

Dietary influences on serum lipids and lipoproteins

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Abstract Substantial data are available to indicate that the diet influences serum levels of cholesterol and lipoproteins. These data are derived from studies in laboratory animals, from epidemiologic studies, and from human investigations. Most research has focused on effects of diet on serum total cholesterol concentrations. In recent years, however, attention has shifted to individual lipoproteins, i.e., low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Three nutritional factors have been identified that raise serum LDL levels; these are saturated fatty acids, cholesterol itself, and excess caloric intake leading to obesity. The major cholesterol-raising saturated fatty acid in the diet is palmitic acid. Several nutrients can be substituted for saturated fatty acids to produce a reduction in LDL-cholesterol levels. These are polyunsaturated fatty acids, monounsaturated fatty acids, carbohydrates, and even one saturated fatty acid, stearic acid. The latter appears to be converted rapidly into a monounsaturated fatty acid in the body. Any of these nutrients can be used for replacement of cholesterol-raising saturated fatty acids in the diet. However, their relative effects on other metabolic processes remain to be determined fully. At present it appears that carbohydrates and monounsaturated fatty acids represent the preferred replacements for saturated fatty acids, although modest increases in polyunsaturated fatty acids and stearic acid, at the expense of cholesterol-raising saturates, probably are safe and may provide for greater variety in the diet.—**Grundy, S. M., and M. A. Denke.** Dietary influences on serum lipids and lipoproteins. *J. Lipid Res.* 1990. 31: 1149–1172.

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The physiological actions of various nutrients are the subject of continuing interest because of the widely held view that diet plays a major role in causation of coronary heart disease (CHD) and in other chronic disorders. That diet affects the serum cholesterol concentration has been known for many years. Approximately 80 years ago, Anitschkow and Chalataw (1) showed that feeding cholesterol to rabbits caused atherosclerosis. Since then, numerous studies have revealed that high intakes of dietary cholesterol cause severe hypercholesterolemia and atherosclerosis in many animal species (2); this response even extends to nonhuman primates (3–8), which has led some

investigators to believe that high-cholesterol diets contribute importantly to the high prevalence of CHD in affluent societies. A few epidemiologic studies are consistent with this latter concept (9).

A critical role of dietary cholesterol in causation of the “mass hypercholesterolemia” of affluent populations, however, is not universally accepted because of reports that humans in general respond less to dietary cholesterol than do most other primate species. A few workers have even suggested that dietary cholesterol has almost no influence on serum cholesterol levels in humans (10–12). This claim almost certainly is not true, but in the 1950s research showed that serum cholesterol concentrations in humans respond more to the major dietary nutrients than to dietary cholesterol itself. For instance, Kinsell et al. (13, 14) reported that vegetable oils markedly reduce serum cholesterol levels when substituted for animal fats in the diet. This finding was extended by Ahrens et al. (15), who identified polyunsaturated fatty acids as the critical component in cholesterol lowering. This basic observation has been confirmed repeatedly by other investigators (16–20).

In the 1960s, Keys, Anderson, and Grande (21) and Hegsted et al. (22) carried out systematic investigations on how the major nutrients affect levels of serum cholesterol in normal humans. They compared responses to different fatty acids, saturated, monounsaturated, and polyunsaturated fatty acids, with those to low-fat, high-carbohydrate intakes. They concluded that carbohydrates have a “neutral” effect on total cholesterol levels, i.e., they neither raise nor lower total cholesterol concentrations. Their work included isocaloric exchange of a variety of fats for dietary carbohydrates and, based on responses, relative effects of different fatty acids on serum cholesterol levels were estimated. They reported that monounsaturated fatty acids do not alter total cholesterol levels when

Abbreviations: CHD, coronary heart disease; VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; FCR, fractional catabolic rate; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-x, corresponds to ω -x unsaturated fatty acids.

exchanged for carbohydrates; thus, monounsaturates likewise were called "neutral." Saturated fatty acids, in contrast, raised serum cholesterol levels, compared to carbohydrates (and monounsaturates), whereas polyunsaturated fatty acids lowered the levels. According to Keys et al. (21), saturated fatty acids raise serum cholesterol concentrations about twice as much as polyunsaturated fatty acids lower them. Hegsted et al. (22) found similar responses, although they reported that saturated fatty acids raise cholesterol levels somewhat less than reported by Keys et al. (21), whereas polyunsaturates lower them somewhat more. The two groups developed similar equations to quantify changes in total cholesterol levels as they occur in response to alterations in diet composition (Table 1). In effect, only the saturated and polyunsaturated fatty acids were used in these equations; carbohydrates and monounsaturated fatty acids were left out because of their apparently "neutral" action on serum cholesterol. From these equations many nutritionists concluded that the polyunsaturated-to-saturated (P/S) ratio is a key determinant of serum cholesterol levels.

Subsequently, a large number of investigations, carried out under metabolic ward conditions, have proven that saturated fatty acids raise serum total cholesterol concentrations relative to other nutrients. This same pattern of response has emerged from epidemiologic studies. In the Seven Countries Study (23), for example, intakes of saturated fatty acids correlated highly with serum cholesterol levels. Higher cholesterol levels occurred in populations consuming diets rich in saturates, whereas lower levels were noted in populations having diets high in either carbohydrates or monounsaturates. In this study (23), no populations were found that habitually ingested large amounts of polyunsaturated fatty acids.

For many years interest in dietary effects on serum lipids centered on total cholesterol levels. Unfortunately, serum lipid measurements in dietary studies generally have lagged behind advances in our understanding of cholesterol transport via lipoproteins. Most results have been expressed in terms of total cholesterol levels. For whole populations, serum levels of total cholesterol correlate highly with concentrations of low density lipoprotein (LDL) cholesterol (24). This correlation led most investigators to assume that diet-induced changes in total cho-

lesterol levels must yield essentially the same alterations in LDL-cholesterol concentrations. For some diet modifications this similarity of response indeed may hold, but we nonetheless must ask whether other dietary changes alter lipoprotein patterns in ways not revealed by total cholesterol levels. Recently, several investigators, including ourselves, have begun to reexamine the influence of various nutrients on lipid metabolism with emphasis on serum lipoproteins and apolipoproteins. The present review will therefore consider effects of diet on lipoproteins as well as total cholesterol, and it will attempt to integrate recent findings with those obtained previously for total cholesterol only. The influence of diet on total cholesterol and LDL-cholesterol levels will be considered first, and this will be followed by a review of actions of various nutrients on triglycerides and on high density lipoproteins (HDL); finally, effects of diet on other metabolic pathways will be examined as they influence general dietary recommendations.

This review will consider primarily investigations carried out in humans in controlled settings. There are large bodies of data from laboratory animals and epidemiologic studies that are beyond the scope of this report. In some instances, research in laboratory animals will be mentioned when it is germane to mechanism, but our review will not attempt to thoroughly incorporate results from experimental animals. The same will hold for epidemiologic data.

TOTAL CHOLESTEROL AND LDL-CHOLESTEROL

Dietary cholesterol

Abundant evidence exists from studies in laboratory animals that dietary cholesterol raises serum cholesterol concentrations in many species. The literature on dietary cholesterol and experimental atherosclerosis is vast and cannot be reviewed adequately in this paper. Atherosclerosis induced by dietary cholesterol has been reported in several species including nonhuman primates (3, 5, 6). Coronary atherosclerosis in primates not only resembles human lesions (5) but can even produce myocardial infarction (4). Evidence that dietary cholesterol is highly atherogenic in many species including primates has bolstered the view that high cholesterol intakes may also be atherogenic in humans.

In primates the major effect of dietary cholesterol is to raise LDL-cholesterol levels. Not only do high intakes of cholesterol increase the number of circulating LDL particles (8), but they can also change the size and composition of these particles. LDL particles become larger in size and enriched in cholesteryl esters. One mechanism for the increase in LDL cholesterol levels is a suppression of LDL receptor activity. Studies in tissue culture have demonstrated that increasing the cholesterol content of cells will

TABLE 1. Equations for predicting effects of diet on total serum cholesterol

Equation of Keys et al. (21)
$\Delta \text{Cholesterol (mg/dl)} = 2.7\Delta S - 1.35\Delta P + 1.5\Delta C^{1/2} \text{ mg/1000 cal-day}$
Equation of Hegsted et al. (22)
$\Delta \text{Cholesterol (mg/dl)} = 2.16\Delta S - 1.65\Delta P + 0.068\Delta C_{\text{mg/day}}$
Where S = saturated fatty acids (% of total calories); P = polyunsaturated fatty acids (% of total calories); C = dietary cholesterol.

down-regulate synthesis of LDL receptors (25, 26). The same presumably occurs *in vivo*; indeed, experimental data indicate that the hepatic LDL-receptor activity is suppressed in cholesterol-fed animals (27, 28). Another reason for the rise in serum cholesterol levels in animals fed high-cholesterol diets is that newly secreted lipoproteins become enriched with cholesteryl ester at the expense of triglyceride (29–32). Apparently the latter change is not accompanied by an increase in the number of lipoprotein particles secreted into plasma. For example, in monkeys, high-cholesterol diets seemingly do not increase abundance of mRNA for apoB in the liver, whereas these diets cause approximately 50% lower levels of hepatic LDL-receptor mRNA (28).

Effects of dietary cholesterol on raising serum levels of total cholesterol and LDL-cholesterol are much less pronounced in humans than in most primate species. In fact, several investigations carried out in the outpatient setting suggested that dietary cholesterol has little or no effect on serum cholesterol levels (10–12). When investigations are performed under metabolic ward conditions, however, increasing the intake of cholesterol consistently produces a rise in serum total cholesterol levels (22, 33–45).

The quantitative relation between cholesterol intake and cholesterol levels nonetheless remains a matter of some dispute. According to Keys, Anderson, and Grande (38), the serum total cholesterol response is correlated to the square root of cholesterol intake, whereas Hegsted et al. (22, 39) and Mattson, Erickson, and Kligman (36) reported a linear relationship. Among primates, some animals are high-responders whereas others are low-responders to dietary cholesterol (46–48). In humans, a marked variability in responsiveness seemingly does not exist (41–45). Still, several studies in humans suggest that individual variability in processing of dietary cholesterol may be a factor determining the serum cholesterol response (40, 49).

The reason for the rise in LDL-cholesterol concentration in humans fed cholesterol presumably is similar to that in laboratory animals, i.e., suppression in activity of LDL receptors. Only a few investigations, however, have addressed the effects of dietary cholesterol on LDL metabolisms in humans. In one study, Ginsberg et al. (50) found no influence of dietary cholesterol on LDL metabolism in humans who were essentially “nonresponders” to excess cholesterol in the diet. In another investigation, Packard et al. (51) reported that raising cholesterol intake causes both an increase in production rate for LDL and a decrease in fractional catabolic rate (FCR) for LDL. The fall in FCR for LDL is suggestive of a decrease in LDL-receptor activity, whereas the higher production rate for LDL raises the possibility of an increase in the hepatic synthesis of apoB-containing lipoproteins. As shown in Fig. 1, however, an increment in input rate for

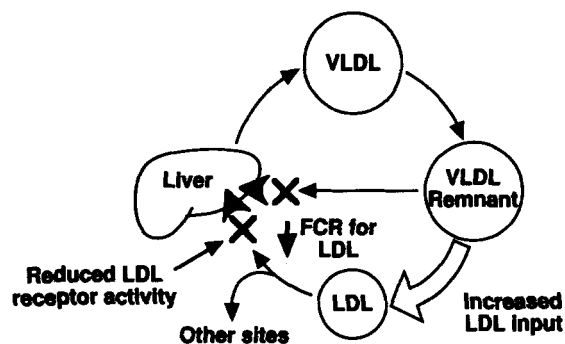


Fig. 1. Mechanism of increase in LDL-cholesterol levels with high cholesterol intakes. An increase in hepatic cholesterol content, secondary to excess dietary cholesterol, suppresses synthesis of LDL receptors. This retards uptake of both LDL and VLDL remnants. The result is a decrease in fractional catabolic rate (FCR) for LDL and increased conversion of VLDL remnants to LDL. The latter is measured as an enhanced input rate for LDL.

LDL per se does not necessarily mean heightened synthesis of lipoproteins in the liver. Since VLDL remnants are partially removed by LDL receptors, a decrease in LDL-receptor activity should allow for an increased conversion of VLDL remnants to LDL; this change will be seen kinetically as an overproduction of LDL. In other words, a high production rate for LDL can be caused by a reduced LDL-receptor activity. This phenomenon is illustrated by the very high production rates for LDL in patients with homozygous familial hypercholesterolemia who are completely devoid of LDL receptors (52–54). Thus, it is not necessary to evoke an oversynthesis of apoB to explain an increased input of LDL.

Saturated fatty acids

The action of dietary saturated fatty acids as a lipid class to raise total cholesterol levels, compared to carbohydrate, is well established. The early reports of Ahrens et al. (15), Keys et al. (21), and Hegsted et al. (22) indicating that saturated acids increase total cholesterol concentrations have not been contradicted by subsequent investigations. Recent reports (55–57), moreover, indicate that LDL-cholesterol levels, as well as total cholesterol concentrations, are raised by saturated fatty acids in the diet. Increases in LDL-cholesterol levels on the average appear to be quantitatively similar to those described previously for total cholesterol concentrations. The mechanisms whereby saturated fatty acids raise LDL levels are not completely understood. A strong probability, however, is that they interfere with LDL receptor-mediated clearance of LDL (Fig. 2). The serum cholesterol-raising action of saturated fatty acids is manifest largely in the LDL fraction; these fatty acids generally do not raise triglyceride concentrations, as might be expected if they were to stimulate the synthesis of very low density lipoprotein (VLDL), the precursor of LDL. Isotope-kinetic studies of LDL apolipoprotein B-100 (apoB) in humans indicate that the

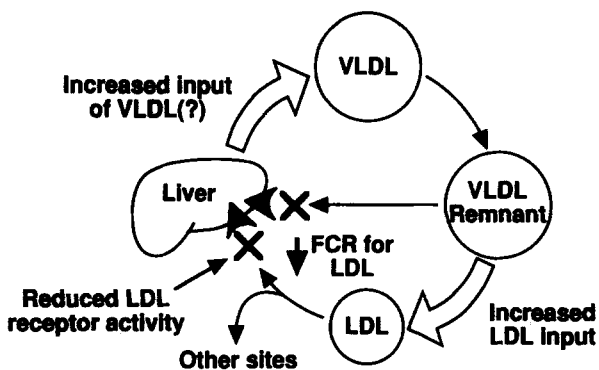


Fig. 2. Mechanisms of increase in LDL-cholesterol levels with high intakes of saturated fatty acids. The major effect of saturated fatty acids appears to be a reduced activity of LDL receptors. This change reduces the fractional catabolic rate (FCR) for LDL and enhances conversion of VLDL remnants to LDL. The possibility that saturated fatty acids promote the synthesis of apoB-containing lipoproteins has not been ruled out, although evidence to support this mechanism is minimal.

LDL-raising action of saturated fatty acids is due mainly to impaired removal of LDL from the circulation (58). In accord, in laboratory animals, diets high in saturated fatty acids seemingly suppress LDL-receptor-mediated clearance of LDL (59, 60). Nonetheless, saturated fatty acids theoretically could act by a second mechanism, namely, by enhancing synthesis of apoB-containing lipoproteins. Research in humans and animals does not yield unequivocal evidence that the only mechanism for the increase in LDL levels is a reduced clearance through the LDL-receptor pathway; thus, an action of saturated fatty acids on synthesis of lipoproteins will remain a possibility until excluded by definitive experiment.

One difficulty with the concept that saturated fatty acids suppress the activity of LDL receptors is that this putative action does not fit into known schemes whereby synthesis of LDL receptors is down-regulated. As indicated before, the major regulator of LDL-receptor synthesis is the amount of cholesterol within a cell (25, 26, 61, 62) or, more likely, the amount of an oxygenated sterol derived from cholesterol (63). Clearly, experimental evidence shows that factors that increase the cellular content of cholesterol, and hence oxysterols, suppress LDL-receptor synthesis. If dietary saturated fatty acids likewise suppress LDL-receptor synthesis, perhaps they exert their action by redistributing cholesterol among various cellular compartments to favor its inhibitory action on receptor synthesis. If this mechanism pertains, feeding saturated fatty acids might be expected to reduce the abundance of mRNA for LDL receptors, as occurs with cholesterol feeding (28); indeed, a reduced mRNA for LDL cholesterol receptors was found with feeding of saturated fatty acids in one investigation in baboons (64) but not in another in African green monkeys (28). Additional research, therefore, is needed to determine with certainty

whether saturated fatty acids alter transcription of the LDL-receptor gene.

An alternate mechanism for the cholesterol-raising action of saturated fatty acids has been postulated by Loscalzo et al. (65); on the basis of in vitro studies, these workers suggested that enrichment of cell-membrane phospholipids with saturated fatty acids interferes with the normal function of LDL receptors within the cell membrane, possibly by reducing binding or internalization of circulating LDL. The failure to find a decrease in mRNA for LDL receptors in monkeys fed saturated fatty acids was considered to support a cell-membrane effect (28). Still, proof that the total saturation of cell-membrane phospholipids can be increased in vivo by feeding of diets high in saturated fatty acid is lacking (66).

As indicated before, Sorci-Thomas et al. (28) reported that a diet high in saturated fatty acid does not increase hepatic abundance of mRNA for apoB in monkeys. In the same study, livers were perfused and rates of secretion of apoB-containing lipoproteins were determined; the pre-feeding of saturated fatty acids did not increase secretion of apoB-containing lipoproteins during perfusion. In another study in hamsters, Spady and Dietschy (67) indicated that dietary saturated fatty acids simultaneously reduce clearance of LDL by receptor-mediated pathways and raise production rates for LDL. As shown by Fig. 2, however, a fall in LDL-receptor activity should enhance conversion of VLDL to LDL, which will be measured as increased LDL "production." The latter study (67), therefore, does not prove that saturated fatty acids enhance the synthesis of apoB-containing lipoproteins in the liver.

The above studies on mechanism pertain to saturated fatty acids as a class. One must keep in mind, however, that the diet contains saturated fatty acids of different chain lengths, and all saturates may not affect serum levels of total cholesterol and LDL cholesterol equally. Each type of saturated fatty acid, therefore, deserves to be considered separately.

Palmitic acid (16:0). The principal saturated fatty acid in most diets is palmitic acid. It is the major saturate in animal fats, but also occurs in vegetable oils. Since palmitic acid is the principal saturated acid in the diet, it is the chief saturated component used to develop the diet equations (21, 22). Keys et al. (21) and Hegsted et al. (22) basically agree on the extent to which palmitic acid raises total cholesterol levels; later studies from our laboratory (55–57) have shown clearly that palmitic acid increases LDL-cholesterol levels in parallel with total cholesterol concentrations when it is substituted for carbohydrates or monounsaturates in the diet.

Myristic acid (14:0). Less data are available on the actions of myristic acid than for palmitic acid. Keys et al. (21) and Hegsted et al. (22) both indicated that myristic acid raises total cholesterol concentrations; but whereas the former (21) equated myristic and palmitic acids, the

latter (22) proposed that myristic acid raises the total cholesterol even more than does palmitic acid. The latter claim was based mainly on the finding that butter fat, which is rich in myristic acid, increases the cholesterol level more than would be predicted if myristic acid has an effect equal to palmitic acid. Unfortunately, no investigations have directly and specifically examined the actions of myristic acid on cholesterol levels, and available data on comparative effects of myristic and palmitic acids remain few. In any case, diets of most people contain relatively small quantities of myristic acid, its major source being butter fat (Table 2).

Stearic acid (18:0). This saturated fatty acid, in contrast to palmitic acid, seemingly does not raise the total cholesterol level. Early evidence to this effect came from the work of Ahrens et al. (15) who found that cocoa butter is less hypercholesterolemic than butter fat. This difference might be attributed to differences in their cholesterol contents because both fats contain a similar high percentage of total saturated fatty acids. However, cocoa butter is unusually rich in stearic acid which opened the possibility that this saturated acid does not increase serum cholesterol levels. Indeed, further studies in both humans (21, 22, 68, 69) and animals (70–72) strongly suggested that stearic acid, in contrast to other saturated fatty acids, does not raise the serum total cholesterol. Keys et al. (21) indeed proposed that stearic acid be subtracted from the dietary mix of saturated fatty acids when calculating the serum cholesterol response; although their equation was modified accordingly, stearic acid subsequently was rarely removed when the equation was used by others to predict responses to diet.

Even though earlier studies raised doubts that stearic acid increases the serum cholesterol level, as does palmitic acid, this lack of effect was not widely acknowledged or accepted simply because stearic acid is a saturated acid. This prompted Bonanome and Grundy (57) to specifically test for relative actions of stearic acid and palmitic acid. A chemically randomized fat that is high in stearic acid was manufactured for this study. The fat had a stearic

acid content that was as high as the palmitic acid content of palm oil, which also was tested. Both fats were compared to high-oleic safflower oil. Relative to the palm oil response, the high-stearic fat lowered total cholesterol levels as much as the high-oleic oil. LDL-cholesterol concentrations responded similarly. This comparison, therefore, confirmed that stearic acid, like the monounsaturated oleic acid, acts as “neutral” and thus fails to increase total cholesterol or LDL-cholesterol concentrations.

The reason stearic acid differs from palmitic acid in its action on cholesterol levels must be considered. One possibility is that stearic acid is poorly absorbed and does not enter the body. Stearic acid is more insoluble than other fatty acids, and thus may be less absorbable. Certainly tristearin resists hydrolysis in the intestine and thereby escapes absorption. On the other hand, investigations in laboratory animals (73) have shown that stearic acid in mixed triglycerides generally is well absorbed, although perhaps somewhat less so than other fatty acids (74, 75). The report of Bonanome and Grundy (57) indicated that stearic acid in the high-stearic fat is well absorbed in humans. In a more recent study, Bonanome and Grundy (76) obtained direct evidence in humans that stearic acid in naturally occurring fats is highly absorbed. In our view, therefore, another mechanism must explain the failure of stearic acid to raise serum cholesterol levels. For one example, stearic acid may be more rapidly converted to oleic acid than are other saturates. The conversion of palmitic acid to oleic acid requires two steps, elongation and desaturation. Elongation may be relatively slow, whereas desaturation is rapid. If so, stearic acid would be converted quickly to oleic acid, whereas palmitic acid would accumulate in tissues. This, in fact, appears to be the case. In humans, triglycerides contain considerably more palmitic acid than stearic acid (57). Further, one study in rats confirms that stearic acid is converted much more rapidly in the liver to oleic acid than is palmitic acid (77).

Since stearic acid does not raise LDL-cholesterol levels, it might be used as a replacement for palmitic acid in diets designed to lower the cholesterol level. In spite of a com-

TABLE 2. Fatty acid compositions of several fats

Fat	4–10:0 ^a	12:0	14:0	16:0	16:1	18:0	18:1	18:2	18:3	Other
	% of total fatty acid									
Butter fat	9.2	3.1	17.7	26.2	1.9	12.5	28.2	2.9	0.5	
Palm kernel oil	8.2	49.6	16.0	8.0		2.4	13.7	2.0		0.1
Coconut oil	14.9	48.5	17.6	8.4		2.5	6.5	1.5		0.1
Palm oil		0.3	1.1	45.1	0.1	4.7	38.8	9.4		0.5
Beef fat	0.1	0.1	3.3	25.5	3.4	21.6	38.7	2.2	0.6	4.6
Pork fat (lard)	0.1	0.1	1.5	24.8	3.1	12.3	45.1	9.9	1.1	3.0
Chicken fat		0.2	1.3	23.2	6.5	6.4	41.6	18.9	1.3	0.6
Mutton fat	0.2	0.3	5.2	23.6	2.5	24.5	33.3	4.0	1.3	5.1
Cocoa butter			0.1	25.8	0.3	34.5	35.3	2.9		1.1

^aThe numbers for the fatty acids represent carbon chain length: number of double bonds.

mon belief to the contrary, hydrogenation of vegetable oils does not necessarily transform them into cholesterol-raising fats because stearic acid, not palmitic acid, is the saturated acid produced by hydrogenation (57). This assumes of course that *trans* unsaturated fatty acids, also formed during hydrogenation, do not raise cholesterol levels. Margarines and shortenings enriched in stearic acid might be developed for use in the place of butter, lard, or beef tallow. Among the latter, lard and beef tallow have considerable amounts of stearic acid, and less than one-third of their total fatty acids is of the cholesterol-raising type (Table 2). These fats consequently are less hypercholesterolemic than butter fat. Even so, they deserve to be classified as cholesterol-raising fats because they have appreciable amounts of palmitic acid, i.e., 25 to 30%.

Lauric acid (12:0). The influence of lauric acid on serum cholesterol concentrations is uncertain. Keys et al. (21) judged that lauric acid raises cholesterol levels as much as palmitic acid, but Hegsted et al. (22) submitted that it has only a small effect on levels. No studies have specifically addressed this issue. The question is perhaps of more importance than that for myristic acid because of the high content of lauric acid in two tropical oils, coconut oil and palm kernel oil (Table 2). Still, both of these oils contain almost as much cholesterol-raising saturates as beef tallow and lard, and regardless of the action of lauric acid, they cannot be called "neutral" fats. Indeed, Reiser et al. (78) demonstrated that coconut oil raises LDL-cholesterol levels more than beef fat; this response, however, might be due more to the high myristic acid content of coconut oil than to its lauric acid content (Table 2). If lauric acid itself is eventually shown not to increase cholesterol concentrations, it too could have utility in "synthetic" fats as a replacement for palmitic acid.

Medium-chain fatty acids (8:0 and 10:0). Butter fat is relatively rich in medium-chain fatty acids, and since butter fat causes a marked rise in cholesterol levels, Ahrens et al. (15) postulated that medium-chain acids increase serum cholesterol concentrations more than other saturates. Subsequent investigations, however, failed to verify this suggestion. In fact, research both in laboratory animals (79) and in humans (80) reveals that medium-chain fatty acids act more like carbohydrates than saturates, i.e., they do not raise serum cholesterol. If these limited data are confirmed by further investigation, medium-chain fatty acids also could be substituted for cholesterol-raising saturated fatty acids in certain foods.

Hyperresponsiveness to saturated fatty acids: Does it exist? Many animal species respond excessively to high cholesterol intakes by developing severe hypercholesterolemia. Other species resist dietary cholesterol and fail to show striking rises in serum cholesterol levels. Within species that are sensitive to dietary cholesterol, the degree of sensitivity varies among individual animals. Some animals are "high-responders," i.e., they show marked rises in

cholesterol levels when fed excessive cholesterol; others are "low-responders." This difference depends in large part on genetic factors (81-83). In humans, individual variability in responsiveness to dietary cholesterol probably exists, but the degree of difference between high and low responders is much less than for many animals (41-43). Since humans in general appear to be more sensitive to dietary saturated fatty acids than to dietary cholesterol, the question might be asked whether some people are high responders to saturated fatty acids whereas others are low responders.

Grundy and Vega (56) recently reported that variability exists among individuals in their sensitivity to saturated fatty acids. The data from this report are summarized in Fig. 3. Total cholesterol and LDL-cholesterol levels were compared on diets high in monounsaturated fatty acids or saturated fatty acids. Almost all patients showed a rise in cholesterol levels when the diet was high in saturated fatty acids, but some showed a greater increase than others. This suggests that some individuals are high responders to saturated fatty acids, whereas others are low responders. Those who had higher cholesterol levels on the

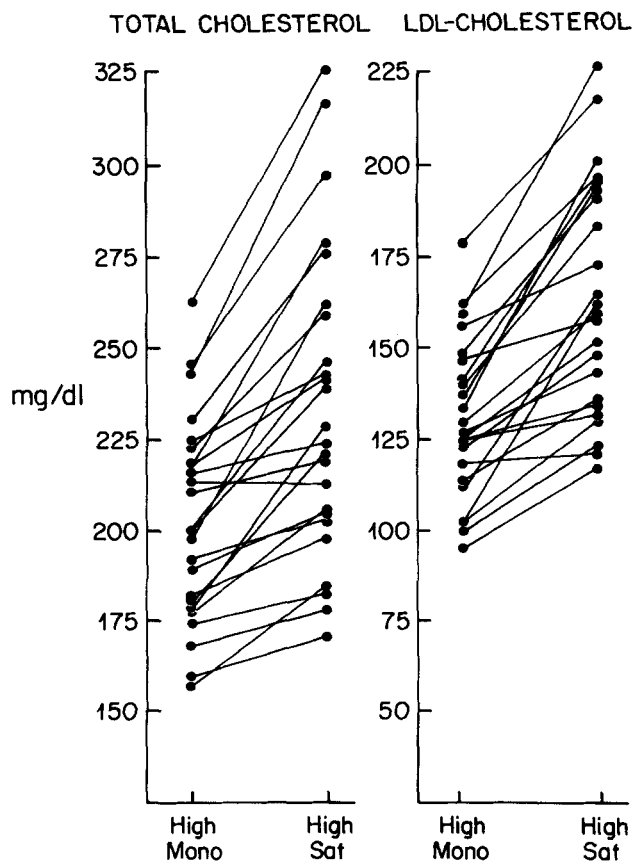


Fig. 3. Effects of exchange of diets high in monounsaturated fatty acids (High Mono) for saturated fatty acids (High Sat) on plasma total cholesterol and LDL cholesterol. Some patients (high responders) had a marked increase in cholesterol levels, but others (low responders) had a lesser increase. Modified from Grundy and Vega (56).

diet high in monounsaturates generally demonstrated the greatest response to dietary saturated fatty acids. This latter phenomenon was reported before for total cholesterol levels by Keys et al. (21). On the basis of these studies (21, 56), it appears that sensitivity to saturated fatty acid is variable, and this variability could have a genetic basis. Some people, for example, could have genetic defects that make them unusually sensitive to the action of saturated fatty acids to suppress the activity of LDL receptors, and thus respond to dietary saturates with a marked increase in cholesterol levels.

The above interpretation, however, has been questioned by Beynen and Katan (84). Although these workers admit to some variability in inherent responsiveness to saturated fatty acids within the population, they propose that the range of variability is relatively small and is of little or no practical importance (44, 85, 86). They further suggest that sizable differences in responsiveness, such as those reported by Grundy and Vega (56), occur not from true differences in sensitivity to saturated fatty acids, but instead reflect normal fluctuations in cholesterol levels within the population; in other words, those who appear to be high responders may have been studied at the "top" of their normal fluctuation; if studied at another time, their apparent sensitivity to saturated fatty acids could have disappeared. This response can be likened to the well-known "regression to the mean" phenomenon. Still, these workers (44, 85, 86) agree that some variability does exist in responsiveness to saturated fatty acids and, in our view, it may be considerable. Many questions nonetheless remain to be answered about diet responsiveness. For example, is variability in responsiveness determined genetically or is it environmentally affected? Do older people generally respond to dietary saturated fatty acids with a greater rise in cholesterol levels than do younger people? Are men more sensitive than women? Are those with higher baseline levels of LDL more sensitive than those with lower levels? And beyond these issues, the question of mechanism must be raised. Do some individuals have a defective catabolism of saturated fatty acids so that they accumulate these acids in the body? Are the defects in the regulation of LDL-receptor activity (e.g., abnormalities in the promoter region of the LDL-receptor gene) that lead to oversuppression of LDL-receptor synthesis by saturated acids? Do some people accumulate excessive amounts of cholesteryl ester in LDL particles secondary to down-regulation of LDL-receptor activity by saturated fatty acids? All of these questions and others must be addressed before the scope of the issue of diet responsiveness can be fully understood.

Monounsaturated fatty acids

Oleic acid (n-9, cis 18:1). The major monounsaturated fatty acid in the diet is oleic acid. As indicated before, oleic acid has been considered "neutral" in its influence on

total cholesterol levels. All studies (21, 22, 35, 87, 88) nonetheless indicate that oleic acid "lowers" plasma cholesterol when substituted for palmitic acid. By convention, however, palmitic acid is designated a cholesterol-raising fatty acid, whereas oleic acid is called "neutral" because it affects total cholesterol levels similarly to the effect of carbohydrates. If LDL-receptor activity is the prime variant, oleic acid presumably allows for the natural expression of receptor activity, whereas palmitic acid actively reduces the activity.

Elaidic acid (n-9 trans 18:1). Hydrogenation of vegetable oils rich in polyunsaturated fatty acids produces considerable quantities of elaidic acid, a *trans* monounsaturated fatty acid. Several other *trans*-unsaturated isomers are formed as well. Reports on effects of *trans* unsaturates on cholesterol levels in humans are inconsistent. One study (89) suggested that they raise cholesterol concentrations, whereas others (90-94) found that *trans* monounsaturates, like oleic acid, are "neutral" and do not increase serum cholesterol levels. In our view, more definitive studies are needed because at present a few percent of total calories in the American diet come from *trans* unsaturated fatty acids. If these acids should be found to raise cholesterol levels, new processes for hardening of vegetable oils would be needed.

Polyunsaturated fatty acids

Two types of polyunsaturated fatty acids occur in the diet, n-6 and n-3 polyunsaturates. The predominant n-6 fatty acid is linoleic acid (18:2) which comes mainly from plant oils. Animal fats may also contain small quantities of linoleic acid, which likewise originate from plant sources. The parent n-3 polyunsaturate is linolenic acid (18:3), and it also occurs in certain vegetable oils. Soybean oil, rapeseed oil, and linseed oil are particularly rich sources of linolenic acid. The fish oils contain large amounts of very-long-chain polyunsaturates that have their origins from linolenic acid of plant sources. Major n-3 fatty acids in fish oils are eicosapentaenoic acid (EPA) (20:5 n-3) and docosahexaenoic acid (DHA) (22:6 n-3). Together they constitute about 26% of fish oil fatty acids.

Linoleic acid. For many years, linoleic acid was considered a "cholesterol-lowering" fatty acid. This concept grew out of early studies of Kinsell et al. (13, 14, 95) and Ahrens et al. (15, 96) which showed that vegetable oils rich in linoleic acid lower the serum cholesterol level when substituted for dietary saturated fatty acids. This notion was extended by other workers (97, 98) and was refined by Keys et al. (21) and Hegsted et al. (22) who attempted to quantify the cholesterol-lowering action of linoleic acid. The work of the latter two groups (21, 22) suggested that linoleic acid lowers total cholesterol levels more than oleic acid or carbohydrates. In general, using oleic acid as a baseline, they estimated that linoleic acid lowers the cholesterol level about half as much as saturated fatty acids

raise it (Table 1). It was later assumed that the cholesterol-lowering action of linoleic acid occurs mainly in the LDL fraction. Since the time of these investigations of the late 1950s and early 1960s, linoleic acid has been thought by most investigators to be an LDL-lowering fatty acid.

Once the concept was established that linoleic acid reduces total cholesterol and LDL-cholesterol concentrations, the question naturally arose as to the mechanism for this action. Investigations designed to answer this question were performed in several areas of cholesterol and LDL metabolism. There is no doubt that when linoleic acid replaces saturated fatty acids in the diet, the major portion of cholesterol lowering occurs in the LDL fraction (99). Most mechanistic studies were based on the assumption that linoleic acid possesses a unique ability to reduce the LDL-cholesterol concentration, perhaps similar to that of some hypocholesterolemic drugs.

One of the first questions to be addressed was whether serum cholesterol lowering induced by linoleic acid occurs in a safe way. For example, what happens to the cholesterol that disappears from the blood stream? Is it excreted from the body, or is it redistributed into tissues? If the latter, might not this excess cholesterol enter into the arterial wall and promote atherosclerosis? These questions stimulated the development of the cholesterol-balance technique, a method that measures rates of excretion of cholesterol and its products, neutral steroids and bile acids, from the body. Cholesterol-balance studies, unfortunately, gave inconclusive data. In some people, e.g., normal subjects (100) and hypertriglyceridemic patients (101), substitution of linoleic acid for saturated fatty acids enhanced excretion of fecal steroids, suggesting a "safe" mechanism for serum cholesterol lowering. Patients with hypercholesterolemia, on the other hand, did not show this response, i.e., cholesterol balance was unchanged (102). The question of whether exchange of polyunsaturates for saturates consistently promotes excretion of steroid products thus was never resolved.

Another action of dietary linoleic acid was proposed by Spritz and Mishkel (103). These workers postulated that when serum lipids are enriched with polyunsaturates they occupy more space within lipoprotein particles than when the lipids are poor in polyunsaturates; consequently, in the presence of polyunsaturates, fewer cholesteryl ester molecules can reside in the core of LDL particles. If this mechanism holds, the number of LDL particles in plasma should not be reduced by polyunsaturates, but rather the cholesterol content of each particle would be decreased. Subsequent studies (58, 104–106) yielded data consistent with this hypothesis, but Vega et al. (99) and Kuksis et al. (107) demonstrated unequivocally that dietary exchange of polyunsaturates for saturates reduces the number of LDL particles in circulation, as revealed by a definite fall in LDL-apoB concentrations. Exclusion of cholesteryl es-

ters from LDL particles thus cannot be the only mechanism whereby polyunsaturates "lower" LDL levels. Vega et al. (99) nonetheless did note that feeding of polyunsaturates reduced LDL-cholesterol/apoB ratios in some patients, which implies some degree of cholesterol depletion in LDL. A change in proportions of lipids and protein in LDL particles during polyunsaturate feeding, however, is not invariable as shown by the recent studies of Mattson and Grundy (55).

Yet another mechanism whereby polyunsaturates might lower LDL levels is by inhibition of hepatic synthesis of apoB-containing lipoproteins. Decreased synthesis of VLDL-apoB, for example, should ultimately reduce formation of LDL apoB. High intakes of polyunsaturates may decrease serum triglyceride concentrations (101, 108), and they can decrease production of VLDL-apoB (109). This change apparently occurs in some individuals, but in many others polyunsaturates have little or no effect on VLDL levels (see section on Triglycerides). LDL-lowering by linoleic acid, therefore, probably cannot be due primarily to an inhibition of hepatic secretion of VLDL particles.

Finally, available evidence suggests that substitution of linoleic acid for saturated fatty acids causes an increase in LDL-receptor activity. In accord, polyunsaturates enhance the fractional clearance rate for LDL when they are substituted for saturates in the diet of humans (34). Although some individuals may show a reduced conversion of VLDL to LDL on polyunsaturates (110), this too could be the result of enhanced direct removal of VLDL remnants via VLDL receptors. Studies in laboratory animals (27) further indicate that exchange of linoleate for saturated acids raises receptor-mediated uptake of LDL. These observations, however, do not prove that linoleic acid actively stimulates LDL-receptor activity, analogous to HMG-CoA reductase inhibitors (111). In fact, when linoleic acid is fed in large quantities to monkeys, there is no evidence for an increase in mRNA abundance for LDL receptors (28). The effects of linoleic acid, therefore, could be entirely passive, which is to say, saturated fatty acids may actively suppress activity or function of LDL receptors by mechanisms yet to be determined, whereas linoleic acid is neutral. If so, linoleate would have no greater effect on LDL-receptor function than oleic acid.

The notion that linoleic acid has unique LDL-lowering properties was called into question by Mattson and Grundy (55). They compared three diets that were relatively high in palmitic acid, linoleic acid, or oleic acid; each diet used a different fat, namely, palm oil, high-linoleic safflower oil, and high-oleic safflower oil. These diets were all liquid formula diets having 40% of calories as fat. In this investigation, substitution of oleic acid for palmitic acid resulted in a lowering of LDL-cholesterol levels similar to that predicted by Keys et al. (21) and

Hegsted et al. (22). The LDL-cholesterol concentration, however, was not lower on the high-linoleate diet than on the high-oleate diet. This unexpected finding suggested that the unique “cholesterol-lowering” property of linoleic acid may not extend to LDL-cholesterol levels. This concept is supported by a recent report from Mensink and Katan (112); these workers also found that oleic acid and linoleic acid have essentially identical effects on LDL-cholesterol levels. Two preliminary reports (113, 114) suggest the same identity of LDL response to dietary oleic and linoleic acids. In addition to comparisons of linoleate with oleate, studies by Brussaard et al. (115, 116), Grundy et al. (117), and Weisweiler, Janetschek, and Schwandt (118) have cast doubt that linoleic acid is more hypocholesterolemic than carbohydrate. Thus, linoleic acid may not uniquely lower the LDL-cholesterol level as was previously thought.

The findings of Mattson and Grundy (55) at first were not accepted by many who held to the view that linoleic acid has a greater LDL-lowering action than oleic acid. One study by Becker et al. (119) supports this latter view. Criticisms of the study of Mattson and Grundy (55) are that the bulk of previous data support a contrary result, that the study had too few patients, and that liquid formula diets blunted the effect of linoleic acid (although not of oleic acid). These criticisms stimulated Mensink and Katan (112) to carry out a larger study in outpatients using solid food diets; but the results of this study again showed that the LDL-lowering actions of linoleic acid and oleic acid are identical. We suggest, therefore, that the calculations of Keys et al. (21) and Hegsted et al. (22) may have underestimated the response to oleic acid, compared to linoleic acid. High-oleate oils were actually used in a few of their studies and their experimental design may have been weighted against a “cholesterol-lowering” property of oleic acid since in regression analyses intakes of oleate were closely linked to saturated fatty acids because both are present in animal fat (i.e., lard and beef tallow). This linkage contrasts to a separation of linoleic acid and saturated fatty acids when high-linoleate diets were used.

Carbohydrates

The absorbable carbohydrates consist of monosaccharides, disaccharides, and polysaccharides (starches). As noted before, the carbohydrates were early designated neutral in their action on cholesterol levels (21, 22). In the light of subsequent investigations (87, 117, 120, 121), this seems reasonable. There are no data to indicate that different types of absorbable carbohydrate differ in their effects on LDL-cholesterol concentrations. Carbohydrates and oleic acid generally induce indistinguishable responses in LDL-cholesterol concentrations (87, 117, 120, 121). Even so, the two nutrients do not necessarily affect LDL metabolism in the same way. Since carbohydrates

tend to raise triglyceride concentrations (122), they may reduce the mean particle size of LDL (123). If so, LDL particles will be relatively reduced in cholesterol content relative to apoB. Indeed, Kuusi, et al. (124) found that low-fat, high-carbohydrate diets lower LDL-cholesterol levels more than LDL-apoB concentrations when compared to a diet high in saturated fatty acids. In this study (124), the low-fat diet caused little if any lowering of LDL-apoB concentrations. In contrast, substitution of monounsaturates for saturates induces equal lowering of LDL cholesterol and LDL apoB (55).

More studies are needed to confirm or refute the findings of Kuusi et al. (124). If future studies should prove that substitution of carbohydrate for saturated fatty acids does in fact lower LDL-apoB concentrations, besides reducing LDL-cholesterol levels, the mechanisms will require an explanation. High-carbohydrate diets could allow for a return of LDL-receptor activity to normal levels, although the reason why this should be is not immediately obvious. The feeding of high-carbohydrate diets may not reduce body stores of palmitic acid, because the body can synthesize palmitate from carbohydrate. Of course, absolute amounts of palmitic acid in the liver might selectively be reduced by high-carbohydrate diets, which could allow for derepression of LDL-receptor activity. Clearly, little is known about the effects of low-fat, high-carbohydrate diets on LDL metabolism even though these diets are widely advocated for LDL lowering.

Fig. 4 summarizes our proposed mechanisms whereby the various nutrients described above, stearic acid, oleic acid, linoleic acid, carbohydrates, result in a lowering of LDL-cholesterol levels when they replace cholesterol-raising saturated fatty acids in the diet. The available data suggest that their primary mode of action is through LDL

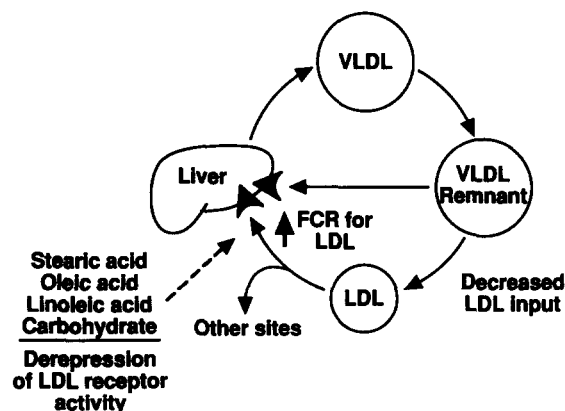


Fig. 4. Alternative nutrients for cholesterol-raising saturated fatty acids. These include stearic acid, oleic acid, linoleic acid, and carbohydrates. When any of these nutrients replace saturated fatty acids in the diet, the level of serum LDL cholesterol falls. The primary mechanism for LDL lowering for each nutrient apparently is a release of suppression of saturated fatty acids on LDL receptor activity. If cholesterol-raising saturates promote the synthesis of apoB-containing lipoproteins, this action likewise may be reversed by alternative nutrients.

receptor-mediated clearance of LDL. However, they seemingly do not actively stimulate LDL-receptor activity, but instead, they reverse the suppression of receptor activity induced by cholesterol-raising saturated fatty acids. This allows for a rise in FCR for LDL and a reduction in LDL input. If saturated fatty acids stimulate the synthesis of apoB-containing lipoproteins, these various nutrients likewise could reverse this effect. It should be noted, however, that there is little support for this latter mechanism.

Overnutrition and obesity

Obesity, as a reflection of overnutrition, is widely believed to raise the serum level of total cholesterol. An effect of obesity per se on serum total cholesterol, and particularly LDL-cholesterol concentrations, however, is not universally accepted. Many obese people do not have an elevated serum cholesterol, and some very obese individuals actually have unusually low cholesterol concentrations. Early epidemiologic studies did not reveal a consistently strong relationship between body weight and total cholesterol levels (124, 126). Nonetheless, subsequent evidence has been accumulating that increasing body fatness is accompanied by rising cholesterol levels. This connection was noted in some populations of the Seven Countries Study (127), the Framingham Heart Study (128–130), the Western Electric Study (131), and other investigations (132). Visceral obesity may be particularly hypercholesterolemic, but this remains to be documented. When all available data are integrated, it seems probable that obesity contributes significantly to the “mass hypercholesterolemia” typical of the American public and similar affluent societies (132). Indeed, from one-third to one-half of the elevation in cholesterol concentrations that occurs in these societies, compared to less affluent societies, could be the result of overnutrition and obesity.

Direct evidence that weight gain can raise the serum cholesterol level comes from studies of Anderson, Lawler, and Keys (133). These workers induced weight gain by the simple feeding of excess calories to young men, and they noted that total cholesterol concentrations rose approximately 4 mg/dl for every kilogram gained. Since very obese individuals rarely have severe hypercholesterolemia, their results suggest that the greatest rise in cholesterol levels occurs as people increase their weight from the desirable weight to mild obesity. In support, epidemiologic data (132) indicate that marked obesity is not associated with much higher cholesterol concentrations than is mild-to-moderate obesity.

Further support for the concept that obesity raises cholesterol levels comes from weight-reduction studies. Of interest, however, is the observation that effects of weight reduction on serum cholesterol are related to the composition of the diet. For example, weight loss in the setting of a diet low in saturated fatty acids and cholesterol will en-

hance responsiveness in serum cholesterol lowering to caloric restriction. As demonstrated in both the Multiple Risk Factor Intervention Trial (134) and the National Diet-Heart study (135), weight reduction combined with favorable change in diet composition results in twice as much serum cholesterol lowering as occurs from alteration of diet composition alone. Weight loss with exercise also may lower the LDL-cholesterol level (136). In contrast, Wolf and Grundy (137) reported that weight loss in obese normolipidemic patients who do not change their percentage intake of saturated fatty acids generally does not reduce their LDL-cholesterol levels. All of these results taken together suggest that diet composition and excess energy intake are linked in their actions on LDL-cholesterol concentrations.

Another factor that may influence LDL-cholesterol response to the obese state is one's inherent sensitivity to a high-caloric intake. In the study of Wolf and Grundy (137), for instance, most subjects had relatively normal levels of LDL cholesterol when they were obese, and hence it might not be surprising that weight loss failed to induce a striking decrease in LDL concentrations. In contrast, Davis et al. (138) reported that weight loss, even without a change in diet composition, caused a distinct reduction in LDL-cholesterol levels in patients with primary hypercholesterolemia. Thus, some individuals may be overly sensitive to effects of a high-caloric intake just as others are excessively sensitive to saturated fatty acids in the diet.

At least two mechanisms can be responsible for higher cholesterol concentrations in obese individuals (Fig. 5). One is hepatic overproduction of lipoproteins containing apoB-100. This mechanism is reflected by the increased production of VLDL-apoB (139, 140) and LDL-apoB (141) noted in overnourished, obese individuals. A second factor is excessive intake of saturated fatty acids and

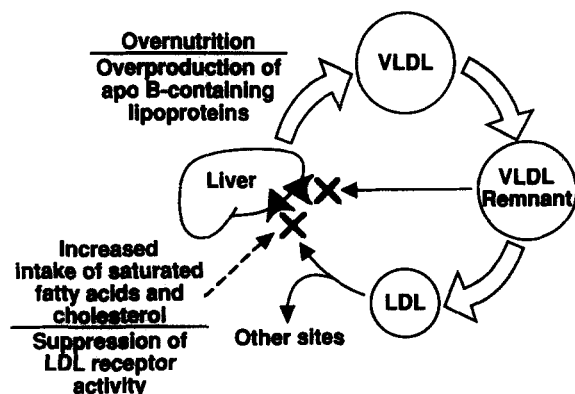


Fig. 5. Mechanisms for the rise in serum cholesterol levels in obese individuals. The primary action is an overproduction of apoB-containing lipoproteins by the liver. If the excessive intake of nutrient energy includes saturated fatty acids and cholesterol, a second action, suppression of LDL-receptor activity, will accentuate the rise of LDL-cholesterol levels.

cholesterol, common in obese Americans, and both of these will suppress LDL-receptor activity. Obese people consuming a typical American diet consequently will have both increased production of apoB-containing lipoproteins and reduced activity of LDL receptors; as a result, they will have two factors acting simultaneously to raise LDL levels.

TRIGLYCERIDES

Less attention has been given to the influence of diet on plasma triglyceride levels than to dietary effects on cholesterol levels; this is partly due to the widely held view that elevated triglycerides are not a risk factor for CHD. This view, however, has been modified in recent years and the possible link between triglyceride levels and occurrence of CHD has received renewed attention. This resurgence of interest comes from new epidemiologic data and from an increased appreciation of how triglyceride-rich lipoproteins may promote atherogenesis. Most epidemiologic investigations reveal a significant positive correlation between serum triglyceride concentrations and CHD risk (142-145); on the other hand, triglyceride levels typically correlate with other lipid risk factor, as for example, low HDL-cholesterol concentrations, and thus, in multivariate analysis, high triglycerides often "fall out" of the equation, i.e., they do not emerge as an independent risk factor for CHD (146). More recent epidemiologic studies, nonetheless, reveal that elevated triglyceride concentrations do indeed predict CHD independently of other known risk factors (147). High serum triglycerides, moreover, appear to be the underlying cause of several putative lipid risk factors for CHD, for instance, reduced concentrations of HDL cholesterol and raised levels of chylomicron remnants, VLDL remnants, intermediate density lipoproteins (IDL), and small, dense LDL (123, 148). If any or all of these lipoprotein changes heighten risk for CHD, and if elevated triglycerides are their cause, then high triglycerides probably deserve to be called a risk factor. This view is gradually being accepted, and thus the influence of diet on triglyceride concentrations should become a subject of greater interest in the future.

To comprehend the influence of diet on metabolism of serum triglycerides, the basic mechanisms responsible for raised triglyceride levels must be understood. In the fasting state, most serum triglycerides are carried in the VLDL fraction, and two factors determine serum levels of VLDL triglycerides, specifically, rates of hepatic secretion of VLDL triglycerides and one's capacity for hydrolyzing circulating triglycerides. One cause of hypertriglyceridemia thus is hepatic overproduction of VLDL triglycerides, and this can occur in two ways. First, the total number of VLDL particles secreted by the liver can be increased; in this case, amounts of both VLDL triglycerides and VLDL apoB entering the circulation are in-

creased, but the overall composition of VLDL particles remains normal. Alternatively, the triglyceride content of each VLDL particle, but not the total number of particles synthesized, is increased; in this instance, the quantity of VLDL apoB entering the bloodstream remains normal, but VLDL-triglyceride input rises. Either change induces hypertriglyceridemia, but the net effect on the overall lipoprotein pattern differs for the two types of defects. Diet-induced hypertriglyceridemia theoretically could occur by either mechanism.

A second general reason for hypertriglyceridemia is defective lipolysis of triglyceride-rich lipoproteins (148). The lipolytic cascade for serum triglycerides is a complicated process and involves interaction of lipoproteins with lipoprotein lipase and hepatic triglyceride lipase. Defective lipolysis of VLDL triglycerides can result from abnormalities or deficiencies in either of these two enzymes (149-151), a genetic deficiency of apoC-II (the activator of lipoprotein lipase) (152, 153), or perhaps abnormalities in triglyceride-rich lipoproteins that render them poor substrates for lipolytic enzymes. Diet could adversely affect any of these processes in various ways to raise triglyceride levels. The different nutrients in the diet thus can be examined briefly for their influence on lipoprotein metabolism.

Dietary fat and specific fatty acids

In patients with severe deficiencies in lipoprotein lipase or apoC-II, a high intake of any type of dietary fat will cause marked hypertriglyceridemia with chylomicronemia (154). In the absence of a severe lipolytic defect, high-fat diets, in comparison with high-carbohydrate diets, generally do not raise serum-triglyceride levels; indeed dietary carbohydrates typically increase triglyceride concentrations more than does fat (122, 155). Reasons for differing effects of fats and carbohydrates on serum triglyceride concentrations are not entirely clear, but the two nutrients may differ in their actions on hepatic synthesis of triglycerides; for example, dietary fat may not drive triglyceride synthesis in the liver as much as carbohydrate (122). Even so, the different types of fatty acids could differently affect serum triglycerides, and each kind must be examined separately.

Saturated fatty acids do not uniquely raise serum triglycerides as they do total cholesterol levels. An exception is medium-chain saturates which increase triglyceride levels to about the same extent as do carbohydrates (156). Studies in laboratory animals further indicate that coconut oil, which is rich in lauric acid, raises triglyceride concentrations (157, 158). Thus, when considering effects on triglyceride levels, lauric acid perhaps belongs with the medium-chain fatty acids. As indicated before, the failure of long-chain saturates (e.g., palmitic acid) to raise serum triglycerides, compared to monounsaturates, suggests that the action of saturated acids to increase LDL-

cholesterol levels does not stem from overproduction of VLDL particles.

Monounsaturated fatty acids. According to studies carried out in our laboratory (55, 57, 87, 117, 159), diets high in oleic acid do not increase serum triglyceride levels in either normotriglyceridemic or hypertriglyceridemic subjects, when they are compared to saturated fatty acids. They do, however, lower serum triglyceride concentrations relative to carbohydrates (87). In patients with hypertriglyceridemia, monosaturates reduce LDL-cholesterol levels, when compared to saturated fatty acids (55). High intakes of oleic acid, therefore, could have utility as a replacement for both saturated fatty acids and carbohydrates in the management of hypertriglyceridemia. It must be noted that obesity frequently is a contributing factor to hypertriglyceridemia, and reduction of total caloric intake is required for most patients. Therefore, if oleic acid is to be substituted for other nutrients, it must be done in the context of total caloric restriction to achieve a desirable weight.

Polyunsaturated fatty acids. The n-6 polyunsaturates, specifically linoleic acid, have been reported to reduce serum triglycerides in some patients with hypertriglyceridemia (101, 108). This reduction can occur relative to either carbohydrates or saturated fatty acids. A triglyceride-lowering action for polyunsaturates, however, is not a consistent phenomenon; indeed, many patients with hypertriglyceridemia do not respond with a lowering of serum triglycerides when fed a diet high in linoleic acid (55). When triglyceride lowering does occur in response to dietary linoleic acid, the mechanism is unclear; perhaps high intakes of n-6 polyunsaturates reduce hepatic synthesis of VLDL triglycerides (108). Alternatively, serum triglycerides containing polyunsaturated fatty acids could be better substrates for lipoprotein lipase than those high in saturated acids; this too could account for some triglyceride lowering.

N-3 polyunsaturates, particularly very-long-chain fatty acids (EPA and DHA), have a greater influence on triglyceride metabolism than the n-6 variety. High intakes of n-3 polyunsaturates markedly reduce triglyceride levels (160), especially when fed to individuals with hypertriglyceridemia (161). The mechanism for triglyceride lowering appears to be inhibition of secretion of VLDL triglycerides (162, 163). N-3 polyunsaturates presumably interfere with synthesis of triglycerides in the liver (164). These fatty acids may be poorly incorporated into triglycerides themselves, and yet competitively inhibit the synthesis of triglycerides (164). Their action to lower triglyceride concentrations seemingly is confined to a reduction of triglyceride content of VLDL particles; the total number of apoB-containing lipoproteins secreted into plasma by the liver is not necessarily reduced. The latter is suggested from studies on effects of n-3 polyunsaturates on serum lipoprotein levels. Whereas these fatty

acids usually lower VLDL-apoB levels, concentrations of LDL-apoB actually may be increased (165). In metabolic terms, a reduction in hepatic secretion of VLDL-apoB may be offset by input of more triglyceride-poor, IDL-apoB, the latter being rapidly converted to LDL. In studies in monkeys, Parks et al. (166) also reported that fish oils reduce the cholesteryl ester content of lipoproteins, but again not the numbers of lipoprotein particles secreted into serum. A compensating increase in secretion of smaller apoB-containing lipoproteins may limit the usefulness of fish oil polyunsaturates in the treatment of hyperlipidemia because the overall lipoprotein pattern may not be improved.

Carbohydrates

Diets high in carbohydrates and low in fat have the paradoxical action of raising serum triglyceride levels (122, 155, 167, 168). For individuals with normal serum triglyceride concentrations, high-carbohydrate diets produce only mild increments in triglyceride levels. Some investigators suggest that the rise of serum triglyceride accompanying high-carbohydrate intake is transitory (169), but this remains to be demonstrated by epidemiologic studies comparing populations consuming high- and low-fat diets. The higher triglyceride levels typically seen on high-carbohydrate diets probably result from enhanced hepatic synthesis of VLDL triglycerides; several studies (170-172) support this mechanism. Higher production rates for VLDL triglycerides upon ingestion of high-carbohydrate diets seemingly are not accompanied by enhanced production rates for VLDL-apoB (173); thus, whereas triglyceride content of each VLDL particle is increased, the number of VLDL particles entering the circulation apparently is not raised. A few reports (174, 175) further suggest that high-carbohydrate intake reduces lipoprotein lipase activity, or otherwise retards lipolysis of triglyceride-rich lipoproteins (167). High-carbohydrate diets thus may raise triglyceride levels by more than one mechanism. Sane and Nikkila (176) recently reported that lipolytic capacity for serum triglyceride varies greatly among individuals within the whole population, and this variability is to a large extent determined genetically. The degree of increase of triglyceride concentration on a high-carbohydrate diet thus may depend on an individual's inherent capacity to hydrolyze serum triglyceride.

Several reports suggest that serum triglyceride concentrations are affected differently depending on the type of dietary carbohydrate. In rats and other laboratory animals, for example, high intakes of sucrose or fructose raise triglyceride levels more than does glucose (177, 178). Similar claims are made for humans (179-183). The latter reports, however, are not entirely convincing. Further research will be required to prove a definite difference between dietary glucose and fructose on triglyceride levels in humans. Simple sugars have been claimed to cause a

greater increase in serum triglycerides than complex digestible carbohydrates, i.e., starch (179, 180); but again, evidence in support of this claim is relatively weak, and it is by no means proven that simple sugars are more hypertriglyceridemic in humans than starches.

Alcohol

Like carbohydrates, consumption of moderate-to-large quantities of ethanol raises triglyceride levels. This response is most pronounced in people with an underlying defect in triglyceride metabolism. Also, like carbohydrate, the primary reason for alcohol-induced hypertriglyceridemia is overproduction of hepatic VLDL triglycerides (184–187). There are no convincing data that high intakes of ethanol interfere with lipolysis of VLDL triglycerides; in this regard, Crouse and Grundy (188) found no reduction in either post-heparin lipoprotein lipase or hepatic triglyceride lipase after ingestion of 20% of calories as alcohol for 1 month. Finally, whereas alcohol stimulates synthesis of hepatic VLDL triglycerides, it apparently does not enhance production of VLDL-apoB. Alcohol does not increase concentrations of either LDL-apoB or LDL-cholesterol (188); such as might be expected if it were to increase hepatic synthesis of any or all apoB-containing lipoproteins.

Overnutrition (obesity)

The most common cause of elevated triglyceride levels undoubtedly is overnutrition and resulting obesity. Ingestion of more calories than needed not only increases adipose triglyceride pools, but promotes triglyceride synthesis by the liver. The latter underlies overproduction of serum VLDL triglycerides in obese people (139, 140, 189). But, in contrast to carbohydrates and alcohol, obese individuals seemingly have increased hepatic secretion of VLDL apoB as well as VLDL triglycerides (140); thus, generalized overnutrition increases the number of VLDL particles secreted into the circulation, and not just amounts of triglyceride per particle. The driving force behind overproduction of VLDL triglycerides most likely is a constant increased influx of nutrients into the liver; an excess of nutrient energy is derived from the diet in the postprandial state and from an increased plasma flux of free fatty acids in the fasting state. An increased input of fatty acids into the liver may be accentuated by visceral obesity, because visceral adipose tissue directly releases fatty acids into the portal circulation.

Fig. 6 summarizes the mechanisms whereby various nutrients affect serum triglyceride levels. Dietary carbohydrates and ethanol stimulate the production of VLDL triglycerides by the liver, although neither appears to increase the number of VLDL particles secreted by the liver. Overnutrition resulting in obesity likewise stimulates the synthesis of VLDL triglycerides, but, in addition, raises the number of VLDL particles secreted into

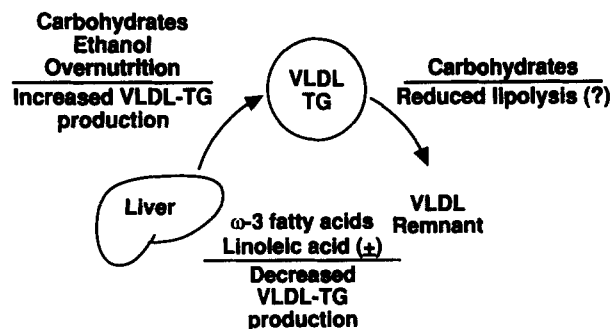


Fig. 6. Actions of various nutrients on serum triglyceride levels. Dietary carbohydrates, excess total calories, and ethanol stimulated the synthesis of VLDL triglycerides. In contrast, ω -3 (n-3) polyunsaturates, and to a lesser extent, linoleic acid, inhibit the synthesis of VLDL triglycerides. Finally, the rise in VLDL triglycerides on low-fat, high-carbohydrate diets may be due, in part, to a reduced synthesis of lipoprotein lipase.

the circulation. In contrast, n-3 polyunsaturates inhibit the synthesis of VLDL triglycerides, and in some cases, linoleic acid may do the same, although less consistently and to a lesser magnitude. A few reports suggest that high-carbohydrate diets reduce the synthesis of lipoprotein lipase which may interfere with lipolysis of triglyceride-rich lipoproteins.

HIGH DENSITY LIPOPROTEINS

A strong inverse correlation exists between levels of HDL cholesterol and rates of CHD in high-risk populations (190–192); consequently, there is a growing interest in causation and management of low HDL cholesterol. Although low HDL levels may be inherited in some people, for most people lifestyle factors appear to be the predominant determinants of reduced HDL-cholesterol concentrations. The latter include several dietary factors. One unresolved issue is whether reduction of HDL levels by diet will promote development of atherosclerosis, or whether dietary reduction of serum HDL concentration is benign. These questions arise because certain populations in the world, which habitually consume low-fat diets, have low levels of both LDL and HDL, and also have low rates of CHD (193–195). This finding has led some workers to conclude that diet-induced lowering of HDL levels does not enhance coronary risk.

If the latter is true, it reveals how little is known about the relation between low HDL concentrations and atherogenesis. However, several competing theories have been developed in the attempt to explain how low serum HDL is linked to CHD. One theory evokes the system known as reverse cholesterol transport; this is the process whereby cholesterol is transported from peripheral tissues to the liver for its excretion. HDL is thought by many to be an acceptor of cholesterol in peripheral tissues, and this could be the first step in reverse cholesterol transport

(196–198). If HDL does in fact play this role, a high HDL level could accelerate removal of cholesterol from the arterial wall and thus retard development of atherosclerosis. To date, however, this theory remains unproven. An alternate hypothesis holds that low HDL levels merely signify an excess of other atherogenic lipoproteins, notably increased levels of small VLDL (VLDL remnants) and IDL (199–204) and small, dense LDL (205, 206). Without doubt these other lipoproteins circulate in excess in many individuals having low HDL levels. If this theory holds, HDL per se may not be a determinant of atherogenesis, but rather it represents a marker for atherogenic lipoproteins. A third hypothesis is that the ratio between LDL cholesterol and HDL cholesterol is the critical determinant of atherogenesis (207). When the ratio is high, the risk for CHD is increased, and vice versa. This concept also supports the view that low HDL is not atherogenic in the presence of a low LDL because the ratio would not be increased.

In low risk populations in which diet-induced lowering of HDL occurs, the question can be asked how low HDL levels relate to each of these theories. First, little is known about the mechanisms whereby HDL accepts cholesterol from the arterial wall. If there is a unique subfraction of HDL that is the cholesterol acceptor, and if this subfraction is not reduced by diet, then perhaps diet-induced reduction of total HDL-cholesterol levels is not atherogenic. Second, if dietary reduction of HDL is not accompanied by an increased level of putative atherogenic lipoproteins, again HDL lowering might not promote atherogenesis. And third, if dietary lowering of HDL simultaneously lowers LDL levels, then the LDL/HDL ratio would remain constant, and thus coronary risk might not be enhanced. Unfortunately, we do not know how to test for the first mechanism, but for the latter two, it should be possible to determine the effects of dietary change. These concepts will be taken into account in the following consideration of effects of diet on HDL metabolism. Each of the major dietary constituents will be examined for its actions on HDL.

Dietary fat

Dietary fat affects HDL-cholesterol concentrations according to the fatty acid composition of the fat. The response also depends on the percentage of fat in the diet. Since low-fat diets generally reduce HDL concentrations (87, 120, 193–195), one argument in favor of higher fat intake is to maintain higher levels of HDL cholesterol. Further, the composition of the fat is another factor affecting HDL concentrations, and high-fat diets will not necessarily maintain relatively high HDL levels unless they have the appropriate fatty acid mix. Each class of fatty acids, therefore, will be considered for its effects.

Saturated fatty acids. In general, saturated fatty acids appear not to reduce HDL-cholesterol levels. In populations

consuming diets high in saturated fatty acids, levels of both LDL and HDL tend to be high (194). In metabolic ward investigations, HDL-cholesterol concentrations typically are the highest when the diet is rich in both total fat and saturated fatty acids (87, 117). Concerning the type of saturated acid, similar levels of HDL cholesterol are obtained whether the predominant fatty acid is palmitic acid or stearic acid (57). A high level of HDL cholesterol in populations consuming diets high in saturates, nevertheless, does not protect individuals from CHD if LDL-cholesterol concentrations are concomitantly increased (194). This is one argument that dietary alterations of HDL levels do not modify coronary risk, whether they raise or lower HDL concentrations. Nonetheless, even in those populations having relatively high concentrations of both LDL and HDL, individuals with the lowest concentration of HDL are those at greatest risk for CHD (208).

Monounsaturated fatty acids. Studies from our laboratory (55, 87, 117) noted that dietary monounsaturated fatty acids (i.e., oleic acid) do not lower HDL-cholesterol levels when substituted for saturated fatty acids. Since exchange of oleic acid for saturated acids will reduce concentrations of LDL-cholesterol, the result of this exchange will be a decrease in LDL/HDL ratio. This favorable modification of the lipoprotein ratios theoretically should decrease coronary risk, and low rates of CHD in populations consuming high intakes of oleic acid provide support for this concept (209). A recent report indicates that diets high in oleic acid not only maintain high concentrations of HDL-cholesterol, but they do the same for apolipoproteins A-I and A-II (121).

Polyunsaturated fatty acids. In contrast to monounsaturated fatty acids, high intakes of n-6 polyunsaturates (linoleic acid) reduce HDL-cholesterol concentrations (55, 99, 210, 211). Some workers postulate that lower intakes of polyunsaturates will not evoke this change (116, 212), but the degree of reduction of HDL-cholesterol may be less than can be detected in small clinical studies. A review of the literature suggests that HDL-cholesterol levels are reduced about 1% for every 2% of total calories in which polyunsaturated fatty acids substitute for saturated or monounsaturated fatty acids (55, 99, 210, 211). If this is a valid estimate, substitutions of polyunsaturated fatty acids would have to be substantial before a decrease in HDL could be detected clinically. In large populations, however, even a small reduction in HDL-cholesterol levels could produce a slight increase in CHD risk. This of course depends on the assumption that lowering of HDL-cholesterol levels by polyunsaturates will, in fact, increase the risk for CHD, an assumption yet to be proven.

The way in which linoleic acid lowers HDL-cholesterol concentration is not well understood. In one report by Shepherd et al. (210), apoprotein kinetics for HDL were determined in subjects on diets high in linoleic acid and

then high in saturated fatty acids. The major effect was a reduction in the synthesis rate of apoA-I by polyunsaturates. Even so, a decrease in apparent synthesis rate for apoA-I in plasma does not necessarily mean a true decrease in synthesis of apoA-I by the liver or intestine. Other interpretations of the isotope-kinetic data are possible. Still, the data of Shepherd et al. (210) appear most consistent with a decrease in apoA-I production as one mechanism whereby linoleic acid reduces the HDL cholesterol concentration. In accord with this mechanism, Johnson, Babiak, and Rudel (213) observed in liver perfusion studies that the livers of polyunsaturated fat-fed monkeys secrete fewer HDL precursor particles than do those of saturated fat-fed monkeys. The actions of n-3, long-chain polyunsaturates on HDL-cholesterol levels appear to be similar to those of linoleic acid; some studies, but not others, report a reduction in HDL-cholesterol concentrations (162, 163). It might be noted that when polyunsaturates of either kind reduce HDL-cholesterol levels they do not raise concentrations of VLDL- and IDL-cholesterol (55, 99). Thus, if a low HDL-cholesterol is merely a marker for other atherogenic lipoproteins, the lowering of HDL by polyunsaturated fatty acids should not be atherogenic. On the other hand, if a high HDL is directly protective against atherosclerosis, then HDL lowering by polyunsaturates might be of concern.

Dietary carbohydrate

When dietary carbohydrates are substituted for either saturated or monounsaturated fatty acids, the serum level of HDL-cholesterol falls (87, 116, 120, 124, 212, 214). The reduction extends to both apoA-I and apoA-II levels (121). Lower HDL-cholesterol concentrations are seen during the feeding of either simple sugars or complex carbohydrates (87, 117, 120); reductions not only occur in metabolic ward and/or short-term outpatient studies, but also in populations that habitually consume low-fat, high-carbohydrate diets (194, 215, 216). Even though such populations may have lower HDL-cholesterol levels than populations consuming high-fat diets, rates of CHD typically are lower in those countries that habitually consume low-fat diets. Still, in some populations, when low-fat diets are routinely ingested, caloric intake only marginally meets energy demands, and the resulting thinness of people partially mitigates the HDL-lowering action of a high-carbohydrate diet (194).

The mechanism for HDL lowering by dietary carbohydrate may relate to the influence of carbohydrate on triglyceride metabolism. The rise in serum triglycerides on high-carbohydrate intakes likely promotes cholesteryl ester-triglyceride exchange between HDL and triglyceride-rich lipoproteins, and thereby reduces HDL-cholesteryl ester concentrations. At the same time, apoA-I may be transferred in excess to triglyceride-rich lipoproteins and thus may be drained away by catabolism of these lipopro-

teins. Whether low-fat, high-carbohydrate diets reduce the synthesis of apoA-I (apoA-II) is not known with certainty, but conversely high-fat diets have been reported to stimulate the synthesis of apoA-I in the intestine (217). A reduction of fat intake thus may decrease the quantity of apoA-I entering with chylomicrons, and this effect might ultimately lower the concentration of HDL cholesterol and apoA-I.

Overnutrition (obesity)

HDL-cholesterol concentrations frequently are reduced in obese patients (137). Several mechanisms might be responsible. Obesity promotes synthesis of VLDL triglycerides, which could drain away HDL-cholesteryl esters and HDL apoA-I by mechanisms just described. But, in addition, obesity has a long-term effect of HDL levels that appears to be unrelated to triglyceride metabolism. For example, during weight loss in obese individuals, serum triglyceride levels fall to the desirable range within a few days or weeks, but HDL-cholesterol concentrations do not rise into the normal range until weeks or months later when almost all excess body fat has been lost (137). The possibility, therefore, might be considered that excess adipose tissue may actually remove HDL from the circulation and thereby lower serum HDL levels. If this mechanism pertains, the HDL concentration may not rise until most excess adipose tissue has been eliminated.

PRACTICAL CONSIDERATIONS

Investigations over the past three decades have proven without question that certain saturated fatty acids, particularly palmitic acid, raise LDL-cholesterol levels, and because of the positive correlation between LDL levels and CHD rates, recommendations to reduce intakes of saturated fatty acids seem fully justified. Reduction in intakes of saturated fatty acids generally will decrease consumption of dietary cholesterol as well. Since saturated fatty acids and cholesterol in the diet appear to interact synergistically to raise LDL levels (218), this is a further advantage of decreasing intake of saturated fatty acids. Most current recommendations are for a reduction in intake of total saturated fatty acids to below 10% of total calories (24, 219–221), which would generally translate into an intake of cholesterol-raising saturates of 7% or below. An important question not fully resolved is what is the best replacement for cholesterol-raising saturated acids in the diet. Four major possibilities are stearate, polyunsaturates, monounsaturates, and carbohydrates (Fig. 4). The decision about the proper mix of these latter nutrients will depend on several factors, and not on their effects on cholesterol levels alone. The arguments for and against each of these nutrients can be summarized briefly.

Stearic acid. The demonstration that stearic acid does not raise the LDL-cholesterol level raises the possibility that it can be used as a replacement for cholesterol-raising saturated fatty acids. For example, stearic acid is the end product of hydrogenated vegetable oils. By exhaustive saturation of vegetable oils, large quantities of stearic acid can be produced relatively inexpensively and, by transesterification with high-oleic or high-linolenic oils, fats can be synthesized that will have the consistency of "saturated fats" without cholesterol-raising properties. These could be used in new margarines and shortenings and in a host of bakery products. Saturated fatty acids are needed to add texture and consistency to food products, and stearate should have the properties to be a desirable substitute for cholesterol-raising saturates. Investigative experience with diets high in stearic acid is limited, and more research on metabolic responses to dietary stearic acids is required before it can be increased substantially in the diet. Nonetheless, a modest replacement for cholesterol-raising saturated fatty acids probably will not be harmful.

Linoleic acid. Over the past two decades concern has been increasing about recommendations for high intakes of polyunsaturated fatty acids in spite of their putative cholesterol-lowering action. Perhaps the greatest concern is that no large population has ever consumed high amounts of linoleic acid for long periods with proven safety. Claims have been made that high intakes of linoleic acid have other potential benefits, such as reducing the blood pressure (222) or perhaps preventing cardiac arrhythmias (223), but these few reports do not justify recommendations for increased intakes of linoleic acid. Certainly these possible influences are worthy of further investigation, but currently they do not have sufficient support to overcome reservations about high intakes of linoleic acid.

Studies in laboratory animals raise further concerns about use of large amounts of linoleic acid in human diets. For example, high intakes of linoleic acid have been shown to suppress the immune system in some species (224). Investigations in our laboratory (224) have suggested that this action is not primary, but rather, linoleic acid accentuates the immune suppression induced by other agents. Even if this is true for humans, it is of concern, particularly in older people in whom the immune system may be compromised. Moreover, several reports (226, 227) suggest that linoleic acid in the diet can promote development of tumors in laboratory animals. Whether tumor production is related to the action of linoleic acid to suppress the immune system has not been determined. Finally, in humans, high intakes of linoleic acid can lower HDL-cholesterol levels, and they may predispose to gallstone formation (101, 228). These various factors have led many workers to suggest that intakes of linoleic acid be limited to less than 10% of total

calories. The National Research Council (221) recently recommended that the average intake for the American public should not increase above the current intake of 7% of total calories. This level allows for a partial but not total replacement of saturated fatty acids by linoleic acid.

Carbohydrate. High-carbohydrate diets are widely consumed throughout the world, and since they generally are associated with relatively low rates of CHD, most investigators believe they are safe. When they are taken in the form of vegetables and fruits, intakes of essential vitamins should be adequate. Further, many workers hold that low-fat diets may help to prevent obesity in populations, and some epidemiologic surveys (229, 230), as well as investigations in laboratory animals (231, 232), are suggestive that low-fat diets may reduce the risk for certain kinds of cancer (e.g., breast, colon, and prostate cancers). These considerations add support to the concept that all populations would benefit from consumption of low-fat, high-carbohydrate diets.

On the other hand, when most populations are given the opportunity to select freely between different types of nutrients, they typically choose diets higher in fats. Low-fat diets apparently do not offer as much variety, palatability, and satiety as diets higher in fat. Moreover, since populations consuming high-carbohydrate diets generally have limited food availability or habitually engage in heavy exercise, the lack of obesity may be the result of these latter factors and not of high-carbohydrate diets per se. Moreover, a common finding in many populations that habitually eat high-carbohydrate diets is a high prevalence of hypertension. Although salt may be used in preservation of food in these populations, the question might be raised whether excess quantities of salt are used also for the purpose of making the diet more palatable. Moreover, a high-carbohydrate diet per se may accentuate a rise in blood pressure by its tendency to cause sodium retention (233). At the very least more research is needed on effects of dietary carbohydrate on blood pressure.

We might consider further whether low-fat, high-carbohydrate diets increase the risk for osteoporosis either directly or indirectly. Such diets could affect the metabolism of calcium in several ways. First, intake of calcium may be marginal in high-carbohydrate diets as these diets are currently consumed world-wide. Second, complex carbohydrates and fiber consumed with many high-carbohydrate diets may interfere with calcium absorption. Third, the high-salt intake, which often accompanies low-fat diets, can promote a "renal leak" of calcium and thereby cause depletion of body stores of calcium (234). Fourth, high intake of carbohydrate per se could induce a renal leak of calcium (235, 236), although a recent study from our laboratory (237) does not support this mechanism. And finally, if low-fat diets do result in low body weight, this effect could facilitate development of osteo-

porosis by reducing the stimulus of weight on bone growth.

In another sphere, diets high in carbohydrate have a tendency to raise serum triglycerides and to reduce HDL-cholesterol levels, both of which could be potentially detrimental. Although many of these potential adverse effects of high-carbohydrate diets can be overcome by careful attention to overall nutrient intake and by use of supplements, the potential detrimental effects of high-carbohydrate diets must be thoroughly considered before they can be recommended without reservation. This caution may be especially necessary for very low-fat diets.

Oleic acid. Finally, consideration must be given to oleic acid as a replacement for saturated fatty acids in the diet. Compared to linoleic acid, oleic acid will produce as much LDL-lowering as linoleic acid when either replaces saturated acids. Moreover, high intakes of oleate do not lower HDL levels, as can linoleate. The same is true when oleate is compared to carbohydrate, and the latter also can raise triglycerides, which oleate does not. Since the upper limits of linoleate intake have largely been defined (221), i.e., less than 10% of total energy, the primary issue appears to be what is the desirable ratio of carbohydrate to oleic acid in the diet. To achieve realistic diets, oleic acid content can vary between 10 and 20% of total calories. Since stearic acid appears to be rapidly converted into oleic acid in the body, its intake can be counted with monounsaturates. A lower intake of oleic acid (i.e., 10% of total calories) might favor weight reduction and prevention of cancer; although, regarding the latter, there is no evidence that oleic acid promotes tumor formation as does linoleic acid. On the other hand, an intake of oleic acid up to 20% of calories may add palatability to the diet, promote satiety, add variety, reduce triglycerides, and maintain higher levels of HDL cholesterol. Perhaps the widely recommended 30% of calories from total fat (or about 15% from monounsaturates) represents a reasonable compromise between these pros and cons.

There may be certain benefits to allowing more liberal quantities of oleic acid (and stearic acid) in the diet, namely, a greater variety of food choices. Already, oleic acid is the major fatty acid of most diets. Vegetable oils that are highest in oleic acid include olive oil, rapeseed (canola) oil, high-oleic forms of safflower and sunflower seed oils, and to a lesser extent, peanut oil. Beef tallow, lard, and chicken fat, although high in saturated fatty acids, likewise are relatively high in oleic acid (Table 2). Recent studies have shown that the oleic acid content of lard can be increased at the expense of saturated fatty acids by feeding high-oleic fats to pigs (238). This approach could make pork and pork fat more acceptable for cholesterol-lowering diets. Further, the oleic acid content of other vegetable oils, that currently are high in linoleic acid, can be increased by selection of seeds that uniquely produce high-oleic oils. This change has already been

made for safflower and sunflower seed oils, and the same procedure could be extended to soybean oil for example. ■

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