less mechanically efficient in comparison with cycle net ME values reported for non-obese groups (i.e., 18.8 - 24%) [58]. Gross efficiency values in this study (i.e., range = 10.1 - 16.6%) were a bit lower but similar to those reported in the literature for moderately obese women (i.e., range = 9 - 24%) [122] and lean men (i.e., range 12 - 19.3%) [58].

Several causes of the elevated oxygen cost of muscular work in obesity have been suggested. Dempsey et al. [39] found that morbidly obese men used a great deal of energy just to stabilize their posture in an upright position on the cycle ergometer. They discovered that a significant portion of the energy expended by the obese person "with large segmental fat deposits over the suprailiac and abdominal regions" could be accounted for by the "extensive shifting of the heavy masses of the trunk which accompanied alternating leg extension during cycling" [39, pg. 1819]. Thus, the obese subjects had a higher overall cost of exercise (i.e., lower efficiency) compared to normal weight controls even though they were performing while sitting on a cycle. This is in contrast to what is normally accepted about cycle mechanical efficiency. Usually, mechanical efficiency on the cycle ergometer is considered to be relatively constant because the subject does not

carry his/her own weight while exercising, and the VO_2 (per unit of work output) is considered independent of body size. However, Dempsey et al. [39] concluded that for obese individuals "muscular work and thus energy expenditure on the bicycle ergometer may not be entirely independent of body mass..." [39, pg. 1819]. The results from Freyschuss & Melcher [56] also supported this assumption. They found a lower oxygen uptake (i.e., increased efficiency) during supine exercise compared to sitting exercise in an obese population which would indicate that there is indeed a "postural component" to the cost of exercise. In general, Freyschuss and Melcher [56] concluded that the improved ME in supine exercise and after weight reduction in obese individuals indicated that body weight per se was the most important factor for the increased oxygen cost of muscular work in obesity. They stated that decreased efficiency was "...partly due to an increased cost of keeping the body stable in the upright position and partly due to the cost of moving the heavy limbs" [56, pg. 758].

In the present investigation all the subjects were obese yet the UB group, in comparison to the LB group, truly had a predominance of fat on the trunk and abdomen which protruded over the suprailiac crest while sitting on the cycle. The literature reporting mechanical efficiency in obese subjects is limited [37,39,56,145,175] and no studies could be found which measured ME between body-fat distribution sub-groups of obese individuals. The observation by Dempsey et al. [39] that excessive body mass may influence ME during cycling, led to the speculation that obese individuals who are primarily UB fat may perform cycling tasks with less efficiency than those who primarily hold their weight in their buttocks and thighs. Theoretically, differences in gross efficiency would have been

noted in the present investigation if there were differences in an unmeasured "resting" or postural component in the energy cost of cycling between the groups. However, there were no differences in the overall caloric cost of cycling (i.e., gross mechanical efficiency) between the two groups at any work rate. In addition, net efficiency, which is a measure of the cost of cycling minus the resting level, was virtually identical between the groups. This would suggest that both groups had a similar influence from unmeasured postural work components throughout the exercise periods. The current data do not support the hypothesis that differences in body-fat distribution alter gross or net mechanical efficiency on a cycle ergometer.

Finally, the reduced mechanical efficiency in obesity has been found to be unassociated with an actual reduction in the efficiency of the muscles. Dempsey et al. [39], tested this by measuring ME during low levels of arm exercise where postural adjustments were negligible. In this situation they found normal efficiencies in the obese subjects. Also, the hypothesis that a low muscular efficiency is the cause of the lowered overall mechanical efficiency in obesity has been previously rejected on the basis of the finding of a normal slope of the $\text{VO}_2^2/\text{load}$ regression line [56]. In other words, a certain increment in work load (i.e., delta efficiency) has been found to give an identical increase in oxygen uptake in the obese and in the normal weight subject [56]. In the present investigation, cycle delta efficiency was not different between the groups. In comparison to lean groups [159], absolute delta efficiency values at comparable work rates were lower in the obese group of women studied. However, the relative slope of the decline in delta efficiency was not different between the lean athletic men reported by Stuart

et al.[159] and the group of obese sedentary women in this study. It is unknown what significance this lower delta efficiency may have. More research on the exercise response of obese women is necessary to help clarify this question. Ultimately the implications of this finding are that obese women are relatively inefficient and thus fully capable of expending calories by weight supported exercise. The findings imply that both groups responded to increments of work on the cycle in a similar manner and effectively nullifies the proposition that one group may be more efficient than the other during exercise.

Treadmill

The caloric cost of exercise on the treadmill is known to be directly related to body weight. The energy cost of weight-bearing exercise has been shown to be similar for lean and obese men of similar body weight because the work done is a function of the total amount of weight that has to be carried [144]. For normal weight men, the efficiency of uphill treadmill walking has been measured in the range of 20.6 - 43.0% depending upon speed and grade of the treadmill [43]. In the obese population, the ME of walking uphill on a treadmill has not been previously described. Net ME for treadmill walking, in the current study, ranged between 10.1 - 18.4% in obese women, which was lower than that reported by Donovan & Brooks [43]. Perhaps an added energy cost of "just moving" the large limbs, the adjustment of upright posture and an increased rotation of the pelvis around the sagittal axis may have enhanced the energy requirements and decreased ME for walking in obese individuals. Indeed, adding extra weight on the limbs has

been shown to increase the energy expenditure of climbing a laddermill in normal weight men [75].

The finding by Kamon et al. [75] that added weight on the extremities can influence mechanical efficiency, led to the idea that perhaps there may be a relationship between walking ME and body weight location (i.e., body-fat distribution). The energy cost of moving the body or limbs during level walking is not included in the calculation of external work on the treadmill [124]. Although, according to Freyschuss & Melcher [56], a considerable amount of unmeasured work is demonstrated in obese subjects walking on the treadmill and may account for the marked elevation of oxygen consumption found during treadmill exercise in obese individuals.

No studies could be found that evaluated the differences in ME during weight bearing exercise between body-fat distribution groups. In the current investigation, no association was found between body fat distribution and treadmill ME. Mechanical efficiency expressed as both gross and net values were virtually identical for the sub-groups in this study. This can be explained by the fact that ME in weight bearing exercise is primarily a function of body weight. All the subjects in this study were of similar body weights. Any subtle differences in the energy cost of postural stability or unmeasured cost of moving the limbs between the groups may have been too small to detect. As with the cycle data, there was no evidence that the intrinsic muscular efficiency was different between the groups because delta efficiencies were comparable in both groups. Also, the absolute delta efficiency values at comparable work rates in this investigation (i.e., 25.7 - 30.0%) were similar to those presented by Donovan and Brooks [43] (i.e., 23.4 -31.6). In

addition, the relative pattern of the decline in delta efficiency was not different from that of the lean men reported by Donovan and Brooks [43]. The similarity of delta efficiency of walking between previously reported lean subjects [43] and the obese women in this study indicates that the obese show no signs that they are more economical in terms of expending calories during exercise than their lean counterparts.

In summary, the results of this investigation give no indication that mechanical efficiency is influenced by differences in body fat distribution. The net, gross and delta efficiencies in both weight carrying and weight bearing exercise were not different between body-fat distribution groups. Thus, exercise of either a weight bearing type or a weight supported type will illicit a work stress able to stimulate comparable caloric expenditure in both groups of obese subjects. In addition, the data a) confirm the observation by others [37,39,56,175] that obesity lowers overall cycle ME compared to non-obese subjects but b) do not support the suggestion that differences in muscular efficiency exist between sub-groups of obese subjects.

Fuel Utilization

An estimation of the relative contribution of carbohydrate and fat to total energy metabolism was obtained by measurements of the metabolic respiratory quotient, RQ, during 60 minutes of steady-state exercise. The findings in this part of the study indicated that while the rate of caloric expenditure over the prolonged walking remained constant, utilization of fat as an energy substrate increased with time. The percentage of kcals utilized as fat during 60 minutes of prolonged

walking at an intensity of 55 - 60% of the subject's $\text{VO}_{2\text{MAX}}$ ranged between 35.8% during minute 10, to 63.1% during minute 60 in both groups of obese women studied. Although no previous research was found in the literature that specifically evaluated substrate utilization during prolonged exercise in obese women, the fat utilization percentages in the present investigation were similar to those reported by Blatchford et al. [21] on normal weight untrained women (i.e., % fat utilization = 60 - 68%). In addition, the RQ values reported in this study corresponded to values reported by other investigators for normal weight men and women [33,125,163]. Thus, the obese women in this study were physiologically capable of the typical metabolic shift from carbohydrate utilization early in exercise toward an increased use of fat as a substrate over time.

Body fat from the abdominal region has been recognized as being much more labile (i.e., lipolytic) than adipose tissue from the gluteal-femoral regions [7,113,155]. It was speculated in this investigation that women characterized as UB obese would have a higher lipolytic potential (e.g., greater fat mobilization) than women who were LB obese. Theoretically, this phenomenon would be manifested during prolonged walking when the physiological stressors are ideal for the enhancement of fat utilization. The results from this study did not support this hypothesis. Although the prolonged walking did induce the expected profile of increased fat utilization over time, there were no differences in fuel utilization/mobilization between the two body-fat groups noted in this study.

Failure to see differences in fat mobilization *in vivo* between the body fat distribution groups is probably a result of the extensive complex of redundant hormonal and neural systems regulating fuel metabolism in the body. The

interactions of mechanisms involved with metabolic regulation during prolonged exercise are complex. Prolonged exercise is known to stimulate a flux of metabolites through the energy-producing pathways in muscle [111]. For example, the intracellular rate of ATP production to ATP utilization must be precisely regulated by the interacting mechanisms of the mitochondria (i.e., Krebs cycle, and electron transport chain) simultaneously with those controlling glycolysis. In addition, the overall rate of systemic fuel mobilization must be precisely regulated to correspond with the rate of fuel oxidation by the working tissues [111]. The mobilization of fatty acids is primarily achieved through the action of hormones delivered through the blood to act on the various fat deposits throughout the body [105]. Thus, even though the LB women primarily held their fat in the gluteal-femoral region which is considered "virtually unresponsive to both insulin and catecholamines in normal subjects" [154, pg.147], they still had a significant amount of fat in the abdominal area capable of being mobilized. Therefore, during prolonged walking in the fasted state, when the need for fat utilization is high, all the adipose stores in the body would be stimulated to increase lipolysis to the same degree in both groups of subjects. If abdominal fat is more labile than gluteal-femoral fat, then FFA would be mobilized from the abdominal region in both groups equally. This hypothetical situation could explain why no differences were seen in RQ between the groups.

In conclusion, RQ and fat utilization during prolonged walking were not different between the body-fat distribution groups. In addition, there was no indication of an impaired ability in the obese subjects to mobilize and utilize fat as fuel during a prolonged bout of moderate intensity walking.

Adrenergic Regulation of Metabolism

Obesity is a condition often distinguished by metabolic disorders resulting from disturbances of the multi-faceted energy regulation control systems of the body [98]. The control mechanisms involve interactions between hormonal and sympathetic nervous system (SNS) processes to regulate energy homeostasis, adipocyte-related substrate fluxes and adrenoreceptor function in adipocytes [98]. In this part of the investigation, a measure of the adrenoreceptor function was evaluated. Specifically, the study was designed to assess differences in the role of the SNS in the mobilization of fat between two groups of obese women at rest and during prolonged exercise.

The catecholamines and their extensive complex of tissue receptors are known to play a role in both systemic energy balance and the specific anatomic distribution of stored fat [98,161]. The adrenergic receptors found in the plasma membranes of human adipocytes are primarily β_1 and α_2 [48,161]. Both are activated by the naturally occurring catecholamines, epinephrine and norepinephrine. However, these two receptors have opposing effects on lipolysis when activated: β stimulates, and α_2 inhibits [91]. The amount of lipid stored within any given adipocyte may reflect the net influence of these receptors. In addition, the metabolic effects may be mediated by the concentration of catecholamines (i.e., amount of sympathetic activity) combined with the number, sensitivity and affinity of the receptors.

Beta Blockade and RMR

The influence of the SNS on metabolism can be evaluated by pharmacologically blocking the adrenoreceptors known to activate specific

metabolic responses and then compare the responses to a control or un-blocked state [162]. In one study, RMR was found to be unaltered following propranolol administration [1]. However, another group of researchers found that propranolol administration produced a decrease in RMR in a group of Caucasian men but not Pima Indian men [31]. Interestingly, Christin et al. [31] observed that the effect of propranolol on reducing RMR may have been influenced by body-fat distribution. The authors noted that the reduction in RMR with propranolol was "blunted" in men with a higher abdomen to thigh ratio (A/T) (i.e., upper body fat). They proposed that the men with a higher A/T ratio may have had an elevated basal SNS activity which could overcome the effect of the beta-blockers through "alpha-mediated stimulation" [31, pg. 442].

In the current investigation, it was thought that resting SNS activity would be lower in the LB obese group compared to the UB obese group and that this would induce an overall lower resting metabolic rate in response to propranolol. The results from this study do not confirm this hypothesis. Theoretically, without measuring resting levels of circulating catecholamines, differences in resting SNS activity between groups could be estimated from dissimilar effects of propranolol administration on heart rate or RMR. Resting heart rate was not significantly different between body-fat groups in this study. Although propranolol administration substantially reduced resting heart rate in both groups (e.g., 9.6 bpm), treatment with propranolol did not significantly lower resting metabolic rate. In addition, there were no differences between the groups in RMR either before or after treatment with propranolol. This is similar to what was observed by Acheson

[1]. Thus, there was no indication that resting SNS activity was elevated in the UB group nor that propranolol administration selectively reduced RMR in the LB group.

Christin et al. [31], suggested that the "lack of a decrease in metabolic rate in response to propranolol infusion" (in the A/T group) "may be explained by a persistent alpha-adrenergic stimulation overcoming the effect of beta-blockade on the RMR" [31, pg. 442]. However, no literature could be found that supported the idea that unobstructed alpha stimulation (i.e., following beta-blockade) would increase RMR or would be able to counteract the overall acute effect of beta-inhibition. An alternative explanation for the lack of effect of propranolol on RMR may be that, at rest, when the levels of circulating catecholamines are low, cell metabolism may be controlled by intrinsically regulated mechanisms rather than being mediated hormonally. The effect of circulating catecholamines at rest may act to "fine tune" energy regulation/ metabolism rather than initially stimulate or control it. In the resting state, neither of the adrenergic receptors (alpha or beta) on metabolically active tissues, would be highly responsive to catecholamine activation. Thus, acute beta-blockade would have little effect on the regulation of energy metabolism until the levels of plasma catecholamines became more pronounced (e.g., during exercise).

In conclusion, the evidence from the current investigation supports the view that resting metabolic rate under the influence of beta blockade is not different between body-fat distribution groups. It has been shown that the lipolytic activity of the beta-adrenergic receptors in response to catecholamines was higher in fat extracted from abdominal areas [89]. In addition, the basal release of FFA in UB obese women has been shown to be considerably higher than in LB obese women

[69]. However, beta-blockade in this study did not selectively influence resting metabolism between groups of UB and LB obese women. The findings suggest that the regulation of energy metabolism at rest may be mediated by an intrinsic cellular mechanism rather than by basal levels of catecholamines. Further research relating body-fat distribution and catecholamine action/ kinetics are needed to help decipher these metabolic mechanisms.

Beta Blockade and Fuel Utilization

Acute non-selective beta blockade with propranolol has been shown to cause a distinct decrease in lipolysis and FFA mobilization [31,38,73]. During exercise, propranolol administration is known to lower the heart rate but does not usually alter low-level, submaximal oxygen consumption [27,28,47]. According to Brusasco, et al. [27], beta-blockade, does not appear to reduce total body metabolism during constant steady-state submaximal exercise. However, propranolol decreases the potential contribution of free fatty acids as a metabolic substrate during exercise [38]. Exercise induced lipolysis during prolonged exercise has been shown to be inhibited by beta-blockade [28,73,103,167] and in particular, by propranolol [95]. The finding that lipolysis during exercise is affected more by non-selective beta-blockers (e.g., propranolol) rather than selective β_1 blocking agents (e.g., atenolol) has been interpreted as evidence that a small population of β_2 receptors in adipose tissue may be of increasing importance in situations where sympathetic tone is significantly increased (i.e., during exercise) [95].

The results from the current study indicated that exercise heart rate was reduced by about 19% following propranolol administration in both groups. This is

comparable to the results by Epstein et al. [47], who found submaximal exercise heart rates to be decreased by about 20% following propranolol infusion. The primary hypotheses in this part of the investigation were that a) the normal shift in fuel utilization (i.e., carbohydrate to fat) during prolonged walking would be altered following propranolol administration, and b) the effect of beta-blockade would be more pronounced in the UB obese group compared to the LB obese group. These ideas were derived from the conclusions of Christin et al., [31]. Christin and colleagues [31] determined that the decrease in FFA production rate with propranolol infusion was evidence for the proposition that the SNS is involved in the mobilization of FFA from fat stores. The authors assumed that the magnitude of the decrease in FFA turnover with propranolol was a reflection of the role played by the SNS in the mobilization of FFA [31]. They interpreted the larger decrease in FFA turnover rate in the more obese subjects as an indication of a higher basal SNS activity. The subjects in Christin's [31] study were all men and so the fat distribution for the obese subjects in their study was most likely the upper body/abdominal variety. Therefore, if an enhanced SNS activity does exist in obese individuals, it is conceivable that it is an upper body obesity phenomenon. Given that the UB group may have an enhanced SNS activity and a greater potential for mobilization of fat, then the anti-lipolytic effect of propranolol treatment would be enhanced in UB obese women.

The processes by which beta-blockade limits lipolysis are considered to be two distinct mechanisms: a) by directly blocking the β_1 adrenoreceptors of fat cells thereby directly decreasing lipolysis, and b) by an indirect mechanism where the circulating catecholamines are "allowed" to interact with the α_2 receptors to

produce results that are unopposed by the counteractive influence of the beta receptor activity, resulting in a net inhibition of lipolysis [31,138]. A number of investigators [89,99,127,155] have documented anatomic site-related differences in the relative activities of adrenergic receptors. Specifically, α_2 receptor activity has been shown to be higher in tissue obtained from the gluteal/femoral regions than from the abdominal adipose regions [127]. In addition, beta receptor activity was shown to be greater in the abdominal fat tissues compared with gluteal tissue. Theoretically, these findings would support the notion that lipolytic activity and fuel mobilization between the two body fat distribution groups in this study would be different following beta receptor blockade.

The results of this study demonstrated that propranolol did significantly alter fuel utilization during prolonged walking in both groups. In general, the amount of kcals utilized as fat during 60 minutes of walking following propranolol treatment were reduced by about 23 percent compared with walking under control conditions. There were no specific group differences in the rate of change of RQ over time with beta-blockade. This would indicate that throughout the exercise period, the compromising effect of beta-blockade on lipolysis was similar in both groups. These findings suggest that during prolonged, low-intensity exercise with beta-blockade, body fat distribution (and perhaps as a corollary, adrenergic receptor status) does not effect fuel mobilization. There was no evidence that the UB group had a higher SNS activity, or a higher degree of fat mobilization during prolonged exercise than the LB group.

The *in vivo* nature of this investigation must be emphasized when attempting to understand why no differences in fuel utilization were observed between the

groups in this study. During exercise, the entire body is stimulated and precise adjustments must be made in many regulatory systems in order to meet the increased energy demands. All the energy storage systems (i.e., all fat and carbohydrate depots in the body) would be "bathed" in and potentially stimulated by the increased levels of circulating catecholamines. Thus, during exercise, following beta-blockade, it is conceivable that the LB group would show decreases in lipolysis in the same fashion as the UB group. Theoretically, although the LB group may have had an abundance of alpha-receptor activity in the gluteal/femoral region and perhaps fewer overall beta receptors, the beta receptors they did have would have been blocked fully by propranolol. This would have left a relatively larger number of adipose cell alpha receptors fully "exposed" to the effects of the circulating catecholamines. The equivalent rate of fuel mobilization noted in both groups in this study is an indication that fat mobilization/ utilization was not impeded in the women with primary gluteal/femoral fat deposits. During prolonged walking when the stimulus for exercise induced lipolysis is high, fat will be mobilized from the most available and efficient sources. Hypothetically, during propranolol treatment, beta-blockade would reduce the beta effects of the abdominal area and the femoral area equally. The net response of the unobstructed alpha receptors from all available fat depots (i.e., gluteal/femoral and abdominal) would be a considerable decrease in overall lipolysis. Both groups of women in this study had essentially identical responses to the exercise stimulus during propranolol treatment. According to Leibel et al. [96], *in vivo* regulation of fat cell metabolism "reflects a complex interplay of the effects of many hormones, autocrine regulators and other local factors" [96, pg. 436]. They considered the "first order" character

of triglyceride loss and mobilization *in vivo* to be proportional to regional adipocyte number and size. Therefore, *in vivo*, the regulation of energy metabolism during exercise is controlled by several redundant and interactive mechanisms.

Summary and Implications

The overall findings of this study suggest that despite the well-defined differences in metabolic activity shown *in vitro* between various adipose tissue sites, the manifestation of energy regulation mechanisms *in vivo* is much more obscure. The data collected in this study can be interpreted to mean that obese women with distinctly different body fat distribution patterns have similar physiological potentials for energy expenditure during rest and during exercise. There was no indication from the current findings that one group was more energy efficient than the other. In addition, both groups of women showed equal capabilities for performing prolonged exercise with the typical (and appropriate) metabolic shift in fuel utilization. Thus, there was no indication that the obese women volunteers in this study had an impaired ability for substrate mobilization/ or fuel utilization during exercise. Finally, there was no foundation for the belief that SNS activity or catecholamine levels were enhanced in the UB obese group either at rest or during exercise.

The results from this study hold implications for those individuals, clinicians or researchers who work with obese populations. First, the results from the RMR tests suggest that LB obese women expend similar amounts of energy at rest as do UB obese women and therefore are probably not more "resistant to slimming" than those with UB obesity. Second, the type of exercise modality utilized (i.e., walking

or cycling) seem to be equally valid therapeutic prescriptions for obese women regardless of where they hold their body fat. In other words, the amount of kcals expended during either weight supported or weight bearing exercise is not influenced by the primary location of one's body weight/fat. Third, prolonged low-intensity exercise is an appropriate and viable method for burning calories as fat in obese women regardless of where they hold their body fat.

A major problem of weight loss treatment programs is continued long-term weight maintenance. A significant percentage of those who do lose weight on any treatment program will fail to maintain this weight loss [25]. Several physiological factors such as lowered resting metabolic rate, increased mechanical efficiency, body fat distribution, fat cell type and size, and lipoprotein lipase activity have been associated with recidivism. Most likely these factors interact with several behavioral factors and/or genetic factors in contributing to the overall difficulty relapsers have in maintaining their lowered body weight. Prospective studies which examine the interplay between genetic and physiological differences on one hand and the psychological, social, cognitive and behavioral factors on the other could help to define the most appropriate treatments for obese individuals. Perhaps with continued multi-disciplinary research treatments for the obese can become curative and not simply palliative [25].

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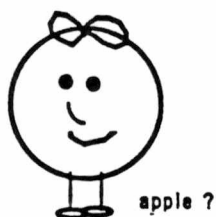
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Appendix A

OVERFAT WOMEN

WHERE DO YOU HOLD YOUR FOLDS??

DO YOU LOOK LIKE AN



OR A



DO YOU WANT TO
DUMP YOUR PLUMP??

You are Wanted For a Research Project on
Body Fat Distribution and Exercise

REQUIREMENTS:

"Apple" or "Pear" Shaped Women, 18-35 Yrs Old
Good Health, No Exercise Limitations
Able to Volunteer 5 Sessions of 1-2 Hours Each

BENEFITS:

Measurement of Resting Metabolic Rate
Measurement of Exercise Capacity
Measurement of Body Composition
Help in designing a diet/exercise program
for weight loss

FOR MORE INFORMATION:

Contact **PAM SWAN**
Dept. of Human Performance and Sport
Studies
University of Tennessee Knoxville

Phone:

974-5111 (Office)
974-5091 (Lab)

Swan recruits overweight women to compare body fat with exercise

By JOEL MOORE

Staff Researcher Editor

An exercise physiologist in the UT Department of Human Performance and Sports Studies is currently recruiting overweight women for a study on body fat distribution and exercise.

Pam Swan, a doctoral student, is seeking healthy "apple" or "pear" shaped women ages 18-35 to volunteer for five 1 or 2 hour sessions. In return for participating in the study, volunteers will learn about their exercise capacity and body composition. Help in designing a diet and exercise program for weight loss will also be offered.

One of the purposes of Swan's study is to compare fat metabolism rates in people with mostly upper body fat with those in people with mostly lower body fat.

"Most research shows that there is a high association of diabetes and high blood pressure with the upper body fat pattern," Swan said. "Most women hold their weight lower than men, but some do hold their fat in the abdominal area. These are more at

"My interest is in how to lose fat. Dieting works to some extent. However, there are conflicting opinions on whether exercise alone elicits fat loss. A lot of women complain that they do everything to lose their rear end but can't. There may be metabolic reasons for which they may not be able to."

Pam Swan

risk for cardiovascular disease."

"My interest is in how to lose fat. Dieting works to some extent. However, there are conflicting opinions on whether exercise alone elicits fat loss. A lot of women complain that they do everything to lose their rear end but can't. There may be metabolic reasons for which they may not be able to," Swan said.

Swan described three main parts of her study, the first of which is determining participants' resting metabolic rate (RMR). This is an assessment of the amount of energy used by the body during rest. Swan

determines this by having participants lie down for 40 minutes.

"This accounts for a very high percentage of total calories consumed during a day. RMR is an important indicator in determining if one is maintaining, losing or gaining weight," Swan said. "Our facilities on campus are the only place in East Tennessee where this can be done."

The second part of Swan's study determines mechanical efficiency or the caloric cost of exercise at different levels of exertion.

"If someone holds their weight high vs. low, that may change their

efficiency. There are different kinds of walks for different shaped people," Swan said.

For the third part of the study, Swan looks at mechanisms of fuel utilization.

"I'm interested in finding out if people are using carbohydrates or fat as sources of energy. If weight loss is facilitated with exercise, I would expect a higher use of fat as energy," she said.

To qualify as a participant in the study, volunteers need to be able to pedal a stationary bicycle and walk continuously at a moderate pace for about an hour. They can't be diabetic and should not have signs of heart disease or asthma. Anyone currently dieting or participating in a weight loss program will not be accepted. Smokers are also ineligible. The study will include a blood test.

The first session will be held before Christmas break. The final four sessions will be held Spring Semester, two in January and two in February. Sessions will be set up around a student's individual schedule. Interested persons should contact Swan in 356 HPER Building. ■

UT researcher seeks 'apples, pears' for study

By WENDY C. FARMER

of The Journal staff

Have you ever heard the phrase, "It's like comparing apples and oranges?"

Well, when body shape is the name of the game, it's more like comparing apples and pears.

At least that's what University of Tennessee researcher Pam Swan is looking for. Swan is currently recruiting women for volunteers in a study on fat metabolism and exercise.

An exercise physiologist, Swan is working toward her doctoral degree in the department of human performance and sport studies at UT.

Her study is based on recent research indicating that body-fat distribution may be associated with cardiovascular disease in obese people.

According to a press release, "People with a preponderance of fat located centrally or abdominally (apples) have a higher risk of developing high blood pressure, diabetes mellitus and high blood-lipid (fat) levels compared with those who hold the majority of their fat lower, in the hips, buttocks and thighs (pears)."

The study will examine relationships between body-fat distribution with fat metabolism in response to exercise. Also the mechanisms involved with exercise as weight-loss therapy will

"People with a preponderance of fat located centrally or abdominally (apples) have a higher risk of developing high blood pressure, diabetes mellitus and high blood-lipid (fat) levels compared with those who hold the majority of their fat lower, in the hips, buttocks and thighs (pears)."

UT press release

be investigated.

Swan requests that volunteers for the study be "apple or pear shaped women" between 18 and 35 years of age.

"If your waist circumference measurement is bigger than your hip/buttocks measurement then you are probably an 'apple,'" read the description in the press release.

Swan also requests that volunteers be "healthy, with no cardiovascular, respiratory or metabolic problems."

Study conditions include being able to pedal a stationary bicycle and to walk continuously at

a "moderate pace" for one hour. Also, commitment to five two-hour sessions in the lab for both resting and exercise tests is mandatory.

Swan also requests that volunteers "not be currently dieting or actively engaged in a weight-loss program."

The listed benefits to participating in the study are many.

"In general you will be helping with research undertaken to understand the association of body fat distribution with the serious metabolic problems of obesity," according to the press release.

Also, on a more personal level, volunteers will receive an evaluation of resting metabolic rates, body composition and exercise capacity. From this information, caloric needs can be determined and will be used to design a personalized exercise program for losing weight.

For more information, call 974-3111.

Appendix B

Body Fat Distribution Study

INFORMATION TO PARTICIPANTS

Description of the project:

This study is designed to study the effects of body fat distribution on metabolism both at rest and in response to exercise. The cardiovascular health risks of obesity are related in part to the metabolic aberrations associated with high levels of circulating fat (hyperlipidemia), high blood sugar levels (diabetes mellitus), and high blood pressure (hypertension). In addition, these metabolic complications are strongly associated with the pattern of distribution of adipose tissue on the body. Specifically, risk of developing cardiovascular health problems increases for those with upper body obesity (abdominal, stomach) than those who hold their fat lower in the thighs, hips or buttocks. Of interest are the mechanisms underlying the development of these obesities as well as the therapies used to treat them. The major objective of this study is to examine the effects of body fat distribution on the mechanisms involved with exercise as an anti-obesity therapy. The study is divided into five sessions which require 1 to 2 hours each. The basic procedures as well as what will be expected of you are described below.

Prior to each visit: Do not eat or exercise.

FOR ALL OF THE TESTING SESSIONS YOU WILL NEED TO COME INTO THE LAB HAVING FASTED FOR AT LEAST 4 HOURS PREVIOUSLY. YOU SHOULD NOT HAVE HAD ANY CAFFEINATED BEVERAGES, SMOKED CIGARETTES OR TAKEN ANY MEDICATIONS. ALSO, YOU SHOULD NOT EXERCISE THE DAY THAT YOU COME IN FOR YOUR TEST.

Recommended Clothing:

YOU SHOULD WEAR LOOSE FITTING EXERCISE CLOTHING SUCH AS A T-SHIRT, SHORTS, TENNIS SHOES AND SOCKS SO THAT YOUR COMFORT AND SAFETY CAN BE ASSURED. ON DAY TWO YOU WILL NEED TO BRING A BATHING SUIT AND TOWEL FOR UNDERWATER WEIGHING.

Body Fat Distribution Study

INFORMATION TO PARTICIPANTS

Day one: orientation & consent form
 demographic information
 circumference & skinfold measures
 health history questionnaire
 diet recall
 menstrual history recall

Day two: resting metabolic rate test = 40 minutes
 underwater weight test = 20 minutes
 1 of the energy efficiency tests = 60 minutes
 (ie. the cycle or treadmill)
 ** (the maximal exertion test follows
 the treadmill test)

Day three: the other of the energy efficiency
 tests (ie. the cycle or treadmill) = 60 minutes
 ** (the maximal exertion test follows
 the treadmill test)

Day four: resting metabolic rate test = 40 minutes
 with placebo or propranolol*
 prolonged walking test = 60 minutes

Day five: resting metabolic rate test = 40 minutes
 with placebo or propranolol*
 prolonged walking test = 60 minutes
 & random assignment

**** At least 2 days will separate the exercise tests. ****

YOU ARE SCHEDULED TO COME INTO THE LAB ON THE FOLLOWING DAYS AND TIMES. Please call if you need to reschedule. Thanks.

Pam Swan

Phone: 974-5111 (office)
 974-5091 (lab)
 945-5812 (home)

Day 2: _____

Day 3: _____

Day 4: _____

Day 5: _____

Final meeting and summary.

Body Fat Distribution Study

INFORMATION TO PARTICIPANTS

Orientation:

You will be given information about the procedures, risks, and benefits of the study. You will be allowed and encouraged to try out the exercise equipment, see the testing apparatus and ask any questions you want. After all of your questions have been answered you will be asked to read and sign an informed consent form.

You are reminded that you are a volunteer and that if at any time, for any reason, you wish to withdraw from the study you may do so without penalty or prejudice.

Following the orientation and consent form you will be asked to complete a health history questionnaire. If there is nothing in your health history (ie. no cardiovascular disease, no diabetes, no asthma or hay fever) that would make you ineligible for participation in this study then you may continue. However, if there is any chance that you may be pregnant you will need to take a pregnancy test before any testing is started.

First, you will have your body circumference and skinfolds measured. Also you will be asked to recall your daily dietary intake periodically each time you come into the lab. Finally, you will be asked to recall your normal menstrual cycle history for the past 2-3 months.

Resting Metabolic Rate (RMR):

There will be a total of three of these tests. Each time you will come into the lab having had no physical exercise nor any food or liquid except water for at least 4 hours previously. On two of the RMR tests you will be given a pill to take orally. One will be 80 mg of propranolol and the other will be a placebo pill. You will recline on a lounge chair as motionless as possible, without sleeping, for a total of 40 minutes. During the last 20 minute period you will be asked to put a mouthpiece in your mouth and breathe through a valve attached to a hose and collecting bag so that your expired air can be collected and analyzed.

Body Composition:

This test consists of measuring your body weight while you are submerged underwater. First the amount of air trapped in your lungs following full exhalation is measured. Next you will climb into a tank of warm water. You will sit on a scale on the bottom of the tank. You will be asked to blow out your air and exhale fully as you completely submerge your head and body underwater (about 10 seconds) so a measurement of your weight underwater can be made.

Mechanical Efficiency--Cycle Ergometer:

You will be asked to sit motionless on an exercise cycle breathing through a mouthpiece and valve while baseline measurements of expired gasses are made. You will have a strap

Body Fat Distribution Study

across your chest which will measure your heart rate via a "heart watch" digital monitoring device. You will also wear a blood pressure cuff so periodic blood pressure measurements can be made.

The exercise test will consist of pedaling at 4 intensities (increased resistance) of 6 minutes each with a 10 minute rest time between each. You will be asked to pedal consistently following a set speed of leg revolutions. Gasses will be collected the last 2 minutes of each workload.

Mechanical Efficiency--Treadmill Walking:

You will again breathe through a mouthpiece and valve but this time you will walk on a treadmill. Again you will have the heart watch monitor your heart rate and a blood pressure cuff on your arm. After baseline measures are taken you will walk a set pace on the treadmill for 4 intensities (increased slope) of 6 minutes each with a 10 minute rest period between each. Gasses will be collected the last 2 minutes of each workload.

Maximal Exercise Capacity Test:

This test directly follows the treadmill part of the energy efficiency test. After your last workload on the treadmill, instead of resting, you will be asked to continue to exercise until you cannot go on any more. Every 2 minutes the treadmill will increase in slope and you will be asked to keep the same walking pace as before. When you can no longer keep the pace up because you are fatigued you will have completed the test. You will then be asked to gently walk and cool down so you do not shock your body by suddenly stopping at the end of heavy exercise.

In this test you will have four adhesive electrode patches placed on your chest to measure your exercise electrocardiogram (ECG).

Prolonged Walking: (2 tests--placebo and propranolol)

Following the administration of either a placebo pill or an 80 mg dose of the drug propranolol, you will participate in another RMR test as described earlier. Then you will be asked to walk on the treadmill for 60 minutes at a set speed and grade. The tests will be done in a randomized fashion so you will not know which test (placebo or propranolol) is which. The speed and grade will have been determined by how you did on the maximal exercise test. You will be kept at 60% of your maximal exercise capacity for the entire 60 minutes. Heart rate and blood pressure will be continuously monitored. Gasses will be collected in ten minute intervals for two minutes each. Some adjustments in grade or speed may be made to keep the exercise level at 60% of your maximal capacity.

Possible Risks and Discomforts:

You will probably feel localized muscular fatigue in your legs up to two days following the higher intensity cycle and

Body Fat Distribution Study

treadmill tests. You may feel some discomfort or awkwardness at first with the mouthpiece or noseclip used to collect gasses. Also there may be a slight uncomfortable pulling of the skin when the electrodes are removed at the end of the maximal exercise test. The risks involved with maximal exercise include the chance of cardiac incident, which means that you may have heart arrhythmias or possibly cardiac failure, but this risk is very slight for someone without cardiovascular disease. You may be uncomfortable with the underwater weighing technique if you do not like water. However, all precautions are taken to assure your safety and this test is very common and done regularly on "non-swimmers".

The drug propranolol will cause a decreased heart rate and blood pressure. There are risks involved in taking this drug, although they are rare for healthy, non-elderly subjects and the one time, low dosage which will be used here. You may not participate in this study if you have bronchial asthma or allergic reactions (hay fever) during the pollen season. Also you cannot be taking any other medications. Please read the patient information sheet on propranolol (next page).

Should any emergency develop while you are participating you will be given immediate emergency first aid and transported to the nearest health facility (UT Student Health Center or UT Hospital).

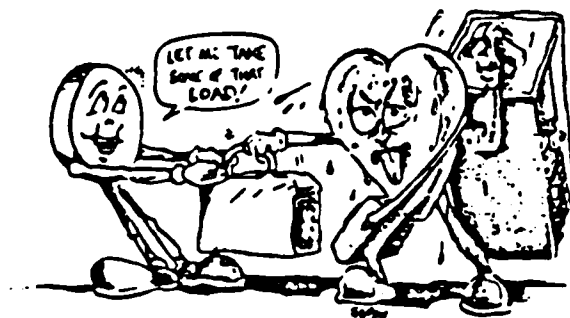
Benefits:

In general, this study will provide information helpful in understanding the association of body fat distribution with the serious metabolic problems of obesity. Results from this study will help elucidate the mechanisms underlying the treatment of obesity by exercise therapy.

Specifically, you will be given a complete anthropometric and body composition evaluation. You will also receive a detailed analysis of your resting metabolic rate which will allow us to calculate a good estimate of your individual daily caloric needs. This information is valuable for anyone truly wanting to lose weight. Finally, you will receive information about your exercise capacity. This knowledge can serve to motivate and perhaps "demystify" exercise as a therapy to help you lose weight.

The services and benefits provided to you in this study are those usually sought by and recommended to overweight people intending to lose weight. You will be given help in designing a weight loss program that you can understand and stay on to help you reach your goal to lower your weight.

After reading this information, are there any questions you want to ask...?



Inderal

Inderal (propranolol hydrochloride) is a synthetic beta-adrenergic receptor blocking agent.

This drug is normally prescribed for heart patients. However, in this study only one dose of 80 mg will be administered. This is much less than is normally prescribed for heart patients with high blood pressure or angina. Thus, you need to be aware of its effects, side effects and cautions, but many of the side effects only occur after repeated doses.

Actions:

This drug blocks the actions of the nervous system (brain and nerves) which can cause high blood pressure. Thus, it will reduce blood pressure. This medication affects the heart by slowing the heart beat. It helps decrease the number and severity of angina attacks by decreasing the workload on the heart. It does this by making the heart contract (squeeze) with less force. Also this medication is used to help your heart beat with the proper rhythm.

In this study we are interested in the actions of the blocking of the nervous system on the metabolism of fat and not on the drug's effect on the heart.

Side effects:

According to the package insert, Information to Patients on Inderal, most adverse effects of Inderal have been mild and transient and have rarely required the withdrawal of therapy. However, you may feel dizzy or tired. You may get cold hands or feet. You may get constipation, diarrhea or an upset stomach. Also your heart rate and blood pressure will go down.

Cautions:

- ** Do not take this medication if you have:
 - bronchial asthma, hay fever, or any other respiratory trouble
 - diabetes
 - low blood pressure
 - slow heart rate
 - or if you are pregnant
- ** Do not take any other drugs the day you take the propranolol.

Information sources: Baptist Health System Heart Center,
Physician's Desk Reference, Patient Package Insert on
 Inderal.

Appendix C

Body Fat Distribution Study**CONSENT FORM**

I have read the above information carefully. I have read and discussed the information given to patients on propranolol. I understand my role in the experiment and the risks involved. The procedures have been explained to me and my questions have been answered to my satisfaction. In addition, I am aware that:

- 1) My participation is entirely voluntary. No coercion of any kind has been used to obtain my cooperation
- 2) Data collected may be used in research presentations or publications but that my identity will remain completely confidential
- 3) I am entitled to have any further inquiries answered regarding the experiment
- 4) I may withdrawal from this study at any time for any reason without penalty or prejudice toward me
- 5) In the event of injury because of my participation in this study, financial compensation is not available and medical treatment is not provided free of charge

I wish to give my voluntary cooperation as a participant.

Date

Signature

Date

Witness

Project Director:

Pam Swan
350 HPER Building
Dept. of Human Performance and Sport Studies
University of Tennessee, Knoxville
974-5111 (office)
974-5091 (lab)
945-5812 (home)

Appendix D

Body Fat Distribution Study

PERSONAL INFORMATION SHEET

Social Security Number

Date

Legal Name

Nickname

Address

Phone (hm)

Date of Birth _____

Phone (wk)

Race: (please circle)

Race: (please circle) Caucasian Hispanic Oriental Other
Am. Indian Black

Personal Physician

Phone

Person to contact in emergency

Phone

Activity Questionnaire

Do you exercise? _____

Circle the total time spent in each category for an average week.

Light activities such as:

slow walking, golf, slow cycling, doubles tennis, easy swimming, gardening

Hours per week: 0 1 2 3 4 5 6 7 8 9 10+

Moderate activities such as:

moderate walking, moderate cycling, singles tennis, moderate swimming, weight lifting

Hours per week:	0	1	2	3	4	5	6	7	8	9	10+
-----------------	---	---	---	---	---	---	---	---	---	---	-----

Vigorous activities such as:

fast walking/jogging, fast cycling, court sports, fast swimming

Hours per week:	0	1	2	3	4	5	6	7	8	9	10+
-----------------	---	---	---	---	---	---	---	---	---	---	-----

Can you walk one hour without stopping?_____

Do you have any physical conditions which may limit your ability to participate in the exercises described in this study? _____
Explain if yes.

Body Fat Distribution Study

HEALTH HISTORY QUESTIONNAIRE

Name: _____ Age _____

SMOKING STATUS:

DO YOU SMOKE? NO, NEVER _____
 YES _____ PACKS PER DAY = _____
 I USED TO _____ BUT I QUIT _____ YEARS AGO

Please check (YES / NO) if you presently have or you have ever been diagnosed with any of the following diseases or symptoms:
 (Have or Had)

<u>SYMPTOM</u>	<u>YES</u>	<u>NO</u>
Coronary Heart Disease	_____	_____
High blood pressure	_____	_____
Heart murmur	_____	_____
Rheumatic fever	_____	_____
Any heart problems	_____	_____
Varicose veins	_____	_____
Stroke	_____	_____
Lung disease	_____	_____
Epilepsy	_____	_____
Anemia	_____	_____
Irregular heart beat	_____	_____
Diabetes	_____	_____
Bronchial asthma	_____	_____
Kidney disease	_____	_____
Liver disease	_____	_____
Hay fever	_____	_____
Orthopedic problems	_____	_____
Date of last medical physical exam	_____	

Body Fat Distribution Study

How long have you been overweight? _____

What is the most and least you have ever weighed?

_____ Most	_____ Date	_____ Least	_____ Date
---------------	---------------	----------------	---------------

Have you lost or gained weight in the past 6 months? How much?

Please list all medications you are currently taking or have taken the last month: _____

How many pregnancies have you had to full term? _____

Is there any chance that you are currently pregnant? _____

Have you recently experienced any of the following symptoms?
Yes or No

Chest pain	_____
Shortness of breath	_____
Heart palpitations	_____
Leg or ankle swelling	_____
Coughing of blood	_____
Low blood sugar	_____
Feel faint or dizzy	_____

Do you have discomfort, shortness of breath or pain with moderate exercise? _____ If yes explain _____

Have you ever been hospitalized? _____ For what? _____

Do you have any medical condition not listed here? _____
If so please describe. _____

Appendix E

Body Fat Distribution Study

id# _____

MENSTRUAL STATUS

Place an X over the days of the month where menstrual bleeding is noticed. Record any "spotting" or "light" days by circling the X. Note the current month and try to recall menstrual history for at least 2 previous months if possible.

JAN.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
FEB.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
MARCH	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
APRIL	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
MAY	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
JUNE	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
JULY	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
AUG.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
SEPT.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
OCT.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
NOV.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
DEC.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Appendix F

Body Fat Distribution Study

DIET RECALL

Instructions For diet recall:

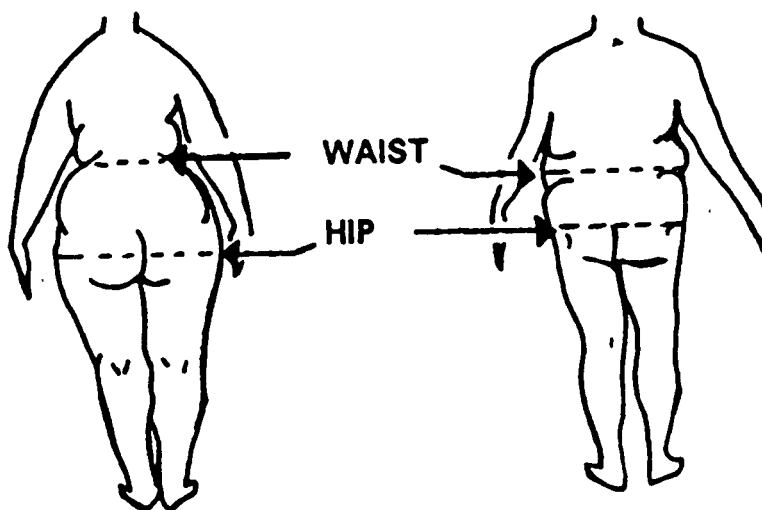
For a 24 hour period (yesterday) please try to recall all food and drink ingested. Also, we know that it is not uncommon for individuals who become aware of their food habits while recording daily dietary intakes to make changes in their normal patterns of eating. If you do this it will defeat the purpose of this part of the study. Try not to alter your usual eating or activity habits over the time that you are in this study. We need you to stay within your normal, everyday meal and activity patterns as possible.

Appendix G

Measurement of Waist to Hip Ratio

**LOWER BODY
OBESE**

**UPPER BODY
OBESE**



Appendix H

Appendix H-1

Repeated Measures Analysis of Variance for Cycle Gross Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	0.571692	0.571692	1.47	.35
S(GRP)	2	.776339	.388169		
<u>Within</u>					
Wkload	3	17.491795	5.830598	7.89	.02
Grp*Wkload	3	1.556161	0.518720	0.70	.58
Error	62	218.202622	3.519397		

Appendix H-2

Repeated Measures Analysis of Variance for Cycle Net Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	2.918798	2.918798	1.70	.32
S(GRP)	2	3.426027	1.713014		
<u>Within</u>					
Wkload	3	7.334544	2.444848	0.83	.52
Grp*Wkload	3	10.333284	3.444428	1.17	.40
Error	62	539.614496	8.703460		

Appendix H-3

Repeated Measures Analysis of Variance for Cycle Delta Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	63.110798	63.110798	1.33	.31
S(GRP)	2	69.152292	34.576146		
<u>Within</u>					
Wkload	2	32.961156	16.480578	1.24	.38
Grp*Wkload	2	.875315	.437657	0.03	.97
Error	45	893.658390	19.859075		

Appendix H-4

Repeated Measures Analysis of Variance for Treadmill Gross Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	.000128	.000128	0.00	.99
S(GRP)	2	3.116180	1.558090		
<u>Within</u>					
Wkload	2	19.079005	9.539502	15.53	.01
Grp*Wkload	2	1.278148	0.639074	1.04	.43
Error	44	36.225060	0.823297		

Appendix H-5

Repeated Measures Analysis of Variance for Treadmill Net Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	5.158290	5.158290	1.97	.17
S(GRP)	2	13.472719	6.736360		
<u>Within</u>					
Wkload	2	21.104890	10.552445	6.98	.05
Grp*Wkload	2	3.346075	1.673037	1.11	.41
Error	44	115.445494	2.623761		

Appendix H-6

Repeated Measures Analysis of Variance for Treadmill Delta Mechanical Efficiency

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	45.662583	45.662583	2.21	.28
S(GRP)	2	41.349981	20.674990		
<u>Within</u>					
Wkload	1	412.484164	206.242082	2.46	.20
Grp*Wkload	2	233.912829	116.956414	1.39	.35
Error	43	3342.853253	77.740773		

Appendix H-7

Repeated Measures Analysis of Variance for Resting Metabolic Rate ($\text{kcal}\cdot\text{day}^{-1}$)

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	187156.08	187156.08	2.19	.15
S(GRP)	2	116229.77	58114.88		
<u>Within</u>					
Treatment	1	30919.16	30919.16	0.36	.55
Grp*Treatment	1	6638.35	6638.35	0.08	.78
Error	34	2905428.48	85453.78		

Appendix H-8

Repeated Measures Analysis of Variance for Resting Metabolic Rate ($\text{kcal}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$)

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	.009859	.009859	1.12	.30
S(GRP)	2	.053176	.053176		
<u>Within</u>					
Treatment	1	.011022	.011022	1.25	.27
Grp*Treatment	1	.000017	.000017	0.00	.96
Error	34	.299019	.008795		

Appendix H-9

Repeated Measures Analysis of Variance for Resting Metabolic Rate (kcal·kg FFM⁻¹·hr⁻¹)

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	.001428	.001428	0.07	.79
S(GRP)	2	.167488	.0837438		
<u>Within</u>					
Treatment	1	.019847	.019847	1.01	.32
Grp*Treatment	1	.001974	.001974	0.10	.75
Error	34	.667006	.019618		

Appendix H-10

Repeated Measures Analysis of Variance for Respiratory Quotient

SOURCE	df	SS	MS	F	p
<u>Between</u>					
GRP	1	.000991	.000991	0.22	.69
S(GRP)	2	.009174	.004587		
<u>Within</u>					
Treatment	1	.073131	.073131	18.52	.05
Grp*Treatment	1	.000657	.000657	0.17	.72
S*Treat(Grp)	2	.007899	.003949		
Time	6	.104536	.017422	57.24	.0001
Grp*Time	6	.002617	.000436	1.43	.28
S*Time(Grp)	12	.003653	.000304		
Treat*Time	6	.029438	.004906	2.37	.03
Grp*Treat*Time	6	.006731	.001122	0.54	.76
Error	230	.475370	.002067		
<u>Contrasts</u>					
<u>10 min</u>					
UB-C vs LB-C	1	.000002	.000002	0.00	.97
UB-C vs UB-T	1	.001901	.001901	1.39	.25
UB-T vs LB-T	1	.000072	.000072	0.05	.82
LB-C vs LB-T	1	.002554	.002554	1.87	.18

<u>Contrasts</u>	df	SS	MS	F	p
<u>20 min</u>					
UB-C vs LB-C	1	.001786	.001786	1.03	.32
UB-C vs UB-T	1	.002622	.002622	1.50	.23
UB-T vs LB-T	1	.000732	.000732	0.42	.52
LB-C vs LB-T	1	.014526	.014526	8.34	.006
<u>30 min</u>					
UB-C vs LB-C	1	.000088	.000088	0.06	.80
UB-C vs UB-T	1	.006588	.006588	4.77	.04
UB-T vs LB-T	1	.000396	.000396	0.29	.59
LB-C vs LB-T	1	.012202	.012202	8.84	.005
<u>40 min</u>					
UB-C vs LB-C	1	.000911	.000911	0.66	.42
UB-C vs UB-T	1	.008167	.008167	5.92	.02
UB-T vs LB-T	1	.000008	.000008	0.01	.94
LB-C vs LB-T	1	.013654	.013654	9.89	.003
<u>50 min</u>					
UB-C vs LB-C	1	.000490	.000490	0.33	.57
UB-C vs UB-T	1	.007512	.007512	5.08	.03
UB-T vs LB-T	1	.000117	.000117	0.08	.78
LB-C vs LB-T	1	.014242	.014242	9.64	.004
<u>60 min</u>					
UB-C vs LB-C	1	.000135	.000135	0.11	.74
UB-C vs UB-T	1	.006188	.006188	5.15	.03
UB-T vs LB-T	1	.000080	.000080	0.07	.80
LB-C vs LB-T	1	.009835	.009835	8.18	.007

UB = Upper Body; LB = Lower Body; C = Control; T = Treatment

VITA

Pamela Diane Swan was born in San Francisco, California on December 16, 1955. She lived in Redwood City, California and graduated from San Carlos High School in 1974. She went on to receive a Bachelor of Science degree in physical anthropology from the University of California - Santa Barbara in 1978 and her California teaching credentials in social studies in 1979. After graduating, Pam contributed to society as a school teacher in California for several years. Eventually she relocated to North Carolina to pursue a career change and received a Master's Degree in physical education (exercise physiology) from the University of North Carolina at Greensboro in 1987. In 1988 she enrolled at the University of Tennessee, Knoxville, to complete a doctoral degree in exercise physiology. Her current research interests include the metabolic and cardiovascular adaptations to acute and chronic exercise stress in various special populations such as the aged and the obese.

She has currently accepted a faculty position at the University of Colorado at Boulder to begin in August, 1991.