THE EFFECTS OF SERUM LIPID LEVELS ON THE EXERCISE STRESS TEST RESULTS IN HYPERLIPIDEMIC SUBJECTS

by

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CHAPTER I

INTRODUCTION

The exercise stress test is often used as a non-invasive method of discovering latent coronary artery disease (CAD) in asymptomatic patients or confirming suspected CAD in symptomatic patients. When used for these purposes, the exercise stress test is said to be positive, meaning predictive of CAD, when there is abnormal S-T segment depression on the exercise electrocardiogram (E-ECG) (Constant, 1973; Ellestad, 1975).

Patients with hyperlipidemia are reportedly at increased risk of developing CAD (Gotto, Phil, Gorry, Thompson, Cole, Trost, Yeshurun, & Debakey, 1975). Subsequently, they may be advised to undergo an exercise stress test as a screen for CAD. Carlson, Ecklund, and Ollson (1975) found that exercise induced S-T segment depression was more frequent in asymptomatic hyperlipidemic men than in asymptomatic normolipidemic men. They suggested that the increased frequency of S-T segment depression in the hyperlipidemic men was due to myocardial ischemia caused by a presumed greater amount of coronary atherosclerosis secondary to their elevated serum lipid levels. However, Borer, Brensike, Redwood, Itscoitz, Passamani, Stone, Richardson, Levy, and Epstein (1975)

found that of 30 asymptomatic hyperlipidemic patients who all had S-T segment depression on the E-ECG, only 11 had significant CAD by angiography. In some hyperlipidemic patients then, S-T segment depression on the E-ECG occurs in spite of no or insignificant CAD. This observation makes one question the validity of the exercise stress test in predicting the presence or absence of CAD in hyperlipidemic patients. Additionally, it makes one wonder what is causing the S-T segment depression on the E-ECG in some hyperlipidemic patients, if not CAD.

There are conditions other than CAD, such as those which obstruct coronary blood flow, decrease cardiac output, or disturb cardiac cell function, which have been found to bring about S-T segment depression on the E-ECG (Constant, 1973; Ellestad, 1975). Elevated serum lipid levels, such as those of patients with hyperlipidemia, have been found to be associated with some of these conditions (Constantino, Merskey, Kudzma, & Zucker, 1977; Cullen & Swank, 1954; Forrest & Cushley, 1977; Gerrity & Schwartz, 1977; Mustard, Moore, Packham, & Kinlough-Rathbone, 1977; Shattil, Anaya-Calindo, Bennet, Colman, & Cooper, 1975). For instance, elevated serum lipid levels are associated with increases in platelet aggregation and thrombi formation (Constantino, et al, 1977; Shattil et al., 1975), and these two conditions may cause obstruction of coronary blood flow and subsequently may result in S-T segment depression on the E-ECG. It appears, then, that there is a relationship between elevated serum lipid levels and

some of the conditions other than CAD which cause S-T segment depression on the E-ECG. If this is true, there may also be a relationship, independent of CAD, between the elevated serum lipid levels of some hyperlipidemic patients and the S-T segment depression seen on their E-ECGs. The focus of this study is to investigate the relationship between elevated serum lipid levels and S-T segment depression on the E-ECG.

Review of the Literature

Reviewed in this section is the literature dealing with the following topics: the genesis of S-T segment depression, the mechanisms which cause S-T segment depression and the clinical conditions and medications associated with S-T segment depression on the E-ECG, the relationship between serum lipid levels and conditions associated with S-T segment depresssion on the E-ECG, the validity and reliability of the exercise stress test in detecting CAD, the relationship between elevated serum lipid levels and S-T segment depression on the E-ECG, the relationship of serum lipid levels to the progression and regression of coronary atherosclerosis, the genesis and treatment of hyperlipidemia, and compliance with lipid lowering diets.

The Genesis of S-T Segment Depression:

The electrocardiogram (ECG) is a recording of the electrical activity produced by the depolarization and repolarization of the cardiac cells working as a unit,

a phenomenon that involves the regulated flow of ions across each cell membrane. Constant (1973) suggests that there is normally no significant flow of ions during the middle part of the repolarization process, which is represented by the S-T segment; all other ECG segments represent ionic influx and/or efflux (see Appendix B, Figure 7). The regulation of ionic flow across the membrane is determined by what Constant calls the "dielectric property" of the membrane, "the ability of the membrane to keep ions or electrons more on one side than the other" (Constant, 1973, p. 225). This dielectric property appears to be dependent on intra and extracellular fluid, electrolyte, and solute concentrations, membrane permeability, and, in particular, the energy dependent sodium pump (Hillis & Braunwald, 1977). Constant (1973) theorized that the loss of the membrane's dielectric property results in abnormal ionic flow. Since the S-T segment represents a phase where there is normally no important ionic flow, ECG changes secondary to abnormal ionic flow will be seen in any or all segments except the S-T segment. Subsequently, when the electrocardiographic changes elevate the baseline, the S-T segment will appear depressed; conversely, when they depress the baseline, the S-T segment will appear elevated (see Appendix B, Figure 8). S-T segment depression usually represents electrical (ionic) disturbances in the subendocardial cells, whereas S-T segment elevations usually represent a disturbance of the epicardial cells (Constant, 1973; Ellestad, 1975).

The Mechanisms Which Cause S-T Segment Depression and the Clinical Conditions and Medications Associated with S-T Segment Depression on the E-ECG:

S-T segment depression is caused by the mechanisms of myocardial ischemia, myocardial hypoxia, direct disturbance of the dielectric property of the subendocardial cell membranes, and possibly some unknown mechanisms. Conditions which are associated with S-T segment depression may in some way initiate or promote one of these mechanisms.

Myocardial ischemia and hypoxia can disturb the dielectric property of the subendocardial cell membranes and thereby cause S-T segment depression (Constant, 1973). Because the subendocardium and the rest of the myocardium function under a system of strict oxygen supply and demand, the S-T segment depression caused by ischemia or hypoxia may appear whenever the myocardium's demand for oxygen exceeds its supply. At rest, the myocardium extracts a large percentage of the oxygen in the resting coronary blood flow, leaving little reserve to draw upon when its demand for oxygen is increased. Subsequently, under conditions of increased demand, the myocardial oxygen supply is normally increased by a compensatory increase in the coronary blood flow (Ellestad, 1975). Myocardial ischemia occurs whenever the coronary blood flow does not meet the oxygen demand. Myocardial hypoxia occurs whenever the oxygen supply is inadequate to meet the demand despite an adequate perfusion (Hillis & Braunwald, 1977).

Myocardial oxygen demand is increased by conditions which cause an increase in heart rate, blood pressure, cardiac output, myocardial contractility, and/or left ventricular work (DeVries, 1966). Exercise increases all of these parameters. Aortic stenosis increases left ventricular work by obstructing the flow of blood out of the heart. Hyperthyroidism may increase some or all of the above parameters by increasing the metabolic rate; hyperthyroidism is associated with an earlier onset of S-T segment depression on the exercise ECG, especially in the presence of CAD (Ellestad, 1975).

Coronary perfusion is decreased or its increase in response to an increase in demand is limited, by conditions which decrease or limit cardiac perfusion pressure and/or cardiac output, and by conditions which obstruct coronary blood flow. Tachy and brady arrhythmias and aortic stenosis can limit cardiac output and perfusion pressure. Alcohol, especially in chronic abusers with underlying heart disease, has been shown to limit cardiac output during exercise (Ellestad, 1975). Coronary blood flow can be obstructed by arterial stenosis secondary to CAD or other causes, such as arterial obstruction, thrombi, microemboli, and increased blood viscosity. Platelet and erythrocyte aggregation are causes of microemboli and increased blood viscosity.

An inadequate myocardial oxygen supply despite adequate perfusion is caused by anemia and/or conditions

that decrease the oxygen-carrying capacity of the erythrocyte.

Myocardial ischemia and hypoxia are not the only mechanisms which can cause S-T segment depression on the E-ECG. Kawaii and Hultgren (1964) studied the effect of digitalis on the S-T segments of patients with known or suspected cardiac disease and a group of normal controls. Over 50% of the normal subjects developed S-T segment depression on the E-ECG when taking digitalis. Initially they hypothesized that the digitalis had caused the S-T segment depression by causing myocardial ischemia or hypoxia because the amount of S-T segment depression was increased by hypoxia and reduced by oxygen administration. However, when they found that nitroglycerine did not reduce the amount of S-T segment depression during exercise and that hypoxia did not produce S-T segment depression during exercise in the subjects when they were not taking digitalis, it became clear that their hypothesis was inaccurate. Kawaii and Hultgren then theorized that digitalis may cause potassium loss from the myocardium and thereby cause S-T segment depression on the E-ECG. Another explanation for digitalis-induced S-T segment depression is related to the observation that digitalis causes calcium ions to be retained in the myocardial cells, an effect which "may inhibit the cell from complete relaxation" (Ellestad, 1975, p. 244). This would allow less time between contractions for myocardial cell per-

fusion, which may lead to myocardial ischemia. From the above, it may be suggested that digitalis has some acute effect that may directly disturb the dielectric property of the cardiac cell membrane to cause abnormal potassium efflux, calcium retention, or some other ionic imbalance that can cause S-T segment depression on the E-ECG.

The following conditions are all associated with S-T segment depression on the E-ECG; the actual cause of S-T segment depression in each of these conditions is unknown. Acute myocarditis and pericarditis may be associated with S-T segment changes which are occasionally seen as S-T segment depression (Constant, 1973). Alkalosis, especially if secondary to hyperventilation or diuretic-induced potassium depletion, may be associated with S-T segment depression at rest or with exercise (Ellestad, 1975). Phenothiazines are associated with S-T segment depression, T-wave flattening, and Q-T interval prolongation. This effect of phenothiazines may be due in part to their ability to block the uptake of catecholamines by the cells, producing elevated circulating levels of the catecholamines, particularly norepinephrine (Ellestad, 1975). Lithium is associated with T-wave flattening or inversion, Q-T prolongation, and S-T segment depression, especially with large doses and underlying heart disease. Although the serum potassium is normal, there is evidence of intracellular potassium depletion with lithium adminstration (Ellestad, 1975). Ingestion of food, particularly food

containing glucose, can be associated with abnormal S-T segment depression and T-wave inversion even in normal patients at rest. In this instance, the effects usually occur about one hour past the meal, and are exaggerated in patients with heart disease (Constant, 1973). Quinidine and Procainamide may both prolong the P-R interval, widen the QRS complex, and produce S-T segment and T-wave changes (Gettes, 1971).

From the above discussion, it can be suggested that S-T segment depression on the E-ECG can be caused by conditions which cause myocardial hypoxia or ischemia, by conditions which directly disturb the dielectric property of the cardiac cell membrane, or by conditions which cause some other unknown effect.

The Relationship Between Serum Lipid Levels and the Conditions Associated with S-T Segment Depression on the E-ECG:

Coronary atherosclerosis can cause myocardial ischemia and thereby cause S-T segment depression on the E-ECG. There is considerable evidence that suggests a positive correlation between chronic hyperlipidemia and coronary atherosclerosis. Platelet survival time is shortened in CAD (Richie & Harker, 1977). Mustard and Murphy (1962) found that platelet survival time was lengthened by changing from a diet rich in saturated fat and cholesterol to one low in saturated fat and cholesterol but rich in unsaturated fat. Platelet survival time was

further lengthened by changing to a low fat diet. Steele and Rainwater (1978) found that "men with CAD and increased serum cholesterol and triglyceride levels have more abnormal average values for platelet survival time than men with CAD who do not have hyperlipidemia" (p. 366). They also found that decreases in serum triglyceride and cholesterol levels were associated with increases in platelet survival time. At the present time it is unclear if lipids directly alter platelet survival time. However, it is known that platelet survival time is directly decreased by endothelial cell injury (Ross & Harker, 1976). This introduces another relationship between elevated serum lipid levels and coronary atherosclerosis, that of the association of elevated serum lipid levels to endothelial cell injury. Endothelial cell injury is the primary event that initiates the process of atherosclerosis. Mustard, Moore, Packham, and Kinlough-Rathbone (1977) believe that hyperlipidemia potentiates and may even initiate endothelial cell injury. They noted that in the presence of hypercholesteremia, one mechanically induced endothelial cell injury produced an atheroma that could only be produced by six mechanically induced injuries if the cholesterol level was normal. Gerrity and Schwartz (1977) found that alterations in the aortic endothelium of pigs occurred as early as two weeks after the initiation of a hypercholesteremia diet. They suggested that this early endothelial injury "may involve

alterations in the membrane function resulting in increased permeability /of the membrane/..." (p. 217). Hyperlipidemia is also associated with other components of the atherosclerotic process including platelet aggregation and thrombi formation, which are described below (Carvalho, Colman, & Lees, 1974; Constantino, Merskey, Kudzma, & Zucker, 1977). It is apparent from the above discussion that hyperlipidemia is positively associated with coronary atherosclerosis. Coronary atherosclerosis may represent a chronic indirect method by which hyperlipidemia may cause myocardial ischemia and subsequently S-T segment depression during exercise.

Platelet aggregation may be associated with S-T segment depression because of its role in the development of atherosclerosis, but also it may be associated with S-T segment depression through more acute causes of myocardial ischemia, such as increased blood viscosity, microemboli occlusion of small vessels, and obstruction of blood flow in larger vessels. Iacano (in Pritkin, Kern, Pritkin, and Kaye, Note 1) changed the diet of normolipidemic subjects from the standard American diet of 40-45% fat to a 25% fat diet. He found a 50% decrease in platelet aggregation associated with the decrease in serum cholesterol that occurred on the low fat diet. When the standard diet was resumed, the platelet aggregation returned to the previous level. Renaud, Kinlough-Rathbone, and Mustard (1970) studied the effects of a high

lipid diet on platelet adhesiveness and thrombotic tendency in rats. They found that the rats had more platelet sensitivity to thrombin, as manifested by an increase in platelet aggregation, when on a high saturated fat diet than when on a low saturated fat/high unsaturated fat diet. Renaud et al. suggested that saturated fats may alter the fatty acids in the platelet membrane which might increase platelet aggregation. Carvalho et al. (1974) found that hyperlipidemia was associated with an increased platelet sensitivity to aggregation. Shattil, Anaya-Calindo, Bennet, Colman, and Cooper (1975) later found that in hyperlipidemic patients, the increased sensitivity of the platelets to aggregation was associated with a higher cholesterol content in the platelet membrane, a finding similar to that suggested by the study of Renaud et al. (1970). The positive association between hyperlipidemia and platelet aggregation suggests that platelet aggregation may be an acute indirect method by which hyperlipidemia may cause myocardial ischemia and subsequently S-T segment depression during exercise.

Thrombi formation may cause myocardial ischemia by obstructing coronary blood flow and thereby causing S-T segment depression during exercise. If there is a positive correlation between hyperlipidemia and platelet aggregation, it follows that there will also be a positive correlation between hyperlipidemia and thrombi formation. This is because "the platelet aggregate serves as a focus for the local acceleration of the coagulation

mechanism..." (Mustard et al., 1977). Platelet aggregation allows membrane phospholipoprotein (platelet factor 3) to become available for the clotting mechanism; platelet aggregation also releases a number of clotting factors which are closely associated with the platelet surface. As noted before, hyperlipidemia is positively associated with endothelial cell injury. Endothelial injury contributes to thrombi formation by exposing subendothelial collagen. When platelets interact with subendothelial collagen, clotting factor XI can be activated (Mustard et al., 1977). Hornstra (in Renaud, 1977) noted that a diet high in saturated fats predisposes animals to thrombosis. O'Brien (in Steele & Rainwater, 1977) noted that clotting time was shortened after the ingestion of a meal heavy in saturated fats; conversely, clotting time was prolonged after the ingestion of a meal low in saturated fats but high in unsaturated fats. Constantino, Merskey, Kudzma, and Zucker (1977) measured levels of blood coagulation factors in people with hyperlipidemia. High cholesterol levels were associated with high levels of prothrombin and Factor X; high triglyceride levels were associated with high levels of prothrombin and factors X, VIII, and IX. As with platelet aggregation, it appears that thrombi formation may be an acute indirect method by which ischemic S-T segment depression during exercise may be related to hyperlipidemia.

Arterial and arteriolar constriction can limit myocardial perfusion and thereby cause myocardial ischemia and S-T segment depression. Two factors involved in platelet aggregation, prostaglandin endoperoxides and thromboxane A_2, can cause contraction of arterial smooth muscle (Mustard et al., 1977). Possibly because hyperlipidemia is associated with an increase in platelet aggregation, hyperlipidemia may also be associated with arterial constriction and the ischemic S-T segment depression it can cause.

Erythrocyte aggregation, like platelet aggregation, can obstruct coronary blood flow to cause myocardial ischemia and S-T segment depression. Cullen & Swank (1954) fed hamsters meals high in saturated fat and then observed the effects on erythrocytes through their transparent cheek pouches. Within four to seven hours after the meal, the erythrocytes had formed aggregations large enough to block many capillaries. The amount of oxygen carried by the erythrocytes was also decreased, possibly due to the decreased surface area of the erythrocytes or due to the slower flow of the blood. Reflecting this, the arterial PO_2 fell 32%; it did not return to the pre-meal level for up to 72 hours later. It may be that erythrocyte aggregation is another acute indirect method by which hyperlipidemia may be associated with myocardial ischemia and S-T segment depression during exercise.

Conditions which increase myocardial oxygen demand will cause myocardial hypoxia or ischemia and S-T segment depression if the coronary blood oxygen supply cannot meet the demand. Henry (1977) studied the effect of hypercholesteremia on the oxygen consumption of rabbits. He concluded that "hypercholesteremia may be associated with a generalized hypermetabolic state, but /it/ does not appear to increase the myocardial uptake /of oxygen/ under controlled conditions" (p. 294). This would suggest that hypercholesteremia may cause an effect similar to that of hyperthyroidism, which, as discussed previously, increases the myocardial oxygen demand. This may suggest that when coronary perfusion or coronary blood oxygenation is limited, as by CAD or anemia respectively, hypercholesteremia may cause myocardial hypoxia or ischemia and subsequently S-T segment depression during exercise by increasing the myocardial oxygen demand.

As observed previously, S-T segment depression may occur in conditions which do not cause myocardial ischemia or hypoxia. Constant (1973) noted that S-T segment depression may represent a disruption of the dielectric property of the cardiac cell membrane. Conditions which interfere with the cardiac cell membrane functions may disturb this dielectric property. Hyperlipidemia appears to alter the membrane functions on endothelial cells, platelets, and erythrocytes (Cullen & Swank, 1954; Gerrity & Schwartz, 1977; Renaud et al., 1970; and

Shattil et al., 1975). Could hyperlipidemia alter the membrane function in cardiac cells? Alivisatos, Papastavrou, Drouka-Lipati, Molyvdas, and Kikitopoulou (1977) studied the effects of a small increase in the cholesterol content of the membranes of dog purkingie fibers in vitro. They found that the spontaneously generated action potentials of these fibers were increased both in amplitude and frequency with an increase in membrane cholesterol. Stevens and Shinitzky (1977) studied the effect of increasing the cholesterol content of the membranes of snail ganglia, which have a dielectric property like that of the cardiac cell membranes. With cholesterol enrichment, the action potential height decreased, an effect opposite to that found in the study of Alivisatos et al., Stevens and Shinitzky noted that there was no alteration in the resting membrane potential. Subsequently they suggested that cholesterol enrichment of the membrane did not affect the sodium-potassium pump but rather disturbed the "channels and gates which are essential for action potential production" (p. 268), indicating that cholesterol decreases active inward ionic flow. They further suggested that increasing the membrane cholesterol content increases membrane microviscosity and decreases membrane fluidity, to alter cellular activity. Forest and Cushley (1977) found that in a model membrane, increasing the saturated cholesterol ester content in relation to the free cholesterol content increases the membrane's permeability to

ions tenfold. An increase in membrane permeability to ions would undoubtably disturb the dielectric property of the membrane. The opposite results of Alivisatos, et al., and Stevens and Shinitzky were perhaps caused by the use of different cholesterol preparations. In any case, these studies suggest that hyperlipidemia may alter cell membrane lipid composition, membrane function, and possibly the dielectric property of some cell membranes. While it is not known at this time if hyperlipidemia induces any of these changes in cardiac cell membranes in vivo, in theory hyperlipidemia could directy disturb the dielectric property of the cardiac cell membrane to cause S-T segment depression.

Validity and Reliability of the Exercise Stress Test:

The validity of a test is the degree to which it measures what it is designed to measure, whereas the reliability of a test is the degree to which independent measurements of the same phenomenon are consistent (Smith, 1975). In much of the exercise stress test literature these terms are confused; exercise stress test validity is often referred to as reliability and there is usually no term used to denote what is actually the reliability. Reliability and validity will be used here as defined by Smith (1975).

It has been generally assumed that significant S-T segment depression on the E-ECG (a positive stress test) predicts the presence of CAD, while no or insignificant S-T segment depression on the E-ECG (a negative stress test) predicts the absence of CAD. Subsequently, the

validity of a stress test is its accuracy in predicting the presence or absence of CAD in a given population; it can be determined by comparing the stress test results with the standard of coronary angiography (this comparison is limited in that the former measures physiological changes, which is an indirect reflection of the anatomical changes measured by the latter). Positive stress test in patients with positive angiograms (significant coronary atherosclerosis by angiography) are called true positive stress tests. Positive stress tests in patients with negative angiograms (no or insignificant coronary arteriosclerosis by angiography) are called false positive stress tests. Negative stress tests in patients with negative angiograms are called true negative stress tests, while negative stress tests in patients with positive angiograms are called false negative stress tests. The sensitivity of a stress test is its validity in predicting the presence of CAD in a given population; it is the number of patients with true positive stress tests out of the total number of patients with positive angiograms (true positives plus false negatives) expressed as a percent. The specificity of a stress test is its validity in predicting the absence of CAD; it is the number of patients with true negative stress tests out of the total number of patients with negative angiograms (true negatives plus false positives) (Ellestad, 1975).

Zohman and Kattus (1975) reviewed the factors affecting the validity of the stress test. Validity was found to be increased by (1) stressing patients to symptom-limited maximal effort rather than submaximal (85% of maximal) effort;

(2) allowing patients a trial test to familiarize themselves with the procedure; (3) allowing patients enough time to achieve a steady state at a workload before taking measurements; and (4) eliminating patients with known causes of false negative or false positive tests. Other factors affecting the validity of the stress test include (1) the degree of S-T segment depression required to call a stress test positive; (2) the use of other parameters in the criteria for positivity; e.g., hypotension and angina; (3) reliability factors; e.g., discrepancies due to intra and interobserver variation in interpretation of the E-ECG: and (4) the prevalence of CAD in the population. In addition, the validity of the stress test is determined by the validity of the angiogram. Angiogram validity is affected by (1) the degree of coronary atherosclerosis required to consider an angiogram positive; e.g., 50% occlusion is less likely to cause myocardial ischemia than 75% occlusion; and (2) the reliability factors; e.g., the discrepancies in intra and interobserver variation in interpretation of the angiograms. The reader is referred to their article for additional information.

It is understandable from the above discussion of the number of factors affecting the stress test validity that the validity of the stress test in predicting the presence or absence of CAD is currently being debated in the cardiovascular literature (Bonoris, Greenberg, Christison, Castellanet, & Ellestad, 1978; Borer, Brensike, Redwood, Itscoitz, Passamani, Stone, Richardson, Levy, &

Epstein, 1975; Epstein, 1979; Erikssen, Enge, Forfang, & Storstein, 1976; McNeer, Margolis, Lee, Kisslo, Peter, Kong, Behar, Wallace, McCants, & Rosate, 1978; Weiner, Ryan, McCabe, Kennedy, Schloss, Tristani, Chaitman, & Fisher, 1979; Zohman & Kattus, 1977). Those who question the validity of the stress test largely focus on its failure to predict the presence or absence of CAD in certain populations. They did not attempt to suggest what could have caused the S-T segment depression on the E-ECG, if not CAD. It must be remembered that S-T segment depression on the E-ECG is a reflection of electrical disturbances in the subendocardium, and these disturbances can be caused by a number of conditions other than CAD (Constant, 1973; Ellestad, 1975). In the foregoing review of the literature, elevated serum lipid levels were found to be associated with several of the conditions other than CAD that are known to cause S-T segment depression on the E-ECG. The next few studies are reviewed to determine if there is a relationship between elevated serum lipid levels and S-T segment depression on the E-ECG.

The Relationship Between Elevated Serum Lipid Levels and S-T Segment Depression on the E-ECG:

Carlson, Ekelund, and Olsson (1975) studied the frequency of exercise-induced S-T segment depression in asymptomatic men with various forms of primary hyperlipidemia. One hundred and thirty men with fasting serum cholesterol levels more than 350 mg/dl or fasting serum

triglyceride levels more than 3.5 mmol/l, and 59 age-matched normolipidemic controls, performed maximal exercise stress tests on a bicycle ergometer. S-T segment levels were measured at 0.08 seconds after the J point and were classified into seven levels according to slope and voltage. Their results showed first that exercise-induced S-T segment depression increases in frequency with age in both hyperlipidemic and normolipidemic men. Second, exercise-induced S-T segment depression (more than 0.05 mV) is significantly more common in men of all hyperlipidemic types than in normolipidemic men. It is particularly more frequent in younger men with types IIa and IV hyperlipidemia and in older men with types IIb and III.

James, Glueck, Fallat, Millett, and Kaplan (1976) studied the relationship between hyperlipidemia and exercise-induced S-T segment depression in children. One hundred and three normolipidemic children and 82 children with familial hyperlipoproteinemia (74 with primary hypercholesteremia and 8 with primary hypertriglyceremia) performed maximal stress tests on a bicycle ergometer. S-T segment depression of 1 mm or more, 0.06 seconds after the J point, below the P-Q segment, was considered positive. S-T segment depression was not present before the exercise in any of the children. Exercise-induced S-T segment depression was three times more frequent in the hyperlipidemic boys than in the normolipidemic boys; it was no more frequent in the hyperlipidemic girls than in the normolipidemic girls.

Borer, Brensike, Redwood, Itscoitz, Passamani,

Stone, Richardson, Levy, and Epstein (1975) studied the relationship between hyperlipidemia, exercise-induced S-T segment depression, and coronary atherosclerosis. Eighty-nine patients with type II hyperlipoproteinemia underwent maximal exercise stress tests which were followed within three days by coronary angiography. The exercise stress tests were performed on a bicycle ergometer and were considered positive "if, 0.08 seconds after the J point, the S-T segment was depressed 0.1 mV or more below the resting baseline value, with the slope equal to or less than zero" (p. 368). Coronary angiography appeared to be considered positive, or indicative of hemodynamically significant coronary atherosclerosis, if the coronary narrowing in one or more vessels was 50% or more. The patients were placed in one of three groups based on their cardiac history. Group A included 43 patients with histories of documented myocardial infarction and/or typical angina. Out of the 43, there were 13 true positive, no false positive, four true negative, and 26 false negative stress tests. Subsequently the sensitivity was low, 33%, while the specificity was high, 100%. Group B included 16 patients with typical angina. There were three true positive, one false positive, 10 true negative, and two false negative stress tests; the sensitivity was fair at 60%, and the specificity was high at 91%. Group C included 30 asymptomatic patients who all had positive stress tests. There were 11 true positive and

19 false positive stress tests. The sensitivity, therefore, was low at 37%, and, because there were no negative stress tests, specificity was not measurable. Borer et al. concluded that the validity of the stess test as they used it was low because it was not sensitive in identifying the presence nor specific in identifying the absence of hemodynamically significant CAD in all three of their groups of hyperlipidemic subjects.

The underlying purpose of the above studies by Carlson et al. and James et al. was to suggest the differences in the frequency of CAD between asymptomatic hyperlipidemic subjects (who are at high risk of developing CAD) and asymptomatic normolipidemic subjects (who are at lower risk of developing CAD) by comparing the differences in the frequency of their S-T segment depression on the E-ECG. But in the study by Borer et al., of 30 asymptomatic normolipidemic subjects with positive stress tests (significant S-T segment depression on the E-ECG) only 11 had significant CAD; 19 had normal or only minimally changed arteries by angiography. Therefore, it cannot be assumed that the S-T segment depression seen in the studies of Carlson et al. and James et al. is only caused by CAD. What is the cause of the S-T segment depression on the E-ECGs of some hyperlipidemic patients, if not CAD? Since S-T segment depression on the E-ECG is more frequent in hyperlipidemic than normolipidemic

subjects, and since elevated serum lipid levels are associated with conditions other than CAD which cause S-T segment depression on the E-ECG, perhaps there is a relationship, independent of CAD, between the elevated serum lipid levels of some hyperlipidemic patients and the S-T segment depression seen on their E-ECG's.

Kuo and Joyner (1955) studied the effects of a high fat meal on the occurrence of angina and ECG changes in 14 persons with angina pectoris. While at rest three to five hours after a high fat meal, six patients had anginal attacks, and in all cases the attack occurred at or near the peak plasma lactescence level. Three of the six had S-T segment depression during their attacks. On another morning, the same patients were given a fat-free meal, identical in calories and bulk to the high fat meal. After five hours, there were no increases in plasma lactescence, no anginal attacks, and no ECG changes. Although this study did not involve exercise or hyperlipidemia, it documents a case in which the presence of high lipid levels was associated with the onset of myocardial ischemia and S-T segment depression and in which the absence of high lipid levels, under similar conditions, was associated with the lack of onset of myocardial ischemia or S-T segment depression. This study also serves to illustrate a method of studying the relationship between serum lipid levels and S-T segment changes on the exercise ECG. Specifically, this method involves

the measurement of exercise-induced S-T segment changes when serum lipid levels are elevated and then when serum lipid levels are lower. A later section will discuss how serum lipid levels can become elevated and subsequently how they can be lowered.

The Relationship of Serum Lipid Levels to the Progression and Regression of Coronary Atherosclerosis:

Of concern to the use of a lipid-lowering treatment as a means of studying the relationship between serum lipid levels and S-T segment depression on the E-ECG, is the effect of lowering serum lipid levels on the progression or regression of coronary atherosclerosis. This is because changes in coronary atherosclerosis may affect myocardial perfusion and thereby alter the S-T segments on the E-ECG. A study of 25 patients with hyperlipoproteinemia showed that, after 13 months of dietary and drug treatment to lower lipid levels, regression occurred in only 13 patients who had successfully lowered and maintained lowered serum lipid levels, while progression occurred in those who had not. The rates of regression were all 2.08% a month or less, except for one patient who had a regression rate of 4.11% a month (Barndt, Blankenhorn, Crawford, & Brooks, 1977; Blankenhorn, Brooks, Selzer, & Brandt, 1978). Therefore, significant regression of coronary atherosclerosis could occur in the relatively short time period of a few months to a year

when serum lipid levels are lowered and maintained at a lower level.

The Genesis and Treatment of Hyperlipidemia:

The amount of fat, cholesterol, and calories in a meal directly affects the post-prandial serum cholesterol and triglyceride elevation. Dietary saturated fat and cholesterol increase the serum cholesterol level, while it is decreased by polyunsaturated fats. Dietary cholesterol may increase the serum triglyceride levels, particularly in type IV hyperlipidemia. Fat and excess calories increase serum triglyceride levels and can increase cholesterol levels (Connor & Connor, 1972; 1977). Normally, if saturated fat and cholesterol are withheld, and if the caloric intake is not excessive, the body will clear the blood of excess serum lipids and synthesize only that amount of triglyceride and cholesterol that it needs; this is manifested by a fall in the serum triglyceride and cholesterol levels to the normal range. Hypercholesteremia (fasting serum cholesterol levels greater than 210 mg%) and hypertriglyceremia (fasting serum triglyceride levels greater than 160 mg%) are conditions which occur whenever the body is unable to clear the blood of any excess cholesterol and triglycerides, respectively, within a 12-hour fasting period. This may be due to either a high intake of cholesterol, saturated fats, and/or excess calories before the fast, or due to a dysfunction

in the body's ability to clear these substances, or both (Frederickson, Levy, & Lees, 1967; Connor & Connor, 1972; 1977).

Currently diet, exercise, and drug therapies are used to lower serum lipid levels in patients with hyperlipidemia. Because exercise and drug therapies may in some way interfere with the performance or interpretation of the exercise stress test, they will not be used as methods for lowering serum lipid levels in this study.

Serum cholesterol and triglyceride levels can be significantly lowered by restricting cholesterol, fat, saturated fat, and excess caloric intake (Connor & Connor, 1977). The typical American diet is high in cholesterol (600-800 mg/day) and fat (40% of the total daily calories); a large percentage of the daily fat ingested is in the form of animal fats, which are saturated fats (Connor & Connor, 1977). Connor and Connor (1977) have had considerable success in the treatment of all types of hyperlipidemia with their "Alternative Diet." This diet restricts cholesterol intake to 100 mg/day, fat intake to 20% of the daily calories, and saturated fat to only 5% of the daily calories. The diet also restricts caloric intake to that required to achieve or maintain normal weight. For a comprehensive description of the conceptual basis and the application of the "Alternative Diet," the reader is directed to Connor and Connor (1972; 1977) and to the manual published by the American Heart Association (1973, Note 2).

Compliance with Lipid Lowering Diets:

Serum lipid levels can be significantly reduced within two to six weeks if the fat, cholesterol, and caloric intake of the hyperlipidemic patient is controlled within the hospital setting. Outpatients, by controlling their own dietary intake, can also reduce their own serum lipid levels if they strictly adhere to the dietary regimen (Connor, 1966; Note 5). Unfortunately, many hyperlipidemic patients have difficulty adhering to their diet (Fey, Carmody, Connor, & Matarrazzo, Note 3). Compliance with any treatment regimen is determined by three major factors: the nature of the disease being treated, the nature of the treatment regimen, and the patient's health beliefs about the disease and the treatment (Haynes, 1979).

Hyperlipidemia is a chronic disease with no or few symptoms in the early course and a prognosis for the remote future which may range from no or minor symptoms of the primary disease manifestations (usually related to atherosclerosis) to severe disability or death from the secondary disease manifestations (usually end organ damage, e.g., myocardial infarction or cerebral ischemia).

The dietary treatment regimen now considered necessary to prevent hyperlipidemia and its manifestations, e.g., the "Alternative Diet," not only restricts caloric intake, but it requires the elimination of some of the most typical

American foods, such as bacon and eggs, hamburger and fries, and ice cream. Certainly people can live without certain foods, but it is the pleasure that is derived from eating those foods that is difficult to give up, particularly when there is no comparable substitute. As Connor and Connor (1972, p. 67-68) stated so succintly, "eating... is one of the most satisfying and pleasure producing activities that mankind pursues during the course of daily living."

The hyperlipidemic patients' compliance with therapy ultimately hinges on their health beliefs. The patient must decide which alternative he perceives to be more tolerable, a treatment regimen that requires long-term major changes in eating habits or the possibility of a seriously debilitating and/or death-producing disease in the distant future (Fey et al., Note 3).

Compliance with lipid reducing diets is complicated because it is difficult to measure. While it might appear that serum cholesterol and triglyceride levels would be direct measures of the patient's compliance with the diet, it must be remembered that serum lipid levels are not only affected by cholesterol and fat intake but also by the patient's caloric state, certain medications, exercise, genetic factors, and normal individual and day-to-day variations in lipid metabolism (Connor & Connor, 1972; Ellestad, 1975). In 1966, Connor

gave six normolipidemic men strictly controlled cholesterol-free and high cholesterol diets. He found that significant changes in serum cholesterol levels occurred within 10 to 14 days after dietary changes and that lipid levels in all the men were labile, with upward and downward changes by as much as 40 mg/dl, despite continued strict adherence to the diet (Connor, 1966; see Figure 6, Appendix A). Other measures of compliance with lipid-lowering diets include: patient interviews, daily written dietary records, verbal reports by the patient, and the physician's subjective assessment of the patient's compliance (Gordis, 1979).

There are three main strategies used to improve compliance: patient education, patient supervision, and behavior modification. The first two are components of most traditional diet therapies; the latter is a promising but still relatively new and less tested strategy. While there are no literature reviews available on the effect of different compliance strategies on adherence to lipid-lowering diets, there have been reviews on the effect of different compliance strategies on adherence to weight reduction diets. Strunkard (1958, p. 79) reviewed the traditional strategies for weight reduction and concluded that "...most patients will not remain in treatment. Of those who remain in treatment, most will lose no weight, and of those who lose weight, most will regain it." In 1972, Strunkard again reviewed compliance strategies for

weight reduction but concluded that "both greater weight loss during treatment and superior weight loss after treatment indicate that behavior modification is more effective than previous treatment methods for obesity" (p. 398). In 1979, however, Fey et al. (Note 3) were less optimistic when they noted that /the more recent/ "...reviews of the behavioral treatment weight loss literature have noted mixed results" (p. 14).

The effectiveness of patient education on compliance appears to be dependent on the provider of the education, the method in which the information is presented, and the nature of the information. Information addressing the patients' health beliefs about their illness and the value of the treatment, and information directed not only to why one should comply but also to how one can change behavior, to comply with a treatment, may be more effective than simple factual information (Fey et al., Note 3; Haynes, 1979).

The effectiveness of patient supervision on compliance appears to be dependent on how specific the supervision is. This is achieved by chiefly organizational methods, such as increasing the frequency of visits, arranging for patients to visit the same health professional at each visit, and, if necessary, hospitalizing non-compliant patients (Haynes, 1979).

Behavior modification includes a number of strategies which, by changing the stimuli for behavior or the consequences of behavior, attempt to eliminate non-compliant

behavior and build up the desired compliant behavior. Although there are many behavior modification strategies, the following are some of those most frequently used to improve compliance with diet therapies. "Reinforcement" is the backbone of behavior modification; a reinforcer is any consequence that increases the possibility of a behavior being repeated. Positive reinforcers, such as praise or rewards, when applied, increase the probability of a behavior occurring. Negative reinforcers, such as pain or punishment, are consequences which, when removed, increase the possibility of a behavior occurring. "Shaping" describes a reinforcing strategy whereby positive reinforcement is applied as goals are met to build up desired behavior. "Extinction" describes a strategy in which the positive and/or negative reinforcers that normally maintain an undesirable behavior are removed in an attempt to eliminate the undesirable behavior. "Family-peer support" is a specific method of promoting positive reinforcement. It is limited, however, by how generally it is applied; it may inadvertently serve to promote non-compliant as well as compliant behavior. For example, a mother who praises her child for eating everything on his plate because she is trying to promote good manners may inadvertently also promote overeating (Agras, 1972; Dunbar, Marshal, & Hovel, 1979; Fey et al., Note 3). "Tailoring" provides a means of allowing a

patient to control his treatment regimen; the prescribed regimen is tailored or adapted to meet the needs, routine, and characteristics of the patient rather than making the patient adapt to the regimen (Dunbar et al., 1979). "Contracting" sets up behavioral rules for the patient to follow which, if met, result in a positive consequence and, if not met, result in a negative consequence (Dunbar et al., 1979; Fey et al., Note 3). "Graduated regimen implementation" allows the patient to slowly change from non-compliant to compliant behavior. It sets up progressive realistic goals which the patient meets on his own time schedule, but once each goal is met, the requirements for adequate performance are gradually increased. It often works in conjunction with shaping. (Dunbar et al., 1979) "Self-monitoring" requires that the subject observe and record his own behavior, analyze the record for compliance and non-compliance, and then use this feedback to help himself to eliminate non-compliant behavior and increase compliant behavior in the future (Dunbar et al., 1979; Fey et al., Note 3).

Fey et al. (Note 3) did an extensive review of the problems of adhering to diets restrictive in cholesterol and fats, in calories, and in salt, the reasons for these problems, and the compliance strategies available to decrease these problems. They concluded that "if dietary intervention is to be effective and compliance rates increased, treatment must involve procedures

designed to promote initial compliance, family support, stress reduction, behavioral control, and long-term adherence" (p. 37).

Summary and Justification for the Study:

S-T segment depression on the E-ECG occurs more frequently in hyperlipidemic patients than in normolipidemic patients (Carlson et al., 1975; James et al., 1975). Since chronically elevated serum lipid levels are associated with the development of CAD, and since CAD can cause myocardial ischemia which is reflected as S-T segment depression on the E-ECG, it is generally assumed that the S-T segment depression seen on the E-ECGs of hyperlipidemic patients is due to CAD (Ellestad, 1975). Recently, however, it was found that S-T segment depression occurred on the E-ECGs of some hyperlipidemic patients who had no or insignificant CAD on angiography (Borer et al., 1975). This observation makes one question the validity of using S-T segment depression on the E-ECG in the detection of the presence or absence of CAD in hyperlipidemic patients. In addition, it makes one wonder what is the cause of the S-T segment depression on the E-ECGs of some hyperlipidemic patients, if not CAD.

There are a number of conditions other than CAD which can cause S-T segment depression on the E-ECG, such as those which cause myocardial ischemia or hypoxia, and those which directly disturb the dielectric property of

the cardiac cell membrane (Constant, 1973; Ellestad, 1975). Elevated serum lipid levels, such as those of patients with hyperlipidemia, have been found to be associated with some of these conditions. For example, elevated serum lipid levels have been associated with increases in platelet aggregation, which can cause arterial spasm, microemboli or thrombi formation, or increased blood viscosity, all of which can cause myocardial ischemia and subsequently S-T segment depression on the E-ECG (Carvalho et al., 1977; Ellestad, 1975; Mustard et al., 1977; Renaud et al., 1977). Elevated lipid levels are also associated with erythrocyte aggregation, increases in basal metabolism, and changes in the cell membrane cholesterol content, all of which may cause S-T segment depression on the E-ECG (Alivisatos et al., 1977; Cullen & Swank, 1954; Henry, 1977; Mustard et al., 1977). It is possible then that there is a relationship, independent of CAD, between the elevated serum lipid levels of some hyperlipidemic patients and the S-T segment depression seen on their E-ECG's.

In order to see significant progression or regression of CAD, serum lipid levels must be maintained significantly elevated or reduced, respectively, for months to years (Barndt et al., 1977; Blankenhorn et al, 1978). But increases and decreases in platelet aggregation, erythrocyte aggregation, basal metabolism, and cell membrane cholesterol content can be seen within hours to

days of reaching significantly elevated or reduced serum lipid levels (Alivisatos et al., 1977; Carvalho et al., 1977; Cullen & Swank, 1954; Henry, 1977; Mustard et al., 1977; Renaud et al., 1977). Subsequently, elevated serum lipid levels may be related to S-T segment depression on the E-ECG, both chronically, by association with CAD, and acutely, by association with platelet aggregation or some of the other conditions which cause E-ECG S-T segment depression.

Serum lipid levels can be significantly reduced within two to six weeks if the fat, cholesterol, and caloric intake is strictly controlled (Connor, 1966; 1979). The acute relationship between elevated serum lipid levels and S-T segment depression on the E-ECG could, therefore, be demonstrated if the elevated serum lipid levels of hyperlipidemic patients were significantly reduced and if within a few days this reduction was associated with significantly less S-T segment depression on their E-ECGs. The demonstration of a relationship, independent of CAD, between elevated serum lipid levels and S-T segment depression on the E-ECG would help direct lipid and cardiovascular research; it would particularly suggest a need to further examine the acute effects of hyperlipidemia on the body. It would also suggest a re-evaluation of the purposes and usefulness of exercise stress testing in hyperlipidemic patients. Thus, determining the relationship between different serum lipid levels and S-T segment changes on the E-ECG is important to all health professionals concerned with the care of hyperlipidemic patients.

Purpose of the Study

The primary purpose of this study was to explore the effect of acute dietary reduction of fasting serum lipid levels on the amount of S-T segment depression seen on the E-ECGs of hyperlipidemic subjects, as a means of demonstrating a relationship, independent of CAD, between elevated serum lipid levels and E-ECG S-T segment depression. In addition, because this was a pilot study, a secondary purpose was to explore and describe the factors affecting the fasting serum lipid levels and the S-T segment depression on the E-ECGs of each subject over the course of the dietary treatment, to benefit further research in this area.

Hypotheses

1. In type IIa and IIa-b hyperlipoproteinemic subjects, success in achieving and maintaining significant reductions (20%) in fasting serum cholesterol levels will be associated with significant decreases in the amount of S-T segment depression on the E-ECGs; the exercise stress tests will become negative.

2. In type IIa and IIa-b hyperlipoproteinemic subjects, lack of success in achieving and maintaining significant reductions (20%) in fasting serum cholesterol levels will be associated with no significant decrease in the amount of S-T segment depression on the E-ECGs; the exercise stress tests will remain positive.

3. In type IV and V hyperlipoproteinemic subjects, success in achieving and maintaining significant reductions (50%) in the fasting serum triglyceride levels will be associated with significant decreases in the amount of S-T segment depression on the E-ECGs; the exercise stress tests will become negative.

4. In type IV and V hyperlipoproteinemic subjects, lack of success in achieving significant reductions (50%) in the fasting serum triglyceride levels will be associated with no significant decrease in the amount of S-T segment depression on the E-ECGs (the exercise stress test will remain positive).

CHAPTER II

METHODOLOGY

Subjects

The sample of this study was drawn from a population of male and female hyperlipoproteinemic in-patients and out-patients at the University of Oregon Health Sciences Center (UOHSC) hospitals and clinics. Those who met the following criteria were asked to participate:

1. 18 years old or more;
2. Type IIa or type IIa-b hyperlipoproteinemia with 12-hour fasting serum cholesterol levels of greater than 260 mg%;

   or

   Type IV hyperlipoproteinemia with 12-hour fasting serum cholesterol levels of 210-260 mg% and fasting serum triglyceride levels of greater than 400 mg%;

   or

   Type V hyperlipoproteinemia with 12-hour fasting serum cholesterol levels greater than 300 mg% and fasting serum triglyceride levels of greater than 100 mg%;
3. A positive exercise stress test: E-ECG S-T segment

depression of 1.0 mm or more below the baseline, or below the level of the resting ECG (R-ECG) S-T segments if they are abnormally elevated or depressed, at 0.08 seconds past the J point (see Appendix B, Figure 9).

Patients with the following characteristics were excluded from serving as subjects:

1. Those with medical conditions which preclude stress testing, such as overt heart disease, recent acute infection, hyperthyroidism, or a debilitating disease;
2. Those with medical conditions which affect stress testing, such as hypothyroidism, hyperthyroidism, electrolyte disturbances, obstructive lung disease, valvular heart disease, and anemia;
3. Those taking medications that affect stress test results, such as digitalis, quinidine, thyroid, amyl nitrate, phenoxybenzamine, phenothiazines, lithium, and alcohol in chronic or copious ingestion.

The original intent was that, of those who met the criteria for inclusion in the study, the first 10 type IIa or type IIa-b hyperlipoproteinemic volunteers would be studied as "Group A"; the first 10 type IV hyperlipoproteinemic volunteers would be studied as "Group B"; and the volunteers with type V hyperlipoproteinemia would be studied as "Group C". However, due to the time restrictions on the study and the unexpectedly small number of subjects from the population who met all the criteria, the four patients

who were eventually studied as subjects, all fell into Group A.

Sources of Data

Selected Demographic and Medical Data:

The selected demographic and medical data of age, sex, type of hyperlipoproteinemia, past and present medical conditions and medications were obtained from the subjects' medical records. These data were recorded in separate files for each subject and were used to describe the subjects' pre-diet characteristics and document the control variables.

Serum Lipid Level Data:

The independent variable for Group A subjects was their fasting serum cholesterol levels; their fasting serum triglyceride levels served as a control variable. Blood for fasting serum lipid levels was drawn after the subject had fasted for 12 hours and had abstained from significant exercise for 48 hours (Ellestad, 1975). Subsequently, the blood for serum lipid levels was always drawn before the exercise stress test. The measurement for the fasting serum lipid levels was performed by the standardized techniques of the Lipid-Atherosclerosis Lab at UOHSC. There was no charge to the subjects for blood tests that were not part of their normal care.

The study required that the subjects lower their fasting serum cholesterol levels to a significant degree. Adopting the criterion espoused by Connor (Connor, 1978),

a significant reduction in the fasting serum cholesterol level was specified as a 20% decrease from the pre-diet level of each Group A subject.

Subjects were asked to comply with a diet restricting cholesterol intake to 100mg/day or less, fat intake to 20% of the total daily calories or less, saturated fat intake to only 5% of the daily calories or less, and caloric intake to that required for the subject to achieve or maintain normal weight. Since this was a radical change in most subjects' eating habits, they were assisted in dietary compliance by instruction in planning, purchasing, and preparing meals suited to their individual diet prescription. This instruction was given verbally and in the written form of the American Heart Association dietary manual (Connor, Brown, Fredrickson, Steinberg, Connor, and Bickel, Note 2). Verbal instruction was based on the "Alternative Diet" (Connor & Connor, 1977). Subjects were also given instruction, guidance, and support in procedures designed to increase dietary compliance based on the behavior modification techniques suggested by Fey et al. (Note 3).

Exercise Stress Test Data:

Exercise stress test measurements were obtained from a maximal exercise stress test on a standard motor-driven treadmill. The Bruce protocol (Appendix B), with all its inherent benefits and limitations (Bruce, 1971; Bruce, Blackmon, Jones, & Strait, 1963; Bruce & Hornstein,

1969), was used with standard electrocardiographic and blood pressure monitoring.

The dependent variable of this study was the S-T segment level on the E-ECG. S-T segment levels were measured in fractions of millimeters and designated as significantly depressed or not significantly depressed: E-ECG S-T segment depression of 1.0 mm or more below the baseline, or below the level of the R-ECG S-T segment if it was elevated or depressed, at 0.08 seconds past the J point, was considered significant (Ellestad, 1975). The exercise stress test was considered positive if there was significnat S-T segment depression on the E-ECG. Otherwise, it was considered negative. The exercise stress tests were done in the presence of a cardiologist who also read the E-ECGs.

The parameters of maximum blood pressure (Max BP), maximum heart rate (Max HR), T wave changes, arrhythmias, exercise tolerance time (ETT), and the symptoms or signs which were the reason for terminating the test, were all recorded during the exercise stress tests of each subject and served as control variables.

Exercise, weight change, and the passage of time were three variables which may have affected the exercise stress test results. Subjects were asked to maintain but not change their pre-study exercise habits. All subjects were asked to abstain from significant exercise for 48 hours before the lipid determinations and the exercise stress test. This is because exercise may increase or decrease serum cholesterol levels and exercise can decrease serum

triglyceride levels (Ellestad, 1975). Since weight reduction is part of the treatment regimen for many hyperlipidemic patients, subjects were not asked to maintain the pre-diet weight. Instead, before and after diet measurements of the subjects' weight were taken, and changes in weight were considered in the data analysis. Attempts were made to limit the time between the stress tests. This was done to control for the possible regression of latent coronary atherosclerosis. A training exercise stress test was done on all subjects prior to the pre-test to control for the variable of experience (Zohman and Kattus, 1975).

Design and Procedure

The original design of this study utilized a longitudional pre-test, post-test design, with three study groups, each serving as its own control. The potential subjects were to have been purposely sampled to meet the criteria of (1) type IIa or type IIa-b hyperlipoproteinemia-Group A, type IV hyperlipoproteinemia-Group B, or type V hyperlipoproteinemia-Group C, and (2) a positive trial exercise stress test. The independent variable for Group A was the fasting serum cholesterol levels of the subjects; for Group B it was to have been the fasting serum triglyceride levels of the subjects; and for Group C it was to have been both fasting serum cholesterol and triglyceride levels. The elevated serum lipid levels of all groups were to have been reduced by the same dietary

intervention. As the study progressed, adaptations were made in the design to accomodate the single study group, Group A, and a second post-test. There was no control for age or sex in the sample population. The dependent variable was the amount and the significance of the S-T segment depression on the pre-test and post-test E-ECGs of the subjects. Significant S-T segment depression on the E-ECGs constituted a positive exercise stress test; all subjects had a positive trial test and pre-test exercise stress tests. The first post-test was performed when the independent variable, the fasting serum cholesterol level, had been reduced significantly or when eight weeks had elapsed since the pre-test, whichever came first. The second post-test was performed when it was thought that the fasting serum cholesterol level was most likely to be reduced significantly. Every effort was made to help subjects lower their fasting serum cholesterol levels in as short a time as possible.

The procedure of the study focused on four areas: (1) subject participation, e.g., the subjects' understanding of the study and willingness to participate; (2) lipid determinations, e.g., the preparation for, collection of, and measurement of fasting serum lipid levels; (3) exercise stress test, e.g., the treadmill exercise stress test protocol; and (4) the diet, e.g., dietary instruction and patient compliance. The procedure schedule is summarized below.

Prospective subjects were identified for all criteria except the positive exercise stress test. Since a training exercise stress test must be done on all subjects to control for experience, a trial exercise stress test was used both to identify prospective subjects with a positive test and to serve as a training test for the subjects with a positive test. Since fasting serum lipid levels must always be drawn before exercise, all prospective subjects had the blood samples drawn before the trial test. These samples were processed only if the trial test was positive or if the subject's physician requested that the samples be processed.

On the day of the trial exercise stress test, subjects had blood samples for fasting serum lipid levels drawn, and the trial exercise stress test was performed according to the Bruce protocol. If the prospective subject had a positive exercise stress test, the study was explained to the subject both verbally and in detail on the study consent form (see Appendix C). Study subjects met with the nurse investigator for review of the study schedule, and for instruction and discussion of the diet and the compliance procedures. Subjects were asked to study the diet for the next week, but they were not started on the diet until after the second exercise stress test, the pre-test, one week later.

On the day of the pre-test, subjects had blood samples for fasting serum lipid levels drawn and the pre-test exercise stress test was performed according to the Bruce

protocol. Subjects were asked to start the diet after the pre-test and to return weekly for serum lipid determinations and diet review.

Subjects returned weekly for fasting serum lipid determinations. At this time the subjects' diets were reviewed and efforts made to help them comply with the diet. It was estimated that it would take between three and six weeks for subjects to significantly reduce their fasting serum cholesterol levels if they strictly complied with the diet. Subjects continued to return for weekly serum lipid determinations until either their fasting serum cholesterol levels decreased significantly or until eight weeks had elapsed since the pre-test, whichever came first. At this time the first post-test was performed. A second post-test was performed several weeks later if the fasting serum cholesterol levels were not significantly decreased at the time of the first post-test.

On the day of the post-test, subjects had blood samples for fasting serum lipid levels drawn, and then they performed the exercise stress test according to the protocol. Time was allowed for further diet review if the subject wished to continue the diet. At the end of the study, subjects were given the option of being followed in the Lipid Clinic in order to maintain their dietary compliance and decreased serum lipid levels (if applicable). A summary of the study results was sent to the subject when the study was completed.

Data Storage and Analysis

All subject data and forms were kept in a locked office at the University of Oregon Health Sciences Center.

The study utilized parametric statistics (interval scale data) on repeated measurements on the same subjects. Analysis of variance was chosen as the appropriate statistic. It was recognized that the sample size of the group was small. In light of the fact that there were no other studies of the relationship between acute changes in the serum lipid levels and acute changes in the S-T segment levels, this study was considered as useful pilot work despite the small sample size.

CHAPTER III

RESULTS AND DISCUSSION

The primary purpose of this study was to explore the effect of acute dietary reduction of fasting serum lipid levels on the amount of S-T segment depression seen on the E-ECGs of hyperlipidemic subjects, as a means of determining if there could be a relationship, independent of CAD, between elevated serum lipid levels and E-ECG S-T segment depression. Four hypotheses were proposed for use in studying this phenomenon, but, due to factors which will later be explained, the hypotheses could not be tested as planned. Because this was a pilot study, there was also a secondary purpose which was to explore and describe the factors affecting the fasting serum lipid levels and the S-T segment depression on the E-ECGs in each subject over the course of the dietary treatment, to benefit further research in this area. To facilitate the reader's understanding of the findings, they will be presented in the order of the subject procedure and will include the subject identification data, the individual subject data, and the comparisons of the individual subject data.

Subject Identification Data

Of the 145 hyperlipidemic patients seen in the UOHSC Lipid Clinid during the subject identification period of March 15, 1979 to May 31, 1979, 11 met all the initial

criteria (lacking only the exercise stress test result) for inclusion in the study. These 11 were all given exercise stress tests according to the Bruce protocol. Of the 11, 5 had negative tests, 2 had equivocal tests, and 4 had positive tests. The demographic, medical, fasting serum lipid levels, and exercise stress test data for these 11 potential subjects are summarized in Table 1.

The small sample size was attributed to both the limited time period for subject identification and the nature of the population at the Lipid Clinic, e.g., most of the patients were referred for aggressive work-up and treatment. Subsequently, many of the clinic patients did not meet subject criteria because they were already on medications which interferred with either the performance or interpretation of the stress test or which were known to affect serum lipid levels.

It was notable that most of the sample subjects had type IIa or IIa-b hyperlipoproteinemia. While this is the most common type of hyperlipoproteinemia, it had been expected that there would also be a few potential subjects with type IV, which is not uncommon, but there were none. The reader is referred to the article by Fredrickson et al.(1967) for a complete discussion of hyperlipoproteinemia.

Despite the small number of potential subjects, a few trends did emerge when the subjects with positive exercise stress tests were compared to those with negative exercise stress tests. The subjects with positive tests tended to

TABLE 1

Demographic, Medical, Fasting Serum Lipid, and Exercise Stress Test Data for all Potential Subjects

Stress Test	Subject	Age	Race/Sex	HPL Type	Family History	Chol mg%	TG mg%
	1	43	W / F	IIa-b	-	298	157
Positive	2	46	W / M	IIa-b	+	550	232
	3	51	B / F	IIa	-	264	121
	4	32	W / F	IIa	-	356	87
	Range	32-57				264-550	87-232
	Mean	43				367	149
	5	41	I / M	IIa-b	-	279	199
Negative	6	33	W / M	IIa	+	472	177
	7	35	W / M	V	+	520	1570
	8	30	W / M	IIa	+	340	50
	9	36	W / F	IIb	+	396	392
	Range	30-41				279-520	50-1570
	Mean	35				402	478/204*
	10	52	O / F	V	+	1400	14,000
Equivocal	11	66	W / F	IIa	-	415	88

* 478 is the mean when 1570 is included, 204 is the mean when 1570 is not included in the calculations.

HPL Type - Hyperlipoproteinemia type
Chol - Fasting serum cholesterol level
TG - Fasting serum triglyceride level
W - White
B - Black
I - Asian Indian
O - Oriental

be older (the mean age was 43) and female (3 of 4), with lower fasting serum cholesterol (the mean was 367 mg%) and triglyceride (the mean was 149 mg%) levels, and a negative family history of hyperlipoproteinemia. The subjects with negative tests tended to be younger (the mean age was 35) and male (4 of 5), with higher fasting serum cholesterol (the mean was 401 mg%) and triglyceride (the mean was 478 mg%, or 204 mg% if Subject 7's very high level was not included) levels, and a positive family history for hyperlipidemia.

Carlson et al. (1975) found that S-T segment depression on the E-ECG increased in frequency with age and was more frequent in hyperlipidemic men than in normolipidemic men; age was a more significant determinant for S-T segment depression than the elevated serum lipid levels. The relationship between S-T segment depression on the E-ECG and increasing age may be attributable to an increased incidence of CAD, but it may also be due to a more limited tolerance of exercise and/or elevated serum lipid levels.

Ellestad (1975) noted that the reported incidence of S-T segment depression on the E-ECG is higher in females than in males, despite the general belief that males have a higher incidence of CAD. This finding could imply that females have a higher incidence of CAD than reported or it could point to the presence of a condition, other than CAD, that causes S-T segment depression on the E-ECGs of females. As postulated earlier, this condition could be hyperlipidemia.

There are no known studies to suggest why the subjects

who had positive stress tests tended to have lower fasting serum cholesterol and triglyceride levels and negative family histories for hyperlipoproteinemia. These trends may not be true for the general population.

Although the above trends are based on the characteristics of a small number of subjects, they provide a basis for further studies to investigate the presence or absence of relationships between age, sex, hyperlipidemia and E-ECG S-T segment depression.

Individual Subject Data

The pre-diet characteristics, the pre-test measurements, the study goals, and the course of the dietary treatment are described in the following section for each subject. Figures 1-4 are graphical illustrations of the changes in the subjects' fasting serum cholesterol, triglyceride, and weight levels over the course of the dietary treatment for subjects 1-4 respectively. These figures are discussed in the text with reference to the diet, the compliance strategies, the changes in the S-T segment depression on the E-ECG, and other related factors.

Subject 1:

Pre-diet characteristics: Subject 1 was a 43-year-old white female with type IIa-b hyperlipoproteinemia. Her history was notable for persistent obesity since age 25 and mildly to moderately elevated fasting serum cholesterol levels for two and a half years prior to the study despite attempts at dietary restriction of cholesterol, fats, and

calories. She complained of fatigue, occasional orthostatic dizziness, and a vague chest pain which was occasionally related to exertion, but she had no physical signs hyperlipidemia. Her only other medical problem was menstrual irregularity. She did not take any medications, smoke, drink, or engage in any regular exercise. Her CBC and chemistry screen were within normal limits. It was postulated that her hypercholesterolemia was related to her longstanding obesity and the dietary habits which presumably contributed to the obesity. It was interesting, therefore, that her pre-study 24 hour dietary recall revealed an intake of 1090 calories, 28 mg cholesterol, 12% fat, 15% protein, and 73% carbohydrate; values well within the guidelines of the Alternative Diet.

Pre-test measurements: On the morning of the pre-test, her fasting serum cholesterol and triglyceride levels were 298 mg% and 157 mg% respectively, and she weighed 167 pounds (her height was 5 feet 1 inch). The R-ECG was normal with baseline S-T segments and T inversion on standing. She tolerated 8 minutes 2 seconds of exercise (Stage III), at the end of which time the Max BP was 178/80, the Max HR was 140 (as compared with the predicted Max HR of 180 for her age and sex), the E-ECG showed S-T segments depressed 1.5 mm below the baseline, T wave inversion, but no arrhythmias, and the test was terminated due to lightheadedness, leg pains, and fatigue. The exercise stress test was considered positive because the S-T segments on the E-ECG were depressed

1.5 mm below the level of the S-T segments on the R-ECG.

Study goals: The study goals for Subject 1 were: 1) to achieve and maintain a significant reduction (20%) in her fasting serum cholesterol level, e.g., from 298 mg% to 239 mg%, and 2) to see a significant decrease in the amount of S-T segment depression on the E-ECG, e.g., E-ECG S-T segments depressed less than 1.0 mm below the level of the R-ECG S-T segments: a negative stress test.

Course of the dietary treatment: (See Figure 1)

Diet: Subject 1 modified her usual diet to meet the guidelines of the Alternative Diet. After five weeks, however, she was discouraged by the lack of significant reduction in both her weight and her fasting serum cholesterol level, so she decided to try the Rice-Fruit Diet. This diet was within the guidelines of the Alternative Diet, but it was thought to be simpler to follow because the only food was three cups of fruit and three cups of rice each day. Subject 1 followed the Rice-Fruit Diet for two weeks, and although she lost weight, her fasting serum lipid levels rose and she complained of an uncomfortable fullness after each meal. Thereafter, when home, she followed a self-designed diet, which consisted of two cups of rice and two cups of fruit a day, and a vegetable salad without dressing. During her vacations, she allowed herself a larger selection of foods, but tried to stay within the guidelines of the Alternative Diet. She admitted to periodic cheating and some days of total non-compliance, particularly when on vacation.

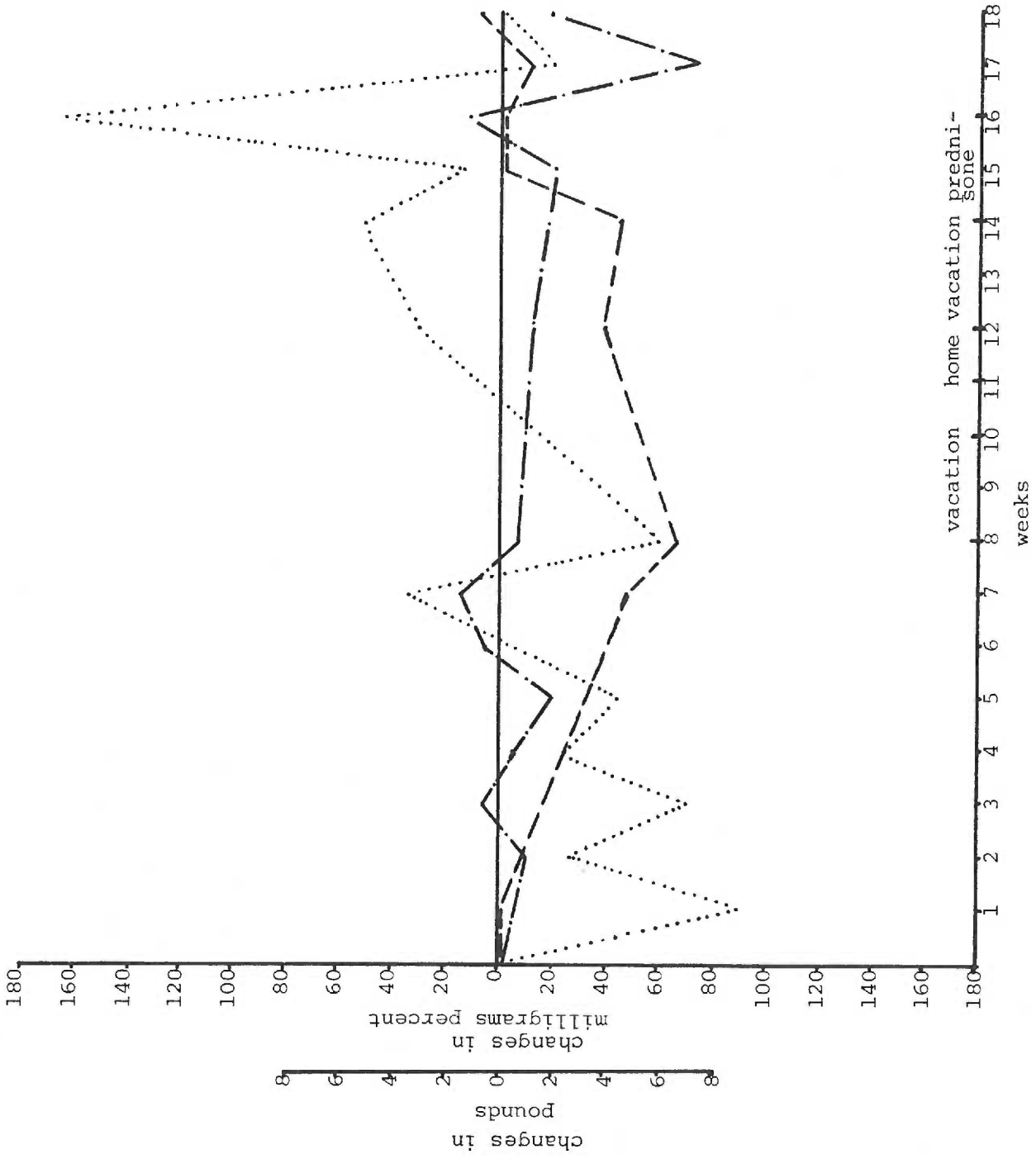
Figure 1: Course of the dietary treatment for Subject 1

Pre-diet fasting serum cholesterol, triglyceride, and weight measurements, together on one baseline.

Fasting serum cholesterol levels in mg% from the pre-diet level.

Fasting serum triglyceride levels in mg% from the pre-diet level.

Weight measurements in pounds from the pre-diet level.


changes in pounds
8 6 4 2 0 2 4 6 8
changes in milligrams percent
180 160 140 120 100 80 60 40 20 0 20 40 60 80 100 120 140 160 180
vacation home vacation prednisone
weeks
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Compliance strategies: 1) Subject education: Subject 1 was familiar with the terms hyperlipidemia and atherosclerosis and the prognostic implications of her disease. She had tried the Alternative Diet before, but was re-instructed in the food group restrictions and encouraged to measure the quantities of food she ate, particularly the meats and fats. The health beliefs of Subject 1 were such that her desire to lose weight often appeared to be more important than her desire to prevent further disease by decreasing her fasting serum cholesterol level. 2) Subject supervision: Subject 1 met with the investigator weekly either at the UOHSC Lipid Clinic or at her work site. The investigator made two visits to the subject's home to observe and give feedback on the subject's preparation of Alternative Diet meals. 3) Behavior modification: The subject was given positive reinforcement in the form of praise from the investigator for reported compliance with the diet and for documented reductions in fasting serum cholesterol levels and/or weight. The family support from her husband and children was limited to praise for weight loss. Tailoring was perhaps the most effective compliance strategy used; once the subject began to design the diet to fit her needs she reported an improvement in her attitude toward the diet.

Serum lipid, weight, and exercise stress test measurements: For the first eight weeks of the diet, the fasting serum cholesterol level fluctuated both above and below the pre-diet level of 298 mg%, with the largest reduction being 22 mg% to the level of 276 mg%. The fasting serum tri-

glyceride level fluctuated weekly but was usually below the pre-diet level of 157 mg%. The weight appeared to decrease steadily, but only three measurements were taken. On the day of the first post-test, eight weeks after the pre-test, her fasting serum cholesterol and triglyceride levels were 291 mg% and 96 mg% respectively and she weighed 159 pounds. The R-ECG was normal with 0.5 mm S-T segment elevation above the baseline and T inversion on standing. Subject 1 tolerated 10 minutes 27 seconds of exercise (Stage IV), at the end of which time the Max BP was 190/80, the Max HR was 150, the E-ECG showed S-T segments depressed 0.5 mm below the baseline, T wave inversion, but no arrhythmias, and the test was terminated due to leg pains and lightheadedness. The exercise stress test was considered positive because the S-T segments on the E-ECG were depressed 1.0 mm below the level of the S-T segments on the R-ECG.

During the next six weeks while the subject was twice on vacation, the fasting serum cholesterol level appeared to stabilize between 10 mg% and 20 mg% below the pre-diet level; however there were only two measurements taken during this period. The fasting serum triglyceride levels and the weight both rose while this subject was on vacation. At the end of the subject's second vacation, she developed a severe case of poison ivy, for which she was inadvertently given high dose Prednisone therapy for three days, followed by decreasing doses until it was discontinued at the end of two weeks. After the first week of Prednisone therapy, the

fasting serum cholesterol level had fallen slightly, the fasting serum triglyceride level had fallen 50 mg%, and the subject had gained four pounds. One week after the Prednisone therapy was discontinued, the fasting serum cholesterol and triglyceride levels had both fallen sharply, and the subject had lost one pound. Her fasting serum cholesterol level at this time was reduced 71 mg% to the level of 227 mg%, which was below the subject's goal of 239 mg%. Unfortunately, this was not maintained. On the day of the second post-test, eighteen weeks after the pre-test, the fasting serum cholesterol and triglyceride levels both had risen to 284 mg% and 185 mg% respectively and she weighed 168 pounds. The R-ECG was normal with 0.5 mm S-T segment elevation above the baseline and flat T waves on standing. Subject 1 tolerated 9 minutes of exercise (Stage III), at the end of which time the Max BP was 180 systolic, the Max HR was 150, the E-ECG showed S-T segments depressed 1.0 mm below the baseline, flat T waves but no arrhythmias, and the test was terminated due to leg pains and lightheadedness. The exercise stress test was considered positive because the S-T segments on the E-ECG were depressed 1.5 mm below the level of the S-T segments on the R-ECG.

In summary, Subject 1 was a 43-year-old white woman with type IIa-b hyperlipoproteinemia, whose moderately elevated fasting serum cholesterol levels were presumably related to her longstanding obesity and the dietary habits that contributed to her obesity. She attempted to comply with the Alternative Diet, in several forms, for 18 weeks.

Despite the use of the compliance increasing strategies of dietary instruction, weekly supervision, positive reinforcement, family support, and tailoring, the subject admitted to periodic cheating and some days of total non-compliance, particularly when on vacation. Over the course of the dietary treatment, her fasting serum cholesterol level was labile, fluctuating from week to week, primarily below but occasionally above the pre-diet level. The fasting serum cholesterol level was reduced significantly (20%) only once, on the seventeenth week, but this appeared to be a rebounding fall from a rise associated with the prednisone therapy. Therefore, Subject 1 was unsuccessful in achieving and maintaining a significant reduction (20%) in her fasting serum cholesterol level by dietary means. It was notable that the prednisone therapy was associated initially with a rise in the weight and then a delayed rise in both the fasting serum cholesterol and triglyceride levels. When the prednisone therapy was stopped, all three parameters dropped together. Otherwise, there was no apparent relationship between the changes in the fasting serum cholesterol level and the changes in the fasting serum triglyceride level and/or the weight, during the dietary treatment.

Although both the R-ECG and the E-ECG S-T segments showed changes in their relationship to the baseline from the pre-test to the post-tests, all the E-ECG S-T segments remained depressed 1.0 mm or more below the levels of the R-ECG S-T segments. Therefore, there was no significant

decrease in the amount of S-T segment depression on the E-ECGs and the exercise stress tests all remained positive. All the other exercise stress test parameters also remained essentially unchanged from the pre-test to the two post-tests, except that there was a slight increase in the exercise tolerance time, the Max BP, and the Max HR on the first post-test. This occured concurrently with a slight but not significant improvement in the amount of S-T segment depression on the E-ECG (from 1.5 mm to 1.0mm depression), and with an eight pound weight loss; the fasting serum cholesterol levels though were close to the pre-diet level. It is notable that Subject 1's Max HR did not at any time reach the predicted Max HR for her age. Perhaps her stress test results would have been different had she been able to give a maximal rather than sub-maximal effort.

Subject 2:

Pre-diet characteristics: Subject 2 was a 46-year-old white man with type IIa-b hyperlipoproteinemia, with a strong family history of both hyperlipidemia and heart disease (his father diet of a myocardial infarction at age 45). Over the five-year period of 1967-1972, Subject 2 was treated aggressively with diet, exercise, and medication regimens (including Atromid S, Choloxin, and Questran). Although his weight fell from 210 to 165 pounds, his fasting serum cholesterol level remained in the range of 350-465 mg%. In 1972, he became disgusted with this lack of progress and refused all lipid lowering forms of treatment until 1979 when he was

referred the the UOHSC Lipid Clinic. He denied any symptoms, but signs of his longstanding severe hyperlipidemia included severe xanthomas, corneal arcus, mild arteriosclerotic fundi changes and mild obesity. His only other problem was hypertension, for which he took Inderal 20 mg QID and Diazide 50 mg BID. He often had wine with dinner and occasionally drank socially, he did not smoke, and he regularly played tennis and handball. His CBC and chemistry screen were within normal limits. It was thought that his severely elevated fasting serum cholesterol levels were probably related to his strong family history of hyperlipidemia, which might suggest a genetic defect in his cholesterol metabolism. However, he also had eating habits that could promote his hyperlipidemia, including frequent red meat meals (he hunted venison) and frequent lunches in fast food restaurants while traveling on the job. He reported a pre-study 24 hour dietary recall revealing an intake moderately high in calories (2331), fat (46%), cholesterol (258mg), and alcohol (17.7%), slightly low in protein (12%), and low in carbohydrate (25%).

Pre-test measurements: On the morning of the pre-test, the fasting serum cholesterol and triglyceride levels were 550 mg% and 232 mg% respectively and he weighed 206.5 pounds (his height was 6 feet 2 inches). The R-ECG was normal with baseline S-T segments. He tolerated 8 minutes of exercise (Stage III), at the end of which time the Max BP could not be obtained, the Max HR was 142 (he had taken 20mg of Inderal earlier that morning), the E-ECG showed S-T segments depressed

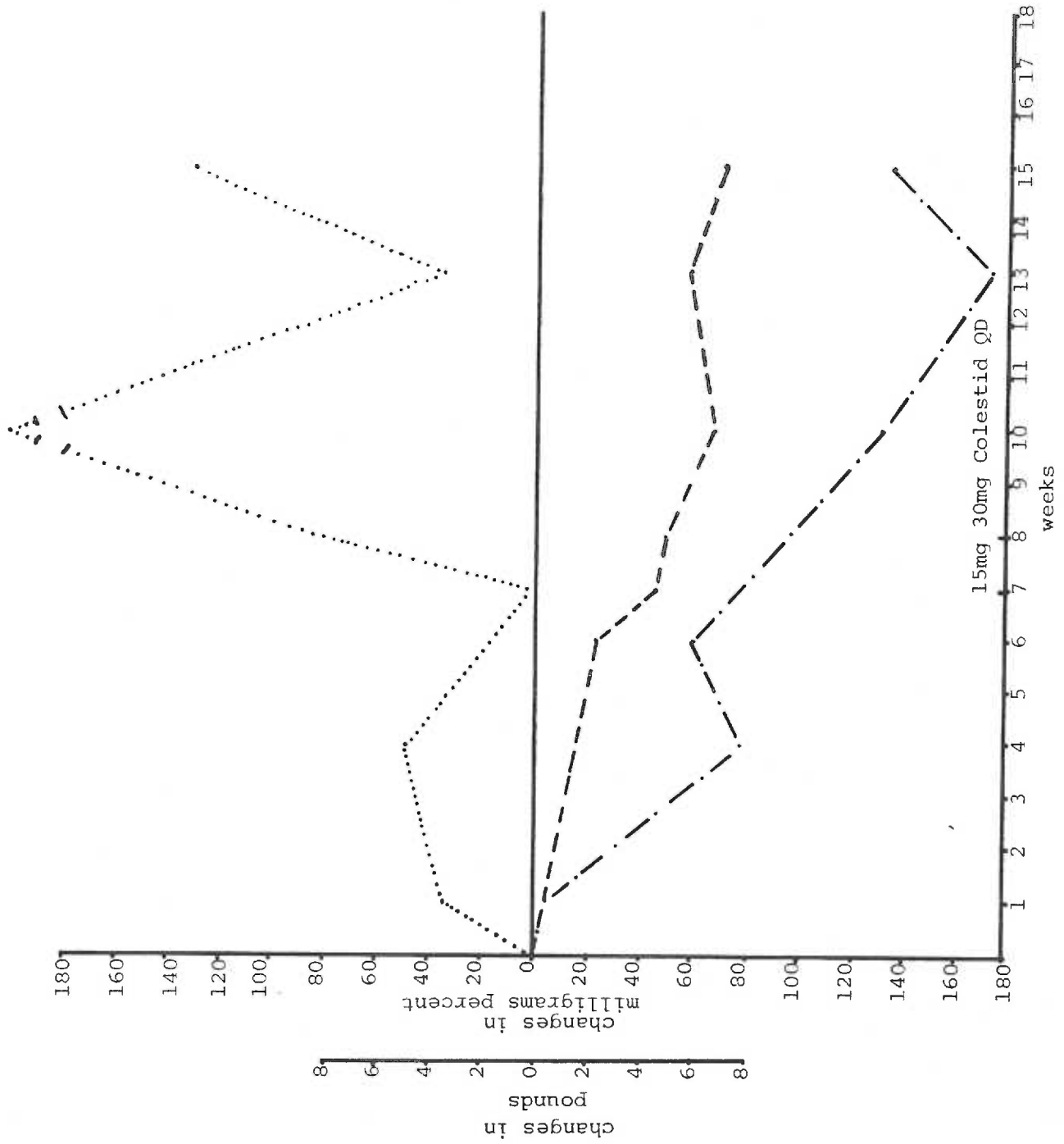
Figure 2: Course of the dietary treatment for Subject 2

Pre-diet fasting serum cholesterol, triglyceride, and weight measurements, together on one baseline.

Fasting serum cholesterol levels in mg% from the pre-diet level.

Fasting serum triglyceride levels in mg% from the pre-diet level.

Weight measurements in pounds from the pre-diet level.


15mg 30mg Colestid QD
weeks
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
changes in milligrams percent
180 160 140 120 100 80 60 40 20 0 20 40 60 80 100 120 140 160 180
changes in pounds
8 6 4 2 0 2 4 6 8

1.0 mm below the baseline and 3 premature ventricular beats, and the test was terminated due to fatigue. The exercise stress test was considered positive because the S-T segments on the E-ECG were depressed 1.0 mm below the level of the S-T segments on the R-ECG.

Study goals: The study goals for Subject 1 were: 1) to achieve and maintain a significant reduction (20%) in his fasting serum cholesterol levels, e.g., from 550 mg% to 440 mg% and 2) to see a significant decrease in the amount of S-T segment depression on the E-ECG, e.g., E-ECG S-T segments depressed less than 1.0 mm below the level of the R-ECG S-T segments; a negative exercise stress test.

Course of the dietary treatment: (See Figure 2)
Diet: Subject 2 followed the Alternative Diet throughout the course of the dietary treatment, but he tailored it to meet his business and traveling needs.

Compliance strategies: 1) Subject education: Subject 2 was knowledgeable about his disease and its prognosis. He understood the principles and restrictions of the diet. His wife was given instruction in the preparation of the Alternative Diet meals, and the subject was given additional tips for compliance with the diet while away from home. The health beliefs of Subject 2 were such that he had a strong desire to lower his serum cholesterol levels in order to avoid serious disease in the future. However, since previous lipid-lowering treatments had failed, he was skeptical of the benefits of another lipid-lowering diet.

2) Subject supervision: Because of a busy work schedule and frequent business trips, Subject 2 came to the UOHSC Lipid Clinic infrequently. When he did come, he was seen by the investigator, a physician, and frequently by a dietician. 3) Behavior modification strategies: Family support, tailoring, and self-monitoring were the primary strategies used with Subject 2, because they could be used with limited investigator supervision.

Serum lipid, weight, and exercise stress test measurements: After four weeks on the diet, the fasting serum cholesterol level had fallen 76 mg% from the pre-diet level of 550 mg% to 474 mg%. It stayed within 15 mg% of this new low level for the next three weeks but never reached the goal of 440 mg%. On the day of the first post-test, seven weeks after the pre-test, the fasting serum cholesterol had fallen to 473 mg%, the fasting serum triglyceride level which had earlier risen was back to the pre-diet level of 232 mg%, and the weight had decreased 4.5 pounds to 202 pounds. The R-ECG was normal with baseline S-T segments. Subject 2 tolerated 9 minutes 38 seconds of exercise (Stage IV), at the end of which time the Max BP was unobtainable, the Max HR was 133 (he had taken 20 mg of Inderal earlier that morning), the E-ECG showed S-T segments depressed 1.5 mm below the baseline but no arrhythmias, and the test was terminated because of fatigue and dyspnea. The exercise stress test was considered positive because the S-T segments on the E-ECG were depressed 1.5 mm below the level of the S-T segments on the R-ECG.

Although Subject 2's fasting serum cholesterol level had fallen on the diet, it had not fallen significantly, and it was thought that it was in his best interest to start him on a medication therapy after the first post-test. He began taking 15 grams of Colestid daily during the eighth week of the study, and during the ninth week he achieved the desired dose of 30 grams a day. Over the next several weeks, on both the diet and the drug therapy, the fasting serum cholesterol fell an additional 95 mg% to 379 mg%, which was below his 20% reduction goal of 440 mg%, thereby constituting a significant reduction. In sharp contrast, the fasting serum triglyceride level was consistently elevated above the pre-diet level, at one time rising to 662 mg%, which was 430 mg% above the baseline of 232 mg%. It was later thought that this strikingly high fasting serum triglyceride level might represent a laboratory error. The weight fell and additional 1.5 pounds and then appeared to stabilize. On the day of the second post-test, fifteen weeks after the pre-test, his fasting serum cholesterol and triglyceride levels were 405 mg% and 377 mg% respectively and he weighed 199 pounds. The R-ECG was normal with baseline S-T segments. He tolerated 9 minutes 17 seconds of exercise (Stage IV), at the end of which time the Max BP was unobtainable, the Max HR was 138 (he had take 20 mg of Inderal earlier that morning), the E-ECG showed S-T segments depressed 1.5 mm below the baseline but no arrhythmias, and the test was terminated because of dyspnea. The exercise stress test was considered positive because the E-ECG S-T segments were depressed 1.5 mm

below the level of the S-T segments on the R-ECG.

In summary, Subject 2 was a 46-year-old man with type IIa-b hyperlipoproteinemia, whose severely elevated fasting serum cholesterol levels were thought to be primarily caused by a genetic defect (as suggested by his strong family history of hyperlipidemia), and secondarily caused by his habit of eating meals high in cholesterol and fat. He attempted to comply with the Alternative Diet for 15 weeks, the last eight of which he was also on Colestid therapy (it is noted that Colestid is not absorbed from the GI tract into the circulation). The compliance improving strategies of dietary instruction, tailoring, family support, and self-monitoring appeared to be helpful because his fasting serum cholesterol level fell steadily during the time he was on the dietary treatment alone, which suggested a good dietary compliance. Since the weight fell at this time also, and continued to fall slowly but consistently with the fall in the fasting serum cholesterol levels during the Colestid therapy, it is probable that his dietary compliance continued throughout the study. Interestingly, the fasting serum triglyceride level was elevated above the pre-diet level during the entire dietary treatment. There was little lability in the fasting serum cholesterol, triglyceride, or weight levels over the course of the diet; this may have reflected the infrequence of the measurements rather than a lack of fluctuation. Subject 2 was unsuccessful in achieving and maintaining a significant reduction in his fasting serum cholesterol on the dietary treatment alone; however he did achieve and maintain a significant reduction when Colestid was added.

The R-ECG S-T segments were at the baseline on all the exercise stress tests; but the E-ECG S-T segments showed more depression from the baseline on the post-test than on pre-test (from 1.0 mm depression on the pre-test to 1.5 mm on the post-tests). Subsequently, since all the E-ECG S-T segments remained depressed 1.0 mm or more below the level of the R-ECG S-T segments, there was no significant decrease in the amount of S-T segment depression on the E-ECGs and the exercise stress tests all remained positive. The other exercise stress test parameters did not change significantly. The Max HR which on the pre-test was 142, decreased to 133 and 138 on the first and second post-tests respectively, despite an increase in the exercise tolerance time on both the post-tests. The low Max HR were thought to be caused by the Inderal therapy. Had he been off the Inderal therapy he may have been able to give a more maximal effort, and bring his Max HR up to the predicted Max HR for his age of 177.

Subject 3:

Pre-diet characteristics: Subject 3 was a 51-year-old black woman with type IIa hyperlipoproteinemia and no outstanding lipid related characteristics. She was first found to have mildly elevated cholesterol two months prior to the study. She complained of infrequent vague chest pains, occasionally related to exertion; she had bilateral corneal arcus and grade II arteriosclerotic fundi changes. Although she was not obese at the time of the study, she reported a history of obesity during most of her adult life. Her other

medical problems of decreased mobility and back and joint pains were related to an old cervical spine injury and osteoarthritis, for which she took Tolectin TID and Norflex PRN. She was able to enjoy daily walks for exercise. She did not take any other medications, she was a social drinker and had smoked occasionally until six years ago. Her CBC and chemistry screen were within normal limits. Because of her negative family and medical history for hyperlipidemia, it was thought that her hypercholesterolemia was related to her earlier obesity and the dietary habits that had contributed to the obesity. Her pre-study 24 hour dietary recall revealed an intake moderate in cholesterol (178mg), protein (18%), and carbohydrate (44%), low in calories (1257%), and high in fat (38%). She described herself as a "health food nut" with a weakness for sweets.

Pre-test measurements: On the morning of the pre-test, her fasting serum cholesterol and triglyceride levels were 264 mg% and 121 mg% respectively and she weighed 120 pounds (her height was 5 feet 1 inch). The R-ECG was normal with 0.5 mm S-T segment elevation above the baseline and T inversion. She tolerated 6 minutes of exercise (Stage III), at the end of which time the Max BP was 140 systolic, the Max HR was 136, the E-ECG showed S-T segments depressed 0.5 mm below the baseline, T wave inversion, but no arrhythmias, and the test was terminated because of fatigue, leg pain, and dyspnea. The exercise stress test was considered positive because the E-ECG S-T segments were depressed 1.0 mm below the level of the R-ECG S-T segments.

Study goals: The study goals for Subject 3 were: 1) to achieve and maintain a significant reduction (20%) in her fasting serum cholesterol levels, e.g., from 264 mg% to 211 mg% and 2) to see a significant decrease in the amount of S-T segment depression on the E-ECG, e.g., E-ECG S-T segments depressed less than 1.0 mm below the level of the R-ECG S-T segments; a negative exercise stress test.

Course of the dietary treatment: (See Figure 3)

Diet: Subject 3 followed the Alternative Diet with a self-imposed-1000 calorie limit. This was to facilitate a desired loss of five pounds.

Compliance strategies: 1) Subject education: Because she had only recently learned that she had hyperlipidemia, she was given instruction in the genesis, manifestations, prognostic implications, and dietary treatment of hyperlipidemia. Subject 3 believed that the dietary treatment would be beneficial in helping her avoid the possibility of a stroke or a heart attack in the future. 2) Subject supervision: Subject 3 came to the UOHSC Lipid Clinic weekly for meetings with the investigator; she saw a dietician intermittently. 3) Behavior modification strategies: Subject 3 tailored the diet to meet her needs and, with the investigator's help, calculated the number of exchanges in each food group that would be allowed in a day. This food plan was written on index cards in such a way that the subject could check off the exchanges eaten from each food group as the day went on. These daily food plan cards then

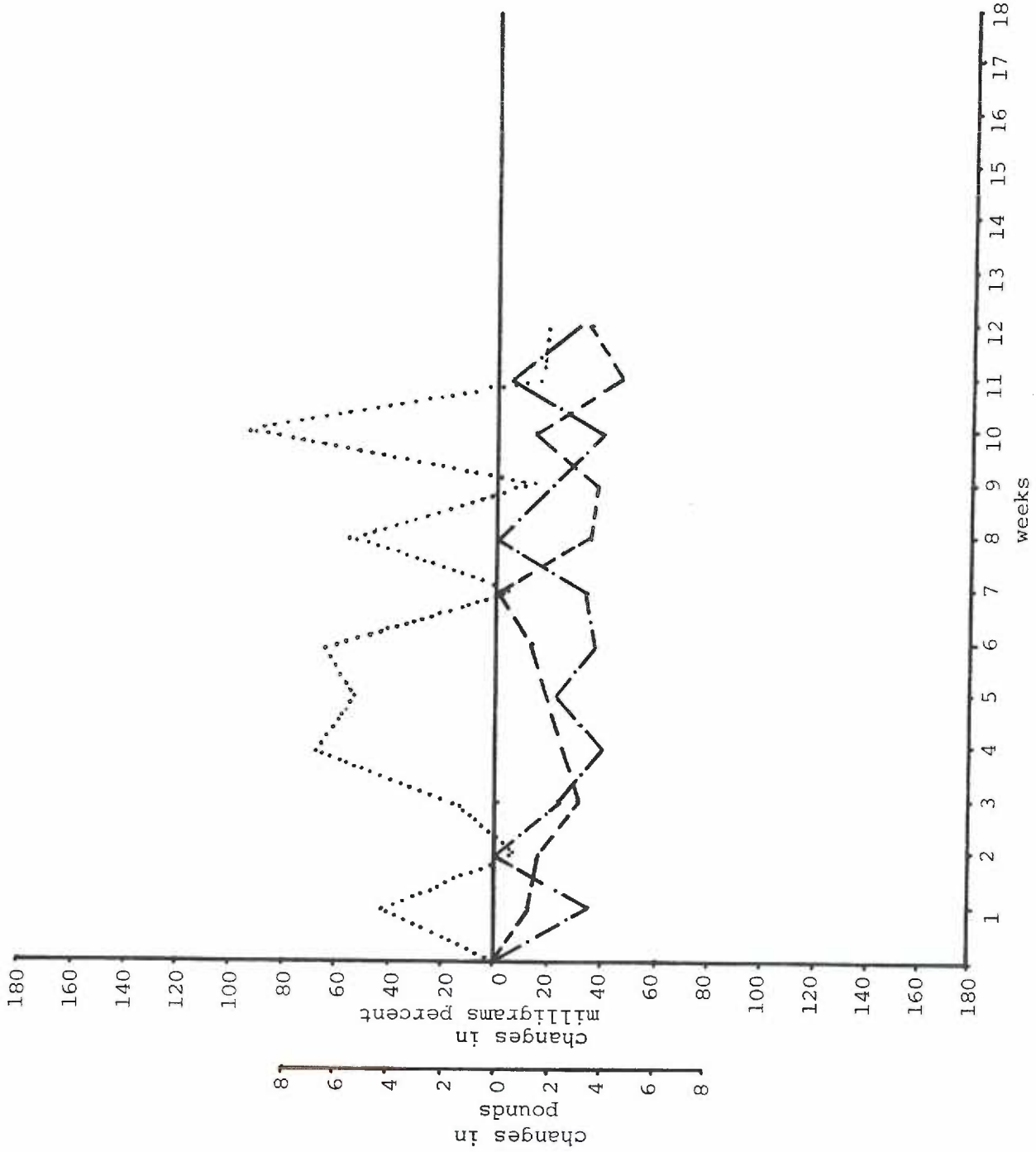
Figure 3: Course of the dietary treatment for Subject 3

Pre-diet fasting serum cholesterol, triglyceride, and weight measurements, together on one baseline.

Fasting serum cholesterol levels in mg% from the pre-diet level.

Fasting serum triglyceride levels in mg% from the pre-diet level.

Weight measurements in pounds from the pre-diet level.


changes in pounds
8 6 4 2 0 2 4 6 8
changes in milligrams percent
180 160 140 120 100 80 60 40 20 0 20 40 60 80 100 120 140 160 180
weeks
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

served as a record from which she could monitor her dietary intake. Positive reinforcement was given by the investigator in the form of praise for good compliance with the diet, as indicated by the subject's diet record, the fasting serum cholesterol levels, and/or weight loss.

Serum lipid, weight, and exercise stress test measurements: Throughout the twelve weeks of the dietary treatment, the fasting serum cholesterol level fluctuated at or below the pre-diet level of 264 mg%. Although at times it fell as much as 40 mg%, the fasting serum cholesterol level never reached the 20% reduction study goal of 211 mg%. The fasting serum triglyceride level fluctuated from just below the pre-diet level of 121 mg% to as high as 214 mg%. The weight fluctuated below the pre-diet weight of 121 pounds, with the lowest weight being 115 pounds. On the day of the first post-test, eight weeks after the pre-test, the fasting serum cholesterol and triglyceride levels were 263 mg% and 176 mg% respectively and she weighed 116.5 pounds. The R-ECG was normal with 1.0 mm S-T segment elevation above the baseline and T wave flattening. She tolerated 6 minutes, 57 seconds of exercise (Stage III), at the end of which time the Max BP was unobtainable, the Max HR was 147, the E-ECG showed S-T segments depressed 1.0 mm below the baseline, T wave flattening, but no arrhythmias, and the test was terminated because of leg fatigue. The exercise stress test was considered positive because the E-ECG S-T segments were depressed 2.0 mm below the level of the S-T segments on the R-ECG. On the day of the second post-test, twelve

weeks after the pre-test, the fasting serum cholesterol and triglyceride levels were 231 mg% and 102 mg% respectively and she weighed 116.5 pounds. The R-ECG was normal with 1.0 mm S-T segment elevation above the baseline and T wave flattening. She tolerated 7 minutes 15 seconds of exercise (Stage III), at the end of which time the Max BP was 110/80, the Max HR was 150, and the E-ECG showed depressed S-T segments but because of a wavy baseline, the amount of S-T segment depression could not be determined. There were no arrhythmias and the test was terminated because of light-headedness, leg fatigue and hypotension. The exercise stress test could not be interpreted because the E-ECG S-T segment depression could not be measured.

In summary, Subject 3 was a 51-year-old black woman with type IIa hyperlipoproteinemia, whose mildly elevated fasting serum cholesterol levels were probably related to the dietary habits that she had developed when obese. Subject 3 tried to comply with the Alternative Diet for a total of 12 weeks. Although her daily diet records showed that she was complying with the diet, it was unclear how effective the compliance improving strategies of dietary instruction, weekly supervision, tailoring, positive reinforcement, and self-monitoring were because the fasting serum cholesterol levels were very labile. Her fasting serum triglyceride and weight levels were also labile, but whereas the weight and fasting serum cholesterol levels fluctuated below the pre-diet level, the fasting serum triglyceride levels fluctuated

above the pre-diet level. There did not appear to be any pattern or relationships between the fluctuations of the three parameters. Subject 3 was unsuccessful in achieving and maintaining a significant reduction (20%) in her fasting serum cholesterol level by dietary means.

Although the R-ECG and the E-ECG S-T segments showed changes in their relationshipto the baseline from the pre-test to the post-test, all the E-ECG S-T segments remained depressed 1.0mm or more below the levels of the R-ECG S-T segments. Therefore, there was no significant decrease in the amount of S-T segment depression on the E-ECGs and the exercise stress test remained positive. Some of the other exercise stress test parameters did change from the pre-test to the first post-test. The T waves which were inverted on the pre-test R-ECG and E-ECG, were flat on the post-test R-ECG and E-ECG. The Max HR increased from 136 on the pre-test to 147 on the first post-test, still less than the predicted Max HR of 174 for her age. The increase in Max HR may have been due to the increase in her exercise tolerance time which was also seen on the first post-test. It was unfortunate that the E-ECG S-T segments on the second post-test could not be interpreted, because she had even more improvement in her Max HR and exercise tolerance time on that test.

Subject 4:

Pre-diet characteristics: Subject 4 was a 32-year-old white woman with type IIa hyperlipoproteinemia whose past

history was remarkable for renal failure and hypertension until a renal transplant in 1968. Since the transplant she had taken maintenance doses of Imuran and Prednisone. She was essentially well, except for progressive obesity, until one to two years prior to the study when she noticed the onset of intermittent vague chest pains. This developed into angina with moderate activity over the four months prior to this study. During that time she had a positive exercise stress test, was found to have severe triple vessel coronary artery disease by angiography, and was started on Inderal 40 mg QID and Isordil 20 mg Q 4 hours. Interestingly, although she had no physical signs of hyperlipidemia, her chart showed records of fasting serum cholesterol levels as high as 491 mg% since December 1976. She did not remember any instructions to limit her fat or cholesterol intake before the positive stress test. She denied any other medical problems. She was able to enjoy walking and light tennis; she admitted to light social drinking and she smoked five cigarettes a day (she had smoked up to two packs per day before the onset of her chest pains). Her CBC and chemistry screen were within normal limits. Although she was obese, the severely elevated fasting serum cholesterol levels of Subject 4 were thought to be primarily related to her renal transplant and post-transplant maintenance medications rather than her dietary habits. Her pre-study 24-hour dietary recall revealed an intake low in cholesterol (96 mg), moderate in protein (18%) and carbohydrates (42%), and high

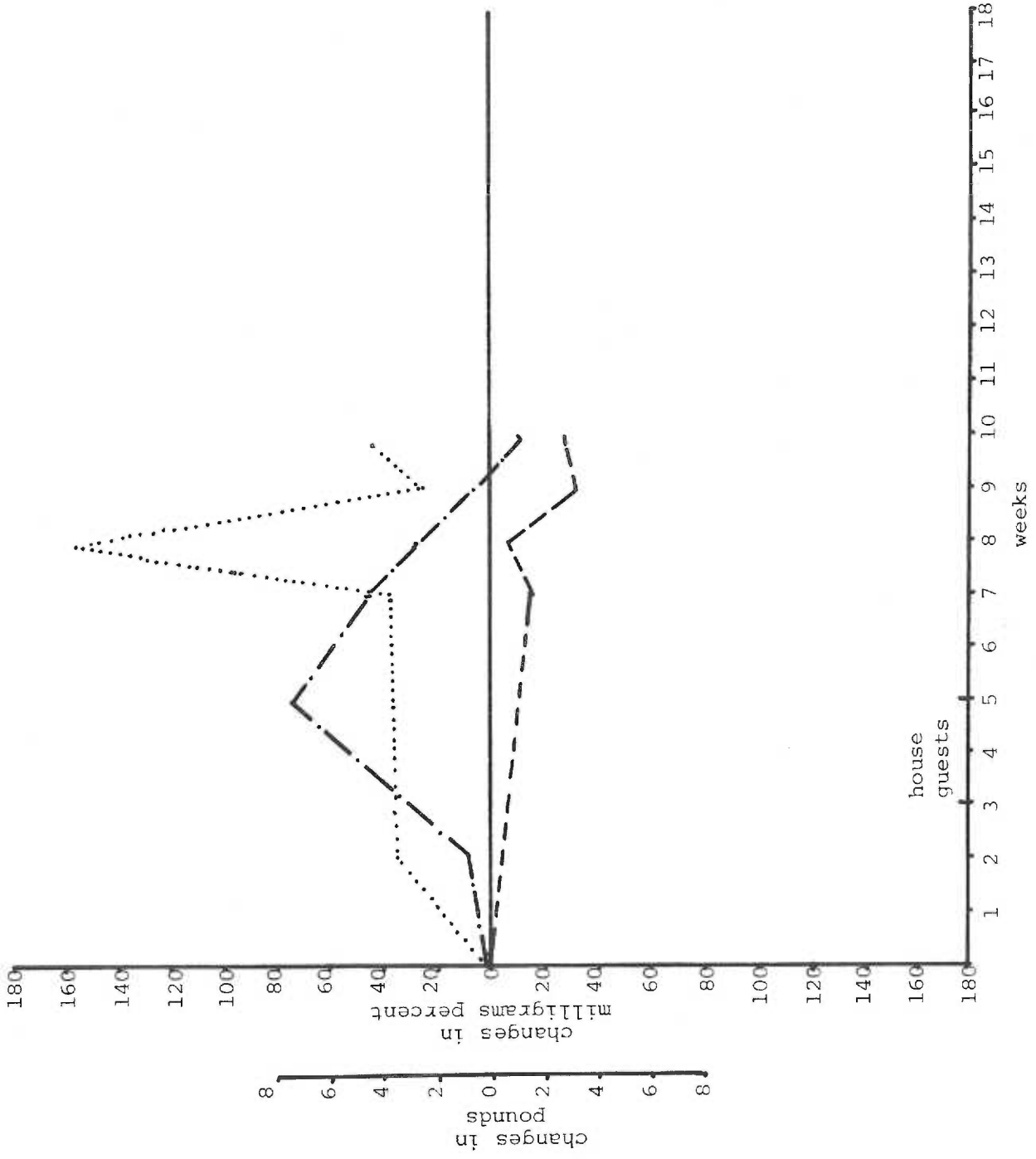
Figure 4: Course of the dietary treatment for Subject 4

Pre-diet fasting serum cholesterol, triglyceride, and weight measurements, together on one baseline.

Fasting serum cholesterol levels in mg% from the pre-diet level.

Fasting serum triglyceride levels in mg% from the pre-diet level.

Weight measurements in pounds from the pre-diet level.


changes in pounds
8 6 4 2 0 2 4 6 8
changes in milligrams percent
180 160 140 120 100 80 60 40 20 0 20 40 60 80 100 120 140 160 180
house guests
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
weeks

and fifth week of the diet and to straying from the cholesterol and fat restrictions one to two times a week at fast food restaurants.

Compliance strategies: 1) Subject education: Subject 4 was given instruction in the genesis, manifestations, prognostic implications, and dietary treatment of hyperlipidemia. In particular, she was told of the probable correlation between her hyperlipidemia and the chest pain and CAD that she now had. Her main motivations for following the diet were to avoid additional medications and/or surgery and to lose weight. 2) Subject supervision: Because she lived more than an hour from UOHSC, the subject's visits were infrequent, but when she was able to come she met with the investigator, and often a dietician. 3) Behavior modification strategies: Positive reinforcement was given for any reported compliance, irrespective of the subject's fasting serum cholesterol level. Because of the subject's irregular and infrequent contacts with the investigator, she was encouraged to independently tailor the diet to meet her needs, and to maintain dietary records as a self-monitoring system. While she apparently did tailor the diet to her needs, the subject's dietary records were irregularly kept.

Serum lipid, weight, and exercise stress test measurements: Subject 4 was on the Alternative Diet for a total of 10 weeks. During that time, her fasting serum cholesterol and triglyceride levels both rose above their pre-diet levels. The reason for this increase is unclear, except

that the subject reported difficulty complying with the diet when entertaining house guests over the fourth and fifth weeks of the diet. Interestingly, she lost rather than gained weight during this time. The fasting serum cholesterol, triglyceride, and weight levels did not appear to be labile, but this may reflect the infrequent measurements more than a lack of fluctuations in the parameters. On the morning of the post-test, ten weeks after the pre-test, the fasting serum cholesterol and triglyceride levels were 350 mg% and 130 mg% respectively, and she weighed 145.5 pounds. The R-ECG was normal with baseline S-T segments. She tolerated 4 minutes of exercise (Stage II), at the end of which time the Max BP was unobtainable, the Max HR was 105 (probably reflecting the Inderal she had taken earlier as well as the low level of exercise), the E-ECG showed S-T segments depressed 3.0 mm below the baseline, normal T waves, and no arrhythmias, and the test was terminated because of fatigue, chest pain, and dyspnea. The chest pain disappeared when the exercise was stopped. The exercise stress test was considered positive because the E-ECG S-T segments were depressed 3.0 mm below the level of the R-ECG S-T segments.

In summary, Subject 4 was a 32-year-old white woman with type IIa hyperlipoproteinemia, whose severely elevated fasting serum cholesterol levels were thought to be primarily related to her renal transplant and post-transplant maintenance medications and secondarily related to her obesity

the dietary habits that contributed to her obesity. She had documented CAD that was probably caused by her hypercholesterolemia and smoking. Subject 4 tried to comply with the Alternative Diet for 10 weeks. The compliance strategies of disease and dietary education, positive reinforcement, tailoring, and self-monitoring were not used effectively by the subject; this may have been due to infrequent subject supervision. She admitted to periodic cheating, particularly when she had house guests. Over the course of the dietary treatment the fasting serum cholesterol and triglyceride levels were consistently above the pre-diet level, but her weight slowly but steadily decreased. Subject 4 was unsuccessful in achieving and maintaining a significant decrease in her fasting serum cholesterol levels by dietary means.

Although both the R-ECG and the E-ECG S-T segments showed changes in their relationship to the baseline from the pre-test to the post-test, the E-ECG S-T segments remained depressed 1.0 mm or more below the level of the R-ECG S-T segments. Therefore, there was no significant decrease in the amount of S-T segment depression on the E-ECGs and the exercise stress test remained positive. The other exercise stress tests remained unchanged except for the Max HR which was much less on the post-test (104 as compared with 136 on the pre-test); this probably paralleled the decrease in the exercise tolerance time (from 5 to 4 minutes). The predicted Max HR for her age was much higher (189) than her Max HR on either test.

in fat (40%). She reported that she enjoyed sweets and eating out in fast food restaurants.

Pre-test measurements: On the morning of the pre-test, the fasting serum cholesterol and triglyceride levels were 356 mg% and 87 mg% respectively and she weighed 148 pounds (her height was 5 feet 4 inches). The R-ECG was normal with 0.5 mm S-T segment depression from the baseline. She tolerated 5 minutes of exercise (Stage II), at the end of which time her Max BP was unobtainable, her Max HR was 136 (she had taken Inderal and Isordil earlier that morning), the E-ECG showed S-T segments depressed 4.0 mm below the baseline, normal T waves, and no arrhythmias, and the test was terminated because of fatigue, chest pain, and dyspnea. She was given one Nitroglycerine 1/150 sublingually, which relieved the chest pain. The exercise stress test was considered positive because the E-ECG S-T segments were depressed 3.5 mm below the level of the R-ECG S-T segments.

Study goals: The study goals for Subject 4 were: 1) to achieve and maintain a significant reduction (20%) in her fasting serm cholesterol levels, e.g., from 356 mg% to 285 mg% and 2) to see a significant decrease in the amount of S-T segment depression on the E-ECG, e.g., E-ECG S-T segments depressed less than 1.0 mm below the level of the R-ECG S-T segments; a negative exercise stress test.

Course of the dietary treatment: (See Figure 4)
Diet: Subject 4 followed the Alternative Diet throughout the study. She did admit to straying from the caloric restrictions when she had house guests during the fourth

Individual Subject Data Comparisons

The Effect of the Dietary Treatment on Fasting Serum Cholesterol Levels and on S-T Segment Depression on the E-ECG:

Table 2 lists the raw data of the fasting serum cholesterol levels at the time of the exercise stress tests for each of the subjects. Analysis of variance was computed on this data to determine if the dietary treatment produced a significant change in the levels from the time of the pre-test to the time of the first post-test and the second post-test, for all the subjects combined. The results of the analysis of variance are summarized on Tables 3 and 4. Initial calculations (Table 3) found that the dietary treatment was effective overall in significantly reducing the fasting serum cholesterol levels ($F=6.9$, $p \leq 0.05$). However, when the analysis of variance was recalculated (Table 4), omitting the fasting serum cholesterol level of Subject 2 that was taken while the subject was on the Colestid therapy (405 mg%), it was found that the dietary treatment was not significantly effective in reducing the fasting serum cholesterol levels ($F=-2.26$, $p \geq 0.05$).

Table 5 lists the raw data of the E-ECG S-T segment depression before and during the course of the diet treatment. The exercise stress test in all subjects remained positive throughout the course of the study. Analysis of variance (Table 6) was computed on this raw data to determine if there was any significant improvement in the amount of S-T segment depression over the course of the

TABLE 2

Raw Data: Fasting Serum Cholesterol Levels at the Time of the Exercise Stress Tests

Subject	Trial Test Cholesterol	Pre-Test Cholesterol	1st Post-Test Cholesterol	2nd Post-Test Cholesterol
1	333 mg%	298 mg%	291 mg%	284 mg%
2	-	550 mg%	473 mg%	405 mg% *
3	248 mg%	264 mg%	263 mg%	231 mg%
4	-	356 mg%	350 mg%	-

* On Colestid drug therapy as well as the diet.

TABLE 3

Summary of Analyses of Variance: Fasting Serum Cholesterol Levels at the Time of the Exercise Stress Tests

Source	SS	df	MS	F
Total	108179	12		
Between Subjects	95700	3		
Within Subjects	12479	9		
Treatments	9680	3	3226.7	6.9 **
Error	2799	6	466.5	

** significant at α = .05; calculated with the measurements taken on Colestid drug therapy included.

TABLE 4

Summary of Analyses of Variance: Fasting Serum Cholesterol Levels at the Time of the Exercise Stress Tests (Excluding the Measurements taken on Colestid Therapy)

Source	SS	df	MS	F
Total	102551	11		
Between Subjects	97633.5	3		
Within Subjects	4917.5	8		
Treatments	18556.2	3	6185.4	-2.26
Error	-13638.7	5	-2727.74	

TABLE 5

Raw Data: E-ECG S-T Segment Depression *
Before and During the Course of the Dietary Treatment

Subject	Trial Test S-T Segment Depression	Pre-Test S-T Segment Depression	1st Post-Test S-T Segment Depression	2nd Post-Test S-T Segment Depression
1	1.5 mm	1.5 mm	1.0 mm	1.5 mm
2	-	1.0 mm	1.5 mm	1.5 mm
3	1.5 mm	1.0 mm	2.0 mm	-
4	-	2.5 mm	3.5 mm	3.0 mm

* E-ECG S-T Segments were measured in millimeters below the baseline or below the level of the R-ECG S-T segment if it was elevated or depressed.

TABLE 6

Summary of Analyses of Variance: E-ECG S-T Segment Depression
Before and During the Course of the Dietary Treatment

Source	SS	df	MS	F
Total	7.31	12		
Between Subjects	5.92	3		
Within Subjects	1.39	9		
Treatments	.81	3	.27	2.78
Error	.58	6	.097	

dietary treatment for all subjects combined. There was no significant decrease in the amount of S-T segment depression on the E-ECG ($F=2.28$, $p \leq 0.05$).

Factors Affecting the Changes in the Fasting Serum Cholesterol Level Measurements:

The 4 type IIa or IIa-b hyperlipoproteinemic subjects in this study were unsuccessful in achieving and maintaining a significant reduction (20%) in their fasting serum cholesterol levels when asked to voluntarily comply with the Alternative Diet. In a comparible study by Connor (1966), 6 normolipidemic men were successful in achieving significant reductions in their fasting serum cholesterol levels within 10-14 days when they were on a strictly controlled cholesterol-free diet. However, the fasting serum cholesterol levels of these subjects were labile, with upward and downward deflections by as much as 40 mg% despite continued strict adherance with the diet. The factors affecting the changes in the fasting serum cholesterol level measurements are illuminated when these two studies are compared.

The diet: Connor's subjects were all on a cholesterol-free diet (the fat and caloric intake was not specified). In contrast, the subjects in the present study followed the Alternative Diet which included a daily intake of 100mg cholesterol, 20% fat (5% saturated, 15% unsaturated), and only enough calories to achieve or maintain a desirable weight for the subject's height. Therefore, although the

Alternative Diet is much lower in cholesterol, fat, and calories than the typical American Diet of 800mg cholesterol, 40% fat, and 2400 calories (Connor & Connor, 1972), it still presents some cholesterol that is available for absorption, some saturated fat to facilitate absorption of the cholesterol, and some calories to serve as a substrate for triglyceride synthesis (increasing the lipoproteins which carry triglyceride and also cholesterol), to increase the serum cholesterol. In subjects who have a dysfunction in their ability to metabolize cholesterol, it could be possible that even the small amount of cholesterol in the Alternative Diet would be enough to slow or interfer with the reduction in fasting serum cholesterol levels. Perhaps this is one reason why the subjects in this study were unsuccessful in achieving significant reductions in their fasting serum cholesterol levels.

Dietary compliance: In Connor's study, the dietary intake of each subject was strictly controlled by the investigator, e.g., the subjects had no control over their diet; they were given cholesterol-free meals and were not allowed to eat any food containing cholesterol. Hence, Connor's study was designed to eliminate the variable of dietary compliance by insuring that each subject had one-hundred percent compliance with the diet. In the present study, the dietary intake of each subject was self-controlled, e.g., although the subjects were asked to comply with the diet, they had complete control over their diet; they could

eat any food that was not on the diet if they so desired.

According to Haynes (1979), compliance with any treatment is determined by three factors: the nature of the disease being treated, the nature of the treatment, and the patient's health beliefs about the disease being treated.

All of the subjects in this study had hypercholesterolemia, a chronic disease which, if untreated, results in severe disability or death in the near or distant future. Hypercholesterolemia can be caused by an excess intake of cholesterol, saturated fat, and/or calories or it can be caused by a dysfunction in the body's ability to metabolize these substances (Fredrickson et al., 1967; Connor & Connor, 1972, 1977). The cause of the hypercholesterolemia in each subject was different.

The nature of the treatment, the Alternative Diet, was the same for each subject, as discussed earlier. It affected dietary compliance in that it required a major change in the subjects' eating habits and changed their lifestyle to the extent that they had to give up the individual and social pleasures derived from the typical American Diet. Their treatments differed in that the compliance improving strategies of education, supervision, and behavior modification were individualized to meet the needs of each subject.

The subjects' health beliefs about the disease and the treatment varied on specifics, but were similar to the extent that they each saw the Alternative Diet as a means of preventing or delaying the deleterious effects of hypercholesterolemia. As noted by Fey et al. (Note 3), based on their

health beliefs, the subjects had to decide which alternative was more tolerable; the major change in eating habits and lifestyle required by the diet or the risk of severe disability or death resulting from chronically elevated fasting serum cholesterol levels.

Because this study did not utilize a standardized measure of dietary compliance, it was difficult to determine the degree to which the subjects complied with the diet, and the extent to which the factors described by Haynes affected their dietary compliance. However, a rough estimate of each subject's dietary compliance was made from the changes in the fasting serum cholesterol levels and the subjects' reports of good compliance and/or compliance difficulties.

Subject 2's hypercholesterolemia was thought to be caused primarily by a genetic defect in his ability to metabolize cholesterol and secondarily by his dietary habits. He appeared to have a good initial reduction in his fasting serum cholesterol levels, but they were not significantly reduced by dietary means. He also reported good dietary compliance. Since his hypercholesterolemia was in part due to his dietary habits, it is probable that improvement in these habits (compliance with the diet) accounted for the initial reduction in the fasting serum cholesterol levels. The lack of significant reduction may have been caused by a slowing or inhibiting of the diet's effects by the genetic defect, compliance difficulties, or simply not enough time on the diet.

Subject 4's hypercholesterolemia was caused primarily by the effects of her renal transplant and the post-transplant medications and secondarily by her dietary habits. Her fasting serum cholesterol levels were consistently above their pre-diet level during the diet and she admitted to occasional cheating on the diet and non-compliance particularily when entertaining house guests. Interestingly, her weight slowly decreased over the course of the diet. It appeared that Subject 4 had difficulty complying with the diet, and perhaps had more trouble complying with the cholesterol and fat restrictions than the caloric restriction, judging from her weight loss. She may have had difficulty breaking old dietary habits, particularly when entertaining, It is unlikely that her renal transplant or post-transplant medications were the cause of the increased fasting serum cholesterol levels.

Subjects 1 and 3 both had hypercholesterolemia that was presumably caused by their poor dietary habits. Although both subjects reported good dietary compliance (with the exception of some minor cheating and some non-compliance by Subject 1 while on vacation), their fasting serum cholesterol levels did not become significantly reduced; they fluctuated from week to week, primarily below the pre-diet level. The fluctuations in the fasting serum cholesterol levels could be caused by mixed dietary compliance. But it should also be noted that Connor (1966) found that fasting serum cholesterol levels can be naturally labile even with strictly enforced dietary compliance.

From the above discussion, it appears that dietary compliance is an important variable in the reduction of fasting serum cholesterol levels by dietary means. Future studies in this area need to more closely examine the factors which affect dietary compliance and develop a standardized, valid means of measuring dietary compliance.

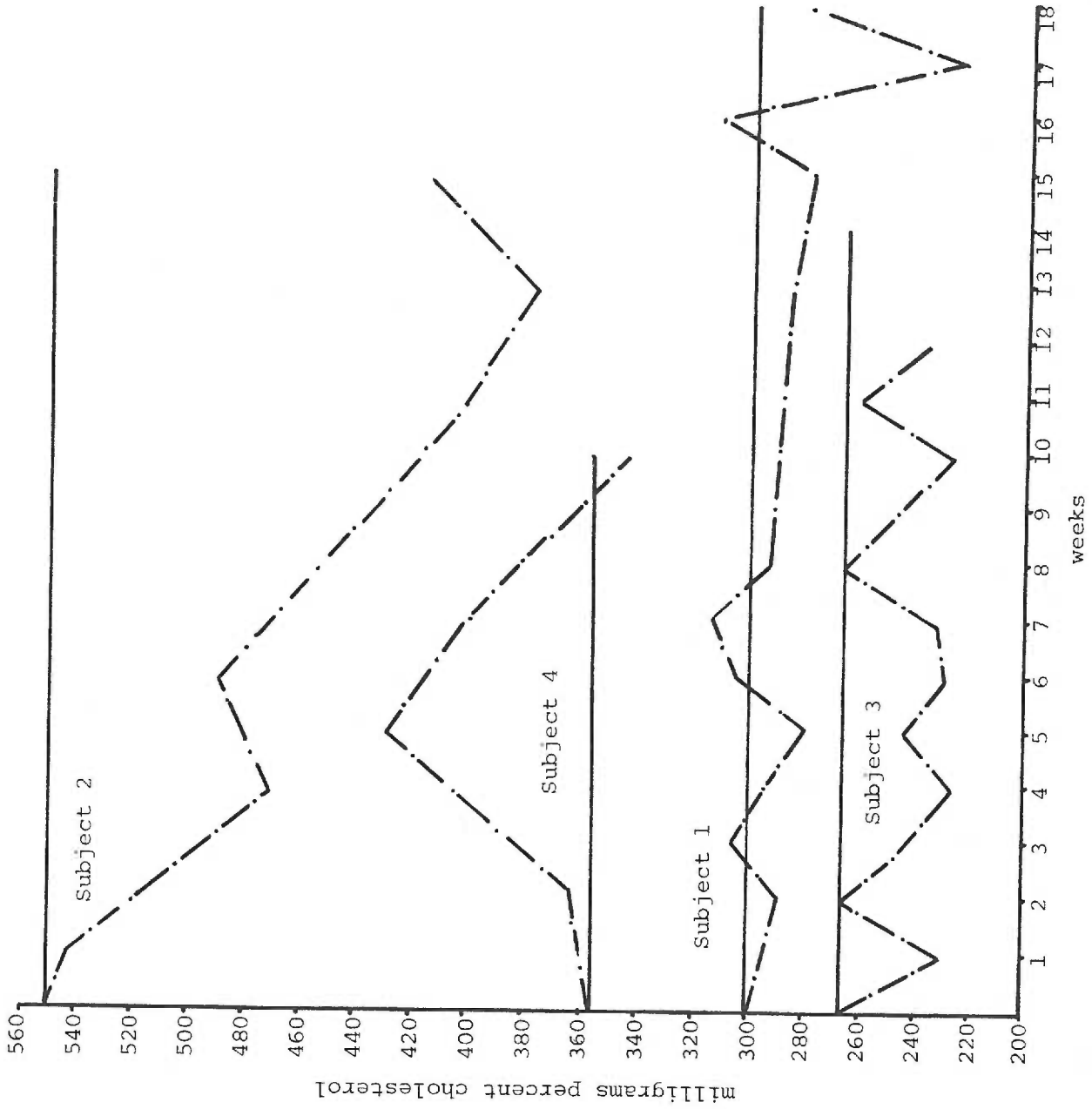
The lability of fasting serum cholesterol levels: As mentioned earlier, Connor (1966) found that the fasting serum cholesterol levels of his six men showed upward and downward fluctuations by as much as 40 mg%, despite strict adherence to the diet (see Figure 6, Appendix A). The fasting serum cholesterol levels of Subjects 1 and 3 of this study were also found to fluctuate as much as 40 mg% from week to week, despite reports of good compliance (see Figure 5). The fasting serum cholesterol levels of Subjects 2 and 4 did not appear to fluctuate, but it is possible that this was due to the infrequent measurements rather than the lack of fluctuations. Therefore, the natural lability of fasting serum cholesterol levels should be considered when trying to determine the effectiveness of lipid lowering treatments.

The medications: The elevated fasting serum cholesterol levels of Subject 4 were primarily attributed to her renal transplant and post-transplant maintenance medications. It is interesting that prednisone, which was one of Subject 4's medications, was associated with a striking increase in the fasting serum cholesterol levels of Subject 1. This increase was noted to follow and increase in the subject's weight and

Figure 5: Course of the dietary treatment for all subjects combined, showing changes in the fasting serum cholesterol levels from the pre-diet levels.

Pre-diet fasting serum cholesterol level.

Fasting serum cholesterol levels measured over the course of the diet.


milligrams percent cholesterol
560
540
520
500
480
460
440
420
400
380
360
340
320
300
280
260
240
220
200
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
weeks
Subject 2
Subject 4
Subject 1
Subject 3

parallel an increase in the fasting serum triglyceride level. Further study needs to be done on the effect of prednisone therapy on fasting serum cholesterol and triglyceride levels and the means, if any, of blocking the lipid increasing effects in order to prevent CAD in patients on long-term prednisone therapy.

Time: In Connor's study (1966), the 6 normolipidemic men were able to significantly reduce their fasting serum cholesterol levels within 10-14 days when on a strictly controlled cholesterol-free diet. The reduction in the fasting serum cholesterol levels of the subjects in the present study were limited because the subjects were hyperlipidemic (they had some dysfunction in their ability to metabolize cholesterol), the diet was not entirely cholesterol-free, and dietary compliance was not strictly enforced. It was originally thought that 8 weeks would be long enough for the subjects to adjust to the diet and succeed in reducing their fasting serum cholesterol levels significantly. But even 18 weeks did not prove long enough for Subject 1. Further studies in this area may need to allow more time for the reduction of fasting serum cholesterol levels, or find better methods of improving dietary compliance.

Factors Affecting the Changes in the Measurements of S-T Segment Depression on the E-ECG:

The measurement of S-T segment depression: In this study, E-ECG S-T segments were considered significantly

if they were 1.0 mm or more below the baseline, or below the level of the R-ECG S-T segments if they were abnormally elevated or depressed, at 0.08 seconds past the J point. Since this was a pilot study, there was no precedent for the use of the criteria for significance described above. Other investigators may want to change the amount of S-T segment depression that was considered significant, or measure S-T segment depression only from the baseline, irrespective of the R-ECG S-T segments. In the present study, if the R-ECG S-T segments were not considered in the measurement of S-T segment depression on the E-ECG, Subject 1 would have had a negative first post-test, and Subject 3 would have had a negative pre-test.

There are several difficulties encountered in the measurement of S-T segment depression on the E-ECG. Since the subject is moving on the treadmill while the E-ECG recording is being taken, it is often impossible to get a steady recording without artifact: the baseline may be inconsistent, the amount of S-T segment depression may vary, or the S-T segments may be too erratic to be measured (see Appendix B, Figure 10). In addition, the intervals being measured, fractions of millimeters, are very small, and subsequently subject to errors in judgement. All of these factors, alone and combined may result in intra and inter observer variations in the interpretation of S-T segment depression. In this study, an attempt was made to increase the reliability of the measurements of S-T segment depression on the E-ECG by consistently having the two readers.

TABLE 7

Pre-Test, Study Goal, and Post-Test
Fasting Serum Cholesterol Levels

Subjects	Pre-Test Cholesterol	Study Goal Cholesterol	1st Post-Test Cholesterol	2nd Post-Test Cholesterol
1	298 mg%	239 mg%	291 mg%	284 mg%
2	550 mg%	440 mg%	473 mg%	405 mg% *
3	264 mg%	211 mg%	263 mg%	231 mg%
4	356 mg%	285 mg%	350 mg%	-

* on Colestid and diet therapy.

Study goals: Table 7 lists the pre-test, study goal, and post-test fasting serum cholesterol levels for subjects 1-4. Although the study goal was different for each subject in milligrams percent cholesterol, in each case it represented a significant reduction (20%) in their fasting serum cholesterol level. All of the subjects were unsuccessful in achieving and maintaining their study goal by dietary means and, as noted earlier, there was no significant decrease in the amount of S-T segment depression on their E-ECGs. Subject 2 did achieve and maintain a significant reduction in his fasting serum cholesterol level with the help of the Colestid therapy. Despite this, however, there was still no significant decrease in the amount of S-T segment depression on his E-ECG. It would appear that the significant reduction in Subject 2's fasting serum cholesterol levels was not adequate enough to affect the S-T segment depression on his E-ECG, if the two are related. But a fasting serum cholesterol level of 405 mg% is still severely elevated. It might have been more appropriate

to the purposes of this study, to have the study goal be the reduction of the fasting serum cholesterol levels to the normal range. If there was still a significant amount of S-T segment depression on the E-ECG when the fasting serum cholesterol levels were within the normal range, then it would be unlikely that the elevated fasting serum cholesterol level had any causative effect on the amount of S-T segment depression on the E-ECG.

The other exercise stress test parameters: The exercise stress test parameters other than S-T segment depression were all evaluated for change from the pre-test to the post-tests on each subject. The R-ECGs remained normal in all subjects. Subject 3's T waves changed from being inverted on the pre-test R-ECG and E-ECG to being flat on the post-test R-ECG and E-ECG; there were no changes in the other subjects' T waves. The Max BP was increased from the pre-test to the post-test for Subject 1 only, but it is noted that the Max BP was unobtainable in the other subjects on most of the tests. The exercise tolerance time increased from the pre-test to the post-test in Subjects 1, 2, and 3 but it was decreased in Subject 4. The exercise tolerance time was paralleled by an increase in the Max HR in Subjects 1 and 3, but the Max HR decreased in Subjects 2 and 4. Since Subjects 2 and 4 were on Inderal, which slows the heart rate, their decreased Max HR may have been caused by the medication. It was noted that none of the subjects reached the Max HR that was predicted for their age. All of the subjects stopped their

post-tests for essentially the same reasons that they stopped their pre-tests. The changes in these exercise stress test parameters did not appear to have any pattern, or to relate to the changes in the fasting serum cholesterol levels. Since there was no significant decrease in the amount of S-T segment depression on the E-ECGs, it could not be determined if there was any relationship between the S-T segment depression and the other exercise stress test parameters.

It is evident from the foregoing that hypothesis 1 could not be accepted or rejected because the pre-condition of a significant reduction in the fasting serum cholesterol levels was not met. Hypothesis 2 was guardedly accepted because the lack of success in achieving and maintaining a significant reduction in the fasting serum cholesterol levels by dietary means was associated with no significant decrease in tha amount of S-T segment depression on the E-ECG. Hypotheses 3 and 4 could not be tested because there were no subjects with elevated fasting serum triglyceride levels.

CHAPTER IV

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

This study was concerned with the relationship between the elevated fasting serum lipid levels and the S-T segment depression on the E-ECGs of hyperlipidemic subjects. A review of the literature revealed that hyperlipidemic patients have an increased incidence of S-T segment depression on the E-ECG. Since chronically elevated serum lipid levels are associated with the development of CAD, and since CAD can cause myocardial ischemia which is reflected as S-T segment depression on the E-ECG, it is generally assumed that the S-T segment depression seen on the E-ECGs of hyperlipidemic patients is due to CAD. However, it was recently found that S-T segment depression occured on the E-ECGs of some hyperlipidemic patients who had no or insignificant CAD by angiography. Based upon this finding, it was suggested by the investigator that there could be a relationship, independent of CAD, between elevated fasting serum lipid levels and S-T segment depression on the E-ECGs of hyperlipidemic subjects. In support of this, it was found in the literature that there are a number of conditions other than CAD which can cause S-T segment depression on the E-ECG and that acute elevations and reductions in fasting serum lipid levels are associated with acute increases and decreases, respectively, in some of

these conditions, including platelet aggregation, arterial spasm, microemboli or thrombi formation, and erythrocyte aggregation. It was therefore proposed that the acute relationship, independent of CAD, between elevated serum lipid levels and S-T segment depression on the E-ECG would be demonstrated if a reduction in the elevated serum lipid level was associated with a decrease in the amount of S-T segment depression on the E-ECG. A further review of the literature revealed that elevated serum lipid levels could be reduced significantly within several weeks if the patient strictly complied with a diet low in cholesterol and saturated fat and restrictive in calories.

The primary purpose of this study was to explore the effect of acute dietary reduction of fasting serum lipid levels on the amount of S-T segment depression seen on the E-ECGs of hyperlipidemic subjects, as a means of demonstrating a relationship, independent of CAD, between elevated serum lipid levels and E-ECG S-T segment depression. In addition, because this was a pilot study, a secondary purpose was to explore and describe the factors affecting the fasting serum lipid levels and the S-T segment depression on the E-ECGs of each subject over the course of the dietary treatment, to benefit further research in this area. Hypotheses 1 and 3 proposed that if the subjects were successful in achieving and maintaining a significant reduction in their fasting serum cholesterol and triglyceride levels, respectively, there would be an associated decrease in the amount of S-T segment depression on their E-ECGs. Hypotheses 2 and 4 proposed that if they were unsuccessful in achieving and maintaining a significant reduction in their

fasting serum cholesterol and triglyceride levels respectively, there would be no associated decrease in the amount of S-T segment depression on their E-ECGs.

Four type IIa or IIa-b hyperlipoproteinemic patients with significant E-ECG S-T segment depression (1.0 mm or more below the baseline, or below the level of the R-ECG S-T segments if they were elevated or depressed, at 0.08 seconds past the J point) on their pre-test, and no excluding characteristics, served as subjects. They ranged in age from 32 to 51-years-old; the mean age was 43 years. Three of the subjects were women and one was a man· the man was the only subject with a family history of hyperlipidemia. Their fasting serum cholesterol levels ranged from 264 to 550 mg%; the mean was 367 mg%. These subjects all fell into one group whose common characteristics were elevated fasting serum cholesterol levels and positive stress tests. Because there was not a group of subjects with elevated fasting serum triglyceride levels, Hypotheses 3 and 4 could not be tested.

Therefore, in its final form, the present study utilized a longitudional, pre-test, post-test design with one group of subjects in which each subject served as his own control. Each subject was asked to voluntarily comply with the treatment, the Alternative Diet, for a minimum of 7 weeks, during which time serial fasting serum cholesterol levels would be measured. The pre-test and post-tests consisted of measurements of the independent variable, the fasting serum cholesterol level, and the dependent variable, the amount of S-T segment depression on the E-ECG. The pre-test measurements were taken before the

subjects started the diet, the first post-test measurements were taken during the seventh or eighth week of the diet, and the second post-test measurements were taken when it was thought that the fasting serum cholesterol level was most likely to be reduced significantly.

The results of this study were inconclusive with relation to its primary purpose: all of the subjects were unsuccessful in achieving and maintaining a significant reduction (20%) in their fasting serum cholesterol levels by dietary means and there was no significant decrease in the amount of S-T segment depression on their E-ECGs. One of the subjects, Subject 2, was successful in achieving and maintaining a significant reduction (20%) in his fasting serum cholesterol level (from 550 to 405 mg%) with the help of Colestid therapy, but there was no associated decrease in the amount of S-T segment depression on his E-ECG. It was noted that, although a fasting serum cholesterol level of 405 mg% was a significant reduction for Subject 2, it still was severely elevated and therefore could be related to the S-T segment depression on his E-ECG. It may have been more appropriate to the purposes of this study to reduce the fasting serum cholesterol levels to the normal range and then determine if there was an associated decrease in the S-T segment depression on the E-ECG.

Considering only the findings resulting from the dietary treatment, Hypothesis 1 could not be accepted or rejected because the pre-condition of a significant reduction in the fasting serum cholesterol levels was not met. Hypothesis 2 was guardedly accepted because the lack of success in achieving

and maintaining a significant reduction in the fasting serum cholesterol levels by dietary means was associated with no significant decrease in the amount of S-T segment depression on the E-ECG. Therefore, this study did not fulfill its primary purpose of demonstrating a relationship, independent of CAD, between the elevated fasting serum cholesterol levels and the S-T segment depression on the E-ECGS of the hyperlipidemic subjects. However, in order to benefit further research in this area, the secondary purpose of this study was fulfilled.

Briefly stated, the factors affecting the changes in the fasting serum cholesterol level measurements included: the Alternative Diet, the dietary compliance, the lability of the fasting serum cholesterol levels, the medication prednisone, and the time allowed for the dietary treatment. The factor of dietary compliance in itself was affected by the nature and cause of the subject's hypercholesterolemia, the nature of the Alternative Diet, the compliance strategies, the subject's health beliefs about the Alternative Diet and his hypercholesterolemia, and the lack of a standardized, valid measure of dietary compliance.

The factors affecting the measurements of S-T segment depression on the E-ECG included: the method of measuring S-T segment depression on the E-ECG, the criteria of significance, the difficulties encountered in measuring S-T segment depression on the E-ECG, the fasting serum cholesterol level study goals, and the relations between the changes in the fasting serum cholesterol levels and the changes in the other

exercise stress test parameters.

The most major problems and limitiations encountered in this study were related to dietary compliance. It is probable that the subjects in this study were unsuccessful in achieving and maintaining a significant reduction in their fasting serum cholesterol levels primarily because they were unable to consistently and strictly comply with the Alternative Diet. Therefore, it is suggested that future studies in this area eliminate the variable of dietary compliance by strictly controlling the dietary intake of the subjects. It is also recommended that the fasting serum cholesterol levels be reduced to within the normal limits rather than the 20% reduction used in this study. Future investigators will need to be aware of the natural lability of fasting serum cholesterol levels and the difficulties encountered in measuring S-T segment depression when comparing these two parameters.

Although this study was unsuccessful in demonstrating a relationship, independent of CAD, between elevated fasting serum lipid levels and S-T segment depression on the E-ECG in hyperlipidemic subjects, it is hoped that it will be of benefit to further lipid and exercise stress test research.

ABSTRACT

THE EFFECT OF SERUM LIPID LEVELS ON THE EXERCISE STRESS TEST RESULTS IN HYPERLIPIDEMIC SUBJECTS

The primary purpose of this study was to explore the effect of acute dietary reduction of fasting serum lipid levels on the amount of S-T segment depression on the E-ECGs of hyperlipidemic subjects, as a means of demonstrating a relationship, independent of CAD, between elevated serum lipid levels and S-T segment depression on the E-ECG. In addition, because this was a pilot study, a secondary purpose was to explore and describe the factors affecting the fasting serum lipid levels and the S-T segment depression on the E-ECGs of each subject over the course of the diet. Hyperlipidemic patients have an increased incidence of S-T segment depression on the E-ECG, but in some hyperlipidemic patients, the E-ECG S-T segment depression is not caused by CAD as usually assumed. S-T segment depression can be caused by conditions other than CAD, and elevated serum lipid levels are associated with some of these condition. This study tested two hypotheses: 1: success in achieving and maintaining significant reductions (20%) in fasting serum cholesterol levels will be associated with significant decreases in the amount of S-T segment depression on the E-ECGs and 2: lack of success would be associated with no associated decrease in the amount of S-T segment depression on the E-ECGs. Four type IIa or IIa-b hyperlipoproteinemic patients with S-T segment depression of 1.0 mm or more below the baseline as 0.08 seconds past the J point on a E-ECG and pre-diet fasting serum cholesterol levels greater than 260 mg% served as subjects. The study utilized a longitudional, pre-test, post-test design with one group of subject in which each served as his own control. The subjects attempted to voluntarily comply with the Alternative Diet (100 mg cholesterol, 20% fat) for a minimum of 7 weeks. The pre-test and post-test measurements consisted of measurements of the independent variable, the fasting serum cholesterol level, and the dependent variable, the amount of S-T segment depression on the E-ECG. The results of the study were inconclusive: all of the subjects were unsuccessful in achieving and maintaining a significant reduction in their fasting serum cholesterol levels by dietary means and there was no significant decrease in the amount of S-T segment depression on the E-ECGs. Hypothesis 1 could not be tested, becasue the fasting serum cholesterol levels did not fall. Hypothesis 2 was guardedly accepted. A number of factors were found to affect the changes in the fasting serum cholesterol level and the S-T segment measurements. Of these, dietary compliance was the major problem.

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APPENDICES

APPENDIX A

Lability of Serum Cholesterol Levels:
Figure 6

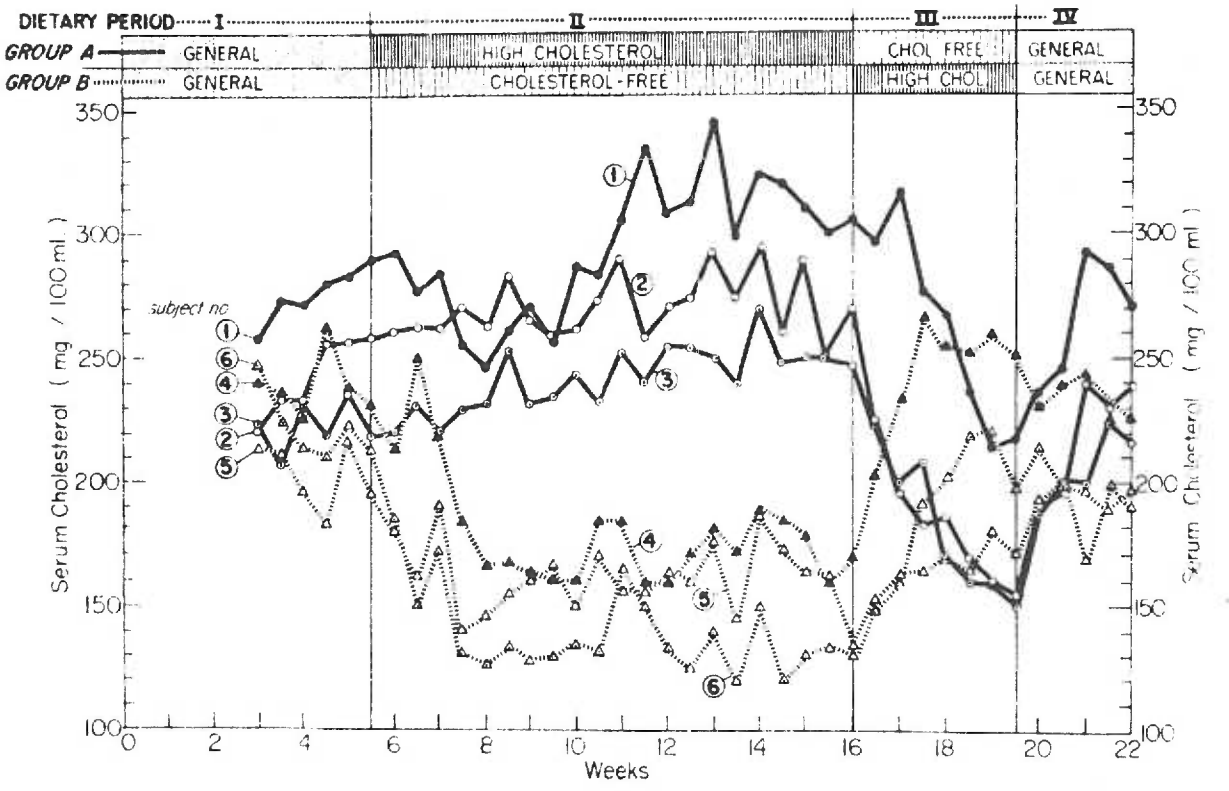

Figure 6: The serum lipid levels of six normolipidemic men who received a series of diets containing differing amounts of cholesterol but were balenced as regards nutrients. Note that when on the cholesterol-free diet, the fasting serum cholesterol levels declined significantly (from a mean of 220mg% to a mean of 156mg%) within 10 to 14 days. The low fasting serum cholesterol levels continued for the duration of the cholesterol-free diet, but the week to week variations showed lability of the fasting serum cholesterol levels in all the subjects. Reprinted with permission from W.E. Connor (1966).

APPENDIX B

EXERCISE STRESS TEST DATA COLLECTION FORMS

Treadmill Exercise Stress Test Protocol
Informed Consent For Electrocardiography
Exercise Electrocardiography Worksheet
Table 8: Desirable Weights for Heights
Table 9: Ages and Maximal Heart Rate
Figure 7: The Normal Electrocardiography Complex
Figure 8: The Evolution of S-T Segment Depression and Elevation
Figure 9: The Measurement of S-T Segment Depression
Figure 10: Difficulties Encountered in Interpreting E-ECG Tracings

TREADMILL EXERCISE STRESS TEST PROTOCOL

INTRODUCTION

The following protocol is that developed by Bruce and his colleagues at University of Washington, for exercise testing of normal and cardiac patients (Bruce, 1971; Bruce, Blackman, Jones, & Strait, 1963; Bruce & Hornstein, 1969). The written format of the protocol has been adapted from Erbele (Note 4). Other references include Blackburn (1969), Constant (1973), and Ellestad (1975). The Bruce protocol has been modified to meet the specific needs of this study. This protocol is designed to achieve the following objectives in subjects with elevated and then lowered lipid levels:

1. Assessment of the amount of S-T segment depression as progressive levels of exercise impose increasing myocardial demand for oxygen.
2. Assessment of the amount of change in heart rate (HR), blood pressure (B), other ECG measurements, and symptoms, with progressive levels of exercise.
3. Subjective observation of the subject's response to exercise.

SCHEDULING

The test requires approximately one hour of the subject's time. Scheduling will be done with the nurse investigator. Because exercise may increase or decrease serum cholesterol levels and because exercise has been shown to decrease serum triglyceride levels for up to 48 hours (Ellestad, 1975), the exercise stress test will be performed after the fasting lipid levels are drawn. All tests will be done in the morning in order to make it easier for the subjects to fast for 12 hours before the fasting serum lipid levels are drawn. Subjects will also be required to abstain from coffee, tea, and tobacco for 3 hours prior to the test. In scheduling the test time, consideration will be given to the convenience of the subject.

PATIENT INSTRUCTIONS

1. Before the scheduled time for the fasting serum lipid determinations and the exercise stress test, subjects will:
   a. abstain from exercise of significance for 48 hours (Ellestad, 1975);
   b. abstain from all food and caloric beverages for 12 hours;
   c. abstain from coffee, tea, and tobacco for 3 hours (Constant, 1973);
   d. arrange to bring shorts and gym shoes, if

desired; hospital scrub pants and gown tops will be provided if needed;
e. take all prescribed medications as on any normal day.

2. At the time of the test, the exercise stress test will be described to the subject both verbally and in the written form on the consent (see Appendix). Time will be allowed for discussion of the test. The subject, the physician, and a witness must sign the consent before the exercise stress test can be performed.

METHODOLOGY OF THE TEST

1. Patient supine and resting for ten (10) minutes.
2. Blood samples drawn for fasting serum lipid levels.
3. Resting 12 lead ECG with rhythm strip taken.
4. Cardiovascular history and physical performed, with attention to changes in food or medication intake, symptoms, and/or physical findings. A summary will be recorded in the subject's file (and chart if applicable).
5. Contraindications to performing the test (Erbele, Note 4):
   a. Changing cardiac conditions on the resting ECG.
   b. Evidence of congestive heart failure.
   c. Arrhythmias:
      (1) Third degree AV block.
      (2) Second degree AV block.
      (3) Paroxysmal atrial tachycardia, at rest.
      (4) Atrial flutter or fibrillation, at rest.
6. Predicted maximal heart rate of subject determined from the "Age and Maximal Heart Rate" table (Ellestad, 1975, p. 68; see Appendix B).
7. Subject attached to monitoring equipment as follows:
   a. Electrode attachment:
      (1) six electrodes, one in each of the standard V_1-V_6 positions.
      (2) one electrode, below the V_5 electrode, to represent the left leg lead.
      (3) one electrode, on the sternum, to represent the right leg (ground) lead.
      (4) two electrodes, one on each shoulder, to represent the right arm and left arm leads.
   b. Blood pressure cuff attached to upper right arm.
8. ECG monitor (oscilloscope) and defibrilator turned on.
9. Subject made aware of available safeguards including the experienced cardiologist and nurse, the emergency drugs, and the emergency equipment.
10. Control blood pressure and rhythm strip of V_1, II, V_5 taken when subject:
    a. Sitting
    b. Standing
    c. Hyperventilating (for 20 seconds, standing).

All measurements recorded on the Exercise Electrocardiography Report (see Appendix B).

11. Start treadmill.
12. Explanation and demonstration of method of stepping on, walking on, and getting off the treadmill.
13. Subject assisted on to the treadmill (speed 1 MPH).
14. Begin Stage I, increase speed and grade every three minutes as listed below. ECG recording and blood pressure obtained at the end of every stage.

Stage	Speed	Grade	Duration
I	1.7 MPH	10%	3 minutes
II	2.5 MPH	12%	3 minutes
III	3.4 MPH	14%	3 minutes
IV	4.2 MPH	16%	3 minutes
V	5.0 MPH	18%	3 minutes
VI	5.5 MPH	20%	3 minutes
VII	6.0 MPH	22%	3 minutes

15. Continuing and terminating the test:
During the test, subjects will be continuously reassured, notified about the time to go, and upcoming changes in speed and grade, and encouraged to continue until they feel they can go no farther. Subjects will be instructed to stop when they have significant dyspnea, leg fatigue, or chest pain, or when they feel lightheaded, dizzy, nauseated, or have visual disturbances. The cardiologist and nurse will closely observe the patient, the oscilloscope, and the other measurements. They will terminate the test early if any of the following events occur (adapted from Ellestad, 1975, p. 72; Erbele, Note 4, p. 58):
    a. Multifocal PVC's, PVC's in pairs, PVC's in increasing frequency, or PVC's in runs of 3 or more.
    b. Atrial tachycardia, fibrillation, or flutter.
    c. Second or third degree AV block.
    d. S-T segment depression 6.0mm or 7.0mm more severe.
    e. Pale, moist skin and/or progressive decrease in heart rate and systolic blood pressure, suggesting vasoconstriction and falling BP.
    f. Extreme increase in systolic and diastolic BP and/or headache and blurred vision.
    g. Ataxia or head nodding, indicating cerebral ischemia.

If early termination is not indicated, the subject will be encouraged to continue until he/she reaches or exceeds the predicted maximal heart rate and/or all stages are completed.

16. At the time of the exercise termination, the ECG recorder is turned on and left running until the subject is assisted to the chair and the blood pressure is taken and recorded.
17. Blood pressure and ECG recordings taken at the end of each minute for at least 8 minutes and until the subject is stable and comfortable. If light-headedness or hypotension occur, the subject should be put in trendelenburg position.
18. Monitoring equipment removed from subject.
19. Cardiologist measures S-T segment depression on recordings as well as other abnormal ECG changes. Results recorded on the Exercise Electrocardiography Report (see Appendix B).
20. Test results explained to subject and subject thanked.
21. Chart note written to record test date, title, purpose, results, reason terminated, assessment, and plan.

EMERGENCY DRUGS AND EQUIPMENT TO BE AVAILABLE

Isuprel
Aramine
Propranolol Hydrochloride (1cc amps)
Neo Synephrine 0.2%
Nitroglycerine
Digoxin 0.5 mg (vials)
Pronestyl
Xylocaine 2%
Atropine Sulfate
Pacemaker
Ambu Bag, Airway
Cedilanid
Epinephrine

University of Oregon Health Sciences Center
Hospital and Clinics

Date Bldg. f17 Rm.

Informed Consent for Exercise Electrocardiography

Unit No.
Name
Birthdate

I hereby authorize and request the physicians and surgeons of the University of Oregon Health Sciences Center Hospital and Clinics to perform Exercise Electrocardiography on

_____ my _____
(Name of Patient) (Relationship)

It has been explained to me and I understand that:

1. During the procedure I will pedal a bicycle ergometer or walk or run on a treadmill while my electrocardiogram is recorded.

2. The exercise will be carried to a limit at which my heart beat is rapid, or I am tired and breathing heavily, or I have discomfort or pain in my chest, or certain changes in the electrocardiogram appear.

3. If heart irregularity occurs, the test will be terminated and I will receive prompt treatment if necessary to reverse any complication. If there is chest pain, I will be permitted to stop the exercise when I feel uncomfortable continuing.

4. The procedure carries a small but significant risk of complication such as prolonged chest pain, heart attack, or heart rhythm irregularity. The risk of serious complication is very small. If any special problems apply, a physician or cardiologist will discuss them with me.

5. I hereby acknowledge that all of my questions have been answered to my satisfaction and that no guarantees have been made concerning the results of this procedure.

_____ M.D. _____
Witness Signature of Patient

Date_____ _____
Signature of Parent or Guardian,
if patient is a minor

Time_____ a.m. p.m.

☐ Please check (X) if this is a telephone monitored consent.

6.A-6

6.A-6-1/77

(See instructions on reverse side)

EXERCISE ELECTROCARDIOGRAPHY REPORT

STANDARD 12 LEAD _____ CM5 _____ OTHER _____

RATE _____ PR _____ QRS _____ QT _____ AXIS _____

NORMAL _____ ABNORMAL _____

_____

EXERCISE ECG TREADMILL	STAGE	Minutes	Speed	Grade	Blood Pressure	Rate
	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____

Maximum ST depression _____ mm: lead _____

Maximum ST segment elevation _____ mm; lead _____

Arrhythmia _____

Other changes in P-QRS-T _____

CHEST PAIN No _____ Yes _____

INTERPRETATION Negative _____ Positive _____

Equivocal _____ Inadequate rate response _____

Remarks: _____

_____

_____

_____

M.D.

_____

(Standard report form of the UCHSC Electrocardiography Lab)

TABLE 8

Desirable Weights for Heights

Height in Inches	Weight in pounds	
	Male	Female
60		109±9
62		115±9
64	133±11	122±10
66	142±12	129±10
68	151±14	136±10
70	159±14	144±11
72	167±15	152±12
74	175±15	

Modified from Table 80, Hathaway and Ford, 1960, Height and Weight of Adults in the U.S. (Home Economics Research Report No. 10 ARS USDA) in Turner, D., 1965.

TABLE 9

Ages and Maximal Heart Rate (MHR)

Age	MHR	Age	MHR	Age	MHR
20	200	37	185	54	171
21	199	38	184	55	171
22	198	39	183	56	170
23	197	40	182	57	170
24	196	41	181	58	169
25	195	42	180	59	168
26	194	43	180	60	168
27	193	44	180	61	167
28	192	45	179	62	167
29	191	46	177	63	166
30	190	47	177	64	165
31	190	48	177	65	164
32	189	49	176	66	163
33	188	50	175	67	162
34	187	51	174	68	161
35	186	52	173	70	160

Adapted from Ellestad, 1975, p. 58.

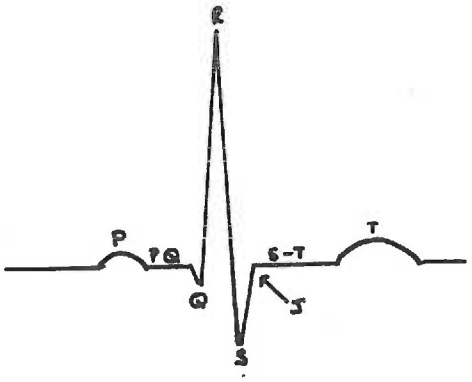

Figure 7: The normal electrocardiographic complex showing the P, Q, R, S, and T waves and the P-Q and S-T segments.

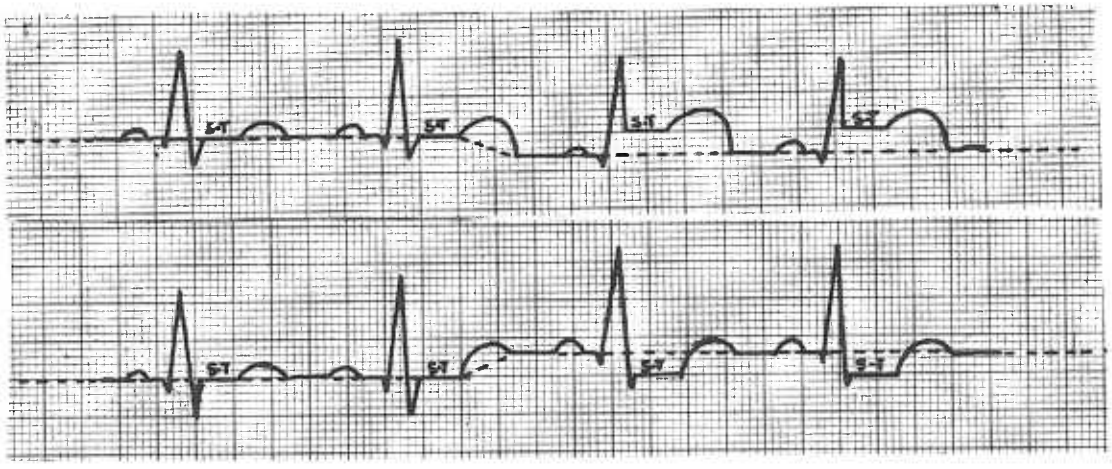

Figure 8: Evolution of S-T segment elevation (top-strip) and depression (bottom strip) as theorized by Constant (1973). Note that the baseline, which is always at the level of the P-Q segment, changes but the S-T segment remains at the same level.

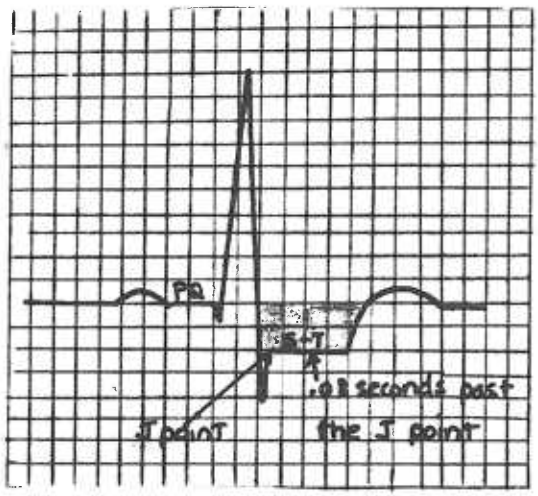

Figure 9: The measurement of S-T segment depression. The S-T segment is measured from the baseline (which is at the level of the P-Q segment) to the S-T segment at 0.08 seconds past the J point. In this figure the S-T segment is depressed 2.0mm

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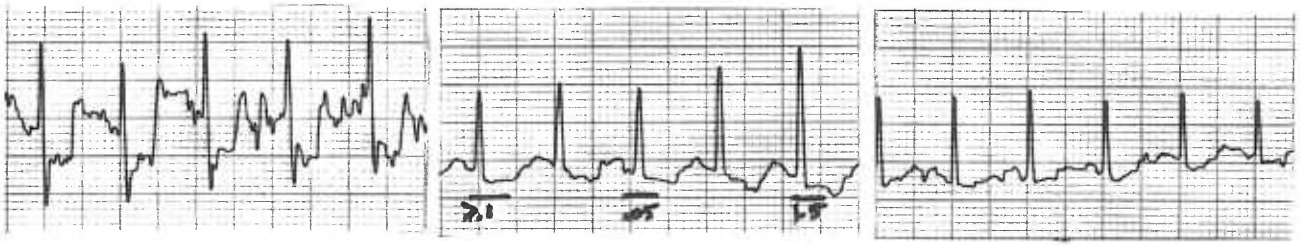

A B C

Figure 10 Three E-ECG strips showing the difficulties encountered when interpreting E-ECG tracings for S-T segment depression. In strip A, there is no consistent baseline: in strip B, the amount of S-T segment depression varies:and in strip C, the S-T segments are too iratic to be measured.

APPENDIX C

CONSENT FOR HUMAN RESEARCH PROJECT

CONSENT FOR HUMAN RESEARCH PROJECT

I, _____, agree to participate in the study entitled "The Effects of Serum Lipid Levels on the Exercise Stress Test Results in Hyperlipidemic Subjects," conducted by Pamela Peters Barnett under the supervision of Doctors McAnulty, Connor, and Rawlinson. The study is designed to determine if there are any improvements in the exercise stress test results of hyperlipidemic subjects who reduce the amount of serum lipids (cholesterol and/or triglycerides) in their blood by reducing the amount of cholesterol and fat in their diet.

I understand that the study will take three to eight weeks, during which time I will be required to follow a low cholesterol, moderately low fat diet. In addition, I will be required to perform three exercise stress tests, two at the start of the study and one at the end. Each exercise stress test will require about one hour of my time. The study will be completed when the amounts of serum lipids in my blood are reduced significantly (20% for cholesterol, 50% for triglycerides) or when eight weeks has passed since the start of the study, whichever comes first. In order to know when the serum lipids in my blood are reduced enough, the study requires that I have fasting serum lipid blood tests done weekly. These tests will each require less than one tablespoon of my blood and will take only five to ten minutes of my time. On the days of the blood tests, additional time may be used for discussion of my diet.

I understand that the exercise stress test carries a very small but significant risk of complications, such as prolonged chest pain, changes in the rhythm of the heart, and heart attack. I understand that an experienced cardiologist and a nurse will be present for the exercise stress test to ensure my welfare; should complications occur, the test will be terminated immediately and the complications treated.

I understand that the low cholesterol, moderately low fat diet may require a significant change in my eating habits, but I will be given as much guidance, instruction, and support as I need to help me follow the diet.

All information that I give will be handled confidentially.

This study may be of benefit to me in allowing my doctors and nurses to better manage my medical problems. In addition, I will contribute to new knowledge that may benefit other patients with hyperlipidemia.

Pamela Peters Barnett has offered to answer any questions I might have about the tasks required of me in this study.

I understand that I may refuse to participate or withdraw from this study at any time without affecting my relationship with, or treatment at, the University of Oregon Health Sciences Center. I have read and fully understand the foregoing information and agree to participate in the study.

Date	Signature of Subject
Date	Signature of Witness