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THE EFFECT OF CHRONIC ENDURANCE EXERCISE ON HIGH DENSITY LIPOPROTEIN CHOLESTEROL AND THE HDL-CHOLESTEROL : TOTAL CHOLESTEROL RATIO

by

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Honours B.Sc., Carleton University, 1975

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SIGNATURE PAGE

DEDICATION

I would like to dedicate the thesis to several people. First, I would like to thank my mom, Mrs. Jeannine Murdoch, my sister, Ann Sanderson, and Don Oxorn, for their continued support as well as their endless practical help throughout the study and in the preparation of the thesis. I would also like to thank the subjects themselves and particularly those that participated in the exercise class who were so consistent in attending the class as well as being extremely co-operative. Thanks everyone.

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ABSTRACT

The purpose of the study was to determine the effect of chronic endurance exercise on high density lipoprotein cholesterol (HDL-cholesterol) and the HDL-cholesterol : total cholesterol ratio. Changes in total cholesterol, LDL-cholesterol, triglycerides and certain physiological and exercise performance variables were measured as well.

The 22 subjects who participated in the study were men, ages 25 to 59, who had a history of high cholesterol but had normal triglyceride levels and glucose tolerance, and were of average body weight. The subjects were divided into two groups, an experimental and a control group. The experimental group was composed of 12 subjects. They participated in a 12 week fitness program which was held for one hour, three times a week. The subjects were asked to jog at a heart rate which was equivalent to 60% of their maximum heart rate, which was derived from a calculation using their resting heart rate (RHR) and maximum heart rate (MHR) (i.e.60% MHR = .6 (MHR - RHR) - RHR). The subjects ran an average of 1.1 Km (.7 miles) in 9.6 minutes at the beginning of the study and 4.0 Km (2.5 miles) in 23.4 minutes at the end of the study. The control group was made up of 10 subjects. These subjects were asked to maintain their normal level of physical activity during the study period. All subjects were also asked to maintain their normal dietary regime. Pre- and post-training dietary records of the experimental group were obtained to determine if any changes had actually occurred.

Significant changes in HDL-cholesterol, the HDL-cholesterol: total cholesterol ratio, total cholesterol and triglycerides, as well as changes in several physiological and exercise performance variables were determined for the experimental group by comparing their pre- and post-training values to those of the control group. The statistical analysis utilized was an Analysis of Covariance.

The results indicated that HDL-cholesterol did not change significantly with the training program, nor did plasma triglycerides. Total cholesterol and LDL-cholesterol both decreased 24 mg%. The HDL-cholesterol:total cholesterol ratio increased from .242 to .276. None of the physiological variables observed (resting heart rate, percentage body fat, systolic blood pressure and diastolic blood pressure) changed significantly. All of the exercise performance variables measured increased. These variables included maximum oxygen uptake expressed in l/min and ml/kg/min, maximum carbon dioxide production and maximum oxygen pulse. Maximum oxygen uptake increased from 2.8 to 3.1 l/min and 36.0 ml/kg/min to 39.5 ml/kg/min. There were no significant changes in the dietary intake of the experimental group and few changes in smoking habits, medication and dietary adherence in both groups.

The findings were discussed in relation to the exercise-related mechanisms that may have resulted in the changes that were observed in the blood lipids over the study period. The changes in total cholesterol and the HDL-cholesterol/total cholesterol ratio were discussed with reference to the subjects' coronary heart disease (CHD) risk profile, and it was suggested that the increase in the HDL-cholesterol:total cholesterol ratio was the most significant finding of

the study in relation to reducing the CHD risk since the increase in the ratio indicated that exercise had resulted in a trend towards a "normalization" of the subjects' plasma lipoprotein profiles.

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CHAPTER I

THE PROBLEM

Introduction and Rationale

The prevention of Coronary Heart Disease (CHD) through a reduction in the development of atherosclerosis is a major medical goal, particularly in the Western countries. Several risk factors have been related to a higher incidence of CHD. Recently, High-Density Lipoprotein (HDL), a carrier of plasma cholesterol, has been identified as as anti-risk factor (Miller & Miller, 1975). The presence of a higher level of HDL (or HDL-cholesterol) has been repeatedly linked with a lower incidence of CHD, while total plasma cholesterol and the major plasma cholesterol carrier, Low-Density Lipoprotein (LDL), have been associated with a higher incidence of CHD (Kannel et al, 1979). HDL is thought to exert a protective effect in the development of atherosclerotic lesions, although the mechanism is not well understood (Levy, 1978). It has been postulated that HDL may exercise its effect in two manners, both resulting in a reduction in the availability of cholesterol to the cells of the arterial wall. HDL is the natural substrate and activator of the enzyme Lecithin Cholesterol Acyl Transferase (LCAT), which esterifies free cholesterol (Eisenberg & Levy, 1975). It has been suggested that this HDL-LCAT interaction provides a mechanism whereby free cholesterol can be taken up from the intercellular space or cell membrane in the periphery, and transported as esterified cholesterol to the liver, where it is degraded to bile

acids, and eventually excreted (Glomset, 1968). In vitro studies have shown that loss of cholesterol to the medium is enhanced in the presence of HDL (Stein et al, 1976A). The second theory is related to the interaction of HDL with LDL, the "atherogenic" lipoprotein (Small, 1977). HDL does not bind as readily to human skin fibroblasts or to rat and porcine smooth muscle cells as does LDL, and HDL is internalized even more poorly (Stein & Stein, 1976; Steinberg et al, 1976). It has been found that HDL also inhibits the uptake of LDL by porcine arterial smooth muscle cells and human endothelial cells in culture (Carew et al, 1976; Stein & Stein, 1976; Steinberg et al, 1976). Considering these observations, HDL may exert its effect by competing with LDL for receptor sites on the cell membrane, decreasing the amount of LDL that is bound and consequently internalized (Miller et al, 1977B).

Interest has also arisen in factors that influence HDL plasma concentrations. As well as finding higher HDL levels in premenopausal women (Castelli et al, 1977A), lean people (Gordon et al, 1977A), and non-smokers (Garrison et al, 1978), HDL has been found to be higher and LDL lower in long-distance runners (Wood et al, 1976) and cross-country skiers (Enger et al, 1977). Although few comprehensive training studies have been completed to date, HDL has been reported to increase with aerobic training (Ratliff et al, 1978).

Physical activity has been linked with a lower incidence of CHD, although the causative factors have not been clearly elucidated (Wilhelmsen, 1976; Gotto, 1979). An increase in HDL may contribute to this protective effect of exercise. It may also explain, in part, the variable effect or the little change that exercise exerts on plasma cholesterol (Naito, 1976). If HDL (and HDL-cholesterol) is

increased with a specific type of exercise program, while LDL is decreased, plasma cholesterol may remain unchanged or decrease very slightly, while the cholesterol-carrier profile has been altered to a more desirable one(Lopez-S et al,1974).This profile would be more desirable since a greater percentage of the total cholesterol would be carried by HDL after training. The percentage of total cholesterol carried by HDL (expressed as the HDL-cholesterol : total cholesterol ratio) may actually be more important than the absolute amount of plasma HDL-cholesterol in relation to the postulated role of HDL in the prevention of atherosclerosis, since it better reflects the relationship of HDL with respect to the plasma cholesterol levels.

Statement of the Problem

This study will attempt to determine whether a regular controlled aerobic training program comprised of jogging at 60% MHR, accompanied by calesthenics, will significantly affect the plasma HDL-cholesterol concentration or the HDL-cholesterol : total cholesterol ratio of the trained group as compared to the control group.

Sub-problems

1. To evaluate the effect of the exercise program on total triglycerides, cholesterol and LDL-cholesterol.
2. To examine the effect of the training program on several physiological variables including resting heart rate, percentage body fat, systolic blood pressure and diastolic blood pressure.
3. To determine the effect of the training program on several

exercise performance variables, including maximum oxygen uptake (l/min and ml/Kg/min), maximum carbon dioxide production and maximum oxygen pulse.

4. To examine: A) the correlations between HDL-cholesterol and total cholesterol, total triglycerides, maximum oxygen uptake (l/min and ml/Kg/min) and percentage body fat;

and B) the correlations between the HDL-cholesterol : total cholesterol ratio with total triglycerides, maximum oxygen uptake (l/min and ml/Kg/min) and percentage body fat.

The correlations were calculated for the pre-training values, for the post-training values and for the changes in the values over the study period.

Delimitations

The subjects were selected in a non-random way from a restricted, normal population since they were volunteers derived from the patient population of Dr. John Biro and were selected according to the criteria laid down in the methodology (Chapter III). Therefore, the results of the study apply to non-obese males, ages 25-60, who had a history of high cholesterol and whose cholesterol may have been elevated at the time of the study but who demonstrated normal levels of plasma triglycerides and normal glucose tolerance.

Limitations of the Study

1. An increase in HDL-cholesterol does not necessarily indicate an increase in the number of HDL micelles. It could be due to an increased ability of the individual HDL micelle to carry cholesterol because of an increased amount of apoprotein per micelle. Or, it may reflect a change in the cholesterol binding ability of the lipoprotein micelle.

2. The composition of the diet and caloric intake were not strictly controlled. All subjects were asked to establish a set dietary pattern and maintain it throughout the program. They were also required to complete a questionnaire before and after the program, concerning their dietary adherence, and to complete a seven-day diet report, pre- and post-training. These precautions do not rule out the possibility that a subtle change in the diet of one group could cause a change in HDL-cholesterol or the other lipid parameters measured.

3. Since the factors controlling human HDL metabolism are largely unknown at the present, suggested mechanisms behind the biochemical effect of exercise on HDL-cholesterol are purely theoretical.

4. The effect of exercise on LDL-cholesterol cannot be clearly assessed, since LDL was estimated on the assumption that VLDL-cholesterol was approximately equal to the total triglycerides ,

which may not be the case for all individuals. Since the rela-

tion of HDL with CHD appears to be independent of LDL, this fact does not detract from the importance or validity of the study.

5. There was a displacement of time between the fitness-testing and procurement of blood samples of the exercise group and that of the control group. Consequently, the presence of any seasonal variation may not be completely reflected by the data.

6. Ultracentrifugation is the most accepted and repeatable technique for HDL-cholesterol analysis. It is used as the reference method from which two or three other techniques have been developed. The technique used in this study had a .82 correlation with ultracentrifugation (Lopez-Virella et al, 1977B).

Definition of Terminology

1. Coronary Heart Disease (CHD): A term designating cardiac disease resulting in an insufficient coronary blood flow, which is commonly (99% of the cases) due to atherosclerotic narrowing of the coronary arteries.

2. Plasma Lipoproteins: Plasma lipids conjugated with carrier proteins which allow for the transport of these lipids, namely cholesterol, triglycerides and phospholipids, in the blood.

3. Plasma Cholesterol: A sterol carried in the blood, largely by LDL and HDL. Normal values for plasma cholesterol range up to 250 mg% (100-250 mg%). Plasma cholesterol occurs in the free and esterified form in a ratio of 1:3.

4. Plasma Triglycerides: Fasting triacylglycerols that normally range in plasma concentration from 0-150 mg% (70-150 mg%). VLDL is the major carrier of endogenous triglycerides, while the chylomicrons are the major carriers of exogenous triglycerides.

5. High Density Lipoproteins (HDL): Lipoproteins isolated by ultracentrifugation in the density range of 1.063-1.21 gm/ml. They represent the alpha (α) lipoproteins on electrophoresis. They are comprised of 50% protein, 20% cholesterol, 8% triglycerides, 22% phospholipids. They contain the apoproteins A-I, A-II, C-I, C-II, C-III, D and E.

6. Low Density Lipoproteins (LDL): Lipoproteins isolated in the range of d. 1.006-1.063 gm/ml. They constitute the beta (β) lipopro-

teins. They are comprised of 20% protein, 46% cholesterol, 11% triglycerides, 22% phospholipids. They contain largely apoprotein B.

7. Very Low Density Lipoproteins (VLDL): These lipoproteins of density .95-1.006 gm/ml are the pre-beta lipoproteins. They contain 9% protein, 22% cholesterol, 50% triglycerides, 18% phospholipids. Their apoprotein constituents are apoprotein B, C-I, C-II and C-III, and E.

8. Chylomicrons: Lipoproteins of density < 0.94 gm/ml which are not present in fasting plasma. They contain 2% protein, 8% cholesterol, 83% triglycerides, 7% phospholipids. They are made up of apoproteins B and C-I, C-II and C-III, and possibly small amounts of A and E.

9. Lecithin Cholesterol Acyltransferase: An enzyme that catalyzes the transfer of a polyunsaturated fatty acid molecule from the 2-position of lecithin (phosphatidycholine) to free cholesterol, resulting in the production of lysolecithin and esterified cholesterol. HDL is the natural activator of this enzyme, due to the presence of apoprotein A-I. The cholesterol, once esterified, is thought to move to the core of the HDL micelle and lysolecithin is carried off by albumin.

10. Maximum Oxygen Uptake (MVO_2): That level of oxygen uptake after which an increase in work-load does not elicit a further increase in oxygen uptake. It is measured in absolute terms of litres per minute, and in relative terms of ml/Kg/min.

11. Maximum Carbon Dioxide Production ($MVCO_2$): That level of carbon dioxide production achieved when oxygen uptake is at its maximum. It is expressed in litres per minute.

12. Maximum Oxygen Pulse: The oxygen uptake attained per heart beat at the point when oxygen uptake is maximal. It is expressed in millilitres per beat. An increase in this variable is considered to generally reflect an increase in stroke volume as well as an increase in the ability of the working muscles to take up oxygen from the blood.

13. Percentage Body Fat: The percent of body composition composed of both essential and non-essential body fats. It is calculated from the subject's skin-fold measurements, according to the following equation: Body Density = 1.08847 - .007123 (MIDAXILLA (mm.)) - .004834 (CHEST (mm.)) - .005513 (TRICEP (mm.)) and then body density is converted to percentage body fat (Pascale et al, 1956).

14. Friedwald's Equation: An estimation of LDL-cholesterol where VLDL-cholesterol is estimated as being equal to the total fasting triglyceride concentration divided by five. This calculation does not give an accurate value for VLDL-cholesterol, per se, but does closely reflect the LDL-cholesterol concentration if total triglycerides do not exceed 400 mg%. The equation is as follows: LDL-cholesterol = Total Cholesterol - $\frac{\text{Total Triglycerides}}{5}$ - HDL-cholesterol (Friedwald et al, 1972).

The calculation of LDL-cholesterol, using this estimation method, was found to have a .98 correlation with the LDL-cholesterol concentration obtained by the ultracentrifugation method (Friedewald et al, 1972).

CHAPTER II

REVIEW OF THE LITERATURE

Atherosclerosis and Plasma Cholesterol

Atherosclerosis has become a major source of concern to the fields of medical science and public health (Gordon & Thorn, 1975), since it is the leading cause of myocardial and cerebral thromboses and infarcts. Such conditions develop since atherosclerosis progressively reduces the arterial diameter via the formation of mineral and lipid laden plaques in the arterial wall (Kottke & Subbiah, 1978).

The atherosclerotic process is difficult to study since it progresses asymptomatically from early childhood and continues at varying rates throughout life. Moreover, the experimental models, using animals, cannot be directly compared with the human form, due to differences in lipid metabolism and formation of the plaques (Kottke & Subbiah, 1978).

The primary cause of the atherosclerotic lesions is unknown, but the process appears to involve the initiation of smooth muscle and fibrous connective tissue proliferation in the intima of the artery, with subsequent deposition of lipid in the cells and in the necrotic extracellular area below (Adams, 1973). The initiating factors may be related to some form of stress or injury imposed on the endothelium of the artery (Ross & Glomset, 1976) but the further formation of the plaque involves the progressive deposition of the lipid, that of cholesterol esters in particular (Zilversmit, 1968). This cholesterol is thought to be derived more from the plasma than from local synthesis (Field et al, 1960).

The incidence of Coronary Heart Disease (CHD), due to atherosclerosis, has been related to the presence of certain risk factors, the major ones being high plasma cholesterol, hypertension and cigarette smoking. Other currently accepted risk factors include obesity, high plasma triglycerides, family history, hyperglycemia (diabetes mellitus), personality type A, sedentary lifestyle, stress and softness of drinking water (Report, 1972). Recently, HDL has been delegated the role of an anti-risk factor (Miller & Miller, 1975). Risk factors have been correlated with the incidence of CHD, but their precise role in the etiology of atherosclerosis remains to be determined. Risk factors may be primary or secondary contributors to the development of the plaques. On the other hand, some factors may simply mirror the presence of other factors, while the other factors may be more directly related to the development of atherosclerosis. Statistically, a single risk factor increases one's chance of developing CHD by a certain percentage, but the presence of a second or third factor increases one's chances geometrically (Report, 1972). This is especially important for the major risk factors.

Plasma cholesterol has received much attention in the past in relation to CHD. Such interest lies in the fact that atherosclerotic lesions do contain an accumulation of cholesterol and its esters. High cholesterol diets have also been known to result in the development of cholesterol-rich lesions in the arteries of several animal species (Kottke & Subbiah, 1978). However, the cholesterol metabolism of these animals differed from that of humans (cholesterol absorption in particular, and the lipoprotein carrier profile as well), and the lesions lacked the fibrous connective tissue proliferation characteristic of the human form (Kottke & Subbiah,1978). Moreover, susceptibility to atherosclerosis also varies a

great deal from species to species, as outlined in Table I. It was not until 1970 that plaques which did resemble the human form were actually reversed in primates after feeding them a low-cholesterol, low-saturated fat diet (Report, 1972).

Epidemiological studies show CHD incidence to increase in a stepwise manner with increasing cholesterol levels (Borhani, 1977) over the full range of values, although the most sensitive levels are above 200 mg% (Report, 1972). Quite recently, a review by Kannel et al(1979) on the role of plasma cholesterol in the prediction of atherosclerotic heart disease, has reinforced the strong relationship between CHD risk and plasma cholesterol, but suggests that it is only applicable for individuals up to the age of fifty. These conclusions were based on data from several prospective studies using large population samples, including those of the Framingham cohort. Demonstrating, as Kannel et al(1979) did, that a person has an increased risk of an early heart attack due to the presence of an elevated plasma cholesterol, is not the equivalent of proving that the risk will be diminished if the elevation in plasma cholesterol is corrected. Therefore, the actual role of cholesterol in the development of atherosclerosis remains controversial, since intervention studies, for the most part, have not confirmed the epidemiological and prospective findings (Rifkind, 1977). The studies that did find a positive relationship between a reduction in plasma cholesterol and a reduction in the incidence of CHD were poorly controlled for other risk factors and/or attrition was high, according to Rifkind (1977), Borhani (1977) and Gotto (1979). The lack of consistency in demonstrating a lowering of CHD incidence with a reduction in plasma cholesterol may be due to the degree of damage that has already occurred in the

TABLE I

RELATION OF PLASMA CHOLESTEROL AND LDL-CHOLESTEROL TO THE DEVELOPMENT OF ATHEROSCLEROTIC LESIONS IN DIFFERENT SPECIES

TABLE 1

	Cholesterol in mg/100 ml (Approximate)	% LDL Cholesterol	Atherosclerotic Lesions
Human:			
*Coronary Disease	240+	90	} Spontaneous
In health	180	70	
Monkey	120	60	With saturated fat feeding
Rabbit	40	50	With cholesterol feeding only
Dog	140	30	With cholesterol feeding + thyroid depression
Rat	50	10	Rarely produced

(Oliver, 1978)

arteries of the participants at the beginning of the study (Kannel et al, 1979). It could also be due to the presence of other risk factors that are not removed with a lowering of plasma cholesterol and which continue to stimulate the progression of atherosclerosis. While either of these hypotheses is possible, the first one may apply more specifically to the secondary intervention studies (Gotto, 1979).
In the case of primary intervention studies, researchers have favoured the latter theory, that other risk factors must be involved (Gotto, 1979). This latter explanation would be even more reasonable if the factor was one that was related to cholesterol metabolism, but not directly associated with plasma cholesterol levels, and thus not affected by the protocol of the intervention studies. The plasma lipoproteins that carry cholesterol in the blood have consequently received much attention in recent years.

Atherosclerosis and Plasma Lipoproteins

The major cholesterol-carrying lipoproteins of fasting plasma are LDL, HDL and VLDL, which normally carry 65% (55%-75%), 25% (15%-35%) and 10% (8%-12%), respectively, of the total plasma cholesterol.

The role of VLDL in cholesterol deposition and uptake is controversial but is not considered to be as important as that of LDL and HDL(Eisenberg&Levy, 1975; Kannel et al, 1979). VLDL-cholesterol has been shown to have a strong relationship with CHD incidence very infrequently (Nestel & Poyser , 1978). VLDL carries the major portion of endogenous plasma triglyceride, and its primary effect appears to be on triglyceride rather than cholesterol metabolism. Elevated VLDL-cholesterol can occur

with hypercholesterolemia, but, when elevated, VLDL-cholesterol usually correlates with the elevation in total cholesterol(Carlson & Ericsson,1975).

There is experimental evidence that the relationship of atherosclerosis to hypercholesterolemia is due, in part, to the infiltration of LDL into the arterial wall, with a resultant cholesterol deposition (Walton & Williamson,1968). LDL and its cholesterol content became the popular lipoprotein for a number of years, because it could be related to the lipid infiltration theory of Virchow (1856), and because LDL-cholesterol was found to be a better predictor of CHD incidence than total cholesterol in some studies (Gofman et al,1966). But LDL-cholesterol is also directly related to the level of total plasma cholesterol, since it carries approximately two-thirds of the total amount (Eisenberg & Levy, 1975). It would then have been affected in the cholesterol-lowering studies, as was the case for VLDL, since it would decrease as the total cholesterol fell.

On the other hand, HDL-cholesterol appears to be independent in its relationship to total plasma cholesterol, and has been found to be inversely related to CHD (Kannel et al,1979). Thus it fulfills the requirements of a factor that is related to CHD incidence and to cholesterol metabolism, but varies independently of the plasma cholesterol level. In cholesterol-lowering studies, possibly HDL levels failed to normalize, even though total cholesterol fell, which would maintain an abnormal and consequently undesirable lipoprotein profile.

High Density Lipoprotein and Coronary Heart Disease

Epidemiological Studies:

In the early 1950's, several researchers suggested that an inverse relationship existed between HDL (or alpha-lipoprotein) and the incidence of

CHD (Gofman et al,1950; Barr et al,1951; Nikkila,1953; Jenks et al,1956). It was found that even in CHD patients with normal serum cholesterol and triglycerides, HDL-cholesterol was lower than normal (Nikkila,1953).

Gofman et al (1966) observed this relationship, but gave HDL-cholesterol little importance as a risk (or anti-risk) factor as compared with LDL-cholesterol or total cholesterol.

Brunner and coauthors (1966), in their study of normal and CHD individuals in an Israeli kibbutz,demonstrated that in this population the alpha-lipoprotein-cholesterol, expressed as a percentage of the total cholesterol, was a more reliable parameter than total cholesterol in the prediction of CHD. The total cholesterol of this group was lower, on the average, than that of most Western populations. Alpha-lipoprotein-cholesterol levels that represented less than 20% of the total cholesterol were associated with CHD irrespective of the total cholesterol values.

In 1968, Glomset also observed this inverse relationship between plasma HDL and the occurrence of CHD, and postulated a possible role for HDL in slowing the progression of atherosclerosis, by providing a mechanism for reverse or "centripetal" cholesterol transport.

Despite such observations, HDL received little attention as an "anti-risk" factor, for a number of years, since any carrier of cholesterol was considered to be involved in the deposition of cholesterol in the atherosclerotic plaques. The relationship of HDL with CHD and cholesterol metabolism remained elusive until 1975, with the review of Miller and Miller. They determined the relation of body cholesterol pools to the mean plasma levels of cholesterol, triglycerides, VLDL-, LDL- and HDL- cholesterol in eight middle-aged hypercholesterolemic

patients. A two-pool model was used where pool A equilibrates rapidly with plasma cholesterol (plasma cholesterol comprising 10% of the total body cholesterol) and pool B equilibrates slowly. Cholesterol in the arterial wall is that of pool B. The cholesterol pool size was found to be unrelated to plasma cholesterol, triglycerides, VLDL-cholesterol or LDL-cholesterol concentrations. However, pool A and B both demonstrated a strong negative correlation with plasma HDL-cholesterol. They noted that HDL is often reduced in several conditions associated with CHD risk, such as hypercholesterolemia, hypertriglyceridemia, male sex, obesity, diabetes mellitus and physical inactivity. They suggested, as did Glomset (1968), that HDL may be necessary for the normal clearance of cholesterol from tissues, including the arterial wall and atheromatous lesions.

The relationship of HDL with CHD has frequently been investigated since this review of Miller & Miller (1975). HDL has continued to demonstrate an inverse association with the incidence of CHD (Castelli et al, 1975; Nikkila, 1976; Rhoads et al, 1976; Castelli et al, 1977B), and with the incidence of a myocardial infarction alone (Carlson & Ericsson, 1975; Albers et al, 1976; Berg et al, 1976A&B;Rhoads et al, 1976; Brunner et al, 1979; Noma, 1979). The relationship applied when HDL was expressed as HDL-cholesterol (Carlson & Ericsson, 1975; Castelli et al, 1975; Albers et al, 1976; Castelli et al, 1977B; Brunner et al, 1979; Noma et al, 1979), alpha-lipoprotein-cholesterol (Nikkila, 1976; Rhoads et al, 1976), or as Apoprotein A-I, the major apoprotein constituent of HDL (Albers et al, 1976; Berg et al, 1976A&B). When expressed as HDL-cholesterol, subjects with levels of 30 mg% demonstrated twice the incidence of CHD when compared to those whose HDL-cholesterol was 60 mg% (Castelli et al, 1975). In a later study, Castelli and coauthors (1977B) noted that subjects whose HDL-cholesterol levels were less than 25 mg%

had twice the incidence of CHD than those with intermediate (35-65 mg%) or higher levels (>75 mg%). In this study, HDL-cholesterol was consistently lower in the CHD cases than in the healthy control, but the average difference was small (3-4 mg%).* When HDL-cholesterol was measured in a CHD group made up solely of survivors of a myocardial infarction (MI), the mean level was 27 mg% (Albers et al, 1976). When alpha-lipoprotein was measured, it was 38.5 mg% in CHD subjects, as compared to 52.6 mg% in the healthy controls (Nikkila,1976). Rhoads and co-authors (1976) found these same alpha-lipoprotein-cholesterol levels to be 42 mg% and 46 mg%, respectively, in their study of the incidence of CHD in Hawaiian Japanese men.

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* It should be noted that, due to the observation of such small differences between CHD cases and non-cases in some studies, the use of the HDL-cholesterol level as a diagnostic tool may not be pertinent to a routine clinical assessment, but may find its use in more specific but nevertheless common situations (Kannel et al, 1979). For example, the measurement of HDL-cholesterol may be very useful in subjects over the age of 50, when total cholesterol loses its effectiveness in the prediction of the future incidence of CHD (Kannel et al, 1979). After this age, HDL-cholesterol becomes the more potent predictor. Another example of its specific utilization may be in the prescription of the therapy administered to individuals who have moderately elevated total plasma cholesterol (Kannel et al, 1979). If HDL-cholesterol is high, the severity of the therapy prescribed for that individual would not be as great as it would be for the individual who demonstrated a very low level of HDL-cholesterol. Furthermore, it may be the percentage of total cholesterol carried by HDL that is the more important clinical index of CHD risk rather than the absolute serum level of HDL-cholesterol.

Observations of the Apoprotein A-I (Apo A-I) levels in MI survivors showed that, as well as being reduced in these subjects, Apo A-I carried less cholesterol per mole of protein than it did in the healthy controls (Albers et al, 1976).

Coronary angiographic studies have substantiated the previous findings of an inverse association of HDL and CHD incidence (Berg et al, 1976C; Jenkins et al, 1978; Pearson et al, 1979). A consistent and significant trend of decreasing HDL-cholesterol with the number of diseased coronary arteries was observed by Pearson et al (1979). Jenkins and coauthors (1978) found that HDL-cholesterol demonstrated a strong inverse association with the Coronary Artery Score which was based on the number and severity of the lesions in eight proximal segment of the coronary circulation. Berg et al (1976C) examined Apo A-I levels and found that they were significantly lower in subjects who had angiographically demonstrable changes, when compared to subjects whose angiographic results were negative.

The conflict that pervaded the investigations into the relationship of HDL with CHD was due to the contention of some researchers that HDL was not an independent factor, but merely reflected the levels of other blood lipids such as LDL-cholesterol, total cholesterol or total triglycerides (Carlson & Ericsson, 1975; Nikkila,1976).

The independence of HDL from LDL-cholesterol and from total cholesterol soon became apparent when expressed as HDL-cholesterol (Castelli et al, 1975; Albers et al, 1976; Castelli et al, 1977A&B), alpha-lipoprotein-cholesterol (Rhoads et al,1976) or as Apo A-I (Berg et al, 1976B). Not only were the plasma concentrations of HDL shown to be independent of those of LDL-cholesterol and of total cholesterol, but HDL

was also shown to be independent of these blood lipids in its contribution to the prediction of CHD incidence (Rhoads et al, 1976; Castelli et al, 1977B; Jenkins et al, 1978). When expressed as alpha-lipoprotein-cholesterol, Rhoads and co-authors (1976) found, by multivariate analysis, that it made a highly significant contribution to the prediction of CHD cases over and above that of total cholesterol, and continued to do so even after taking into account the contributions of age, cigarettes smoked per day, sum of skinfolds and systolic blood pressure. Castelli et al (1977B) observed that the inverse association of HDL-cholesterol with CHD was more uniformly present in the six study populations than was the positive relationship of LDL-cholesterol, total cholesterol and triglycerides with CHD. In this study, LDL-cholesterol and HDL-cholesterol were found to be independent of each other in their contribution to CHD prediction. In Jenkins and co-authors' study (1978) of angiographic findings, HDL-cholesterol was more strongly correlated with the Coronary Artery Score than were LDL-cholesterol and total cholesterol, as determined by multivariate analysis. Moreover, a further demonstration of the independence of HDL-cholesterol from these two blood lipids is found in two studies of MI survivors whose total cholesterol levels were actually similar to the healthy controls and in the normal range, while HDL maintained its inverse relationship with CHD incidence (Brunner et al, 1979; Noma et al, 1979). Brunner and colleagues (1979) noted that the percentage of total cholesterol carried by HDL was also inversely related to the incidence of an MI. From these observations of normal cholesterol and reduced HDL-cholesterol in MI survivors, Brunner et al (1979) hypothesized that a redistribution of cholesterol from HDL to LDL and VLDL may be one of

the first steps in the development of an atherogenic lipoprotein pattern which is later followed by an increase in total cholesterol. This later increase in total cholesterol is carried mainly by LDL.

The case for the independence of HDL from total triglycerides was not resolved quite so easily, since plasma triglycerides were frequently demonstrated to be inversely related to HDL levels (Carlson & Ericsson, 1975; Nikkila, 1976; Castelli et al, 1977A), and triglycerides had also been found to be directly correlated with the incidence of CHD in some cases (Report, 1972; Castelli et al, 1977B ; Jenkins et al, 1978). But, despite the fact that HDL had been negatively correlated with triglycerides, its independence from triglycerides in relation to CHD incidence was demonstrated in three studies (Albers et al, 1976; Rhoads et al, 1976; Castelli et al, 1977B). Albers and co-authors (1976) found that the MI survivors in their study who had normal plasma triglycerides continued to demonstrate reduced levels of HDL-cholesterol. In the subjects of Rhoads et al (1976), the triglycerides of the CHD patients were similar to those of the control group, forcing him to conclude that plasma triglyceride levels could not account for the observed differences in alpha-lipoprotein-cholesterol between the two groups. Castelli and colleagues' study (1977B) was the most comprehensive of all of these, due to the large populations utilized. It was also the most conclusive. Although they found a moderately negative correlation between plasma triglycerides and HDL-cholesterol (-.28 to -.44), it was discovered that in these populations the relationship of triglycerides with CHD was dependent on HDL-cholesterol levels, rather than the reverse, since at any triglyceride level, HDL-cholesterol continued to contribute to the prediction of CHD but this was not the case for the opposite situation.

Therefore, from the studies reviewed, HDL, expressed as HDL-cholesterol, alpha-lipoprotein-cholesterol or Apo-A-I, appears to be inversely related to the incidence of CHD, MI alone, or to demonstrated angiographic changes, and the relationship is independent of LDL-cholesterol, total cholesterol and triglyceride levels. However, there are several weaknesses inherent in the experimental designs that make a conclusive statement concerning the relationship of HDL to CHD impossible. In the studies of CHD incidence, HDL could be lower due to changes in diet, medication or level of physical activity that occurred after the presentation of the symptoms rather than be a predisposing characteristic of CHD. Such factors were not mentioned. The angiographic studies would also warrant this criticism, since subjects who underwent coronary angiography had undoubtedly exhibited severe symptoms of CHD and were likely receiving treatment for it. Angiographic studies are more accurate than the CHD incidence studies which are based on clinical symptoms since the angiographic studies can directly determine the presence and degree of coronary artery disease. Both types of studies failed to mention, in many cases, the smoking habits, alcohol intake or percentage body fat of the subjects, as well as the type of diet, level of physical activity or medication, as previously mentioned. Any of these factors could affect HDL levels (see section entitled Factors Affecting HDL Levels). Therefore, the lower HDL observed in all these studies could as easily be interpreted as being a consequence of the development of atherosclerosis, as it could be identified as a factor that contributes to the development of this vascular disease.

Prospective Studies:

While it is possible to correlate HDL levels with CHD incidence, a conclusive statement regarding such a relationship would require an investigation into the HDL levels of individuals who are initially free of CHD but who develop it at a later date. Four such prospective studies have been completed to date. Their findings generally support the findings of the epidemiological studies that HDL was inversely related to CHD incidence (Medalie et al, 1973; Roseman et al,1975; Gordon et al, 1977A; Miller et al, 1977A). An outline of these studies can be found in Table II.

Miller and colleagues' study (1977A) had several weaknesses. The subjects were followed for a relatively short period of time. Only eleven subjects who were initially free of CHD developed it over the study period. Finally, the samples were analyzed for HDL-cholesterol after being frozen for two years. Such a long storage period can definitely decrease the accuracy of the results (Reckless et al, 1977). Despite these shortcomings, the results of Miller et al are still noteworthey since they found that HDL-cholesterol was 35% lower in CHD cases than in the controls, who were matched for age and physical activity, but total cholesterol and triglycerides were no different. The lipoprotein-cholesterol of d<1.063 was higher in the CHD cases and represents mainly the cholesterol carried by LDL, but also that of VLDL to a certain extent. The subjects ranged in age from 20-49. The mean initial HDL-cholesterol of the CHD cases was 25.8 mg% as compared to 40.6 mg% in the subjects who remained asymptomatic. Using discriminant function analysis, it was found that only HDL-cholesterol and the cholesterol of the d<1.063 lipoproteins contributed significantly to the prediction of future MI incidence. The relationship of both these lipoprotein fractions

TABLE II

HDL-CHOLESTEROL AND CHD INCIDENCE - Prospective Studies

AUTHOR	YEARS	DATA	SUBJECTS: CHD CASES: Description	CHD CASES: Age	CHD CASES: #	CONTROLS: Description	CONTROLS: Age	CONTROLS: #	Initial HDL levels were related to CHD incidence	Most potent risk factor	Other risk factors	HDL levels were independent of other risk factors in relation to CHD	NOTES
Miller et al (1977A)	1974-1976	2	Tromso Residents (developed MI)	20-49	11	Tromso Residents (matched for levels of physical activity also)	age matched	2 per MI individual	yes	HDL-cholesterol	cholesterol of d<1.063 lipoproteins	yes, when triglycerides, systolic blood pressure and diastolic blood pressure were considered (both groups had similar body weight and smoking habits)	total cholesterol and triglycerides were not related to the future incidence of a MI
Gordon et al (1977A)	1970-1974	4	Framingham Residents (developed clinical CHD)	49-83	79 M & 63 F	Framingham Residents	49-83	remainder of 1025M & 1445F	yes	HDL-cholesterol	LDL-cholesterol; triglycerides, but its relation to CHD was due to other risk factors	yes, when they controlled for cholesterol, triglycerides, systolic blood pressure, left ventricular hypertrophy, relative body weight and diabetes	total cholesterol was not related to CHD incidence
Medalie et al (1973)	1963-1968	5	Israeli Residents (developed MI)	40 and over	10000 M	Israeli Residents	40 and over	yes, as well as the HDL-cholesterol : total cholesterol ratio	total cholesterol	total cholesterol; beta-lipoprotein cholesterol	not calculated	triglycerides were not mentioned; they calculated the incidence rate at different levels of the variables under study & determined if significant differences were present with respect to CHD at different levels
Goldbourt & Medalie (1979)	extrapolated the results of the study of Medalie et al (1973)			(1) Gp 1: 40-49 Gp 2: 50 + (2) Gp 1: 40-44 Gp 2: 45-54 Gp 3: 55-64				multivariate analysis	no: age 40-49 yes: age 50 + no: age 40-44 yes: age 45-54 yes: age 55-64			yes, for subjects over the age of 45, when they controlled for age, smoking habits, systolic blood pressure, relative weight and diabetes	
Rosenman et al (1975)	1960-1969	8.5	California Residents (demonstrated manifest CHD)	39-59	257	California Residents	39-59	remainder of 3154	not measured; looked at β:α lipoprotein ratio instead	not measured	β:α lipoprotein ratio; total cholesterol; total triglycerides	not measured	

with CHD was found to be an independent one, but HDL-cholesterol made a three-fold greater contribution to the discrimination of subjects who were likely to develop CHD in the following two year period than did the cholesterol of d<1.063. This would indicate that the percentage of total cholesterol carried by HDL may be a very important indicator of the future development of CHD, since it reflects both HDL cholesterol levels and also those of the d<1.063 lipoproteins.

The results of Gordon and co-authors (1977A) were very similar to those of Miller and colleagues (1977A), in that HDL-cholesterol was the major potent risk factor due to the inverse association it demonstrated with the future development of CHD. This association continued even after other blood lipids (LDL-cholesterol and triglycerides) and risk factors (systolic blood pressure, left ventricular hypertrophy, relative weight and diabetes) were taken into consideration. Once again, LDL-cholesterol was positively related to CHD but the association was not as strong as that of HDL and CHD. The subjects of Gordon et al (1977A) were older than those of Miller et al (1977A) and more in the range of the subjects in the other two studies. The findings of Gordon and colleagues would again indicate that it is the percentage of total cholesterol carried by HDL that may be the important indicator of the future CHD risk.

Medalie et al (1973) found that total cholesterol had the strongest association with future MI incidence, unlike Miller et al (1977A) and Gordon et al (1977A), but they also found alpha-lipoprotein-cholesterol to be significantly and inversely related to future MI incidence, and the association was devoid of a cut-off point in that it was effective over a continuum of values. The same was true when HDL-cholesterol was expressed as a percentage of the total cholesterol, which reflects

the findings of Miller et al (1977A) and Gordon et al (1977A). Beta-lipoprotein-cholesterol (reflecting LDL-cholesterol) was once again positively related to the future incidence of a MI. No mention was made of triglyceride levels. The relationship of alpha-lipoprotein-cholesterol (referred to as HDL-cholesterol in this case) to the future incidence of a MI in the subjects of Medalie et al (1973) was further investigated by Goldbourt and Medalie (1979). For a more comprehensive evaluation of the results, they divided the subjects into various age groups. When this was done, HDL-cholesterol was significantly related to MI incidence in subjects of age 50 and older, but it was not related in subjects of ages 40-49. After controlling for age, total cholesterol, smoking habits, relative weight and diabetes, and having divided the subjects into three age groups, initial HDL-cholesterol levels demonstrated a significant negative relationship to the future occurrence of a MI in subjects of ages 45-54 and 55 and older, but were not associated with MI incidence in subjects of ages 40-44.

Although Rosenman and colleagues' study (1975) was the longest and therefore perhaps the most informative of all four prospective studies, they did not measure HDL per se but only looked at the beta:alpha-lipoprotein ratio (which is approximately equivalent to the LDL:HDL ratio). They also failed to determine the independence of the ratio from other possible contributory factors related to CHD incidence. They did find the ratio to be positively related to the future incidence of CHD, but this was also true for total cholesterol and triglycerides. An elevation of the beta:alpha-lipoprotein ratio could indicate that there was an elevation of beta-lipoprotein, a reduction of alpha-lipoprotein or both, since LDL and HDL are virtually independent of one another

(Castelli et al, 1977A). This ratio can be considered somewhat similar to (but the reverse of) the HDL-cholesterol/total cholesterol ratio, since LDL-cholesterol and total cholesterol are so closely correlated (Castelli et al, 1977A).

The findings of these prospective studies lead to several conclusions. (1) HDL-cholesterol can be the most potent risk factor, in some cases, in its negative relationship with the future incidence of CHD (Gordon et al., 1977A; Miller et al, 1977A) while total cholesterol and triglycerides may not always be directly related to the future CHD occurrence (Gordon et al, 1977A; Miller et al, 1977A). LDL-cholesterol (Gordon et al, 1977A) or the cholesterol of d<1.063 can also be related to CHD incidence (positively), but HDL-cholesterol is more strongly related and is independent of LDL-cholesterol in its ability to predict future CHD occurrence (Gordon et al, 1977A; Miller et al, 1977A). These findings confirm the observations of the epidemiological studies of the independence of the role of HDL, in the prediction of future CHD, from LDL, total cholesterol and triglycerides. (2) HDL-cholesterol levels may not be predictive of CHD development in subjects younger than 44 (at least in subjects between the ages of 40 and 44) (Goldbourt & Medalie, 1979), although the subjects of Miller et al, (1977A) were of ages 20-49 and HDL-cholesterol was found to be a highly significant risk factor (negative) in these subjects. (3) The percentage of total cholesterol carried by HDL may be a very important indicator of the chances of a future CHD incident, since it reflects not only HDL-cholesterol levels but also total cholesterol levels and, indirectly, the LDL-cholesterol levels. Its importance lies in the fact that in the previous studies both HDL-cholesterol and LDL-cholesterol were significantly related to

the future incidence of CHD, even when total cholesterol was not a factor (Gordon et al, 1977A; Miller et al, 1977A). Possibly the HDL-cholesterol / LDL-cholesterol ratio would be an even stronger indicator. These comments and conclusions on the findings of the prospective studies must be moderated by the following considerations. As in the epidemiological studies, the prospective studies failed to account for initial differences in physical activity (except for that of Miller et al, 1977A), diet or medication, all of which could also affect HDL-cholesterol levels. The longest prospective study was of an eight and one-half year duration, which may not be an extensive enough period to carry out a proper prospective study of factors related to the development of CHD, since the atherosclerotic process is one that progresses over decades and may take a prolonged period of time before it becomes symptomatic.

Inherited HDL Variations and their Relation to CHD

Conditions with low HDL:

Familial hypercholesterolemia results in elevated levels of LDL-cholesterol and hypertriglyceridemia is characterized by elevations of VLDL, but both conditions often demonstrate a reduced level of HDL and a higher than normal incidence of CHD (Carlson & Bothinger, 1972; Frederickson & Levy, 1972). The percentage of total cholesterol carried by HDL is also significantly reduced in hypercholesterolemics (Brunner et al, 1979; Lehtonen & Viihari, 1978A), since the percentage which it carries decreases as total cholesterol increases (Brunner et al, 1979).

In individuals of ages 19-25 whose parents had a history of MI or angina, HDL-cholesterol was lower than in the normal subjects (Shaw, 1979). A reduction in HDL-cholesterol was also seen in the offspring of participants who developed CHD in the Framingham study (Feinleib et al, 1976).

Conditions with high HDL:

Individuals with hyper-alpha-lipoproteinemia or with hypo-beta-lipoproteinemia, characterized by high levels of HDL-cholesterol or low levels of LDL-cholesterol, respectively, have been found to have a higher than normal life expectancy. Males and females with hyper-alpha-lipoproteinemia had life expectancies 5 and 7 years longer than normal, and 9 and 12 years longer for male and female hypo-beta-lipoproteinemics (Glueck et al, 1975A; Glueck et al, 1975B). Morbidity and mortality rates were three times greater in the normal control kindred than in the kindred with either condition. On observing the lipoprotein profiles of 22 octogenarian kindred who were randomly selected from the population, Glueck et al (1977) observed a much higher than normal incidence of hyper-alpha- and hypo-beta-lipoproteinemia than would normally be seen in the population (14 out of 22). In the kindred of these 14 octogenarians, life expectancy was 10 years longer and mortality from a myocardial infarction was reduced in the first degree relatives.

High Density Lipoprotein - Structure, Characteristics, Metabolism and Function

Structure and Characteristics:

The structure and characteristics of the plasma lipoproteins, including HDL, are outlined in Table III. High density lipoproteins are defined as those lipoproteins with densities between 1.063 and 1.21 gm/ml on ultracentrifugation and alpha$_1$ mobility on electrophoresis. The average concentration of HDL in the plasma is 263 mg% for males and 320 mg% for females (Eisenberg & Levy, 1975). HDL is composed of 50% lipid and 50% protein on the average, but its two subclasses HDL_2 (d =1.063 - 1.125) and HDL_3 (d=1.125 - 1.210) actually have protein:lipid ratios of 40:60 and 55:45, respectively.

Aproprotein A-I (Apo A-I) and Apoprotein A-II (Apo A-II) are the two major protein constituents of HDL and account for more than 90% of the total protein content (Eisenberg & Levy, 1975). Apo-I and Apo A-II are present in a ratio of 3:1, but the ratio varies with the subfractions being higher in HDL_2 than in HDL_3 (Albers et al, 1978). In the other lipoprotein classes, Apo A-I and Apo-A-II are minor protein constituents except for the case of chylomicrons where Apo A-I, in the lymph, can be a major protein also (Schaefer et al, 1978). Apoprotein C-I, C-II and C-III are minor proteins comprising 2%, 2% and 6%, respectively, of the total HDL protein (Eisenberg & Levy, 1975). The Apo C's, although present in relatively small amounts, account for one-half of the total Apo C pool of fasting human plasma. The other half of the Apo C pool is located largely in VLDL, but also in chylomicrons to a certain extent. For VLDL and chylomicrons, Apo C is a major protein constituent. Apoprotein D

TABLE III

CHARACTERISTICS AND COMPOSITIONS OF THE PLASMA LIPOPROTEINS

A. Lipoprotein Characteristics[1]

	Chylomicrons	VLDL	LDL		HDL	
electrophoretic mobility	origin	pre-β	β		α_1	
density (gm/l)	<1.006	<1.006	1.006-1.063		1.063-1.21	
subclasses	none	none	IDL*	LDL	HDL_2	HDL_3
density of subclasses (gm/l)	--	--	1.006-1.019	1.019-1.063	1.063-1.125	1.125-1.210
molecular weight	$>0.4 \times 10^9$	$5-10 \times 10^6$	$3.9-4.8 \times 10^6$	2.7×10^6	3.9×10^5	1.8×10^5
lipoprotein concentration (mg%) female	?	69	41	330	83	237
male		173	57	380	37	226
diameter (Å)	>750	250-750	220-240	200-225	60-140	40-100

B. Percentage Composition (weight %) (approximate)[2]

	Chylomicrons	VLDL	LDL	HDL
percentage protein	2%	10%	20%	50%
percentage free & esterified cholesterol	2 + 4 = 6%	6 + 16 = 22%	10 + 40 = 50%	3 + 15 = 18**
percentage triglyceride	84%	50%	8%	7%
percentage phospho	8%	18%	22%	25%

C. Apoprotein Composition (% of total of lipoprotein protein)[3]

	Chylomicrons		VLDL		LDL		HDL	
Apo AI	7.4***	(minor)[4]	TRACE***	(minor)	--		67	(major)
Apo AII	4.2	(minor)	TRACE	(minor)	--		21	(major)
Apo B	22.5	(major)	36.9		98 (major)		TRACE	
Apo CI	15		3.3	(major)	TRACE		1-3	
Apo CII	15	(minor)	6.7		TRACE	(minor)	1-3	(minor)
Apo CIII	36		39.9		TRACE		3-5	
Apo D	-		-	(minor)	--		+	(minor)
Apo E	- ****		13.0	(major)	TRACE		+	(minor)

1. adapted from Eisenberg & Levy, 1975; Osborne & Brewer, 1977.
2. adapted from Faergeman, 1977.
3. adapted from Schaefer et al, 1978; Smith et al, 1978.
4. major & minor classification according to Smith et al, 1978.

* = this subclass is not always included, but it is presently gaining acceptance as an intermediate density lipoprotein (IDL) remnant lipoprotein.

** = others report a free: esterified cholesterol ratio of 1:3 (Eisenberg, 1978A)

*** = can be a major protein but only if intestinal in origin, and in the lymph (Eisenberg et al, 1978).

**** can be a major protein according to Faergeman, 1977.

(Apo-D), also known as the thin- line peptide or Apo A-III, and Apoprotein E (Apo E) which is also called the arginine-rich peptide, are present in minute amounts in plasma HDL. This contrasts with nascent HDL, which has recently been secreted from the liver (rat), where Apo E is a major protein comprising 50% of the total HDL protein mass (Schaefer et al,1978). In nascent rat HDL, the Apo E : Apo A ratio is 5 : 1 as compared to the ratio in plasma HDL which is in the range of 1 : 5 (Havel et al, 1978). Apo E is also a minor protein of plasma VLDL. Apoprotein B, a major protein of the chylomicrons, VLDL and especially LDL, is absent in HDL (Eisenberg & Levy, 1975; Eisenberg, 1978; Eisenberg et al, 1978).

Of the total lipoprotein mass, 20% is cholesterol (esterified : free cholesterol in a ratio of 3:1), 22% is phospholipid and 8% is triglyceride (Eisenberg & Levy, 1975). The average range of plasma HDL-cholesterol in adults is 30-60 mg% (Castelli et al, 1977A).

Structurally, plasma HDL is a spherical globule, approximately 100-110 $\mathring{A}$ in a diameter, with cholesterol esters and triglycerides forming an inner core (Scanu, 1978). This liquid core is thought to have a radius of approximately 20 $\mathring{A}$ (Scanu, 1978) and is surrounded by an outer shell of apoproteins, phospholipids and free cholesterol (Morissett et al,1975 & 1977). The free cholesterol and phospholipids form a monolayer, with their closely packed hydrophobic ends on the surface of the inner core (Scanu, 1978). Thus, the phospholipids are oriented with their hydrocarbon chains close to the core and their head groups at the plasma-lipoprotein interface. The organization of the apoproteins at the interface is less clear (Scanu, 1978). The major forces in the protein-lipid interaction appear to be hydrophobic (Levy et al, 1976). Cholesterol esters are

considered to be responsible for the spherical structure of mature HDL, as these esters do not easily form stable bilayers (Eisenberg & Levy, 1975). Nascent HDL, containing predominantly free cholesterol rather than esterified cholesterol, is disc shaped. It is only after this HDL disc is subjected to the action of certain plasma enzymes, specifically Lecithin-Cholesterol-Acyl-Transferase (LCAT), that its spherical shape takes form (Hamilton et al, 1976) due to the consequent formation of esterified cholesterol which moves to the centre of the disc bilayer.

The absolute and relative concentrations of all lipoproteins vary with the species, probably reflecting major differences in the lipoprotein metabolism. As an example, in dogs and rats, HDL is high, VLDL is low and LDL is very low (Eisenberg & Levy, 1975). These animals are also quite resistant to atherosclerosis (Oliver, 1978). In humans and guinea pigs, LDL is in the greatest concentration, then HDL, followed by VLDL (Eisenberg & Levy, 1975). Notably, humans and guinea pigs are quite susceptible to atherosclerosis. Due to these differences in lipoprotein profiles, caution must be used when extrapolating results obtained from animal studies to the human situation.

Synthesis and Catabolism:

Detailed knowledge of lipoprotein metabolism, especially that of HDL metabolism, has only begun to appear in the literature since 1975 when HDL began to gain importance as an anti-atherogenic lipoprotein. Information regarding the specifics of HDL synthesis, metabolism and degradation in man is still rather disjointed, but certain characteristics of it have been determined from observations made on animal models. For a detailed comparison of the general synthetic and catabolic routes of the

major plasma lipoproteins, as well as their probable roles, refer to Table IV.

i) Synthesis

A short review of general lipoprotein synthesis may facilitate the comprehension of the synthetic, metabolic and degradation pathways that have been suggested for HDL.

The major sites of synthesis of the various lipoproteins are the liver, small intestine and plasma.

Chylomicrons, which primarily carry exogenous triglycerides but also transport dietary cholesterol, are synthesized in the small intestine (Gangl & Ockner, 1975). In the intestinal lymph chylomicrons have an appreciable amount of Apo A-I, but after circulating for a short time in the plasma they contain little Apo A-I (Tall & Small, 1978). Most of this Apo A-I is eventually found in the HDL density range (Tall & Small, 1978). In the plasma, through the action of the enzyme Lipoprotein Lipase (LPL) on chylomicron triglycerides, chylomicrons are slowly degraded. As the degradation proceeds, triglycerides, phospholipids, unesterified cholesterol and certain proteins (Apo C and Apo A, in particular) are removed (Eisenberg, 1978; Eisenberg et al, 1978; Tall & Small, 1978). This degradation product, termed a remnant particle, is thought to be almost completely removed from the plasma by the liver where its cholesterol esters are hydrolyzed and Apo B is removed (Faergeman, 1977). Chylomicron remnants are the major lipoprotein regulators of hepatic cholesterol synthesis in the rat when compared to LDL and HDL (Anderson et al, 1979). LDL and HDL did regulate the synthesis, but the

TABLE IV

LIPOPROTEIN SYNTHESIS AND METABOLISM

Table 2 Lipoprotein synthesis and metabolism

Lipoprotein	Location	Process	Major components
Chylomicron	Intestine	assembly, secretion	apoA, apoB, phospholipid, cholesterol, cholesteryl ester, triglyceride
	Lymph	transfer	apoC, apoE[a]
	Plasma	transfer	apoC, cholesterol
	Endothelial cell	hydrolysis[b]	triglyceride, phospholipid
		transfer	fatty acid, cholesterol, phospholipid, apoC, apoA, apoE[a]
VLDL	Liver	assembly, secretion	apoB, apoC, cholesterol, phospholipid, triglyceride, cholesteryl ester
	Plasma	transfer	apoC[a], apoE[a], cholesteryl ester
	Endothelial cell	hydrolysis[a]	triglyceride, phsopholipid
		transfer	fatty acid, cholesterol, phospholipid, apoC, apoE[a]
LDL	Plasma	formation	from VLDL and chylomicrons
		exchange	cholesterol, phospholipid
	Peripheral tissues, liver[a]	uptake, degradation, regulation	cholesterol, cholesteryl ester
HDL	Liver	assembly, secretion	apoA, apoE, phospholipid, cholesterol
	Plasma	formation[a]	from chylomicrons[a]
		acyltransfer[c]	phosphatidylcholine, cholesterol
		transfer	cholesteryl ester, apoC, apoE[a]
		exchange	apoC, cholesterol, phospholipid
	Liver, peripheral tissues[a]	uptake, degradation	cholesterol, cholesteryl ester

[a] Inferred but not determmed.
[b] Lipoprotein lipase (triacylglycerol hydrolyase, apoC-II activated).
[c] Lecithin cholesterol acyltransferase.

(Smith et al, 1978)

cholesterol carried in chylomicrons was fifty times more effective, due to its higher rate of transport into the liver.

VLDL can be synthesized in the small intestine, but its major site of synthesis is considered to be the liver (Roheim et al, 1966). VLDL carries endogenous triglycerides derived from hepatic synthesis. Plasma free fatty acids are the major contributors to endogenous triglyceride formation. But the triglycerides of VLDL can also arise from de novo hepatic synthesis utilizing hepatic fat stores, or from fatty acids originating from the triglycerides of VLDL and chylomicrons (Barter & Nestel, 1972). Intestinal VLDL derives its fatty acids from bile and gastrointestinal mucosal shedding (Havel et al, 1970). VLDL, like chylomicrons, is degraded in the plasma via the action of the endothelial enzyme LPL. As triglycerides are degraded and removed, there is a concomitant loss of free cholesterol, phospholipids and apoproteins (Apoprotein C, in particular) (Eisenberg et al, 1978). VLDL is converted by this process to an intermediate density lipoprotein (IDL) which retains the full complement of the VLDL Apo B and the major portion of VLDL Apo E (Schaefer et al, 1978). This intermediate density lipoprotein (IDL) is either metabolized by the liver, as were the remnant particles of chylomicrons, or further degraded to LDL (Schaefer et al, 1978). All Apo B in LDL has been shown to be derived from VLDL (Eisenberg et al, 1978). Whereas Apo B remains during the degradation of VLDL to LDL, only minute amounts of Apo E and Apo C are detectable in the LDL end product (Schaefer et al, 1978). LDL is considered to be catabolized principally in the periphery by cellular uptake and degradation (Sniderman et al, 1974; Stein et al, 1977).

HDL may arise from several synthetic routes or may be derived from a combination of these pathways. Nascent HDL has been observed to

be secreted from the liver in rats (Hamilton et al, 1976), but this form is rarely seen in humans except in individuals who are deficient in the enzyme LCAT (Forte et al, 1971). Nascent HDL is discoidal in shape since cholesterol esters are absent when it is secreted. Without cholesterol esters present, a central core does not occur, and as a result, nascent HDL takes the form of a lamellar bilayer composed of phospholipids and free cholesterol with its apoproteins randomly situated on the surface (Hamilton et al, 1976). The apoproteins of nascent HDL are the same as those of plasma HDL, but nascent HDL has a much higher Apo E : Apo A-I ratio then that of plasma HDL (Havel, 1978). On entering into the plasma, the surface free cholesterol is esterfied by the action of LCAT with the concomitant partial hydrolysis of phosphatidylcholine (Havel, 1978). The cholesteryl esters formed cannot occupy an interfacial position, and move into the centre of the disc forming a pseudo-micellular particle with a cholesteryl ester core. The lysophosphatidycholine formed leaves HDL due to its high affinity for plasma albumin (Havel, 1978). But if nascent HDL is the precursor of the plasma HDL, the action of LCAT cannot be the only mechanism involved in the transformation, since Apo A is much higher than Apo E in plasma HDL (Havel, 1978). The average particle of nascent HDL contains approximately 5 molecules of Apo E and 1 of Apo A-I, whereas plasma HDL contains less than 1 molecule of Apo E and 5 molecules of Apo A-I (Havel, 1978). Therefore, Apo E must be lost in the plasma and Apo A must be added at a site other than the liver or from another source (Eisenberg, 1978 ;Eisenberg et al,1978).Apo A-I is a major apoprotein of rat lymph chylomicrons and is contained to a minor extent in VLDL (Kostner & Holasek, 1972), particularly in VLDL derived from the intestine (Glukman & Green, 1977). Due to the presence of Apo A-I

in these lipoproteins, it has been suggested that formation of mature HDL requires the transfer of Apo A-I from the triglyceride-rich lipoproteins and possibly partial removal of Apo E (Eisenberg et al, 1978; Havel, 1978). This is substantiated by the finding that, during lipolysis of chylomicron triglycerides, Apo A and Apo C as well as phospholipids are rapidly transferred to plasma HDL (Tall & Small, 1978). The case for the transfer of Apo A-I from VLDL is not quite as clear since VLDL contains little Apo A, but transfer of Apo C during VLDL degradation is well documented (Havel et al, 1973) and in vitro lipolysis of VLDL triglyceride leads to the transfer of phospholipid to HDL (Chajek & Eisenberg, 1978).

Eisenberg et al (1978) carry the hypothesis of HDL transformation via the addition of triglyceride-rich lipoprotein components one step further. They have observed that, as VLDL is metabolized, the product particle (post-lipolysis VLDL) retains all the Apo B of the precursor VLDL particles, but that lipolysis results in a loss of both the core components (cholesteryl esters and triglyceride) and surface constituents (Apo C, etc.). The surplus surface constituents (phospholipid, Apo C and free cholesterol), after lipolysis, were found in the plasma in the HDL range. Eisenberg and associates (1978) suggest that these surplus surface fragments that dissociate from VLDL during lipolysis associate or fuse with HDL. They conclude that the contribution of chylomicron and VLDL surface components to HDL formation may account for the origin of some, most or even all of the circulating HDL. They also note that LCAT may play a key role in the transfer of cholesterol from the surface of HDL, LDL or VLDL fragments to the core of HDL.

Tall and Small (1978) also agree with Eisenberg and coauthors' (1978)

hypothesis on the possible synthetic routes of HDL. They have outlined a possible mechanism for the transfer of the surplus surface components of chylomicrons to HDL during lipolysis of the chylomicron triglycerides (Figure 1). VLDL may follow a similar route. Tall and Small further suggest that HDL may become unstable due to a loss of its Apo A-I(possibly to the plasma phospholipids) from the surface. Due to this instability, HDL may fuse with other lipoprotein particles which would result in the deposition of the HDL cholesteryl ester core into the particles. If the recipient particle was a chylomicron, this mechanism would provide a route for the transportation of esterified cholesterol back to the liver in the form of a remnant particle. Since chylomicron remnants have been reported as being lipoproteins which are most effective in the control of hepatic cholesterol synthesis (Anderson et al, 1979), such interrelationships of chylomicrons with HDL could be very important in the control of overall cholesterol metabolism. Presently, any such interrelated control mechanisms are virtually unknown.

Tall and Small (1978), Nikkila et al (1978A) and Nikkila (1978) all suggest that an increase in the concentration of HDL may be due to an increase in the activity of the enzyme LPL. An increase in LPL activity would increase the rate of peripheral catabolism of VLDL and chylomicrons. If, in humans, HDL is actually derived either partially or completely from the degradation of these triglyceride-rich lipoproteins, this increase in their catabolic rate would result in an increase in the synthetic rate of plasma HDL.

Another possible source of HDL may be the intestine, since it has been suggested that Apo A-I —phopholipid particles that have been found to arise from this site may fuse with Apo C —Apo E—unesterified cholesterol fragments of VLDL and chylomicrons to form a new HDL molecule (Tall & Lange, 1978).

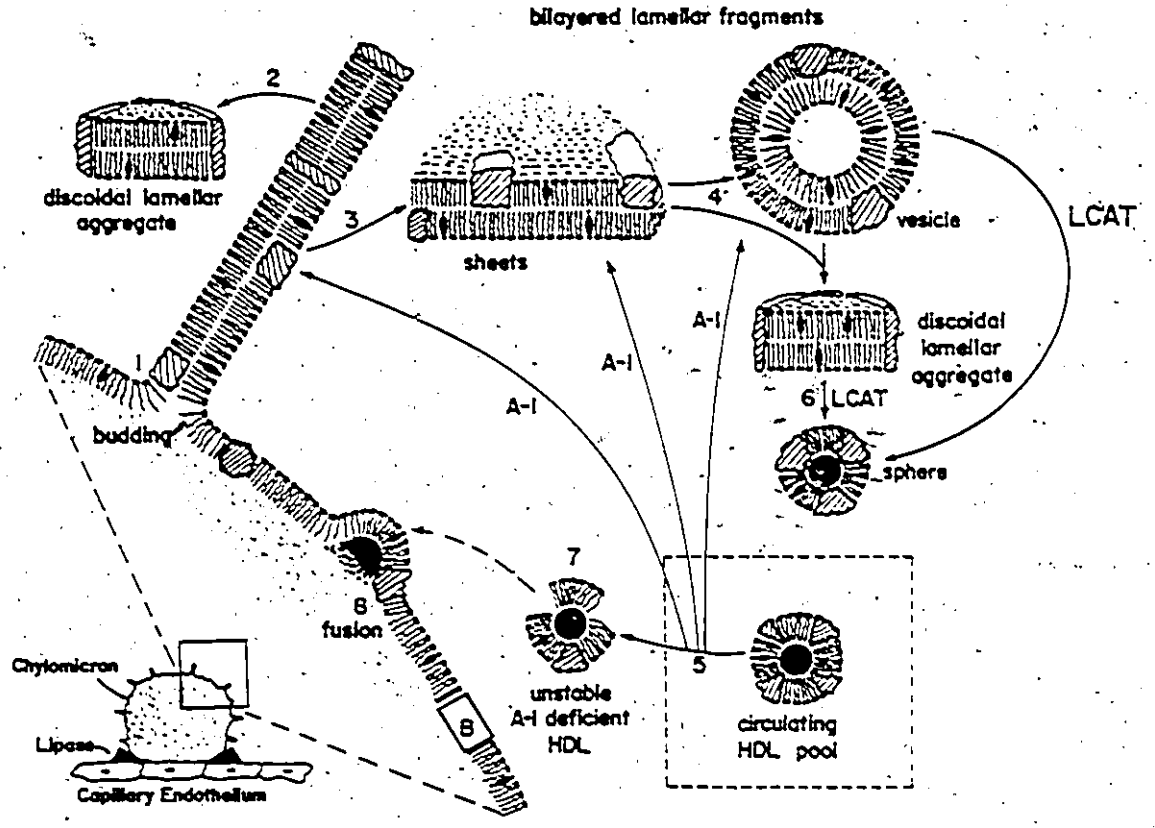


Figure 1. Possible Mechanism for the Transfer of Surface Compoments from Chylomicrons to HDL Fraction during Lipolysis of Chylomicron.

Lipoprotein lipase situated in the capillary endothelium hydrolyzes chylomicron triglyceride (lower left). The surface of the chylomicron contains phospholipids, free cholesterol, soluble A and C apoproteins (shown as hatched bodies) and apo B protein (labeled B). In 1, as triglyceride is removed, during lipolysis, the core shrinks, and the redundant surface constituents form lipid bilayer folds projecting from the chylomicron. In 2, a disklike particle could be formed directly from the apoprotein and phospholipids of the surface of the chylomicron. In 3, however, most of the excess material probably comes off as unstable bilayered sheets. In 4, these sheets seal to form vesicles — a more stable form of the bilayer. In 5, the circulating spherical high-density lipoprotein may interact with any of these bilayered lamellar structures (redundant folds, sheets or vesicles), donating A-I apoprotein. In 6, any of these bilayered fragments (sheets, vesicles or disks) are good substrates for the LCAT reaction if some A-I apoprotein is present. Thus, the pool of high-density lipoprotein helps to convert the bilayer fragments to new spherical high-density lipoprotein. In 7, however, the apo A-I-depleted spherical HDL has lost a large fraction of its surface and is thus unstable. Such particles could potentially fuse with various other lipoproteins disgorging their cholesterol ester core into such particles. In 8, if fusion occurred with the chylomicron, cholesterol esters, originally present in the circulating HDL, could be transported back to the liver in the remnant.

Figure 1 Tall & Small (1978)

Therefore, several routes for HDL synthesis in humans may exist. Nascent HDL may be formed in the liver and be transformed to mature HDL in the plasma by the addition of Apo A and C, cholesterol and phospholipid, and removal of Apo E. On the other hand, HDL may be partially or completely synthesized from the products of the triglyceride-rich lipoprotein lipolysis. Finally, HDL may be formed by the fusion of an Apo A-I — phospholipid particle with fragments from triglyceride-rich lipoprotein lipolysis. Notably, all these pathways require the involvement of LPL at some stage which initiates triglyceride hydrolysis and the subsequent removal of the excess surface components from the triglyceride-rich lipoproteins. Furthermore, LCAT may be necessary in HDL formation as well, since it appears to be needed for the esterification of free cholesterol of nascent HDL. It may also be required in the process of the removal of free cholesterol from the other lipoproteins and the transfer of this cholesterol, once esterified, from the surface into the HDL core. In all cases, a transfer to HDL of Apo A, Apo C, phospholipid and cholesterol is also involved. It should be noted that, since individuals with abeta-lipoproteinemia (lacking the Apo B containing lipoproteins, i.e., chylomicrons, VLDL and LDL) still possess the pseudo-micellular HDL particles in their plasma, it is possible for the apoprotein components of HDL to be secreted independently of the triglyceride-rich lipoproteins if necessary (Scanu et al,1974). None of the pathways outlined may be the actual one for HDL synthesis in humans, or HDL may be derived by a combination of the pathways. The synthetic routes may also differ for the two subfractions of HDL (HDL_2 and HDL_3), since there is some evidence that HDL_2 could be the end product of the in-

teraction of the surplus surface components of the triglyceride-rich lipoproteins and HDL_3, resulting in the formation of IDL and HDL_2 (Patsch et al, 1979). On the other hand, discoidal HDL_2, but not HDL_3, has been found to be secreted from the liver into the sphlachnic bed, in man, indicating that HDL_2 may originate from the liver while HDL_3 may be formed in the plasma (Turner et al, 1979). Since the two HDL subfractions have basically the same components (but HDL_2 has a higher lipid to protein ratio and a higher Apo A-I to Apo A-II ratio), free exchange of their components can occur and has been observed (Shepherd, 1978). But direct interconversion of the two subfractions has not been found (Shepherd, 1978), so the occurrence of a product-precursor relationship remains to be established.

ii) Catabolism

HDL circulates with a half-life of approximately 5.8 days before being catabolized (Blum et al, 1977). In a study of the turnover rate of human HDL, Furman and co-authors (1964) observed HDL half-life to be least in individuals with the lowest plasma HDL level suggesting that a diminished HDL pool size is related to an increased turnover rate. In a more recent study of human HDL metabolism, subjects demonstrated a reduced HDL half-life when fed a high carbohydrate isocaloric diet (Blum et al, 1977). Plasma HDL was reduced 20% in those individuals, due to an increased catabolic rate but an unchanged rate of synthesis.

The HDL degradation site has been determined in several animal studies (Roheim et al,1971; Rachmilewitz et al, 1972;Eisenberg et al,1973). The liver participates most actively in HDL catabolism.

Labelled HDL was observed by radioautography to be localized in rat hepatocytic organelles, especially in the secondary lysosomes (Eisenberg et al, 1973). A significant amount of HDL may also be removed by other organs such as the kidney and the small intestine (which seems to be of particular importance in rats) (Roheim et al, 1971; Eisenberg et al, 1973). Peripheral catabolism of HDL is possible since HDL has been found to be taken up to a certain extent by smooth muscle cells and skin fibroblasts, but the uptake was of a non-specific type (Miller, 1977B). In humans, Apo A-I and Apo A-II are degraded simultaneously and this occurs in both a plasma and non-plasma compartment (Blum et al, 1977).

The mechanisms involved in the clearance of HDL lipids from the circulation are unknown. It is thought that cholesterol carried by HDL can be removed in the liver for excretion as bile acids or biliary cholesterol, without the concurrent degradation of the remaining HDL particles (Schwartz et al, 1978). This would allow HDL to return to the circulation and take up more cholesterol, providing a "reverse cholesterol transport mechanism" (Miller & Miller, 1975) along the lines of Glomset's proposal (1968). Another possible mechanism for HDL lipid removal by the liver may be that suggested by Tall and Small (1978) where unstable HDL particles fuse with chylomicron remnants and disgorge their cholesteryl ester core into the remnant. The remnants would then carry this cholesterol to the liver for removal. The peripheral removal of HDL lipids is even less clear. Unlike LDL, which is readily bound and internalized by extrahepatic tissue with subsequent loss of its cholesterol to the cell and degradation of its protein moiety, HDL is not as easily or as specifically internalized or degraded in swine aortic smooth muscle cells (Carew et al, 1976), rat smooth muscle cells (Stein et al,

1976A) or in human skin fibroblasts (Stein et al, 1976B). This difference between LDL and HDL degradation in the periphery is even more marked in human cells (Stein et al, 1976A; Miller et al, 1977C). Peripheral removal of HDL lipids may also arise from exchange with or loss of lipids to other circulating lipoproteins (Eisenberg & Levy, 1975; Tall & Small, 1978).

High Density Lipoprotein Activity:

As described in the previous section, HDL in the circulation can undergo constant change. Along with the generation of cholesteryl esters within the HDL particle, exchange of free and esterified cholesterol, phospholipid and certain apoproteins occurs among the lipoproteins and between lipoproteins and tissue cells.

The exact role of HDL in lipid and lipoprotein metabolism is unclear but it may be reflected by the activity of its constituent proteins.

Apo A-I appears to be more related to function and Apo A-II plays more of a structural role. These respective roles are based on the observations that Apo A-I is loosely bound and easily separated from HDL, while Apo A-II is more tightly associated and is more efficient in binding phospholipid (Assman & Brewer, 1974). The ratio of Apo A-I : Apo A-II may therefore be important in determining the capacity of HDL to bind lipids since the interaction of Apo A-I with lipids is much less avid than that of Apo A-II (Eisenberg & Levy, 1975). However, this does not explain why there is a higher lipid : protein ratio in HDL_2 which has a higher Apo A-I : Apo A-II ratio than does HDL_3. Apo A-I is the apoprotein that is most frequently investigated, possibly because it is in the highest concentration (60% of HDL lipoprotein as compared to 30% for Apo A-II) but also because of the role it plays

in cholesterol esterification. Apo A-I is an activator of LCAT, an enzyme of major importance in the esterification of cholesterol in the plasma, which catalyzes the transfer of a fatty acid from phosphatidycholine to unesterified cholesterol (Fielding et al, 1972). Because of its high Apo A-I content, HDL is a natural activator of this enzyme as well, and HDL and LCAT are thought to circulate in close association with one another. HDL can transfer, nonenzymatically, this esterified cholesterol to the lower density lipoproteins. But the cholesteryl ester content of newly secreted VLDL and chylomicrons can easily account for the cholesterol content of all remaining Apo B - containing metabolites (Eisenberg & Levy, 1975). From these observations, it has been suggested that the LCAT-HDL system may be more responsible for the removal of excess unesterified cholesterol and phosphatidycholine from the system, rather than for the transfer of esterified cholesterol to other lipoproteins (Eisenberg & Levy, 1975). These findings would support the hypothesis that HDL plays a key role in the removal of excess cholesterol from the periphery and in the transport of it to the liver (Glomset, 1968).

The C apoproteins appear to be more related to triglyceride metabolism. Apo C-II (with phospholipids) is the specific plasma protein cofactor required for the activation of adipose tissue Lipoprotein Lipase (LPL) (Larosa et al, 1971). Apo C-I may also activate the enzyme, while Apo C-III may be inhibitory (Ganeson et al, 1971; Brown & Baginsky, 1972). The role of the Apo C proteins of HDL is unclear, but, since a two-way transfer of these apoproteins between VLDL and HDL occurs very easily, it has been postulated that HDL serves as a reservoir for Apo C between tides of high plasma triglyceride levels (Eisenberg et al, 1972).

Apoprotein D has been isolated from HDL_3 (Schaefer et al, 1978). Apo D is similar to another Apo A, called Apo A-III, which has been reported to activate LCAT also (Schaefer et al, 1978). The role of Apo D is presently unknown.

Apo E appears to shuttle between HDL and VLDL in a manner similar to Apo C. Nascent HDL may transfer Apo E to VLDL, which may be transferred back to HDL during the cholesterol esterification process that occurs as IDL is transformed to LDL. The exact role of Apo E is unknown but it may be to increase the binding affinity of HDL to LDL receptors and improve HDL's ability to compete with LDL for binding sites (Mahley & Innerarity, 1977). Normal human plasma HDL contains only a small amount of Apo E (Havel, 1978; Schaefer et al, 1978).

HDL activity, as determined by the function of its apoproteins, plays a role in cholesterol and triglyceride metabolism. HDL may simply act as a carrier molecule for the transfer of cholesterol from tissue to tissue or, as the proponents of the role of HDL as an anti-risk factor suggest, HDL may provide a transport mechanism for the removal of cholesterol from the periphery to the liver with the subsequent excretion of its cholesterol content in the bile.

High Density Lipoprotein Activity in Relation to Atherosclerosis:

Due to the presence of large deposits of plasma cholesterol in atherosclerotic lesions, the role of HDL in cholesterol metabolism is of great interest.

Emphasis in the past has been placed on factors affecting cholesterol uptake in the arteries, which would further the progression

of atherosclerosis. Total cholesterol and LDL have received much attention since cholesterol has been found to filter into the atherosclerotic intima in proportion to its plasma concentration. (Zilversmit, 1968). LDL reflects the total plasma cholesterol level since it usually carries 65 - 70 % of the total amount (Eisenberg & Levy, 1975).

Little attention had been paid to the processes affecting the removal of cholesterol from cells, until the proposals of Glomset (1968) and Miller and Miller (1975). This function in cholesterol metabolism is vital since cholesterol cannot be metabolized in peripheral cells (except in the formation of steroid hormones) and must be removed from the cells and transported to the liver, which is the sole site of cholesterol degradation and excretion.

Glomset (1968) proposed that HDL, through its interaction with LCAT, provides a mechanism whereby unesterified cholesterol is taken up from peripheral tissues and transported as cholesteryl esters to the liver. The steps would involve: 1) HDL uptake of free cholesterol from the peripheral cell membrane, after a loss of phospholipid to albumin, 2) loss of esterified cholesterol to the liver (and uptake of phospholipid), 3) esterification of the newly acquired cholesterol in the circulation by LCAT, and transfer of it to the core of the HDL particle, 4) replacement by new free cholesterol from the periphery on the outer shell of HDL, 5) loss of the recently esterified cholesterol to the liver, etc.....(Figure 2). Glomset's view of the role of HDL in centripetal cholesterol transport has since become a popular explanation for the role of HDL in cholesterol metabolism.

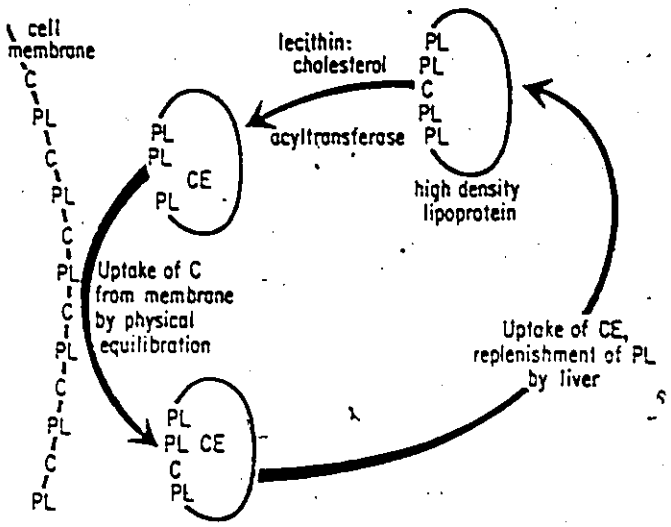


FIG. 2. Postulated mechanism for the transport of cholesterol from membranes of peripheral cells to the liver. Lecithin:cholesterol acyltransferase reacts with circulating lipoproteins to form cholesteryl esters from unesterified cholesterol and lecithin. The lipoproteins subsequently pick up unesterified cholesterol from cell membranes, circulate through the liver, and release esterified cholesterol. C, unesterified cholesterol; CE, cholesteryl ester; PL, phospholipid.

Figure 2

Glomset (1968)

While further studies have continued to add to the growing knowledge of the possible mechanisms whereby HDL may play a role in the prevention of atherosclerosis, certain studies should be noted for their unique contribution to such an explanation.

i) Studies in Humans

Miller and Miller (1975) reported an inverse relationship of the body cholesterol pool and CHD with HDL cholesterol levels, and noted that the development of atherosclerosis may be accelerated by a decreased clearance of cholesterol from the arterial wall, secondary to a reduction in plasma HDL concentrations.

The role of HDL as a "sink" for excessive cholesterol was suggested by an investigation of the serum cholesterol-binding reserve of healthy subjects as compared to cardiac patients (Hsai et al., 1975). The serum lipoproteins of cardiac patients bound less cholesterol than the normal controls, when incubated in vitro with a cholesterol preparation. For both groups, the serum cholesterol-binding reserve was located in the lipoproteins of the VLDL and HDL density ranges, and bound 51% and 29% respectively, of the total cholesterol bound. LDL appeared to be saturated, since it failed to take up any of the excess cholesterol, but LDL was not stable under these experimental conditions so this result is inconclusive. The authors postulated that VLDL and HDL may act as a buffer for excess cholesterol. Cardiac patients would then have a reduced ability to expand their serum cholesterol-binding reserve when presented with an increase in the cholesterol load, which would result in a deposition of the excess plasma cholesterol in the arterial wall.

In reference to the more direct role of HDL in centripetal cholesterol transport, HDL was found to be the principal plasma acceptor of adipocyte cholesterol during weight reduction in two obese subjects (Nestel & Miller, 1978). The subjects were infused with radiolabelled

cholesterol seven weeks prior to the commencement of a seven day caloric restriction period. The design was based on previous findings that, seven weeks after such an infusion, the specific activity of adipocyte cholesterol exceeds that of plasma cholesterol by 50% - 100%. It was also based on the knowledge that the cholesterol content of adipocytes decreases with decreasing cell size and triglyceride content. The specific activity of plasma cholesterol was measured during the seven day diet period. As the subjects lost weight, a rise in the specific activity of plasma cholesterol was only seen in the HDL fraction while it remained unchanged or decreased in the d<1.063 lipoproteins (VLDL & LDL). An absence of an increase in plasma HDL-cholesterol was interpreted to mean that the rate of HDL-cholesterol disposal had increased. Based on the assumptions of the experimental design, this study provides the most direct evidence for the role of HDL as a cholesterol acceptor in the reverse transport of tissue cholesterol (i.e. in the removal of cholesterol from the periphery). The limitation of this interpretation lies in the possibility that HDL may be removing cholesterol but depositing it in another peripheral location rather than transporting it to the liver for excretion. The results would be more conclusive if a concomitant increase in the specific activity of biliary cholesterol and bile acids would have been measured as well.

Pertaining once again to the role of HDL in the peripheral removal of cholesterol, the utilization of labelled free cholesterol from HDL and LDL for the production of biliary cholesterol was compared in a case study of a bile-fistula patient (Schwartz et al, 1978; Halloran et al, 1978). The experimental design was such that the liver had time to selectively extract the specifically labelled free cholesterol

of HDL and LDL prior to the complete exchange of the free cholesterol among the lipoproteins. It also allowed for the collection of bile that could be derived only from hepatic synthesis rather than from recirculation. Free cholesterol from HDL was incorporated into biliary cholesterol much more rapidly than that of LDL, indicating a selective utilization of free cholesterol from HDL in the cholesterol degradation pathway. The reason they measured free cholesterol uptake was because they had previously found that 70% of the cholesterol used in the formation of bile acids and biliary cholesterol was derived from the plasma cholesterol and 60% was from free cholesterol while only 10% was from esterified cholesterol. Consequently, their view of the role of HDL differs from that of Glomset (1968), in that they propose that HDL acts as a shuttle in the transport of free cholesterol, rather than esterified cholesterol, from the periphery to the liver since free cholesterol appears to be the favoured precursor of the biliary excretion products. They substantiate their proposal by noting that HDL selectively binds free cholesterol while LDL does not have this property.

To add further question to the specifics of Glomset's hypothesis (1968), on the role of LCAT in the egression of cholesterol from tissues and its removal by the liver, it has been demonstrated that the presence of LCAT in the medium is not necessary for the removal of cholesterol by HDL from human skin fibroblasts and rat aortic smooth muscle cells (Stein et al,1978A; Stein et al,1978B). Cholesterol esterification, therefore, is not necessary for the removal of cholesterol from cells. The authors suggest that LCAT may play a key role in cholesterol transport between the lipoproteins in the circulation rather than in the transfer of cholesterol from tissues to the lipoproteins since as much cholesterol was removed from cells in the absence as in the presence of the enzyme. Possibly, LCAT serves to keep the surface of HDL low in free cholesterol,which would facilitate the transfer of free cholesterol from

the cell membrane to the surface of the HDL micelle.

ii) Cell Incubation Studies

Although cell incubation studies are by no means representative of the in vivo situation, they can provide information that cannot be obtained from the intact animal which may reflect how the various lipoproteins could affect cellular cholesterol content as well as how they interact with each other in this regard. The cell incubation studies noted below indicate that HDL could exert an antiatherogenic effect via a variety of possible mechanisms. The majority of the cell incubation studies have focused either on the way in which HDL could 1) prevent cholesterol deposition, or 2) aid in cholesterol removal, from peripheral cells.

Plasma HDL-cholesterol levels have been observed to be inversely proportional to the human arterial tissue cholesterol content ($r = -.80$) while LDL-cholesterol levels were directly proportional to the cholesterol content ($r = -.55$) (Bondjers et al, 1976). Such correlations for serum cholesterol, triglyceride and VLDL were all low to moderate ($r = .43$, $.28$, and $.47$) and were not significant. These measurements were carried out on the mesenteric arteries of obese subjects who showed no signs of CHD. Therefore, the high negative correlation of HDL cholesterol with the arterial cholesterol content suggests that a decrease in HDL-cholesterol may precede the development of vascular disease. This study does not indicate whether HDL exerted its effect by preventing cholesterol uptake or acting in its removal.

Cholesterol removal from cells has been found to be facilitated

in the presence of HDL. Human skin fibroblasts and rat aortic smooth muscle cells, incubated with HDL as the sole lipoprotein source, demonstrated a greater loss of cholesterol to the medium than when LDL or whole plasma was utilized (Stein et al, 1976B). HDL has also been found to promote a cholesterol efflux from cells in several other studies (Glomset, 1970; Stein et al 1975 & 1976A). Not only has HDL been found to facilitate the efflux, but it also appears to be obligatory in order to achieve a net removal of cholesterol from healthy human intimal arterial tissue (Bondjers & Bjørkerud, 1975). This later observation of the obligatory role of HDL in net cellular cholesterol removal is interesting but questionable, due to observations of the cellular cholesterol content in subjects with Tangier's disease. Tangier's disease is characterized by a lack of (normal) HDL. These patients are not considered to exhibit a higher than normal incidence of CHD, and excessive cholesterol deposition is usually only observed in the reticulo-endothelial system (Ferrans & Frederickson, 1975), which makes one question if HDL does affect arterial cholesterol removal. It may also be that, in these individuals, there is an alternate cholesterol "clearing" mechanism that becomes active with this type of disease. Another explanation may be that, since LDL-cholesterol is also very low in these individuals, the HDL-cholesterol : LDL-cholesterol ratio would probably still be high enough for adequate peripheral cholesterol removal to occur.

Following the hypothesis that HDL influences cellular cholesterol removal, the destination of this cholesterol becomes of interest. HDL could deposit the cholesterol in other peripheral cells or, as suggested by Glomset (1968), transport it to the liver for excretion. The latter route would be the final step if HDL was truly involved in

"reverse cholesterol transport". Liver cells, primarily non-hepatocytes, have been shown to catabolize HDL in vitro and do so to a much greater extent than for LDL (Van Berkel et al, 1977). This observation may indicate that, unlike LDL which is primarily catabolized in the periphery, the majority of HDL catabolism may take place in the liver resulting in the deposition of its cholesterol content at this site and, possibly, the further removal of the cholesterol into the bile.

The suggestion that the major site of HDL catabolism may be non-peripheral is further substantiated by the finding that HDL is interiorized very poorly in human skin fibroblasts, as compared to LDL (Miller et al, 1977B). The difference in uptake between HDL and LDL is due to the presence of LDL-specific receptors in the cell membrane. These receptors allow for the rapid binding and interiorization, via endocytosis, of LDL with the subsequent degradation of its protein moiety and release of cholesterol to the cell (Brown et al, 1975; Goldstein & Brown, 1977; Small, 1977) (Figure 3). HDL uptake, on the other hand, is rather non-specific since it occurs by way of gross fluid endocytosis. and does not appear to favour a specific receptor (Miller et al,1977B).

HDL may prevent cholesterol accumulation via a second route, by preventing the uptake of cholesterol from the plasma. Cholesterol uptake was found to decrease in porcine coronary arteries when HDL was added to the plasma medium (Sarma et al, 1978). This does not provide information regarding the net uptake of cholesterol, but it does reflect a difference in the permeability of the arteries to the various

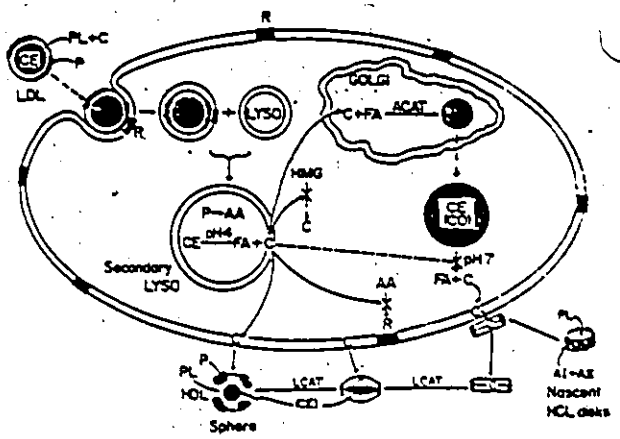


Figure 3. Cellular Uptake, Metabolism and Removal of Cholesterol.[5-7,9,10,34,35]

Low-density lipoprotein (LDL) is composed of a core of cholesterol ester (CE) and triglyceride[32] and a shell of phospholipid (PL), free cholesterol (C) and protein (P). Once LDL binds to a receptor (R) on the cell surface, the receptor-LDL complex migrates to become an endocytotic vesicle and fuses with a lysosome (LYSO). In the acid interior of the lysosome, P is hydrolyzed to amino acids (AA) and CE to fatty acids (FA) and C. The C must then translocate to the outer side of the lysosome so that it can be transported to other parts of the cell. As excess C emerges from the lysosome, it first inhibits synthesis of new C from hydroxymethylglutarate (HMG) and then stimulates formation of CE, consisting mainly of cholesteryl oleate (CO), by the acyl coenzyme A : cholesterol acyltransferase (ACAT) system. In addition: the excess C inhibits synthesis of new receptors and perhaps blocks cytoplasmic hydrolysis of newly formed CE. The broken line indicates that this pathway has not been fully established.

The acceptors for C, disk-shaped nascent high-density lipoprotein (HDL) and intact spherical plasma HDL, pick up C and possibly PL from the outer leaf of the plasma membrane. As C enters nascent or intact HDL, lecithin-cholesterol acyltransferase (LCAT) converts surface C to CE, which leaves the surface to form the core of HDL. The removal of CE from the surface permits the particle to pick up more C.

Figure 3 (Small, 1977)

lipoproteins in the medium. When human skin fibroblasts and rat smooth muscle cells were incubated with a physiological concentration of HDL, HDL produced little or no increase in the cellular cholesterol content, whereas with LDL the cholesterol content increased considerably (Miller et al, 1977C). HDL may decrease cholesterol uptake not only by its inability to be efficiently bound and interiorized by the cells but also by inhibiting the uptake of LDL. HDL has been found to decrease LDL uptake in human endothelial cells (Stein & Stein, 1976), human fibroblasts and rat smooth muscle cells (Stein et al, 1976A; Steinberg et al, 1976). It has been suggested that HDL may prevent LDL uptake by inhibiting the binding of LDL to the receptor sites on the cell membrane. This inhibition of LDL binding has been observed in several studies (Carew et al, 1976; Stein & Stein, 1976; Miller et al, 1977C) using human skin fibroblasts, rat aortic smooth muscle cells and vascular endothelium. Due to this inhibition of LDL or via some alternative mechanism, HDL may inhibit the interiorization of the LDL particle as a result. This would prevent the excessive deposition of LDL-cholesterol in the cell.

HDL could also affect atherosclerosis by preventing the formation of the plaque structure. The interaction of LDL with glycosaminoglycans has been related to the development of the atherosclerotic plaque (Ross & Glomset, 1976). When LDL was incubated with aortic glycosaminoglycans, in vitro, the resultant complex formation decreased as the concentration of HDL was increased in the medium (Bihari-Varga,1978). Addition of HDL to the serum medium inhibited the formation of these insoluble complexes in proportion to the amount of HDL added. Furthermore, HDL may also affect non-cellular cholesterol accumulation

in atherosclerotic plaques since incubation of HDL with cholesterol crystals was shown to lead to the eventual destruction of the crystal structure via the formation of liposome buds on the surface of the crystal(Abdulla & Adams, 1978; Adams & Abdulla, 1978). This breakdown of the cholesterol crystal was not observed during incubation with LDL or VLDL.

Therefore, HDL may be effective in the prevention of cellular and extracellular cholesterol deposition. It may do so by playing a significant role in the centripetal transport of cholesterol from the periphery to the liver for excretion. It may also act by inhibiting the cellular uptake of LDL. The degree that either mechanism is utilized in vivo is presently unknown, but studies of humans have at least indicated that HDL can be involved in the reverse cholesterol transport pathway, particularly during weight loss.

Factors Affecting High Density Lipoprotein Concentrations

Miller & Miller (1975) noted that HDL or HDL-cholesterol levels are generally lower than normal in conditions associated with a high incidence of CHD, and are higher in conditions characterized by a low incidence of CHD. These relationships are outlined below.

Conditions of Low HDL-Cholesterol and High CHD Incidence:

HDL-cholesterol is sometimes lower in subjects with hypercholesterolemia (Miller & Miller, 1975) and hypertriglyceridemia (Miller & Miller, 1975). With regard to total plasma cholesterol, HDL-cholesterol shows little relationship (Castelli et al, 1975; Albers et al, 1976; Berg et al, 1976A; Nikkila, 1976; Rhoads et al, 1976A; Castelli et al, 1977B; Gordon et al, 1977A). This may be due to the fact that as total cholesterol increases, the percentage of total cholesterol carried by HDL decreases but appears to do so in an inconsistent manner (Goldburt & Medalie, 1979). In the case of total plasma triglycerides, HDL demonstrates a consistent but low negative correlation (-.35 and -.40) (Albers et al, 1976; Rhoads et al, 1976; Castelli et al, 1977A &B; Gordon et al 1977A; Berenson et al, 1979; Hjermann et al, 1979). Diabetes Mellitus has been associated with a low HDL-cholesterol level in some individuals (Lopez-Virella & Colwell, 1976; Gordon et al, 1977B; Lopez-Virella et al,1977A). Diabetics, who demonstrated low levels of HDL-cholesterol, increased their levels with insulin treatment but such an effect was not observed with other oral hypoglycemic drugs (Stanton, 1978). HDL-cholesterol increased when blood sugar

levels were lowered in some maturity onset diabetics but the response was not consistent in all subjects and appeared to be very individualized (Michael et al, 1979). HDL-cholesterol is lower in children of CHD parents (Feinleib et al, 1976) or in children of CHD mothers specifically (Mjøs et al, 1977). Obese subjects have lower HDL-cholesterol (Wilson & Lees, 1972), HDL has an inverse relationship with relative body weight (Wood et al, 1976; Gordon et al, 1977A & B; Mjøs et al, 1977; Van Gent et al, 1978), body mass index (Hulley et al, 1979) or with the sum of several skinfolds (Rhoads et al, 1976). Patients in chronic hemodialysis also demonstrate reduced HDL-cholesterol which is not related to raised triglyceride levels (Rapoport et al, 1978).

Conditions of High HDL-Cholesterol and Low CHD Incidence:

HDL-cholesterol is higher in premenopausal women (Castelli et al, 1977A; Mjøs et al, 1977; Van Gent et al, 1978; Rifkind et al, 1979) due to an increase in HDL_2-cholesterol (Cheung & Albers, 1977). Males have higher levels of HDL-cholesterol than females up to the age of fourteen where a switch over occurs (Rifkind et al, 1979). After this age, HDL-cholesterol begins to fall for men (age 14 55 mg% age 50 46 mg%) but continues to rise for women (age 14 53 mg% age 50 64 mg%) (Berenson et al, 1979; Rifkind et al, 1979). This difference between male and female cholesterol levels in the adult is thought to be due to a hormonal influence. This conclusion is based on the findings that estrogen therapy can increase HDL-cholesterol but progesterone therapy decreases it (Bradley et al, 1978). The difference in response is due to an increase in the HDL_2 subfraction with estrogen administration and a decrease in HDL_2 with progesterone administration (Krauss et al, 1979). Women on oral contra-

ceptives have also been reported to have reduced levels of HDL-cholesterol (Bradley et al, 1978; Van Gent et al, 1978), but the response is related to the formulation of the contraceptive administered and is related to the opposing effects that estrogens and progestins appear to have on HDL-cholesterol (Bradley et al, 1978). HDL-cholesterol is higher in non-smokers than smokers (Enger et al, 1977; Bradley et al,1978; Garrison et al, 1978; Van Gent et al, 1978; Hulley et al, 1979) and the relationship is independent of alcohol intake (Garrison et al, 1978; Hulley et al, 1979) and body mass index or subscapular skinfold thickness (Garrison et al, 1978; Hulley et al,1979). In the study of Enger et al (1977), this relationship with smoking was only observed in physically active men. Two studies did not find such a relationship among smokers (Gordon et al, 1977A; Mjøs et al, 1977), but the lack of difference between the groups may be due to the contribution of other factors such as a high alcohol intake in smokers, that would mask the relationship. HDL-cholesterol has been found to be higher in physically active individuals (Wood et al, 1976; Martin et al, 1977; Wood et al, 1977; Lehtonen & Viihari, 1978A). Finally, HDL-cholesterol is higher in subjects with a moderate to high alcohol intake (Castelli et al, 1977C; Bradley et al, 1978; Hulley et al, 1979).

Other Conditions Affecting HDL Levels:

There are several other known factors that can influence HDL-cholesterol levels. The ones of interest are those utilized in the treatment of subjects who are at a high CHD risk since risk-reduction therapy may not be worthwhile if its administration concurrently causes

a reduction in HDL-cholesterol or in the percentage of total cholesterol that it carries.

Lipid lowering drugs, such as cholestyramine resin (Wallentin et al, 1978) and clofibrate (Enger et al, 1978) do not seem to change HDL-cholesterol levels. Niacin actually increases HDL (and HDL-cholesterol) by decreasing its intravascular catabolic rate and increasing the Apo A-I: A-II ratio (Blum et al, 1977; Shepherd, 1978). The increase in HDL was principally seen in the HDL_2 subfraction (Blum et al, 1977).

Diets also affect HDL-cholesterol levels. In diets that were fat-controlled with a high polyunsaturated to saturated fat ratio (1;1 or 4:1), HDL-cholesterol was reported to increase (Hjermann et al, 1979; Wallentin et al, 1979), not to change (Hulley et al, 1979) or to decrease (Shepherd, 1978). In all cases total cholesterol fell. The differing responses may be due to the fact that all other studies utilized hypercholesterolemic subjects, while Shepherd studied subjects whose cholesterol levels were in the normal range. With calorie restriction diets, HDL-cholesterol increased in most cases (Wilson & Lees, 1972; Hulley et al, 1979; Wallentin et al, 1978). On the other hand, Taskinen and Nikkila (1979) reported a decrease in HDL-cholesterol during the calorie-restriction period. The decrease was accompanied by a decrease in adipose tissue LPL. Taskinen and Nikkila (1979) explained the discrepancy of their results from those of the other studies as being due to the fact that they measured HDL-cholesterol during the low calorie period rather than after it. They suggest that during negative calorie balance, due to low levels of LPL, HDL-cholesterol is reduced. On resuming an isocaloric diet, LPL may rebound to higher than normal levels resulting in a consequent elevation of HDL-cholesterol.

A high carbohydrate diet reduced HDL by increasing its rate of catabolism without changing its rate of synthesis (Blum et al, 1977).

Cholesterol feeding increases LDL significantly, while it increases HDL only very slightly (Connor , 1977) or does not change HDL-cholesterol (Mahley et al, 1978) in humans. While cholesterol feeding did not increase total cholesterol in all subjects in the study of Mahley and co-authors (1978), it did increase the binding affinity of HDL for LDL receptors. In dogs, cholesterol feeding results in an increase in LDL and IDL, a reduction in normal HDL and the formation of a new HDL sub-fraction called HDL_c (Mahley et al, 1978). HDL_c falls in the LDL flotation range but has α mobility. It contains much more Apo E than usual and it binds avidly to LDL receptors (Mahley et al, 1978).

Therefore, when determining the effect of a given factor on HDL levels, one must ensure that other contributing factors such as those listed in this section can be accounted for and their effect isolated from those of the treatment factors under study.

Coronary Heart Disease and Chronic Physical Activity

Most studies that related CHD incidence to level of inactivity have been retrospective studies that compared the level of occupational physical activity with CHD incidence (Morris, 1960; Froelicker & Oberman, 1972). The design of these studies is weak since it does not consider the possibility that healthier individuals selected the more active jobs rather than the activity in the job being responsible for their lower incidence of CHD. Despite this drawback, several such studies deserve mention. Coronary arteries of men whose occupation required regular physical activity demonstrated less atherosclerotic involvement as compared to those of less active men (Rissanen, 1976). He suggests that coronary atherosclerosis in physically active men fails to reach the threshold level of severity required for the clinical manifestation of its presence as often as it does in sedentary men. Physically active men, on the basis of occupation, were also under represented in two separate population studies of men who had died from ischemic heart disease (Rissanen, 1976).

In longitudinal studies, which should avoid the possibility of a biased selection that could have accounted for the differences in the comparative studies, 2 out 3 found an inverse association between CHD and level of physical activity. Paffenberger and colleagues (1977) followed a group of San Francisco longshoremen for 22 years. They concluded that a higher energy output on the job (as measured by oxygen consumption) was associated with a reduction by one-third of the incidence of a fatal heart attack after accounting for the

contributions of blood pressure, smoking and plasma cholesterol. Wilhelmsen et al (1976) found that low physical activity during leisure time rather than work was a risk factor in an 8 year follow-up study of a group of Swedish men. But, this relationship was lost when other risk factors were included in a multivariate analysis. In a 10 year follow-up study in Finland, (Punsar & Karvonen, 1976) no relation was observed between CHD incidence and degree of occupational physical activity. Recently, in a review of factors that can predict CHD incidence using the Framingham population as part of the sample, physical inactivity was included as one of the three major treatable CHD risk factors, the others being smoking and plasma cholesterol (Gotto, 1979).

Therefore, physical activity has been negatively correlated with the incidence of CHD in some cases. The benefits that arise from physical activity in relation to the prevention of CHD are usually considered to be derived from an improved cardiovascular system and an increased oxygen uptake in the muscle, allowing more physical work to be accomplished at a lower heart rate. But CHD risk factors may also be beneficially affected by exercise, as well, either directly (by decreasing plasma triglyceride levels) (Lopez-S, et al. 1976) or indirectly (by weight loss or cessation of smoking).

Plasma Cholesterol and Chronic Physical Activity

The effect of chronic physical activity on plasma cholesterol has frequently been examined. Only the training studies will be reviewed here because they give a more direct indication of the chronic effects of exercise than the comparative studies which can only relate cholesterol levels to the degree of activity reported. A more comprehensive coverage of the relation of total cholesterol to physical activity can be found in the review article of Naito (1976). The results of the training studies are rather inconsistent in that some studies reported a decrease while other studies found no significant change. The conditions and results of the various studies are listed in Table V.

A number of studies have reported a reduction in plasma cholesterol following the administration of a training program and in all cases the type of activity was of an endurance nature (Golding, 1961; Rochelle, 1961; Naughton & Balke, 1964; Campbell, 1965 ; Campbell, 1966; Altekruse & Wilmore, 1973; Lopez-S et al. 1974; Leon et al. 1977; Roundy et al, 1978; Widhalm et al. 1978). The extent of the decrease appears to be related to the initial level of plasma cholesterol in that the subjects with the highest initial cholesterol level exhibited the greatest reduction. In subjects whose cholesterol levels were high to begin with, cholesterol fell 26% (from 342 mg% to 253 mg%) (Golding, 1961) and 20% (from 260 mg% to 210 mg%) (Naughton & Balke, 1964). A reduction of 23% (from 217 mg% to 167 mg%) was also observed in a group of obese children but their activity program was also accompanied by

TABLE V

PHYSICAL TRAINING AND PLASMA CHOLESTEROL

Author	TRAINING PROGRAM: Type	Duration	Frequency	Intensity & Duration of Session	Tx Test	SUBJECTS: Experimental Group: Description	Age	n	SUBJECTS: Control Group: Description	Age	n	PLASMA CHOLESTEROL: Classification of Initial Level*	Experimental Group: Pre	Post	% change	Control Group: Pre	Post	Significant Difference	NOTES
Studies which observed a reduction in plasma cholesterol																			
Golding, 1961	hard endurance exercise program	25 wks	52 wk	hard endurance exercise for 1 hr		males, sedentary, overweight	adults	4	males, sedentary overweight	adults	4	high	342	253	-26%			yes	(Says consistent exercise over a long period lowered serum cholesterol more than sporadic exercise for a shorter period.)
Revington & Balke, 1966	endurance (running)	16 wks		trained to run 3 miles in 22-28 min (8-9 min/mile)	Yes, VO2 increased from 31.6 to 45.3 ml/kg min	males	21-43 mean = 28	6	absent			high	260	210	-20%	-	-	yes	-mean weight loss 2 kg
Alstrand & Wilmore, 1973	endurance (walk/jog)	10 wks	3 x wk	walk/jog with increasing intensity, with mean jogging rate of 12.1 km/hr & 7.26 m/kg	no 5	males, sedentary	mean = 33	39	absent			high-normal	224	203	-10%	-	-	yes	-lost 1 kg; no formal dietary regime was followed; asked to establish normal diet 1 week before & maintain it throughout -didn't check diet, smoking or alcohol intake
Rockelle, 1961	endurance (running)	5 wks	5 x wk	exhaustive exercise including a timed 2 mile run (12.1o-15 min)	no		20-36	6		20 - 36	6	normal	203	181	-11%	-	-	yes	-no change -saturated fat comprised 35% diet in experimental group and 45% diet in control group
Campbell, 1965	varied: 1) cross-country skiing 2) tennis 3) a) Golf b) Tumbling Gymnastics c) Weight Training d) Wrestling	10 wks			no	males	young adults	20 20 20 17 20 16	males	young adults	20	low-normal	180 169 181 176 165 189	61 62 79 80 68 92	-11% -4% no change	182	190	yes yes no	
Lopez-S et al, 1974	endurance (bicycle, jogging, calisthenics)	3 wks	4 x wk	bicycling 5-10 min; jogging 10-15 min; calisthenics 5-10 min all to maximum capacity.	no	medical students	22	13	absent			low-normal	169	62	-4%	-	-	yes	-adjusted caloric intake to make up for increased energy expenditure
Leon et al, 1977	endurance (treadmill walking)	16 wks	5 x wk	walked on treadmill for 1.5 hrs at 3.2 mph & 0% grade	Yes, VO2 increased 3 ml/kg/min on Balke treadmill Test	males, obese	young	6	absent			low-normal	125	69	-3%	-	-	not stated	-on unrestricted diet but lost 5.7 kg; & body fat decreased
Campbell, 1966	endurance (treadmill running)	10 wks	3 x wk	ran on treadmill at 5 mph & 0%—7.5 mph & 10% for 6x5 min periods, with 5 min. of rest in between.	no	a) obese b) muscular c) lean	young	13 20 20	a) obese b) muscular c) lean	young	59 9 9	-normal -low-normal -low-normal	213 168 180	195 187 177	-12% -no change -no change	219 164 183	218 178 183	yes no no	-changes observed were independent of dietary influence & weight changed
Roundy et al, 1978	endurance (walk/jog)	10 wks	3 x wk	prescribed walking/jogging, average initially 1.4 mile & 1.3) miles, finally 3 min & 2.5 mile		cholesterol, lipoprotein profile: type IIA type IV normal	adults	13 25 27	absent absent absent			type IIA type IV normal	a e i m q u	a' e' i' m' q' u'	-86.1mg% -67.6mg% -46.8mg%			yes yes yes	
Wilmore et al, 1978	vigorous exercise class	3 wks	not mentioned	not explained		children, obese	11-13	14	absent			high for age	b d 217	b' d' 167	-23%			yes	-on weight reduction diet & lost 4.7 kg -diet had high polyunsaturated to saturated fat ratio -compared levels to normal group of children with cholesterol of 209 mg%

* Initial cholesterol levels have arbitrarily been subdivided into different classifications as follows:

high -> 250 mg%
high normal 220 - 250 mg%
normal 180 - 220 mg%
low normal 150 - 180 mg%
low < 150 mg%

TABLE V (cont'd)

PHYSICAL TRAINING AND PLASMA CHOLESTEROL

Author	TRAINING PROGRAM: TYPE	DURATION	FREQUENCY	INTENSITY & DURATION OF SESSION	Fitness Test	SUBJECTS: Experimental Group: Description	Age	#	Control Group: Description	Age	#	PLASMA CHOLESTEROL: Classification of Initial Cholesterol Level	Experimental Group: Pre	Post	% change	Control Group: Pre	Post	Significant Difference	NOTES
Studies which observed no change in plasma cholesterol																			
Brumbach, 1961	(not endurance; some running but not vigorous; & weight lifting)	10 wks	3 X wk	weight lifting & run of .24 to .4 miles (approx.) equal to 5-8 min. at most		students, sedentary		20				normal	199		no change			no	
Fitzgerald et al, (1965)	short bouts of calisthenics; not vigorous	2 wks	daily	60 sec. bout of calisthenics with 30 sec. rest; session length was not recorded		males	20-49	11	absent			normal to high-normal	219		no change			no	diet didn't change
Johnson & Wong, 1961	sprint swimming (not endurance type)		daily	-402-201 meter swim sprints with 5-10 minutes rest in between -1.6 - 3.2 km of running (.6-1.92 miles)		students, competitive swimmers	19.3		absent			low-normal	169		no change			no	
Hollozy et al, 1964	endurance (running or calisthenics)	24 wks	3 X wk	A) endurance running & calisthenics 3.22-5.45 km (2-4 miles	Increased exercise tolerance	males, sedentary	(35-59) 41.7	15	males, sedentary			high-normal	244	256				no	-dieting record of 2 wks prior & told not to change eating habits
				B) endurance running on own; dependent on own capacity; increasing progressively		males, sedentary	(32-70) 42.6	12	males, sedentary		5	high-normal	233	233				no	-didn't change body weight (Group A) -didn't change diet (Group A)
Webster et al, 1978	endurance	12 wks	3 X wk	Jogging at H.R. of 76.4 APHHR-R for 45 min.		males	43	15	males	42	15	not listed for either group						no	changes were independent of weight loss, adipose tissue loss or dietary change
Ratliff et al, 1978	endurance (Jogging)	20 wks	3 X wk	prescribed jogging with increasing duration & intensity	Yes, increased	males, sedentary firefighters	middle-aged	14	males, sedentary firefighters	middle-aged	14	low-normal	170	164	-3.5%	181	178	no	% body fat decreased
Erkelent et al, 1978	endurance (walking & jogging)	12 wks	3 X wk	walking, jogging & calisthenics created 1-15 for 45 minutes	no	survivors of a MI, males		18	absent			normal	216	216	0%			no	
Gilliam & Burke, 1978	endurance (jump rope, run)	6 wks	5 X wk	5 minutes calisthenics; min. rope jump; 10 minutes run; 20 minutes games & activities; 12 minutes run race & rest		girls, normal weight	8-10	14	absent			low ?	139	130	6%			no	- no weight changes - normal diet

* see classification outlined in Table VA

a calorie restricted diet that was low in cholesterol and high in polyunsaturated as compared to saturated fat content (Widhalm et al, 1978). These dietary factors could, at least partially, account for the fall in cholesterol observed. Individuals whose cholesterol levels were in the normal range (150-250 mg%) demonstrated more varying responses but the trend seemed to persist for a greater reduction to occur in subjects who had a higher initial level. Some studies showed a decrease of 10-11% from 224 mg% to 201 mg% (Altekruse & Wilmore, 1973), from 203 mg% to 181 mg%(Rochelle, 1961) and from 177 mg% to 157.5 mg% (Campbell, 1965). A 12% decrease from 213 mg% to 195 mg% was also observed in the obese subjects in Campbell's study in 1966. Interestingly, as compared to the obese subjects, plasma cholesterol did not change significantly in the muscular or lean subjects whose initial cholesterol levels were lower than those of the obese subjects and fell in the normal to "low-normal" range (188 mg% and 180 mg%, respectively (see Table V). The concept of a greater reduction of total cholesterol in subjects demonstrating a higher initial level may be reflected in the results of Roundy and colleagues' study (1978) of type IIA and IV hyperlipoproteinemics and of normal subjects. The initial and final values of total cholesterol were not recorded and only the extent of the decrease that occurred was listed which was expressed in mg%. Type IIA hyperlipoproteinemics, who would presumably have had the highest initial plasma cholesterol of all three groups, demonstrated the greatest reduction in cholesterol. It decreased 86.1 mg% as compared to 62.6 mg% for the Type IV

hyperlipoproteinemics and 46.8 mg% for the normal subjects. In this study the reductions in cholesterol levels were quite large even in the normal subjects. An explanation of such a finding is difficult since the initial levels were not listed and information regarding weight loss or dietary manipulation was absent.

The intensity and type of exercise may be another factor involved in determining the extent of the reduction of plasma cholesterol. Golding (1961) noted that individuals who exercised the hardest and increased their fitness level the most had the greatest decrease in plasma cholesterol but he based this on the results of only four subjects. Nevertheless, his observation was also reflected in Campbell's study (1965) where subjects who trained by cross-country skiing reduced their cholesterol 11%, those trained by playing tennis reduced it 4% and the remaining subjects who either golfed, lifted weights or participated in tumbling gymnastics or wrestling did not demonstrate a significant change whatsoever. Initial plasma cholesterol did not differ much between the different exercise groups and fell in the low-normal range.

Plasma cholesterol did not change significantly in several studies (Brumbach, 1961; Johnson & Wong, 1961; Holloszy et al, 1964; Fitzgerald et al, 1965; Erkelens et al, 1978; Gilliam & Burke 1978; Ratliff et al, 1978; Webster et al, 1978). For many of the studies, possible explanations for the lack of change do exist. In two studies the exercise intensity utilized was not considered to be at all vigorous (Brumbach, 1961; Fitzgerald et al, 1965).

In another study the exercise was not of the endurance type (Johnson & Wong, 1961). Cholesterol did decrease 3.5% from 170 mg% to 164 mg% (Ratliff et al, 1978) and 6% from 139 mg% to 130 mg% (Gilliam & Burke, 1978) but neither of these decreases were found to be significant. In both studies the initial cholesterol level was also quite low which may be a factor but the endurance component was adequate. In the study of Ratliff and co-authors (1978), the results were similar to those of Leon et al (1977) and Lopez-S et al (1974) yet the change in plasma cholesterol was reported by Ratliff et al as being non-significant. A control group, whose cholesterol changed from 181 mg% to 178 mg%, was used by Ratliff and colleagues while a control group was absent from the studies of Leon et al and Lopez-S et al. This could explain the discrepancies to a certain extent. The three remaining studies that found no change in cholesterol with chronic activity were similar in their exercise intensities and endurance components to the studies that did find a decrease, so this could not account for the different results (Holloszy et al, 1964; Erkelens et al, 1978; Webster et al (1978). Plasma cholesterol levels were in the "high-normal" (Holloszy et al, 1964) or normal (Erkelens et al, 1978) range in two of the three studies, which could not explain the lack of response either. The results of Webster et al cannot be commented on, since they failed to record initial and final cholesterol levels. Their intensity may have been low as compared to the other studies which may explain the lack of change, but the specifics of the exercise intensity are not clear.

One of the major reasons for the inconsistency noted in the studies of the cholesterol response to chronic physical activity may be due to differences in the activity programs

administered which did vary in terms of intensity, frequency, duration and type of activity utilized. The inconsistent response may also be due to differing initial cholesterol levels, total caloric intake, type of diet, degree of weight loss and genetic predisposition. Most studies did not record dietary information, weight changes or improvement in fitness level and many lacked a control group as well. Consequently, it was difficult to adequately compare or explain the differing results. On review of the studies that did find a negative relationship between plasma cholesterol and chronic physical activity, it appears that cholesterol may be reduced to a greater extent in subjects who demonstrated a higher initial cholesterol level and/or in subjects who participated in a vigorous, endurance-type, training program. Other factors such as weight loss or diet, as explained previously, are also presumably involved but, when recorded, they did not appear to be as consistently related to the decrease in plasma cholesterol as was physical activity.

High Density Lipoprotein and Chronic Physical Activity

Due to the relatively recent interest in HDL as an anti-risk factor, the relationship between HDL levels and physical activity has not yet been extensively investigated. Information is particularly lacking on the amount, type and intensity of physical activity required to exert an effect on HDL. Despite the lack of detailed information, a number of studies have examined this relationship either by comparing the physical activity levels with HDL concentrations or by observing the response of HDL levels to a training program.

Comparative Studies:

Several studies have examined the relationship between an individual's level of physical activity and HDL (Carlson & Mossfeldt, 1964; Brunner et al, 1966; Hoffman et al, 1967; Wood et al, 1976; Enger et al, 1977; Krauss et al, 1977; Martin et al, 1977A; Mjøs et al, 1977 ; Wood et al, 1977; Lehtonen & Viihari, 1978A & B; Nikkila et al, 1978A; Williams et al, 1979). The conditions and results of these studies are listed in Table VIA.

HDL levels were clearly higher in active subjects for the great majority of the studies (Carlson & Mossfeldt, 1964; Hoffman et al, 1967; Wood et al, 1976; Enger et al,1977;Krauss et al, 1977;Martin et al,1977; Wood et al, 1977; Lehtonen & Viihari, 1978A; Lehtonen & Viihari, 1978B;Nikkila et al, 1978A; Miller et al, 1979; Williams et al, 1979). This was particularly obvious when highly trained endurance athletes were compared to sedentary persons

TABLE VIA

HDL and Physical Activity:

Comparative Studies

Author	Type of Activity	Fitness Test	SUBJECTS: Experimental Group: Description	Age	n	Control Group: Description	Age	n	HDL[1] (mg%): Experimental Group	Control Group	Significant Difference	TOTAL CHOLESTEROL (mg%): Experimental Group	Control Group	Signif-icant Difference	% CHOLESTEROL CARRIED BY HDL: Experimental Group	Control Group	Signif-icant Difference	TRIGLYCERIDES (mg%): Experimental Group	Control Group	Signif-icant Difference	NOTES
Studies that found a positive relationship between HDL and Physical Activity																					
Carlson & Mossfeldt, 1966	Cross-country skiers, well trained (ran 50 km/wk(30 miles/wk) for 12 months before)	no	males, trained		10	absent			63 mg%			201			315		*	1.22 gm/l			- apo lipids are high as compared to normal male population in Sweden
Hoffman et al, 1967	5 61 or participated in tennis, handball, squash or basketball routinely for at least 1 year	no	airforce officers, males, trained	40-55	229	airforce officers, males	40-55	126	measured as alpoproteins 121.6 mg% (lipid portion only)	107.9 mg%	yes in older age group	213	223	yes				101	116	yes	- no significant difference found in seasonal variation
Woods et al, 1976	runners who completed at least 15 miles/week in previous year, mean = 33 miles/week	yes, ran 10 min on treadmill test as compared to 9.4 min for control group	males, trained	35-59 (mean:45)	41	males, randomly selected cohort (for HDL-c and LDL-c, used a sub-group of the group used for cholesterol and triglyceride analysis)	35-59	or HDL-c:147 for total-c TG:743	64	63	yes	200	210	yes	32%	20%	*	70	146	yes	- all runners were non-smokers, low % body fat control group; 42% smokers, higher % body fat than the runners, no diet difference, alcohol intake in runners was greater
Woods et al, 1977	runners who completed at least 15 miles/week in previous year, mean = 31 miles/week	Yes ran 13 min on Bruce treadmill test as compared to 6.7 min in control group	females, trained	30-59	43	randomly selected cohort (for HDL-c used a sub-group of the group used for cholesterol and triglyceride analysis)	35-59	for HDL-c = 50 for total-c & TG = 934	75	54	yes	193	212	yes	39	26	*	56	123	yes	HDL-cholesterol:LDL-cholesterol = .46 experimental; 45 controls; runners were leaner than controls (21% body fat as compared to 32% body fat), more runners were non-smokers; no diet difference; runners' alcohol intake somewhat greater than control
Martin et al, 1977	elite runners (averaging 85 miles/wk) good runners (averaging 60 miles/wk)		elite (males) runners; good (males) runners	26-30	20 8	age matched, males	26-30	72	56 52	49	yes yes	175 185	189	no no	32 28	26	*	76 53	92	yes yes	- no differences in alcohol intake - runners had lower % body fat than controls (correlation of body fat and HDL-c was not significant in older runners)
Esper et al, 1977	competitive cross-country skiers		males, trained	16-74 mean = 41	220	1) healthy males, free of CHD as determined by clinical examination and maximal bicycle test	40-59 (mean = 50)	247	64	1) 53	yes	256	1) 254	yes	28	1)22	yes*				few skiers smoked
						11) subgroup of 1 whose body weight was within 10% of their recommended weight & had normal cholesterol, triglycerides & glucose	40-59 (mean = 50)	87		11) 56	yes*		11)241	no		11)20	yes				
						111) males, 46 of whom were daily smokers (blood donors)	19-59 (mean = 37)	87		111) 51	yes		111)237	no		111)22	yes				
						iv) females, 9 of whom were daily smokers, none use oral contraceptives (blood donors)	19-62 (mean = 36)	23		iv) 59	no		iv) 228	no		iv)27	no				
Lehtonen & Viitasari, 1978A	run or cross-country skied at least 4 X/week for a minimum of 25 km/week for the last 5 years, mean = 83 km/week (50 miles/week)	no	A) males trained	30 +	23	B) males sedentary	30+	55	68.5	54.9	yes	191	262	no	37	29	yes	56(in male /1)	.92	yes	-Experimental group were non-smokers, on normal diet with low or normal alcohol intake -runners had a higher level of plasma free fatty acids & an increased degree of adipose tissue lipolysis; some adiposity in runners & Gp C -alcohol intake, dietary intake or adiposity could not account for the differences -control group were on a normal diet & had 5 smokers in Gp. B & 7 in Gp. C
						C) males who exercise less than 25 km/week	years	10		56.3	yes		176	no		33	no		.66	no	
						D) females		12		59.8			219			28			-		
						E) Type IIA hyperlipoproteinemics: females		7		61.2			333			16			1.7		
						males		11		51.0			334			17			1.4		

TABLE VIA (cont'd)

HDL and Physical Activity:

Comparative Studies

Author	Type of Activity	Fitness Test	SUBJECTS: Experimental Group: Description	Age	#	SUBJECTS: Control Group: Description	Age	#	HDL[1] (mg%): Experimental Group	Control Group2	Significant Difference	TOTAL CHOLESTEROL: Experimental Group	Control Group	Significant Difference	% CHOLESTEROL CARRIED BY HDL: Experimental Group	Control Group	Significant Difference	TRIGLYCERIDES: Experimental Group	Control Group	Significant Difference	NOTES
Miller et al, 1979	varied, most active subjects were cross-country skiers	bicycle ergometer measured VO_2 of 24-85 ml/kg min	males of varying degree of physical activity	mean = 27	11	others			31.15 -7.35 (in males/1) 41-51 mg%											-subjects were non-smokers -correlation of HDL-c and MVO_2 was .81, HDL-c/Apo-I and MVO_2 was .88.
Ernst et al, 1977	runners	no	females trained (premenopausal and not on hormone therapy)	34-46	6	females sedentary (premenopausal and not on hormone therapy)	aged matched		HDL-CHOLESTEROL Apo-I F 218 mg% M 119 mg% HDL- F 220 mg% M 259 mg% Apo A-I F 126 mg% M 163 mg% Apo A-II (identical to runners & controls)	122 mg% 53 mg% 220 mg% 227 mg% 130 mg% 120 mg%	yes yes yes no no yes yes									
			males trained	42-58	7	males sedentary	age/ethnic controls*														
Bilsila et al, 1978A	-world class long distance runners: 1500 m., Marathon running or cross-country track finding (males:100-130 km/wk females: 65-90 km/wk) -world class sprinters: 100-400 m. (ran c 20 - 35 km/wk)		distance runners: females males sprinters: males		6 12 8	[illegible] sedentary males sedentary	matched for age & relative body weight	15 10	74 64 50	61 47	yes yes no	201 213 200	178 186	no no no	37 31 25	34 25	* * *	82 89 128	84 100	no no no	-experimental group had a normal diet, didn't smoke and had a low to moderate alcohol intake. -control group had two smokers and a normal alcohol intake
Lehtonen & Viikari, 1978B	highly active in occupation	no	normal population: lumberjack		12	normal population electricities (similar weight)		12	75	55	yes	222	201	no	34	27	*	64mg%	92mg%	yes	
Williams et al, 1979	leisure time physical activity determined by questionnaire	no	normal population of varying degree of physical activity divided into: very active, active, slightly active	all ages		inactive	all ages		very 57.4 active 57.7 slightly 56.1	53.7	yes				24 23.3 22.2	21.3	yes				HDL-c was highly significant and positively related to degree of physical activity. This was also true of HDL-c & physical activity.
Studies that did not find a positive relationship between HDL and physical activity																					
Brunner et al, 1968	active in occupation		active (not tested 80% of the time during work hours)			sedentary (seated at least 80% of time during work hours)			cholesterol		no			no						no	dietary habits & living conditions were the same
Rijs et al, 1977	participated in regular exercise for more than 4 hours per week		active			sedentary			57.3	46.6	no										

1 most studies expressed HDL as HDL-cholesterol, so values are expressed as cholesterol in mg% unless otherwise stated

2 not given since the authors did not calculate the percentage of total cholesterol carried by HDL

(Carlson & Mossfeldt, 1964; Wood et al., 1976; Enger et al, 1977; Krauss et al, 1977; Martin et al, 1977; Wood et al, 1977; Lehtonen & Viihari, 1978A; Nikkila et al, 1978A; Miller et al, 1979). The HDL-cholesterol levels in these athletes, who trained by long distance running or cross-country skiing, were frequently higher than 60 mg% for males (Carlson & Mossfeldt, 1964; Wood et al, 1976; Enger et al, 1977; Lehtonen & Viihari, 1978A; Nikkila et al, 1978A) and greater than 70 mg% for females (Wood et al, 1977; Nikkila et al, 1978A). Both these HDL-cholesterol levels are well above the mean levels found in the North American population which fall approximately in the range of 30-60 mg% (mean=45%) for males and 40-73 mg% (mean=57 mg%) for females (Castelli et al, 1977A). On the other hand, male world class sprinters did not have HDL-cholesterol levels that were significantly different from those of the control subjects (Nikkila et al, 1978A). The training program of the sprinters, which involved mainly exercises of short duration such as weight lifting but also included some running, had a much lighter endurance component than did the training programs of the athletes in most of the other studies reviewed (Carlson & Mossfeldt, 1964; Wood et al, 1976; Enger et al, 1977; Krauss et al, 1977; Martin et al, 1977; Wood et al, 1977) or than that of the training programs of the long distance runners in the same study of Nikkila et al (1978A). This would indicate that the type and intensity of the exercise is very important in relating HDL-cholesterol to the level of physical activity and that the elevation observed in the endurance athletes is not simply a result of an increased caloric utilization or an

increased rate of energy turnover, but may be due to such general factors as changes in the hormonal axis with endurance training or to such specific factors as the preferential utilisation of fats, an increase in cholesterol excretion in bile, etc. Enger et al (1977) alluded to the fact that the HDL response is dependant on the training program when they noted a trend towards a higher HDL-cholesterol level in the fastest and presumably the best trained skiers, although the trend did not reach statistical significance. This was also indicated in the study of Lehtonen and Viihari (1978A) who observed that the HDL-cholesterol in young men who ran or skied less than 25 km per week (Controls, Group C) was not significantly different from that of the sedentary men over the age of 30 (Controls, Group B). This observation is also notable in reference to the amount of endurance training required to effect a significant increase in HDL-cholesterol. More importantly, Lehtonen & Viihari further noted that HDL-cholesterol was correlated with the number of miles run per week and that, although there was a tendency for all runners to have a higher HDL-cholesterol level on the average, the concentrations were clearly higher than normal when the number of kilometers run per week exceeded 70 (42 miles).

Other studies have observed HDL-cholesterol in subjects selected from the general population rather than utilizing athletes and related these levels to the subject's degree of physical activity either on the job or during their leisure time (Brunner et al, 1966; Mjøs et al, 1977; Lehtonen & Viihari, 1978B; Miller et al, 1979; Williams et al, 1979). HDL-cholesterol was very high

(75 mg%) in men whose occupation demanded a high level of physical activity (Lehtonen & Viihari, 1978B). In men whose leisure time activity was classified according to their response to a questionnaire, HDL-cholesterol was significantly higher in those classified as very active (57.8 mg%) as compared to those classified as inactive (53.7 mg%) but the differences were not large (Williams et al, 1979). The two studies that failed to find a positive relationship between HDL and physical activity also determined the activity level by a questionnaire. Brunner et al (1966) classified their subjects according to degree of activity on the job (sedentary subjects were those who were seated more than 80% of the time). Mjøs et al, (1977B) looked at leisure time activity and classified their subjects as active if they exercised more than 4 hours per week. These studies are similar to those of Lehtonen & Viihari (1978B) and Williams et al (1979) in that all four studies utilized the general population and categorized the individuals by occupational activity or recall of leisure time activity. The studies are dissimilar in that the categorization procedures of Brunner et al (1966) and Mjøs (1977B) may be subject to individual interpretation to a greater extent than those of Lehtonen & Viihari (1978B) or Williams et al (1979). Mjøs et al (1977B) actually have stated that their classification was ambiguous and said that it may have failed to discriminate adequately between the active and inactive individuals.

To more accurately determine an individual's level of endurance fitness, rather than depend on exercise history, measurement of aerobic capacity is necessary. Men of varying degrees of physical activity, from sedentary subjects to cross-country skiers, were examined for both HDL-cholesterol levels as well as for aerobic

capacity by Miller et al (1979). Aerobic capacity was expressed as maximum oxygen uptake (MVO_2) in ml/kg/min. HDL-cholesterol and MVO_2 were found to be significantly and positively related (r=.81). HDL-cholesterol ranged from 44-91 mg%, and MVO_2 from 24-85 ml/kg/min. The ratio of HDL-cholesterol: Apo-AI which they consider to be representative of the ratio of the two subfractions of HDL (HDL_2: HDL_3), was even more positively correlated with MVO_2 values (r=.88). Miller and co-authors suggested that physical activity raises plasma HDL by increasing the synthesis or decreasing the catabolism of the HDL_2 subfraction.

The HDL_2 subclass was measured directly in a study of female and male runners (Krauss et al, 1977). HDL-cholesterol, HDL_3, Apo-AI and Apo-II were measured as well. HDL-cholesterol was significantly higher in both the male and female runners, and it was the HDL_2 subfraction that was greatly elevated rather than HDL_3. Apo-AI levels were also higher in the runners while Apo-AII concentrations were nearly identical to those of the controls. This confirms Miller and colleagues' suggestion (1979) that it is the HDL_2 subclass that is elevated rather than HDL_3.

Not only has HDL-cholesterol been positively correlated with physical activity but this is also true of the HDL-cholesterol: total cholesterol ratio (Enger et al, 1977; Lehtonen & Viihari 1978A; Nikkila et al, 1978A; Williams et al, 1979). This ratio indicates that in active people, a greater percentage of their plasma cholesterol is carried by HDL than in sedentary subjects. The ratio ranged from .28 – .37 in male, endurance-trained, athletes

(Carlson & Mossfelt, 1964; Wood et al, 1976; Enger et al, 1977; Martin et al, 1977; Lehtonen & Viihari, 1978A; Nikkila et al, 1978A). In female long distance runners, the ratio was even higher and ranged from .37-.39 (Wood et al, 1977; Nikkila et al, 1978A). Notably, even sedentary females have a higher ratio than sedentary males as it ranged from .26-.34 in the studies reviewed (Enger et al, 1977; Wood et al, 1977; Nikkila et al, 1978A). Enger found that there was no significant difference in HDL-cholesterol or in the ratio between his competitive cross-country skiers (males) and sedentary female controls (Group IV). In fact, Wood et al (1976) concluded that long distance running resulted in a lipoprotein profile in their middle aged male runners that was desirable with respect to CHD prevention since it resembled the lipoprotein profile of a young, healthy female. In active males, selected from the general population, the ratio was not as high as that seen in the male endurance-trained athletes but it was still significantly higher than that of the inactive controls (.24 and .21, respectively) (Williams et al, 1979).

Training Studies:

The results of the various training studies are of greater interest than those of the comparative studies since an actual change in HDL can be demonstrated in the training studies, which avoids the possibility that an elevated level of HDL is merely a characteristic of individuals who tend to be active rather than be a result of the activity.

HDL increased significantly with endurance training programs of varying lengths (6-20 weeks), frequencies (3-5 times per week)

and intensities in the majority of the studies (Altekruse & Wilmore, 1973; Lopez-S et al, 1974; Leon et al, 1977; Erkelens et al, 1978; Gilliam & Burke, 1978; Ratliff et al, 1978; Roundy et al, 1978). It failed to change significantly in the remainder of the studies which were 3-17 weeks long, held 2-7 times per week and varied in intensity (Lewis et al, 1976; Webster et al, 1978; Widhalm et al, 1978). The conditions and results of these studies are listed in Table VIB.

When HDL was expressed as a percentage of the total lipoprotein content, it was found to increase 18.6% from 36.5% to 55.5% (Altekruse & Wilmore, 1973). When expressed as alpha-lipoprotein, it increased 16% from 286 mg% to 332 mg% (Lopez-S et al, 1974) or it increased 71 mg% in type IIA hyperlipoproteinemics, 49 mg% in type IV hyperlipoproteinemics and 51 mg% in normal subjects (Roundy et al, 1978). The results of the study of Roundy et al are notable since total cholesterol decreased a good deal in all subjects, while alpha-lipoprotein increased. The alpha-lipoprotein increase in this study could be related to the decrease in plasma triglycerides in the type IIA and IV subjects but could not explain the increase seen in the normal subjects since their triglycerides did not change. Even the increase in type IIA and IV subjects could not be completely due to the triglyceride change, since in the type IIA subjects total cholesterol decreased the most and alpha-lipoprotein increased the most but triglycerides fell to a lesser extent than in the type IV subjects (who did not demonstrate as great an increase in alpha-lipoprotein as that of the type IIA subjects).

HDL-cholesterol was measured in the majority of the studies

TABLE VIII

...ess and Physical Activity:

...tudies

Author	TRAINING PROGRAM: Type	Duration	Frequency	Intensity & Session Length	FITNESS TEST	SUBJECTS: Experimental Group: Description	Exp. Age	Exp. n	SUBJECTS: Control Group: Description	Ctrl. Age	Ctrl. n	HDL (mg%): Experimental Group: Pre	Exp. Post	Exp. Increase	HDL (mg%): Control Group: Pre	Ctrl. Post	Significant Difference	TOTAL CHOLESTEROL (mg%): Experimental Group: Pre	Exp. Post	TOTAL CHOLESTEROL (mg%): Control Group: Pre	Ctrl. Post	Significant Difference	% CHOLESTEROL CARRIED BY HDL: Experimental Group: Pre	Exp. Post	% CHOLESTEROL CARRIED BY HDL: Control Group: Pre	Ctrl. Post	Significant Difference	TRIGLYCERIDES (mg%): Experimental Group: Pre	Exp. Post	TRIGLYCERIDES (mg%): Control Group: Pre	Ctrl. Post	Significant Difference	NOTES:
Studies that observed an increase in HDL with training																																		
Altekruse & Wilmore, 1973	endurance (jogging)	10 wks	3 X wk	mean = 15 min at 7.5 mph (5.6-8.9 mph) = 5 Calories/min (range = 4-6 Calories/min)	no	males sedentary	17-59 means 33	35	absent								yes	224	220			yes						164	167			no	mean weight loss = 1 kg (not checked for diet, smoking or alcohol intake)
Lopez-S et al, (1974)	endurance (bicycle & jogging)	7 wks	4 X wk	30 minutes per session intense exercise of bicycling 5-10 min, jogging 10-15 min, calisthenics 5-10 min. (intensity = 7 METS)	no	males	22	13	absent								yes	169	182			yes	25	37			*	110	83			yes	dietary intake was adjusted to maintain caloric balance no change in % body fat or weight
Roundy et al, (1978)	endurance (jogging)	10 wks	3 X wk	1: run 1/4 wk. 1: 1.32 miles in 21.6 mins/1/4 wk. 10: 2.58 miles in 34 min/ 4.3 to 7.6 miles/week)	no	sedentary hyperlipoproteinemic adults: Type II & Type IV Normals		13 25 27	absent absent absent								yes yes yes	decreased: -86.1mg% -62.6mg% -41.8mg%				yes yes yes					yes yes yes	decreased: -29 mg% -105mg% -7.2mg%				yes yes no	
Pollock et al, (1978)	endurance (jogging)	20 wks	3 X wk	prescribed jogging with increasing duration & intensity	yes, VO_2 increased	males sedentary firefighters	early middle aged	14	males sedentary firefighters	early middle aged	16	42	50	19%	43	41	yes	170	164	181	178	no	25	30.5	24	23	*	97	84	114	109	no	-% body fat decreased in experimental group -change in HDL-c not positively correlated with VO_2 r = .28
Leon et al, (1977)	endurance (walking)	16 wks	5 X wk	treadmill walking at 3.2 mph & 10% grade for 1.5 hours (= 24 miles/ week)	yes, VO_2 increased (3 ml/kg on average)	obese men	young	6	absent			32	37	15%			yes	175	169			not stated	18%	22%			*	165	148			not listed	diet intake not restricted % body fat decreased 3% lost 5.7 kg
Lewis et al, (1976)	endurance (jogging)	12 wks	2 X wk	jogged at 80% MHR and did calisthenics & 2.5 miles/wk	yes, VO_2 increased (6 ml/kg on average)	mildly obese females	30-52	22	absent			49.0%	51.5%	5%			no	204	201			no	24	27			*	89	97			no	-HDL-c : LDL-c ratio increased from .30 to .4 (significant change) -diet did not change -lost 4.2 kg
Gilliam et al, (1978)	strenuous activity (skipping & running)	8 wks	5 X wk	physical activity program: 40 minutes of skipping 5 minutes of running 10 min calisthenics per session & 1, 12 min run/wk	no	girls normal height & weight	8-10	14	absent			30	36.4	21%			yes	139	139			no	22	29			yes						maintained normal diet
Ekblom et al, (1978)	endurance (walking & jogging)	12 wks	3 X wk	jogging or walking at intensities graded 1-15 for 45 minutes per session	no	male survivors of a MI		18	absent			35	41	17%			yes	216	216			no	16	19			*	128	178			no	HDL-c increased to 40 mg% at end of 1st week
Studies that found no change in HDL with training																																		
Klimain et al, (1978)	vigorous exercise class	3 wks	daily	intense daily sports program	no	obese children (average = 28% overweight)	11-13	14	absent			69	61.5	-11%			no	217	167			yes	32	37			*	89	92			no	on diet: -low cholesterol -low calories -high P/S to fat ratio -lost 6.2 kg
Webster et al, (1978)	endurance (jogging)	12 wks	3 X wk	jogging (5 minutes per session at 74.6% ($\dot{V}O_2$max -R)		males	mean: 43	15	males	mean: 42	15	not listed	48.7		not listed	43.2	no	not listed				no	not listed					not listed	130	not listed	127	yes	changes were independent of weight loss, adipose tissue loss or dietary change

* not given since the authors did not calculate the percentage of total cholesterol carried by HDL

(Lewis et al,1976; Leon et al,1977; Erkelens et al,1978; Gilliam & Burke, 1978; Ratliff et al,1978; Webster et al 1978; Widhalm et al, 1978). HDL-cholesterol increased significantly in most of the studies and this increase ranged from 17-21% from 42 mg% to 50 mg% (Ratliff et al,1978) from 32 mg% to 37 mg% (Leon et al,1977) from 30 mg% to 36.4 mg% (Gilliam & Burke, 1978) and from 35 mg% to 41 mg% (Erkelens et al,1978). Ratliff et al (1978) and Leon et al (1977) used adult sedentary males, Gilliam & Burke (1978) utilized children and Erkelens et al (1978) studied MI survivors. The initial HDL-cholesterol levels in all these studies were in the low-normal range. HDL-cholesterol did not increase significantly in Lewis & colleagues' study (1976) of obese women (pre-training = 49.8 mg%, post-training = 54.5 mg%), but the HDL-cholesterol: LDL-cholesterol ratio rose significantly from .38 to .43. In a study of obese children placed on a low cholesterol, low saturated fat, calorie-restricted diet, HDL-cholesterol did not change significantly either (pre-training = 69 mg%, post-training = 61.5 mg%) (Widhalm et al,1978). Webster and co-authors (1978) also did not find a change in HDL-cholesterol. Only the post-training level of 48.7 mg% was listed. Webster et al noted that there was a trend for an increase in HDL-cholesterol seen in the first three weeks and suggested that a training threshold may exist for the exercise-induced change in HDL-cholesterol.

The HDL-cholesterol: total cholesterol ratio appeared to increase in all studies when it could be calculated from the data given (Lopez-S et al,1974; Lewis et al,1976; Leon et al,1977;

Erkelens et al,1978; Gilliam & Burke, 1978; Ratliff et al,1978; Roundy et al,1978; Widhalm et al,1978) but only two studies actually reported the ratio and determined its significance (Gilliam & Burke, 1978; Roundy et al,1978). It is important to note that in most studies total cholesterol fell and/or HDL-cholesterol increased to varying degrees, resulting in an increase in the ratio (Altekruse & Wilmore, 1973; Lopez-S,1974; Ratliff et al,1978; Roundy et al,1978 [total cholesterol change was not significant]; Lewis et al, 1976 [HDL-cholesterol change was not significant]; Leon et al,1977; Erkelens et al, 1978; Gilliam & Burke, 1978 [total cholesterol change was not significant]). An increase in the ratio with exercise would be considered to be beneficial in respect to CHD risk since HDL would carry a greater percentage of the total cholesterol while LDL and VLDL would carry less. Roundy and co-authors (1978), who looked at the changes in lipoproteins in type IIA and IV hyperlipoproteinemics, noted that endurance training appeared to normalize the serum lipoprotein profile causing a favourable shift from the light pre-beta and beta-lipoprotein densities to the heavier alpha-lipoprotein densities. Such a shift in the profile was also seen by Altekruse and Wilmore (1973) Lopez-S et al (1974), Lewis et al(1976), Leon et al (1977), Ratliff et al (1978). Webster and colleagues (1978), on the other hand, did not observe a change in the profile. The change in the cholesterol-carrying lipoprotein pattern indicates that some change has occurred in the lipoprotein metabolism which causes an increase in HDL synthesis or in LDL catabolism or a decrease in HDL catabolism

or in LDL synthesis. Lopez-S et al (1974) suggested that this switchover in the cholesterol-carrying lipoprotein profile could also explain the lack of a demonstrable change in total cholesterol with exercise, in some cases, since HDL-cholesterol and LDL-cholesterol change in opposite directions.

Therefore, the majority of the comparative and training studies have observed a positive relationship between HDL and endurance exercise.

In the comparative studies, HDL and the percentage of cholesterol carried by HDL were elevated in the endurance-trained athletes. In some cases the runners had a higher alcohol intake (Wood et al, 1976; Wood et al, 1977), a lower percentage body fat (Wood et al,1976; Martin et al,1977; Wood et al,1977)or smoked less than the control subjects(Wood et al, 1976; Enger et al, 1977; Wood et al, 1977; Lehtonen & Viihari, 1978A; Nikkila et al, 1978A),which could account for some of the difference in HDL levels (see section on Factors Affecting HDL Levels, p.60) But these factors could not account for all the differences in HDL levels since HDL and the HDL-cholesterol: total cholesterol ratio were still elevated in studies where the alcohol intake was the same for both groups (Martin et al, 1977; Lehtonen & Viihari, 1977A), relative body weight was the same (Nikkila et al, 1978A),all subjects were non-smokers (Miller et al, 1979) and where dietary intake was very similar for the athletes and control subjects (Wood et al, 1976; Wood et al, 1977; Lehtonen & Viihari, 1978A; Nikkila et al, 1978A; Wood et al (1976). Martin et al (1977) and Lehtonen & Viihari (1978A)noted that the HDL-cholesterol differences could not be directly accounted for by

differences in adiposity. Nikkila and colleagues' study (1978A) of long-distance runners was the most comprehensive one in that the experimental and control subjects were matched for age and relative body weight, their diets were similar and the only smokers were 2 of the 10 males in the control group. In studies utilizing the general population, the differences in HDL between the active and inactive subjects were not as great, but a positive relationship between HDL and level of activity at work (Lehtonen & Viihari, 1978B) or during leisure time (Miller et al, 1979; Williams et al, 1979) was still observed in some studies. Other studies failed to find a significant relationship (Brunner et al, 1966; Mjøs et al, 1977A).

The training studies are of greater interest than the comparative ones since they can be used to suggest a primary cause and effect relationship between physical activity and HDL. The majority of the training studies reported a significant increase in HDL-cholesterol and/or in the ratio of HDL-cholesterol to total cholesterol or to LDL-cholesterol (Altekruse & Wilmore, 1973; Lopez-S et al, 1974; Lewis et al, 1976; Leon et al, 1977; Erkelens et al, 1978; Gilliam & Burke, 1979; Ratliff et al, 1978; Roundy et al, 1978). Either an increase in the absolute level of HDL-cholesterol or in the ratios would be considered beneficial in reference to CHD risk (see section on HDL Activity in Relation to Atherosclerosis, p.48). One training study reported an insignificant decrease in HDL-cholesterol (Widhalm et al, 1978) and one study found no change (Webster et al, 1978). Precise interpretation of many of the results of the training studies is difficult since several

factors are lacking in the experimental design. The relationship of the change in plasma triglycerides with the change in HDL was not determined in any of the studies. Since triglycerides have been found to be negatively related to HDL-cholesterol, an increase in HDL-cholesterol could be a result of a decrease in triglycerides rather than be a direct result of the training. Triglycerides did decrease significantly in some studies (Lopez-S et al, 1974; Leon et al, 1977; Roundy et al, 1978: Type IIA and IV hyperlipoproteinemics). But triglycerides did not change significantly in other studies while HDL-cholesterol still increased (Altekruse & Wilmore, 1973; Erkelens et al, 1978; Ratliff et al, 1978; Roundy et al, 1978: normal subjects) indicating that the HDL-cholesterol increase accompanying endurance exercise is not completely due to a decrease in triglycerides. Another weakness in many of the studies is a lack of a control group (Altekruse & Wilmore, 1973; Lewis et al, 1976; Lopez-S et al, 1974; Leon et al, 1977; Erkelens et al, 1978; Gilliam & Burke, 1978; Roundy et al, 1978; Widhalm et al, 1978), so the possibility still exists in these studies that the changes in lipids and lipoproteins reported could be merely due to a seasonal fluctuation. Several studies failed to mention any dietary changes (Altekruse & Wilmore 1973; Erkelens et al, 1978; Ratliff et al, 1978; Roundy et al, 1978). The outline of the training program was poorly described or impossible to decipher in many of the studies (Altekruse & Wilmore, 1973; Erkelens et al, 1978; Gilliam & Burke, 1978; Ratliff et al, 1978; Webster et al, 1978; Widhalm et al, 1978; Roundy et al, 1978). A number of studies did not record weight loss or change in percentage body fat (Erkelens et al, 1978; Gilliam & Burke, 1978; Roundy et al, 1978).

When such changes were reported, the extent to which this change contributed to the change in HDL-cholesterol was not established (Altekruse & Wilmore, 1973; Lewis et al, 1976; Leon et al, 1977; Ratliff et al, 1978; Widhalm et al, 1978). Only Webster & coauthors (1978) mentioned that any changes observed were independent of weight loss but HDL-cholesterol did not change in their study. None of the studies recorded changes in smoking habits or in alcohol intake. Since HDL-cholesterol has been found to be positively related to alcohol consumption and weight loss (in some cases) and negatively related to cigarette smoking (see section on Factors Affecting HDL Levels), any change in these factors could result in a change in HDL-cholesterol which would be independent of the effect of physical activity or at least be an indirect result. Finally, only three studies (Lewis et al, 1976; Leon et al, 1978; Ratliff et al, 1978) assessed if the endurance training program resulted in an actual change in the subject's level of endurance fitness, which is necessary if one wishes to relate an increase in HDL-cholesterol to an increase in endurance capacity, since participation in an endurance training program does not necessarily ensure that an individual's functional capacity will increase. The training studies also varied a great deal in duration and intensity and in the type of dietary regime utilized, which may significantly affect the outcome. The most complete training study to date, that avoided most of the afore-mentioned shortcomings in experimental design, was that of Ratliff & colleagues (1978). In this study, HDL-cholesterol increased significantly by 8 mg%, on the average, after 20 weeks of an individually prescribed training program. The weakness in this study is that the specifics of the exercise prescription procedure were not included and the

independent contribution of the decrease in percentage body fat to the increase in HDL-cholesterol was not established.

Thus, at present, it is impossible to delineate from the training studies an exercise intensity and frequency that would serve as threshold level after which one can observe a significant increase in HDL-cholesterol or in the percentage of cholesterol carried by HDL. In the comparative studies, the only clue that exists pertaining to the amount of exercise required to elevate HDL-cholesterol is found in Lehtonen and Viihari's study (1978A). They observed that HDL-cholesterol was no higher in young men who ran less than 25 km per week (Group B) than in the older sedentary men (Group A). Most importantly, they noted that the HDL-cholesterol was clearly higher than normal in runners or skiers when the number of kilometers run or skied per week exceeded 70 km. These observations, though informative, still fail to indicate an actual threshold in training intensity and duration after which a significant increase in HDL can be observed. Furthermore, some of the training studies in which subjects ran less than 25 km per week nevertheless observed an increase in HDL (Altekruse & Wilmore, 1973; Lopez-S et al, 1974; Erkelens et al, 1978; Gilliam & Burke, 1978; Roundy et al, 1978). The training study of Lopez-S et al, 1974) should be given particular attention since HDL increased the greatest amount of all the training studies. Although HDL was measured only in the lipoprotein form, the amount of cholesterol it carried could be calculated since values for total cholesterol, LDL-cholesterol and triglycerides were given. HDL-cholesterol appeared to increase 17 mg%. The description of the program indicated that the subjects participated in a very intensive exercise session but further details are rather sparse. Therefore, the question concerning the specifics of the exercise prescription required to elevate HDL-cholesterol remains unanswered at present.

CHAPTER III

METHODOLOGY

Introduction

The purpose of the study was to determine the effect of aerobic exercise on HDL-cholesterol in men. To establish that a change in HDL-cholesterol in the experimental group would be related to the training program rather than to a seasonal variation, as has been found for plasma cholesterol and triglycerides (Warnick & Albers, 1976), a control group was followed concurrently. All subjects underwent a fitness test before and after the training program, but the control subjects did not participate in the exercise class.

Subjects

Subjects were males, age 25-59 (mean age of 40.5; experimental group =41.25; control group =45.5). They had normal levels of triglycerides $\leq$ 150 mg% and had a history of high cholesterol that remained high or was controlled at the time of intake. Subjects did not exceed their recommended weight by more than 20%. They had no history or clinical indication of CHD, uncontrolled hypertension (diastolic $\geq$ 95 mm Hg and systolic $\geq$ 140 mm Hg), orthopedic problems or abnormal glucose tolerance. This profile was selected since HDL-cholesterol is related to sex. It is not related to age in adult men. It has a low negative correlation with plasma triglycerides, while it is not directly related to plasma cholesterol. HDL-cholesterol can be slightly negatively

correlated with body fat and the cholesterol-binding capacity of HDL differs in diabetics. These individuals were considered to be at some risk of CHD due to their age, sex and history of high cholesterol.

All subjects were requested to establish a regular dietary pattern, one month preceding the program, and to maintain it throughout the twelve-week period. They were advised not to change their cholesterol or carbohydrate intake in particular, since a change in the dietary cholesterol content can affect the serum cholesterol levels (Gotto, 1979) and a high carbohydrate diet has been found to lower HDL-cholesterol (Blum et al, 1977). Both groups were requested not to change their habitual level of physical avtivity during the program. Information pertaining to dietary adherence, smoking habits, medications prescribed and physical activity levels of both groups was obtained by a questionnaire (Appendix A) at the beginning and end of the twelve-week period, in order to determine if these parameters had changed significantly over the course of the study. If physical activity levels increased significantly in any of the subjects in the control group, these subjects were excluded from the study. A change in the average daily dietary content was also evaluated by comparing a seven-day record (Appendix B) of their dietary intake at the beginning of the program with one submitted at the end of the program. Their daily pre- and post-training intake of cholesterol, carbohydrates, total fat, unsaturated and saturated fat, protein, alcohol and total calories, and the ratio of unsaturated to saturated fat, were included in this evaluation.

On intake, there were sixteen subjects in the experimental group and fifteen in the control group. Several subjects from each group were lost after their initial fitness test, or during the

remainder of the study period. In the experimental group, two subjects dropped out of the class, one did not attend more than 60% of the classes (while the other participants attended at least 80% of the classes), and one subject's ability to train was prevented due to the presence of chronic obstructive lung disease. In the control group, one subject could not be included due to the occurrence of frequent premature ventricular contractions during his initial fitness test, and a second subject could not complete the test due to the presence of peripheral vascular disease. During the study period, two subjects in the control group trained a sufficient amount so as to be deemed unacceptable to the group. Finally, one subject in the control group refused to undergo the final fitness test. This left twelve subjects in the experimental group and ten in the control group.

The data from the control group was obtained, on the average, one month after that of the experimental group.

Testing Procedures

Subjects received resting ECG's and complete physicals before being accepted into either the experimental or the control group. A full explanation of the study was given and the subjects' informed consent was obtained for the testing and exercise program.

Anthropometric Measurements:

Height, weight, tricep, mid-axilla and chest skin-folds were measured on the subjects, before and after the twelve-week period, in order to estimate their percent body fat and desirable weight. Percentage body fat was determined using the prediction equation of Pascale et al(1956) as outlined on page 10.

Fitness Testing Procedures:

For the pre- and post-training test, the subjects underwent an ECG monitored, volitional maximum oxygen uptake (MVO_2) treadmill test, according to the protocol of the Department of Kinanthropology, University of Ottawa (Appendix C). The results were used in determining their cardiovascular fitness level and training heart rate when required. Resting heart rate, and reclining and sitting blood pressure were measured before the test.

After a 3-minute warm-up at 3.5 miles per hour at 2% elevation, and a 2-minute rest period, the subjects were required to walk on a motor-driven treadmill (Quinton 24-72). while the speed or elevation was increased at the end of each 2-minute interval. Heart rate, ST level. and ST slope were measured each minute, and diastolic and systolic blood pressure were determined every second minute. Expired gas was collected at several stages during the test. and during the last stage in particular.

On termination of the test, the subjects continued to walk for 1 minute at 2.5 mph and 0% elevation. They were then seated for a 5-minute recovery period. Heart rates, ST level and ST slope, diastolic and systolic blood pressure were monitored throughout the recovery period.

If the subjects did not voluntarily end the test, it was terminated according to the guidelines of the American College of Sports Medicine (1975). The major criteria utilized for cessation of the test were:

1. The presence of successive or multifocal premature ventricular contractions (PVC's), the occurrence of 2 PVC's within a 6-second interval, or a PVC falling on a T wave.

2. A rapid continuous fall in the ST_2 segment, below -2mm or an ST_2 segment reading of -2.5mm.
3. A horizontal or downsloping ST_2 slope, with an ST_2 segment depression of -1 mm or more.
4. A rise in the diastolic blood pressure over 100 mm Hg, or a rise of more than 20 mm Hg.
5. A sudden or continuous fall in the systolic blood pressure.
6. Symptoms of significant exertional intolerance such as dizziness, angina, unusual fatigue, claudication or pain.
7. Signs of intolerance, such as staggering, mental confusion, cyanosis, pallor, dyspnea or nausea.

The heart rate was recorded on a Quinton 609 Exercise Cardiotachometer. The ECG was monitored on a Quinton ECG Isolation Amplifier (768-100). ST_2 level and slope were registered on a Quinton ECG Data Computer (740). Expired O_2 and CO_2 were collected in a Tissot Gasometer and analyzed by a Godart Oxygen Analyzer and Godart Capnograph. VO_2, VCO_2, ECG, V_E and breathing frequency were recorded on a Narco Four-B Physiograph. The V_E and breathing frequency were obtained via a potentiometer attached to the Tissot.

Training Program

The experimental group participated in a twelve-week, 3 times per week, aerobic exercise program. Each 45 minute session included a 10 to 20 minute warm-up, 10 to 25 minute jog, 5 to 10 minute cool-down, and 5 minute relaxation period

During the jogging period, the subjects were asked to work at a heart rate corresponding to that of 60% of the maximum heart rate calculated by the equation: $60\%\ MHR = .6\ (MHR - RHR) + RHR$ where MHR = maximum heart rate and RHR = resting heart rate.

The subjects monitored their pulse immediately after the jog and adjusted their pace accordingly.

The initial two-week period was used for acclimatization to jogging for an extended period of time. The subjects jogged for 10 minutes, in 1 minute intervals, with a 30 second walk period in between in the first class, and monitored their 10 second heart rate by carotid palpation. This jogging/walking procedure continued throughout the following two-week period, with gradual extension of the time period for each jog, consequently reducing the number of rest periods (Appendix D). By the beginning of the third week, all subjects jogged for a continuous 10 minute period. For the remaining ten weeks, the jogging duration was gradually increased to 25 minutes, maintaining the prescribed heart rate through adjustment of speed. The total duration and distance of the run were recorded at the end of each session for every subject. The subjects ran an average of .7 miles (1.1 Km) in 9.6 minutes at the end of the third week, and an average of 2.5 miles (4.0 Km) in 23.4 minutes at the end of the twelfth week.

Blood Analysis

Fasting (12 hours) venous blood samples were obtained at the beginning and end of the program, to estimate plasma triglycerides, cholesterol and HDL-cholesterol. A second, non-fasting sample was taken within 10 days of the first, and analyzed for cholesterol and HDL-cholesterol, in order to obtain an average value for these two blood lipids. The serum was prepared by centrifuging the blood at 2,000 RPM for 20 minutes, after remaining for 1 hour at room temperature. The serum was

decanted and frozen at -20° for a maximum of three weeks for most samples. The frozen serum was used for HDL-cholesterol and total cholesterol analysis. Freezing for six weeks (Reckless et al, 1977), two months (Miller, 1977) and up to six months (Wood et al, 1976) has been reported to have little effect on the HDL-cholesterol values, but the precision of the analysis has been found to decrease after six months (Reckless et al, 1977) The pre-training samples of some individuals in the control group were analysed after being frozen for two months. Triglycerides were analysed using fresh serum, within one week of obtaining the sample.

HDL-cholesterol Analysis:

HDL-cholesterol was isolated from VLDL and LDL-cholesterol by a polyanion and bivalent cation precipitation method originally developed by Burnstein and Samaille (1960).

Sodium phosphotungstate and magnesium were used to precipitate VLDL and LDL in this study since the more common heparin and manganese method sometimes fails to precipitate VLDL and LDL completely, due to differences in the heparin preparation utilized (Lopez-Virella et al, 1977B). This resulted in an overstimation of the HDL-cholesterol levels.

The sodium phosphotungstate and magnesium precipitation method of Burnstein et al (1970) has been found to have a .82 correlation with the ultracentrifugation method (Lopez-Virella et al, 1977B), but it may result in an underestimate in some cases (Albers et al, 1978). Sodium phosphotungstate solutions remain stable for six months (Lopez-Virella et al, 1977B) unlike the heparin solutions, so the solution could be used for a large number of analyses, removing one means of variability in the HDL-cholesterol results. It was not possible in this study to use the same solution for all of the analyses, so one solution was used for the pre-training samples of the experimental

and the control group, but a second solution was required for the analysis of the post-training samples of both the experimental and the control group. This second solution was required since the expiry date of the first solution had passed.

100 μl of a sodium phosphotungstate solution (40 grams of phosphotungstic acid (FISHER) per litre of a mixture of 1 M NaOH and distilled water in a 16/84 ratio by volume) and 25 μl of 2 M $MgCl_2$ were added to 1 ml of serum. The tubes were covered and vortexed for 20 seconds. They were then centrifuged for 30 minutes at 1500 x g and at 4^0 C. The supernatants were removed and analysed for cholesterol content. This method is the one outlined in the paper by Lopez-Virella et al (1977B) which compared the HDL-cholesterol results of the precipitation methods to those obtained by the ultracentrifugation analysis.

To determine the reproducibility of the method, 10 aliquots of pooled serum were analyzed for HDL-cholesterol at the same time. The average HDL-cholesterol concentration was 44 mg% with a standard deviation of $\pm$1 mg% and a coefficient of variation of 2.3%.

To determine the validity of the precipitation method, a frozen serum sample that had previously been analyzed for HDL-cholesterol by the ultracentrifugation method (reference method) was supplied by the Biochemistry Department of the Ottawa Civic Hospital. The serum was reported to contain 36 mg% of HDL-cholesterol when measured by ultracontrifugation. When the frozen sample was analyzed using the precipitation method, it was found to contain 37 mg% of HDL-cholesterol. One of these frozen serum samples, of known HDL-cholesterol concentration was included in the analysis of each set of samples. This frozen

sample was considered to serve as a standard for each analysis since its HDL-cholesterol content had been determined by the reference method.

To determine the inter-analysis variability, serum was frozen in 1½ ml aliquots and one of the aliquots was analyzed with the analysis of each set of samples to provide for a quality control. Since there were not many frozen aliquots obtained from each batch of serum, it was necessary to use 3 different serum batches that were frozen and utilized at different times. The mean, standard deviations (S.D) and coefficients of variation (C.V) obtained from the various analysis of these frozen aliquots are outlined below. The results of the analysis of the standard from one time to the next are included as well:

Analysis Number	Serum A	Serum B	Serum C	Standard from Ottawa Civic Hospital
	(mg %)	(mg %)	(mg %)	(mg %)
1	56.4	--	--	--
* 2	54.0	46.1	--	37
* 3	45.0	41.6	--	29
* 4	47.3	43.9	--	44
5	48.4	43.9	--	38
6	--	45	50.6	-
* 7	--	--	55.1	38
* 8	--	--	51.7	36
9	--	--	48.4	33
Mean	50.0	44.2	51.5	36.3
S.D.	± 4.7	±1.5	±2.9	±4.6
C.V.	9.4%	3.4%	5.6%	12.7%

(* The serum samples of the subjects in the study were analyzed at these times.)

It should be noted that the results of these measurements not only reflect the variability of the HDL-cholesterol precipitation method and cholesterol analysis, from analysis to analysis, but may also reflect the effects of freezing to a certain extent. The coefficients of variation reported here are quite high in some cases. Coefficients of variation for the inter-analysis precision of HDL-cholesterol precipitation methods have been reported to range from 4% to 8% (Morrison et al, 1979; Van Gent et al, 1978). Consequently, HDL precipitation methods can have an inter-analysis variability that can be higher in some cases than the level which is considered desirable for good precision (<5%) (Goldberg et al, 1978).

Cholesterol Analysis:

Cholesterol was measured enzymatically (Allain et al, 1974) using an Abbott ABA-100 Automated Analyzer. The reagents and instrumentation utilized were from Abbott Laboratories, North Chicago, Illinois. The error of the method is 2%. When the sample was analyzed in two separate runs, the difference in cholesterol was found to be 3 mg%. When the prepared cholesterol standard of 110 mg% was diluted in half and analyzed, the mean of the results of the different runs (on different days) was 55 mg% with a standard deviation of ± 2.6 mg% and a coefficient of variation of 4.7%. The cholesterol values obtained for HDL-cholesterol were adjusted by a factor of 1.125 to account for the dilution involved in the precipitation method.

~~Triglyceride Analysis:~~

Triglycerides were assayed enzymatically (Eggstein & Kreutz, 1966) using an Abbott ABA-100 Automated Analyzer. The reagents and instrumentation utilized were from Abbott Laboratories, North Chicago, Illinois.

Statistical Analysis

Major Analysis:

An analysis of Covariance (ANCOVA) was carried out on the data of the biochemical, physiological and exercise performance variables, to determine if any of these variables changed significantly in the experimental group as compared to the control group.

Minor Analyses:

Correlation Coefficients, expressed as a Pearson's r , were calculated to determine the relationships between variables which were considered to be relevant to the study. The correlations include those of HDL-cholesterol with total cholesterol, triglycerides, percent body fat and MVO_2 (l/min and ml/kg/min) and of HDL-cholesterol: total cholesterol with triglycerides, percent body fat and MVO_2 (l/min and ml/kg/min). The statistical significance of these correlations was also determined.

The pre- and post-training seven-day dietary reports were analyzed for cholesterol, carbohydrate, total fat, unsaturated and saturated fat, protein and alcohol content, according to the values given in Food Values of Portions Commonly Used by Church and Church (1975). Cholesterol content was supplemented by the values listed in Nutrition et Diétothérapie by Krause and Hunscher (1978). The daily intake of these components was calculated and a Student's t test was used to check for significant differences between the pre- and post-training daily dietary composition.

The pre- and post-training questionnaires listing dietary adherence, smoking habits, medication prescribed, and physical activity

levels were examined for changes in these variables over the study period, but a statistical analysis was not carried out.

For the purpose of this study, a statistically significant difference was considered to be present if the probability level (P level) was found to be less than .05. This applies to the results of all of the different methods of statistical analysis utilized in the study.

CHAPTER IV

RESULTS

Section I: Biochemical, Physiological and Exercise Performance Variables

The pre- and post-training results of the experimental and control groups for the biochemical, physiological and exercise performance variables are contained in Tables VII - IX. The A section of each table includes the results for each individual. The B section contains the means, the standard deviations and the significance of the differences noted.

Since the statistical design was one of an Analysis of Covariance (ANCOVA), reference to the presence of a statistically significant difference is based on the finding that the post-training values of the exercise group were significantly different from those of the control group, after having adjusted all post-training values by their respective pre-training values. When the increase or decrease in a variable of the experimental group is referred to as being statistically significant, this is an interpretation based on the ANCOVA results that if the adjusted post-training values of the experimental group are significantly different from those of the control group, the experimental group values must have changed significantly with respect to the control group values. The level at which the difference between the adjusted post-training values of the two groups is significant is

indicated by a corresponding probability value (P).

Table VII A and Table VII B contain the data for the biochemical variables which include HDL-cholesterol, total cholesterol, the ratio of HDL-cholesterol:total cholesterol, LDL-cholesterol and triglyceride values. The HDL-cholesterol and total cholesterol values listed for the individuals are the mean of a fasting and non-fasting sample. The fasting and non-fasting values are listed separately in Appendix E1 and E2. LDL-cholesterol is an estimate (supra p. 10), therefore more caution is required in the interpretation of the LDL-cholesterol results as compared to those of the other biochemical variables that were measured directly.

Table VIII A and Table VIII B contain the data for the physiological variables which include resting heart rate, percentage body fat, diastolic blood pressure and systolic blood pressure.

Table IX A and Table IX B list the data for the exercise performance variables. These include maximum oxygen uptake measured in litres per minute and, to account for differences in body weight, millilitres per kilogram per minute, maximum carbon dioxide production and maximum oxygen pulse.

Figures 4-16 represent the percentage change (post-training minus pre-training values divided by pre-training values and multiplied by 100), in the variables measured, that occurred for each subject in the experimental and control groups. Mean percentage change in the variable is also included for both groups.

Biochemical Variables:

HDL-cholesterol was 53.6 mg% pre-training and 55.3 mg% post-training in the experimental group, and 57.3 mg% and 57.2 mg% in the control group. HDL-cholesterol did not change significantly in the

TABLE VII A

BIOCHEMICAL VARIABLES: Individual Data

		HDL-CHOLESTEROL mg/100 ml			TOTAL CHOLESTEROL mg/100 ml			HDL-CHOLESTEROL : TOTAL CHOLESTEROL			LDL-CHOLESTEROL mg/100 ml			TRIGLYCERIDES mg/100 ml		
		pre	post	dif.	pre	post	dif.	pre	post	dif.	pre	post	dif.	pre	post	dif.
EXPERIMENTAL GROUP	1	546	517	-29	3070	2125	-945	.178	.243	.065	2360	1423	-937	82	92	10
	2	436	416	-2	2105	1965	-14	.207	.212	.005	1407	1331	-76	131	109	-22
	3	478	517	39	214	228	14	.223	.227	.004	1482	1631	149	90	66	-24
	4	538	523	-15	235	214	-21	.229	.244	.015	1584	1401	-183	114	108	-6
	5	523	557	34	2325	2055	-27	.225	.271	.046	1608	1356	-252	97	71	-26
	6	399	478	79	140	1425	25	.285	.335	.050	847	765	-82	77	91	14
	7	484	568	84	264	207	-57	.183	.274	.091	1866	1294	-572	125	104	-21
	8	776	731	-45	2465	2035	-43	.315	.359	.044	1553	1185	-365	68	58	-10
	9	484	563	79	265	239	-26	.183	.235	.052	2010	1613	-397	78	107	29
	10	489	506	17	198	198	0	.247	.256	.009	1319	1346	27	86	64	-22
	11	602	697	95	1885	1815	-7	.319	.384	.065	1169	987	-182	57	65	8
	12	675	557	-118	215	2025	-125	.314	.275	-.039	1313	1298	-15	81	85	4
	MEAN	536	553	17	2263	2025	-238	.242	.276	.034	1543	1303	-24	905	85	-5.5
CONTROL GROUP	1	605	703	98	205	2155	105	.295	.326	.031	1297	1338	41	74	57	-17
	2	501	517	16	208	205	-3	.241	.252	.011	1255	1297	42	162	118	-44
	3	574	664	90	194	2115	175	.296	.314	.018	1207	1281	74	80	85	5
	4	791	731	-6	1985	1945	5	.417	.376	-.041	976	1032	56	64	91	27
	5	464	433	-31	227	196	-31	.204	.221	.017	1530	1273	-257	138	127	-11
	6	301	349	48	2275	2165	-11	.132	.161	.029	1702	1550	-152	136	133	-3
	7	542	557	15	2385	2175	-21	.227	.256	.029	1561	1394	-167	141	112	-29
	8	553	512	-41	243	245	2	.228	.209	-.019	1599	1598	-01	139	170	31
	9	692	636	-56	2165	2925	76	.320	.217	-.103	1227	1933	706	123	178	55
	10	709	619	-9	2365	2345	-2	.300	.264	-.036	1503	1572	69	77	77	0
	MEAN	573	572	-1	2186	2229	43	.266	.260	-.006	1386	1427	41	1134	1148	14

TABLE VII B

BIOCHEMICAL VARIABLES: Mean Values, Standard Deviations and Significant Differences

		HDL-CHOLESTEROL		TOTAL CHOLESTEROL		HDL-CHOLESTEROL : TOTAL CHOLESTEROL		LDL-CHOLESTEROL		TRIGLYCERIDES	
		mg/100 ml		mg/100 ml				mg/100 ml		mg/100 ml	
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group
MEAN	pre	53.6	57.3	226.3	218.6	.242	.266	154.3	138.6	90.5	113.4
	post	55.3	57.2	202.5	222.9	.276	.260	130.3	142.7	85.0	114.8
MEAN CHANGE		1.7	-.1	-23.8	4.3	.034	-.006	-24.0	4.1	-5.5	1.4
STANDARD DEVIATION	pre	±10.5	±13.9	±42.8	± 18.9	± .05	±.08	±39.8	±22.6	±22.5	±35.6
	post	± 8.7	±12.2	± 24.0	± 29.0	± .05	±.06	± 24.0	± 24.7	± 19.1	± 39.1
P VALUE		<.77		<.025		<.04		<.05		<.16	

TABLE VIIIA

. PHYSIOLOGICAL VARIABLES: Individual Data

		RESTING HEART RATE			PERCENTAGE BODY FAT			SYSTOLIC BLOOD PRESSURE			DIASTOLIC BLOOD PRESSURE		
		beats / minute			%			mmHg			mmHg		
		pre	post	difference	pre	post	difference	pre	post	difference	pre	post	difference
EXPERIMENTAL GROUP	1	64	58	-6	17.2	18.3	1.1	108	110	2	70	74	4
	2	70	60	-10	22.9	24.3	1.4	130	136	6	94	80	-6
	3	64	56	-8	19.3	19.6	.3	138	118	-20	72	66	-6
	4	74	58	-16	18.1	19.2	1.1	120	106	-14	70	88	18
	5	58	76	18	15.7	15.9	.2	122	120	-2	66	68	2
	6	76	72	-4	22.8	23.5	.7	108	110	2	72	60	-12
	7	70	62	-8	17.6	16.9	-.7	118	134	16	70	70	0
	8	66	64	-2	17.2	16.7	-.5	104	108	4	72	66	-6
	9	82	56	-26	20.8	23.5	2.7	120	114	-6	80	76	-4
	10	82	84	2	17.7	18.5	.8	132	104	-28	70	60	-10
	11	66	56	-10	26.0	25.3	-.7	132	126	-6	90	74	-16
	12	88	69	-19	16.2	15.5	-.7	116	110	-6	60	60	0
	MEAN	71.7	64.3	-7.4	19.3	19.8	.5	120.7	116.3	-4.4	73.8	70.2	-3.6
CONTROL GROUP	1	72	68	-4	18.2	16.7	-1.5	100	112	12	70	84	14
	2	68	72	4	19.1	19.6	.5	114	118	4	68	72	4
	3	56	56	0	19.3	20.5	1.2	128	116	-12	78	72	-6
	4	60	58	-2	14.7	16.0	1.3	108	104	-4	66	74	8
	5	72	60	-12	28.3	27.8	-.5	122	98	-24	74	62	-12
	6	76	72	-4	27.1	29.3	2.2	122	118	-4	80	74	-6
	7	72	70	-2	24.9	25.3	.4	152	142	-10	98	82	-16
	8	72	64	-8	22.3	24.6	2.3	124	122	-2	80	88	8
	9	92	76	-16	21.7	24.2	2.5	138	132	-6	90	98	8
	10	72	58	-14	24.5	25.6	1.1	146	138	-8	98	102	4
	MEAN	71.2	65.4	-5.8	22.0	23.0	1	125.4	120.0	-5.4	80.2	80.8	.6

TABLE VIII B.

PHYSIOLOGICAL VARIABLES: Mean Values, Standard Deviations and Significant Differences

		RESTING HEART RATE		PERCENTAGE BODY FAT		SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE	
		beats / minute		%		mmHg		mmHg	
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group
MEAN	pre	71.7	71.2	19.3	22.0	120.7	125.4	73.8	80.2
	post	64.3	65.4	19.8	23.0	116.3	120.0	70.2	80.8
MEAN CHANGE		-7.4	-5.8	.5	1.0	-4.4	-5.4	-3.6	.6
STANDARD DEVIATION	pre	± 8.9	± 9.6	± 3.2	± 4.3	± 10.8	± 16.3	± 9.7	± 11.7
	post	± 9.1	± 7.1	± 3.5	± 4.5	± 10.7	± 14.1	± 8.7	± 12.5
P VALUE		< .69		< .48		< .83		< .11	

TABLE IX A

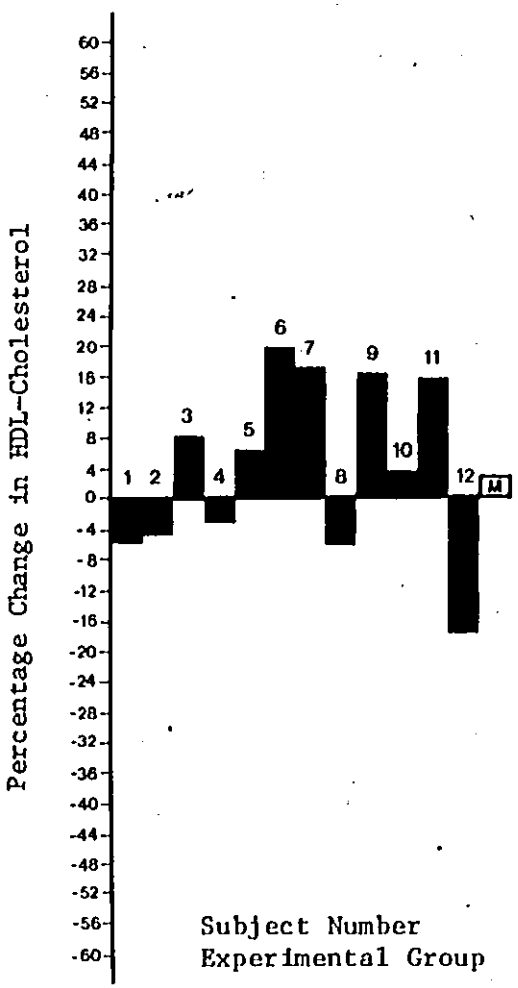
EXERCISE PERFORMANCE VARIABLES - Individual Data

	MAXIMAL OXYGEN UPTAKE l/minute			MAXIMAL OXYGEN UPTAKE ml/Kg/minute			MAXIMAL CARBON DIOXIDE OUTPUT l/minute			MAXIMAL OXYGEN PULSE ml/beat		
Experimental Group	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
1	2.3	2.4	.1	33.3	33.8	.5	2.6	3.1	.5	13.8	14.7	.9
2	3.1	3.9	.8	31.6	40.5	8.9	3.3	4.6	1.3	18.9	22.9	4.0
3	3.0	3.1	.1	39.0	41.3	2.3	3.4	3.6	.2	17.6	20.0	2.4
4	3.2	3.5	.3	42.7	46.3	3.6	3.4	3.7	.3	18.4	19.2	.8
5	1.5	1.6	.1	26.3	28.3	2.0	1.5	2.2	.7	9.8	9.9	.1
6	3.2	3.1	-.1	34.8	33.5	-1.3	3.9	3.7	-.2	18.6	19.7	1.1
7	3.3	3.4	.1	43.3	45.5	2.2	3.3	3.9	.6	17.5	19.7	2.2
8	2.8	3.4	.8	36.5	45.2	8.7	3.3	4.3	1.0	15.5	19.5	4.0
9	2.7	3.3	.6	34.7	41.2	6.5	2.9	3.8	.9	14.1	17.6	3.5
10	2.6	2.8	.2	36.9	38.7	1.8	2.8	3.4	.6			
11	3.5	3.7	.2	37.3	40.5	3.2	3.5	4.5	1.0	17.7	20.1	2.4
12												
MEAN	2.8	3.1	.3	36.0	39.5	3.5	3.1	3.7	.6	16.2	18.3	2.1
Control Group												
1												
2	3.2	3.0	-.2	41.7	38.4	-3.3	3.3	3.7	.4	17.9	16.6	-1.3
3	3.8	3.5	-.3	48.0	43.1	-4.9	4.1	4.1	.0	22.7	21.3	-1.4
4	2.9	2.8	-.1	49.5	46.5	-3.0	3.4	3.4	.0	17.2	16.1	-1.1
5	1.8	1.8	.0	22.1	22.3	.2	2.1	2.1	.0	11.5	11.8	.3
6	1.8	2.0	.2	21.1	23.7	2.6	2.3	2.3	.0	11.1	12.3	1.2
7	2.2	2.3	.1	25.1	25.7	.6	2.6	2.6	.0	13.3	14.7	1.4
8	2.6	2.8	.2	30.3	33.5	3.2	2.8	3.7	.9	17.2	15.7	-1.5
9	2.7	2.9	.2	36.3	38.5	2.2	3.2	3.7	.5	14.3	15.7	1.4
10	2.0	2.0	.0	26.5	26.9	.4	2.1	2.1	.0	11.3	11.5	.2
MEAN	2.6	2.6	.0	33.4	33.2	-.2	2.9	3.1	.2	15.2	15.1	-.1

TABLE IX B

EXERCISE PERFORMANCE VARIABLES: Mean Values, Standard Deviations and Significant Differences

		MAXIMUM OXYGEN UPTAKE		MAXIMUM OXYGEN UPTAKE		MAXIMUM CARBON DIOXIDE PRODUCTION		MAXIMUM OXYGEN PULSE	
		l/minute		ml/Kg/minute		l/minute		ml/beat	
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group
MEAN	pre	2.8	2.6	36.0	33.4	3.1	2.9	16.2	15,2
	post	3.1	2.6	39.5	33.2	3.7	3.1	18.3	15.1
MEAN CHANGE		.3	0	3.5	-.2	.6	.2	2.1	-.1
STANDARD DEVIATION	pre	± .6	± .7	± 4.8	±10.9	± .6	± .7	± 2.9	±3.9
	post	± .7	± .6	±5.6	±8.9	± .7	± .8	±3.6	±3.0
P VALUE		< .02		< .005		< .04		< .002	



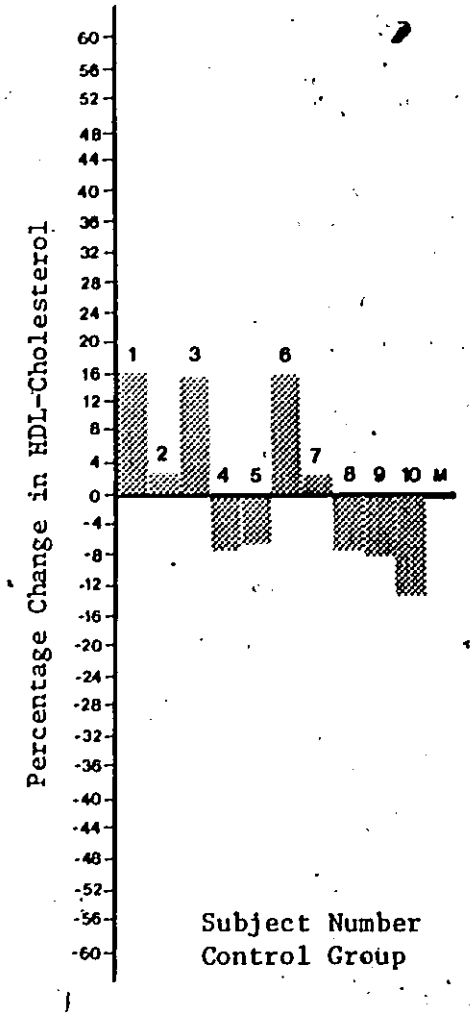


FIGURE 4 : Percentage Change in HDL-Cholesterol

M = mean percentage change

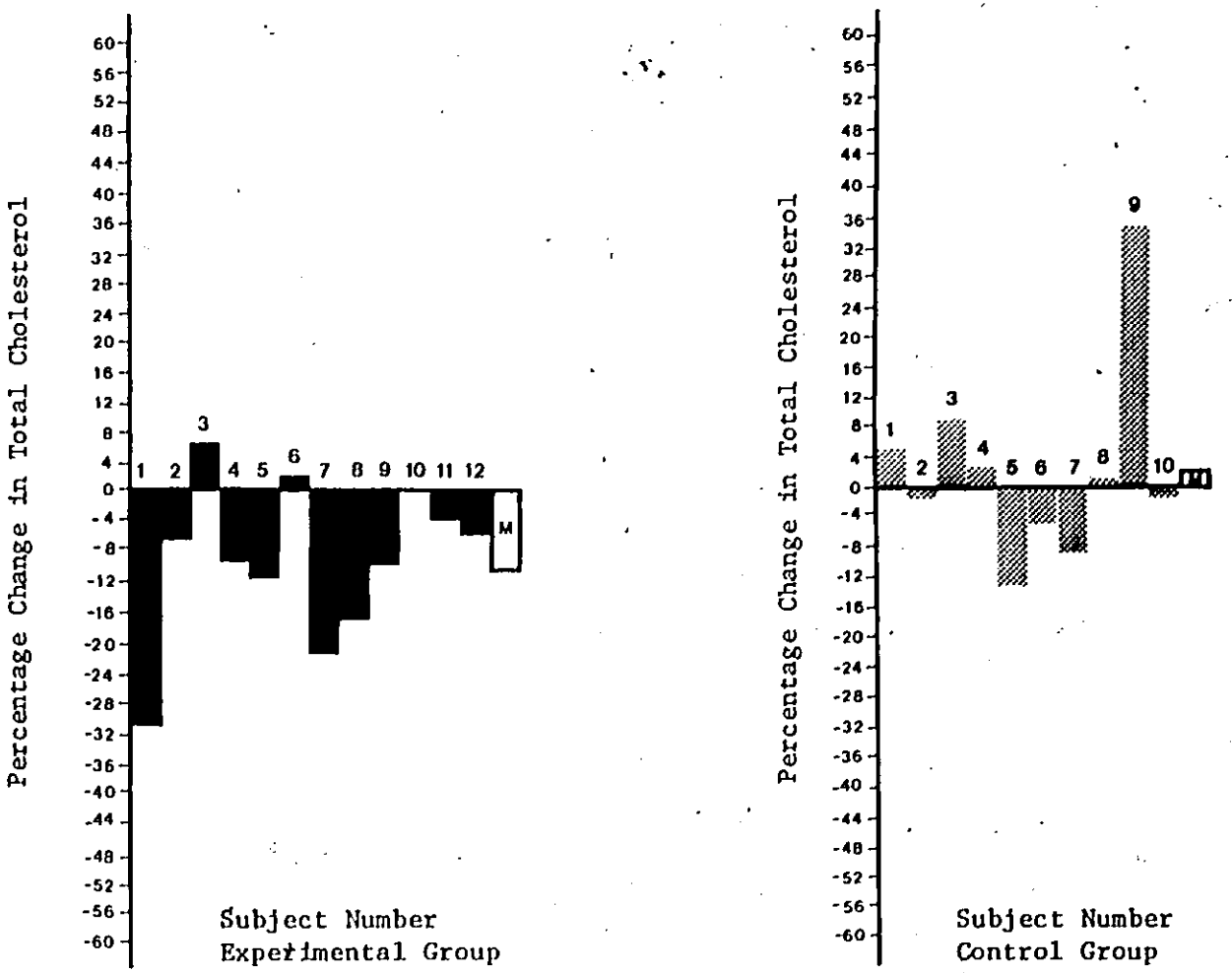


FIGURE 5 : Percentage Change in Total Cholesterol

M = mean percentage change

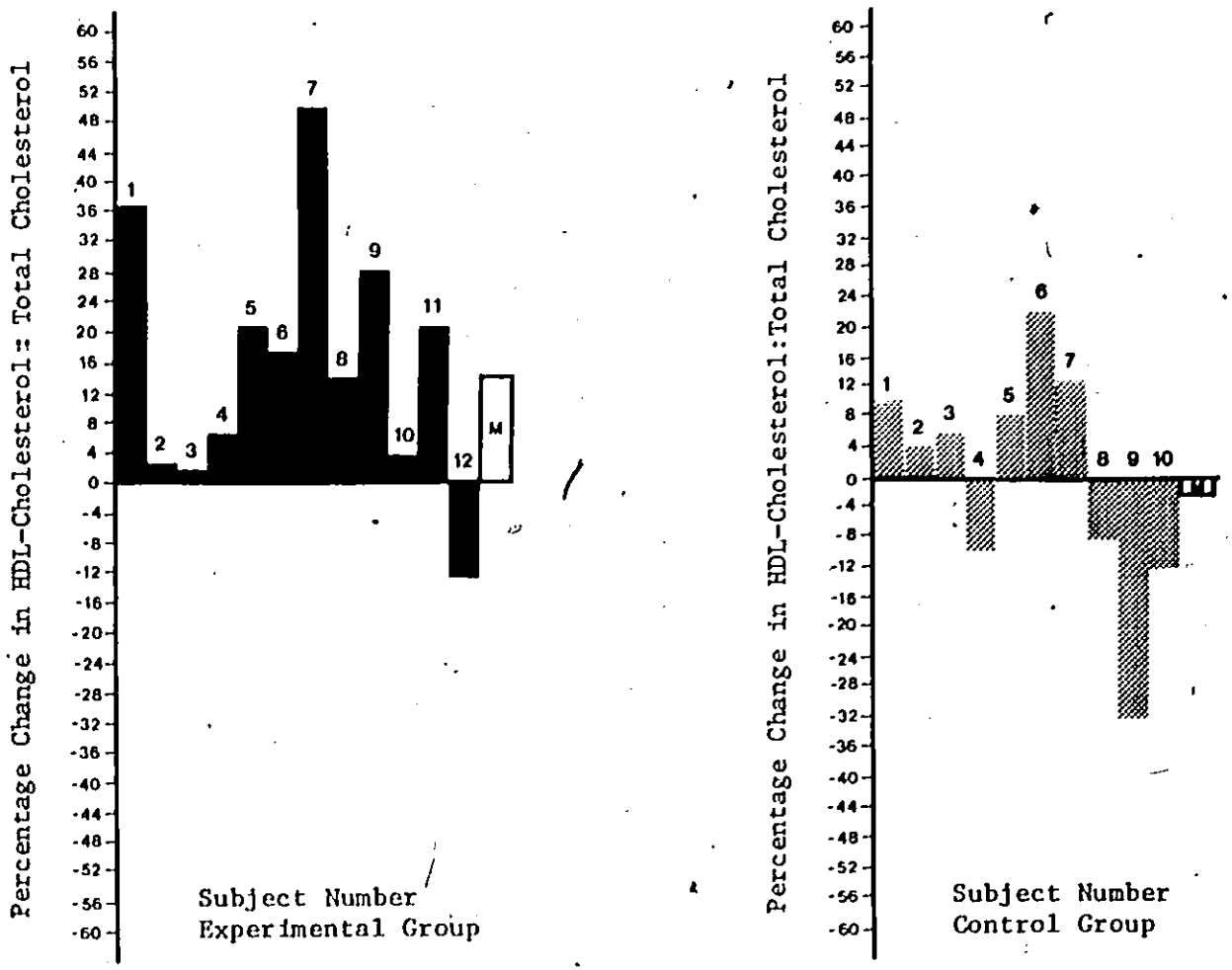
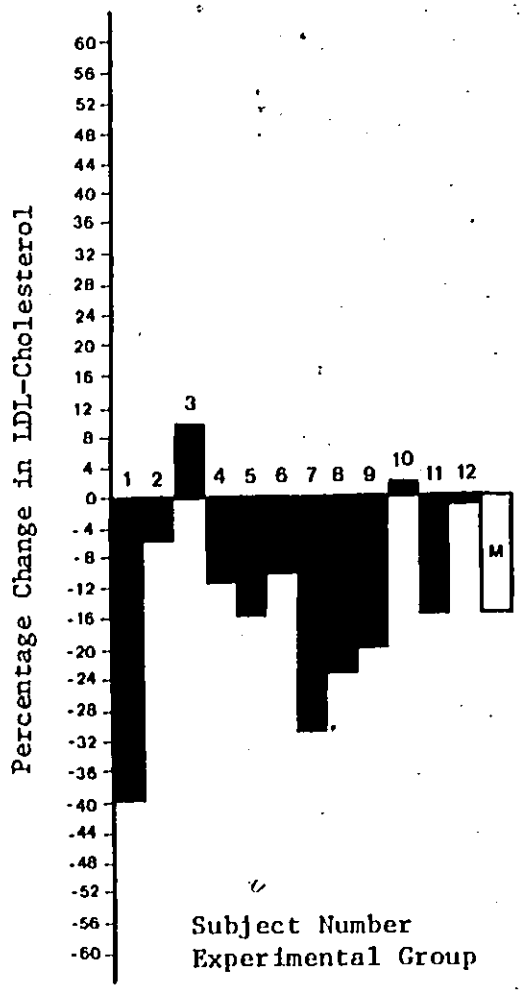


FIGURE 6 : Percentage in the HDL-Cholesterol:Total Cholesterol Ratio

M=mean percentage change



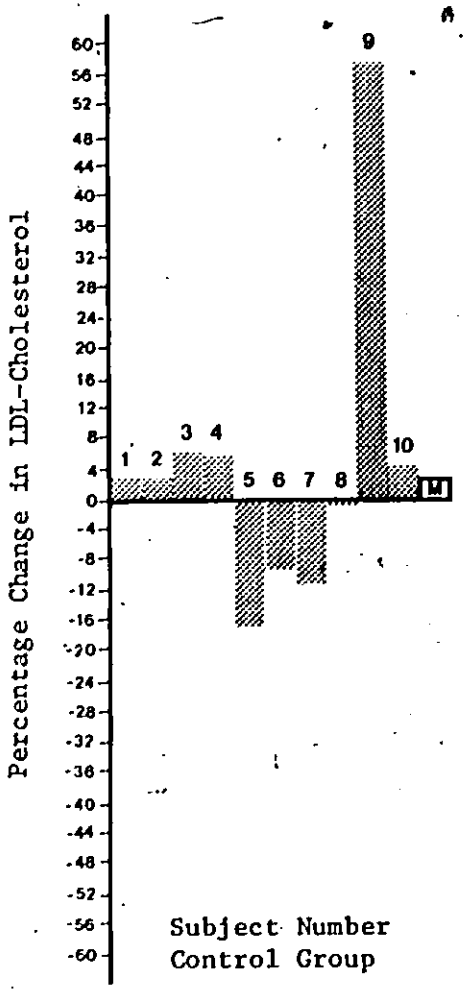


FIGURE 7 : Percentage Change in LDL-Cholesterol

M=mean percentage change

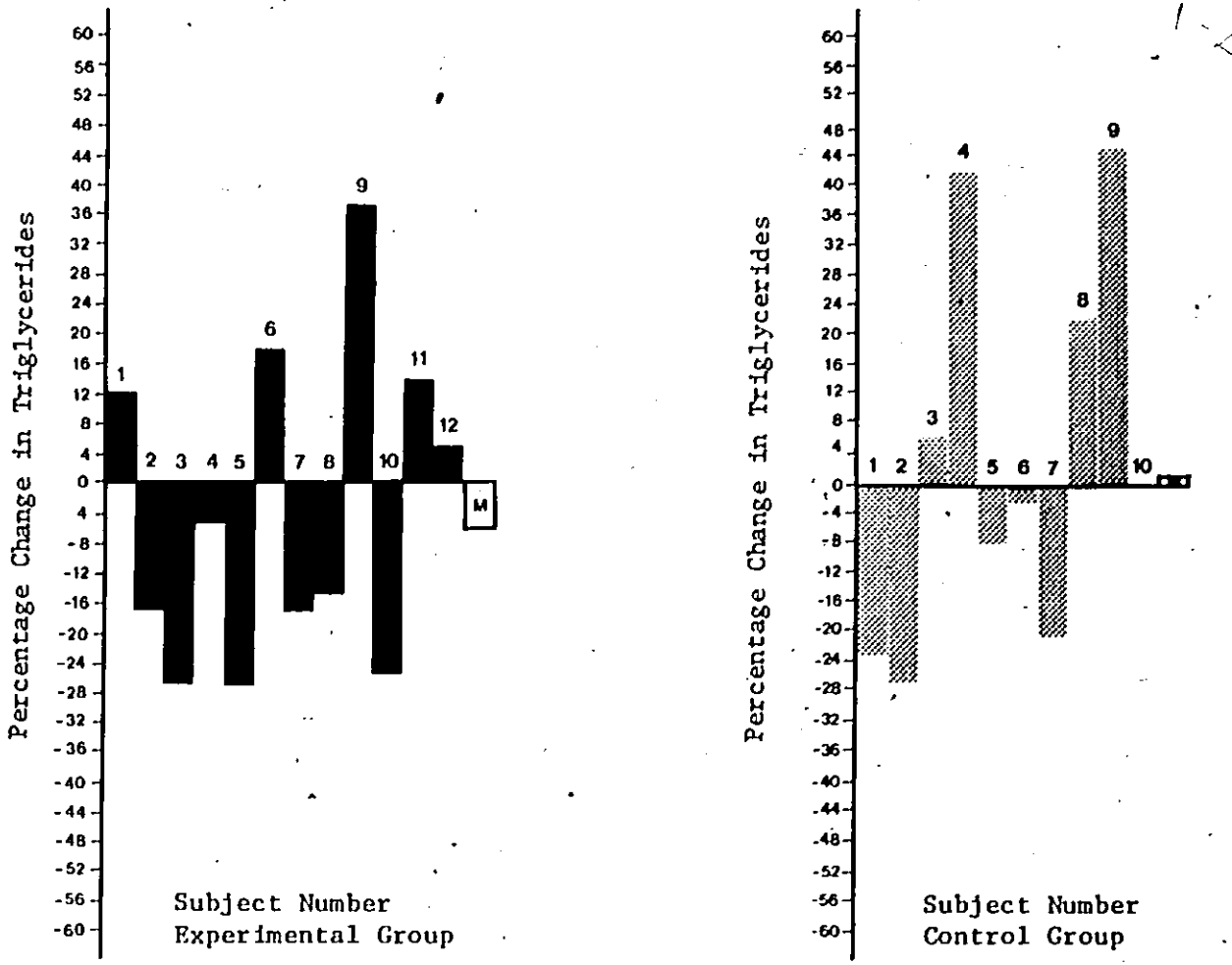


FIGURE 8 : Percentage Change in Triglycerides

M=mean percentage change

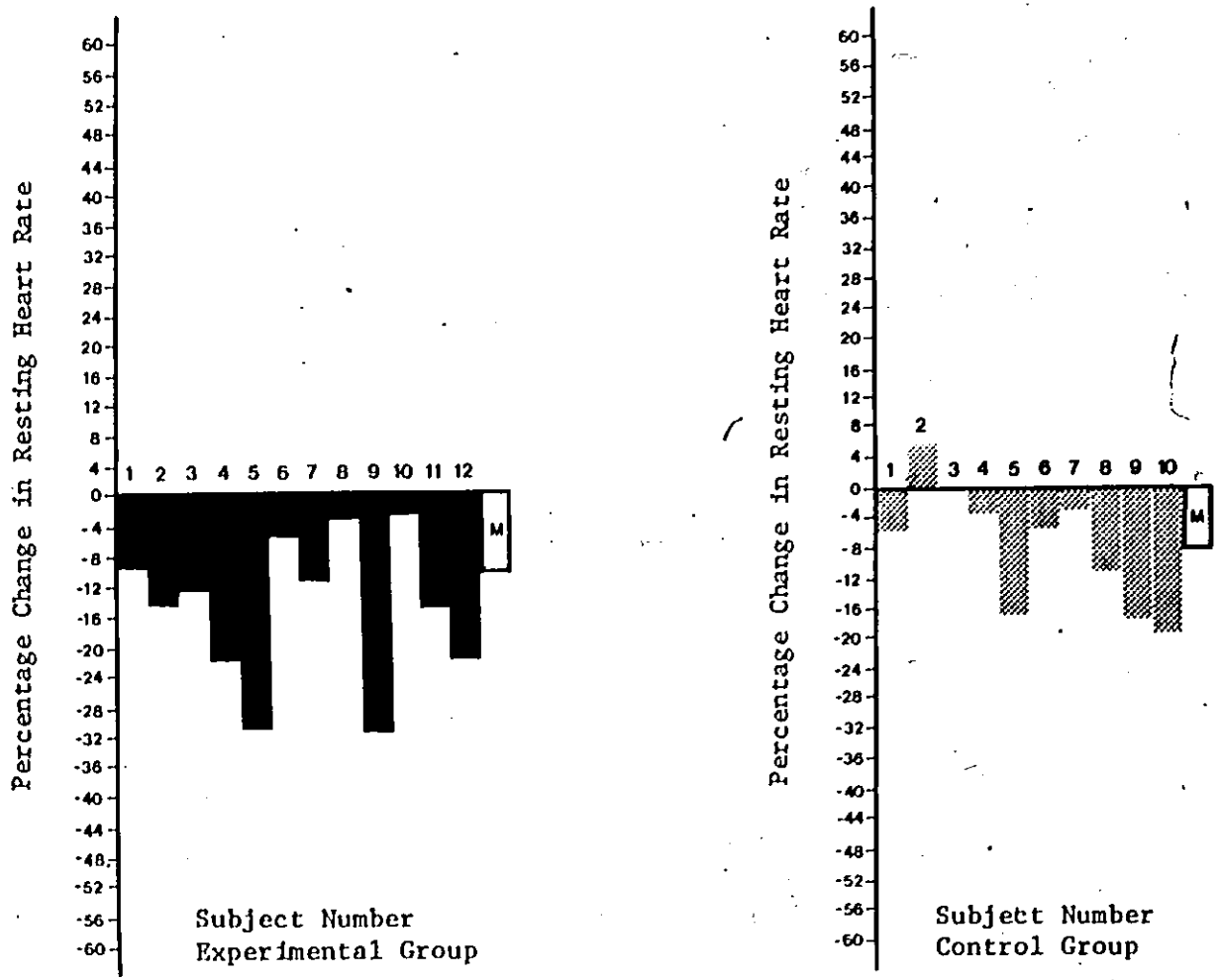


FIGURE 9 : Percentage Change in Resting Heart Rate

M=mean percentage change

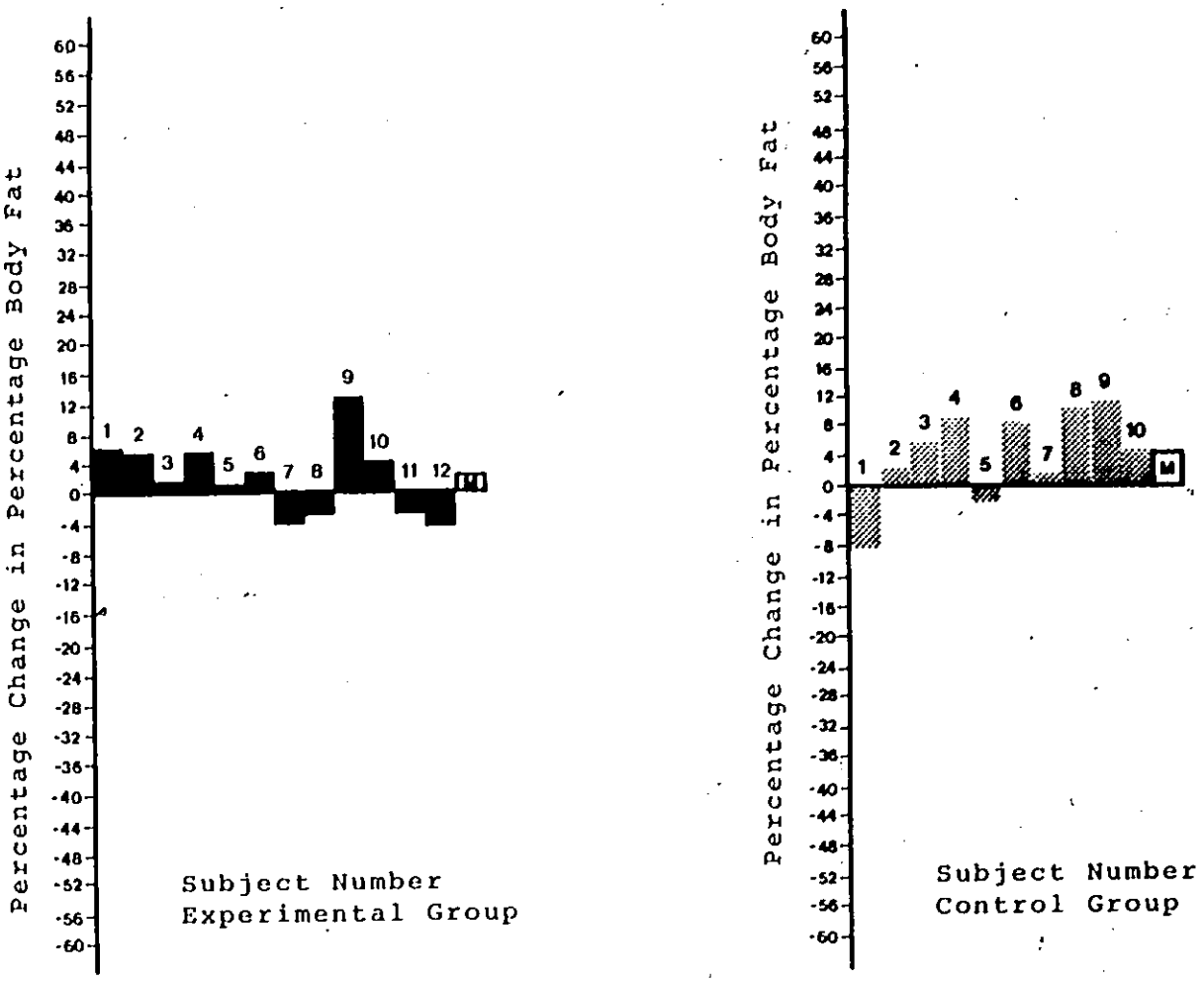
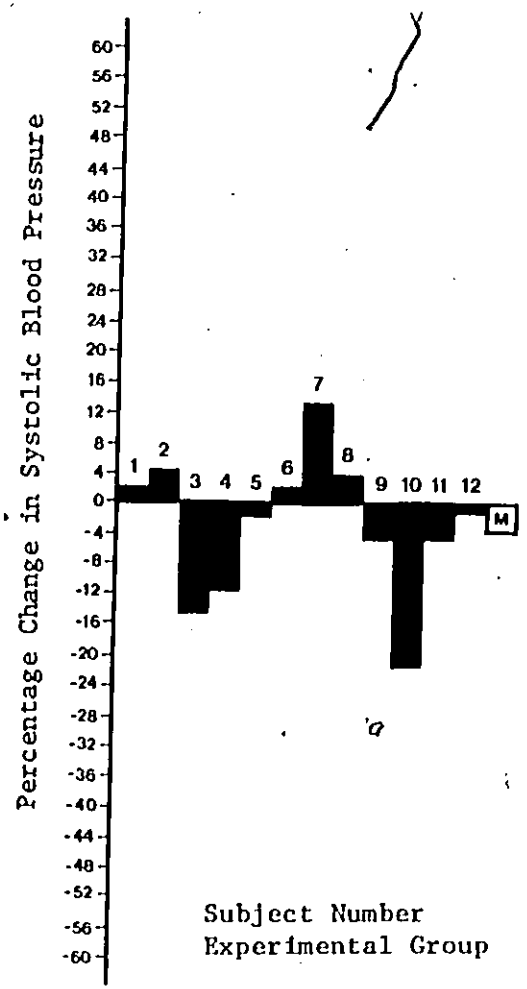


FIGURE 10 : Percentage Change in Percentage Body Fat

M=mean percentage change



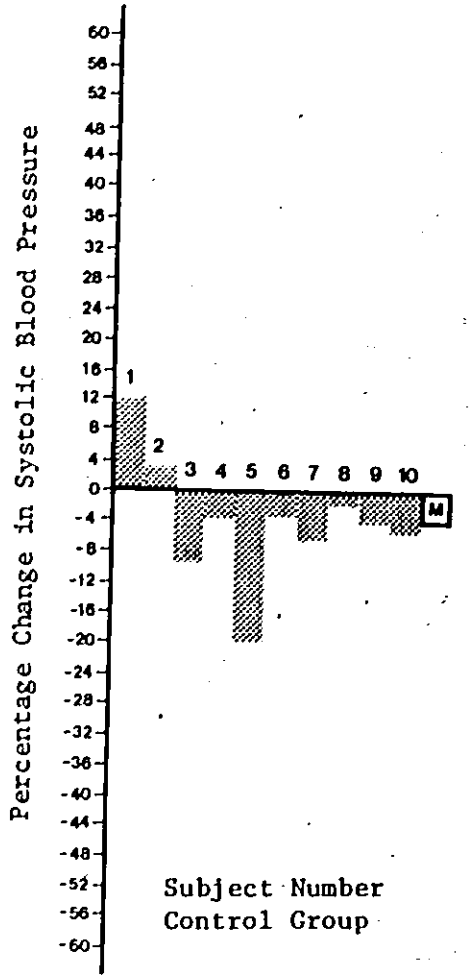
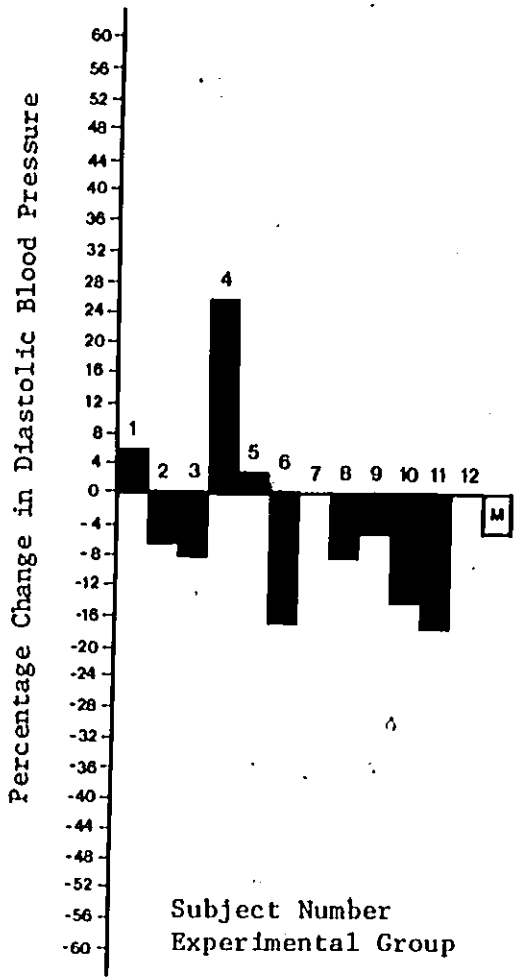


FIGURE 11 : Percentage Change in Systolic Blood Pressure

M=mean percentage change



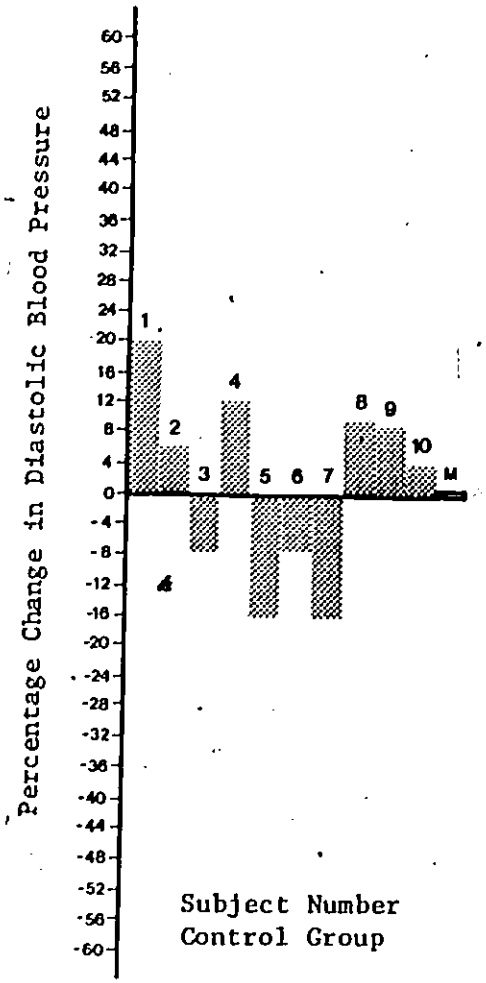


FIGURE 12 : Percentage Change in Diastolic Blood Pressure

M=mean percentage change

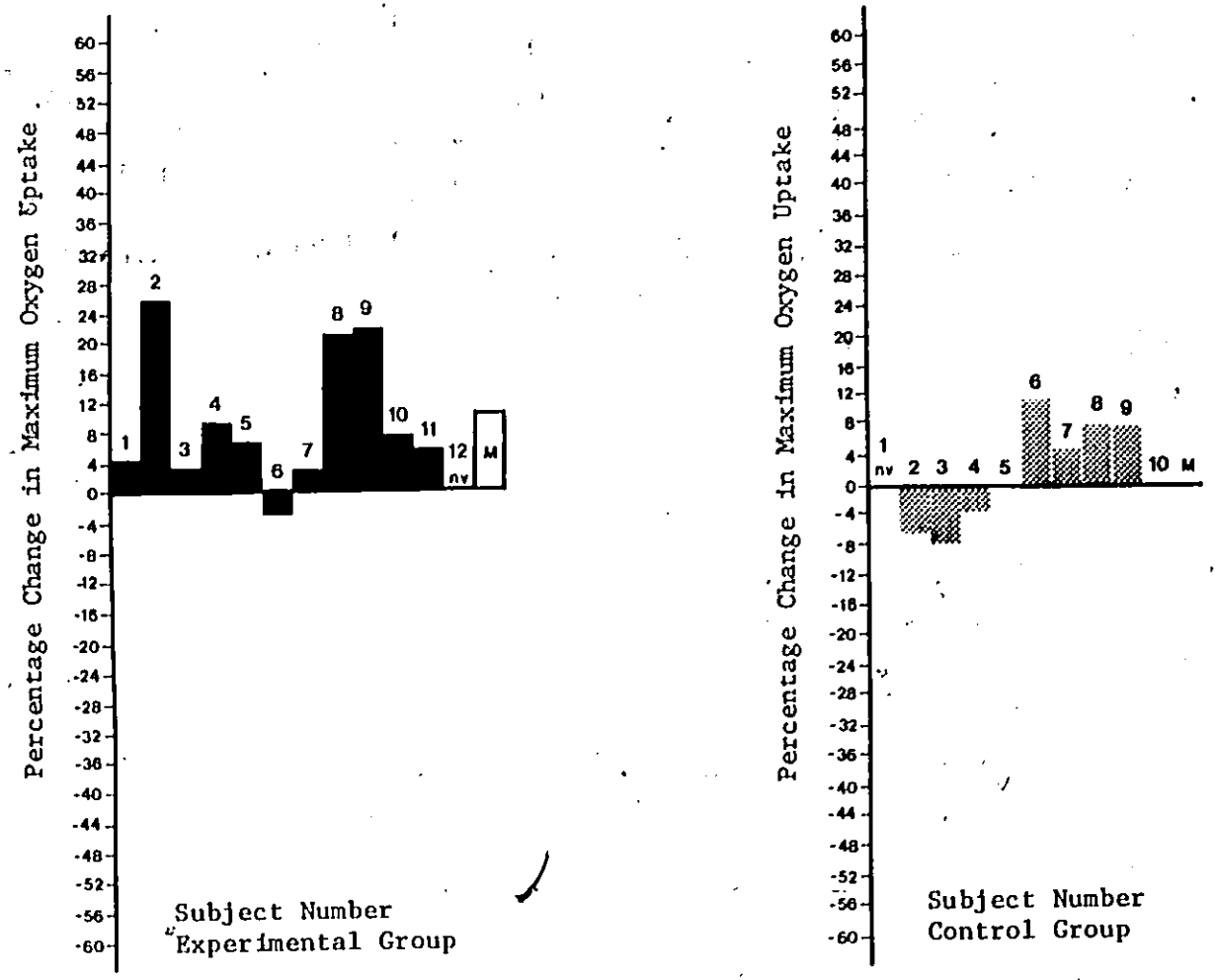
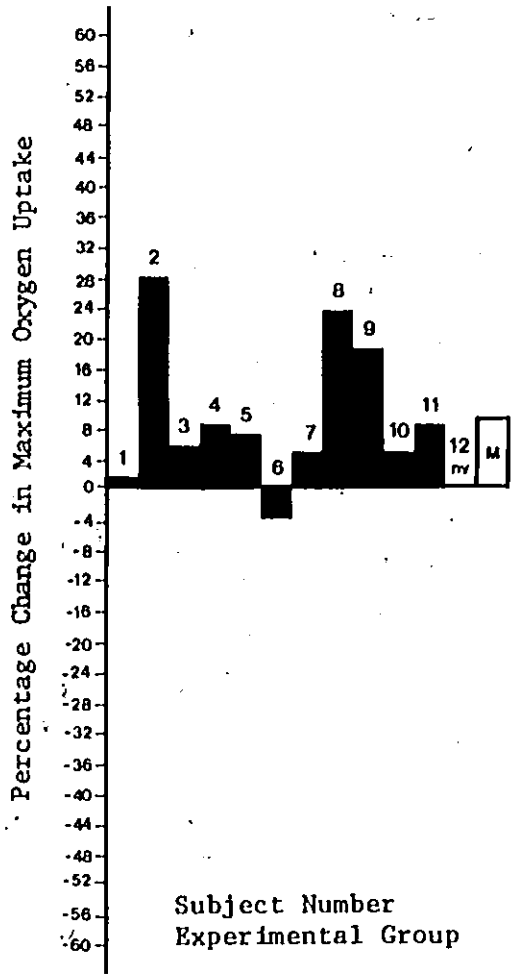


FIGURE 13 : Percentage Change in Maximum Oxygen Uptake (l/min)

M=mean percentage change
nv= no value



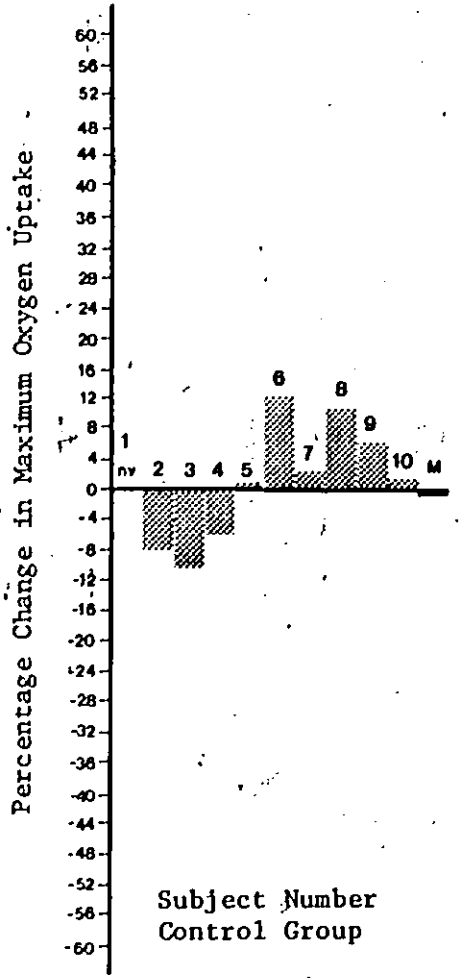


FIGURE 14 : Percentage Change in Maximum Oxygen Uptake (ml/kg/min)

M=mean percentage change
nv = no value

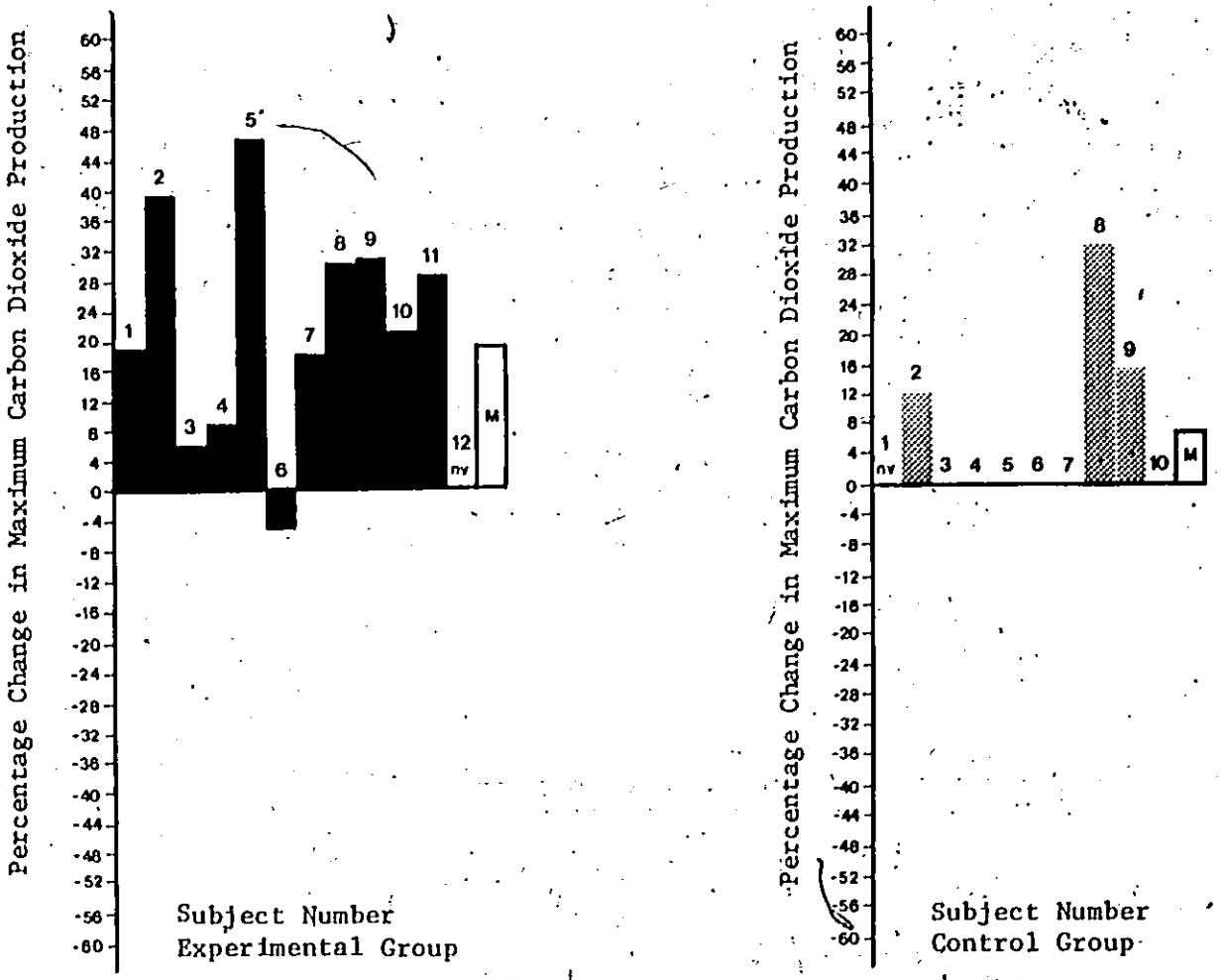


FIGURE 15 : Percentage Change in Maximum Carbon Dioxide Production

M=mean percentage change
nv= no value

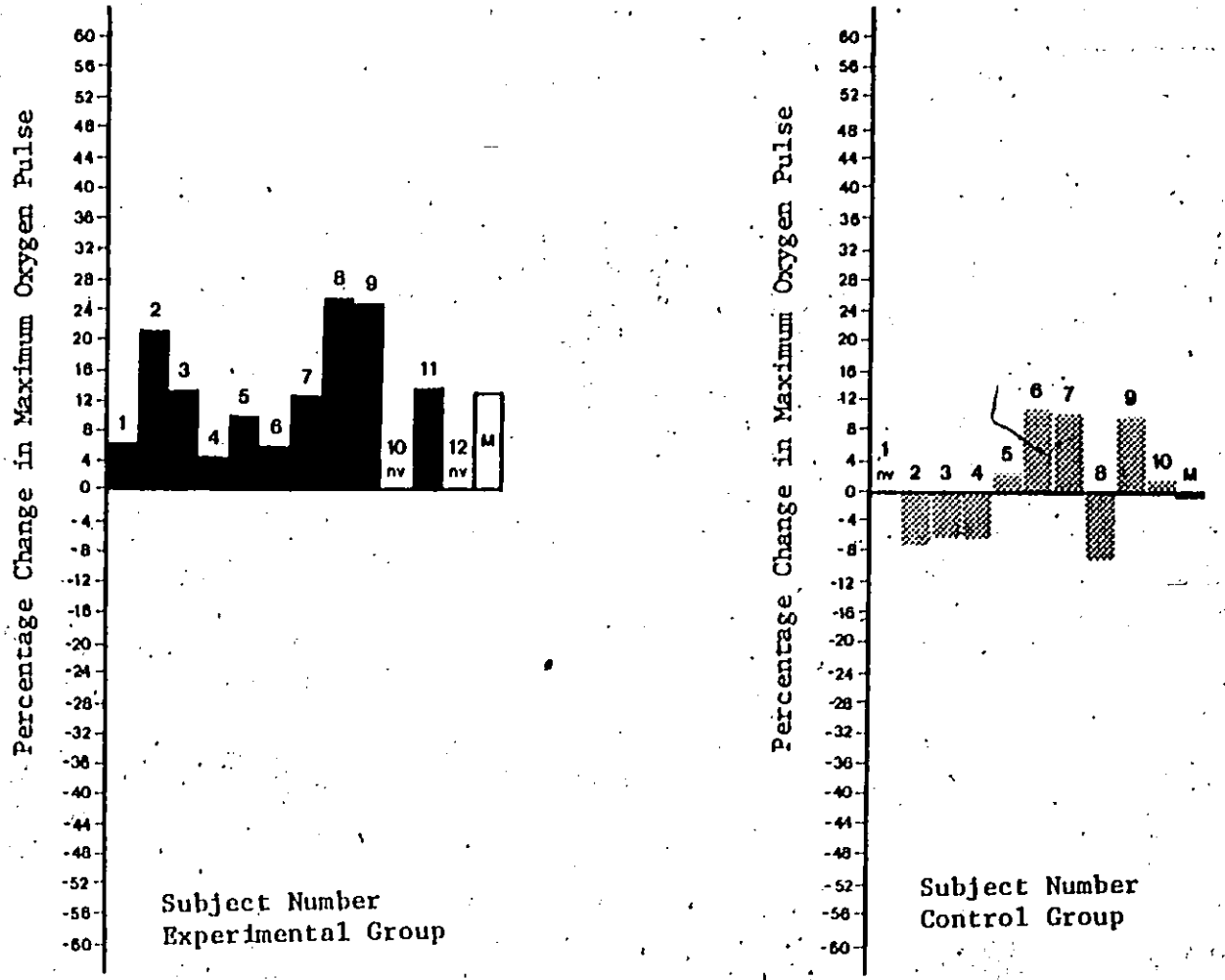


FIGURE 16 : Percentage Change in Maximum Oxygen Pulse

M=mean percentage change
nv = no value

experimental group (P<.77) during the study period as compared to the control group. Individual changes in HDL-cholesterol are outlined in Figure 4.

Total cholesterol decreased significantly (P<.025) in the experimental group as compared to the control group. Cholesterol was lowered an average of 23.8 mg% in the experimental group from 226.3 mg% to 202.5 mg%, while that of the control group rose slightly from 218.6 mg% to 222.9 mg%. Figure 5 outlines the individual changes noted for total cholesterol.

The ratio of HDL-cholesterol:total cholesterol increased significantly (P<.04) from .242 to .276 in the experimental group. This is compared to the ratio remaining quite stable in the control group at .266 and .260. The ratio of the experimental group indicates that 24.2% of their serum cholesterol was carried by HDL at the beginning of the study and this increased to 27.6% at the end of the study period. Individual changes in the ratio are shown in Figure 6.

LDL-cholesterol was estimated using the Friedwald Equation (supra page 10). LDL-cholesterol decreased significantly (P<.05) by 24 mg% in the experimental group, from 154.3 mg% to 130.3 mg%. This is compared to the LDL-cholesterol in the control group which increased slightly (4.1 mg%) from 138.6 to 142.7 mg%. LDL-cholesterol changes for each individual are represented in Figure 7.

Triglyceride levels for the experimental group were at the lower end of the normal range at the beginning of the study (normal fasting triglycerides 75-150 mg%). The decrease observed in

triglycerides for the experimental group over the study period from 90.5 mg % to 85 mg % was not significant ($P < .16$) when compared to the control group triglyceride values, which remained stable with a pre-training value of 113.4 mg % and post-training value of 114.8 mg %. The individual changes in triglyceride levels are indicated in Figure 8.

Physiological Variables:

Resting heart rate in beats per minute (b.p.m.) decreased in both groups by approximately the same amount, so a significant difference ($P < .69$) was not found between the post-training values of the two groups. Resting heart rate in the experimental group decreased from a pre-training heart rate of 71.7 b.p.m. to a post-training one of 64.3 b.p.m. The corresponding values for the control group were 71.2 b p m and 65.4 b p m. Figure 9 represents the individual changes in resting heart rate that occurred over the study period.

Percentage body fat remained stable in both groups. The experimental group demonstrated a 19.3 % body fat content, pre-training, and a 19.8 % body fat content, post-training. The corresponding values for the control group were 22 % and 23 %. Individual changes in percentage body fat are outlined in Figure 10.

Systolic blood pressure decreased 4.4 mm Hg in the experimental group, but this difference was not significant ($P < .83$) since it also decreased 5.4 mm Hg in the control group. Figure 11 shows the individual changes observed in systolic blood pressure.

Diastolic blood pressure decreased slightly but insignificantly ($P < .11$) in the experimental group as compared to the control group, from 73.8 mm Hg to 70.2 mm Hg. It remained stable in the

control group, with a pre-training value of 80.2 mm Hg and post-training value of 80.8 mm Hg. Figure 12 graphs the individual changes in diastolic blood pressure.

Exercise Performance Variables:

Maximum oxygen uptake (MVO_2) increased significantly in the experimental group as compared to the control group, when expressed in either litres per minute ($P < .02$) or millilitres per kilogram per minute ($P < .005$). MVO_2 increased .3 l/min from 2.8 to 3.1 l/min in the experimental group, but remained at 2.6 l/min in the control group. When expressed in ml/kg/min, MVO_2 increased 3.5 ml/kg/min from 36.0 to 39.5 ml/kg/min, while the control group MVO_2 remained stable (33.4 ml/kg/min, pre-training and 33.2 ml/kg/min, post-training). Figures 13 and 14 outline the individual changes in MVO_2 when expressed in l/min and ml/kg/min respectively.

Maximum carbon dioxide production ($MVCO_2$) increased .6 l/min in the experimental group from 3.1 to 3.7 l/min. $MVCO_2$ also increased .2 l/min from 2.9 l/min to 3.1 l/min in the control group, but the post-training value of the experimental group was still significantly different ($P < .04$) from that of the control group. Individual changes in $MVCO_2$ are graphed in Figure 15.

The increase in maximum oxygen pulse was highly significant ($P < .002$) in the experimental group, as it increased 2.1 ml/beat from 16.2 to 18.3 ml/beat. This is compared to maximum oxygen pulse in the control group, which remained static (15.2 ml/beat, pre-training, and 15.1 ml/beat, post-training). The changes observed in maximum oxygen pulse for each individual are outlined in Figure 16.

Section II: Correlations Relevant to the Study

Table X presents the correlation between HDL-cholesterol and total cholesterol, triglycerides, $\dot{M}VO_2$ (l/min and ml/kg/min) and percentage body fat: and between the HDL-cholesterol:total cholesterol ratio and triglycerides, $\dot{M}VO_2$ (l/min and ml/kg/min) and percentage body fat. Table X contains the pre- and post-training correlations and the correlations between the changes that took place in the variables during the course of the study for both the experimental and the control group. The number of subjects used in the various correlations differs since $\dot{M}VO_2$, in l/min and ml/kg/min, and $\dot{M}VCO_2$ values were not available for one subject (#12) in the experimental group and for one (#1) in the control group. Similarly, the values of these two individuals, as well as for one other person (#10) in the experimental group,were unavailable for maximum oxygen pulse.

Each correlation is expressed as a coefficient which represents a Pearson r value. A star (*) next to the coefficient indicates that the correlation is significant at a P level of $< .05$. Significance in a correlation does not necessarily indicate importance of that correlation, but rather that it is stastically different from zero. The significance of the correlation is largely dependent on group size, so correlations that have not been found to be significant should not necessarily be disregarded. Therefore, with the relatively small group size in this study, even relatively high correlations did not reach significance in some cases. However, non-significant trends were noted in the context of the existing literature. The relevance of these high but non-significant correlations nevertheless must remain questionable.

The relationship of HDL-cholesterol with total cholesterol for the exercise group was .26 pre-training, .07 post-training, and .18 for the change in the variables during the program. The correspon-

TABLE X

CORRELATIONS RELEVANT TO THE STUDY

VARIABLES	CORRELATION					
	Experimental Group			Control Group		
	Pre	Post	Difference	Pre	Post	Difference
HDL-cholesterol & total cholesterol	.26	.07	.18	-.35	.11	-.10
HDL-cholesterol & triglycerides	-.47	-.55	.12	-.66*	-.49	-.47
HDL-cholesterol & % body fat	-.33	-.17	.15	-.63*	-.80*	-.41
HDL-cholesterol & $M\dot{V}O_2$ (l/min)	-.07	.12	-.37	.33	.59	-.46
HDL-cholesterol & $M\dot{V}O_2$ (ml/Kg/min)	.08	.30	-.40	.56	.77*	-.38
HDL-cholesterol/total cholesterol & triglycerides	-.61*	-.52	.19	-.73*	-.72*	-.80*
HDL-cholesterol/total cholesterol & % body fat	.20	.12	-.02	-.79*	-.87*	-.57
HDL-cholesterol/total cholesterol & $M\dot{V}O_2$ (l/min)	.31	.17	-.29	.50	.45	-.33
HDL-cholesterol/total cholesterol & $M\dot{V}O_2$ (ml/Kg/min)	.04	.01	-.27	.75*	.71*	-.23

* significant at $P < .05$

ding correlations of the control group were -.35, .11 and -.10. None of these correlations demonstrated a strong relationship between HDL-cholesterol and total cholesterol.

The correlations of HDL-cholesterol with triglycerides in the experimental group were -.47, -.55 and .12 for the pre-training and post-training values, and for the change in the variables during the study. The correlations of the pre-training and post-training values for the control group were in a similar range (-.66 and -.49, respectively), but the correlation of the way in which HDL-cholesterol changed with respect to the direction and magnitude of the triglyceride change was -.47, which differs from that found in the experimental group. The pre-training correlation of -.66 in the control group was significant.

The HDL-cholesterol and percentage body fat correlations in the experimental group were -.33 and -.17 for the pre-training and post-training values. The same correlations in the control group were stronger (-.63 and -.80) and were statistically significant. The correlations between the way in which HDL-cholesterol changed with respect to the change in percentage body fat were .15 for the experimental group and -.41 for the control group.

HDL-cholesterol and maximum oxygen uptake (l/min) demonstrated a -.07 and .12 correlation for the pre-training and post-training values in the experimental group. These correlations in the control group were .33 and .59. The correlation of the change in HDL-cholesterol and the change in MVO_2 (l/min) was -.37 for the experimental group and -.46 for the control group. When MVO_2 was expressed in ml/Kg/min, the pre-training and post-training correlations for the experimental group were .08 and .30. These values were .56 and .77 for the control group. The post-

training correlation of .77 was significant. The correlations between the changes in HDL-cholesterol with the changes in MVO_2 (ml/kg/min) were -.40 for the experimental group, and -.38 for the control group.

The correlations of HDL-cholesterol : total cholesterol ratio with triglycerides for the experimental group were -.61, -.52 and .19 for the pre-training and post-training values and for the changes that occurred over the study period, respectively. The corresponding correlations for the control group were -.73, -.72 and -.80. The pre-training correlation of -.61 in the experimental group and all three correlations in the control group were significant.

The ratio demonstrated a correlation with percentage body fat, in the experimental group, of .20, .12 and -.02, for the pre-training and post-training values and for the changes observed over the study period, respectively. In the case of the control group, correlations were -.79, -.87 and -.57. The pre- and post-training correlations of the control group were significant.

The correlations of the ratio and MVO_2 in l/min for the experimental group were .31 for the pre-training values, -.17 for the post-training values, and -.29 for the changes in the variables that took place. In the control group, the correlations were .50, .45 and -.33.

When MVO_2 was expressed in ml/kg/min, its correlation with the ratio in the experimental group was .04, .01 and -.27 for the pre- and post-training values and for the changes in the variables. The same correlations in the control group were .75, .71 and -.23. The pre- and post-training correlations of the control group were significant.

Section III: Daily Dietary Composition, Dietary Adherence, Smoking and Exercise Habits, and Prescription Medication

Analysis of Daily Dietary Composition:

The results of the analysis of the pre- and post-training seven day dietary reports are contained in Tables XI A and XI B. Table XI A contains the pre- and post-training dietary intake of cholesterol, carbohydrates, total fat, unsaturated and saturated fat, protein, and alcohol, expressed in grams or milligrams consumed per day. Table XI B also contains the pre- and post-training intake of the above-mentioned dietary components, but in this case their dietary composition is expressed as a percentage of the total daily caloric intake. Table XI B also lists the total daily caloric intake, as well as the ratio of poly-unsaturated to saturated fat.

Since there was a poor return of the post-program dietary reports (2 out of 10) in the control group, it was not possible to determine if there were any changes in their dietary habits over the study period, so only the diets of the experimental group were analyzed. Of the two diets returned in the control group, the pre- and post-training daily dietary composition appeared to be very similar, but this is speculative as a statistical analysis could not be carried out. In the experimental group, there were seven subjects who returned both their pre- and post-training dietary reports (subjects #1,3,7,8,9,11 and 12).

The mean of the pre- and post-training values for each dietary component analyzed is given in Tables XI A and XI B, along with the

TABLE XI A

ANALYSIS OF DAILY DIETARY COMPOSITION

(expressed in grams or milligrams consumed per day)

	TOTAL CHOLES-TEROL		TOTAL CARBO-HYDRATE		TOTAL FAT		TOTAL UNSATUR-ATED FAT		TOTAL SATUR-ATED FAT*		TOTAL PROTEIN		TOTAL ALCOHOL	
SUBJECT NUMBER	mgs/day		gms/day		gms/day		gms/day		gms/day		gms/day		gms/day	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1 (#1)	168	138	117	161	73	67	14	17	57	49	85	64	0	2
2 (#3)	317	292	215	172	68	59	6	3	58	44	82	101	8	9
3 (#7)	181	206	208	181	68	57	8	12	61	45	88	61	3	27
4 (#8)	316	313	219	192	80	75	6	6	73	69	110	98	7	10
5 (#9)	233	326	150	99	49	62	3	8	46	55	66	64	35	8
6 (#11)	537	381	139	158	51	48	4	3	47	45	73	63	20	32
7 (#12)	391	427	203	188	121	93	30	15	88	75	175	145	1	0
MEAN	3062	2928	1784	1646	729	645	100	92	614	544	970	852	106	123
STANDARD DEVIATION	±130	± 99	± 42	± 32	± 24	±15	±9	±6	±15	±13	±37	±32	±13	±12
SIGNIFICANCE LEVEL	not sig-nificant		not sig-nificant		not sig-nificant		not sig-nificant		not sig-nificant		not sig-nificant		not sig-nificant	

* also includes monounsaturated fats

TABLE XI B

ANALYSIS OF DAILY DIETARY COMPOSITION

(expressed as a percentage of the total calories consumed per day and as a ratio of polyunsaturated to saturated fat*)

	TOTAL CALORIES		PERCENTAGE CARBOHYDRATE		PERCENTAGE FAT		PERCENTAGE UNSATURATED FAT		PERCENTAGE SATURATED FAT*		PERCENTAGE PROTEIN		PERCENTAGE ALCOHOL		RATIO OF UNSATURATED TO SATURATED FAT	
SUBJECT NUMBER	Kcal/day		% of total Kcal/day		% of total Kcal/day		% of total Kcal/day		% of total Kcal/day		% of total Kcal/day		% of total Kcal/day			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1 (#1)	1461	1467	33	46	47	43	9	11	37	31	33	25	0	1	.24	.36
2 (#3)	1812	1590	49	45	35	29	3	1	30	26	25	36	3	4	.10	.08
3 (#7)	1798	1882	48	40	36	29	4	6	32	23	28	18	1	10	.13	.26
4 (#8)	2059	1869	44	43	37	37	3	3	33	35	30	30	2	4	.08	.09
5 (#9)	1552	1074	40	38	30	54	2	7	28	48	24	34	16	5	.06	.14
6 (#11)	1487	1539	39	43	32	29	3	2	30	28	28	23	9	14	.09	.06
7 (#12)	2548	2120	33	37	45	41	11	7	32	33	39	39	3	0	.34	.20
MEAN	18168	16485	41.0	41.5	323	326	40	52	317	318	296	291	5	5	.15	.17
STANDARD DEVIATION	±387	±343	±7	±3	±6	±9	±3	±3	±3	±8	±5	±7	±6	±5	±.10	±.11
SIGNIFICANCE LEVEL	not significant		not significant		not significant		not significant		not significant		not significant		not significant		not significant	

* also includes monosaturated fats

standard deviations from the mean, and the presence of any significant differences between the pre- and post-training values.

The daily cholesterol intake before the study was 306.2 mg and 297.8 mg afterwards. The mean daily carbohydrate content was 178.6 gms at the beginning and 164.6 gms at the end of the study, which was equivalent to 41.0% and 41.5% of the total daily caloric intake, respectively. Total fat intake per day was 72.9 gms, pre-training, and 64.5 gms, post-training. This represents a daily fat intake that made up 37.3% and 37.6% of the total calories. Unsaturated fat intake was 10 gms/day before the study and 9.2 gms/day afterwards, corresponding to 4.9% and 5.2% of the total calories. Saturated fat intake was 61.4 gms/day before and 54.4 gms/day after the training period, which was equivalent to 31.7% and 31.8% of the daily caloric intake. Protein intake, pre-training, was 97 gms/day and 85.2 gms/day, post training. Protein comprised 29.6% and 29.1% of the total calories consumed per day. Alcohol intake was 10.6 gms/day before and 12.3 gms/day after the study. Both of these amounts represented 5% of the total daily caloric intake. The total daily caloric intake was 1817 Kcal/day initially, and 1649 Kcal/day at the end of the study. The ratio of unsaturated to saturated fat was .15, pre-training, and .17, post-training. The ratio is an underestimate since often the polyunsaturated fat content of the food was not listed. None of the dietary components were found to have changed significantly over the course of the study, as indicated in Tables XI A and B, when the P level was set at $<.05$.

Dietary Adherence
Smoking and Exercise Habits
and Prescription Medication:

Of the questionnaires (Appendix A) returned for this section, twelve out of twelve subjects in the experimental group completed both pre- and post-training questionnaires. This was the case for seven out of ten subjects in the control group.

Dietary Adherence:

Dietary composition was covered in the previous section, but the subjects were also required to give a subjective analysis of their dietary composition and adherence. As indicated by the questionnaire responses, the dietary composition was not reported to have changed for the majority of the subjects in the experimental and control groups. One subject (#2) in the experimental group had begun a low calorie and low sugar diet 3½ weeks before the end of the study period. This subject did not return his post-training daily dietary record, so confirmation of this change was not possible. One subject (#6) in the experimental group had returned to a low cholesterol diet one week prior to the beginning of the program. In the control group, two subjects (#5 and #8) indicated that they were following a low sugar diet, only in the post-training questionnaire. Dietary adherence in both groups did not change over the study period.

Smoking Habits:

In the experimental group, smoking habits did not change during the training period. One subject (#3) had ceased smoking four months prior to the inception of the study. In the control group, one

subject (#8) increased his cigarette consumption by 15 cigarettes per day. Two subjects (#2 and #10) in the control group also reported that they had stopped smoking cigarettes 2-3 weeks before the beginning of the study.

Exercise Habits:

In the experimental group, there were no changes in exercise habits other than those implied by the training program. In the control group, subject #1 indicated that he had increased his degree of physical activity from the pre-training level by adding 30 minutes of tennis and 40 minutes of fast walking to his weekly exercise routine. Unlike two other subjects in the control group, who were excluded from the study since they reported on the post-training questionnaire that they had begun an intensive training program during the study period, this subject (#1) was still included as it was decided that the extent of the increase in his training was not great enough to necessitate the exclusion of his data from the results. A change in his aerobic capacity could not be determined since he could not complete the post-training test due to a back problem.

Prescription Medication:

In the experimental group, the medication of subject #9 had been changed from Inderal, Donnatol and Diovol to Progethyroxin. Subject #11 began Allopurinol therapy and subject #12 began to take Motrin therapy during the training period. In the control group, subject #3 was taking Zyloprim at the beginning of the study but had ceased

taking it at the end. The prescription of subject-#4 had been changed from Inderal to Beminal during the study period.

CHAPTER V

DISCUSSION

The endurance training program administered in this study demonstrated a chronic effect on several of the variables measured. Exercise was accompanied by an increase in maximum aerobic capacity (expressed in l/min and ml/kg/min),maximum carbon dioxide production, maximum oxygen pulse and an increase in the HDL-cholesterol:total cholesterol ratio. It decreased total cholesterol and LDL-cholesterol. HDL-cholesterol, total triglycerides and percentage body fat were not significantly changed. A lack of change was also seen in resting heart rate, systolic blood pressure and diastolic blood pressure.In the present study, unlike many other studies of the chronic effect of aerobic exercise on biochemical variables, the efficacy of the treatment (i.e. the aerobic training program) was determined and found to have been significant since the aerobic capacity of the experimental group increased while that of the control group remained unchanged. This measurement allows one to more directly relate the changes that accompanied the treatment to an increase in aerobic fitness and avoids the possibility that the treatment failed to produce the desired effect. But, noting that aerobic capacity has increased does not immediately allow one to assume that this change in aerobic fitness is the sole cause for the changes obesrved in the biochemical variables since other factors such as changes in diet,dietary adherence,exercise outside of the treatment period,smoking habits or prescription medication

could also have effected the results. It is desirable, consequently, to check these factors as well. In the present study there were very few changes in dietary adherence, exercise habits, smoking habits or prescription medication during the study period in either group and there did not appear to be a definite relationship between the few changes that occurred in these factors with the changes observed in the biochemical parameters. In reference to dietary changes, the dietary intake of the experimental group, whether expressed in absolute amounts or as a percentage of the total caloric intake, did not change significantly over the study period, so it is unlikely that the changes observed in the biochemical variables are attributable to changes in diet alone. Such a conclusion is dependent upon the following assumptions: 1) that the diets of the seven experimental subjects who returned both pre- and post-study diets were representative of the diets of all twelve subjects in this group; 2) that, since the dietary changes of the control group could not be assessed due to a poor return of their dietary records, a seasonal variation in one of the biochemical variables was not masked by a consistent change in the diets of the control group in such a way as to obviate the appearance of a seasonal change. Furthermore, the use of a control group was necessary in order to reflect the normal seasonal variations that may occur in the parameters measured. Its use in this study is dependent on the assumption that the displacement of time of one month between the procurement of the blood samples of the experimental group and of the control group did not affect the ability of the control group to reflect the normal seasonal variations of the biochemical parameters for both groups. Reports of the seaasonal variation over the periods of 1) March 1 to April 1, 2) June 1 to July 1, and 3) March-April to June-July show very little variation in total cholesterol (Warnick&Albers,1976).

According to the same report, (Warnick & Albers, 1976), there is also little seasonal variation in triglycerides for the periods of March 1 to April 1 and June 1 to July 1. There is a seasonal decrease in triglycerides over the March-April to June-July period but this decrease would be seen in both groups. In the case of the seasonal variations of HDL-cholesterol, samples obtained from a Danish population at the beginning of March were slightly higher than those obtained at the beginning of April (+3.5 mg %)(Van Gent, et al, 1978). Conversely, HDL-cholesterol was 2 mg% lower in samples obtained at the beginning of June than those taken at the beginning of July. There was also a seasonal increase from the March-April to the June-July period but, as in the case of triglycerides, this increase would have occurred in both groups. Therefore, it is unlikely that the one month displacement in sampling times between the experimental and control group would have greatly affected the results.

Total Cholesterol

The decrease in total cholesterol observed here reflects the findings of several other studies that attempted to determine the chronic effect of endurance exercise on total plasma cholesterol. Not only was the response of total cholesterol similar in direction of change, but the magnitude of change was similar to that seen in several studies as well. Notably, in the studies that reported a similar percentage reduction, initial cholesterol levels were in the same range as the levels in this study. In the present study, total cholesterol fell 10.5% (from 226.3 mg% to 202.5 mg%) which is similar to the reduction recorded by Altekruse & Wilmore (1963)(10% decrease, from 224 mg% to 201 mg%), Rochelle et al. (1961)(11% decrease, from 203 mg% to 181 mg%),

Campbell et al (1966)(12% decrease, from 213 to 195 mg%, and Campbell (1965) (11% decrease, from 180 mg% to 161 mg%). In studies where a greater degree of reduction was observed, the initial plasma cholesterol levels were generally higher as seen in the studies of Golding (1961) (26% decrease, from 342 mg% to 253 mg%) and Naughton & Balke (1964)(20% decrease,from 260 mg% to 210 mg%). The findings of a similar degree of reduction occurring in subjects with similar initial cholesterol levels appears to support the previous suggestion (see chapter II, p. 67) that the extent of cholesterol reduction following an endurance exercise program may be positively related to the initial cholesterol level. Unlike many of the training studies which failed to account for other possible confounding factors, it is unlikely that in this study the reductions observed were due to weight loss, change in diet or seasonal fluctuation. Such is the case since 1) the subjects didn't lose weight or decrease their percentage body fat, 2) the pre and post-program diets were not significantly different and 3) a control group was utilized whose total cholesterol did not change over the study period.

The mechanism whereby endurance exercise effects a reduction in plasma cholesterol is generally not known. Some studies have suggested that the decrease is due to the increased output of cholesterol and bile acids into the bile and the increase in bile flow which is seen during acute but prolonged endurance exercise in rats (Malinow et al,1972) and in humans (Simko and Kelley, 1979). Since bile acids are reabsorbed much more readily than cholesterol, Simko (1978) states that cholesterol, but not necessarily bile acids, would be lost to the feces as a result of and during regular exercise. Due

to the increased bile acid output and bile flow during exercise as well as its rapid reabsorption, it is thought that there would be an increase in the number of circulations of the bile acid pool which would inhibit the hepatic and intestinal biosynthesis of cholesterol. Such an explanation of a reduction in cholesterol synthesis would only be possible if the cholesterol returning with the increased number of circulations is adequate, since a low return of cholesterol in the bile acids to the liver would stimulate hepatic cholesterol synthesis. Also, an increased return of bile acids to the liver could inhibit the hepatic synthesis of more bile acids from cholesterol unless there was also an accompanying increase in the loss of bile acids to the feces. Simko (1978) goes on to suggest that a decrease in plasma cholesterol could be due not only to a decrease in hepatic synthesis but also a decrease in the absorption of exogenous cholesterol. To provide support for the various mechanisms suggested, Simko (1978) notes that as a result of chronic endurance exercise in rats, in the resting state, there is a decrease in biliary and hepatic cholesterol, a decrease in adipose and red blood cell cholesterol and no change in bile acid concentration in the bile. The decrease of adipose and red blood cell cholesterol is considered to be indicative of an increase in cholesterol transport from the periphery, while the decreased hepatic concentration suggests that exercise promotes hepatic cholesterol catabolism. In humans, a decrease in red blood cell cholesterol has also been observed as a result of acute endurance exercise (Simko & Kelly, 1979). One cannot exclude the possibility, though, that these observations indicate the converse i.e. that a decrease in cellular cholesterol uptake and a decrease in the synthesis of hepatic cholesterol could have occurred .

But, one would tend to favour the previous suggestion of an increase in cellular cholesterol loss since exercise can promote the utilization of fatty acids from adipocyte stores and it has been demonstrated that the cholesterol is removed concomitantly as triglycerides are lost from adipocytes during calorie-restricted regimens (Nestel & Miller, 1978). To substantiate this suggestion, it is notable that an increase in peripheral cholesterol transport has been related to the enzyme LCAT and to HDL (Glomset, 1968) and both increase with endurance exercise (Lopez-S, et al, 1974). Interestingly, the cholesterol lost from adipose tissue during weight reduction was carried largely by HDL (Nestel & Miller, 1978). From these observations, it may be the case that HDL and LCAT are intricately related to the peripheral effect of endurance exercise on total body cholesterol, although the evidence is hypothetical.

An alternative explanation for the reduction of plasma cholesterol and increased bilary cholesterol output during exercise has been put forth by Simko (1978) that these effects may be related to the decrease in splanchnic blood flow that occurs during moderate to severe exercise since it may increase the efficiency of transport (i.e. the extraction ratio) of substrates from the sinusoids to the hepatocytes. This may occur because each blood component remains in contact with the hepatic sinusoids for a longer period, resulting in a more complete extraction of bile acids and cholesterol from the blood. An increased extraction would inhibit hepatic cholesterol synthesis and increase the biliary output of bile acids and cholesterol during the exercise period.

Such suggested mechanisms are interesting but it is probable that there are various other chronic effects of endurance exercise that

may also play a role in the reduction of plasma cholesterol by reducing its hepatic synthesis, increasing its peripheral removal or increasing its catabolism and output.Possibly there is a hormonal effect since growth hormone and thyroxine have been found to decrease plasma cholesterol (Dugan & Porter,1977) and growth hormone and thyroxine both rise during prolonged endurance exercise and remain elevated for some time afterward (Terjung & Tipton,1971;Hartley et al,1972). Glucocorticoids and glucagon also rise with exercise (Bottger et al,1971;Hartley et al,1972) and they have been found to inhibit hepatic cholesterol synthesis (Dugan & Porter,1977).Exercise reduces plasma insulin (Hartley et al,1972) and insulin has been found to stimulate hepatic cholesterol synthesis (Dugan & Porter,1977). On the other hand,catecholamines,which stimulate hepatic cholesterol synthesis (Dugan & Porter,1977)also increase with exercise (Hartley et al,1972). It should be noted that the individual contributions of these hormones to overall cholesterol metabolism,as well as their interplay,have not been thoroughly elucidated. Finally,an increase in the formation of remnant particles(with a concomitant. increase in HDL,according to Tall and Small [1978],due to elevated levels of LPL with endurance exercise(Nikkila et al,1978A),would also result in an increased rate of inhibition of hepatic cholesterol synthesis (Anderson et al,1979)

A reduction in total cholesterol may be due to a combination of the previously stated mechanisms.In some cases it may also be due to weight loss and a negative caloric balance that can be a result of exercise,although this is not the case in the present study or in that of Lopez-S et al (1974) or that of Campbell(1966). Generally,the mechanisms behind the exercise-induced decrease in total plasma cholesterol remains unclear.

The initial cholesterol levels of the subjects in this study were in the normal range since,although previously classified as hypercholesterolemics, their cholesterol levels were well under control.But it should be remembered that

a cholesterol level of 226 mg% carries with it a certain degree of risk since the relationship of CHD with plasma cholesterol is one that is effective over a continuum of values (Gotto, 1979; Kannel et al, 1979). Consequently, the reduction seen in this study from 226.3 mg% to 202.5 mg%, which is similar to the degree of reduction that often accompanies dietary management (Gotto, 1979), is considered to be a more desirable level than the initial one with respect to CHD risk. Actually, an even further reduction would probably be beneficial since it has been suggested that the plasma cholesterol levels which we define as "normal" in the Western countries are well above the optimal levels (Cooper, 1979). Cooper (1979) has stated that optimal plasma cholesterol would be less than 180 mg% and refers to the fact that animals with low plasma cholesterol are relatively resistant to the natural as well as the experimental development of atherosclerosis. In terms of reducing plasma cholesterol to our presently-defined normal levels, one wonders if chronic aerobic exercise, which in this study reduced plasma cholesterol by an amount similar to that achieved by a cholesterol-lowering diet (Gotto, 1979), could substitute for part of the dietary control and therefore lessen the severity of the dietary regime. Or, on the other hand, possibly a combination of endurance exercise and diet could have an additive effect on plasma cholesterol that would be great enough so as to remove the requirement for cholesterol-lowering drugs.

LDL-Cholesterol

The LDL-cholesterol values were arrived at by a calculation rather than by a direct measurement and the calculation

assumes that VLDL-cholesterol is approximately equal to total triglycerides divided by five. Such values must be considered with somewhat more caution than those of the other blood lipids that were measured directly. Nevertheless, the calculation for LDL-cholesterol has been reported as being quite reliable for subjects whose triglyceride levels fall in the normal range. (Friedwald et al, 1972). The significant decrease in LDL-cholesterol from 154.3 mg% to 130.3 mg% agrees with the observations that LDL-cholesterol and total cholesterol are highly positively correlated (Castelli et al, 1977A), and with the findings that LDL-cholesterol also decreases with endurance training when total cholesterol falls (Altekruse & Wilmore, 1973; Lopez-S et al, 1974; Roundy et al, 1978). The fall in total cholesterol in this study, as in others, was therefore specific to the LDL fraction since HDL-cholesterol did not change significantly. The mechanism behind the specificity for the cholesterol-carrying lipoprotein (i.e. LDL rather than HDL) that is reduced with an exercise-induced decrease in total cholesterol is unknown. This specificity may be related to the factors that have been postulated to be responsible for the increase in HDL-cholesterol that is often seen with endurance training and which occurs even when total cholesterol is reduced.

Total Triglycerides

Total triglycerides did not change significantly. Triglycerides are often reduced by endurance exercise but the greatest reduction is said to occur in subjects whose triglyceride

levels are high to begin with (Wood et al, 1976). In the present study the subject's initial triglyceride levels were in the low to middle level of the normal range,so they may not have been as responsive to the stimulus imposed by the endurance exercise program. Triglyceride reductions were seen by Lopez-S et al (1974) (from 110 mg% to 83 mg%), Roundy et al (1978) (Type IIA decreased 29 mg%; Type IV decreased 105 mg%), Leon et al (1976) (from 165 mg% to 144 mg%) and Webster et al (1978) but were not observed in the studies of Erkelens et al (1978)(stable at 178 mg%),Lewis et al (1976)(from 89 mg% to 97 mg%), Ratliff et al (1978)(from 97 mg% to 84 mg%) and Roundy et al (1978)(normals decreased, nonsignificantly, 7.2 mg%). The initial triglyceride levels in this study were similar to those of Lewis et al (1976) and Ratliff et al (1978). The non-significant variation observed in the study of Ratliff and co-authors (1978) was very similar to the one observed in the present one (from 90.5 mg% to 85 mg%). The mechanism behind the reduction in triglycerides seen with endurance training is thought to be due to an increased utilization of hepatic fatty acids as a result of the exercise with a consequent decrease in the synthesis of hepatic triglycerides (Lopez-S,1976). A triglyceride reduction with exercise may also be related to weight loss, as is the case for plasma cholesterol, in some studies. But the exercise effect cannot solely be due to this factor since Lopez-S et al (1974) and Webster et al (1978) observed a triglyceride decrease in the absence of or irrespective of weight loss, respectively. An increase in triglyceride catabolism,with or without changes in synthesis, would also cause a decrease in plasma triglycerides and

this may be occurring with endurance exercise due to the observed increase in the activity of the enzyme Lipoprotein Lipase (LPL) (Nikkila, 1978). Such an increase in LPL has been recorded in both the adipose tissue and skeletal muscle of long distance runners (Nikkila, 1978; Nikkila et al, 1978A).

HDL- Cholesterol

HDL-cholesterol levels remained stable. HDL-cholesterol varied insignificantly from 53.6 mg%, pre-training, to 55.3 mg%, post-training. There was a greater increase seen in some subjects (subjects #6,7,9,11 increased their HDL-cholesterol by 7.9 mg%, 8.4 mg%, 7.9 mg% and 9.5 mg%, respectively) which may indicate a trend toward a HDL-cholesterol elevation but possibly the intensity or total exercise volume wasn't adequate enough for all subjects to demonstrate such an effect(see Figure 4). Most endurance training studies did find an increase in HDL or HDL-cholesterol (Altekruse & Wilmore, 1973; Lopez-S et al , 1974; Leon et al , 1977; Erkelens et al , 1978; Gilliam et al , 1978; Ratliff et al , 1979; Roundy et al , 1978). The findings of the present study are similar to those of Lewis and co-authors (1976) who found that the change in HDL-cholesterol from 49.8 mg% to 54.5 mg% was not significant, but the HDL-cholesterol: LDL-cholesterol ratio (HDL-C/LDL-C) was significantly increased. In the present study, the HDL-cholesterol change was also non-significant while the HDL- C:Total-C ratio did increase significantly. The HDL-cholesterol:LDL-cholesterol ratio was not determined since LDL-cholesterol values were derived from a calculation and total cholesterol supplied similar information

HDL demonstrates an interesting response to endurance training in that total cholesterol is often reduced but HDL-cholesterol not only remains stable, as it did in this study, but actually increases (see Chapter II, p. 81). The present study is most similar in design to that of Ratliff et al, (1978), although it is impossible to compare the specifics of the training intensities utilized, since Ratliff did not record the method of exercise prescription nor the extent of the increase in MVO_2 that resulted from the training program. But, though the studies are similar, Ratliff did observe a significant increase in HDL-cholesterol from 42 mg% to 50 mg% while the control group varied from 43 mg%, pre-training, to 41 mg% post-training. In the present study, the comparable HDL-cholesterol levels of the control group were 57.3 and 57.2 mg%. The absence of a significant increase in HDL-cholesterol in this study may be due to several factors, the major ones being:

1. Initial HDL-cholesterol levels were relatively high.
2. The total exercise volume of the exercise was not adequate.
3. Total triglycerides were not significantly reduced.
4. Percentage body fat was not significantly reduced.

1. As HDL-cholesterol was relatively high to begin with, it may have been less amenable to change than a lower level would have been. Most training studies that found an increase recorded initial HDL-cholesterol levels that were in the lower ranges, i.e. 42 mg% (Ratliff et al, 1978), 32 mg% (Leon et al, 1977), 30 mg% (Gilliam & Burke, 1978) and 35 mg% (Erkelens et al, 1978). Calculating HDL-cholesterol from the values given for total cholesterol, triglycerides and LDL-cholesterol, in the study of Lopez-S and co-authors (1974), results in an initial HDL-cholesterol level of 43 mg%. In the studies that did not find a significant

change, the initial levels were higher, i.e. 49.8 mg% (Lewis et al, 1976) and 48.7 mg% (approximately) (Webster et al, 1978). These levels are closer to the initial HDL-cholesterol level of the experimental group of 53.6 mg% in the present study, which is somewhat higher than the average levels reported for white North American males (Castelli et al, 1977A).

But a lack of response of HDL to the training program cannot be simply due to a lack of malleability of the relatively high initial levels of HDL-cholesterol, since it fails to explain the extremely high levels of HDL-cholesterol (greater than 60 mg%) frequently observed in long-distance runners and cross-country skiers (Wood et al, 1976; Martin et al, 1977; Wood et al, 1977; Lehtonen & Viihari, 1978A). It would appear, as suggested by Webster and colleagues (1978), that a training threshold may exist for HDL-cholesterol so that, as one works with higher and higher initial levels of HDL-cholesterol, it is necessary to impose a greater demand, in terms of exercise volume, in order to observe an exercise-induced elevation in HDL-cholesterol with training. This leads into the second possible explanation for the lack of change in HDL-cholesterol seen in this study, i.e. that the total exercise volume was insufficient.

2. Therefore, the overall exercise volume may not have been adequate to elicit a demonstrable elevation in HDL-cholesterol. This suggestion is based on Lehtonen and Viihari's (1978A) observation that the HDL-cholesterol of young males who ran less than 25 kilometres per week (15 miles) was not significantly different from that of the older sedentary men. In the present study, the subjects only ran an average of 12 kilometres per week (7.5 miles) at the end of the training period, with a maximum of 16.7 kilometres per week (10 miles) (subject #4).

Also, Lehtonen and Viihari (1978A) noted that consistent and obvious elevations in HDL-cholesterol in the group of long distance runners and skiers were only apparent when the number of kilometres ran or skied per week exceeded 70 (43 miles). Yet, despite these observations of Lehtonen and Viihari (1978A), in other studies that did find an increase in HDL-cholesterol and where the number of miles covered per week could be calculated, HDL-cholesterol was elevated when the number of miles run per week varied from 5.6 (9 km) (Altekruse & Wilmore, 1973) and 4.1 to 7.6 (6.8 to 12.7 km) (Roundy et al, 1978) to 24 (40 km) (Leon et al, 1977). Of course it is not only the distance covered that would be important but also the total duration, frequency, duration of each session and the intensity of the exercise that must be considered and this is why the term exercise volume was referred to. It is difficult to separate these various components since one component can only be compared across several studies if the other components are equalized — exercise intensity in particular — which is not the case since all these components vary throughout the studies and the intensities are not always possible to assess. Therefore, the following comments in the contribution of the individual exercise components to elevations in HDL-cholesterol must be considered to be general and only inferential.

Total duration does not appear to be directly related to elevations in HDL-cholesterol, since Webster et al (1978) saw no change after 12 weeks and Lewis et al. (1976) observed a non-significant increase after 17 weeks, yet HDL-cholesterol increased significantly after 7 weeks (Lopez-S et al, 1974) and after 10 weeks (Altekruse & Wilmore, 1973; Roundy et al, 1978).

This lack of a direct relationship with HDL-cholesterol elevations may also apply to exercise frequency, since Webster et al, (1978) found no change in HDL-cholesterol while Erkelens et al, (1978), Ratliff et al, (1978) and Roundy et al, (1978) did find an increase, yet all four studies exercised their subjects three times per week.

The duration of each session does not seem to be directly related either, since the subjects of Webster et al, (1978) exercised for 45 minutes per session and demonstrated no increase in their HDL-cholesterol while the studies that observed an increase had exercise sessions that were of the same length (Erkelens et al, 1978) or of even shorter duration (Lopez-S et al, 1974; Roundy et al, 1978). The difficulty in the interpretation of the duration of the various exercise sessions lies in the fact that the amount of the total time spent on the endurance exercise component is not always clarified (Erkelens et al, 1978; Webster et al, 1978).

Exercise intensity is perhaps the most important factor in relation to the effect of physical training on blood chemistries. This is particularly true in the case of the blood lipids since the type of metabolism utilized by a particular exercise can be very important in determining the effect it will have on these lipids. For example, an anaerobic training program had no effect on plasma cholesterol (Johnson & Wong, 1961; Campbell, 1965) and HDL-cholesterol was not elevated in sprinters whose training program was largely anaerobic (Nikkila et al, 1978A). HDL-cholesterol was elevated in those athletes who had a heavy endurance component as the major part of the training program (Enger et al, 1976; Wood et al, 1976; Martin et al, 1977; Wood et al, 1977; Lehtonen and Viihari, 1978A; Nikkila et al, 1978A).

Therefore, in the case of HDL-cholesterol, it seems that an endurance - type of training program is a very important factor in the exercise-induced elevation of HDL-cholesterol. All of the training studies reviewed appear to utilize such a program type, except for that of Widhalm et al(1978) whose type of program could not be determined. The idea of an "intensive training program" as indicated in the study of Lopez-S et al(1974),who observed the greatest increase in HDL-cholesterol and in the HDL-cholesterol/total cholesterol ratio, must also be considered but a specific intensity could not be determined from their description of the training program. The program appeared to be largely aerobic but high in intensity which may provide a clue to the exercise prescription required to elevate HDL. The problem, with respect to determining the intensity of the endurance activity required to elevate HDL, lies in the fact that it is impossible to compare the intensities from study to study, since the description of the exercise intensities prescribed ranged from moderately clear (Lewis et al,1976) to non existent (Erkelens et al,1978; Ratliff et al,1978; Widhalm et al,1978).

Therefore, conclusions concerning the total exercise prescription required to elevate HDL-cholesterol are rather difficult to make, at present, particularly in reference to the specific intensity and total work accomplished per week. Nevertheless, it seems probable that an increase in the general exercise volume (i.e. a combination of an increase in the total duration and an increase in intensity) beyond that utilized in the present study, but staying within the confines of an endurance - type of training program, would be advisable in order to demonstrate an exercise-induced elevation in HDL-cholesterol. This would increase the total work accomplished per week (and aerobic capacity) which would tie in with the results of the study of Lehtonen and Viihari (1978A).

3. Triglycerides were not significantly reduced by exercise, which may be another factor behind the lack of a demonstrable change in HDL-cholesterol.

The reason for such a suggestion is due to the recent interest and subsequent theories on the role of HDL in triglyceride metabolism. As previously described (see Chapter II, p.38), HDL metabolism appears to be intricately involved in that of VLDL and chylomicrons, especially during the process of lipolysis of their core triglycerides. For these triglyceride-rich lipoproteins, the triglyceride breakdown is dependent on the presence of the enzyme Lipoprotein Lipase (LPL) which uses Apo C-II as a cofactor (Apo C-II is an apoprotein of VLDL, chylomicrons and HDL). LPL catalyzes the breakdown of triglycerides to mono and diacyl glycerols with the release of fatty acids to the cells and plasma. During triglyceride lipolysis, it appears that HDL receives the surplus surface fragments which include mainly Apo C-II, phospholipid and free cholesterol. It has been suggested that these surface fragments may not only contribute to the formation of mature plasma HDL (Tall & Small, 1978) but may actually represent the origin of some, the majority or all of the plasma HDL (Eisenberg et al, 1978). The fragments may also affect the HDL subfraction distribution (Eisenberg, 1978). Therefore, HDL levels should be positively related to LPL levels since an increase in LPL would increase the catabolism of the triglyceride-rich lipoproteins, resulting in an increase in the rate of formation of plasma HDL. In many cases, such a positive relationship has been observed, in that LPL was found to be elevated in: females as compared to males; long-distance runners as compared to sedentary controls or sprinters; and in insulin treated diabetics as compared to hyperglycemic diabetics (Nikkila, 1978; Nikkila et al, 1978B). In all these cases, HDL-cholesterol was higher in the group exhibiting the higher LPL activities. (It must be pointed out, at this stage, that this relationship between

HDL, LPL and the triglyceride-rich lipoproteins should not be considered to account for all of the HDL formation since, in the case of estrogens, their effect on HDL is independant of LPL activity [Nikkila, 1978] and HDL is still present in individuals who lack the Apo-B containing lipoproteins [i.e. LDL, VLDL & chylomicrons in non-fasting plasma] . Nevertheless, the mechanism may normally make a very significant contribution to the determination of plasma HDL levels). The elevation of LPL in long distance runners is of interest, since LPL was not elevated in sprinters who also failed to demonstrate any elevations in their HDL-cholesterol levels (Nikkila et al, 1978A). Such a difference between long distance runners and sprinters would indicate, as previously explained, that it may not only be an increase in energy turnover with exercise that is important in elevating HDL, but it is more likely a specific combination of intensity and duration, which utilizes exercise of an endurance nature, that increases HDL.. The differences between sprinters and long distance runners also indicate that the elevation of HDL-cholesterol with exercise may truly be related to an increase in LPL. According to the proposed mechanism, an increase in LPL would lead to an increase in the catabolism of the triglyceride-rich lipoproteins, so total triglycerides, VLDL and chylomicrons should be consequently reduced. In several endurance training studies an increase in HDL or HDL-cholesterol was accompanied by a fall in total plasma triglycerides as outlined below in Table XII.

TABLE XII

STUDIES WHERE HDL INCREASED AND TRIGLYCERIDES DECREASED WITH EXERCISE

Author	HDL* (mg%)			TRIGLYCERIDES (mg%)		
	Pre	Post	Difference	Pre	Post	Difference
Lopez-S et al, (1974)	286	332	+46 mg%	110	83	-27 mg%
Roundy et al, (1978) IIA			+71 mg%			-29 mg%
IV			+49 mg%			-105 mg%
Leon et al, (1977)	32	37	+ 5 mg% (HDL-c)	164	144	-20 mg%

*HDL- lipoprotein unless otherwise stated

But the exercise induced change in HDL cannot always be related to a change in total triglycerides since Erkelens et al, (1978) found HDL-cholesterol to increase significantly from 35 mg% to 41 mg% while triglycerides remained unchanged. Altekruse and Wilmore(1973) also found similar results. Moreover, even though Webster et al(1978) failed to observe an increase in HDL-cholesterol, triglycerides decreased significantly.

4. Percentage body fat did not change significantly (nor did body weight) and HDL has been inversely related to both these variables (Wood et al, 1976; Rhoads et al, 1976; Gordon et al, 1977A & B; Bradley et al, 1978; Van Gent et al, 1978). The effect of weight loss without exercise is somewhat contradictory since one study recorded a decrease in HDL-cholesterol(Taskinen & Nikkila,1979)while another observed an increase(Wilson & Lees, 1972). Interestingly, in the study where HDL-cholesterol decreased, LPL in adipose tissue was also reduced. It was therefore

suggested that the relationship between weight loss and HDL-cholesterol may be related to the catabolism of the triglyceride-rich lipoproteins in the same manner that triglycerides were related to HDL-cholesterol. HDL did increase in several training studies, as well, where percentage body fat or body weight decreased, as outlined below in Table XIII:

TABLE XIII
STUDIES WHERE HDL INCREASED AND % BODY FAT OR WEIGHT DECREASED WITH EXERCISE

Author	Weight Change	% Body Fat Change	HDL-Cholesterol (mg% Change
Leon et al, (1977)	lost 5.7 kg	decreased 3%	increased from 32 mg% to 37 mg%
Altekruse & Wilmore (1973)	lost 1 kg	----	increased from 36.9 mg% to 55 mg%*
Ratliff et al, (1978)	---	decreased	increased from 42 mg% to 50 mg%

*HDL is expressed as a percentage of the total lipoprotein in this case.

But, as was the case for triglycerides, the relationship between body weight or percentage body fat with HDL was not consistently demonstrated in all of the training studies as seen in Table XIV:

TABLE XIV
STUDIES WHERE HDL INCREASED AND % BODY FAT OR WEIGHT DID NOT CHANGE WITH EXERCISE

Author	Weight Change	% Body Fat Change	HDL-Cholesterol (mg%) Change
Lopez-S et al, (1974)	absent (isocaloric diet)	no change	increased from 286 to 332 mg%*
Gilliam & Burke, (1978)	absent (normal diet)	---	increased from 31 mg% to 39 mg%

*HDL is expressed as lipoprotein in this case.

This demonstrates, as was the case for total triglycerides, the fact that the lack of change in HDL-cholesterol observed in the present study cannot be solely attributed to a lack of change in percentage body fat or body weight.

Therefore, the factors that induce a change in HDL or HDL-cholesterol with endurance training may be related to initial HDL levels, exercise volume (including the utilization of a training intensity that lies within the endurance range of exercise), or changes in triglycerides and body fat metabolism. It is likely that an increase in the total exercise volume is the most important factor in relation to inducing an increase in HDL-cholesterol, since a change in triglycerides or percentage body fat cannot always account for the exercise-induced change in HDL-cholesterol and it seems probable that individuals with relatively high HDL-cholesterol can increase it further, given the sufficient exercise stimulus. Furthermore, it is also likely that there are other factors which come into play that are not necessarily directly related to triglyceride metabolism. These factors may exert their effect by increasing the formation or decreasing the catabolism of plasma HDL, but they may also affect HDL and/or HDL-cholesterol more directly by increasing the rate of its apoprotein synthesis or the production of nascent HDL. Such factors could be related to the altered hormonal secretion profile that occurs with endurance exercise as outlined previously in relation to changes in total cholesterol (supra p.144). For example, growth hormone and thyroid hormone are elevated during prolonged endurance exercise and remain elevated for a period afterward (Hartley et al, 1972; Terjung & Tipton, 1971) but their relationship with HDL

metabolism has not yet been investigated. Insulin is reduced during this type of exercise (Hartley et al, 1972), but according to the LPL hypothesis, this would cause a decrease in HDL-cholesterol since insulin stimulates LPL activity (Nikkila, 1978). Possibly the insulin related effect may be due to an increased insulin sensitivity in the enzyme and cell membrane, that may occur as a result of the exercise program (Nikkila et al, 1978B). Other hormones, such as glucagon, corticosteroids, etc..., that change with endurance exercise (Hartley et al, 1972; Bottger, 1971), may also exert an effect on HDL but their role in HDL metabolism is also unknown. A more general effect of endurance training, that is related to the change in the hormonal axis, is the preferential utilization of fats rather than carbohydrates during endurance exercise. This reduced utilization of carbohydrates as compared to fats could possibly effect an increase in HDL-cholesterol since subjects placed on an isocaloric but high carbohydrate diet demonstrated a reduced level of HDL (Blum et al, 1977). The HDL distribution also shifted in favour of HDL_3 on a high carbohydrate diet. Whatever the factors may be that affect HDL or HDL-cholesterol with training, they are probably specifically related to endurance exercise since well-trained sprinters, who were generally anaerobically trained relative to long-distance runners, failed to demonstrate any significant differences in HDL-cholesterol levels from those of the control group while long-distance runners in the same study had levels that were quite high (Nikkila et al, 1978A).

At this point, a comment on the HDL subfractions and the effect of exercise on these subfractions is necessary since the factors that affect HDL during exercise seem to be specific to the

HDL_2 subfraction. Previously, the subfractions of HDL were not measured separately but assessment of these distributions has gained importance since it has been noted that most of the elevations of HDL in women (Cheung & Albers, 1977) and long distance runners (Krauss et al,1978) have been due to elevations of the HDL_2 subfractions specifically, and reduced levels of HDL in CHD patients are mainly due to reductions in the HDL_2 subfractions (Gofman et al,1966).(Nicotinic acid, used in the treatment of hypercholesterolemia, shifts the HDL subfraction distribution towards HDL_2 and high carbohydrate intake shifts it to HDL_3 [Blum et al,1977]). The characteristics of the HDL_2 subfraction are that it has a higher Apo A-I to Apo A-II ratio, and a higher content of Apo E and Apo C than does HDL_3. The elevations of HDL_2 noted in male and female long distance runners were accompanied, as well, by elevations in Apo A-I but not in Apo A-II (Krauss et al,1978). Apo-I has also been found to be reduced in CHD patients (Berg et al,1976A & B). To carry the relationship of exercise and the HDL subfractions one step further, it has been observed that the HDL-cholesterol : Apo A-I ratio (reflecting the ratio of HDL_2 : HDL_3) was positively related to aerobic capacity, specifically,in a survey of individuals of varying degrees of physical fitness (Miller et al,1978). Therefore, endurance exercise must increase the synthesis or decrease the catabolism of Apo A-I preferentially, along with affecting the formation of HDL_2 specifically. These two effects may be interrelated since HDL_2 does have a higher ratio of Apo A-I: Apo A-II than HDL_3. The exercise-induced elevations in HDL_2 and Apo A-I may be importantin relation to CHD risk,since the subfraction and apoprotein which one

desires to elevate are specifically increased by exercise treatment. In the present study, although HDL-cholesterol did not change, alterations in the subfraction distributions cannot be ruled out.

HDL-cholesterol/Total Cholesterol Ratio

The most significant finding of the study was the significant increase in the HDL-cholesterol:total cholesterol ratio (HDL-C/total-C ratio) that accompanied the training program (see Figure 6). The increase in the ratio from .242 to .276 was due to the fact that total-cholesterol decreased while HDL remained stable. Such an increase in the ratio of HDL-C/Total-C or HDL-C/LDL-C was seen in many studies (Lopez-S et al, 1974; Lewis et al, 1976; Leon et al, 1977; Erkelens et al, 1978; Gilliam & Burke, 1978; Ratliff et al, 1978; Roundy et al, 1978; Widhalm et al, 1978) and the significance of the change was determined and found in two (Gilliam & Burke, 1978; Roundy et al, 1978). The ratio infers that at the beginning of the study HDL carried 24.2% of the total plasma cholesterol while at the end it carried 27.6% of the total amount. Such an increase in the ratio is quite desirable with respect to reducing the CHD risk since the ratio has been inversely related to CHD incidence (Brunner et al, 1966; Medalie et al, 1973; Kannel et al, 1979) and it may reflect the risk profile more specifically than would the separate measurements of total cholesterol and HDL-cholesterol. This is considered to be especially true in subjects whose total cholesterol is in the normal to moderately elevated range (Kannel et al, 1979). In this range, the ratio can be quite indicative of the severity of the medical treatment required in an individual whose total cholesterol is moderately elevated, since the therapy prescribed would be more

moderate if a relatively large percentage of the individual's total cholesterol was carried by HDL. Notably, the larger number of CHD cases have plasma cholesterol levels that fall in the high normal to moderately elevated range (200-300 mg%) where the ratio is considered to be quite significant in determining CHD risk (Gotto, 1979). The importance of the ratio also lies in the fact that although higher total cholesterol levels are accompanied by higher HDL-cholesterol levels, the HDL-cholesterol does not increase as fast or as consistently as does total cholesterol, so one observes a reduction in the percentage of total cholesterol carried by HDL as one goes from the low to high ranges of total cholesterol. This reduction in the percentage carried by HDL, as total cholesterol increases, is undesirable in reference to th CHD risk and to the postulated role of HDL in peripheral cholesterol removal. Possibly, chronic endurance exercise could obviate this situation by preventing a decrease in the ratio from occurring, as total cholesterol gradually follows the normal North American pattern of increasing with age.

Finally, the ratio as well as the LDL-cholesterol measurement indicates that there has been a beneficial change in the lipoprotein profile, since HDL-cholesterol was unchanged while LDL-cholesterol decreased. With respect to CHD, it is considered desirable to have a lipoprotein profile wherein the HDL fractions are elevated and the lipoproteins of the lower densities are reduced (Brunner et al, 1979). This profile would simulate the profile of premenopausal, healthy women who are practically free of CHD. It would also tend towards the lipoprotein profile of animals which

exhibit a low incidence of atherosclerosis (supra p. 15) and away from that of animals which demonstrate a high incidence. Possibly the most important treatment, with respect to plasma lipids and CHD risk, as opposed to reducing solely the total cholesterol levels, would be to "normalize" the lipoprotein profile by shifting the lipoprotein distribution from the lower density lipoprotein to the higher density lipoproteins. Support for this suggestion is based on the lipoprotein profiles seen in animals which are relatively free of atherosclerosis and on the suggestion by several authors (Brunner et al, 1979; Gotto, 1979) that a redistribution of cholesterol to the beta-lipoproteins from the alpha-lipoproteins is the first step in the development of an atherogenic lipoprotein profile, preceeding the elevations in total cholesterol. Further support for this hypothesis lies in the fact that, in a study of atherosclerotic regression in monkeys, (Malinow et al, 1978) treatment that resulted in a reduction in total cholesterol failed to reduce the rate of development of atherosclerosis unless there was a concomittant normalization of the lipoprotein pattern (i.e. an increase in HDL and a decrease in LDL and VLDL). Therefore, the change in the lipoprotein profile demonstrated in the present study may be as important, in relation to CHD risk, as an absolute increase in HDL-cholesterol alone would have been.

Correlations Observed

The relationship of HDL-cholesterol to total cholesterol was similar to that reported in many studies (Castelli et al, 1975; Albers et al, 1976; Berg et al, 1976A; Nikkila, 1976; Rhoads

et al,1976A; Castelli et al,1977A & B; Gordon et al, 1977A) in that such a relationship in most cases was negligible.

HDL-cholesterol and triglycerides demonstrated the commonly reported (Albers et al,1976; Rhoads et al,1976; Castelli et al,1977A & B; Gordon et al,1977A; Berenson et al,1979; Hjermann et al,1979) moderate negative correlation in both groups. The only situation where this differed was for the correlation of the way in which HDL-cholesterol changed with respect to triglycerides in the experimental group during the study period, which fell in the negligible range (.12). This lack of a demonstrable relationship between the way in which HDL changes with triglycerides conflicts with the proposed mechanism of LPL, HDL and triglyceride-rich lipoprotein interaction. But, the relationship may not be apparent, in this case, since HDL-cholesterol and triglycerides, on the average, were not actually significantly changed.

Percentage body fat only demonstrated a significant and negative correlation with HDL-cholesterol for the pre-and post- training values of the control group. A negative correlation of percentage body fat with HDL-cholesterol (as reflected by the sum of several skinfold measurements) has been observed by Rhoads et al (1976) and Woods et al (1976).

HDL-cholesterol was not significantly correlated with maximum aerobic capacity when expressed in l/min or ml/kg/min in most cases. Only the post-training correlation between HDL-cholesterol and MVO_2 (ml/kg/min) for the control group was significant (.77). The negative (non-significant) correlation seen in both groups (experimental group = -.37 & -.40; control group=.46 & -.38) of the way HDL-cholesterol

changed with maximum aerobic capacity (expressed either in l/min or ml/kg / min) is not explainable. The lack of relationship between HDL-cholesterol and maximum aerobic capacity was also observed by Erkelens et al, (1978) after a training program. On the other hand, Miller et al, (1978) found a highly significant relationship (.81) between the two variables in a survey of individuals of widely varying aerobic capacities. The correlation was even higher (.88) when the HDL-cholesterol: Apo A-I ratio was correlated with MVO_2 (in ml/kg/min). The HDL-cholesterol to Apo A-I ratio is considered to be representative of the HDL_2: HDL_3 ratio. Ratliff and co-authors (1978) observed that the change in HDL-cholesterol and MVO_2 (ml/kg/min), as a result of an endurance training program, was significantly and positively related (.78). Williams et al, (1979) also found that both HDL-cholesterol and the HDL-c/total-c ratio were positively related to the degree of physical activity in a population survey.

The correlations comparing the HDL-c/total-c ratio with the various parameters measured were similar to those seen for HDL-cholesterol and in several cases the use of the ratio served to strengthen the correlations. The negative correlation of the ratio with the triglycerides became stronger and reached significance in most cases. But the change in triglycerides still failed to show a relationship with the change in HDL-cholesterol (.19) in the experimental group, yet it was highly negatively correlated in the control group (-.80). The negative correlations of percentage body fat for the pre- and post-training values of the control group were also higher when

the ratio was utilized but remained negligible in the experimental group. The correlations of the ratio with MVO_2 (ml/kg/min) were higher as well for the pre and post-training values in the control group than those observed for HDL-cholesterol and MVO_2 (ml/kg/min). The lack of a relationship between the ratio and MVO_2 (in l/min or ml/kg/min) for the pre- and post-training correlations of the experimental group continued, and the way in which the ratio changed with the change in MVO_2 (in l/min or ml/kg/min) for both groups remained negative (non significant) but was slightly reduced.

It is notable that the correlations between the variables observed in the control group appear to be in agreement, in many cases, with those recorded in the literature but this was not the case for the correlations observed in the experimental group. The reason behind such a difference is unclear since both groups were selected from the same population and in the same manner.

CHAPTER VI

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Summary

The purpose of the study was to determine the effect of a twelve week endurance training program on HDL-cholesterol and on the HDL-cholesterol:total cholesterol ratio. The effects of the training program were also determined on several other biochemical variables (LDL-cholesterol, total cholesterol and total triglycerides), physiological variables (resting heart rate, percentage body fat, systolic blood pressure and diastolic blood pressure) and exercise performance variables (maximum oxygen uptake, maximum carbon dioxide production and maximum oxygen pulse).

The effect of chronic endurance exercise on HDL-cholesterol and on the HDL-cholesterol:total cholesterol ratio was of interest since they have both demonstrated an inverse association with the incidence of CHD in epidemiological as well as in prospective studies. Elevated levels of HDL-cholesterol and of the HDL-cholesterol:total cholesterol ratio have been observed in long distance runners and cross-country skiers but not in sprinters, and both variables have frequently been seen to increase as a result of endurance training. Consequently, the question arose pertaining to the degree of training that is required to elevate either HDL-cholesterol or the HDL-cholesterol:total cholesterol ratio and, more specifically, whether a typical 12 week jogging program would have a significant effect on HDL-cholesterol or on the percentage of the total cholesterol which HDL carried.

Twenty-two non-obese men, ages 25-59, participated in the study. They had a history of high cholesterol and had either high or normal cholesterol on intake. Their glucose tolerance was normal, as were their plasma triglycerides. The subjects were divided into an experimental group (N=12) and a control group (N=10). The experimental group participated in a jogging program for 1 hour, 3 times a week. The control group maintained their habitual level of physical activity. All subjects were asked to maintain their normal dietary regimen and this was confirmed in the experimental group by comparing their pre-training and post-training seven-day dietary records. All variables were measured pre-training and post-training, and a significant difference was determined for the values of the experimental group as compared to those of the control group. Correlations of interest to the study were calculated for th pre-training and the post-training values, as well as for the way in which one variable changed in respect to another variable over the study period.

Conclusions

Within the scope of the study, the following may be concluded in relation to the effects of the training program on the variables measured:

1. HDL-cholesterol was not significantly affected by the type of endurance training program utilized in this study. An increase of 8 to 9 mg% was observed in certain individuals which may represent a trend that possibly would have become significant if the total exercise volume (i.e. intensity and number of miles run per week) had been greater.

2. The HDL-cholesterol:total cholesterol ratio increased significantly. This observation of an increase in the percentage of total cholesterol carried by HDL is considered to be the most significant result of the training program, since it indicates that the subjects' cholesterol-carrying lipoprotein profiles have been altered in such a manner so as to reduce their CHD risk. The increase in the ratio was due to the fact that, although total cholesterol decreased, only LDL-cholesterol decreased while HDL-cholesterol remained stable.
3. Total cholesterol and LDL-cholesterol both decreased significantly and in appriximately equal amounts.
4. Total plasma triglycerides did not change significantly.
5. Resting heart rate, percentage body fat, systolic blood pressure and diastolic blood pressure were not significantly altered.
6. The treatment was considered to have been effective since aerobic capacity definitely increased as a result of training. This was demonstrated by the significant increase observed in maximum oxygen uptake, when expressed in either litres per minuter or in millitres per kilogram/minute. Maximum carbon dioxide production and maximum oxygen pulse both increased as well.
7. The correlations observed were similar, in many cases, to those observed in the literature. HDL-cholesterol was not related to total cholesterol. It had a moderate negative correlation

with plasma triglycerides. HDL-cholesterol was negatively related to percentage body fat in the control group. HDL-cholesterol was not significantly related to maximum aerobic capacity, in most cases, which differs from the positive relationship which has sometimes been reported. The HDL-cholesterol:total cholesterol ratio demonstrated similar relationships with these variables, and in most cases the use of the ratio strengthened the correlation.

Additional Observations

1. The absence of a significant increase in HDL-cholesterol may be due to the presence of high initial levels of HDL-cholesterol, an inadequate exercise volume (a combination of intensity and duration) or due to a lack of a decrease in total triglycerides or in percentage body fat.
2. Other factors, such as hormonal changes, changes in Lipoprotein Lipase, etc..., may also be involved in an exercise-induced change in HDL-cholesterol, but information regarding the factors that are involved in HDL-cholesterol metabolism during exercise is not available at present.
3. Due to this lack of knowledge concerning the effect of various factors on HDL metabolism during exercise, and due to the inadequacy of the descriptions of the training programs utilized to elicit an increase in HDL-cholesterol, it is not possible to recommend a specific intensity or exercise duration that would be required to elevate HDL-cholesterol.
4. Despite the lack of a significant change in HDL-cholesterol,

the training program administered in this study succeeded in reducing the subjects' CHD risk factors, since total cholesterol decreased as did LDL-cholesterol and the percentage of total cholesterol carried by HDL increased. This resulted in an improved lipoprotein profile due to the fact that the lipoprotein concentrations in the blood have been redistributed away from the lower density lipoproteins and towards the higher density lipoproteins.

RECOMMENDATIONS

1. Futher clarification of the exercise prescription required to elevate HDL-cholesterol and the HDL-cholesterol:total cholesterol ratio is necessary. This includes the elucidation of the intensity, duration and frequency,as well as the degree of aerobic fitness that are required to induce an elevation in HDL-cholesterol and in the ratio. From the studies that investigated the relationship of exercise with HDL-cholesterol, it appears advisable to increase the exercise volume beyond that utilized in the present study by increasing the intensity or,possibly more importantly, the total number number of miles run per week. It appears that an endurance type of exercise is necessary and an increase in HDL-cholesterol becomes obvious when the number of miles run per week exceeds 40, but this is the extent of the details that have been established concerning the exercise prescription required to elevate HDL-cholesterol.
2. Clarification of the relationship of HDL with exercise is required in relation to the mechanism whereby exercise affects HDL metabolism and the HDL subfraction distribution.

3. The true role of HDL in cholesterol transport is presently unknown since it is not clear whether HDL serves in the transport of cholesterol from the periphery to the liver for excretion,or simply redistributes its cholesterol among the other plasma lipoproteins.
4. Further research into the relationship of HDL with CHD is required since, in certain studies, the inverse relationship reported for these two variables is not always apparent since:
    i) subjects with Tangiers Disease, who lack HDL, are not considered to have an increased incidence of CHD. This may also be due to the low levels of LDL that these patients also demonstrate.
    ii) in Hawaiian Japanese men, Castelli et al (1977B) noted that the differences seen in HDL-cholesterol could not account for differences in CHD incidence.
5. Information regarding the importance of the HDL subfraction distribution in relation to CHD is required, since data relating to the differences in HDL composition, the lipid:protein ratio and the number of micelles per subfraction between normal subjects and CHD patients is sparse at present.
6. Further to Recommendation #5, clarification of the factor which is related to HDL metabolism and is most strongly correlated with CHD incidence is required,since several factors have been implicated,i.e. HDL, HDL-cholesterol, the HDL-cholesterol: total cholesterol ratio, the HDL-cholesterol:LDL-cholesterol

ratio, the HDL_2 concentration, the HDL_2:HDL_3 ratio, the apoprotein A-I concentration or the Apo A-I:Apo A-II ratio.

7. The accuracy of the HDL-cholesterol precipitation methods requires improvement, since differences in HDL-cholesterol between CHD subjects and healthy subjects are not always large. Furthermore, the precipitation methods can have an inter-analysis variability that is quite high in some cases, and is greater than the level which is considered to be desirable for good precision.

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APPENDIX A

Clinical Conditioning Program Questionnaire

APPENDIX A

CLINICAL CONDITIONING PROGRAM QUESTIONNAIRE

NAME:

ADDRESS:

TELEPHONE: (home) (work)

AGE:

HEIGHT:

WEIGHT:

SMOKING:
1) Do you smoke cigarettes? ___
   Number per day ___
   Number of years smoked ___
2) Do you smoke cigars? ___
   Number per day ___
   Number of years smoked ___
3) Do you smoke a pipe? ___
   Amount smoked ___
   Number of years smoked ___
4) If you have stopped smoking, how long ago was this? ___ ___

DIET: Are you on any kind of diet? ___
If so 1) What type of diet is it?

2) How well do you adhere to it?
   Little adherence ___ Partial adherence ___ Full adherence ___
   Comments:

3) How long have you been following this diet? ___ ___

PHYSICAL ACTIVITY:
1) Do you take part in regular or structured physical activity? ___
   If so, in which category does this activity fall?

	NUMBER OF MINUTES PER SESSION
daily	___
3-4 times per week	___
1-2 times per week	___
a few times a month	___
about once a month	___

2) In what other types of activities do you take part?
   PLEASE NOTE THAT PHYSICAL ACTIVITY CAN REFER TO PARTICIPATION IN A TEAM SPORT, BUT IT CAN ALSO INCLUDE WALKING (BRISKLY), JOGGING, RUNNING, SWIMMING, SAILING, CANOEING, BICYCLING, CALISTHENICS, ETC.
   How much time do you spend on each of these activities?

MEDICATION: Are you on any type of medication?

NAME OF PRESCRIPTION	REASON	DOSAGE

APPENDIX B

Sample of Seven-Day Dietary Record

Sample of Seven Day Dietary Record

Tuesday . Wed . Thurs . Fri . Sat . Sun . Mon

Breakfast

* 10 oz cereal + milk no. reg.	* 8 oz cereal	* cereal	* cereal	* cereal	* cereal
1 egg 2 bacon		1 egg 3 bacon	1 toast	2 toast	1 toast
* 1 decaff. coffee	* 1 coffee	2 toast	1 small	* 1 coffee	1 " + peanut butter
1 white toast	1 wh. toast	* 1 coffee	banana	apple juice	1/2 cup coffee
1 wh. wt +	1 wh wt +				* 4 oz. orange juice

Lunch

Chicken noodle	tuna	mich. stew	breaded	1 - slice roast beef	bowl cabbage soup
rice, carrot	sandwich	french fries	pale	1 " bread	1 - slice roast beef
cabbage	6 oz 1%	turnips	mixed veg.	2 cups milk	1 - " bread
10 oz skim + milk, roll	milk	10 oz skim milk, roll	fr. fries	+ 4 tsp's ovaltine	2 - glasses of milk
+ butter (2)		+ 2 pats butter	salad +	1 - hamburg	* 1 - coffee
			1 - butter	1 - orange	1 small banana
					+ 1/2 cup crushed pineapple
Supper					
* 3 oz salmon	baked	roast beef	boiled	2 - scotch + soda	
1/2 cup rice	baked	mashed pot.	chowder	1 - beer	1 - pork chop
1 raisin bread	small	corn	2 slices bread	* 1 plate chinese food	serving broccoli
* 1 decaff coff.	serving of broccoli + cauliflower	1/2 c yogurt + 1/2 cup	1 glass milk	(small servings of veg + meat)	+ potatoes
	+ 1/2 c fresh fruit	+ pineapple (WS)	banana +		+ mixed veg.
	1 slice toast	+ coffee	2 slices bread.	milk	1 - banana
Snacks	+ coffee			+ tea	1 glass milk
2 oz roasted nuts	roasted nuts	* coffee	4 cups * coffee	1 - apple	1 - graham sand.
1/2 cup yogurt	skim pretzels	cinnamon pill	+ 2 cups tea	1 toast	* 1 - coffee
1 salmon sand.	glass of milk	10 oz nuts	2 crackers	1 " + peanut butter	
1 cracker + cheese	1 Salmon sand.	1 apple	+ cheese	1 orange	
+ 3 cups coffee	+ 3 cups coffee	1 glass milk	10 oz nuts	1 small bowl of chips	
* no sugar		1 small bowl of chips			
* decaff/butter coffee					

APPENDIX C

Outline of Aerobic Fitness Test

APPENDIX C

DEPARTMENT OF KINANTHROPOLOGY

CLINICAL FITNESS RESEARCH APPRAISAL PROGRAMME

EXERCISE STRESS TEST RECORDING FORM

NAME: LAB NO: WEIGHT:

EXAMINER: DATE: TIME:

		Mph/% Grade	H R b/min	B P mmHg	ST_2 Level mm	S-T slope mm/sec.	Symptoms/ Comments
Sitting							
Warm up	(1)	3.0 / 2.5					
Warm up	(2)	/					
Warm up	(3)	/					
Post Warm up	(1)						
Post Warm up	(2)						
Stage 1	(1)	3.0 / 2.5					
	(2)						
Stage 2	(1)	3.0 / 5.0					
	(2)						
Stage 3	(1)	3.0 / 7.5					
	(2)						
Stage 4	(1)	3.5 / 7.5					
	(2)						
Stage 5	(1)	3.5 /10.0					
	(2)						
Stage 6	(1)	3.5 /12.0					
	(2)						
Stage 7	(1)	3.5 /14.0					
	(2)						
Stage 8	(1)	3.5 /16.0					
	(2)						
Stage 9	(1)	3.75/16.0					
	(2)						
Stage 10	(1)	3.75/18.0					
	(2)						
Stage 11	(1)	3.75/20.0					
	(2)						
Stage 12	(1)	3.75/22.0					
	(2)						
Stage 13	(1)	3.75/24.0					
	(2)						
Stage 14	(1)	3.75/26.0					
	(2)						
Post Ex Walking		2.5/ 0					
Sitting							
Recovery	(1)						
Recovery	(2)						
Recovery	(3)						
Recovery	(4)						
Recovery	(5)						
Recovery	(6)						
Recovery	(7)						
Recovery	(8)						

APPENDIX D

Protocol of Jogging Program

APPENDIX D

PROTOCOL OF JOGGING PROGRAM

Week	Day	Jogging Time (in minutes)	Rest Time (in seconds)	Total Time (in minutes)
1	1	1	30	10
	2	1	30	10
		1	30	
		2	45	
		2	45	
		2	45	
		2		
	3	1	30	10
		2	45	
		2	45	
		2	60	
		3		
2	4	2	45	10
		2	45	
		3	90	
		3		
	5	2	45	10
		3	60	
		5		
	6	5	120	10
		5		
3	7	10		10
	8	10		10
	9	10		10
4	10	11		11
	11	11		11
	12	12		12
5	13	12		12
	14	13		13
	15	13		13
6	16	14		14
	17	14		14
	18	15		15
7	19	15		15
	20	16		16
	21	16		16
8	22	17		17
	23	18		18
	24	19		19
9	25	20		20
	26	21		21
	27	22		22
10	28	23		23
	29	24		24
	30	25		25
11	31	25		25
	32	25		25
	33	25		25
12	34	25		25
	35	25		25
	36	25		25

NOTE: The rest period may have been extended beyond the time listed, in order for the subjects' heart rate to fall below their prescribed jogging heart rate.

APPENDIX E

Fasting and Non-Fasting Values of HDL-Cholesterol and Total Cholesterol

1) HDL-Cholesterol

2) Total Cholesterol

APPENDIX E1

Fasting and Non-Fasting Values for HDL-Cholesterol

HDL-Cholesterol **

Subject Number	Pre-Training		Post Training	
	Fasting (mg%)	Non-Fasting (mg%)	Fasting (mg%)	Non-Fasting (mg%)
Experimental Group				
1	56.3	52.9	55.0	48.4
2	* 45.0	* 42.2	40.5	42.7
3	50.6	45.0	51.7	51.7
4	* 52.5	55.1	52.9	51.7
5	54.0	50.6	56.3	55.1
6	40.5	39.4	48.4	47.3
7	48.4	48.4	61.9	51.7
8	77.6	77.6	78.7	67.5
9	47.3	49.5	57.4	55.1
10	48.4	49.5	48.4	52.9
11	64.1	56.3	72.0	67.5
12	70.9	64.1	58.5	52.9
Control Group				
1	* 56.8	* 64.1	70.9	69.7
2	* 51.2	* 48.9	56.3	47.3
3	60.7	54.0	67.5	65.3
4	* 85.8	* 72.4	78.7	67.5
5	* 46.7	* 46.1	46.1	40.5
6	* 29.8	* 30.4	34.9	34.9
7	* 54.4	* 54.0	56.3	55.1
8	* 53.3	* 57.4	52.9	49.5
9	69.7	68.6	66.4	60.7
10	* 72.0	* 69.7	64.1	59.6

* these values are the mean of 2 or 3 measurements.

** all values listed are the values obtained in the lab x the dilution factor of 1.125 of the method.

APPENDIX E2

Fasting and Non-Fasting Values for Total Cholesterol

Total Cholesterol

Subject Number	Pre-Training		Post-Training	
	Fasting (mg%)	Non-Fasting (mg%)	Fasting (mg%)	Non-Fasting(mg%)
Experimental Group				
1	265	349	226	199
2	229	192	205	188
3	224	204	234	222
4	238	221	218	210
5	218	247	208	203
6	142	138	146	139
7	271	257	218	196
8	237	256	219	188
9	262	268	245	233
10	201	195	192	204
11	204	173	187	176
12	215	215	208	197
Control Group				
1	199	211	228	203
2	224	192	213	197
3	201	187	213	210
4	204	175	207	182
5	247	207	214	178
6	230	225	221	212
7	244	233	200	235
8	241	245	240	250
9	203	230	334	251
10	238	235	242	227