acylglycerol concentrations are normal. Although this disorder certainly exists, many subjects who present with this phenotype have had hypertriglyceridemia in the past or have an older (or more obese) first-degree relative who has both low HDL and increased triacylglycerol levels. Hence, carefully conducted family studies and long-term follow-up may be necessary to identify individuals who truly have primary reductions in HDL cholesterol. The basis for such reductions is unknown except for extremely rare situations in which genetic mutations in the area of the apo A-I gene have been described. Other rare disorders in which HDL cholesterol is severely reduced include Tangier disease and lecithin:cholesterol acyltransferase (LCAT) deficiency.

Epidemiology of Atherosclerosis

General Overview. Extensive reviews of the epidemiology of atherosclerosis are available in both journals and textbooks (National Research Council, 1989). The 20th century has seen a disappearance of several infectious diseases in Western societies and the emergence of chronic diseases, particularly atherogen. In the early part of the century, the rising incidence of coronary heart disease (CHD) paralleled increased caloric intake, particularly intake of saturated fats. Natural experiments attest to the importance of these factors; during World War II the incidence of CHD fell dramatically in occupied countries. By contrast, after the war, Japanese men who migrated to Hawaii and then to California consumed increased quantities of saturated fats, had increases in their plasma cholesterol levels, and began to suffer more and more from CHD. In the United States, the switch from a farming to an industrial society, together with a switch from a high-carbohydrate to a high-fat diet paralleled our epidemic of CHD in the 1950s through 1970s. During the past decade, reductions in dietary consumption of fat have correlated with the reduction in coronary artery disease (CAD) observed in the United States (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 1993).

Risk Factors for Atherosclerotic Cardiovascular Disease. Numerous, long-term prospective studies, including the Framingham Study, the Honolulu Heart Study, and the Chicago Gas and Electric Company Study, have provided unique data regarding the role of genetic and environmental factors that increase risk for developing atherosclerotic cardiovascular disease (ASCVD) (National Research Council, 1989). Hypertension, smoking, hypercholesterolemia, and diabetes are the major risk factors for CAD and stroke. A low level of HDL cholesterol is also an important risk factor. Although prevalence of individual risk factors may differ by race or gender, the major risk factors are usually of similar importance in whites and blacks and in men and women. Age has a major impact in women, with premenopausal women having lower total and LDL cholesterol levels and higher HDL cholesterol concentrations than postmenopausal women. Hormone replacement therapy lowers total and LDL cholesterol and raises HDL cholesterol. A list of major risk factors from the National Cholesterol Education Program report is shown in Table 41–2.

Lipids and Lipoproteins as Risk Factors. As described earlier in this chapter, disorders of lipoprotein metabolism can lead to alterations in plasma cholesterol and triacylglycerol levels, and these disorders are usually associated with increased risk of cardiovascular disease. The association of plasma total cholesterol with CAD is quite robust, but this association is confounded by the distribution of cholesterol among the lipoprotein classes. High total cholesterol levels in blood are usually paralleled by high plasma concentrations of LDL cholesterol, and LDL levels are strong indicators of risk for atherosclerosis. On the other hand, HDL cholesterol levels are inversely related to risk for CAD, and extremes in HDL cholesterol, either at the low or high end, can confound the relationship between total cholesterol and risk. The issue of plasma triacylglycerols as a risk factor has been controversial for many years (Hall, 1995). This controversy stems from an absence of triacylglycerols in vessel wall lesions, the close inverse relationship between triacylglycerols and HDL cholesterol, and the lack of strong
NUTRITION INSIGHT

Risk Factors for Vascular Disease

Classic independent risk factors for cardiovascular disease include hypercholesterolemia, smoking, and hypertension. Over the past decade, numerous studies have demonstrated that an elevated plasma total homocysteine level is also a strong and independent risk factor for vascular disease. Results of a recent multicenter case-control study that involved 19 centers in 9 European countries and that included both men and women of all types of atherosclerotic vascular disease (cardiac, cerebral, and peripheral) demonstrated this relationship between homocysteine and vascular disease (Graham et al., 1997; Boers, 1997). When the relationship between plasma total homocysteine level and the risk of all categories of atherosclerotic vascular disease was considered, subjects with plasma total homocysteine levels in the top quintile had a risk that was double that of all other subjects combined (relative risk, or the ratio between the two risks, was ~2). When the top 10% of the fasting plasma total homocysteine distribution was compared with the lowest 10%, the relative risk was 3 instead of 2. The level of risk associated with hyperhomocysteinemia was equivalent to that associated with hypercholesterolemia or smoking, whereas hypertension was associated with a higher excess risk.

The relationships between smoking or fasting plasma cholesterol level and vascular disease are continuous; risk increases as the number of cigarettes smoked daily or the plasma cholesterol concentration increases. Similarly, a dose-response relationship is observed between plasma total homocysteine level and risk of vascular disease. Interactions of plasma homocysteine level and risk of vascular disease. Interactions of plasma homocysteine with other risk factors were also observed in the European multicenter study; an increased fasting homocysteine level showed a more-than-multiplicative effect on risk in smokers and in subjects with hypertension.

Benefits of smoking cessation, cholesterol reduction, and antihypertensive treatment in reducing risk of cardiovascular disease events have been well documented. Demonstration of the benefits of reductions of plasma homocysteine levels, possibly by administration of B vitamins (folate, vitamin B₆, and vitamin B₁₂), in reducing risk of vascular disease is currently being evaluated.

evidence that triacylglycerols are independent predictors of disease. The cholesterol transported in VLDL with triacylglycerols based on animal and cell studies can accumulate in arterial wall macrophages, and thus, elevated triacylglycerol levels may be a marker of increased delivery of non-LDL cholesterol to lesion sites.

The observation that HDL cholesterol levels are inversely related to CAD has led to numerous studies of HDL subclasses in an effort to identify the "truly antiatherogenic" type of HDL. HDL₃ (density of 1.063 to 1.12 g/mL) and HDL₄ (density of 1.12 to 1.21 g/mL) were the first major subclasses studied. Although several studies have indicated that only the larger, more cholesteryl ester-enriched HDL₄ is protective, other investigators have failed to see a difference between the two types of HDL (Silverman et al., 1983; Wilson et al., 1991). More recently, studies in which HDL was subdivided according to apoprotein composition have raised the possibility that particles with apo A-I but not apo A-II are antiatherogenic, whereas particles with both apoproteins A-I and A-II are not; this work remains controversial (Lagrost et al., 1995).

Investigators studying LDL have also looked closely at heterogeneity in LDL. Small dense LDL, which are commonly found in individuals with higher triacylglycerol and lower HDL cholesterol levels, have been proposed as the "more" atherogenic LDL (Austri et al., 1990). It is possible, based on studies showing greater penetration into the artery wall or increased predisposition for oxidative modification, that small, dense LDL are more atherogenic than "normal" LDL. On the other hand, patients with familial hypercholesterolemia have large, cholesteryl ester-enriched LDL that seem to be quite atherogenic.
TABLE 41-2
Risk Status* Based on Presence of CHD Risk Factors Other than LDL Cholesterol

Positive Risk Factors
- Age:
  - Men: ≥ 45 years
  - Women: ≥ 55 years, or premature menopause without estrogen replacement therapy
- Family history of premature CHD (define myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (≥ 140/90 mm Hg.† or on antihypertensive medication)
- Low HDL cholesterol (≤ 35 mg/100 mL)
- Diabetes mellitus

Negative Risk Factor‡
- High HDL cholesterol (≥ 60 mg/100 mL)

*High risk, defined as a net of two or more CHD risk factors, leads to more vigorous intervention. Age (defined differently for men and for women) is treated as a risk factor because rates of CHD are higher in elderly than in young people and higher in men than in women of the same age. Obesity is not listed as a risk factor because it operates through other risk factors that are included (hypertension, hyperlipidemia, decreased HDL cholesterol, and diabetes mellitus), but it should be considered a target for intervention. Physical inactivity is similarly not listed as a risk factor but it too should be considered a target for intervention, and physical activity is recommended as desirable for everyone.

†Confirmed by measurement on several occasions.
‡If the HDL cholesterol level is > 60 mg/100 mL, subtract one risk factor (because high HDL cholesterol levels decrease CHD risk).


EFFECTS OF DIET ON PLASMA LIPIDS AND LIPOPROTEINS

The amount and type of fatty acids in dietary fat, the dietary cholesterol level, as well as the caloric content and macronutrient composition of the diet, can influence the composition, concentration, and metabolism of plasma lipoproteins.

Dietary Fat and Fatty Acids

Dietary fatty acids are often divided into three major classes: saturated, monounsaturated, and polyunsaturated, and the ratio (by weight) of polyunsaturated fatty acids to saturated fatty acids is referred to as the P:S ratio. The major fatty acids found in dietary triacylglycerols (fats and oils) are listed in Table 41-3.

A number of studies have been used, alone and together, to generate equations that predict the changes in total and lipoprotein cholesterol that will occur in response to changes in intake of dietary fatty acids and cholesterol. These equations are given in Table 41-4.

Effects of Saturated Fatty Acids on Plasma Total and LDL Cholesterol Concentrations. The classic studies of Keys et al. (1965) and Hegsted et al. (1965) demonstrated clearly

Finally, it cannot be overlooked that all the studies concerned with lipids, lipoproteins, and risk for CAD have used fasting blood samples for determination of lipid and lipoprotein levels. In recent years, increased interest in the postprandial period has led to a number of reports that link postprandial triacylglycerol levels to CAD (Fatsch et al., 1992). This link may have its pathophysiologically basis in the accumulation of atherogenic chylomicron remnants, the concomitant fall in HDL cholesterol, and/or the production of smaller, denser LDL during the postprandial period. Further studies, particularly ones focused on the effects of diet on postprandial lipoprotein metabolism, are needed.

TABLE 41-3
The Major Dietary Fatty Acids by Class

<table>
<thead>
<tr>
<th>Saturated Fatty Acids</th>
<th>Monounsaturated Fatty Acids</th>
<th>Polyunsaturated Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauric acid (12:0)</td>
<td>Oleic acid (18:1n-9)</td>
<td>Omega 6</td>
</tr>
<tr>
<td>Myristic acid (14:0)</td>
<td>trans 16:1n-9 and trans 18:1n-9</td>
<td>Linoleic acid (18:2n-6)</td>
</tr>
<tr>
<td>Palmitic acid (16:0)</td>
<td></td>
<td>Omega 3</td>
</tr>
<tr>
<td>Stearic acid (18:0)</td>
<td></td>
<td>α-Linoleic acid (18:3n-3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eicosapentaenoic acid (20:5n-3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docosahexaenoic acid (22:6n-3)</td>
</tr>
</tbody>
</table>
Predictive Equations for Estimating Changes in Plasma Cholesterol and Lipoprotein Cholesterol in Response to Dietary Fatty Acids and Cholesterol*

(A) Keys Equation
\[ \Delta TC = 1.35(2\Delta S - \Delta P) + 1.52\Delta C \]

(B) Hegsted Equation
\[ \Delta TC = 2.16\Delta S - 1.65\Delta P + 0.067\Delta C - 0.53 \]

(C) Mensink and Katan Equations
\[ \Delta TC = 1.51\Delta S - 0.12\Delta M - 0.60\Delta P \]
\[ \Delta LDL-C = 1.29\Delta S - 0.24\Delta M - 0.55\Delta P \]
\[ \Delta HDL-C = 0.47\Delta S + 0.34\Delta M + 0.28\Delta P \]

(D) Yu Equations
\[ \Delta TC = 2.02a_{12:0} + 16.0 - 0.03a_{18:0} - 0.49a_{16:0} - 0.98\Delta P \]
\[ \Delta LDL-C = 1.46a_{12:0} + 16.0 + 0.07a_{18:0} - 0.60\Delta M - 0.96\Delta P \]
\[ \Delta HDL-C = 0.62a_{12:0} + 16.0 - 0.06a_{18:0} + 0.39\Delta M + 0.24\Delta P \]

*Where \( \Delta TC \), \( \Delta LDL-C \), and \( \Delta HDL-C \) = changes in plasma total, LDL, and HDL cholesterol in mg/100 ml; \( \Delta S \) = change in percentage of daily energy from saturated fatty acids; \( \Delta M \) = change in percentage of daily energy from monounsaturated fatty acids; \( \Delta P \) = change in percentage of daily energy from polyunsaturated fatty acids; \( \Delta C \) = change in the square root of dietary cholesterol in mg/1000 kcal; \( \Delta C \) = change in dietary cholesterol in mg/day (Hegsted).

Equations are from the following sources:

that increases in the percent of calories from saturated fat are associated with increases in total plasma cholesterol levels. Substitution of saturated fat for polyunsaturated or monounsaturated fat or carbohydrates will raise total plasma cholesterol levels. Although numerous studies (Mensink and Katan, 1992; Yu et al., 1995) have been carried out since these original investigations, the regression coefficients proposed by Hegsted et al. (1965) and Keys et al. (1965) have generally stood the test of time. The response in total cholesterol is mirrored by changes in LDL cholesterol and apo B levels and is similar in men and women, older and younger individuals, pre- and postmenopausal women, and whites and blacks (Ginsberg et al., 1998). Children also respond to changes in dietary saturated fat intake with the predicted changes in total and LDL cholesterol levels.

The mechanisms by which saturated fatty acids raise LDL cholesterol levels have been investigated intensely (Woollett et al., 1992a, 1992b). In a variety of animal models, down-regulation of LDL receptors, coupled with increased production of cholesterol-carrying lipoproteins by the liver, accounts for the rise in plasma LDL levels. In hepatocytes from rats fed saturated fat, LDL receptor mRNA levels are depressed; similar effects have been observed in other rodents and in nonhuman primates. Less is known about the mechanisms underlying increased production of lipoprotein cholesterol; data concerning effects of intracellular cholesterol on apo B secretion are conflicting.

Several studies of the effects of saturated fats on human lipoprotein metabolism have been conducted. In a study of normal and hypercholesterolemic men, Turner et al. (1981) found that high-fat diets with very low P:S ratios were associated with increased rates of production and slightly reduced rates of clearance of LDL apo B compared with diets with very high P:S ratios. Shepherd et al. (1980) found that similar diets altered LDL clearance rates in normal subjects. Cortese et al. (1983) fed high-fat diets with varying P:S ratios to hyperlipidemic men; they observed that saturated fats increased both the number of VLDL secreted by the liver and the conversion of VLDL to LDL.

In the same series of studies from which Keys et al. (1965) and Hegsted et al. (1965) generated regression coefficients for saturated fats, coefficients were estimated for each of the individual saturated fatty acids from C12 through C18. In the succeeding years, interest in the individual saturated fatty acids increased intermittently; recently interest has peaked once again, in part because of technological advances that allow production of specific fatty acid blends that may be used in food production.

Palmitic (C16:0), myristic (C14:0), and lauric (C12:0) acids all seem to be hypercholesterolemic compared with monounsaturated
TABLE 41-2

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Hypertension (≥ 140/90 mm Hg,† or on antihypertensive medication)
Low HDL cholesterol (≤ 35 mg/100 mL)
Diabetes mellitus

Negative Risk Factor:†
High HDL cholesterol (> 60 mg/100 mL)

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†If the HDL cholesterol level is > 60 mg/100 mL subtract one risk factor (because high HDL cholesterol levels decrease CHD risk).


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Dietary fatty acids are often divided into three major classes: saturated, monounsaturated, and polyunsaturated, and the ratio (by weight) of polyunsaturated fatty acids to saturated fatty acids is referred to as the P:S ratio. The major fatty acids found in dietary triacylglycerols (fats and oils) are listed in Table 41-3.

A number of studies have been used, alone and together, to generate equations that predict the changes in total and lipoprotein cholesterol that will occur in response to changes in intake of dietary fatty acids and cholesterol. These equations are given in Table 41-4.

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TABLE 41-3

The Major Dietary Fatty Acids by Class

Saturated Fatty Acids
- Lauric acid (12:0)
- Myristic acid (14:0)
- Palmitic acid (16:0)
- Stearic acid (18:0)

Monounsaturated Fatty Acids
- Oleic acid (18:1n-9)
- trans 16:1n-9 and trans 18:1n-9

Polyunsaturated Fatty Acids
- Omega 6
  - Linoleic acid (18:2n-6)
  - Omega 3
  - ωLinoleic acid (18:3n-3)
- Eicosapentaenoic acid (20:5n-3)
- Docosahexaenoic acid (22:6n-3)
TABLE 41-1
Predictive Equations for Estimating Changes in Plasma Cholesterol and Lipoprotein Cholesterol in Response to Dietary Fatty Acids and Cholesterol

(A) Keys Equation
\[ \Delta TC = 1.35(2\Delta S - \Delta P) + 1.52\Delta Z \]

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\[ \Delta TC = 2.16\Delta S - 1.65\Delta P + 0.67\Delta C - 0.53 \]

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\[ \Delta TC = 1.51\Delta S - 0.12\Delta M - 0.60\Delta P \]
\[ \Delta LDL-C = 1.28\Delta S - 0.24\Delta M - 0.55\Delta P \]
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(D) Yu Equations
\[ \Delta TC = 2.02\Delta 12:0-16:0 - 0.93\Delta 18:0 - 0.48\Delta M - 0.96\Delta P \]
\[ \Delta LDL-C = 1.46\Delta 12:0-16:0 + 0.07\Delta 18:0 - 0.83\Delta M - 0.95\Delta P \]
\[ \Delta HDL-C = 0.62\Delta 12:0-16:0 - 0.06\Delta 18:0 + 0.39\Delta M + 0.24\Delta P \]

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In the same series of studies from which Keys et al. (1965) and Hegsted et al. (1965) generated regression coefficients for saturated fats, coefficients were estimated for each of the individual saturated fatty acids from C12 through C18. In the succeeding years, interest in the individual saturated fatty acids increased intermittently; recently interest has peaked once again, in part because of technological advances that allow production of specific fatty acid blends that may be used in food production.

Palmitic (C16:0), myristic (C14:0), and lauric (C12:0) acids all seem to be hypercholesterolemic compared with mono-unsaturated...
fatty acids (i.e., oleic acid), but the relative potency of these three individual saturated fatty acids in raising plasma cholesterol is not certain. They all seem to act by suppressing receptor-dependent LDL cholesterol clearance from the circulation and by increasing VLDL cholesterol secretion by the liver.

In the original studies by Keys et al. (1965) and Hegsted et al. (1965), contrasting effects of lauric acid (C12:0) were indicated; Keys assigned lauric acid a coefficient equal to that of palmitic acid and myristic acid, whereas Hegsted found it to have only a mild cholesterol-raising effect. More recent studies have not resolved the cholesterol-raising of lauric acid relative to palmitic acid but suggest that lauric acid does have an LDL cholesterol-raising effect compared with monounsaturated fatty acids (i.e., oleic acid) and a more or less equivalent LDL cholesterol-raising effect as compared with that of palmitic acid.

Data from both Keys et al. (1965) and Hegsted et al. (1965) suggested that myristic acid (C14:0) may be four to six times more cholesterolemic than palmitic acid. In a recent trial (Welty et al., 1995), the effect of myristic acid was tested on a large group of volunteers. Compared with both palmitic and oleic acids, myristic acid significantly raised both total and LDL cholesterol levels. Myristic acid was about 1.5 times as cholesterol-raising as was palmitic acid. Furthermore, several other investigators have reported that palmitic acid (C16:0) was less hypercholesterolemic than a combination of lauric acid and myristic acid when substituted for lauric plus myristic acid over a range of 5% to 18% of energy intake (Sundaram, 1994). However, there are also reports of no increase in total and LDL cholesterol when myristic acid was substituted for palmitic acid, and the cholesterol-raising effects of myristic acid relative to the other major saturated fatty acids remain in question.

Both the studies of Keys et al. (1965) and Hegsted et al. (1965) assigned a neutral role to stearic acid (C18:0), and this has been confirmed by more recent studies (Bonanome and Gandy, 1988). It must be pointed out, however, that relative to polyunsaturated fatty acids such as linoleic acid, stearic acid raises total cholesterol and LDL cholesterol. Recently, Yu et al. (1995) developed a new regression equation based on 18 studies that reported data on stearic and other fatty acids. In that equation, stearic acid was found to be neutral. The lack of a cholesterol-raising effect of stearic acid is due, in part, to its desaturation to oleic acid shortly after absorption as well as its higher incorporation into phosphatidylycholine (versus triacylglycerol and cholesteryl esters) compared with palmitic acid.

**Effects of Polyunsaturated Fatty Acid on Plasma Total and LDL Cholesterol Concentrations.** Human feeding studies in the early 1950s suggested that polyunsaturated fats had unique properties in that they reduced plasma cholesterol concentrations. Keys et al. (1965) and Hegsted et al. (1965) both estimated negative regression coefficients for this class of fatty acids. Although the reductions in total cholesterol that occurred when diets high in polyunsaturated fats were fed were confirmed in many studies by concomitant reductions in HDL cholesterol (Mensink and Katan, 1992), LDL cholesterol levels fell as well. Indeed, the reductions in LDL levels appear to be not only a response to replacement of saturates by polyunsaturates in many studies, but also a direct result of some activity of polyunsaturated fatty acids. Meta-analysis of a number of well-controlled diet studies in humans have confirmed a direct LDL-lowering effect of an increase in the amount of polyunsaturated fatty acids in the diet, but this effect is not as potent as that obtained by reducing the amount of saturated fat in the diet (Mensink et al., 1992; Yu et al., 1995). This effect may be difficult to observe in single studies in which modest increases in dietary polyunsaturates are achieved. Additionally, polyunsaturates may be potent only when they are added to diets initially lacking or extremely low in this class of fats: Hayes (1992) suggested that 5% of calories from polyunsaturated fatty acids represents the upper end of the dose-response curve for the LDL cholesterol-lowering effect. The mechanisms for LDL lowering by consumption of diets high in polyunsaturates are the opposite of those demonstrated for saturates: increased LDL receptor function and reduced lipoprotein-cholesterol secretion from the liver.
Effects of Monounsaturated Fatty Acids and trans Fatty Acids on Plasma Total and LDL Cholesterol Concentrations. There has been much recent interest in the effects of monounsaturated fatty acids because of the low rates of atherosclerotic cardiovascular disease in the Mediterranean area where diets are high in fat but the fat is mainly olive oil. In the studies by Keys et al. (1965) and Hegsted et al. (1965), monounsaturated fats, specifically oleic acid, were found to have negligible independent cholesterol-lowering effects. This was accepted as a fact until the mid-1980s, when other investigators demonstrated that monounsaturates could lower total and LDL cholesterol in subjects fed diets in which monounsaturated fatty acids replaced saturated fatty acids. Ginsberg et al. (1990), in a study with young, healthy men, found that replacing 7% of calories from carbohydrates with oleic acid in an otherwise American Heart Association (AHA) Step 1 diet did not result in lower plasma total or LDL cholesterol. This finding is in accord with the predictive regression coefficient based on a meta-analysis of the effects of fatty acids published by Mensink and Katan (1992), although Yu et al. (1995) recently developed a predictive equation in which monounsaturates were given a small cholesterol-lowering value. Although replacement of saturated fat with monounsaturated fat has a cholesterol-lowering effect, the addition of a moderate amount of oleic acid to the diet (in the range of 5% to 10% of total calories as a replacement for carbohydrate calories) is unlikely to have a discernible effect on total or LDL cholesterol. Other monounsaturates, such as palmitoleic acid, are found in very low amounts in typical American diets; palmitoleic acid levels are higher in diets high in many types of nuts.

A unique, but commercially important, monounsaturated fatty acid is the trans isomer of C18:1n-9, elaidic acid. This fatty acid results from the commercial process to partially hydrogenate linoleic acid in the production of margarines. Early work by Mattson et al. (1975) in the 1960s led to the belief that elaidic acid acted like the cis isomer of oleic acid; it had no effect on plasma cholesterol concentrations. However, work published a few years later suggested a slight cholesterol-raising effect of trans fatty acids. Finally, in 1990, Katan and colleagues (Mensink and Katan, 1990) published the first of a series of papers indicating that trans fatty acids might behave more like saturated fatty acids. LDL levels increased in a dose-response manner when dietary oleic acid was replaced by moderate to large amounts of elaidic acid (5% to 20% of total calories). HDL levels fell and Lp(a) levels increased on the high elaidic acid diet. These findings for LDL have been confirmed in other studies (Judd et al., 1994; Nestel et al., 1992), whereas the fall in HDL was observed in some (Judd et al., 1994; Lichtenstein et al., 1993) but not all studies (Nestel et al., 1992). Additionally, an increase in Lp(a) was not seen in the study by Lichtenstein et al. (1993), although it was observed by Nestel et al. (1992). The relevance of these findings to the American diet is unclear because the average intake of trans fatty acids is estimated at 2% to 4% of calories, which is appreciably lower than the intake of saturated fatty acids. On the other hand, some epidemiological data indicate a negative effect of trans fatty acid intake on morbidity and mortality. Estimates of the average intake of trans fatty acids from various food sources are listed in Table 41-5.

Effects of Fatty Acids on HDL Cholesterol Concentration. In their early studies, Keys et al. (1965) and Hegsted et al. (1965) examined only total plasma cholesterol levels on different diets. Indeed, it wasn't until the late 1970s, after the rediscovery of the importance of HDL cholesterol as a protective factor for CAD, that studies of the effects of dietary fatty acids on HDL cholesterol began to be conducted. In many of the early studies, large quantities of polyunsaturated fatty acids (up to 20% to 30% of total calories) were used to replace saturated and monounsaturated fatty acids; these studies demonstrated reductions in HDL cholesterol concentrations (along with lowering of LDL cholesterol levels). In the studies by Mattson and Grundy (1985) in which monounsaturated fatty acids were compared with polyunsaturated fatty acids as replacements for saturated fats, the "high poly" diets were associated with much lower HDL cholesterol levels than were the "high mono" diets.