Physical exercise and the prevention of atherosclerosis and cholesterol gall stones

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Summary

There is accumulating evidence in man and experimental animals that even mild exercise, if regularly repeated, may alter the metabolism of lipids. Exercise has been reported as decreasing peripheral tissue cholesterol in red blood cells, working muscle, lungs and the liver. During physical activity, the output of cholesterol and bile acids into the bile increases. This probably leads to higher faecal losses of sterols which may lead to lower cholesterol levels in the peripheral tissues and in the bile, when exercise is repeated regularly. Preferential release of unsaturated fatty acids from the adipose tissue during exercise and the linoleic acid-dependent LCAT enzyme (transporting plasma cholesterol) may be partly responsible for this effect of exercise. The experimental data reviewed provide supportive basis for epidemiological studies reporting on the beneficial effect of regular exercise.

Physical activity is an important factor in the phylogeny of all animal species, secondary only to food intake and reproduction. Exercise is readily available to all population groups. There is good evidence that the amount of exercise required for a protective effect is easily accessible for time-pressured and older individuals. Short bursts of activity repeated several times a day may be equally or more beneficial than prolonged exhaustive exercise. Modified exercise is also beneficial for patients with coronary heart disease and for elderly patients, provided this is done under strict medical supervision. To be effective, physical exercise should be regular and continuous throughout life.

PHYSICAL inactivity is considered among the major risk factors contributing to the development of coronary heart disease in technically developed countries (Fox, Naughton and Gorman, 1972). The decrease in energy requirements and the diminishing of physical exertion in our society have been so gradual that we may not be fully aware of the consequences of this change for our habits, health and lives. Since there is a good possibility that habitual physical exercise protects in some degree against degenerative disorders, this is taken by many

authorities to be adequate justification for recommending regular exercise. Significant correlation exists between exercise-saving factors, such as the national income, number of cars, radios and TV sets, and the risk of a coronary attack (Brunner *et al.*, 1967). The existence of associations proved by epidemiological methods does not establish a cause-and-effect relation and we have to seek for additional evidence obtained by other investigative techniques. Mann (1975) claims the most probable cause of the rise of coronary heart disease to be the leisurely life. However, for the food and pharmaceutical industry with its large research funds, it is much less profitable to seek remedies against physical inactivity than against dietary risk factors and diseases such as hypertension. White (1972), always a strong proponent of 'walking to wisdom', expressed hopes that an adequate interest will develop for more scientific studies on exercise which for too long have played third or fourth fiddle to the greater amount of research on dietary and nutritional factors.

Most of the experimental data available until 1970 on the effect of exercise on lipid metabolism have already been summarized by the author (Simko, 1970).

The years since 1970 have shown a continued interest in the preventive role of physical exercise in degenerative diseases of man. New epidemiological and clinical studies have been designed to document the value of regular exercise in reducing coronary-pulmonary-circulatory risk factors (Morris *et al.*, 1973; Paffenberger and Hale, 1975; Brunner *et al.*, 1974; Cassel *et al.*, 1971). Alarming reports were published on the poor physical fitness of young men from the U.S. compared to men in other countries, and speculations were made on the possible association with the high prevalence of mortality from heart attacks in the United States (Cooper, 1970). 'Jogging' has become increasingly popular, and various physical fitness programmes have been springing up all over the American continent. Practical tests for physical fitness and cardiac performance have been proposed (Sharrock, Garrett and Mann, 1972).

Exercise is now an important part of cardiac rehabilitation, beginning in the coronary care unit and early ambulation after myocardial infarction is strongly endorsed. Some proponents of exercise go even further and report on the beneficial effects of distance running in cardiac patients with bypass grafts and after myocardial infarction (Bassler and Scaff, 1975). Physical exercise became an important diagnostic tool in routine evaluation of the pulmonary functions (Jones, 1975) and the data on ventilatory mechanics during exercise in healthy elderly men were described in detail (de Vries and Adams, 1972b).

However, many important questions about exercise remain unanswered. If exercise has a protective potential, what are the responsible metabolic mechanisms? How much exercise is enough to halt coronary disease and other degenerative disorders? How long does the protective effect of exercise persist when previously exercising individuals become inactive? How much exercise is needed to prevent obesity? How much exercise is harmful in health and in disease?

The gross stress of extreme long-distance running may lead to diseases from maximal exercise unveiling disposition to some disorders (musculo-skeletal, cardio-vascular, renal, neuro-psychiatric) which would not otherwise become manifest. Exercise tests for evaluation of heart disease are fraught with a mortality of about 1/10 000 tests (Rochmis and Blackburn, 1971). Consequently, the Committee on Exercise and Physical Fitness of the American Medical Association (Editorial, 1972) and others (Cooper and Zechner, 1971) published guidelines for participation in an exercise programme.

The animal body has a remarkable potential to conserve energy from the diet: most marathon runners require only about 2400 to 3600 kcal to complete a 26-mile run (Costill, 1972). From calculations of caloric expenditure at various types of exercise it seems that unless exercise is very strenuous and prolonged, prevention of obesity still requires moderation in the dietary intake. Thus, the potential benefits of exercise obviously are related more to specific changes in the intermediary metabolism rather than to simple 'burning' of calories.

More recently, Paffenberger and Hale (1975) published a study on the relative advantage of heavy physical work to prevent the syndrome of sudden-death from a coronary accident. This study, of 6351 longshoremen for 22 years, stressed the potential importance of short bursts of high energy output. Although not all possible variables could have been accounted for in the experimental design, this study provides solid evidence that individuals with adequate endurance fitness may be spared the clinical disasters of coronary heart disease.

Another study on the apparent protective effect of vigorous exercise against rapidly fatal heart attacks was reported in a survey of almost 17 000 male executive workers in Britain (Morris *et al.*, 1973). Peak exercise levels considered 'vigorous' were close to the 5.0–7.0 kcal/min category reported from the longshoremen by Paffenberger and Hale (1975).

In 1974, Brunner *et al.* reported a 2–4 times higher incidence of coronary heart disease and its complications in 5288 middle-aged sedentary males when compared to their physically active counterparts. This study, performed for 15 years in the controlled environment of the Israeli collective settlements, showed that this effect of exercise was specific: food was the same for the whole community and there were no differences in body weight between the sedentary and physically active employees. In a follow-up study on the incidence of coronary heart disease in Evans County, Georgia, Cassell *et al.* (1971) suggested that sustained physical activity above a certain critical threshold was protective against coronary heart disease.

Keys (1970) analysed critically the epidemiological studies of the 1960s relating coronary heart disease to physical inactivity. His criticism included large studies published before 1969: the study on U.S. railway employees (Taylor, 1967), the Framingham Study (Kannel, 1967), and the Health Insurance Plan Study in New York City (Frank *et al.*, 1966). He found serious faults in the analyses of the data and felt there was no epidemiological scientific basis for the hypothesis that lack of physical exercise was a major cause of coronary heart disease.

What supportive evidence for the beneficial effect of physical exercise is there in the animal and clinical studies? De Vries and Adams (1972a) summarized the available evidence that physical work improved cardiac function, oxygen transport and working capacity in men (Saltin *et al.*, 1968). He concluded that age was not a limitation for physical activity: at any given workload the work of the heart was not significantly different in healthy normotensive older men than in the young (although maximal physical work capacity of the elderly men was considerably lower).

Studies on longevity in exercising versus sedentary rats (Edington, Cosmas and McCafferty, 1972) indicated an increased life span when regular exercise was started at a young age. Intensive exercise initiated in old rats decreased their survival. Not only the 'threshold' age (Edington *et al.*, 1972) may be a limiting factor for starting an exercise programme but the intensity of the programme is also significant.

Anthropometric and biochemical data collected in seventy-five adults were used to study the metabolic importance of inactive muscle mass versus body fat

(Simko, 1973). The results indicated that the amount of body fat was metabolically more important than the amount of inactive lean body mass. In order to exert significant metabolic effect the muscle mass must be engaged in regular activity.

In another study (Simko, Merrifield, and Stouffer, 1974) college students were subjected to a daily exercise routine for nine weeks. Compared with non-exercising controls, mild exercise significantly decreased the skin fold measurements (subcutaneous fat) overlying the working muscles. No changes were induced in other skin fold areas, in plasma cholesterol and free fatty acid response to glucose (probably because of the low energy requirements of the exercise).

This attractive possibility of 'spot reduction' of body fat by localized exercise, while reported by others (Olson and Edelstein, 1968) was not confirmed in a study in tennis players (Gwinup, Chelvam and Steinberg, 1971) who had no difference between the skin folds of the hypertrophied and those of the 'normal' forearm. However, there is a substantial difference in the exercise pattern reported in these two studies. Playing tennis actively involves many other muscle groups, whereas lifting a weighted boot (Simko *et al.*, 1974) is a much more selective exercise which may increase lipolysis or inhibit lipogenesis in the adipose tissue adjacent to the working muscle groups.

Physical fitness is attainable for middle-aged and older individuals without the need for time- and energy-consuming intensive exercises (Mann, Garrett and Long, 1971). In this study, physical fitness was achieved by an initial programme of exercise five times 60 min/week at 380–450 kcal/hr and it could be maintained with three 20-min exercise per week, each at 600–900 kcal/hr.

More recently, several reports were published indicating that exercise may affect the high density lipoproteins (HDL) which pick up cholesterol from body cells and carry it in the plasma to the liver. Excretion of cholesterol via the liver then may provide protection against cholesterol-related disorders.

In a study on young healthy men, Simko, Kelley and Connell (1976) reported that 30 min of a mild physical exercise decreased the cholesterol and phospholipid concentration of the red blood cells and increased the bile acid and cholesterol output in the bile. There was a trend to a decrease in saturation of the bile with cholesterol. Exercise intensity required to promote these changes was equivalent to walking 5.5 km in one hour. At 4.7 kcal/min it was close to the amount of exercise reported by Mann *et al.* (1971) as that required to achieve an adequate physical fitness. When exercise increased the output of bile acids and cholesterol in the bile and decreased the red blood cell lipids there was a trend to a

decrease in plasma cholesterol and phospholipids (Simko *et al.*, 1976). Thus in man, relatively mild exercise probably promotes the transport of cholesterol from the peripheral tissues via liver into the bile. This study also indicates that lack of physical exercise may be a pathogenetic factor in degenerative disorders affecting the gastrointestinal system, namely in the pathogenesis of cholesterol gall-stones.

Studies in experimental animals provided supportive evidence for the effect of exercise on bile composition and red blood cell lipids observed in humans. In rats (Malinow, McLaughlin and Pierovich, 1972) the immediate effect of exercise was an increase in bile flow and an increase in the incorporation of cholesterol label into bile acids. There is abundant evidence that chronic intermittent exercise decreases cholesterol concentration and cholesterol output in the bile. In rats exercised for 2 hr, bile collected in the subsequent 24-hr period demonstrated a significantly decreased cholesterol output with no changes in the bile acid output (Simko and Chorvathova, 1968a, b). Rats exercised regularly for 105 days had decreased cholesterol output in their resting bile sample compared to sedentary controls (Simko *et al.*, 1970). In two separate experiments, rats regularly exercised for 24 days (Simko and Kelley, 1977a) or 47 days (Simko and Kelley, 1977b) had significantly lower cholesterol and phospholipid concentration in their bile with no changes in the bile flow and biliary bile acids. These changes in bile composition significantly decreased the cholesterol saturation of the bile in rats exercising for 24 days.

Exercise probably stimulates bile flow and bile acid and cholesterol output in the bile only during actual muscular activity (Simko *et al.*, 1976). In the rest intervals between periods of exercise, adaptive changes occur which influence metabolism of bile acids and cholesterol. Since the intestinal absorption of bile acids is much more efficient than that of cholesterol, regular exercise may promote faecal losses of neutral sterols and increase the number of circulations of bile acids through the liver. Increased amount of bile acids returning to the liver during exercise may depress the hepatic synthesis of cholesterol. These assumptions which need further experimental support would explain the decrease of tissue cholesterol and an improved cholesterol solubility in the bile reported in the exercise experiments.

As in man (Simko *et al.*, 1976), red blood cell cholesterol was significantly lower in rats subjected to 78 days (Simko and Kelley, 1976) and to 47 days (Simko and Kelley, 1977b) of regular exercise. In these two experiments exercise also induced an increase in the lecithin-cholesterol acyltransferase (LCAT). An increase in plasma LCAT activity induced by exercise was also reported in humans (Lopez *et al.*, 1974). LCAT is probably responsible

for the transport of cholesterol from the peripheral cells to the liver (Glomset, 1970).

A decrease in liver cholesterol in animals exposed to exercise reported previously (Simko, 1970) was confirmed by other authors (Monsen, Arlin and Rumery, 1972). Morgan, Short and Cobb (1969) reported that exercise lowered the content of cholesterol in the skeletal muscle.

What other mechanisms altering lipid metabolism may be induced by physical exercise? Exercise results in a release of fatty acids from the adipose tissue and their rise in plasma (Simko and Chorvathova, 1969; Felig and Wahren, 1975; Fröberg, 1971). Animals showing a significant decrease of liver cholesterol induced by chronic intermittent exercise had an increase in the serum total polyunsaturated fatty acids (Simko and Babala, 1964).

Increased levels of circulating polyunsaturated fatty acids may have a dual role. Long chain fatty acids serve as a major source of energy for the skeletal muscle (Therriault *et al.*, 1973), which in exercise undergoes adaptive enzymatic (Mole, Oscai and Holloszy, 1971) and structural (Gollnick and King, 1969) changes in the mitochondria. In addition to this caloric function, circulating polyunsaturated fatty acids may facilitate transport of other lipids, including cholesterol. Immediately after a marathon run, a rise in plasma unsaturated fatty acids was associated with a reduction in the percentage of stearate and an increase in the percentage of linoleate (Hurter *et al.*, 1972). Even in the resting state, these runners maintained more active adipose tissue lipolysis and more readily disposed of the mobilized fat than did the sedentary subjects.

In exercising rats (Simko *et al.*, 1970), there was an increase in the saturated fatty acids and a decrease in polyunsaturated fatty acids in the adipose tissue triglycerides with a reverse trend in the liver triglyceride fatty acids. The possibility that exercise may preferentially release certain fatty acids from the adipose tissue during exercise was strengthened by data of other authors. Allard *et al.* (1973), observed an increase in the adipose tissue palmitic acid and a decrease in oleic acid in coronary patients subjected to physical training.

The adipose tissue of turkeys subjected to exercise contained significantly more saturated (palmitic and stearic acid) and less oleic and linoleic acid than that of the sedentary controls (Ginter *et al.*, 1973), while the liver triglycerides of the active animals contained less saturated fatty acids and more linoleic acid. That the preferential release of certain fatty acids from the adipose tissue of exercising animals is mediated by norepinephrine is at this point more a speculation than an experimental fact. It appears that physical activity enhances adipose tissue sensitivity to catecholamines (Riddle, Ryan and Schwartz, 1972).

Hunter, Buchanan and Nye (1970) presented evidence that in rats, the rate of release of fatty acids from the adipose tissue depends on their structure. In their study, norepinephrine had little effect on the release of saturated fatty acids but it markedly increased the release of linolenic acid from the adipose tissue. Since physical exercise results in an elevation of circulating norepinephrine, it seems appropriate to put forward the hypothesis of a preferential release of the metabolically more active polyunsaturated fatty acids from the depot fat as a consequence of exercise (Simko *et al.*, 1970). Another supportive evidence that exercise differentially affects saturated and unsaturated fatty acids is derived from studies on tissue lipases (Hunter *et al.*, 1970). Tissue lipases stimulated by humoral effects of exercise may have specificity for a particular ester bond of fatty acid distribution in the triglyceride molecule with an affinity to bonds with unsaturated fatty acids.

Linoleic acid (derived either from the fat depots or the diet) is an important component of the LCAT enzyme in plasma. This enzyme affecting the transport of cholesterol is probably stimulated by unsaturated fatty acids released from fat depots during exercise (Simko and Kelley, 1976, 1977b). Relative physical inactivity in modern man may thus be creating a greater need for polyunsaturated fatty acids in the diet. The cholesterol-lowering effect of exercise as well as the hypocholesterolaemic action of dietary unsaturated fatty acids (Moore *et al.*, 1968) would then have a common denominator in increased faecal loss of biliary sterols. The activity of LCAT depends on HDL in plasma. Recently there appeared several reports that exercise increases the HDL fraction in plasma. Four days of running 3–4 miles in 40 min/day normalized type IV or type V lipoprotein abnormalities (Oscai *et al.*, 1972) but the effect was observed only on the days of exercise. A programme of 17 weeks of jog-walking 2.5 miles twice/week led to an increase in the HDL/low density lipoprotein cholesterol ratio (Lewis *et al.*, 1976). Physical exercise in volunteers decreased the β -lipoproteins and increased α -lipoproteins (HDL) (Vial *et al.*, 1971). Men running more than 15 miles/week had significantly lower plasma cholesterol, lower low-density lipoprotein cholesterol and higher HDL cholesterol (Wood *et al.*, 1976). HDL cholesterol, as opposed to low density lipoprotein cholesterol is negatively related to the incidence of coronary heart disease (Miller and Miller, 1975). Although 30 min of treadmill walking per day for 4 days did not affect the cholesterol distribution in the lipoprotein fractions in plasma (Gyntelberg *et al.*, 1977) there remains a good possibility that exercise is the least harmful way to raise HDL. Increase in HDL due to regular exercise would simulate plasma lipoprotein

patterns of young women (Barr, 1953) and of kindreds with an elongated life span (Glueck *et al.*, 1976).

Many of the diverse and inconsistent results with the effect of exercise on plasma cholesterol may be attributed to the previous lack of our understanding of HDL cholesterol. They also may have been caused by the great variability in the intensity, duration, and type of physical exercise (Naito, 1976).

After these comments on the potential role of adipose tissue fatty acids, plasma LCAT and HDL in exercise let us quote studies on the effect of exercise on the lipogenesis in the adipose tissue. In animals subjected to exercise, reduced lipogenesis may induce lower levels of adipose tissue triglycerides as well as an increased lipolysis (Watt, Foss and Block, 1972). Adipose tissue glucose 6-phosphate dehydrogenase (supplying NADPH required for fatty acid and cholesterol synthesis) was decreased by regular exercise in rats (Askew *et al.*, 1975b; Lopez *et al.*, 1975; Nee and Hartsook, 1971). Exercise also induced in rats an increased activity of α -glycerophosphate dehydrogenase (Lopez *et al.*, 1975). This enzyme could increase the oxidation of α -glycerophosphate which is required for the synthesis of triglycerides. These observed changes in enzymes related to lipogenesis suggest but do not provide evidence for the inhibiting effect of exercise on lipogenesis.

Rapid proliferation of adipose tissue cells in early life provides basis for the development of obesity at a later age. There is some evidence that exercise may modify this process. Exercise in early life reduced the rate at which adipose tissue cells accumulated in young rats (Oscai *et al.*, 1974). This resulted in lower body fat in later life.

The review of more recent literature on the metabolic effects of physical exercise, listed above, leaves little doubt of the potential benefits of regular exercise. Most of the data concern the impact of exercise on the cardiovascular system and on lipid metabolism. However, there are other physiological systems which are also probably subjected to the beneficial effect of exercise.

One of such systems is the gastrointestinal tract. The author and his colleagues have already outlined the effect of exercise on bile composition in man (Simko *et al.*, 1976) and animals (Simko *et al.*, 1970; Simko and Kelley, 1976). There is also evidence that exercise increases faecal excretion of cholesterol in animals (Gollnick and Simmons, 1967; Hebbelinck and Casier, 1966).

Ever since the clinical study of Bock *et al.* (Bock *et al.*, 1928) it has been postulated that increased blood flow to working muscles (related in part to local muscular vasodilatation) must be partially derived from the splanchnic blood flow. Splanchnic

bed is ideally suited for rapid correction of any imbalance between left ventricular output and peripheral distribution of blood flow (Wade and Bishop, 1962). If such exercise-induced redistribution of blood flow away from the splanchnic bed does occur this would potentially affect multiple functions of the gastrointestinal system. Healthy volunteers exercising vigorously on a bicycle ergometer (Hagenfeldt and Wahren, 1973) had a reduced net splanchnic uptake of free fatty acids permitting a redistribution of the body free fatty acid turnover towards greater utilization by muscle.

Splanchnic blood flow studies during exercise utilizing the hepatic sulphobromophthalein excretion (Wade and Bishop, 1962) indocyanine green excretion (Rowell, Blackmon and Bruce, 1964) and measurements of hepatic arteriovenous differences (Bishop *et al.*, 1957) yielded conflicting results depending on the experimental animal and the intensity of exercise. However, in man, moderate to severe exercise led to marked decreases in hepatic blood flow and in the splanchnic flow (Rowell *et al.*, 1964). Decreased blood flow through the liver does not necessarily have to reduce the clearance of a substance (bile acids, cholesterol) from the organ. Clearance depends not only on the blood flow but also on the removal efficiency (extraction ratio) for the particular substance (Rowell *et al.*, 1964). Decreased hepatic blood flow (if this occurs during exercise) may actually increase the extraction efficiency for the substance by the hepatocytes since the erythrocytes and plasma components remain for a longer period in contact with hepatic sinusoids.

Regarding the effect of exercise on digestion and intestinal absorption, for years we have not known more than the old saying 'After dinner rest awhile, after supper walk a mile'. From observations on his patient with a permanent gastric fistula, Beaumont (1838) in his classical study, was convinced that 'moderate exercise conducted considerably to healthy and rapid digestion'. It is amazing how little information on the effect of exercise on digestive functions is to be found in modern textbooks of physiology or internal medicine.

Campbell, Mitchell and Powell (1928) performed studies on gastric acid response to a Boas test meal during exercise and concluded that moderate exercise soon after a light meal delayed the secretion of gastric juice and the rate of emptying of the stomach. Lighter exercise such as walking did not delay the secretion of gastric juice and increased the rate of gastric emptying. Hellebrandt and Hoopes (1934) confirmed that exhausting exercise inhibited the initial gastric secretory response to a meal whereas mild activity increased the acidity or left the peak of acidity unchanged. Fluoroscopic studies of the influence of exercise on gastric motility showed

that mild exercise hastened the gastric emptying time, especially if exercise followed immediately upon the ingestion of a meal (Hellebrandt and Tepper, 1934). Exhausting exercise inhibited gastric peristalsis which was frequently followed by increased emptying activity so that final emptying was not much altered. These findings were essentially confirmed in 1974 (Ramsbottom and Hunt, 1974): severe exercise at a level of 600 kp m/min reduced the gastric acid secretion and gastric emptying.

Rats demonstrated a highly significant increase in the intestinal absorption of labelled lipids during mild exercise induced by swimming (Simko, Ginter and Cerven, 1963). In volunteers subjected to prolonged severe exercise for one hour, there was no effect on gastric emptying, acid secretion and intestinal absorption of glucose, urea, xylose and electrolytes (Fordtran and Saltin, 1967).

There is a good possibility that mild exercise affects the release of gastrointestinal hormones, the function of the entero-insular axis and subsequently the hypothalamic centre of satiety. In repeated experiments it was documented that mild exercise suppressed the appetite and food intake (Simko *et al.*, 1970; Lopez *et al.*, 1975; Mayer *et al.*, 1954). Physically trained individuals have increased tolerance to glucose (Pruett, 1970), and improved utilization of ketone bodies (Askew, Dohm and Huston, 1975a), whereas physical inactivity and prolonged bed rest result in glucose intolerance and reactive hyperinsulinaemia (Lipman *et al.*, 1972).

In conclusion, physical exercise is an important metabolic factor to which we should be exposed regularly and daily. There is now strong evidence that it is beneficial not only in terms of improved cardiac and pulmonary efficiency, it also has favourable effects on hormonal regulations and on the metabolism of lipids, including cholesterol. Experimental data provide sufficient evidence for the claim that lack of physical exercise is one of the major risk factors in the development of degenerative disorders of the technological age.

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