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EFFECTS OF DIET ON LIPOPROTEIN METABOLISM

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INTRODUCTION

The relationship of diet to lipid metabolism and to atherosclerosis has engendered great interest and even controversy for several decades. However, much of the heat has gone out of the controversy because accumulated data now document that dietary factors do indeed affect plasma levels of lipoproteins and lipoprotein metabolism; at the same time the association between plasma lipoprotein concentrations and risk of coronary heart disease has been well established by epidemiological and experimental studies (10, 28, 50, 59). As a result, groups such as the American Heart Association recommend that the public make changes in their eating patterns (31, 33).

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In this review, we discuss major dietary factors affecting lipid metabolism such as dietary cholesterol, fat, saturated fat, polyunsaturated fat, carbohydrate, and protein. The emphasis is on studies in human beings and on information accumulated during the last few years. To aid in the interpretation of data, the metabolism of lipoproteins is first reviewed briefly.

OVERVIEW OF LIPOPROTEIN METABOLISM

The components of the plasma lipid transport system include various classes of lipoproteins, cellular receptors, and enzymes. The lipoproteins are composed of varying amounts of triglycerides, free cholesterol, cholesterol esters, phospholipid, and proteins. The system transports triglycerides, phospholipids and cholesterol from their sites of entrance into the body to the cells where they are required for energy (as in the case of triglycerides) and for membrane structure and hormone synthesis (as in the case of cholesterol). Lipids can enter the system from the diet, the liver, and peripheral tissues.

Dietary cholesterol and the fatty acids hydrolyzed in the intestine from dietary fats are absorbed into enterocytes. The lipids are reesterified in the endoplasmic reticulum and packaged in chylomicrons with several apoproteins, including A-I, A-IV, and the intestinal form of apoB, identified as B48 (41) and phospholipids. Chylomicrons are secreted into the lacteals of the laminal propria of the intestinal villus and enter the venous circulation via the thoracic duct (24, 70). During their movement from lymph to blood, chylomicrons acquire additional apolipoproteins C and E from high-density lipoprotein (HDL) (34). These modified chylomicrons interact with lipoprotein lipase, an enzyme bound to the endothelial surfaces of cells in capillaries in many parts of the body (35). Apolipoprotein C-II located on the surface of the chylomicrons activates lipoprotein lipase, which catalyzes the hydrolysis of triglycerides and phospholipids to free fatty acids, glycerol, and lysophospholipids that are then taken up by tissues (5). In addition to losing most of their triglyceride cores, chylomicrons lose cholesterol and apoproteins A-I, A-IV, and C but retain apoB and apoE. Some of the lost proteins and phospholipids form disc-like lipid bilayer complexes (83) called nascent HDL. The remaining chylomicron particle with most of its triglyceride removed is called a chylomicron remnant. It can interact with the apoprotein E receptor on the surface of hepatic parenchymal cells, and be taken up by endocytosis.

In the hepatocytes, the remnants' triglycerides, cholesterol esters, phospholipids, and proteins experience diverse fates. Triglycerides are hydrolyzed and used for energy; sterols and phospholipids are used for membrane synthesis or secreted into bile; proteins are hydrolyzed to amino acids. Lipid components of remnants also can be recirculated by the liver once they are incorporated into other lipoproteins (79). In addition to entering the liver, chylomicron remnants

also may be removed from the circulation by scavenger cells, particularly when remnants are present in plasma in large concentrations, as in some cases of hypertriglyceridemia.

Very low-density lipoproteins (VLDL) are produced by the liver. The particles contain predominantly triglycerides and apoproteins B, E, and C. Triglycerides are synthesized from free fatty acids from the circulation (72) or from other plasma lipoproteins. A form of apoB called apoB100 is necessary for secretion of VLDL by the liver (41). After release, VLDL acquires apoprotein C and interacts with lipoprotein lipase, losing triglyceride and leading to release of fatty acids and glycerol. As with chylomicrons, nascent HDL also is released, and remnant VLDL particles are formed. In normal individuals, most VLDL remnants are modified to form low-density lipoproteins (LDL) that contain almost exclusively apoB as their apoprotein. In hypertriglyceridemic persons, a large proportion of VLDL remnants are removed from circulation before being converted to LDL. VLDL remnants and LDL interact with specific high-affinity receptors present on cells throughout the body, including the liver (8). The lipoproteins are taken up by the cells and deliver cholesterol used for membrane structure and steroid hormone synthesis. VLDL remnants also may be taken up by scavenger cells. This "scavenger pathway" is probably implicated in atherogenesis.

The sources of the mature, spherical, high-density lipoproteins (HDL) in plasma are the nascent HDL particles, composed of a phospholipid bilayer disc surrounded by apoproteins A and E. These discs are secreted by the liver and intestine, and as pointed out they also are formed during the catabolism of the triglyceride-rich particles, chylomicrons, and VLDL. The HDL matures as cholesterol esters are transferred into the core of nascent HDL. Cholesterol from peripheral cells is removed and esterified by a complex consisting of lecithin cholesterol acyltransferase (LCAT) and apoAI. The resulting esters are transferred to nascent HDL by a transfer protein (11). HDL can be taken up by liver cells where its cholesterol esters can be hydrolyzed and excreted in the bile primarily as neutral sterols. This comprises the reverse transport of cholesterol from the periphery to the liver and into the bile.

DIETARY FAT AND CHOLESTEROL

The relationship between blood cholesterol and dietary intake of cholesterol and fat has been studied in populations and individuals. Older studies examined total cholesterol and triglyceride levels; more recent studies have looked at specific lipoproteins and apolipoproteins. Customary dietary intakes in population studies were assessed by using dietary recalls or diaries and/or by analysis of the foods eaten. Correlations were sought between diet and levels of lipids and lipoproteins in plasma or serum sampled after 12–14 hours of fasting.

Studies of individuals, either as clinic outpatients or inpatients on metabolic wards provide the most information on various acute and chronic effects of diet on lipoprotein metabolism in humans. Animal studies add further insights into mechanisms.

Population Surveys

Studies relating the effect of diet to serum lipid levels and to rates of atherosclerosis in free-living populations have consisted mostly of cross-sectional surveys. Some studies found correlations between dietary fat and serum cholesterol when different groups were compared, e.g. Japanese living in urban and rural areas (86) and Polynesian groups consuming different levels of dietary saturated fat (61). Surveys of single populations such as that of the Western Electric Study showed that a high ratio of polyunsaturated to saturated fat was correlated with plasma lipid levels and with a decreased incidence of coronary heart disease (75), but the correlation coefficients are small. The Tecumseh Study, on the other hand, failed to show a correlation between fat, cholesterol, and other macronutrient intake and serum cholesterol and triglyceride levels (57).

Worldwide cross-sectional surveys, both prospective and retrospective, generally support the concept that low-fat, low-cholesterol diets correlate with lower lipid levels and lower incidence of atherosclerotic heart disease; and they are used to support position papers advocating the adoption of such diets (31). Nevertheless, there are problems in interpreting such studies. It is difficult to assess the part played by other factors such as exercise, total caloric intake, obesity, and stress (29). More useful information concerning the relationships of diets and lipoproteins has come from individual and group feeding studies.

Acute Feeding of High-Fat, High-Cholesterol Diets

Since cholesterol and triglycerides are absorbed from the diet, in the form of chylomicrons, changes in dietary cholesterol and/or fat affect the compositions of the particles and their metabolism. Direct data on lymph chylomicrons in humans are difficult to obtain. A study by Borgström et al (7) involving thoracic duct cannulation in humans showed that a fatty meal increased cholesterol transport in lymph, but that adding cholesterol did not significantly increase lymphatic cholesterol transport. Studies in nonhuman primates showed that increased dietary cholesterol led to an increased cholesterol ester content in chylomicrons and VLDL in lymph. In fact, all lymph lipoproteins had an increased content of cholesterol ester (44, 45). It was postulated that increased cholesterol in chylomicrons would lead to increases in the amount of cholesterol delivered to the liver by chylomicron remnants and eventually to increased cholesterol in LDL. These authors also found a decrease in the amount of endogenous cholesterol transported in lymph; this suggested the

presence of a partial compensatory mechanism for decreasing cholesterol absorption. In rats, increases in dietary cholesterol also led to increased cholesterol ester content in lymph lipoproteins (22). Changes in dietary fatty acids are reflected in the fatty acid compositions of chylomicrons and VLDL of rat lymph, which changes physical properties of the lipoproteins that could affect their metabolism (21).

The response of normal humans to fat loads, such as cream ingestion, is an increase in blood triglyceride, cholesterol, and apoAI. The increase in triglyceride level was gone in eight hours but the rise in apoAI persisted (30). The apoA-I was associated with HDL and presumably represented the transfer of apoprotein AI from chylomicrons to HDL.

The importance of the effects of acute increases in dietary fat and cholesterol may be related to chylomicron remnants. It was proposed that chylomicron remnants are directly atherogenic and deliver cholesterol to arterial walls (94). This has not been clearly demonstrated in humans.

Prolonged Feeding of High-Fat, High-Cholesterol Diets

When animals are fed diets high in saturated fat and cholesterol, changes in lipoproteins are seen. In dogs and rats plasma cholesterol levels can increase to several times normal. Some of the excess cholesterol is carried in the HDL_1 subclass, which under these conditions is called HDL_C. HDL_C contains large amounts of apolipoprotein E, which is usually found only in small amounts in other subclasses of HDL. HDL_C may acquire cholesterol from peripheral tissues in these animals. Another lipoprotein found in cholesterol-fed animals is β-VLDL, a cholesterol rich β-migrating (rather than α-migrating) very low-density lipoprotein. β-VLDL causes cholesterol to accumulate in cultured macrophages and is a potentially important atherogenic lipoprotein (50).

The effects of cholesterol feeding in humans have been extensively studied. Studies have been done in both normal and hyperlipidemic subjects, with various amounts of cholesterol and varying contents of total fat and polyunsaturated and saturated fat. Each dietary factor has independent effects. Because single factors are difficult to alter, it is not always possible to distinguish effects of low dietary fat from the effects of high carbohydrate; or when dietary components are changed from animal to vegetable sources, to distinguish the effects of changes in protein from the effects of changes in fat and/or cholesterol. It is also important to keep in mind that the magnitudes of change are determined not only by the compositions of the experimental diets, but also by the fat and cholesterol contents of the basal diets. The increments in plasma lipoprotein levels obtained for a given experimental diet are inversely related to the fat and cholesterol contents of the basal diet. For example, diet-induced increases in plasma LDL cholesterol are greater when the basal diet contains 50 mg of cholesterol per day than when it contains 400 mg per day.

Ahrens et al (1) first showed that normal subjects had higher serum cholesterol levels when fed saturated-fat as compared to polyunsaturated-fat diets. This was confirmed in both outpatient (63, 65, 84) and inpatient studies. In a study by Anderson et al (2), addition of cholesterol to diets low in cholesterol caused an elevation in serum cholesterol. The effect of adding cholesterol to the diet has been reported as both dependent (71) and independent (23) on the polyunsaturated-to-saturated-fat ratio of the diet. In the study by Schonfeld et al (71), in normal young men eating diets composed of 15% protein, 45% carbohydrate, 40% fat, and 300 mg/dl cholesterol, the ratio of dietary polyunsaturated to saturated fatty acids (P/S) was varied from 0.25, 0.4, 0.8 to 2.5. The addition of 750 mg and 1500 mg of cholesterol to the basal diets had different effects depending on the P/S ratio. The total and LDL cholesterol were increased with the addition of 750 mg of cholesterol to the diets with P/S ratios of 0.25 to 0.40. For the diet with P/S of 0.8 it required 1500 mg of cholesterol to raise the total and LDL cholesterol significantly. Even high amounts of cholesterol did not change the total or LDL cholesterol on diets with P/S ratio of 2.5. While the number of LDL particles increased, qualitative properties of the LDL such as flotation rate and interaction with cell receptors on cultured fibroblasts did not change.

In a similar study by Mistry et al (53), LDL cholesterol increased significantly in subjects fed six eggs per day. In addition, intermediate-density lipoproteins (IDL) increased. VLDL cholesterol did not change. Additional diet effects were found also in terms of lipoprotein-mediated cellular function in cells from men who had eaten a high-cholesterol diet for 14 days. The affinity of blood monocytes for LDL was decreased in cells obtained from men on the diet with more cholesterol, and the activity of HMG CoA reductase in freshly isolated blood mononuclear cells was significantly decreased. Another study of cholesterol feeding confirmed the increases of LDL cholesterol and decreases in LDL receptor activity in mononuclear cells (3).

Somewhat different results were obtained by Fisher et al (23). Normal subjects were fed normal diets containing carbohydrate, protein, and fat from either corn oil (P/S ratio 4:1) or coconut oil, 92% saturated fatty acids. One gram per day of cholesterol was added to those diets for part of the study. The saturated fat diet alone caused elevations of total, IDL, and LDL cholesterol. The addition of dietary cholesterol had no additive effect on plasma levels.

In all of the above studies HDL cholesterol was elevated in the diets that were higher in cholesterol, except for the study of Fisher et al in which the coconut oil diet caused an increase in HDL whether or not cholesterol was added. In the studies reported by Cole et al (12) and Schonfeld et al (71), the addition of eggs to the diet with a low P/S ratio caused a slight to moderate increase in HDL-cholesterol levels and also caused increases in apoE-rich HDL, or HDL_C (12) and the lighter HDL subclass HDL_2 compared to HDL_3. HDL, especially

HDL_2 is felt to be a negative risk factor for atherosclerosis (10, 15, 28, 52) so that the increase of HDL_2 on an atherogenic diet is somewhat paradoxical. This finding was also seen by Mistry et al (53).

Lin & Connor (47) studied the effect of high- and low-cholesterol diets on sterol balance over several months. Total, LDL, and HDL cholesterol all increased as dietary cholesterol was increased from ~50 to 1000 mg of cholesterol per day. Bile aid secretion rose during the high-cholesterol feeding period and cholesterol biosynthesis, as determined by balance studies, fell. Cholesterol absorption was unchanged.

Effects of High-Fat, High-Cholesterol Diets on Apoproteins

Apolipoprotein levels were measured in normal subjects on high-saturated-fat plus or minus high-cholesterol diets in several studies (3, 12, 23, 71). Applebaum-Bowden et al (3) found no difference in apoB, apoAI, or apoAII levels on high-cholesterol diets. This is in contrast with the two studies from our center (12, 71) in which diets with low P/S ratios and high in cholesterol were associated with increases in apoAI and apoB. The increase in apolipoprotein B levels is consistent with the increase in LDL since apoB is the predominant apoprotein of LDL. ApoAII levels were unchanged in both studies. Thus, apoAI/apoAII ratios rose, consistent with rises in HDL_2.

The high-saturated-fat diets affected apoE levels and distribution among the lipoproteins in plasma. The study by Cole et al (12) showed a redistribution of apoE on the high-fat, high-cholesterol diet. Total apoE increased as did the apoE containing lipoprotein, HDL_C. Fisher et al (23) found that apoE was redistributed on the saturated-fat diet, such that apoE in VLDL, IDL, and LDL (combined) were increased while apoE was decreased in heavier HDL fractions. Thus, saturated fat combined with cholesterol may produce alterations different from those produced by saturated fat alone.

Mahley et al (51), using a cell binding assay to detect the presence of HDL_C, also demonstrated the presence of HDL_C in humans fed diets high in cholesterol. HDL_C competes with LDL for occupancy of LDL receptors on human fibroblasts. HDL isolated from human subjects showed displacement of ^{125}I-labeled LDL by HDL_C to a greater extent after cholesterol feeding than before.

Effects of Low-Cholesterol, High-Polyunsaturated-Fat Diets

Studies of increasing dietary cholesterol with or without modifications in dietary fat are numerous. Most recent studies focus on the effects of increasing the proportions of polyunsaturated fatty acids in the diet. In general, they show that polyunsaturated fats lower plasma cholesterol levels (1, 14, 16, 17, 68, 77, 85, 90–92). A number of the important findings are discussed here.

Shepherd et al (77) studied eight normal adult men over two five-week periods using diets containing 20% protein, 40% carbohydrate, 40% fat, and

400 mg of cholesterol per day. The P/S ratio was 0.25 for one diet and 4.0 for the other. On the high-polyunsaturated-fat diet, total plasma cholesterol decreased by a mean of 23%. Most of the reduction was in LDL cholesterol, although VLDL cholesterol and HDL cholesterol decreased as well. Plasma triglyceride levels fell an average of 14%. The fatty acid composition of LDL lipid changed greatly with a decrease in the palmitate (16:0) and oleate (18:1) and an increase in the linoleate (18:2) content of LDL triglycerides, cholesteryl esters, and phospholipids. In addition, the amount of cholesterol decreased in LDL. The fractional catabolic rate of apolipoprotein LDL was also increased by the polyunsaturated-fat diet.

Pownall et al (60) also reported changes in composition of LDL from subjects on a diet high in polyunsaturated fat. There was an increase in unsaturated fatty acids in LDL, and an increase in triglyceride content of LDL. A previous study by Shepherd et al (78) also demonstrated low LDL, VLDL, and HDL cholesterol and changes in composition of HDL, with an increase in phospholipid and decrease in protein. The significance of these changes in composition is not clear. The reasons for the decrease in LDL cholesterol levels with increased levels of polyunsaturated fats in the diet are unknown. Nichaman et al (56a) suggested that increased fat oxidation in men receiving high P/S ratio diets can account for less LDL synthesis. Illingworth et al (38) found decreased synthesis of apoprotein B in normal human subjects fed diets rich in omega-3 fatty acids. Another suggestion postulates a change in catabolism of LDL when dietary fat is modified. Baudet et al (4) found changes in lipoprotein composition when the predominant fats in the diet of Benedictine nuns were changed to more highly saturated fatty acids. They reported decreased binding, internalization, and degradation of LDL by fibroblasts with diets with the lowest P/S ratios.

Several studies showed HDL levels decreased by diets high in polyunsaturated fats. This is disturbing because of the strong correlation between high HDL-cholesterol levels and decreased cardiac risk (10, 15, 28, 52). Plasma apolipoprotein AI and apoB levels and the ratios of HDL_2 to HDL_3 are reduced (78). In hypercholesterolemic patients on polyunsaturated-fat diets, levels of LDL cholesterol, HDL cholesterol, apoB, and apoAI all declined (91). However, at least one study reported no change in the ratio of LDL cholesterol to HDL (91). In most of the above short-term feeding studies, the P/S ratios used were high, up to 4.0, a quite unrealistic and possibly undesirable level for P/S ratios in the long-term treatment of a person with hypercholesterolemia. In a longer feeding study, a diet with cholesterol content of 250 mg per day and P/S ratio 1.0 (vs cholesterol of 370 mg per day and P/S ratio 0.3 in the control diet) was tried in healthy adults (74). After three months, LDL cholesterol was decreased; apoAI, total cholesterol, and HDL_2 and HDL_3 were unchanged, which led to a more favorable balance between LDL and HDL cholesterol. In studies

with normal and hypercholesterolemic children, Stein et al (82) demonstrated that decreases in dietary cholesterol and total fat and increases in P/S ratio could lower plasma LDL cholesterol levels for a sustained period without decreasing HDL cholesterol.

Evidence that HDL levels can decrease over time comes from studies of vegetarians. Lock et al (49) found low levels of HDL cholesterol in vegetarians. There was a greater reduction in HDL_2 than in HDL_3 and apolipoprotein AI/AII ratios were low, particularly in the group with the lowest cholesterol intake and highest P/S ratio. Nevertheless, LDL cholesterol levels were also quite low. Since rates of atherosclerosis are low in complete vegetarians, this suggests that the low LDL levels are protective in spite of low HDL cholesterol levels.

Fish Oils

The fatty acids from seal, whale, and fatty fish such as mackerel, salmon, and trout contain large amounts of unsaturated fatty acids of the omega-3 type. Vegetable oils contain omega-6 fatty acids. Reduced levels of plasma triglycerides and cholesterol are reported in Eskimos and other populations consuming diets high in marine oils (18). The Eskimo population was also found to have prolonged bleeding times and a low incidence of coronary artery disease. This prompted several studies of the effect of fish oil on lipoproteins in Western populations. When fish oils are added to diets of normal subjects or hyperlipidemic patients, there is a decrease in VLDL and LDL cholesterol levels and total triglycerides (38), while effects on HDL are inconsistent (67). In another study, the production of VLDL apolipoprotein B and VLDL triglycerides were decreased, HDL and apoAI fell, but effects on LDL were inconsistent (55). Fish oil in doses of 10 to 20 ml per day also caused an increase in bleeding time, decreased platelet aggregation, and decreased platelet thromboxane B_2 production (66, 67). The combination of decreased lipoprotein production and decreased thrombosis may account for the low incidence of atherosclerosis in Eskimo populations eating their traditional diet. The potential use of fish oil as an antiatherogenic agent is at present under intense investigation.

CARBOHYDRATE

If the percentage of fat in the diet is lowered, there is a compensatory increase in carbohydrate because amounts of protein usually are held relatively constant. Diets high in carbohydrate (60–80% of calories) and low in fats (0–25% of calories) have marked effects on plasma levels of lipoproteins and on lipoprotein metabolism. Plasma triglycerides and VLDL triglycerides rise in both normal and hypertriglyceridemic subjects (6, 19, 20, 25, 27, 37, 42, 48, 73). Hepatic secretion of VLDL increases (72), and the VLDL tend to contain more

triglyceride (69). Typically, VLDL triglyceride, VLDL cholesterol, and VLDL protein rise by factors of 2.4, 1.67, and 1.88 respectively; LDL cholesterol decreases while LDL triglyceride remains the same (19, 25, 42, 73). The elevations in plasma triglyceride reach a peak after one week and decrease after three weeks, although they do not return to baseline levels in that time (42). HDL cholesterol also decreases after a few days on a high-carbohydrate diet (6, 27, 42, 73), with the HDL_2 fraction falling to a greater extent than HDL_3 (27). Thus, in some respects diets high in carbohydrate and those with high P/S ratios both produce similar effects on LDL and HDL, but not on VLDL.

There are significant changes in apolipoprotein concentrations in response to these short-term increases in dietary carbohydrate. Apoproteins of the C family increase in response to high-carbohydrate diets. Plasma levels of apoC-II increase both in normal subjects fed a high-carbohydrate formula diet and in patients with hypertriglyceridemia (19). Kashyap et al (42) found increases in both apoC-II and C-III but the ratio of apoC-III to apoC-II was lower in VLDL and HDL_2 after three weeks of a high-carbohydrate diet; this indicates a relative enrichment of VLDL and HDL_2 with apoC-II. Kashyap et al suggest that the difference in amounts of apoC-III and C-II in HDL_2 subfractions may be due to differences in binding affinities of the different apoC's for HDL subfractions.

ApoC-III is found in at least three isoelectric forms called apoC-III_0, C-III_1, C-III_2. The different forms are due to different amounts of sialic acid in the protein, with the subscript representing the number of moles of sialic acid per mole of protein (88). The degree of sialylation can be altered by diet (58), as can the distribution of the different sialylated forms. ApoC-III_0 increased in VLDL in normal subjects fed high-carbohydrate diets (19, 42). Huff & Nestel (37) found a decrease in the percentage of C-III_2 in VLDL and HDL, whereas Kashyap (42) found no differences in the percentage of apoC-III_1 or apoC-III_2. The reasons for the changes in apoC-III subspecies are not clear. However, the relative increases in apoC-II in VLDL may affect removal of triglyceride from VLDL since apoC-II is required for activation of lipoprotein lipase. Alterations in apoCIII, on the other hand, may affect rates of removal of remnants from plasma; apoCIII inhibits the apoE-mediated recognition of lipoproteins by cellular receptors (76).

Apolipoprotein E distribution is also affected by high-carbohydrate diets. Normal and hypertriglyceridemic subjects fed an 85% carbohydrate formula diet for one week showed no increase in plasma total apoE levels, but the proportion of apoE associated with VLDL did increase at the expense of HDL_1. There was no change in the distribution of apoE subspecies by isoelectric focusing (20).

Apoprotein A-I levels in normal subjects fed high-carbohydrate diets showed a mean decrease of 20%, while apoB levels did not change (73). Plasma apoA-I

to apoA-II ratios fell. The catabolism of HDL increased (6). Again, the effects of diets high in P/S ratio but normal in fat content and of diets higher in carbohydrate (low in fat) are notable.

The falls in HDL in response to these dietary modifications are disturbing in light of the epidemiologic findings on the "protective" role of HDL for coronary heart disease. However, the higher proportion of dietary carbohydrate and lower amounts of dietary fat and cholesterol consumed by vegetarians lead to profound lowering of plasma lipids, including decreased total HDL, HDL_2, and apoAI levels, without any apparent increases in atherosclerotic heart disease (49).

The type of carbohydrate used in the diet significantly affects triglycerides and VLDL responses. On a diet with 70% carbohydrate and with sucrose contributing 55% of calories, VLDL increased in six of seven subjects (56). VLDL apoB also increased. In two subjects there were increases in removal rates of apoB VLDL from the circulation, whereas in four subjects there was decreased removal of apoB VLDL. In most of the studies involving high-carbohydrate diets, sucrose comprised a large part of the additional carbohydrate calories. In a recent study of hypertriglyceridemic subjects, when the sucrose content of the diet was increased from 9 to 15% while total carbohydrate content was increased from 40 to 60%, the degree of fasting hypertriglyceridemia and increase in VLDL triglyceride were greater than if sucrose was kept at a constant percentage of total carbohydrate (48).

PROTEIN

In laboratory animals fed cholesterol-free diets, hypercholesterolemia resulted if the protein used in the diet was derived from animal sources, such as casein compared with soy protein (9). In human subjects with hypercholesterolemia, the use of soy protein as a substitute for animal protein has been reported to lower plasma cholesterol levels (13, 26, 81). Studies in Italy using textured soybean protein as a substitute for almost all animal protein showed plasma cholesterol levels reduced by 20% or more in hypercholesterolemic patients (13). Variations in P/S ratios modified the effectiveness of the cholesterol lowering, with the soy protein having less effect in a diet with a low P/S ratio (81). Another study in hypercholesterolemic patients used isolated soy protein as a substitute for animal protein in an isocaloric diet in which dietary cholesterol, fat, and P/S ratio were held constant. This study showed LDL cholesterol reduced by a mean of 6% and apoprotein B by a mean of 6.3%. Total cholesterol was decreased by 3.5%, but this was not statistically significant (26). The difference in results between these studies may be attributed to the fact that, as protein was changed from animal to soy in the Italian study, simultaneous changes were made in total fat and P/S ratio, and fat and

cholesterol contents of the soy diet were lowered. The vegetable fiber and β sitosterol contained in the textured soybean protein preparation used also could have enhanced the effects of the protein and fat alterations.

In normal subjects, the substitution of soy protein for animal protein in an otherwise identical diet had no effect on levels of total cholesterol, LDL cholesterol, or apoprotein B in four normal subjects studied by Goldberg et al (26). Van Raaij et al (89) studied 57 middle-aged normal subjects fed diets in which 60% of the protein content was supplied as caseinate, soy protein isolate, or soy protein concentrate. The soy isolate diet caused small declines of 6.5 mg/dl in total and LDL cholesterol and increases of 5.8 mg/dl in HDL cholesterol, none of which were significant compared with the diet containing caseinate. Grundy & Abrams (32) found no consistent changes in plasma cholesterol, triglycerides, LDL, or HDL in ten patients with normal triglycercides and varying levels of plasma cholesterol when liquid formula diets containing soy protein were compared with ones containing casein. In contrast, soy protein caused a significant lowering of triglycerides in patients with hypertriglyceridemia. Soy protein caused no change in fecal excretion of neutral, acidic, or total steroids.

In a study of VLDL kinetics in five hypercholesterolemic men, Huff et al (36) compared the effect of a soybean protein diet high in polyunsaturated fat and low in cholesterol with a diet in which the protein was derived from meat and dairy products. Cholesterol content and P/S ratios were similar in the two diets. Fasting serum cholesterol and triglycerides did not differ between the two diets, but the fractional catabolic rate of VLDL apoB was higher during the diet made up of all plant protein. The production rate of apoprotein B was also higher during the plant protein diet, but VLDL apoB pool size was unchanged. This implies that turnover rate of VLDL was increased in spite of the unchanged plasma levels of VLDL.

Sacks et al (64) added equal amounts of either casein or soy protein to the diets of strict vegetarians. Levels of plasma HDL, LDL, and total cholesterol were not altered significantly by either type of protein in spite of an overall increase in daily protein intake from a mean of 59 g to 82 g. VLDL cholesterol decreased and triglyceride increased, so that the ratio of VLDL cholesterol to triglyceride decreased significantly from 0.3 to 0.17. Sacks et al concluded that neither the overall amount of dietary protein, when above minimum requirements, nor whether it is from animal or vegetable sources has an important effect on plasma HDL and LDL in humans.

DIETARY FIBER

There are conflicting reports about the effects of dietary fiber on plasma lipid and lipoprotein levels (39, 40, 43, 46, 54, 62, 80, 87, 93). The dose and the type of dietary fiber used may influence whether it will have any effect on

plasma lipids. Several studies that used diets containing mixtures of different types of fiber in ordinary foods, such as grains, legumes, fruits, and vegetables, have shown no significant effect on cholesterol levels (62, 87). Raymond et al (62) fed normal and hypercholesterolemic subjects formula diets containing either less than 50 mg cholesterol or 1000 mg cholesterol per day. The addition of a large quantity of dietary fiber derived from corn, beans, bran, pectin, and purified cellulose to either diet caused no significant changes in plasma levels of cholesterol or triglycerides. The high-cholesterol diet caused a rise in plasma cholesterol both in the presence or absence of fiber. Total fecal steroid excretion was significantly increased by the addition of fiber in the cholesterol-free diet but not in the 1000-mg cholesterol diet. Intestinal transit time decreased and stool bulk was increased by fiber. Ullrich & Albrink (87) used a high-carbohydrate, high-starch diet with or without added fiber in healthy young men. They found similar slight increases in triglycerides and decreases in cholesterol and HDL cholesterol, independent of fiber content.

Certain types of fiber can affect lipid levels when added to diets of both normal and hypercholesterolemic subjects, while other types have no effect. Soft wheat bran fiber (46), bagasse (fiber from sugar cane) (93), and corn bran (54) had no significant effects on cholesterol and triglyceride levels when added to diets of normal subjects. Diets containing hard red spring wheat bran or soybean hulls as the main source of fiber decreased plasma cholesterol by about 12 and 14% respectively in healthy men. LDL cholesterol decreased by 21% with hard red spring wheat bran (54). In hypercholesterolemic patients, guar gum, a galactomannan storage polysaccharide obtained from the cluster bean, led to reduction in plasma cholesterol of 10.6% after two weeks of administration to ten patients (40). In a long-term study, a preparation of guar gum added to a cholesterol-lowering diet reduced plasma cholesterol levels in patients with hypercholesterolemia by 15% during the initial three months of treatment. This effect was sustained for 12 months. There was a 20% decrease in LDL cholesterol but no change in HDL cholesterol (80). Oat bran fiber has also been shown to decrease both total and LDL cholesterol levels by 13 and 14% respectively in hypercholesterolemic men when added to a diet containing 400 mg of cholesterol per day and with a P/S ratio of 0.6 (43). Fecal excretion of total bile acids was higher on the oat bran diet but neutral steroid excretion was slightly lower.

The mechanism of action of dietary fiber is unclear. In one study, absorption of cholesterol was unchanged by the addition of mixed fiber to the diet (62). In contrast, Simons et al (80) demonstrated a decrease in cholesterol absorption in four out of five hypercholesterolemic subjects after a single dose of guar gum. Other suggested factors are binding of bile salts, increased neutral steroid loss, and decreased postprandial insulin and glucose rises (39). The mechanisms of action of the different types of dietary fiber are still unclear.

FUTURE DIRECTIONS

We have surveyed here the recent literature on the effects of various macronutrients on lipid transport in man. In the overwhelming majority of these studies, more or less discrete alterations are produced in dietary intake, and the concentrations of lipoprotein lipids are measured. In a minority of studies, major lipoproteins VLDL, LDL, and HDL are characterized with respect to their flotation characteristics and compositions. Plasma decay kinetics of VLDL, LDL, and HDL are also reported in a few studies. Rarely, lipoproteins are isolated from plasma and are examined in vitro with respect to interactions with cells or enzymes.

Although a pretty good picture is available on the effects of the macronutrients on the plasma levels for the major lipoprotein classes (VLDL, LDL, and HDL), little information is available on the effects of dietary perturbations on the minor classes of lipoproteins now implicated in atherogenesis, including β-VLDL, Lp(A), and HDL_C. This lack is due in part to the assays, particularly for β-VLDL and HDL_C, which are cumbersome and not easily applicable to large numbers of samples. Therefore suitable assays should be developed promptly. More information is needed on the effects of classes of simple and complex carbohydrates and various proteins on lipoprotein kinetics. Virtually nothing is known about the effect of any dietary perturbations on the subtle structural details of lipoproteins, details that could affect their function at the cell biological or molecular levels. The appropriate experimental techniques for performing such studies are available to those workers interested in the mechanisms of the effects of nutrition on human lipoprotein transport.

Another potentially important area is the examination of the differing susceptibilities to dietary manipulation of various human subpopulations. It is clear that there are major differences among the sexes and the races in population distributions of lipid levels. Between and within races there are wide individual variations. If susceptibility to atherosclerosis is related in any way to dietary responsiveness, the determinants of such variation should be identified. This would allow the identification of groups particularly susceptible to atherosclerosis and the more precise targeting of nutritional interventions.

Literature Cited

1. Ahrens, E. H. Jr., Hirsch, J., Insull, W. Jr., Tsaltas, T. T., Blomstrand, R., et al. 1957. The influence of dietary fats on serum lipid levels in man. *Lancet* 1:943–53
2. Anderson, J. T., Grande, F., Keys, A. 1976. Independence of the effects of cholesterol and degree of saturation of the fat in the diet on serum cholesterol in man. *Am. J. Clin. Nutr.* 29:1184–89
3. Applebaum-Bowden, D., Haffner, S. M., Hartsook, E., Luk, K. H., Albers, J. J., et al. 1984. Down-regulation of the low-density lipoprotein receptor by dietary cholesterol. *Am. J. Clin. Nutr.* 39:360–67
4. Baudet, M. F., Dachet, C., Lasserre, M., Esteva, O., Jacotot, B. 1984. Modification in the composition and metabolic properties of human low density and

high density lipoproteins by different dietary fats. *J. Lipid Res.* 25:456–68
5. Bengtsson, G., Olivecrona, T. 1980. Lipoprotein lipase: Some effects of activator proteins. *Eur. J. Biochem.* 106:549–55
6. Blum, C. B., Levy, R. I., Eisenberg, S., Hall, M., Goebel, R. H., et al. 1977. High density lipoprotein metabolism in man. *J. Clin. Invest.* 60:795–807
7. Borgström, B., Radner, S., Werner, B. 1970. Lymphatic transport of cholesterol in the human being. Effect of dietary cholesterol. *Scand. J. Clin. Lab. Invest.* 26:227–35
8. Brown, M. S., Kovanen, P. T., Goldstein, J. L. 1981. Regulation of plasma cholesterol by lipoprotein receptors. *Science* 212:628–35
9. Carroll, K. K. 1978. The role of dietary protein in hypercholesterolemia and atherosclerosis. *Lipids* 13:360–65
10. Castelli, W. P., Doyle, J. T., Gordon, T., Hames, C. G., Hjortland, M. C., et al. 1977. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* 55:767–72
11. Chajek, T., Aron, L., Fielding, C. J. 1980. Interaction of lecithin: cholesterol acyl transferase and cholesterol ester transfer protein in the transport of cholesteryl ester into sphingomyelin liposomes. *Biochemistry* 19:3673–77
12. Cole, T. G., Patsch, W., Kuisk, I., Gonen, B., Schonfeld, G. 1983. Increases in dietary cholesterol and fat raise levels of apoprotein E–containing lipoproteins in the plasma of man. *J. Clin. Endocrinol. Metab.* 56:1108–15
13. Descovich, G. C., Ceredi, C., Gaddi, A., Benassi, M. S., Mannino, G., et al. 1980. Multicentre study of soybean protein diet for outpatient hypercholesterolemic patients. *Lancet* 2:709–12
14. Durrington, P. N., Bolton, C. H., Hartog, M., Angelinetta, R., Emmett, P., Furniss, S. 1977. The effect of a low-cholesterol, high polyunsaturate diet on serum lipid levels, apolipoprotein B levels and triglyceride fatty acid composition. *Atherosclerosis* 27:465–75
15. Eder, H. A., Gidez, L. I. 1982. The clinical significance of the plasma high density lipoproteins. *Med. Clin. North Am.* 66:431–40
16. Ehnholm, C., Huttunen, J. K., Pietinen, P., Leino, U., Mutanen, M., et al. 1984. Effect of a diet low in saturated fatty acids on plasma lipids, lipoproteins, and HDL subfractions. *Arteriosclerosis* 4:265–69
17. Ernst, N., Fisher, M., Bowen, P., Schaefer, E. J., Levy, R. I. 1980. Changes in plasma lipids and lipoproteins after a modified fat diet. *Lancet* 2:111–13
18. Eskimo diets and diseases. 1983. *Lancet* 1:1139–41 (Editorial)
19. Falko, J. M., Schonfeld, G., Witztum, J. L., Kolar, J. B., Salmon, P. 1980. Effects of short-term high carbohydrate, fat-free diet on plasma levels of apoC-II and apoC-III and on the apoC subspecies in human plasma lipoproteins. *Metabolism* 29:654–61
20. Falko, J. M., Schonfeld, G., Witztum, J. L., Kolar, J. B., Weidman, S. W., et al. 1980. Effects of diet on apoprotein E levels and on the apoprotein E subspecies in human plasma lipoproteins. *J. Clin. Endocrinol. Metab.* 50:521–28
21. Feldman, E. B., Russell, B. S., Chen, R., Johnson, J., Forte, T., et al. 1983. Dietary saturated fatty acid content affects lymph lipoproteins: studies in the rat. *J. Lipid Res.* 24:967–76
22. Fielding, C. J., Renston, J. P., Fielding, P. E. 1978. Metabolism of cholesterol-enriched chylomicrons. Catabolism of triglycerides by lipoprotein lipase of perfused heart and adipose tissues. *J. Lipid Res.* 19:705–11
23. Fisher, E. A., Blum, C. B., Zannis, V. I., Breslow, J. L. 1983. Independent effects of dietary saturated fat and cholesterol on plasma lipids, lipoproteins, and apoprotein E. *J. Lipid Res.* 24:1039–48
24. Friedman, H. I., Cardell, R. R. Jr. 1977. Alterations in the endoplasmic reticulum and Golgi complex of intestinal epithelial cells during fat absorption and after termination of this process: A morphological and morphometric study. *Anat. Rec.* 188:77–102
25. Ginsberg, H. N., Le, N.-A., Melish, J., Steinberg, D., Brown, W. V. 1981. Effect of a high carbohydrate diet on apoprotein B catabolism in man. *Metabolism* 30:347–53
26. Goldberg, A. P., Lim, A., Kolar, J. B., Grundhauser, J. J., Steinke, F. H., et al. 1982. Soybean protein independently lowers plasma cholesterol levels in primary hypercholesterolemia. *Atherosclerosis* 43:355–68
27. Gonen, B., Patsch, W., Kuisk, I., Schonfeld, G. 1981. The effect of short-term feeding of a high carbohydrate diet on HDL subclasses in normal subjects. *Metabolism* 30:1125–29
28. Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B., Dawber, T. R. 1977. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am. J. Med.* 62:707–14
29. Gordon, T., Fisher, M., Rifkind, B. M.

1984. Some difficulties inherent in the interpretation of dietary data from free-living populations. *Am. J. Clin. Nutr.* 39:152–56
30. Groot, P. H. E., Scheek, L. M. 1984. Effects of fat ingestion on high density lipoprotein profiles in human sera. *J. Lipid Res.* 25:684–92
31. Grundy, S. M. 1984. Recommendations for the treatment of hyperlipidemia in adults. A joint statement of the Nutrition Committee and the Council on Arteriosclerosis of the American Heart Association. *Circulation* 69:1065A–90A
32. Grundy, S. M., Abrams, J. J. 1983. Comparison of actions of soy protein and casein on metabolism of plasma lipoproteins and cholesterol in humans. *Am. J. Clin. Nutr.* 38:245–52
33. Grundy, S. M., Bilheimer, D., Blackburn, H., Brown, W. V., Kwiterovich, P. O., et al. 1982. Rationale of the diet-heart statement of the American Heart Association: Report of the nutrition committee. *Circulation* 65:839A–54A
34. Havel, R. J., Kane, J. P., Kashyap, M. L. 1973. Interchange of apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipemia in man. *J. Clin. Invest.* 52:32–38
35. Higgins, J. M., Fielding, C. J. 1975. Lipoprotein lipase. Mechanisms of formation of triglyceride rich remnant particles from very low density lipoproteins and chylomicrons. *Biochemistry* 14:2288–93
36. Huff, M. W., Giovannetti, P. M., Wolfe, B. M. 1984. Turnover of very low density lipoprotein-apoprotein B is increased by substitution of soybean protein for meat and dairy protein in the diets of hypercholesterolemic men. *Am. J. Clin. Nutr.* 39:888–97
37. Huff, M. W., Nestel, P. J. 1982. Metabolism of apolipoproteins CII, $CIII_1$, $CIII_2$ and VLDL-B in human subjects consuming high carbohydrate diets. *Metabolism* 31:493–98
38. Illingworth, D. R., Harris, W. S., Connor, W. E. 1984. Inhibition of low density lipoprotein synthesis by dietary omega-3 fatty acids in humans. *Arteriosclerosis* 4:270–75
39. Jenkins, D. J. A. 1979. Dietary fibre, diabetes and hyperlipidemia. *Lancet* 2:1287–90
40. Jenkins, D. J. A., Leeds, A. R., Slavin, B., Mann, J., Jepson, E. M. 1979. Dietary and blood lipids: reduction of serum cholesterol in type II hyperlipidemia by guar gum. *Am. J. Clin. Nutr.* 32:16–18
41. Kane, J. P., Hardman, D. A., Paulus, H. E. 1980. Heterogeneity of apolipoprotein B: Isolation of a new species from human chylomicrons. *Proc. Natl. Acad. Sci. USA* 77:2465–69
42. Kashyap, M. L., Barnhart, R. L., Srivastava, L. S., Perisutti, G., Vink, P., et al. 1982. Effects of dietary carbohydrate and fat on plasma lipoproteins and apolipoproteins C-II and C-III in healthy men. *J. Lipid Res.* 23:877–86
43. Kirby, R. W., Anderson, J. W., Sieling, B., Rees, E. D., Chen, W.-J. L., et al. 1981. Oat-bran intake selectively lowers serum low-density lipoprotein cholesterol concentrations of hypercholesterolemic men. *Am. J. Clin. Nutr.* 34:824–29
44. Klein, R. L., Rudel, L. L. 1983. Cholesterol absorption and transport in thoracic duct lymph lipoproteins of non-human primates. Effect of dietary cholesterol level. *J. Lipid Res.* 24:343–56
45. Klein, R. L., Rudel, L. L. 1983. Effect of dietary cholesterol level on the composition of thoracic duct lymph lipoproteins isolated from non-human primates. *J. Lipid Res.* 24:357–67
46. Liebman, M., Smith, M. C., Iverson, J., Thye, F. W., Hinkle, D. E., et al. 1983. Effects of coarse wheat bran fiber and exercise on plasma lipids and lipoproteins in moderately overweight men. *Am. J. Clin. Nutr.* 36:71–81
47. Lin, D. S., Connor, W. E. 1980. The long-term effects of dietary cholesterol upon the plasma lipids, lipoproteins, cholesterol absorption, and the sterol balance in man: the demonstration of feedback inhibition of cholesterol biosynthesis and increased bile acid secretion. *J. Lipid Res.* 21:1042–52
48. Liu, G., Coulston, A., Hollenbeck, C., Reaven, G. 1984. The effect of sucrose content in high and low carbohydrate diets on plasma glucose, insulin, and lipid responses in hypertriglyceridemic humans. *J. Clin. Endocrinol. Metab.* 59:636–42
49. Lock, D. R., Varhol, A., Grimes, S., Patsch, W., Schonfeld, G. 1983. ApoA-I/ApoA-II ratios in plasmas of vegetarians. *Metabolism* 32:1142–45
50. Mahley, R. W. 1982. Atherogenic hyperlipoproteinemia. *Med. Clin. North Am.* 66:375–402
51. Mahley, R. W., Innerarity, T. L., Bersot, T. P., Lipson, A., Margolis, S. 1978. Alterations in human high-density lipoproteins, with or without increased plasma-cholesterol, induced by diets high in cholesterol. *Lancet* 2:807–9
52. Miller, G. J. 1980. High density lipoproteins and atherosclerosis. *Ann. Rev. Med.* 31:97–108
53. Mistry, P., Miller, N. E., Laker, M.,

Hazzard, W. R., Lewis, B. 1981. Individual variation in the effects of dietary cholesterol on plasma lipoproteins and cellular cholesterol homeostasis in man. *J. Clin. Invest.* 67:493–502

54. Munoz, J. M., Sandstead, H. H., Jacob, R. A., Logan, G. M., Reck, S. J., et al. 1979. Effects of some cereal brans and textured vegetable protein on plasma lipids. *Am. J. Clin. Nutr.* 32:580–92
55. Nestel, P. J., Conner, W. E., Reardon, M. F., Connor, S., Wong, S., et al. 1984. Suppression by diets rich in fish oil of very low density lipoprotein production in man. *J. Clin. Invest.* 74:82–89
56. Nestel, P. J., Reardon, M., Fidge, N. H. 1979. Sucrose induced changed in VLDL- and LDL-B apoprotein removal rates. *Metabolism* 28:531–35

56a. Nichaman, M. Z., Olson, R. E., Sweeley, C. C. 1967. Metabolism of linoleic acid-1-^{14}C in normolipemic and hyperlipemic humans fed linoleate diets. *Am. J. Clin. Nutr.* 20:1070–83

57. Nichols, A. B., Ravenscroft, C., Lamphiear, D. E., Ostrander, L. D. 1976. Daily nutritional intake and serum lipid levels. The Tecumseh study. *Am. J. Clin. Nutr.* 29:1384–92
58. Patsch, W., Schonfeld, G. 1981. The degree of sialylation of apoC-III is altered by diet. *Diabetes* 30:530–34
59. Pooling Project Research Group. 1978. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. *J. Chronic Dis.* 31:201–306
60. Pownall, H. J., Shepherd, J., Mantulin, W. W., Sklar, L. A., Gotto, A. M. Jr. 1980. Effect of saturated and polyunsaturated fat diets on the composition and structure of human low density lipoproteins. *Atherosclerosis* 36:299–314
61. Prior, I. A., Davidson, F., Salmond, C. E., Czochanska, Z. 1981. Cholesterol, coconuts, and diet on Polynesian atolls: a natural experiment: the Pukapuka and Tokelau Island Studies. *Am. J. Clin. Nutr.* 34:1552–61
62. Raymond, T. L., Connor, W. E., Lin, D. S., Warner, S., Fry, M. M., et al. 1977. The interaction of dietary fibers and cholesterol upon the plasma lipids and lipoproteins, sterol balance, and bowel function in human subjects. *J. Clin. Invest.* 60:1429–37
63. Roberts, S. L., McMurry, M. P., Conner, W. E. 1981. Does egg feeding (i.e. dietary cholesterol) affect plasma cholesterol levels in humans? The results of a double-blind study. *Am. J. Clin. Nutr.* 34:2092–99
64. Sacks, F. M., Breslow, J. L., Wood, P. G., Kass, E. H. 1983. Lack of an effect of dairy protein (casein) and soy protein on plasma cholesterol of strict vegetarians. *J. Lipid Res.* 24:1012–20
65. Sacks, F. M., Salazar, J., Miller, L., Foster, J. M., Sutherland, M., et al. 1984. Ingestion of egg raises plasma low density lipoproteins in free-living subjects. *Lancet* 1:647–49
66. Sanders, T. A. B., Hochland, M. C. 1983. A comparison of the influence on plasma lipids and platelet function of supplements of omega-3 and omega-6 polyunsaturated fatty acids. *Br. J. Nutr.* 50:521–29
67. Saynor, R., Verel, D., Gillott, T. 1984. The long-term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina. *Atherosclerosis* 50:3–10
68. Schaefer, E. J., Levy, R. I., Ernst, N. D., Van Sant, F. D., Brewer, H. B. Jr. 1981. The effects of low cholesterol, high polyunsaturated fat, and low fat diets on plasma lipid and lipoprotein cholesterol levels in normal and hypercholesterolemic subjects. *Am. J. Clin. Nutr.* 34:1758–63
69. Schonfeld, G. 1970. Changes in the composition of very low density lipoprotein during carbohydrate induction in man. *J. Lab. Clin. Med.* 75:206–11
70. Schonfeld, G., Bell, E., Alpers, D. H. 1978. Intestinal apoproteins during fat absorption. *J. Clin. Invest.* 61:1539–50
71. Schonfeld, G., Patsch, W., Rudel, L. L., Nelson, C., Epstein, M., et al. 1982. Effects of dietary cholesterol and fatty acids on plasma lipoproteins. *J. Clin. Invest.* 69:1072–80
72. Schonfeld, G., Pfleger, B. 1971. Utilization of exogenous free fatty acids for the production of very low density lipoprotein triglyceride by livers of carbohydrate-fed rats. *J. Lipid Res.* 12:614–21
73. Schonfeld, G., Weidman, S. W., Witztum, J. L., Bowen, R. M. 1976. Alterations in levels and interrelations of plasma apolipoproteins induced by diet. *Metabolism* 25:261–75
74. Schwandt, P., Janetschek, P., Weisweiler, P. 1982. High density lipoproteins unaffected by dietary fat modification. *Atherosclerosis* 44:9–17
75. Shekelle, R. B., Shryock, A. M., Paul, O., Lepper, M., Stamler, J., et al. 1981. Diet, serum cholesterol, and death from coronary heart disease: The Western

Electric study. *N. Engl. J. Med.* 304:65–70

76. Shelbourne, F., Hanks, J., Meyers, W., Quarfordt, S. 1980. Effect of apoproteins on hepatic uptake of triglyceride emulsions in the rat. *J. Clin. Invest.* 65:652–58
77. Shepherd, J., Packard, C. J., Grundy, S. M., Yeshurun, D., Gotto, A. M. Jr., et al. 1980. Effects of saturated and polyunsaturated fat diets on the chemical composition and metabolism of low density lipopoteins in man. *J. Lipid Res.* 21:91–99
78. Shepherd, J., Packard, C. J., Patsch, J. R., Gotto, A. M. Jr., Taunton, O. D. 1978. Effects of dietary polyunsaturated and saturated fat on the properties of high density lipoproteins and the metabolism of apolipoprotein A-I. *J. Clin. Invest.* 61:1582–92
79. Sherrill, B. C., Innerarity, T. L., Mahley, R. W. 1980. Rapid hepatic clearance of the canine lipoproteins containing only the E apoprotein by a high affinity receptor. *J. Biol. Chem.* 255: 1804–7
80. Simons, L. A., Gayst, S., Balasubramaniam, S., Ruys, J. 1982. Long-term treatment of hypercholesterolemia with a new palatable formulation of guar gum. *Atherosclerosis* 45:101–8
81. Sirtori, C. R., Gatti, E., Mantero, O., Conti, F., Agradi, E., et al. 1979. Clinical experience with the soybean protein diet in the treatment of hypercholesterolemia. *Am. J. Clin. Nutr.* 32:1645–58
82. Stein, E. A., Shapero, J., McNerney, C., Glueck, C. J., Tracy, T., et al. 1982. Changes in plasma lipid and lipoprotein fractions after alteration in dietary cholesterol, polyunsaturated, saturated, and total fat in free-living normal and hypercholesterolemic children. *Am. J. Clin. Nutr.* 35:1375–90
83. Tall, A. R., Small, D. M. 1978. Plasma high density lipoproteins. *N. Engl. J. Med.* 299:1232–36
84. Tan, M. H., Dickinson, M. A., Albers, J. J., Havel, R. J., Cheung, M. C., et al. 1980. The effect of a high cholesterol and saturated fat diet on serum high density lipoprotein-cholesterol, apoprotein AI, and apoprotein E levels in normolipidemic humans. *Am. J. Clin. Nutr.* 33: 2559–65
85. Turner, J. D., Le, N.-A., Brown, W. V. 1981. Effect of changing dietary fat saturation on low-density lipoprotein metabolism in man. *Am. J. Physiol.* 241:E57–E63.
86. Ueshima, H., Iida, M., Shimamoto, T., Konishi, M., Tanigaki, M., et al. 1982. Dietary intake and serum total cholesterol level: Their relationship to different lifestyles in several Japanese populations. *Circulation* 66:519–26
87. Ullrich, I. H., Albrink, M. J. 1982. Lack of effect of dietary fiber on serum lipids, glucose, and insulin in healthy young men fed high starch diets. *Am. J. Clin. Nutr.* 36:1–9
88. Vaith, P., Assmann, G., Uhlenbruck, G. 1978. Characterization of the oligosaccharide side chain of apolipoprotein C-III from human plasma very low density lipoproteins. *Biochim. Biophys. Acta* 541:234–40
89. Van Raaij, J. M. A., Katan, M. B., West, C. E., Hautvast, J. G. A. J. 1982. Influence of diets containing casein, soy isolate, and soy concentrate on serum cholesterol and lipoproteins in middle-aged volunteers. *Am. J. Clin. Nutr.* 35:925–34
90. Vega, G. L., Groszek, E., Wolf, R., Grundy, S. M. 1982. Influence of polyunsaturated fats on composition of plasma lipoproteins and apoproteins. *J. Lipid Res.* 23:811–22
91. Vessby, B., Boberg, J., Gustafsson, I.-B., Karlstrom, B., Lithell, H., et al. 1980. Reduction of high density lipoprotein cholesterol apoliprotein AI concentrations by a lipid-lowering diet. *Atherosclerosis* 35:21–27
92. Vessby, B., Lithell, H., Boberg, J. 1982. Reduction of low density and high density lipoprotein cholesterol by fat modified diets. *Hum. Nutr. Clin. Nutr.* 36C:203–11
93. Walters, R. L., Baird, I. M., Davies, P. S., Hill, M. J., Drasar, B. S., et al. 1975. Effects of two types of dietary fibre on fecal steroid and lipid excretion. *Br. Med. J.* 2:536–38
94. Zilversmit, D. B. 1979. Atherogenesis: A postprandial phenomenon. *Circulation* 60:473–85