Effects of physical activity on serum cholesterol metabolism

A review

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Dawson[1] was one of the first investigators to suggest exercise as a therapeutic agent as well as a preventive measure for circulatory diseases. His description is given verbatim.

> Patients with arterial sclerosis were placed upon a seesaw and gradually tipped up and down. Their symptoms, confusion and headache and their objective signs, color and mental condition were improved. Thus, one is led to ask, might not these gentle oscillations be duplicated in light calisthenics and might not the latter tend to prevent as well as alleviate the condition?

Physical conditioning and physical fitness have been given much attention in the United States in recent years. Research interests have been stimulated by the recognition of the association of obesity, hyperlipemia, and coronary heart disease (CHD) to the lack of physical activity. The volume of research in this area in the past 2 decades is overwhelming. This review will be divided into epidemiologic, human experimental and animal experimental findings on the effects of physical activity on serum cholesterol metabolism.

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Epidemiologic research

Although there are abundant population studies demonstrating the correlation between the incidences of angina pectoris, development of myocardial infarctions (MI), or deaths from CHD and physical activity or inactivity, this section will be primarily limited to the association between cholesterol level and physical activity. Heyden,[2] Fox and Haskell,[3] Fox and Skinner,[4] Holloszy,[5] and Hein and Ryan[6] have reviewed the effects of physical activity or inactivity on MI or CHD.

Although the literature on the effect of exercise on decreased incidences of MI and CHD seems clear,[7-11] the relationship of exercise to serum cholesterol levels seems particularly confusing. This is because many factors other than physical activity affect cholesterol metabolism: diet, sex, age, genetics. The intensity, duration, and kind of physical activity are important considerations when evaluating the salutary effect on cholesterol levels. Separation of the findings into epidemiologic, human experimental, and animal experimental research will also help clarify the relationship. The papers are reviewed in chronologic order.

Positive correlations. Early in 1955, a report on serum lipoproteins and cholesterol concentrations of Central and North Americans by Mann et al[12] made the first inference regarding the relationship of serum total cholesterol levels to physical activity. Total cholesterol and β-lipoprotein measurements of a group of rural Central American subjects subsisting on a largely vegetarian and low-fat diet were compared with those of urban Guatemalan and North American subjects who habitually consumed large amounts of fat (36% and 40% of the total calories coming from fat, respectively). The study revealed an unexpected dissociation of the serum β-lipoprotein and cholesterol levels. Rural Central Americans showed low and almost constant cholesterol levels at all adult ages. The levels, which were near 150 mg/dl for both sexes of that adult population, are characteristic of North American children.[13] In contrast, the serum β-lipoprotein levels in the rural Central Americans were similar to those of the North American subjects when compared according to age and sex. The differences in dietary fat intake among the groups could not be used to explain the inconsistent change in direction of the serum cholesterol and β-lipoprotein levels because of the many reports that both serum cholesterol and β-lipoprotein levels were reduced when dietary fat intake was limited.[14, 15] The only other difference was that the studies in Central America indicated that, although the subjects were thinner than the age- and sex-matched North Americans, the Central Americans consumed more food daily in relation to body size. These facts were interpreted to indicate that the high energy expenditures by the Central Americans must have accounted for weight differences—a reasonable expectation in an agrarian culture. This study indicated that a salutary effect of muscular exercise in regulating serum lipids might be possible.

That same year Mann et al[12] evaluated their hypothesis: the magnitude of the total caloric turnover in human subjects controls the serum lipoprotein levels, and the deposition of the calories supplied in the diet controls the serum cholesterol concentration. When an excess of food calories is converted to body fat, the serum cholesterol level is high and when a caloric balance or deficit is present, the serum cholesterol level is low.[16] Four medical students participated in the 10-week experimental program which consisted of four phases: Phase I, normal caloric intake, normal activity; Phase II, double the normal caloric intake with normal fat intake, and an increase in physical activity to maintain body weight ± 5 lb; Phase III, a caloric intake as in Phase II with a decrease in physical activity to control levels to allow weight gain; Phase IV, caloric restrictions with normal physical activity to allow weight loss. The results showed that serum phospholipid, cholesterol, and β-lipoprotein levels decreased in Phase II, increased in Phase III, and decreased to control values in Phase IV. These observations indicated that young men consuming high caloric diets were able to maintain their serum lipid levels so long as excess energy was dissipated as exercise. These findings do not support the hypothesis proposed, which related serum lipoprotein levels to the magnitude of serum exchange. They do support the concept that serum lipid levels are related to caloric balance of the body.

Similar findings on 46 Nigerian men who had larger muscle mass and greater expenditure of energy compared to an age- and weight-matched group in the United States supported the earlier finding[17] that the diversion of excessive food calories to mechanical energy may be a favorable influence, such as facilitating low serum lipid levels either as a consequence of the increased muscle mass necessary to effect the energy loss or as a by-product of muscular work.

A study was conducted in Africa on serum cholesterol levels of normal Bantu men that were all migrant laborers and normal white men (controls) that were mainly white collar workers from a large Cape Town Insurance Company.[18] The study showed a serum total cholesterol average of 147 mg/dl for the former group and 243 mg/dl for the latter. Total daily caloric intake was relatively similar between both groups. It was concluded that physical activity accounted for the difference in serum cholesterol levels.

Mathur[19] investigated various factors related to CHD in two groups of patients: (1) 553 patients with clinical CHD, and (2) 1,056 persons selected in a field survey of the general population in Agra, India. The incidence of CHD was high in the urban population, in the upper socioeconomic classes, and in persons with the highest amount of total dietary fat consumption. Physical activity was found to be less, and emotional stress and strain were greater in patients with CHD. Business executives formed the largest percentage of the 553 patients with CHD, with physicians, landlords, and high government officials following in that order. In evaluating the amount of physical activity involved in each case study, it was calculated that the higher the stratum of society, the higher the serum cholesterol concentration. This was in marked contrast to the poorer sections of society where type of work and mode of life demanded a greater amount of physical activity.

In 1961, Karvonen et al[20] studied the food consumption of lumberjacks in five camps in eastern Finland. These men had an extremely large average daily food intake, more than 4,700 calories, of which no less than 45% were derived from fat. Yet their serum cholesterol levels were no higher than those of the average Finnish man with a much lower caloric intake, only 35% of which was derived from fat.

The Samburu people of Northern Kenya live on a diet of milk and meat. Shaper et al[21, 22] found that all the males (15 to 60 years of age) had very low serum cholesterol levels (mean, 166 mg/

dl), despite the moderate to high saturated fat intake. It is interesting that at all age levels there is a high degree of physical activity. Their activity is associated with herding, watering, and grazing of cattle. Family migrations usually take place every 6 weeks; the whole settlement moves 16 to 24 km, whereas, seasonally, cattle may be driven by the younger men to areas 80 or even 160 km distant in search of grazing land or water. The task of herding the main stock is undertaken by older boys, warriors, and elders. A day's herding may involve a trek up to 32 km. Warriors and elders who are not herding will assist with watering cattle, and this may involve lifting 1,500 liters of water 1 to 1.5 meters away by hand every other day. Thus, it appears that despite a high fat diet, the high degree of physical activity is an important factor in maintaining low serum cholesterol levels.

Gsell and Mayer[23] compared an extremely active Swiss village population, (Blattendorf) with an urban Swiss population (Basel). The village population, essentially farmers, had a high-fat intake and a daily caloric intake 1,000 calories higher than the urban population. However, the serum cholesterol levels of both men and women were significantly lower than those found in their urbanized countrymen. The farms and pastures are spread on steep slopes varying in altitude from 4,000 to 8,000 feet. All distances have to be walked. The people carry hay, weed, milk, and building materials on their backs. Men frequently carry 45.4 kg and elderly women carry loads 23 to 27 kg up and down the mountain path. It is unlikely that the difference in altitude and climate between Basel and Blattendorf explains the observed differences in serum cholesterol. South African Europeans living in Johannesburg at an altitude greater than 6,000 feet have serum cholesterol levels similar to those in the United States. Climate did not seem to influence serum cholesterol levels in Maine and Florida populations.

Hard physical labor as a way of life of the West Indian Community (St. Kitts, West Indies) revealed a similar inverse relationship with serum cholesterol.[24] Average serum cholesterol level for subjects 20 to 49 years of age was 177 mg/dl, which is considerably lower than North Americans in a similar age-matched group (230 mg/dl).[25]

A 6-year cohort and descriptive epidemiologic study of the Many Farms Navajo Indian population has revealed only four cases of CHD in 508 adults aged 30 years and older.[26] The incidence of CHD was significantly lower when an appropriate age- and sex-matched segment was compared to the Framingham population.[7] The dietary survey indicated that the Navajo had a high animal fat intake of adequate caloric value, but cholesterol levels appeared to be somewhat lower than in the Framingham group. Navajo occupational activity, for the most part, involves moderate to heavy labor, with much walking and horseback riding. It was estimated that Navajos compare with other North American rural groups in physical activity, being considerably greater than that found in a white urban population.

A study was carried out on 26 pairs of white men in Georgia, matched age for age and classified on the basis of high or low serum cholesterol value; the nutrient intake was assessed by dietary interview, and exercise was evaluated on the basis of occupation.[27] Subjects found to have cardiovascular abnormalities during examinations were excluded. Exercise was graded according to occupations: laborers, farm sharecroppers (active); tradesman, service workers (moderately active);

and proprietors, professionals, large farm owners (less active). Although there was no significant correlation between serum cholesterol and the dietary components, a highly significant inverse relationship was found between the degree of physical activity and serum cholesterol level. A significant seasonal difference in dietary constituents was observed which consisted essentially of a decreased caloric intake during warmer months. A possible relationship between the seasonal dietary pattern and the seasonal cholesterol pattern was noted, although their data were inadequate to test the relationship.

In a more extensive study, that same group[28] reported on 3,102 Negro and white subjects in Evans County, Georgia. The white and Negro female groups had similar incidences of CHD, 15 cases/1,000 examined; the white male group had 20 cases/1,000 examined. The prevalence of CHD in nonfarm occupations was highest for professionals, proprietors, and managers and lowest for laborers. Of the farm occupations, prevalence of CHD was highest for farm owners and lowest for sharecroppers and laborers. It was also noted that owners of small farms performed more physically demanding work than owners of large farms for two principal reasons: less mechanization and less available hired help on small farms. Not unexpectedly the incidence of CHD was lower in small farm owners than in the large farm owners. Serum cholesterol values averaged 213.3 mg/dl for the white males, 205.8 mg/dl for Negro males, 229.4 mg/dl for the white females, and 219.2 mg/dl for the Negro females. When subdivided according to occupation, significantly higher serum cholesterol levels occurred among white nonlaborers compared with white laborers. The greater amount of physical work demanded of Negro farm owners as a group when compared to white farm owners revealed higher serum cholesterol levels in the white farm owners. Neither dietary fat intake nor cigarette smoking would explain the differences in CHD prevalence between Negroes and whites.

In 1965, Melichar[29] evaluated the serum cholesterol values of three groups: (1) 67 individuals who had been working for 5 to 10 years in the foundry in Brno, Czechoslovakia, all performing hard physical work; (2) 47 administrative employees who had also been working for 5 to 10 years, but who had, in many cases, some regular form of physical activity; and (3) 56 civil servants who expended great mental exertion and who had no spare time for regular physical exercise. Despite the fact that the highest average and highest consumption of fats (consisting almost exclusively of lard and butter, forming about 45% of the caloric intake), were found in the group doing hard physical work (group 1), the serum total (204 mg/dl) and esterified cholesterol values (138 mg/dl) were the lowest. In the other two groups, fats represented 35% of the total caloric intake. The lipid values of the second and third groups did not differ significantly from group 1. However, in the second and third groups the number of overweight persons was higher. When the serum cholesterol was evaluated only on those who were slightly underweight in the latter two groups, a slight, but positive relationship occurred between the cholesterol concentration and the lack of activity.

If excess weight can be used as an indirect index of inactivity, then other investigations also demonstrated a positive relationship between inactivity and high serum cholesterol levels.[30-36]

Negative correlations. According to Keys et al,[37] differences in physical activity do not explain the large differences in serum total cholesterol found when groups with different dietary habits are compared. In Naples and Malmo, clerical workers, members of the city fire departments, and those who do heavy manual work were studied in parallel. From their study, it appears that dietary and not physical activity is the major factor that influences serum cholesterol concentration.

The following year, Keys et al[38] reported results of a lengthy epidemiologic study on serum cholesterol of men classified by age and physical activity in Minnesota, Malmo, Sweden, Bologna, Naples, the Islands of Sardinia, and three ethnic groups in Cape Province, South Africa. The study was composed of men presumed to be representative of their class in the community and who were judged to be clinically healthy by physical examination that included electrocardiographic measurements. Dietary estimates included the percentage of total calories coming from fat. No estimation of carbohydrate, protein, and caloric intake was reported. Physical activity was classified into three groups: (1) light work (sedentary workers, and men whose jobs make very little demand on muscular effort, e.g., clerks, draftmen, shopkeepers); (2) moderate work (men whose jobs infrequently entail severe muscular effort, but who are fairly active during a good part of the work day, e.g., machine operators, carpenters, painters, janitors, mechanics); (3) heavy work (men whose jobs require much heavy lifting and severe muscular effort in steel mills, shipyards, foundries, coal mines, docks and quarries). These results show that except for the Bantu population who show a somewhat lower serum cholesterol level in the manual labor group as compared to the light work group, there was no significant correlation between physical activity and serum cholesterol levels. Like their previous study, they concluded that habitual diet, especially its fat content, has much more influence than physical activity per se on the concentration of serum cholesterol or β-lipoprotein cholesterol levels.

An epidemiologic survey of the incidence of MI in 8,500 middle-aged members (40 to 65 years of age of Israeli Kibbutzim during a 10-year period showed that the ratio of incidence of MI in sedentary male workers to members engaged in manual work was 3:1.[39] In contrast, the average values of serum total cholesterol had a tendency to be lower in the various age groups of sedentary workers than in the members engaged in heavy or light manual work. According to the constitutions of the cooperative settlements, all members live in absolute equality regarding their nutrition, housing conditions, and all other environmental factors, irrespective of the nature of work or status. In this study the implication of the results of the survey may have a more definite meaning due to the more controlled environmental conditions. However, no explanation was given for the lack of correlation between physical activity and serum cholesterol levels, but a positive correlation between physical activity and MI. They concluded that the preventive effect of long-term manual labor on the incidence of MI in middle-aged people has no parallel expression in different lipid patterns and values.

Lee et al reported[40] that serum cholesterol levels of young (mean age, 21.3 years) and older (mean age, 41.2 years) Buddhist monks and nuns were 119 and 122 mg/dl, respectively. Although these Korean monks and nuns are strict vegetarians consuming an exceedingly low fat diet (7% of total calories), they live very sedentary lives. In contrast, comparison of a more active group, American soldiers (mean age, 21.6 years) and officers (mean age, 43.3 years) had serum cholesterol levels of 192 and 231 mg/dl, respectively. Therefore, they concluded that physical activity did not seem to be the hypocholesteremic factor when the nonactive monks and nuns were compared to the active soldiers and officers. For a more valid comparison, it would have been more appropriate to compare the young and older Buddhist monks and nuns to young and older active Koreans from the same geographic area. The different diet and genetic backgrounds of the American soldiers and Korean monks and nuns complicate the issue of evaluating the hypocholesterolemic effect of physical activity.

In 1966, Cooper et al[41] reported serum cholesterol values of 30 veteran handball players, aged 36 to 68 years. No dietary history was made of the players. Eighteen were businessmen or self-employed. Obesity was rare and half the players were nonsmokers. All played handball two to three times a week, several as much as five times a week. Electrocardiograms were taken during the Double Masters Test by radiotelemeter immediately after 45 to 60 minutes of handball playing. An unexpected finding was the lack of the hypocholesterolemic effect after strenuous handball playing. The mean cholesterol level for the group was 254 mg/dl.

Keyes et al,[42] in 1966, reported that serum cholesterol levels of three groups of United States railroad employees (nonsedentary clerks, sedentary clerks, and switchmen) bore no significant relationship to the activity levels in each of the age groups 40 to 44, 45 to 49, 50 to 54, and 55 to 59 years.

Similarly, Malhotra[43] in 1967 reported serum lipid concentrations in 28 pairs of age-matched railway men, 35 to 45 years of age, from two geographically different Indian population groups (Udaipur and Madras) with extremely high consumption of fats. Although the Udaipur group consumed 10 times more fat (most of which was saturated fat of animal origin) than the Madras group, the latter group had 15 times more ischemic heart disease. The serum cholesterol level was not different in both groups. When compared to the blood donors from the Railway Hospital in Madras, who were essentially sedentary workers, both groups of railway men from Udaipur and Madras had cholesterol concentrations no different from the blood donors. Thus it appears that that particular type of physical activity of the railway men had no effect on maintaining low serum cholesterol levels.

Human experimental research

Numerous human experimental studies have been undertaken on the possible relationship of exercise to serum lipid levels since the initial epidemiologic findings in the early 1950s. Because these types of studies are more structured and the variables are more controlled, the results should form a more meaningful pattern.

Positive correlations. Mann et al[16] reported the effects of vigorous physical exercise on the serum cholesterol levels of four medical students. Their observations indicated that the men were able to consume high fat diets and double their caloric intake without increasing the level of their serum lipids so long as the excess energy was dissipated as exercise. A similar finding was reported by Calvy et al[44] on 101 Marine Corps trainees (mean age, 20.5 years) on a 4,500-calorie diet (10% protein, 45% fat, and 45% carbohydrate). The men followed a strenuous regimen of exercise, even greater than that of the lumberjacks,[2] from the moment of arising at 5:00 a.m. until they went to bed at 9:30 p.m. Although the caloric intake was excessive, the 22 weeks of training inhibited the rise of serum cholesterol (mean, 183 mg/dl). Calvy et al[45] later confirmed these findings.

The effect of increasing the level of daily physical activity on serum cholesterol concentration was studied[46] in nine clinically healthy university students (mean age, 23.3 years). Physical activity was induced by walking on a motor-driven treadmill at a rate which required 1,280 calories for 2 hours. All meals were prepared and measured in the laboratory. The caloric intake was increased by 900 calories to 4,189 calories, but the proportion of calories derived from fat was held constant (43% of total calories). After 4 weeks of physical exercise, there was no significant change in the serum cholesterol level. Before the exercise program, the serum cholesterol level was mean, 158 mg/dl; after the exercise program mean, 162 mg/dl. It appears that the extra calories consumed as fat during the exercise program were utilized during the increased work output. This can be indirectly related to the lack of weight gain, despite the fact that there was an increased consumption of fat (46 g/day).

In 1961 Golding[47] conducted a study to determine the effects of hard endurance exercise program on total serum cholesterol in the instructional staff of the College of Physical Education at the University of Illinois. Serum cholesterol values were determined on four male subjects and four controls before and after the program. The exercised group participated in a 25-week training period in which strength and endurance were stressed. The subjects met for 1 hour of exercise 5 days a week and were encouraged to participate in physical recreation on the weekends. Before the exercise program, the mean serum cholesterol level of the four participants was 342 mg/dl. All four exercised subjects showed significant reduction (26%) in serum cholesterol at the end of the 25-week period. Golding concluded that consistent exercise over a long period of time lowered the serum cholesterol to a greater degree than sporadic or erratic exercise for a shorter period of time. Those individuals who exercised harder and more often had greater gains in physical fitness and greater degree of serum cholesterol reduction. It would be interesting if similar significant reduction in cholesterol levels could be obtained in exercised subjects with initial cholesterol concentration in the normal physiologic range (150 to 250 mg/dl).

The possibility of physical activity having a prophylactic effect on serum cholesterol increase was further supported by Rochelle.[48] Plasma cholesterol levels were followed in six experimental and six control subjects (aged 20 to 36 years) during a 5-week exhaustive exercise program (timed 2-mile run, 5 days/week) and an 8-week detraining period; no specific diet was given. Saturated fat comprised about 35% to 45% of the diet. Plasma cholesterol level of the experimental group for the pretraining period was 203 mg/dl. The plasma cholesterol concentrations were significantly reduced during the course of intensive training (reduction of 11%). A temporary increase in plasma cholesterol during the exercise phase occurred, which was believed to be due to fat mobilization and ultimate utilization during physical exercise. Four weeks after the detraining period, the plasma cholesterol levels returned to the pretraining levels. Rochelle suggested that physical activity, by increasing metabolism, speeds up the process of cholesterol excretion and also prevents synthesis of this sterol.

A study was conducted on 92 male physicians and medical students (mean age, 28 years; range, 21 to 43 years) who were divided into the following groups: (1) sedentary individuals, (2) active (those who had a history of participation in competitive athletics), and (3) sedentary, trained individuals (sedentary subjects who participated in an exercise program and determined trained when they could run 4.83 km in 24 to 28 minutes.[49] The exercise test applied to group 3 was the Maximum Work Capacity Test. The subjects began walking on a 1% treadmill grade at 3.4 mph and the grade was elevated 1% each minute. The exercise period was terminated when the pulse was 180 beats per minute or with the onset of severe dyspnea, fatigue, or claudication. Group 1 had a mean serum cholesterol concentration of 232 mg/dl, whereas group 2 had 208 mg/dl. Before the physical training period, group 3 had a mean serum cholesterol concentration of 260 mg/dl; the post-training value was 210 mg/dl. Thus the normally active individuals in group 2 and individuals on a formal training program in group 3 had lower cholesterol values when compared to the sedentary group.

To determine the influence of several types of physical activity upon the serum cholesterol, Campbell[50] randomly selected 133 male freshmen college students to participate in 10-week programs of cross-country running, golf, tennis, tumbling-gymnastics, wrestling, and weight training. Mean pretraining cholesterol level for the entire group was 177.4 mg/dl. Only cross-country running and tennis produced a significant serum cholesterol reduction, 11% and 4% respectively. This study illustrated the necessity of regular, vigorous physical activity in order to induce a change in serum cholesterol concentration, particularly if the pretraining cholesterol levels are normal.

The following year, Campbell reported on the influence of diet and physical activity on serum cholesterol[51] of 86 young men who were divided into six categories; lean, muscular, and obese individuals who were either physically active or inactive. The active subjects ran from 5 mph at 0 degree elevation to 7.5 mph at 10 degrees on a treadmill three times a week for 10 weeks. There was a significant reduction in serum cholesterol level in the active group as compared with the inactive group. The greatest serum cholesterol reduction at the end of 10 weeks occurred in the obese, active subjects (12% reduction). The muscular, active subjects had a 3.4% reduction and the slim, active group had no change in cholesterol concentration. The reduction of serum cholesterol was independent of dietary influences and weight changes. This study suggests that the serum cholesterol level of subjects of various morphologic configuration is influenced differently when undergoing a similar exercise program, and may thus help explain some of the divergent results in previous studies.

A group of 229 Air Force officers who routinely engaged in a dynamic exercise program for at least 1 year was compared for serum cholesterol differences against 126 officers who were classified as sedentary.[52] The physical activity of the dynamic exercise group required continuous, fast movements such as tennis, handball, squash, or basketball. The average age of the participants ranged from 40 to 55 years. The exercise group had lower levels of total lipid (5%), cholesterol (4%), β-lipoprotein (5%), and triglycerides (11%) than the sedentary group. Alpha-lipoprotein levels increased with exercise.

Similarly, Carlson and Fröberg[53] not

only found a significant decrease in plasma concentration of cholesterol, but also in phospholipids and triglycerides in 12 men who walked 500 km in 10 days. The true significance of the effect of physical activity on the change in cholesterol concentration is difficult to evaluate, since the subjects went without food for the entire period. They subsisted on mineral water, fruit and vegetable juices estimated to be about 200 kilocalories per person per day.

The effect of 10 weeks of physical conditioning on various blood chemistry values was observed in a group of 39 male subjects (mean age, 33 years) at the University of California.[54] The groups were classified as "sedentary" prior to starting the conditioning program. No formal dietary regimen was followed. The exercise program consisted of three conditioning periods each week which consisted of walking and jogging for a prescribed distance. This program was progressively increased in intensity and duration. During the 10-week period the group mean distance covered was 83.3 km in a mean of 413 minutes for a mean jogging rate of 12.1 km/hr. The mean serum total cholesterol decreased from 224 mg/dl (preconditioning) to 201 mg/dl (postconditioning) with no statistically significant changes in the serum triglycerides and phospholipid concentrations. Pre-β-lipoprotein and β-lipoprotein concentrations decreased 7% and 13% respectively; α-lipoprotein levels increased 18.6%. This phenomenon was also observed by others.[52-57] The study also included "fat tolerance tests" which suggested better handling or more rapid metabolism of the exogenous fats, i.e., a given fat load produces an earlier fat peak in the blood, suggesting enhanced digestion and adsorption from the digestive tract. The observed peak serum lipid concentration is of smaller amplitude and the return of the serum values to normal is quicker, suggesting more rapid clearing from the blood and expedited utilization.

It has been reported that the incidence of CHD is higher in physicians than other professional groups.[19, 55] Balart et al[56] conducted a study on 104 undergraduate (mean age, 22.3 years) medical students at Louisiana State University. Dietary intakes were calculated from 7-day dietary histories completed by the students using a computerized method developed at the medical school. Physical activity was assessed by a self-administered questionnaire. An average Work Metabolic Rate/Basal Metabolic Rate ratio was computed from the questionnaire data and used as the index of physical activity. The results indicate that the group as a whole had a high daily caloric intake, high fat intake, and a low index of physical activity. A significant number (one-third) of these students had "abnormally" elevated serum lipids. Thirteen students volunteered to participate in a program of physical exercise consisting of four 40-minute periods of jogging, running, and calisthenics each week for 6 weeks. At the end of this period there was a decrease in β- and pre-β-lipoprotein concentrations. Thus if this trend of higher serum lipid levels occurs in persons in professional occupations, it might be prudent to decrease the serum lipid levels to reduce the risk of CHD. Proper caloric intake and energy expenditure should be reinforced in these groups of professionals.

The effect of exercise on serum lipids and lipoproteins was studied in 13 medical students (mean age, 22 years) participating in a voluntary program of four weekly 30-minute sessions of intense physical exercise consisting of 10 to 15 minutes jogging, 5 to 10 minutes bicycling, and 5 to 10 minutes calisthenics.[57] These tasks were performed each time up to the participants' maximal tolerance during the 7-week program. The results indicate that exercise significantly lowered serum triglycerides (from 110 to 80 mg/dl), pre-β-lipoprotein (42% reduction), β- plus pre-β-lipoprotein cholesterol (29%) and β-lipoprotein (15%), with only modest reduction of cholesterol levels (4%). A concomitant increase in α-lipoprotein levels was observed (14% increase). These investigators interpreted the results to mean that the decrease in serum lipids induced by exercise may be due to its direct effect on the β- and pre-β-lipoprotein fractions. It would have been interesting if they analyzed the cholesterol content in the α-lipoprotein fraction. Since exercise did not substantially lower serum cholesterol, but did decrease β- and pre-β-lipoprotein cholesterol level, it would be important to know whether more cholesterol was actually carried by the α-lipoprotein moiety. Since α-lipoprotein concentration did increase, the data tend to suggest this phenomenon. Therefore, there may be a shift in the functional role of the lipoproteins to carry cholesterol. The relevance of this physiological change to atherogenesis is not clear.

Negative correlations. The effect of a typical training and competitive collegiate swimming program on plasma cholesterol[58] was studied in 12 male varsity swimmers for 14 months. The workout consisted of swimming 1.6 to 3.2 km daily in a series of 402- or 201-meter sprints. The rest interval was from 5 to 10 minutes between sprints. The daily caloric intake was moderately low, averaging 2,559 calories. The investigators concluded that exercise, in the form of varsity swimming, did not significantly lower blood cholesterol levels. Closer examination of the data revealed that the initial serum cholesterol levels of the college swimmers had a mean pretraining value of 169 mg/dl, which was relatively low for that age group (19.3 years). Results of a study by Schilling et al[25] indicated that the average serum cholesterol concentration for that age is 193 mg/dl. Therefore, the pretraining cholesterol values may represent the lower limits of the physiologic range, and to depress that level even further would require greater physical effort than would be the case of a hypercholesteremic group. As with Rochelle,[48] and Naughton and Balke,[49] the authors of this study reported that the blood cholesterol increased with the onset of muscular exercise. They suggested that the body may have a high priority for lipids, including cholesterol, for fuel to supply the increased metabolic needs resulting from acute physical exertion.

Brumbach[59] studied changes in serum cholesterol levels of 40 freshman students from the University of Oregon who failed the university's physical fitness test. Twenty of these subjects remained sedentary (controls). The remaining persons volunteered to take part in an exercise program which met for 35 minutes 3 times a week for 10 weeks. Each subject ate his meals at the university dormitory dining room. Average caloric intake was 2,936 calories. Mean cholesterol levels before the experiment were 201 mg/dl for the control group and 199 mg/dl for the exercise group. Exercise included the U.S. Army Conditioning Exercise Drill No. 1, running (starting with 402.3 meter jogs and gradually increasing the distance to 676.7 meters) and weight lifting. No significant difference in serum cholesterol levels was detected between the control group (190 mg/dl) and the exercised group (196 mg/dl). However, the investigator questioned the "vigorousness" of the physical exercise program.

Holloszy et al[60] determined the effects of a 6-month program of endurance exercise on the serum lipids of middle-aged men. One group (group A) of 15 men (mean age, 41.7 years) who previously led sedentary lives for 3 or more years participated in a progressively strenuous program of endurance calisthenics and distance running (3.22 to 6.45 km), averaging 3.35 times per week for 6 months. Twelve men (group B) in another group (mean age 42.5 years) who also had been sedentary for a number of years, took part in a program of distance running geared to their individual capacities and which increased progressively in intensity. It was estimated that the men expended approximately 1,000 calories per week from participating in the exercise program. Caloric intake was about 2,596 calories per day per individual, of which fat constituted 28% of the total calories. No significant change between the initial serum cholesterol level and the post-training level was found in both groups A and B. There was also no change in body weight. In contrast, there was a significant decrease in the mean fasting triglyceride levels in both groups. Apparently this reduction in serum triglycerides occurred within 2 to 3 hours after exercise and lasted about 2 days. There was some indication that this reduction may have been cumulative, an observation first to be recognized and reported. Similar results were attained by Carlson and Mossfeldt[61] who investigated plasma lipid levels of normal persons who participated in the 1962 and 1963 "Vasaloppet" (an annual ski-racing event). Training consisted of indoor gymnastics 5 months before the experiment. The most pronounced decreases in plasma lipids was in the triglyceride fraction, and this decrease was directly and significantly correlated to the fasting triglyceride concentration. Approximately 75% of the decrease in triglyceride concentration was due to reduction in the amount of triglycerides in the very-low-density lipoproteins. No significant changes were observed in the cholesterol content of any of the lipoprotein fractions.

Fasting total lipids and serum cholesterol levels were studied in 15 medical students, 3 research workers and 2 laboratory technicians who participated in 14 consecutive days of training of short bouts of strenuous exercise.[62] The exercise regimen consisted of nine sets of different calisthenics, each of 60-second duration, with 30-second rest intervals. The results showed that the course of training did not alter the fasting total lipids and serum cholesterol. The authors concluded that this lack of response could possibly be accounted for by the fact that the subjects had initial "normal" serum lipid levels (219.5 mg/dl). It is hardly likely that this conjecture is correct. To expect a hypocholesterolemic effect of this type and duration of physical activity is not reasonable. According to Aastrand and Rodahl[63] the average caloric output due to calisthenics is approximately 4.5 kilocalorie per minute. Therefore about 39.5 calories were expended per training session, a value that can hardly be classified as "strenuous", let alone beneficial. That amount of "work" can be accomplished by milking a cow by hand for 8 minutes.[63] The point is that these types of "exercises" cannot be expected to lower cholesterol levels when the intensity and duration of exercise are in question.

The role of protein, milk intake, and exercise on serum lipid concentrations of 24 university athletes representing the competitive sports of football, basketball, track and field, and wrestling was studied.[64] All subjects were in training for, or were participating in, their respective sports during the entire investigation. Seven basic menus were created, all of which contained 35% of the calories as fat. The menus were adjusted for protein (10.0%, 13.4%, and 16.8% of the total calories) and milk content (no milk, 1 liter, and 2 liters per day per individual) to meet the specifications of each diet. Mean dietary cholesterol intake ranged from 959 to 1,233 mg for no-milk and milk diets. The caloric intake was adjusted to maintain the weight of each subject, and required a range of 3,100 to 4,700 calories. The investigators concluded that no significant effects of the various diets or exercise on serum cholesterol, total lipid, or phospholipids were found. Changes in dietary protein level had little influence on blood lipid values. Although no hypocholesteremic effect was evident through the exercise program, this need not be interpreted as a failure of exercise to have a therapeutic effect. This is especially so when one considers the hypercholesteremic diet given to the athletes (high caloric intake, two eggs per day, high amounts of saturated fats, and large quantities of milk). It has long been known that milk will induce a significant rise in blood cholesterol level.[65-68] Closer examination of the data reveals that in no instance did the serum cholesterol level rise above the initial serum cholesterol concentration even when the special diets were given during the training period. Therefore, one cannot ignore the possibility that the training prevented an increase in serum cholesterol concentration induced by the hypercholesteremic diets.

Animal experimental research

The beneficial effects of physical activity in lowering serum cholesterol concentration are more evident in laboratory animal studies. This can be attributed, primarily, to a more homogeneous sample subjected to a more controlled and symmetrical treatment than the subjects in epidemiologic and human experimental studies.

Positive correlations. Brown et al[69] were the first to report the possible salutary effect of exercise in lowering serum cholesterol. Rabbits were divided into six groups: (1) basal diet, no exercise; (2) basal diet, exercised; (3) 0.1% cholesterol, no exercise; (4) 0.1% cholesterol, exercised; (5) 0.5% cholesterol, no exercise; and (6) 0.5% cholesterol, exercised. A 12-week exercise program consisted of 20 minutes of daily compulsory running in a large, cylindrical, motorized barrel which revolved 12 to 15 times per minute. The results in the six groups at the end of the experimental period were as follows: 36, 42, 350, 192, 1,134, and 581 mg cholesterol/dl, respectively. Serum total cholesterol was increased as the levels of dietary cholesterol were increased. Although no effect was found in the exercised group on basal diet, a hypocholesteremic effect was found in the exercised groups receiving 0.1% and 0.5% dietary cholesterol.

A similar experiment was conducted on cockerels by Wong et al.[70] The birds were separated into three categories: (1) plain mash diet, no exercise (control group); (2) 2% cholesterol + 5% cottonseed oil, no exercise; and (3) dietary regimen similar to group 2, but exercised. Two daily sessions on a motorized treadmill for 7 weeks was the method employed for physical activity. A significant increase was observed in the serum total cholesterol levels of groups 2 and 3 when compared to group 1, and the concentration of cholesterol in group 3 was significantly lower when compared to group 2. In addition, there was a subsequent reduction in formation of atheromatous plaques of the abdominal aorta of the exercised birds. This is in agreement with their earlier finding.[71]

In 1957, Orma[72] reported an extensive investigation on serum lipid levels of 145 cockerels classified into four categories: active and inactive on ordinary diet, and active and inactive on 1.5% cholesterol-supplemented feed. The birds were rendered inactive by restricting the pen area to allow minimal movement. The active birds were allowed a large pen to provide ample motion. It was concluded that there was no difference in either the serum lipid values or the degree of atherogenesis between the active and inactive control groups fed an ordinary diet. In the cholesterol-fed groups the lipid values of the inactive group were significantly higher than those of the active cholesterol-fed group. Moreover, the incidence of atherosclerosis was higher and more severe in the former group. Also, by measuring the relative colloid volume in the thyroid, a much higher volume was found in the active, cholesterol-fed birds as compared to the inactive. This was interpreted as increased thyroid activity, which was the first inference of its kind relating the possible increased thyroid activity associated with exercise.

Rabbits consuming a basal diet had a serum cholesterol concentration of 59 mg/dl, whereas those on a 0.3% cholesterol-supplemented diet had a mean concentration of 903 mg/dl.[73] A cholesterol-fed group who exercised in a motorized drum (alternate periods of rest and exercise every 15 minutes) for 8 hours daily for 2 months experienced a pronounced hypocholesteremic effect, 501 mg/dl, a 45% reduction.

Rabbits given a high-cholesterol diet (750, 250, and 150 mg/day) had a lower serum cholesterol when exercised, only if they were "adequately" exercised.[74] No difference was found in the group of rabbits that had an insufficient amount of physical activity. Moreover, in the adequately exercised group (induced to run continuously in a drum by periodic electrical stimulation) the amount of atherosclerosis in the aorta was distinctly smaller than the sedentary controls.

In an extensive study on the lipid concentration in serum and tissues by Lewis et al[75] at the Cleveland Clinic, four groups of 100 rats each were fed high fat diets containing 22% or 54% saturated coconut oil or unsaturated soya oil. Another 185 rats were fed Hartroft diet, which is a high saturated fat diet (69% of total calories from fat) containing 0.3%, 1.0%, or 3.0% cholate. The 75 chow-fed rats served as controls. Approximately half of each group were exercised on a treadmill 8 hours daily, in which the drum alternately revolved for 2 minutes and stopped for 1 minute. The exercise period lasted for 9 to 14 weeks. Serum and tissue lipid levels of rats were higher with diets containing 54% than 22% fat, and also depended on whether the diet contained coconut or soya oil. The 5-month period of exercise proved effective in lowering elevated serum and hepatic lipids in rats fed high fat diets, but was not long enough to change the levels in rats fed the Hartroft diet. Nine months of exercise resulted in a significant decrease of serum lipids in the latter animals. The effect of exercise differed when the lipid concentrations were either high or normal. Exercise was effective in reducing serum total lipid and cholesterol concentrations only in those animals in which the lipid levels were elevated by high fat intake. When hepatic lipid concentrations were normal, as in rats fed chow diets, exercise had no effect. In rats fed the Hartroft diets, serum but not hepatic lipid accumulation was decreased by exercise. They suggested that in rats fed the Hartroft diet, the relative ineffectiveness of exercise in maintaining low serum and hepatic lipids may be due to a combination of factors. Reduction of serum albumin and increase of β- and γ-globulin concentration in these rats suggests that hepatic damage may have occurred. The Hartroft diet contains several abnormal dietary components, cholate and thiouracil, in addition to an abundance of butterfat. The toxicity of cholate is amply demonstrated. The thiouracil in the diet may have prevented any increase in thyroid activity accompanying exercise.

Montoye et al[76] investigated the effects of exercise on serum cholesterol and correlated those effects with estimates of body fat through experiments with 45 albino weanling rats (15 litter-mate trios). Group A was fed a stock diet and exercised for an hour in the morning and an hour in the afternoon by forced swimming 5 times a week for 12 weeks. Group B was subjected to the same exercise, but a portion of the stock diet was replaced with powdered whole milk so that 30% of the caloric intake was derived from the whole milk supplement. Group C was fed the stock diet but activity was restricted. The total serum cholesterol concentrations at the end of the experimental period were 74.83, 84.90, and 93.08 mg/dl. This clearly indicated that physical activity had a definite hypocholesteremic effect upon the basal diet group as well as the high fat diet group subjected to swimming two hours daily for 12 weeks. The final body weight was less in the exercised group. The additional weight in the nonexercising group was partially due to fat as indicated by the significantly higher specific gravities of the carcasses in the exercised group.

The effect of 15 weeks of regular, vigorous exercise (swimming) on serum and hepatic cholesterol levels of rats was studied.[77] The experimental design included four groups: (1) young, unexercised 13-week-old rats, (2) sedentary adult rats on stock diet, (3) exercised adult rats on stock diet, and (4) sedentary adult rats on a calorie-restricted diet to maintain their weights as closely as possible to the weights of those of the exercising animals in group 3. Growth of calorie-restricted animals was retarded as evidenced by lower ash weight, but their body composition on a percentage basis was almost identical to that of group 2. It was concluded that exercise was effective in preventing most of the increase in body fat and serum cholesterol associated with increasing age. Neither total nor free cholesterol concentration in the liver was affected by physical activity, but the concentration of total hepatic lipids was reduced.

The effects of training programs of various intensities, as well as detraining and terminating training on liver cholesterol levels of rats maintained on high-fat diets were studied.[78] The effect of exercise on the excretion of cholesterol via the feces was also studied. In the first experiment 52 rats with an average initial body weight of about 320 g were divided into four groups equalized with respect to body weight. Groups A, B, and C swam 15, 30, and 60 minutes per day, respectively. Group D served as unexercised controls. Hepatic cholesterol (mg/g wet weight) was 3.06, 3.41, 3.19, and 4.95 respectively, which indicated that the nonexercised animals had the highest concentration. Increasing the daily exercise period beyond 15 minutes did not produce any further statistically significant reduction. Free plasma cholesterol was not altered by training, but total plasma cholesterol was significantly lower only in the group of rats exercised 60 minutes per day (81.91, 78.15, 68.41, and 83.38 mg/dl, respectively). Animals which exercised excreted significantly more sterol in their feces than those which did not exercise. The lack of any difference in sterol excretion between the three exercise groups agrees with the pattern observed for liver cholesterol levels. In the second experiment, rats were trained to run in motor-driven work wheels. The speed and duration of the daily exercise bout were progressively increased until the animals were capable of running for 60 minutes at 1.0 mph. At the end of 8 weeks, one group of rats was taken off the training program, a second group was progressively detrained for 4 weeks by reducing the exercise 2 minutes each day. A third group of rats continued the daily 60-minute run throughout the entire experimental period. Unexercised animals served as controls for the fourth group. Plasma cholesterol was not significantly altered by any of the training programs in which running was used as the exercise. The concentration of cholesterol in the livers of the trained group was significantly lower than that of the untrained group. This change also appeared to be temporary, since the difference between the control group and the group that terminated training at the end of 8 weeks was not significant. It was concluded that the increased excretion of cholesterol via the feces of the exercised rats is one of the means by which the lower hepatic cholesterol level was maintained.

Analogous results on increased cholesterol excretion via the feces in mice were reported by Hebbelinck and Casier.[79] The daily bouts of training which were considered exhaustive consisted of running on a miniature treadmill. Intraperitoneal injection of 4-^{14}C was administered to the animals to examine the effects of exercise on the quantitative distribution of sterol and saponifiable fractions in the liver and excreta. The results were interpreted to indicate that muscular exercise can stimulate the conversion of cholesterol to bile acids and enhance its rate of excretion into the feces. It was inferred that physical activity may increase the rate of cholesterol catabolism. The lower cholesterol content in the liver of exercising animals confirmed other report.[75-78, 80, 81] The data seemed to indicate that it was doubtful whether short duration or single activity might be sufficient to increase the cholesterol catabolism because the differences in excretion of acidic materials and neutral sterol started only after the 6th day of exercise. Only when physical exercise was continued over a longer period was there evidence that cholesterol catabolism and excretion was enhanced.

The effects of strenuous exercise and training were studied on plasma triglyceride, nonesterified fatty acid (NEFA), cholesterol, phospholipids, and lipoprotein in rats.[82] Exercise consisted of 4 hours swimming which lasted for 4 weeks. Another group of animals was subjected to the same exercise treatment, but had a pretraining period to alleviate the possibility of psychic stress due to forced swimming. Kratzing[83] indicated that when rats stood in water for 2½ hours, hepatic lipid and cholesterol values were comparable with those which swam the same length of time. He concluded that factors other than muscular exercise were involved. Similarly, audiovisual stress,[84] emotional stress,[85, 86] psychic stress,[87] and electrical shocks[88] have been known to alter serum lipid and cholesterol concentrations. The results of the experiment of Papadopoulos et al[82] indicated that a sufficiently strenuous exercise and training program may lead to a lowering of serum cholesterol, triglyceride, and certain fractions of lipoproteins in rats. It appeared that there was a relation between the degree of training and the extent to which the plasma cholesterol was lowered, as there was a continuous decrease throughout the exercise period. The apparent rise in plasma cholesterol observed at the end of the 1st week in the untrained group could possibly be related to psychic stress. However, at the end of the experimental period, the hypocholesteremic effect in both the trained and untrained group forced to swim had comparable values. In contrast, the NEFA was significantly higher and triglycerides significantly lower in concentration in the untrained group when compared to the trained group at the end of 4 weeks.

Ahrens and Broxton[89] compared three levels of forced swimming (lead weights 2%, 4%, and 6% of the body weight attached to the tail) to the sedentary controls (immersed in water up to their necks). The young male adult rats were fed a high-fat diet containing 38% of the calories from protein, 50% from fat, and 12% from one of two carbohydrate sources, cornstarch or a mixture diet representative of the typical U.S. "market basket" diets. It was found that exercise (daily bouts of 10 minutes of exercise for 60 days) increased serum cholesterol concentration in the starch fed group, but decreased the concentration in the mixture diet group that was forced to swim with weights equivalent to 6% of their body weight. This group was classified as exhaustively exercised. The control group (immersed) fed the mixture diet had a significantly increased blood cholesterol concentration. Equally confusing was the fact that the moderate level of exercise (2% loading) led to the lowest body weight, the lowest rate of increase in tissue cholesterol, and the lowest accumulation of lipophilic material in the aorta. These results can be attributed to the low water temperature (27 C) to which the rats were subjected during the swimming exercise program. This may have induced a hypothermal stress or some other unnatural physiologic phenomenon. Baker and Horvath[90] studied the influence of water temperature on oxygen uptake of swimming rats and found that the animals swimming in cold water were exhausted before their oxygen uptakes stabilized. Wilber and Hunn[91] reported that there was a positive relationship between decreasing water temperatures and swimming time to exhaustion. Therefore, the performance of the rats, especially those with the heavier load (6%), may have been caused by hypothermic stress, oxygen deficiency, decreased swimming time as compared to the lighter weight-loaded rats, or altered metabolism or both as an adaptation to the metabolic cost of thermogenic activity.

The effects of training on plasma and tissue lipid levels of aging rats was studied.[92] One group of 10 male rats (12 to 13 months old) was trained on a treadmill[92] by running at a speed of 30 cm/sec, 3 hours a day, 5 days a week for 3 weeks. Electrical shocks were employed to induce the rats to run. Another group of 10 rats served as controls. The type of diet was not mentioned, but was assumed to be basal. The high concentration of serum cholesterol of the controls (249 mg/dl) as compared to the trained rats (186 mg/dl) indicated that the hypocholesteremic effect (reduction of 75%) was highly significant.

Malinow et al[93-96] reported that when cholesterol-26-^{14}C was injected intravenously into an animal, the recovered $^{14}CO_2$ in the expired air could be used as a quantitative index of cholesterol side-chain degradation. It was found that treadmill running accelerated cholesterol degradation in rats[93] and in man.[94] Muscular contraction via electrical stimulation of the hindlimbs produced similar results in rats and squirrel monkeys.[95] In 1970, it was reported that oxidation was highly dependent on the adrenal glands, both during rest and exercise, and it was postulated that the hypocholesteremic response to exercise could be mediated through the adrenal glands to increase the rate of cholesterol side-chain cleavage.[96] It was estimated that roughly 80% of the cholesterol oxidation depends on the presence of the adrenal glands in the initial periods of exercise and 20% in the later period. Their latest study on hepatectomized and adrenalectomized rats[96] seemed to support their thesis that the adrenals as well as the liver were mainly responsible for splitting the side-chain of cholesterol during rest and muscular stimulation.

How important are the adrenal glands in promoting increased cholesteroleresis due to increased physical activity? There are some indirect indications that the adrenals may play a role in the hypocholesteremic effect of exercise, and there are several reports on increased adrenal size in rats forced to exercise.[70, 97-102] There is evidence that prolonged physical exercise may stimulate the adrenocortical activity in rats,[103] dogs,[104] and men,[105] whereas in other investigations no such effect was found.[106-108]

Negative correlations. In 1957, Kobernick et al[109] reported the effects of physical activity on cholesterol-fed rabbits (28 g/day). The animals were electrically stimulated to run on a treadmill (50 rpm for 5 minutes, twice daily for a period of 4 weeks). There was no difference in the serum cholesterol and phospholipid concentrations between the sedentary and exercised group.

In contrast to their earlier study[70, 71] Wong et al[110] found no significant effect of physical activity on blood cholesterol level, aortic and coronary atherosclerosis of 45-week-old, egg-laying hens fed an atherogenic diet of 2% cholesterol and 5% cottonseed oil. After 12 weeks the nonexercised hens had the highest incidence of aortic atherosclerosis and marked elevation of blood cholesterol when compared to controls on plain mash diet. The exercised birds on an atherogenic diet did not show a decrease in aortic atherosclerosis or any change in blood cholesterol level.

The serum hypocholesteremic effect of four groups of rats that were fed two different diets was examined by Gollnick.[80] The effect of training (one-half hour daily swimming for 22 weeks) was also examined on serum cholesterol levels. The groups were divided as follows: (1) basal diet, untrained; (2) basal diet, trained; (3) 1.0% cholesterol-0.5% cholate diet, untrained; and (4) 1.0% cholesterol-0.5% cholate diet, trained. The data revealed that training significantly lowered total fat and serum cholesterol in group 2, but produced a rise in both lipid components in the cholesterol-cholic acid fed group.

The effect of fat intake and exercise on serum cholesterol was reported on four groups of rats receiving a high-fat diet and four groups continuing to receive the low-fat diet.[111] Each of the two groups was subdivided into two more groups in which one group was fed *ad libitum* and the other fed 65% of the *ad libitum* group. These four groups, which were trained, also had respective sedentary control groups for comparison. The exercised groups were forced to swim for two 30-minute periods each day for 6 weeks. Their results showed that serum cholesterol was higher in calorie-restricted than in *ad libitum* fed animals and higher in exercised than in sedentary animals. Serum cholesterol was highest in calorie-restricted animals forced to exercise.

There appeared to be a trend toward higher serum cholesterol in rats fed the high-fat diet as opposed to the low-fat diet. Exercise had no effect on either group. It was suggested that the utilization of fat for energy results in accelerated cholesterol biosynthesis. The animals restricted in calories and forced to exercise would have used the greatest amount of body fat for energy, thereby increasing cholesterol biosynthesis which then affects the serum cholesterol level.

Lopez-S et al[112] recently reported on the effects of measured voluntary exercise on serum lipid levels and enzymes related to lipogenesis of rats achieving different levels of exercise for 10 weeks. Both control and exercising young adult male Fischer rats were fed Purina rat chow. Each rat in the exercise group was housed individually in a rodent activity cage allowing voluntary exercise on a revolving drum. Although not by design, the rats were categorized into having done light exercise (ran 0.48 km/day), moderate exercise (1.12 km/day) and heavy exercise (2.72 km/day). Their study showed that food intake was greater in the exercised rats than in their sedentary controls in all three experimental groups. Although the efficiency of weight gain seemed to depend upon initial body weight, a trend of lower efficiency in weight gain was observed in the exercised rats. There were no statistical differences in serum cholesterol levels in the exercising animals in all three groups. The most dramatic effect of physical activity on serum lipids was seen in the triglyceride moiety in which increased effectiveness was seen with increased levels of exercise: 26% reduction at light, 32% at moderate, and 45% at heavier levels of exercise. However, in a subsequent study[113] using the same sex and strain of rats, same mode of physical activity, and same dietary regimen, a lowering of the serum cholesterol was observed ($p < .05$) in the exercised rats. The experiment further showed that this beneficial effect will persist for up to 3 weeks after the exercise is terminated. No explanation was given for the discrepancy in the data between the former study[112] and the latter study.[113] One possibility exists in which if they had used a greater number of experimental animals, the difference in the cholesterol levels between the sedentary group and exercised group would have possibly been nonsignificant due to a possibly larger standard deviation of the values as shown in their former study.[112] These studies emphasize even more the confusing and often contradictory effect of exercise upon serum cholesterol levels.

Hebert et al[114] reported on whether exercise could override the lipogenic differences produced by either a high sucrose (63%) or a high starch (63%) diet. In the first experiment mature Fischer male rats weighing 300 g were used; in the second study young 125-g rats were used. Their findings on both the young and mature rats indicate that rats fed sucrose have higher serum cholesterol levels than rats fed starch ($p < 0.01$). The effect of exercise on serum cholesterol is not clear. Exercise seemed to lower serum cholesterol in the young rats, but raised serum cholesterol levels in the older rats ($p < 0.05$). Exercise caused a highly significant decline in serum triglyceride levels in both the young and old rats. Whether the high carbohydrate diet was sucrose or starch had no effect on the level of serum triglycerides. Liver glucose-6-phosphate dehydrogenase (G-6-PD) was not affected by either diet or exercise in the mature rats. In the younger rats, liver G-6-PD was not affected by exercise, but was significantly affected by diet. Liver malic enzyme (ME) was affected by diet in both age groups, which was higher in the livers of rats fed sucrose than in rats fed starch. It appears exercise did not overcome the liver lipogenic effect induced by sucrose feeding.

Since it is well documented that thyroxine (T_4) is a potent hypocholesterolemic agent[115, 116] and that exercise appears to stimulate thyroid secretion rate,[117, 118] in our laboratory a study was done on the interrelationships of physical activity and thyroid gland on serum cholesterol level.

Five physiological thyroid states were produced in the surgically thyroidectomized male Sprague-Dawley-Rolfsmeyer rats by daily replacement therapy of L-T_4: (1) athyroidism, no L-T_4 replacement; (2) hyperthyroidism, 3.5 μg/100 g BW; (3) euthyroidism, 1.0 μg/100 g BW; (4) hypothyroidism, 0.5 μg/100 g BW; and (5) rats with intact thyroids served as controls. Rats were 220 ± 20 g at the initiation of the experimental period.

The five thyroid groups were further subdivided into four levels of physical activity: (A) nonexercised controls, (B) standing in 7.6 cm of water to check the possibility of water-induced stress, (C) moderate exercise, and (D) exhaustive exercise. Daily swimming was employed in groups C and D. The criterion for rats swimming until exhausted[119] was allowing each rat to swim until it could no longer remain swimming above water. To decrease the swimming time and to stimulate more vigorous swimming, lead weights (4% of body weight) were attached to the tail, and to reduce the buoyancy effect of trapped air under the fur, a wetting agent was added to the water. Moderate exercise was arbitrarily established as one half the mean weekly swimming time of the respective exhaustively exercised groups (group D). The animals swam individually in 20 gallon plastic tanks 6 days a week for 10 weeks. Water temperature was maintained at 37 ± 2 C. The rats were weighed every other day. Daily feed consumption of each rat was recorded. Drinking water and feed (Wayne Lab-Blox) were provided *ad libitum*.

At the end of the experimental period, the rats were bled and then killed. At this time a postmortem check for remaining thyroid tissue was performed in the surgically thyroidectomized animals. The sera and liver were analyzed for total cholesterol[120] content. Serum protein-bound iodine[121] and thyroxine[122] levels were measured.

The results of the study indicate that increased physical activity decreases body weight (*Table 1*) in all thyroid-treated groups with the exception of the athyroid and hyperthyroid groups which were all lean to begin with. Feed intake (*Table 2*) of all thyroid groups did not change with elevated physical activity. However, there was a positive relationship between increasing feed intake and increasing thyroid status. Serum total cholesterol levels (*Table 3*) of all thyroid groups except the control rats did not change with elevated physical activity. The control rats with intact thyroids had progressively lower cholesterol concentrations with increasing physical activity. There was an accumulation of hepatic cholesterol (*Table 4*) in the athyroid animals regardless of the amount of exercise. There were indications of accumulation of hepatic cholesterol in the euthyroid and hypothyroid exhaustively exercised groups. This phenomenon may be due to a decreased efficiency to catabolize cholesterol to bile acid in thyroxine-insufficiency states.[116]

The above data suggest that physical activity will lower serum total cholesterol in rats with intact thyroids. Whether this effect is mediated through increased thyroid secretion rate is not known. The decrease is not a consequence of decreased feed intake, and not a result of weight reduction, because weight reduction occurred in other thyroid groups. Since adrenal weights did not change in the exercised rats as compared to the standing or control rats (*Table 5*), it is also unlikely that the decrease in serum cholesterol concentration was primarily due to increased steroidogenesis by the adrenal glands as suggested by Malinow et al.[93-96]

Unfortunately, the serum PBI and T_4 measurements (*Table 6*) of the nonexercised and exhausted exercised rats only reflect the relative thyroid states and

Table 1. Influence of different levels of physical activity and thyroxine on final body weight (mean ± S.E.M.)

Thyroid status†	Physical activity* No exercise	Standing	Moderate exercise	Exhaustive exercise	Mean (A)
Control	425.2 ± 11.8†	415.7 ± 4.0	393.9 ± 8.4§	366.5 ± 12.3‖	(400.3 ± 9.1)
Athyroid	306.5 ± 21.2	298.4 ± 13.9	284.0 ± 15.6	299.6 ± 14.3	(294.9 ± 16.3)‖
Hyperthyroid	376.7 ± 10.1	378.6 ± 11.3	376.4 ± 10.5	375.5 ± 9.9	(376.8 ± 10.5)‖
Euthyroid	417.6 ± 11.2	409.5 ± 8.9	373.8 ± 10.0‖	359.3 ± 9.7‖	(390.0 ± 9.9)
Hypothyroid	406.1 ± 10.2	393.3 ± 10.9	381.1 ± 11.0	376.1 ± 10.1§	(389.1 ± 10.5)
Mean (B)	(386.4 ± 13.9)	(377.3 ± 13.7)	(361.8 ± 12.7)**	(355.4 ± 9.2)‖	

* lsd (least significant difference, at = .05) for B = 14.63 g.
† lsd for A = 16.36 g.
‡ lsd for AB = 32.65 g.
§ .05 < p < .1.
‖ p < .0005.
** p < .01.

Table 2. Influence of different levels of physical activity and thyroxine on daily feed intake (g/100 g BW)

Thyroid status†	Physical activity* No exercise	Standing	Moderate exercise	Exhaustive exercise	Mean (A)
Control	6.40 ± .40‡	6.50 ± .38	6.66 ± .19§	6.59 ± .18	6.54 ± .29
Athyroid	6.14 ± .27	5.91 ± .19	5.96 ± .04	5.88 ± .13§	5.97 ± .16‖
Hyperthyroid	7.68 ± .14	7.23 ± .26	7.55 ± .13	7.31 ± .01**	7.48 ± .15‖
Euthyroid	6.17 ± .14	6.46 ± .11	6.34 ± .20	6.17 ± .14	6.29 ± .15††
Hypothyroid	6.43 ± .25	6.39 ± .36	6.45 ± .10	6.28 ± .06	6.39 ± .19‡‡
Mean (B)	6.57 ± .24	6.45 ± .26§	6.59 ± .15	6.45 ± .11§	

* lsd for B = 0.11 g/100 g BW.
† lsd for A = 0.12 g/100 g BW.
‡ lsd for AB = 0.24 g/100 g BW.
§ p < .05.
‖ p < .005.
** p < .01.
†† p < .001.
‡‡ p < .02.

therefore cannot answer the question of whether the activity of the thyroids is elevated during exercise. Futhermore, the blood was drawn 18 to 24 hours after the final exercise period. Under these conditions the L-T_4 level may not reflect the increased thyroidal activity due to exercise. Concentration measurements do not indicate turnover rates of these compounds. Although the PBI and T_4 concentrations are lower in control rats with intact thyroids compared with other thyroxine-treated rats, the relative turnover rate in the exercised rats with

Table 3. Influence of different levels of physical activity and thyroxine on serum total cholesterol concentration (mg/100 ml)

	Physical activity*				
Thyroid status†	No exercise	Standing	Moderate exercise	Exhaustive exercise	Mean (A)
Control	57.8 ± 2.1‡	58.1 ± 2.0	54.8 ± 1.4	51.6 ± 2.3§	55.6 ± 1.9
Athyroid	59.3 ± 2.3	59.5 ± 2.5	59.6 ± 2.2	61.5 ± 3.5‖	60.0 ± 2.6**
Hyperthyroid	56.5 ± 2.4	54.4 ± 2.1	54.1 ± 2.0	54.3 ± 1.5	55.6 ± 2.0
Euthryoid	61.1 ± 2.9	56.6 ± 2.0	54.1 ± 1.7††	60.7 ± 2.9‖	58.1 ± 2.44††
Hypothyroid	58.3 ± 2.6	59.2 ± 1.9	59.7 ± 2.0	60.6 ± 1.1‖	59.4 ± 1.9**
Mean (B)	58.6 ± 2.5	57.6 ± 2.2	56.5 ± 1.5	57.6 ± 2.3	

* lsd for B = 4.13 mg/100 ml serum.
† lsd for A = 3.25 mg/100 ml serum.
‡ lsd for AB = 6.51 mg/100 ml serum.
§ $.05 < p < .1$.
‖ $p < .01$.
** $p < .02$.
†† $p < .05$.

Table 4. Influence of different levels of physical activity and thyroxine on total hepatic cholesterol concentration (mg/100 g BW)

	Physical activity*				
Thyroid status†	No exercise	Standing	Moderate exercise	Exhaustive exercise	Mean (A)
Controls	0.86 ± .04‡	0.87 ± .02	0.95 ± .04	.98 ± .03	0.92 ± .03
Athyroid	1.34 ± .09	1.40 ± .08§	1.36 ± .07§	1.35 ± .07§	1.36 ± .08§
Hyperthyroid	0.98 ± .00	0.96 ± .04	0.95 ± .04	1.02 ± .05	0.98 ± .03
Euthyroid	0.90 ± .03	0.97 ± .04	0.97 ± .04	1.07 ± .04‖	0.98 ± .04
Hypothyroid	0.90 ± .04	1.04 ± .05**	1.02 ± .06**	1.13 ± .05††	1.02 ± .05††
Mean (B)	0.99 ± .04	1.05 ± .05	1.05 ± .05	1.11 ± .05§	

* lsd for B = .07 mg/100 g BW.
† lsd for A = .07 mg/100 g BW.
‡ lsd for AB = .15 mg/100 g BW.
§ $p < .0005$.
‖ $p < .05$.
** $.05 < p < .1$.
†† $p < .001$.

Table 5. Total adrenal weights of the 20 treatment combination groups (mg)*

Thyroid status	Physical activity: No exercise	Standing	Moderate exercise	Exhaustive exercise	Mean
Euthyroid control	50.5	44.1	44.2	51.9	47.6
Athyroid	36.8	32.6	30.8	35.0	33.8
Hyperthyroid	40.9	47.4	45.9	46.7	45.1
Euthyroid	41.3	44.6	45.0	44.2	43.7
Hypothyroid	37.1	39.5	48.9	42.8	42.0
Mean	41.3	41.6	42.9	44.1	

* Wet tissue weight (right and left adrenals).

Table 6. Serum thyroxine and protein-bound iodine concentrations in nonexercised and exercised rats

	Nonexercised		Exhaustive exercise	
	T_4 (μg/dl)	PBI (mEq/dl)	T_4 (μg/dl)	PBI (mEq/dl)
Control	2.5 ± 0.3	2.2 ± 0.2	3.0 ± 0.4	3.7 ± 0.2
Athyroid	Trace	Trace	Trace	Trace
Hyperthyroid	6.5 ± 0.5	4.5 ± 0.8	10.0 ± 0.3	8.2 ± 0.2
Euthyroid	4.4 ± 0.4	3.4 ± 0.3	3.6 ± 0.0	4.0 ± 0.0
Hypothyroid	4.4 ± 0.2	4.0 ± 0.4	4.4 ± 1.3	4.4 ± 0.8

intact thyroids may be higher as described by others.[117, 118]

The mechanism by which serum total cholesterol is lowered in rats forced to exercise until exhaustion is still not clear from this study. It does demonstrate that an intact thyroid is necessary for cholesterol reduction. It may be mediated indirectly by increased thyroid activity, which in turn is stimulated by increased release of TSH from the anterior pituitary gland (*Figure*). Exercise may increase TSH release by two possible pathways: (1) by directly stimulating the hypothalamus to release TRF (thyroid releasing factor) via the central nervous system or (2) by increasing the peripheral utilization and fractional turnover rate of thyroxine, reducing the negative feedback on the hypothalamus or adenohypophysis so that TSH is released. Subsequently, hepatocellular binding and fractional turnover rate of thyroxine are increased, allowing hepatic cholesterol degradation and excretion rates to exceed the biosynthetic rate. This causes the serum cholesterol influx into the liver to transcend the rate of efflux so that, ultimately, the cholesterol pool in the serum is lowered. Moreover, this catabolic process occurs mainly in the thyroxine-dependent liver and not in the adrenal glands.

This proposed mechanism does not imply that the thyroid hormone alone regulates cholesterol metabolism. It is very likely that other hormones contribute to the hypocholesteremic effect of exercise. Friedman et al[123] demonstrated that growth hormone was as effective as the thyroid extract in reducing the post-

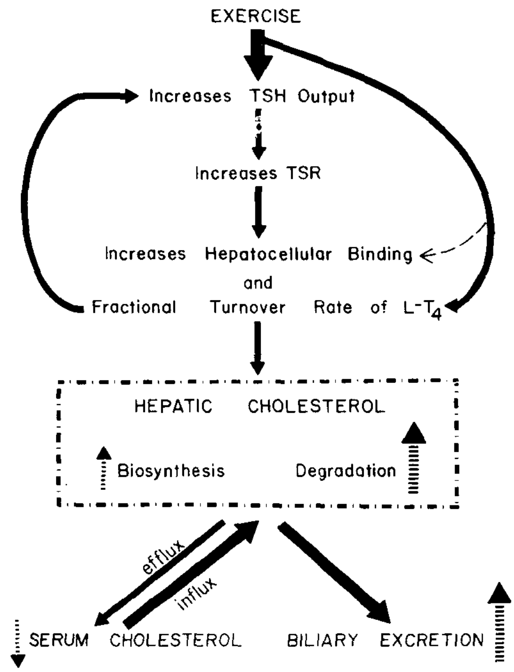

Figure. Suggested mechanism by which hypocholesteremia is mediated by increased physical activity. TSH = thyroid stimulating hormone, TSR = thyroid secretion rate, L-T_4 = L-Thyroxine.

operative hypercholesterolemia of the hypophysectomized rats. Neither hormones alone could completely inhibit the development of the rising cholesterol levels in the hypophysectomized rats. When the two hormones were given in combination, hypercholesterolemia was completely prevented. A serum cholesterol concentration resulted which was similar to that of the control rats with intact thyroid and pituitary glands.

The following year Friedman et al[124] reported that glucagon may be the most potent endogenous agent in the regulation of plasma cholesterol. Chronic administration of glucagon (250 mg/day) reduced the normal plasma cholesterol of stock-fed rats and was capable of preventing hypercholesterolemia in rats subjected to various plasma cholesterol-elevating procedures.

These recent findings are important because of the current reports showing that exercise will increase the level of growth hormone, glucagon, and thyroxine.

Summary

The relationship of exercise to serum cholesterol concentration becomes less confusing when the intensity, duration, and kind of physical activity are considered. Separation of the findings into epidemiologic, human experimental, and animal experimental research also clarifies this relationship. It appears that the higher the initial serum cholesterol level before the exercise program, the more effective was increased physical activity in lowering the cholesterol concentration. Dynamic, vigorous exercise (i.e., cross-country running, tennis, swimming) is more effective than static exercise (i.e., weight lifting, golf, calisthenics, bowling) in lowering serum cholesterol levels. The effectiveness of the exercise program is, to

a large extent, also influenced by total caloric intake, type of diet, and genetic variability. The mechanism by which this hypocholesterolemic effect is mediated through increased physical activity is not known. It could be mediated by way of the endocrine system. Exercise may increase thyroid secretion rate which increases cholesterol degradation to bile acids. This causes the serum cholesterol influx into the liver to transcend the rate of efflux which ultimately lowers the cholesterol pool in the serum.

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