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The Effects of a Moderate Progressive
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Ph.D. degree in the School of Health
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THE EFFECTS OF A MODERATE PROGRESSIVE AEROBIC EXERCISE PROGRAM
ON THE SEVERELY AND MORBIDLY OBESE

By

Chester John Zelasko

A DISSERTATION

Submitted to
Michigan State University
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ABSTRACT

THE EFFECTS OF A MODERATE PROGRESSIVE AEROBIC EXERCISE PROGRAM ON THE SEVERELY AND MORBIDLY OBESE

By

Chester John Zelasko

The purpose of the study was to examine the effects of a progressive aerobic exercise program on the severely and morbidly obese with no planned dietary intervention. The study attempted to determine if obesity-associated risk factors for diabetes and coronary heart disease can be reduced. Twelve severely to morbidly obese male and female volunteers (mean age = 39.8 yrs), who were screened for clinical, ECG or exercise-induced indications of obstructive coronary heart disease, were participants in the study. The exercise program was moderate (50-60% of maximal heart rate) in intensity. The subjects trained by walking on treadmills, riding stationary bicycles and/or cycling a hand-crank ergometer one hour a day, a minimum of four times per week, for six months. All subjects participated throughout the entire study. Serum lipid determinations showed that there were decreases in total cholesterol, triglycerides, and low-density lipoproteins but increases in high-density lipoproteins. The cholesterol:HDL ratio was decreased 13%. Fasting plasma insulin levels were decreased by 55%. Significant differences ($P < .01$) were found in membrane fluidity and the lipid composition of mononuclear leukocyte cellular membranes after exercise training. Changes in membrane fluidity are associated with an increase in insulin sensitivity. The study revealed a trend toward the reduction of obesity-associated risk factors due to the exercise training.

DEDICATION

To the loving memory of my grandmother, Frances Rogacki;
and to my wife, Ginger.

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CHAPTER I

THE PROBLEM

Obesity is considered to be a risk factor for diabetes, coronary heart disease (CHD), hypertension, and cancer. In addition, if the degree of obesity is severe, the capacity for normal day-to-day living may be impaired. Severe obesity can manifest itself in reduced functional capacity and sleep apnea (80). Currently, the primary goal in the treatment of obesity is a reduction of body weight. Obesity typically is treated by reducing caloric intake for a period of time until a target weight is achieved. Severe obesity also is treated with either gastric stapling or intestinal bypass surgery. Recently, a technique has been developed that places a balloon in the stomach to decrease stomach size and to promote satiety. Exercise often is recommended to increase caloric expenditure and thus to aid in weight loss.

While most treatments of obesity can be successful in achieving weight loss, the subsequent maintenance results typically are dismal. Far too many treatments of obesity, even those in clinical settings, treat the symptom of excess body weight without defining manifestations of improved health as desirable concomitant goals. Almost every study that has dealt with exercise as a treatment for obesity has used weight

loss as the sole criterion for success of treatment. The question must be asked: Is weight loss the only criterion or even a necessary criterion to measure the effectiveness of exercise as a treatment for obesity? The reduction of obesity-associated risk factors, regardless of the amount of weight lost, would seem to be an entirely appropriate and desirable goal (6,14,30,34,38,79).

Many studies have examined the effects of exercise on obese populations. Those studies that have dealt with extremely obese populations have achieved mixed results when weight loss was the only research objective. The diversity in the exercise regimens between various studies may account for the differences in the results achieved. The frequency (times per week), duration (minutes per session), and intensity (percentage of maximal heart rate) of the exercise programs, as well as the length of some studies, may not have been sufficient to achieve desired results. Simply stated, the exercise programs in some studies may not have used a sufficient number of calories to induce a substantial weight loss.

While the success of exercise programs evaluated in terms of weight loss in many studies is disappointing, there are indications that risk factors for coronary artery disease and adult-onset diabetes may be reduced. Reductions in plasma insulin, plasma cholesterol, and total plasma triglyceride levels have been observed after exercise programs (7,47,49,50,55,58,74,83,84). Plasma glucose levels have decreased or remained the same (6). Increased high density lipoproteins, lowered resting heart rates, lowered systolic and diastolic blood pressures, and increased maximal oxygen consumption have been reported in various

studies in response to an exercise program (20,23-25,38,45,54,60,78).

The major obstacle to the success of an exercise program is lack of adherence by the subjects to the exercise regimen prescribed. Dropout rates as high as 50% have been reported in studies with severely and morbidly obese populations (10,69). The reasons cited for dropouts in previous studies are injury, discomfort, boredom, embarrassment, and inability to fit the exercise sessions into the participants' schedules (12).

Purpose of the Study

The purpose of this study was to examine the effects of a six-month, progressive aerobic exercise program in the severely to morbidly obese with no planned dietary intervention. The progressive aerobic exercise program was designed to be of sufficient duration, intensity, and frequency to achieve maximal tolerable performances on an individually scheduled basis. Specifically, the study attempted to determine if obesity-associated risk factors for coronary artery disease and adult-onset diabetes can be reduced whether body weight is decreased or not. Those risk factors associated with obesity that were examined are hyperinsulinemia, elevated plasma cholesterol, elevated plasma triglycerides, decreased high-density lipoproteins, and the atherogenic index which is the total cholesterol:high-density lipoprotein ratio. The study cannot answer unequivocally the question of whether an individual can be "fat and fit". However, it is possible to see if there are positive changes in obesity-associated risk factors regardless of whether



or not the participants lose weight.

Research Hypotheses

The study was designed to test the following hypotheses:

1. A progressive aerobic exercise program is a viable treatment for chronic obesity; specifically, obesity-associated risk factors for coronary artery disease and adult-onset diabetes can be reduced through an exercise program whether or not significant weight loss occurs.
2. Persons who are severely obese will adhere to a long-term exercise regimen if they are provided with proper guidance in an environment that is conducive to their participation so that they receive enjoyment from the program.
3. Short-term (1-wk) and long-term (5- and 6-month) changes in insulin binding, membrane fluidity, and cellular lipid composition of mononuclear leukocytes in the severely obese will reflect positive changes in insulin sensitivity in response to an exercise program.

Research Plan

Eight female and four male severely and morbidly obese persons were subjects in the study. The subjects were screened for the presence of CAD. Screening included a physical examination, a medical history, a resting 12 lead electrocardiogram (ECG), various blood analyses, and an



exercise stress test.

Each subject was required to participate in a 6-month, progressive exercise program conducted in the Center for the Study of Human Performance at Michigan State University. The original research design provided that data could be grouped and analyzed from measurements taken prior to the exercise program, at 3 months, and following the completion of the exercise program at 6 months. Due to financial considerations, the 3-month measures of insulin binding, and membrane fluidity of mononuclear leukocytes were delayed until 5 months. However, determinations of blood lipids, body composition, dietary history, and aerobic capacity followed the original design. Insulin binding and membrane fluidity were measured prior to the exercise program, at 5 months, and 6 months.

With the exception of the insulin binding results, the data were analyzed by a repeated measures multiple analysis of variance (MANOVA), by a univariate analysis of variance (ANOVA), and, where appropriate, by a repeated measures analysis of covariance (MANCOVA). Wilk's Lambda was used as the test statistic to determine the overall significance of the MANOVA. A priori contrasts for differences between each test session were performed if an individual ANOVA was statistically significant. The probability of making a type I statistical error was set at .01 for all analyses.



Limitations of the Study

The following limitations apply to the applications of the results of this study:

1. The sample size was limited due to financial and personnel limitations. This resulted in an unequal number of male and female participants.
2. The fasting periods prior to blood sampling were unsupervised. Compliance of the subjects was assumed.
3. The subjects were allowed to eat ad libitum. The dietary histories were assumed to reflect accurately the food consumed. Reliance was placed on the word of the subjects.

Significance of the Study

This study can make significant contributions both to obesity research and to the treatment of obesity. The primary focus of the study places the emphasis for success of the exercise program upon the reduction of obesity-associated risk factors instead of upon weight loss. Considering the usual lack of long-term success achieved by most dietary weight-reduction approaches, health enhancement resulting from a progressive aerobic exercise program can provide a reasonable alternative.

Adherence to a program by the severely obese is the greatest obstacle to the use of exercise as a treatment for obesity. The supervision, leadership, and private environment of the current exercise



program may provide insight that will help facilitate other exercise programs for the obese in the future.

CHAPTER II

REVIEW OF LITERATURE

The volume of research that examines the genesis, related illnesses, and treatment of obesity is extensive. This literature review is concentrated on studies that are related to the severely and morbidly obese. However, where appropriate, other studies that have examined the effects of exercise on lipid and carbohydrate metabolism in normal-weight populations are included in the discussion.

Obesity and Coronary Artery Disease

Obesity is associated with increased morbidity. In fact, many diseases are attributed to the obese state. Coronary artery disease (CAD), adult-onset diabetes (AOD), hypertension, gall bladder disease, arthritis, and increased rates of breast and colon cancer are among the most serious medical problems suffered by the obese (11). What is not clear at the present time is whether the cause of the increased morbidity is obesity itself or the risk factors associated with obesity (14).

Coronary artery disease and adult-onset diabetes are thought to be preventable in obese persons if their excess weight is lost. This assumes that other risk factors such as cigarette smoking or a high-fat

diet are not present after weight loss. Risk factors for CAD and AOD that are associated with obesity revolve around dysfunctions of lipid and carbohydrate metabolism. Physiological manifestations of the abnormal metabolism found in the obese are hypercholesteremia, hypertriglyceridemia, decreased high-density lipoproteins, hyperglycemia, and hyperinsulinemia.

The Framingham Study has provided much of the evidence that has linked obesity to CAD. Hypercholesteremia was found to be a primary risk factor for CAD in both obese and non-obese segments of the population. In 1967, the authors reported that the risk of CAD and sudden death are increased in obese males without hypercholesteremia. When hypercholesteremia and/or hypertension are present, the risk of CAD and sudden death doubles in men and is 64% higher in women (42). In 1979, the authors reported that as a population fattens, atherogenic traits worsen in proportion to the weight gained. Total serum cholesterol has been shown to increase with an increase in weight. Each 1% increase in relative weight is associated with a 1 mg/dl increase of serum cholesterol in males and a .5 mg/dl increase in females (33,40,41).

Decreased levels of high-density lipoproteins have been implicated as another risk factor associated with CAD. Recent studies have found a strong inverse relationship between CAD and high-density lipoprotein levels (32,56). Kannel, Castelli and Gordon (43) stated in 1979, "High-density lipoprotein cholesterol appears to be the most powerful single lipid indicator of cardiovascular risk, at least in ages older than 50 yrs." They further state, "The evidence currently available strongly suggests that the high-density lipoprotein cholesterol findings apply to

those younger than age 50." The mechanism of the anti-atherogenic effect of high-density lipoproteins has yet to be discovered.

Obesity is associated with low levels of high-density lipoproteins. The Lipids Research Clinics Program Prevalence Study found that body mass and high-density lipoproteins are inversely related. High-density lipoproteins decrease as the degree of fatness increases (32). Gordon et al. (33) reported similar findings in the Framingham Study. They reported that in women, the greater the relative weight, the lower the levels of high-density lipoproteins. A similar pattern is found in obese men.

The relationship between total cholesterol and high-density lipoproteins may provide the best atherogenic index at the present time. Castelli et al. (16) have reported that the strong inverse relationship between CAD and high-density lipoprotein cholesterol applies to all levels of total cholesterol. A ratio of total cholesterol to high-density lipoprotein cholesterol which is less than 4.5 is associated with a lower incidence of CAD. This relationship applies even in those persons with low total cholesterol ($< 200\text{mg/dl}$) (14). Arntzenius et al. (4) examined the effects of nutritional modifications on atherosclerotic lesion growth in patients with angina pectoris. No coronary lesion growth was observed in patients whose total cholesterol:high-density lipoprotein ratio was less than 6.9 throughout the experimental period. Those patients who initially had higher ratios but lowered their values below 6.9 through dietary intervention also did not experience lesion growth. Further studies are necessary before an optimal total cholesterol:high-density lipoprotein ratio can be established for

clinical evaluation purposes. However, a ratio of less than 4.5 can be considered to be reasonably associated with a decreased risk of CAD.

Obesity and Adult-Onset Diabetes

Obesity is well recognized as the primary cause of adult-onset diabetes (AOD). The National Institutes of Health recently convened a consensus panel to review data on current treatments of AOD. The panel agreed that AOD is entirely preventable if normal body weight is maintained. The panel further stated that obese persons currently with AOD will see a remission of symptoms if weight is lost (46). The development of AOD in the obese is related to abnormalities in carbohydrate metabolism. Whether due to an increased carbohydrate intake (64), elevated fatty acids (77), decreased physical activity (64), or elevated blood triglycerides (53), the obese become insulin resistant.

The progression of AOD in the obese is unclear at the present time. Factors that appear to interact to produce AOD are hyperinsulinemia and concomitant dysfunction of target tissue insulin receptors. Björntorp (9) recently stated that "... there is no explanation for increased plasma insulin in obesity. There is evidence for decreased insulin sensitivity in all tissues examined so far including adipose tissue, muscle, and lymphocytes. This suggests a generalized decrease of insulin responsiveness at the cellular level." The decrease in insulin responsiveness has been attributed to a malfunction of the cellular insulin receptor. Further research has shown a decreased number of insulin receptors per cell in adipocytes (37,67,68) and lymphocytes

(66,68). The decrease in insulin receptors may be the result of changes in the structure of the target tissue membrane (63). The result of the decreased insulin sensitivity is an elevated blood glucose. Adult-onset diabetes may ensue.

Exercise and Weight Loss

Obesity-associated risk factors for CAD and AOD can be reduced if weight is lost, but the energy balance of the obese must be altered to incur a weight loss. The number of calories ingested and/or the number of calories expended must create a caloric deficit to enable fat stores to be used for energy. Hypocaloric diets are used to decrease the energy intake while exercise has been used to increase the caloric expenditure in obese individuals. However, the long-term results of weight-loss programs, especially in the severely and morbidly obese, have not been encouraging.

In spite of serious physical limitations, persons who have severe weight problems can safely participate in physical training programs. Over the past 20 years, studies involving severely and morbidly obese subjects have been conducted regularly at First Medical Service and the Department of Medical Rehabilitation and Clinical Physiology, University of Göteborg, Sweden (6,7,47,48) and at the University of Michigan Medical Center, Ann Arbor, Michigan (25-27,49,50,74). While the obese can participate in exercise programs, the results achieved in terms of weight loss have been disappointing. Weight loss (47), no change (7), or even weight gain (6,47) have been reported.

Investigators also report that adherence to the exercise programs is

a persistent problem (12,25,26). Dropout rates ranging from 15% to 50% are common in studies involving exercise and obese subjects. The reasons cited by those dropping out of programs are monotony (52) embarrassment (12), and a perceived lack of progress (10). Careful examination of the training programs reveals that the intensity of some programs may have been too severe (75–80% of maximal heart rate) (6,7,47,48). Also, an estimate of the number of calories expended per exercise session shows that even a small increase in caloric consumption (<200 kcal) could negate the energy expended during exercise (6,7,47).

Three studies consistently are cited in review articles of exercise and the obese. These investigations warrant close scrutiny. Gwinup (35) reported a substantial average weight loss (22 lbs) in eleven obese women who exercised a minimum of 30 min per day for at least one year. No attempt was made to control dietary intake and no measurements of blood lipids or carbohydrate metabolism were taken. The initial range of overweight was 10% to 60% according to the Metropolitan Life Insurance Tables. From the descriptive data provided, none of the subjects who completed the study were morbidly obese. Only 11 of the original 34 subjects (29 women and 5 men) completed the study. Gwinup concludes, "Although exercise alone does not provide an easy answer to the problem of obesity, for certain subjects it seems to offer an alternative to dieting that will produce weight loss and may, in addition, provide the other health benefits often attributed to exercise."

Lewis et al. (54) reported a mean weight loss of 4.2 kg in 22 moderately obese middle-aged women (out of 27 who began the study). The subjects exercised three times weekly for 17 weeks. Although no dietary

records were maintained, only 19% of the weight lost was attributed to the exercise program. No statistically significant changes in blood lipids were reported; there was, however, a mean decrease in total cholesterol of 3 mg/dl, a mean decrease in low-density lipoproteins of 5 mg/dl, and a mean increase in high-density lipoproteins of 5 mg/dl. Each of these small alterations occurred in the direction expected with exercise.

Leon et al. (52) examined the effects of a vigorous walking program on young obese men. Six subjects (out of 10) completed a 16-week progressive walking program which was conducted 90 min per day, 5 days per week. The mean weight loss was 5.7 kg and the subjects' average body fat decreased from 23.5% to 18.6%. The subjects experienced mean decreases in total cholesterol, triglycerides, and low-density lipoproteins. A significant ($P < .05$) increase was observed in high-density lipoproteins. The mean fasting insulin and glucose levels decreased after training, indicating an increase in insulin sensitivity.

The previously mentioned studies have yielded mixed results for weight loss in obese subjects. However, encouraging and generally consistent changes in carbohydrate and lipid metabolism took place. The use of exercise for the treatment of obesity-associated risk factors, regardless of weight loss, appears to be warranted.

Exercise, Obesity and Serum Lipids

The fact that a relationship exists between exercise and serum lipids is well established. Increased physical activity typically is

associated with decreased values of serum total cholesterol, low-density lipoproteins, and triglycerides as well as with increased values of high-density lipoproteins. However, prospective studies have been unable to conclusively demonstrate a causal relationship between exercise and blood lipids in normal-weight individuals. This may be due to confounding variables such as unreported dietary changes. The duration, frequency, intensity, and/or the length of some studies may not have been sufficient to achieve desired changes.

There are only a limited number of studies that have examined the effects of exercise on blood lipid levels in the obese. Total serum cholesterol has been the lipid component of blood examined most frequently. Cholesterol levels have been found either to decrease (47,52,54,84) or to remain unchanged (22,78). Serum triglycerides have increased (54,78) or decreased (22,47,52,84) with low-density lipoproteins generally following a parallel pattern. High-density lipoproteins levels in the obese have been reported to increase after an exercise program (52,54,78,84). Weltman, Matter, and Stamford (84) reported a significant decrease in the total cholesterol:high-density lipoprotein ratio in response to an exercise program.

While these studies are encouraging, two possible confounding variables must be addressed. Dietary modifications such as low total caloric intake, a high carbohydrate diet (70), high dietary fiber (3), and low cholesterol diets (4) can all affect serum cholesterol and triglycerides. The research literature seems to indicate that dietary changes can affect the high-density lipoprotein proportion as well. Short-term studies have shown a lowering of high-density lipoproteins in

response to a high carbohydrate diet (19,58,70). Currently, long-term studies are not available to examine the effects of dietary changes on high-density lipoproteins without concomitant weight loss. VanGaal, Vandewoude, and DeLeeuw (82) and VanGaal and DeLeeuw (81) reported an increase in high-density lipoproteins after weight loss. Both studies utilized a protein supplemented hypocaloric diet which was imposed for six months. Decreases in high-density lipoproteins were experienced early in the studies, but the trends had reversed by six months. The interaction between exercise and possible dietary modifications clouds the independent effects of either intervention.

The relationship between weight loss and total serum cholesterol also may confound the results. Decreases in serum cholesterol have been associated with decreases in total body weight (65,83). Vu Tran and Weltman (83) found a strong relationship between weight loss and serum lipids in a meta-analysis of ninety-five exercise-related studies. Total cholesterol, triglycerides, and low-density lipoproteins decreased with exercise when either weight was lost or no change in weight occurred. When weight increased, there were small increases in total cholesterol, triglycerides, and low-density lipoproteins. However, whether weight was lost, remain unchanged, or was gained, the high-density lipoprotein fraction consistently increased with exercise. This relationship becomes even more apparent when the total cholesterol:high-density lipoprotein ratio is examined. In each case, the ratio was decreased by exercise which indicates there was a decrease in atherogenic risk.

Obesity, Exercise, and Risk Factors for Adult-Onset Diabetes

A strong relationship exists between insulin sensitivity and obesity. The greater the degree of obesity, the more insulin sensitivity decreases. That is, obese subjects are more resistant to insulin action than are normal-weight subjects. When severely and morbidly obese subjects participate in exercise regimens, insulin resistance is decreased regardless of whether or not weight is lost. Fasting serum insulin levels in obese subjects have been reported to decrease in response to exercise training (6,7,47,49,52). Furthermore, insulin sensitivity is increased after exercise training whether determined by the oral glucose tolerance test (6,47,52), by the euglycemic clamp technique (49,74), or by changes in insulin receptors on adipocytes or circulating lymphocytes (63). Blood glucose in obese subjects decreases (52) or remains unchanged with exercise (6,7,47).

The mechanism responsible for increased insulin sensitivity after physical training is not yet known. Björntorp (6) has suggested that the increased insulin sensitivity is, in part, due to an increased peripheral uptake by the musculature. Several investigators have reported changes in insulin receptors following acute exercise in adipocytes (10) and mononuclear leukocytes (65). An increased number of insulin receptors, an increased density of receptors per cell, and an increase in the receptor affinity for insulin all have been examined to explain the increased insulin sensitivity, but with no conclusive evidence. Changes in the composition of the membrane structure of target and non-target tissues may provide the key for determining the mechanism of the

increased insulin sensitivity due to exercise training (65).

The evidence supporting the use of exercise as a treatment for obesity-associated risk factors, irrespective of weight loss, is substantial. The risk factors for CAD and AOD that are associated with obesity appear to be modified in response to exercise training. Although the problems associated with getting obese subjects to exercise also are substantial, when the overall failure of severely and morbidly obese persons to maintain weight loss is considered, an exercise-based treatment of obesity-associated risk factors becomes a reasonable alternative. Björntorp (10) recently stated, "An improvement in the associated complications of obesity might be considered at least as important as an improvement of the obesity as such."

CHAPTER III

RESEARCH METHODS

This study was designed to examine the effects of a progressive aerobic exercise program on a group of severely and morbidly obese subjects with no planned dietary intervention. Specifically, the study attempted to determine if the risk factors for coronary artery disease and adult-onset diabetes that are associated with obesity can be reduced by exercise whether or not body weight is decreased.

Subjects

Potential subjects for the study were recruited in various ways. Several were referred by local physicians who had treated these persons for obesity. Others inquired about the study after hearing of it through word of mouth. The remainder responded to an advertisement in a local newspaper. The only criterion for selection as potential subjects was that the person had to appear obese enough to be classified as severely or morbidly obese. Five male and nine female severely and morbidly obese persons were asked to volunteer for the screening portion of the study.

A minimum of two interviews with the primary investigator informed the potential subject about the nature, purpose and possible risks of the

study as well as the type and number of tests involved in the testing sessions. The progressive aerobic exercise program was discussed, and a tour was conducted of the facilities where the testing and exercise sessions were scheduled to take place.

Body Mass Index (BMI), $\text{wt (kg)}/\text{ht (m)}^2$, was used to rate the initial degree of obesity of each potential subject. A value of $\text{BMI} \geq 30 \text{ kg/m}^2$ indicates severe obesity (15,39) and was used as a minimum criterion for inclusion in the study. Body fat values $\geq 35\%$ in male adults and $\geq 40\%$ in female adults indicate severe obesity and were used as alternative criteria for inclusion in the study. All subjects exceeded one or both of the criterion.

Permission for the use of human subjects in the study was obtained from the University Committee on Research Involving Human Subjects. Those potential subjects who decided to volunteer were asked to sign an informed consent form before any screening took place.

Each potential subject was screened by the Special Diagnostics Unit of the Clinical Center at Michigan State University before being allowed to participate in the study. Screening included a physical examination, a medical history, a resting 12-lead electrocardiogram (ECG), several blood analyses, and an exercise stress test. Individuals were not included in the study if they had suffered a cardiovascular event, had juvenile onset diabetes or had clinical, ECG or exercise-induced symptoms of obstructive coronary heart disease. All potential subjects passed the screening procedure and were asked to participate in the study. One person was unable to participate due to personal problems. Another person was severely injured at work and could not participate. Four male

and eight female subjects volunteered to participate in the study.

Preliminary Data Collection

Three 7-ml serum vacutainers of blood were drawn from an antecubital vein after an overnight fast on each of three separate days before an initial exercise treadmill test. These blood samples were analyzed for insulin, glucose, triglycerides, cholesterol, and high density lipoproteins. The initial blood analyses provided baseline data on each subject.

Blood lipids, glucose, and insulin measurements were performed by Advanced Medical and Research Center, Inc., Pontiac, Michigan. Cholesterol, triglycerides, high density lipoproteins, and glucose were determined enzymatically using an ABA-GP (Abbott Industries). Duplicate values were obtained every 24 samples. Low-density lipoproteins were estimated using the formula of Friedewald, Levy, and Fredrickson (29). Insulin was determined by radioimmunoassay (Diagnostic Products kit). Triplicate values were obtained every 25 specimens.

Additionally, 35 ml of blood was drawn in heparinized tubes on the day of the third baseline blood sampling. This blood was packed and shipped via overnight express mail service to the Pediatric Endocrinology Laboratory at Cedar Sinai Medical Center in Los Angeles, CA. This laboratory is under the direction of Dr. Naomi Neufeld. The blood samples were analyzed for insulin binding, membrane fluidity, and cellular lipid composition of mononuclear leukocytes. The specific methods used are provided in the Appendix B. This was repeated after 7

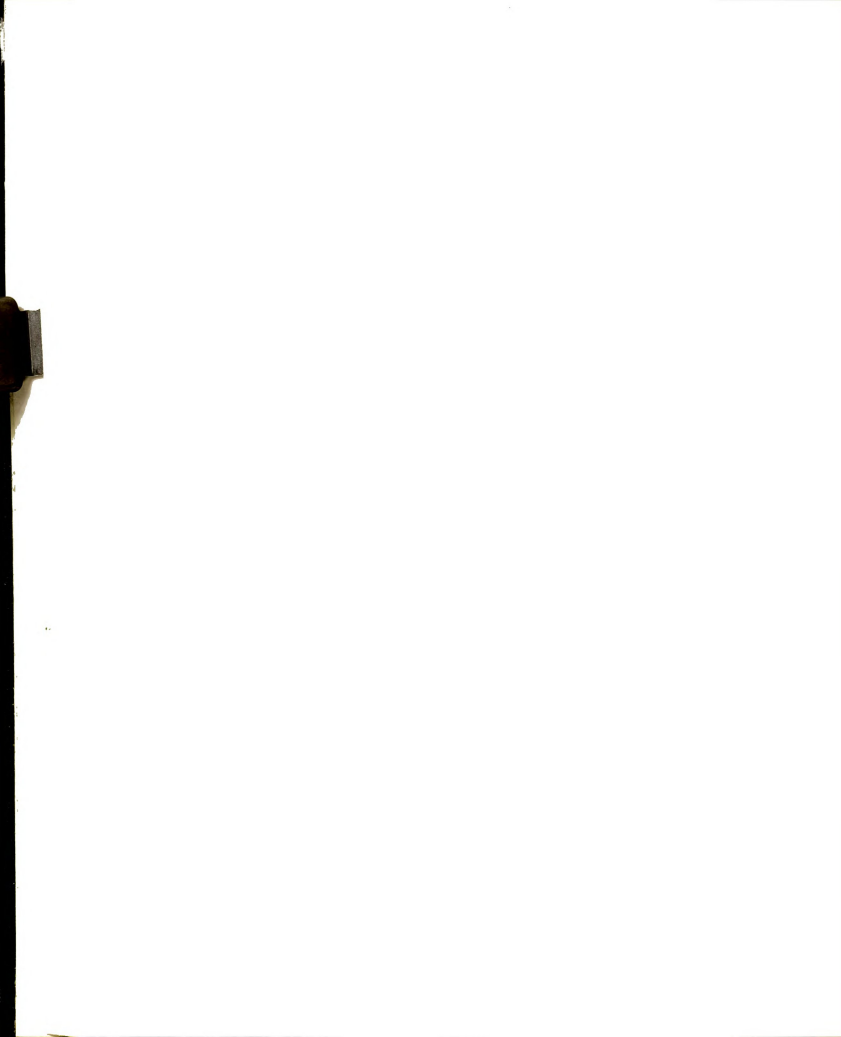
days, after 5 months, and after 6 months of the exercise program.

Nutritional information and eating habits were obtained two weeks to one month before the actual testing began. Dietary intake was determined by a three-day food recall which included two weekdays and one weekend day (44,51,59). Food models were used to determine portion sizes. Weight, resting heart rate and blood pressure was measured twice prior to the exercise test session.

Aerobic Capacity

The subjects were randomly assigned to report for the initial exercise test session at the Center for the Study of Human Performance. After sitting quietly for 10 min with the left hand soaking in warm water to ensure an arterialized sample, a 20-microliter tube of blood was drawn from a finger and immediately analyzed for lactate. The hand then was placed inside a glove to keep the hand warm. Resting heart rate and blood pressure were taken. The subject was fitted with a mouthpiece and head apparatus. After a period of adjustment to the treadmill, the subject began the treadmill test.

The test used a combination of the first two stages of the Naughton (61) and subsequent stages of the Balke (5) substandard and standard treadmill tests (Appendix A). Each stage lasts two minutes. Each subject was asked to walk to exhaustion or until terminated due to one of the following conditions: signs and symptoms of exertional intolerance, ECG changes, or inappropriate blood pressure, heart rate, or respiratory responses. Heart rate and ECG were monitored continuously by a physician



throughout the exercise test. Electrocardiographic recordings were obtained using the CM-5 lead. Blood pressure was taken during the final 15 sec of each level completed.

The subject inspired through a two-way Daniels respiratory valve (R-Pel Company, Los Altos CA). The valve was connected to a four-way automated switching valve by two feet of corrugated tubing. The expired gases were collected continuously in neoprene weather balloons. The bags were changed every 60 sec until the volume of expired gas appeared to exceed the capacity of the bag. The bags then were changed every 30 sec until the test was terminated. During 10 min of recovery, bags were changed every 60 sec.

Expired gases were analyzed for percentages of CO₂ and O₂ using an infrared CO₂ analyzer (Model CD-3A, Applied Electrochemistry, Sunnyvale, CA), and an electrochemical O₂ analyzer (Model S-3A Applied Electrochemistry, Sunnyvale, CA). Helium gas was used for zeroing the analyzers. The analyzers were calibrated with a gas sample that was verified for O₂ and CO₂ content with a Haldane Chemical Analyzer (A. H. Thomas Co. Philadelphia, PA). The volume of gas was measured using a dry gas meter (Model DTM-115 American Meter Co.). The gas was pumped through the dry gas meter at a rate of 50 l/min.

Pulmonary ventilation (V_E) and oxygen consumption (VO_2) were determined continuously throughout the exercise stress test and through 10 min of recovery. The values for V_E and VO_2 were calculated using the equations of Consolazio, Johnson and Pecora (17).

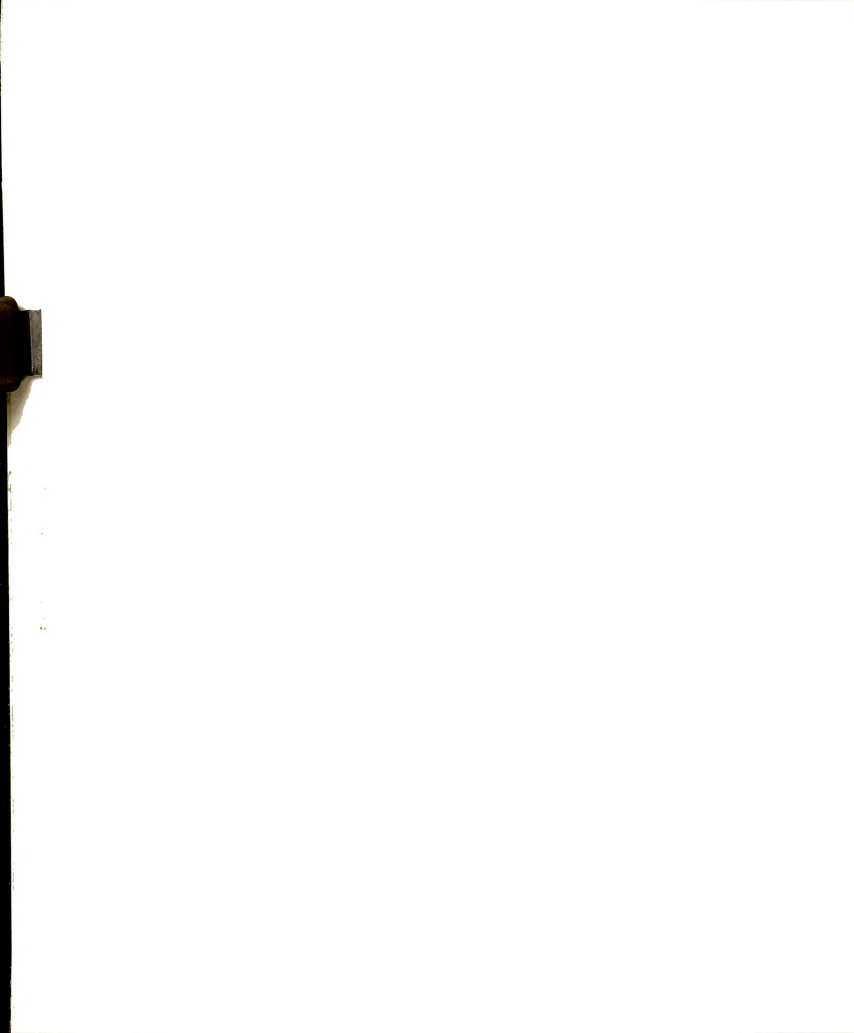
Blood lactate levels were measured before exercise, immediately after exercise, and following 5 min and 10 min of recovery from the

exercise test.

Body Composition

The laboratory was restricted to non-essential personnel during body composition analysis to prevent any possible embarrassment to the subjects. The subjects were asked to change into a swim suit or other suitable apparel that could be worn in water. They then were weighed on a balance beam scale to the nearest .01 kg. The subject proceeded to the underwater weighing tank where body density was measured. The subject practiced the required procedure in the water.

Underwater weight in the Center for the Study of Human Performance (CSHP) at Michigan State University is measured in a seated position with a strain gauge (Model SR-4 Load Cell Type UI-B, Balwin-Lima Hamilton Corp). The signal from the strain gauge is sent to a Wheatstone bridge where it is modified and then sent to a graphic recorder (Model 2115M Allen Datagraph Corp.). Lung volume is measured underwater, at the same time as the underwater weight is recorded, using a modified version of the closed circuit, nitrogen dilution method of Rahn, Fenn and Otis (72). The nitrogen content of a closed circuit rebreathing bag is continuously monitored by a MedScience 505 Nitralizer. Body density is calculated using the Brozek formula (13). Percent fat is calculated using the Siri equation (76). The procedure is repeated three times and the mean of the three trials is reported as the subject's percent fat.



Aerobic Exercise Program

Supervised exercise sessions were conducted in the CSHP laboratory. The CSHP serves as a focal point in the University for the assessment, investigation, and promotion of human health and work performance. The main part of the laboratory is divided into two rooms. One room of 2500 sq. ft. includes a treadmill area to assess energy metabolism and physiological responses to submaximal and maximal work, a hydrostatic weighing area for body composition analysis, an exercise area, and a blood lactate analysis area. The other room of 1000 sq. ft. includes areas for physical examinations, anthropometric measurements, phlebotomy, and meeting facilities. Separate shower and locker room facilities are available for men and women.

The exercise area used in the study is contained within a 400 sq. ft. corner of the larger room in the laboratory. Six-foot tall room dividers enclose the exercise area for subject privacy. The exercise equipment includes three motor driven treadmills, four stationary exercise bicycles, and a hand-crank ergometer.

The primary modes of exercise were walking on a motor driven treadmill, riding a stationary bicycle and/or pumping a hand-crank ergometer. The subjects were encouraged to train utilizing a circuit approach involving all three modes of exercise. This limited the stress in a particular set of joints. Following the American College of Sports Medicine Guidelines for Graded Exercise Testing and Exercise Prescription (2), the subjects were trained at 50% to 60% of the maximal heart rate achieved during the treadmill test. However, due to their low initial

level of fitness, 2 to 8 weeks of training at 40% to 50% of maximal heart rate were needed before more intense exercise was attempted. Initially, the duration of the aerobic portion of each exercise session was 45 min. The duration was increased to 60 min as soon as the physical condition of each subject allowed. Some subjects required up to 4 weeks before 45 continuous minutes of exercise could be performed. The individual exercise programs were adjusted weekly to maintain target heart rates. The subjects participated in a minimum of four exercise sessions per week but were encouraged to participate in exercise sessions on a daily basis.

The warm-up included static stretching and large muscle group movements on the apparatus selected to begin each exercise session. Warm-ups were 5 to 7 min in duration and mild in intensity. The subjects then began the aerobic portion of the session. Heart rates were monitored during the aerobic portion of the exercise session by the supervisory staff. Subjects were taught to monitor their own heart rates and, under guidance of the staff, adjusted the intensity of the workouts to maintain their heart rates within the target zone. The cool-down period involved mild intensity movements on the apparatus the subject was exercising on at the completion of the work period. The cool-down continued until the heart rate had dropped below 100 - 110 beats per minute.

The exercise sessions were held every day of the week. Weekday sessions occurred during three time blocks: 6:30 - 8:30 AM, 11:30 AM - 1:00 PM, and 5:00 - 7:00 PM. The exercise sessions were scheduled to maximize participation and were based on the work and school schedules of the subjects. Any subject who missed a normal session was encouraged to

attend at another time of day if possible. Weekend sessions were scheduled during a single block of time in the morning or afternoon and maximized participation. All subjects who volunteered for the study participated in the exercise sessions as required and in all testing sessions.

Aerobic capacity, blood lipids, glucose, and insulin levels were examined before and following 3 months and 6 months of the exercise program. Glucose, insulin binding, membrane fluidity, and cellular lipid composition of mononuclear leukocytes were examined before and following 7 days, 5 months, and 6 months of the exercise program. Dietary history was monitored once every four weeks throughout the duration of the exercise program. Body composition was assessed prior to the initial exercise test session and then monthly for the duration of the study.

Statistical Analyses

The original research design provided that data could be analyzed from measurements taken prior to the exercise program, at 7 days, at 3 months, and at 6 months (or postexercise program). Due to financial considerations, the measures of insulin binding and membrane fluidity of mononuclear leukocytes scheduled for 3 months were delayed until 5 months. Therefore, blood lipids, body composition, and aerobic capacity were analyzed according to the original design. Insulin binding, membrane fluidity, blood lipids, blood glucose, and body composition data were analyzed from measurements prior to the exercise program, at 7 days, at 5 months, and 6 months.

The data were analyzed by a repeated-measures multiple analysis of variance (MANOVA). Wilk's Lambda was used as the test statistic to determine overall significance. Alpha was set at .01 for all statistical analyses. If the MANOVA indicated the existence of overall statistical significance, then a univariate repeated measures analysis of variance (ANOVA) was used to determine the statistical significance of each dependent variable. A priori contrasts for differences between each test session were performed if the ANOVA yielded a statistically significant F-value. Dependent variables known to be moderately or highly intercorrelated with adiposity also were analyzed using a repeated measures analysis of covariance (MANCOVA) with initial body fat as the covariate.

The data from the membrane fluidity of the mononuclear leukocytes were analyzed as described. The insulin binding data, including total insulin receptors (R_0), high affinity, low capacity receptors (R_1), and low affinity, high capacity receptors (R_2) were not analyzed statistically due to missing data but are presented and discussed in Chapter IV.



CHAPTER IV

RESULTS AND DISCUSSION

The results of the study are presented in the following order: (a) descriptive data, (b) body composition, (c) aerobic capacity, (d) diet, (e) serum lipid measures, and (f) measures of carbohydrate metabolism. A discussion section follows the presentation of results.

Descriptive Data

The means and standard deviations for the ages and heights of the 12 subjects were 39.8 ± 8.7 years and 168.0 ± 4.9 cm respectively. Two subjects (one male and one female) smoked cigarettes, each at the rate of 20 cigarettes per day. Although not encouraged to maintain the habit, both subjects did so for the entire experimental period. One subject had adult-onset diabetes and received twice daily human insulin injections based on measured blood glucose levels.

Body Composition

Data on body weight, percent fat, fat free mass (FFM), and fat weight are presented in Table 4.1. Repeated measures MANOVA and

TABLE 4.1 Effects of Exercise on Body Composition (mean $\pm$ SEM)

	Pre-exercise	Three Month	Six Month
Weight (kg)	108.0 $\pm$ 4.4	107.1 $\pm$ 4.5	107.6 $\pm$ 4.3
Percent Fat	44.8 $\pm$ 2.1	44.0 $\pm$ 2.2	43.4 $\pm$ 2.3
FFM (kg)	59.2 $\pm$ 3.6	59.5 $\pm$ 2.7	60.4 $\pm$ 2.6
Fat Weight (kg)	48.7 $\pm$ 2.4	47.5 $\pm$ 3.7	47.2 $\pm$ 3.7

FFM = Fat Free Mass

subsequent ANOVA revealed that no significant changes occurred in any of the measures over the duration of the study. There was a small decrease in percent body fat (1.4%). This change in percent body fat reflects an 1.2 kg increase in FFM with a concurrent 1.5 kg decrease in fat weight.

Aerobic Capacity

The aerobic capacity results are presented in Table 4.2. Maximal oxygen uptakes (Max $\dot{V}O_2$) are expressed both in liters per minute (l/m) and in milliliters per kilogram of body weight per minute (ml/kg BW/m). The repeated measures MANOVA indicated the existence of overall significance ($P < .01$); however, the univariate ANOVA F-values for the separate expressions of aerobic capacity were not statistically significant. There was a .36 l/min increase in Max $\dot{V}O_2$ between the pre-

TABLE 4.2 Effects of Exercise on Aerobic Capacity (mean $\pm$ SEM)

	Pre-exercise	Three Month	Six Month
$\dot{V}O_2$ (l/m)	2.60 $\pm$.20	2.96 $\pm$.18	3.01 $\pm$.18
$\dot{V}O_2$ (ml/kg BW/m)	24.2 $\pm$ 1.9	27.7 $\pm$ 1.8	28.3 $\pm$ 1.9

exercise and three-month measures. This accounts for 88% of the total increase in Max $\dot{V}O_2$ experienced over the entire study period.

Nutritional Intake

The nutritional intake data are presented in Table 4.3. Due to incomplete dietary recalls, data from only 11 subjects were analyzed. Pre-exercise, 5-month, and 6-month data were used for the analyses. Repeated measures MANOVA and ANOVA revealed no significant changes in total caloric intake, dietary composition, polyunsaturated : saturated fat (P/S), or dietary cholesterol.

TABLE 4.3 Effects of Exercise on Caloric Intake, (mean $\pm$ SEM), Diet Composition, and the Intake of Selected Nutrients (n = 11)

	Pre-exercise	Five Month	Six Month
Total Calories	2360 $\pm$ 231	2071 $\pm$ 231	2435 $\pm$ 295
Protein %	15.5	16.7	17.9
Fat %	40.4	38.5	39.5
Carbohydrate %	41.4	43.5	42.9
Alcohol %	2.6	1.3	0.0
P/S	.36	.45	.39
Cholesterol	458 mg	350 mg	415 mg

P/S = Polyunsaturated : Saturated Fat ratio

Serum Lipids

The data on serum lipids are presented in Table 4.4. The MANOVA for the lipid measures showed there was a significant ($P < .01$) overall treatment effect. However, the univariate F-values were not significant ($P > .01$) for cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), or the atherogenic index, the CHOL/HDL ratio. While the changes observed were not individually statistically significant, it should be noted that all five of these variables were altered in the direction of decreased obesity-related risk factors. The probability of such a consistent pattern occurring purely by chance is only $P = .03$.

Pre-exercise percent fat was used as a covariate in all serum lipid analyses. The results of these analyses showed that the adjusted mean lipid values were not significantly different when pre-exercise adiposity was taken into account.

The results of the serum insulin and serum glucose measurements are presented in Table 4.5. Repeated measures MANOVA showed there was a significant ($P < .01$) overall treatment effect; however, the univariate F-values were not significant for serum insulin or serum glucose. The results of the analyses were unaffected by the inclusion or exclusion of the subject with adult-onset diabetes.

Table 4.6 contains the results of the cellular composition and membrane fluidity measurements. The overall effect, as demonstrated by a repeated measures MANOVA, was significant ($P < .01$). Univariate analyses revealed that there were significant ($P < .01$) reductions in fluorescence

TABLE 4.4 Effects of Exercise on Serum Lipids (mean $\pm$ SEM)

Serum Lipid (mg/dl)	Pre-exercise	Three Month	Six Month
Cholesterol	202.7 $\pm$ 11.3	196.4 $\pm$ 14.3	185.8 $\pm$ 12.6
Triglycerides	135.4 $\pm$ 21.5	129.3 $\pm$ 20.4	117.4 $\pm$ 12.7
HDL	46.8 $\pm$ 4.1	47.0 $\pm$ 3.7	49.0 $\pm$ 4.5
LDL	128.8 $\pm$ 10.1	123.5 $\pm$ 11.9	113.4 $\pm$ 10.8
CHOL/HDL	4.65 $\pm$ 0.45	4.35 $\pm$ 0.37	4.05 $\pm$ 0.40

HDL = High-density Lipoprotein

LDL = Low-density Lipoprotein

CHOL/HDL = Cholesterol : High-density lipoprotein ratio



TABLE 4.5 Effects of Exercise on Serum Glucose and Insulin (mean $\pm$ SEM)

	Pre-exercise	Three Month	Six Month
Glucose (mg/dl)	108.3 $\pm$ 11.3	112.8 $\pm$ 13.1	106.2 $\pm$ 11.0
	(98.0 $\pm$ 7.7)	(102.2 $\pm$ 8.3)	(96.6 $\pm$ 5.9)
Insulin (uU/ml)	31.7 $\pm$ 12.5	24.3 $\pm$ 4.2	14.4 $\pm$ 2.8
	(27.6 $\pm$ 5.0)	(21.1 $\pm$ 2.6)	(12.3 $\pm$ 2.0)

Parentheses = Mean + SEM without Insulin dependent subject

polarization and the phospholipid : protein ratio (PL/PR) as well as a significant increase in the cholesterol : phospholipid ratio (CHOL/PL). Tracer binding of ^{125}I -insulin/ 10^7 monocytes at five months was significantly greater than it was prior to the exercise regimen. Tracer binding at six months was significantly less than it was either pre-exercise or after five months of exercise. Inclusion or deletion of the subject with adult-onset diabetes resulted in no differences in the statistical analyses. The values reported include all twelve subjects.

Discussion

The analyses of the body composition measurements confirms that exercise is not a reasonable treatment to initiate substantial weight loss in severe obesity (6,7,47,74). Although Gwinup (35) and Weltman et

TABLE 4.6 Effects of Exercise on Cellular Composition and Membrane Fluidity (mean $\pm$ SEM)

	Pre-exercise	Five Month	Six Month
Fluorescence Polarization	.316 $\pm$.001	.276 $\pm$.003 ^a	.281 $\pm$.002 ^a
PHOS/PRO	.274 $\pm$.016	.237 $\pm$.012 ^a	.188 $\pm$.008 ^{ab}
CHOL/PHOS	.231 $\pm$.012	.305 $\pm$.012 ^a	.254 $\pm$.006
Tracer Binding	2.353 $\pm$.262	3.513 $\pm$.397 ^a	1.725 $\pm$.165 ^{ab}

PHOS/PRO = Phospholipid : Protein Ratio

CHOL/PHOS = Cholesterol : Phospholipid Ratio

^a = significantly different from Pre-exercise (P < .01)

^b = significantly different from Five month (P < .01)

al. (84) found significant decreases in body weight after exercise interventions, the populations used in those studies were not as obese as the subjects in this or other similar investigations.

The small decreases in percent body fat and fat weight do not reflect the total calories expended during the exercise program. There may be several explanations for this phenomenon. Pi-Sunyer (46) recently reported that when obese people enter an exercise program, they move less during the rest of the day. Another reasonable explanation is that the obese consciously or unconsciously compensate for the increased activity by eating more, but this is not confirmed in the present study. Although fluctuating slightly, the number of calories and the composition of the diet, as reported, did not change over the duration of the study. An alternative and appealing explanation is that obese subjects may become metabolically more efficient as they engage in exercise regimens. The current study provides no data to either support or reject this hypothesis.

The increase in aerobic capacity in the present study represents an overall 16% gain in Max $\dot{V}O_2$. Björntorp (6) reported a 7% increase in Max $\dot{V}O_2$ after an eight-week exercise program. Björntorp (7) found a 19% increase in Max $\dot{V}O_2$ after six weeks of training. The training programs used in those investigations consisted of light work lasting an hour but with three, 5-min exhaustive exercise bouts on an ergometer interjected. This may explain the quick rise in Max $\dot{V}O_2$.

The small increase in Max $\dot{V}O_2$ from the third month to the sixth month is likely a reflection of both the moderate nature of the exercise program (50–60% of max heart rate) and the continued severe obesity of

the participants. That is, the subjects may have achieved the maximal aerobic effect possible for the intensity of the exercise program and the fat mass they maintained.

Figure 1 is a comparison of mean heart rates prior to, after 3 months, and after 6 months of exercise training. The mean heart rates at rest, at each level of the exercise test, and throughout 5 minutes of recovery had decreased after three months of exercise training. A nonparametric sign test was used to analyze the heart rate data. The consistency of the anticipated mean heart rate changes suggests that these obese subjects did achieve a significant ($P < .01$) training effect similar to that in nonobese persons. The decreased mean heart rate response was maintained through 6 months of training, although the data at 3 months and 6 months were not significantly different. The lack of further decreases in mean heart rate responses to given submaximal work loads after 3 months of training may be due to the fact that the intensity of the exercise program was maintained throughout the experimental period at a moderate level of 50% to 60% of maximal heart rate.

Figure 2 is a comparison of mean $\dot{V}O_2$ (ml/kg/m) during the treadmill exercise test and throughout 5 minutes of recovery. The figure shows that small decreases in oxygen uptake occurred at most levels of the treadmill test after both 3 months and 6 months of training. While not statistically significant, the consistent changes in oxygen uptake at submaximal work loads indicate that a metabolic adaptation to the exercise program did occur. The subjects were able to perform at submaximal work loads more efficiently. Although slight increases in $\dot{V}O_2$

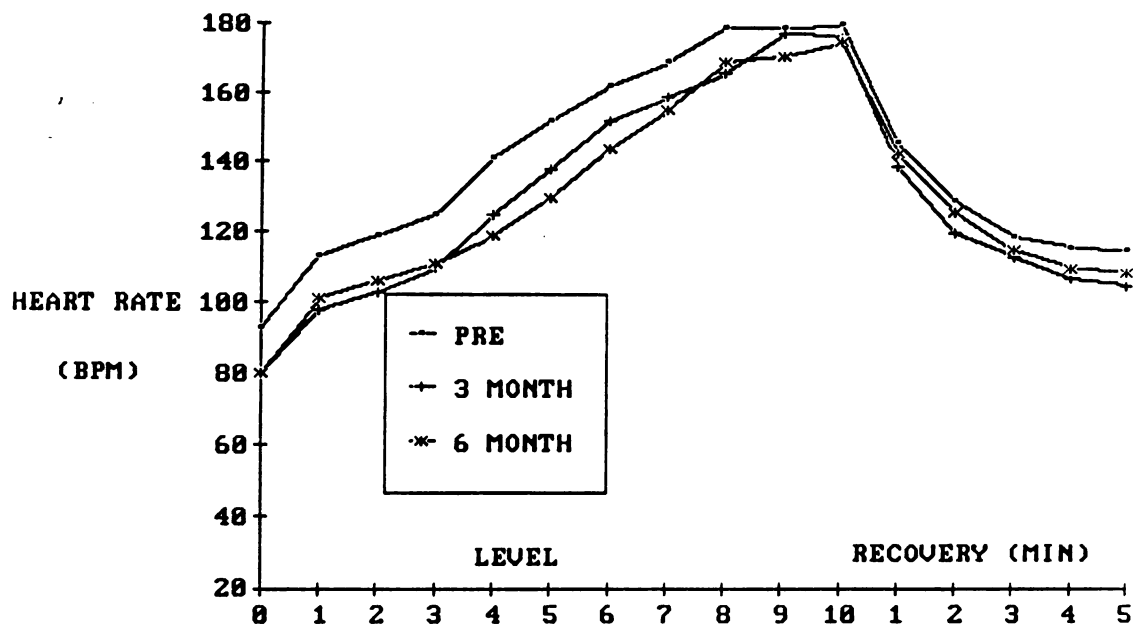


Figure 4.1 Mean Heart Rates During Treadmill Test and Recovery

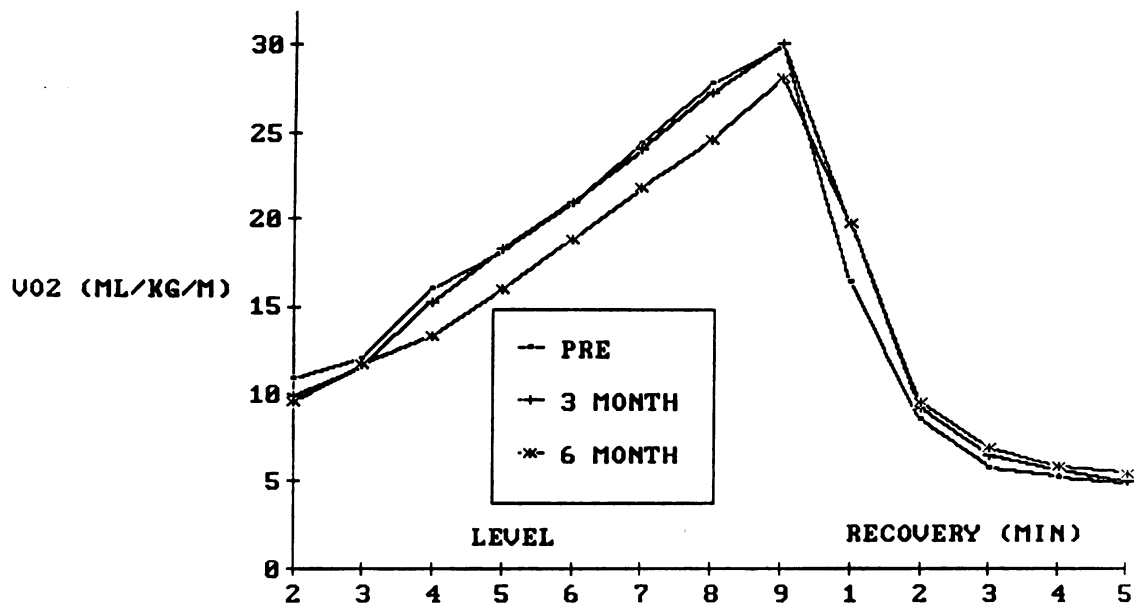


Figure 4.2 Mean $\dot{V}O_2$ During Treadmill Test and Recovery

were observed during the recovery period at 3 months and 6 months, the decline from maximal oxygen uptake through the end of one recovery minute increased 10%. The obese subjects recovered faster from a maximal effort after the training program.

The overall changes in energy metabolism parameters (heart rate and oxygen uptake) indicate that obese persons can experience a desirable training effect in response to moderate exercise. Several studies have yielded similar changes in heart rate and oxygen uptake after an exercise program (6,50,52,78).

Obesity-associated risk factors for CAD decreased independently of weight loss in this study. The primary atherogenic risk factor, the CHOL/HDL ratio, decreased 13%. While not statistically significant, the decrease is clinically important. If a CHOL/HDL ratio greater than 4.5 proves to be a clinical indication for increased risk of CAD (16), then the mean decrease in the present study from 4.65 to 4.05 considerably reduces the risk of CAD for this group of subjects. The results are bolstered by the fact that there was a decrease in CHOL/HDL ratio of all twelve participants. Due to the recent development of the atherogenic index, few studies have used the CHOL/HDL ratio to assess the risk of CAD. Weltman et al. (84) found a similar decrease (15%) in the CHOL/HDL ratio after a 10-week walking program with obese men.

Serum cholesterol has been the most frequently reported measure of serum lipids associated with CAD. Total serum cholesterol has been reported to decrease with weight loss (41,83) but to change little (54) or not at all (22) in exercise studies in which obese subjects did not achieve a loss in weight. The mean decrease in serum cholesterol in this

study was 16.9 mg/dl. While not statistically significant, the 8% decrease in serum cholesterol could be expected to lower the risk of CAD by 16% (73). Ten out of twelve subjects experienced a decrease in serum cholesterol (including both subjects who smoked).

Triglycerides (TG) and low-density lipoproteins (LDL) have been consistently shown to be reduced by exercise training. Decreases in TG and LDL both with (49,83) and without a loss in weight (6,47,83) have been reported. In the current investigation, there were nonsignificant, but clinically important, decreases of 18 mg/dl (13%) in TG and 15.4 mg/dl (12%) in LDL. These results agree with reports of studies on similar populations where weight loss did not occur (6,22,83).

The level of serum high-density lipoproteins (HDL) is inversely related to CAD (33,56). Physical activity is associated with an increase in HDL (36), while obesity is associated with a decreased HDL level (31). Studies of obese populations have reported increases in HDL with (52,78,81-83) and without weight loss (78,83). Controversy surrounds the intensity and frequency of exercise bouts necessary to increase HDL (24,85). Recently, moderate exercise (50-60% of maximal heart rate) has been reported to increase HDL. Sopko et al. (78) reported an increase in HDL in response to a vigorous walking program. Cook et al. (18) found significantly higher HDL levels in mail carriers than in postal workers who do not carry mail. However, Weltman et al. (84) reported no increase in HDL after 10 weeks of moderate exercise.

The mean increase in HDL in the present study was 2.2 mg/dl (5%). While not statistically significant, all subjects maintained or increased their HDL levels without a concurrent loss in weight. Interestingly,

both subjects who smoked experienced an increase in HDL. When combined with the results of other studies that link smoking cigarettes to decreases in HDL (81), this observation suggests that exercise may help to partially overcome at least one detrimental side effect of smoking.

Fasting serum insulin levels have been found to decrease in obese populations after exercise training (6,47,49). The mean decrease in fasting serum insulin in this study was 17.3 uU/ml (55%). The changes in carbohydrate metabolism reflected by the decreased insulin levels can be attributed in part to increased peripheral utilization of insulin by the musculature (6,7,10). Fasting serum glucose did not change over the duration of the study.

Currently, one focus of research is the insulin receptor. The increase in insulin sensitivity after weight loss or in response to exercise has been attributed to an increase in the number of insulin receptors (63,64). Increased membrane fluidity, which is dependent upon lipid constituents, is important in regulating the appearance and behavior of insulin receptors (1,62). Studies of membrane fluidity using hydrophobic probes, such as 1,6-diphenyl-1,3,5-hexatriene (DPH), provide an estimate of the average fluidity of the lipid bilayer within the membrane (63,75).

The acute (one week) effects of exercise on membrane fluidity were examined in six subjects. Fluorescence polarization decreased from .318 to .310 after one week of exercise. Although slight, this fall in fluorescence polarization indicates an increase in membrane fluidity after only one week of exercise. The increase in membrane fluidity was accompanied by a reduction in the PHOS/PRO ratio (.260 to .221) as well

as a slight decrease in the CHOL/PHOS ratio (.242 to .232).

The mean pre-exercise fluorescence polarization value of .316 in this study was significantly greater than that usually seen in normal subjects (62). However, the PHOS/PRO ratio of .274 was more than double that found in normal adults, while CHOL/PHOS ratio of .231 was significantly lower than that found in normal adults (63). Both of these factors would tend to increase rather than decrease fluidity which, in turn, would result in lower fluorescence polarization values.

Fluorescence polarization decreased significantly ($P < .01$) after five months of exercise while tracer binding significantly increased. However, in contrast, the PHOS/PRO ratio decreased significantly, and there was a significant increase in the CHOL/PHOS ratio. Fluorescence polarization was maintained at a reduced level after six months of exercise, whereas tracer binding decreased below pre-exercise levels. The PHOS/PRO ratio continued to decrease further while the increase in the CHOL/PHOS ratio was reversed. The changes in fluorescence polarization cannot be explained on the basis of any lipid changes that were measured. It is clear that exercise does alter membrane fluid behavior, but precisely how is not clear from the measurements taken.

There is another way of looking at these data. It has been shown that when proteins are introduced into a membrane bilayer, the protein contributes to the disorder of the bilayer (75). It is reasonable to consider that increased insulin receptors might have accounted for some of the contradictory changes observed. Furthermore, exercise induces alterations in the fatty acid composition of membranes (63). This also may have accounted for part of the changes recorded during and after the

treatment period.

Exercise introduces profound changes in the membrane physical state as well as in the membrane lipid composition. Such changes are associated with an increase in membrane-associated insulin receptors (37,63). An increase in insulin receptors is known to increase insulin sensitivity both after weight loss and moderate exercise. The results of this study, while not entirely explainable, demonstrate an increase in insulin sensitivity after six months of exercise training in severely and morbidly obese subjects.

Tables 4.7 and 4.8 contain data on insulin binding to monocytes. Missing data prevented statistical analysis. The data are presented because dramatic changes occurred in insulin binding which indicates there was an increase in insulin sensitivity in these obese subjects after exercise training. Table 4.7 presents the percentage of ^{125}I binding/ 10^7 monocytes. After one week of exercise, increases in binding occurred at each concentration of insulin. Binding further increased after 5 months of exercise at all concentrations except 200 ng/ml. The binding decreased below pre-exercise levels after 6 months at 1 and 10 ng/ml but remained slightly above pre-exercise levels at 50, 100, and 200 ng/ml. The small elevations in binding at 100 and 200 ng/ml become important when the number of insulin receptors are calculated from the binding data.

Table 4.8 presents the changes in insulin receptors that occurred after exercise training. Total binding capacity (R_0) increased over 300% after one week of exercise. This increase was due to an almost doubling of the high-affinity, low-capacity receptors (R_1) and over a 400%

TABLE 4.7 Effects of Exercise on the Percentage of ^{125}I Binding/ 10^7 Mononuclear Lymphocytes (number of subjects)

ng/ml	1	10	50	100	200
Pre-exercise	1.56 (12)	1.11 (12)	.62 (8)	.56 (12)	.32 (9)
One-Week	2.31 (6)	1.64 (6)	1.34 (6)	1.18 (6)	.79 (6)
Five Month	2.79 (12)	2.03 (12)	1.41 (11)	1.13 (12)	.73 (10)
Six Month	1.45 (12)	.99 (11)	.64 (10)	.57 (12)	.45 (6)

ng/ml = nanograms per milliliter

TABLE 4.8 Effects of Exercise on Insulin Binding

	Pre-exercise	One Week	Five Month	Six Month
R_0	.747	2.400	2.070	2.138
R_1	.343	.505	.656	.279
R_2	.404	1.895	1.414	1.859

R_0 = Total Binding Capacity

R_1 = High Affinity, Low Capacity Receptors

R_2 = Low Affinity, High capacity Receptors



increase in the low-affinity, high-capacity receptors (R_2). After five months of exercise, R_0 remained elevated due primarily to the 300% increase in R_2 . The value of R_0 remained almost 300% higher than the pre-exercise level after six months of exercise due entirely to increases in the low-affinity, high-capacity receptors. R_1 decreased below pre-exercise levels. Due to missing data, the conclusions that can be drawn from these results are limited. It appears that exercise training does increase the total binding capacity of monocytes in obese subjects. Further, this increase in binding may be the result of increases in R_2 . The increases in R_0 could explain the decrease observed in fasting serum insulin. That is, as insulin binding was stimulated, serum insulin levels might have decreased due primarily to the increase in R_2 .

The research hypotheses can now be examined in light of the results of the study. The study was designed to test the following hypotheses:

1. A progressive aerobic exercise program is a viable treatment for chronic obesity; specifically, that obesity-associated risk factors for coronary artery disease and adult-onset diabetes can be reduced through an exercise program whether significant weight loss occurs or not.

This hypothesis can be partially accepted. There was a trend toward decreased obesity-associated risk factors for CAD. Decreases in the CHOL/HDL ratio, serum cholesterol, TG, and LDL as well as an increase in HDL can all be regarded as beneficial effects, especially in persons who are unable to lose weight. The observed decreases in serum insulin along with any changes in membrane fluidity and membrane composition that are

associated with increased insulin sensitivity and, therefore, a reduction in the risk of adult-onset diabetes also must be considered beneficial.

2. Persons who are severely obese will adhere to a long-term exercise regimen if they are provided with proper guidance in an environment that is conducive to their participation so that they receive enjoyment from the program.

This hypothesis can be accepted. The adherence rate of 100% for the duration of the study establishes the fact that persons with severe weight problems will exercise regularly if they are provided proper supervision and motivation in an environment that affords reasonable privacy.

Due to the lack of adherence to an exercise regimen by obese subjects in previous studies, the success of the exercise program in this investigation merits further discussion. Several factors contributed to the continued participation of all subjects. The supervision and motivation provided by the exercise supervisor was an integral part of the exercise program. The atmosphere provided was free from fear of failure and guilt. That is, there was no reward or punishment associated with weight loss or gain. Participation, regardless of any weight change, was the one and only measure of success.

The immediate feedback on the results of the testing sessions also strengthened participation. Due to a lack of weight loss, changes in blood lipids, heart rates, or aerobic capacity were regarded as important indicators of the success of the program for each individual. Ideally, the subjects participated in the study because they wanted to become healthier. Immediate feedback that demonstrated gains in health-related

measures, however small, was received with enthusiasm and served as inspiration for continued participation.

The secluded environment allowed each subject to participate freely without fear of observation by others not in the study. The exercise sessions were designed to help overcome any fear or embarrassment that the subjects might have felt. Personnel involved in the testing sessions were instructed to avoid any behavior which could be misinterpreted by the subjects as being degrading. There was no concealed laughter for any reason, and there was no staring at subjects who were engaged in any tests.

Finally, the subjects developed a strong bond with the program leader. Typically, exercise leaders are selected because they have achieved a certain level of fitness. They often are the epitomy of good looks as well as health and provide a picture of an unattainable goal for severely obese persons. The exercise program leader was initially overweight and provided a certain 'kinship' with the subjects. While their personal dedication might have wavered, the subjects were committed to the program leader and this relationship was crucial to their continued participation. It may be impractical for all exercise programs to attempt to develop such strong personal relationships. However, if an exercise program is, in fact, worthwhile and important to the health and well-being of the participants, any factor which contributes to the success of the program must be considered important.

3. Short (1-week) and long (5- and 6-month) term changes in insulin binding, membrane fluidity, and cellular lipid composition of mononuclear leukocytes in the severely obese

will reflect positive changes in insulin sensitivity in response to an exercise program.

This hypothesis can be accepted in part. Positive changes in membrane fluidity did occur. These changes may or may not have been due to alterations in cellular lipid composition. However, the exercise training did have a significant impact on insulin sensitivity regardless of the mechanism. Due to a lack of sufficient data, no conclusions regarding insulin binding can be drawn.

CHAPTER V

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The purpose of the current study was to determine if obesity-associated risk factors for coronary artery disease (CAD) and adult-onset diabetes (AOD) can be reduced through participation in a progressive program of moderate aerobic exercise. Twelve severely and morbidly obese men and women, who had been screened for the presence of CAD, participated in the study. The subjects exercised a minimum of one hour per day, four days per week, at 50-60% of their maximal heart rates. The duration of the study was 6 months.

The overall results of the serum lipid measures showed a decrease in total cholesterol, TG, LDL, and the CHOL:HDL ratio along with an increase in HDL. The CHOL:HDL ratio was reduced from 4.65 to 4.05 after six months of exercise. Total cholesterol was reduced 8% over the course of the study which represents a 16% decrease in the risk of CAD.

The results for membrane fluidity and membrane composition of mononuclear leukocytes were significant ($P < .01$). The changes in membrane fluidity suggest an increase in insulin sensitivity after exercise training.

The moderate progressive aerobic exercise program was successful. The twelve subjects completed the entire six months of training. The

study provided a secluded environment for the participants to exercise. The subjects generally felt comfortable in their surroundings, and any embarrassment they might have felt in a more conventional exercise setting was largely eliminated. The exercise program supervisor was firm yet supportive and understanding of the problems extremely obese persons face when exercising. The atmosphere created was critical in overcoming the discomfort and boredom of the exercise regimen and in making the participants feel as comfortable as possible.

Conclusions

1. The moderate progressive exercise program was successful. The success of the program establishes the fact that provided the program is moderate in intensity, and provides a proper environment, proper supervision, and adequate motivation, persons who are severely obese will exercise regularly.
2. There was a small but noticeable trend for normalization of serum lipids after six months of exercise training. This trend was apparent in spite of no decrease in body weight over the course of the study.
3. The changes in membrane fluidity and composition after exercise training are associated with an increase in insulin sensitivity. These changes occurred independently of changes in weight.

Recommendations

1. Further studies should be undertaken with a larger and more homogenous subject population. The small sample size, and the consequent need to pool already heterogenous data across sexes, probably inflated the within group variability which, in turn, may have masked statistical significance in some cases. Consequently, although clinically important results were achieved, the heterogeneity of the sample affected the statistical outcome.
2. While the exercise program was successful, six months may be too long to expect persons who are morbidly obese not to lose weight. "Feeling better physically and an increased aerobic capacity" are insufficient motivational factors when a significant (>50 lb) amount of weight loss is desired.
3. Further research of membrane fluidity and lipid and protein composition of cellular membranes is needed to provide an understanding of the membrane changes associated with the insulin receptor. The exercise training had a profound effect on the lipid composition of the mononuclear leukocytes. Analysis of the fatty acid composition of the lipid membrane components may help to reveal how exercise affects cells to increase insulin sensitivity.

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APPENDICES



APPENDIX A

TREADMILL PROTOCOL



Treadmill Protocol

Stage	Speed (MPH)	Grade	VO ₂ (ml/kg/min)	METS
1	1.5*	0.0	7.6	2.1
2	2	0.0	8.7	2.5
3	2	2.5	11.2	3.2
4	3	2.5	15.1	4.3
5	3	5.0	19.0	5.4
6	3	7.5	22.4	6.4
7	3	10.0	26.0	7.7
8	3	12.5	29.7	8.5
9	3	15.0	33.3	9.5
10	3	17.5	36.7	10.5
11	3	20.0	40.6	11.6
12	3	22.5	44.1	12.6
13	3	25.0	47.6	13.6

This treadmill protocol is a combination of the first two stages of the Naughton* (61) and subsequent stages of the Balke substandard and standard treadmill tests (5). Each stage lasts two minutes.

* This is the lowest speed attainable by the treadmill in the Center for the Study of Human Performance laboratory and replaces the first stage of the Naughton protocol.

Insulin Binding and Membrane Fluidity Methodology

Na-¹²⁵I-iodide was purchased from New England Nuclear Corp. (Boston). Enzymo-Beads for lactoperoxidase iodination were obtained from Biorad Corp. (Richmond, CA). Purified monocomponent insulin was obtained from Novo Corporation (1,6 diphenyl, 1, 3, 5, hexatriene (DPH) (95% pure by thin layer chromatography) and purified phospholipids including phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin were purchased from Sigma Chemical Co. (St. Louis). Silica gel-coated plates (25mm thickness) were obtained from E Merck, Darmstadt, Germany.

Blood in heparinized tubes was received via overnight express mail service. Mononuclear cells were harvested following separation by Ficoll-Hypaque gradients. This cell fraction was used for both insulin binding and cell lipid analysis. Plasma was stored at -40 C for subsequent analyses.

¹²⁵I -insulin was prepared by the lactoperoxidase method. Specific activities of these preparations ranged from 80 to 280 uCi/ug. Insulin binding studies were performed at 25 C. It should be noted that all binding data were obtained using the entire mononuclear leukocyte fraction, but were normalized to a final monocyte concentration of 1×10^7 cells/mL.

Intact mononuclear cells were washed in Tris buffer (pH 7.4) and lipids were extracted by the method of Folch. Cholesterol content was



determined calorimetrically. Phospholipid species were separated and quantitation performed.

Membrane fluid behavior has been shown to correlate with the rotation of the fluorescent dye molecule DPH within the membrane. Resistance to rotation is provided by the surrounding lipid matrix and can be assessed by the relative fluorescent intensities of polarized light emerging parallel and perpendicular from the sample, following excitation by a vertically polarized light. Such measurements were obtained using an Elscint MV-1a microviscosimeter (Hackensack, NJ).

Fluorescence polarization (FP) are provided by the equation:

$$FP = \frac{I_{11} - I_1}{I_{11} + I_1}$$

where I_{11} and I_1 are the fluorescent intensities emerging parallel to the original light source.

For these studies, mononuclear cells were resuspended in phosphate-buffered saline (PBS) pH 7.4 at a concentration of $1 - 2 \times 10^6$ cells/mL. One milliliter of cell suspension was mixed with 1 mL of 2×10^{-6} mol/L DPH in PBS and incubated at room temperature (25 C). Cells were washed twice in PBS before resuspension in 2 mL PBS. The suspension was transferred to quartz cuvette and placed in the MV-1a microviscosimeter for determination of the FP value at 25 C, after correction for light scatterings using a whole-cell suspension.

Plasma membranes were isolated from five preparations on mononuclear cells following cell disruption by means of differential centrifugation.

Use of DPH to assess membrane fluidity under these experimental conditions rests on three assumptions: (1) that this probe localizes within the plasma membrane bilayer and is thus a reflection of the



subcellular locus, (2) that differences in cellular lipid composition of these cells reflect differences within the plasma membrane, and (3) that lipid composition and membrane fluid behavior of a subset of mononuclear cells (ie, monocytes) is comparable to that of the entire mononuclear cell fraction. There is ample evidence to support the assumption that DPH does monitor the fluidity of the area surrounding the insulin receptor.

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