TABLE 4.1-5

<table>
<thead>
<tr>
<th>Estimated Average Daily Intake of Total Fat and trans Fat from Primary Food Sources of trans Fatty Acids***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Source</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Vegetable</strong></td>
</tr>
<tr>
<td>Bread, commercial</td>
</tr>
<tr>
<td>Fried foods†</td>
</tr>
<tr>
<td>Cakes and related baked goods</td>
</tr>
<tr>
<td>Savory snacks</td>
</tr>
<tr>
<td>Margarine, stick§</td>
</tr>
<tr>
<td>Margarine, soft and spreads§</td>
</tr>
<tr>
<td>Cookies</td>
</tr>
<tr>
<td>Crackers</td>
</tr>
<tr>
<td>Household shortening§</td>
</tr>
<tr>
<td><strong>Animal</strong></td>
</tr>
<tr>
<td>Milk</td>
</tr>
<tr>
<td>Ground beef</td>
</tr>
<tr>
<td>Butter</td>
</tr>
</tbody>
</table>

*Values are 3-day averages from the U.S. Department of Agriculture (USDA) Continuing Surveys of Food Intakes by Individuals, 1989-1990 and 1990-1991.
†Fats composition data adapted from Nutrient Data Bank Bulletin Board (USDA/Agricultural Research Service, Riverdale, MD).
‡Total fat intake = 69 g/day; total energy intake = 7,355 MJ/day (1.75 kcal/day).
§Home and food service combined.
††Contributions of these foods do not include use as ingredients in foods already listed in table.

LDL cholesterol concentrations were similar in the two diets. In several studies (Dreon et al., 1990; Wardlaw and Snook, 1990) in which smaller quantities of polyunsaturated fatty acids were added to an AHA Step 1 diet as replacement for saturated or monounsaturated fat, a smaller HDL lowering was observed (Ginsberg et al., 1994a).

A more systematic look at the effects of each class of fatty acids on HDL cholesterol levels can be achieved using the meta-analysis approach. In reports by Mensink and Katan (1992) and Yu et al. (1995), saturated, polyunsaturated, and monounsaturated fatty acids were all shown actually to have HDL cholesterol-raising effects. However, the relative potency of these fatty acid classes in raising HDL cholesterol was saturated > monounsaturated > polyunsaturated. Thus, if monounsaturates are used as a replacement for saturates, a very slight reduction in HDL would result (monounsaturates raise HDL slightly less than saturates); this reduction would likely be statistically insignificant in most of the studies with small sample sizes. If polyunsaturates are used to replace saturates, the fall in HDL cholesterol would be greater because polyunsaturates raise HDL only about 40% as much as saturates; this effect has been statistically significant in most reported studies. This scheme makes it clear why replacement of total fat (of any fatty acid distribution) with carbohydrate (which is neutral regarding HDL cholesterol) results in significant reductions in HDL cholesterol levels: all fats raise the plasma HDL concentration.

Three human studies have addressed the mechanisms by which HDL falls during consumption of diets with different total fat contents. Blum et al. (1977) first studied HDL apo A-I metabolism in subjects consuming a diet very high in carbohydrate (80% of total calories) and low in fat (5% of total calories) or high in fat (40% of total calories) with typical carbohydrate content (40% of total calories). These investigations demonstrated that the fall in plasma concentrations of HDL cholesterol and apo A-I was associated with increased fractional clearance of apo A-I in individuals consuming the lower fat diets. Brinton et al. (1990) performed a similar experiment several years later in which they fed subjects diets in which fat provided 40% or 10% of total calories. They found that the fall in HDL cholesterol levels in subjects on the low-fat diet was associated mainly with reduced apo A-I production, although they also found that fractional clearance of apo A-I was higher in subjects fed the low-fat diet than in subjects fed the high-fat diet. Shepherd et al. (1978) compared diets with very high and very low polyunsaturated to saturated fat ratios and found that the lower HDL levels observed in subjects eating the polyunsaturated fat diet were associated with significantly reduced rates of apo A-I appearance in plasma. Summarizing these studies, the consistent theme that emerges is that all fatty acids somehow increase secretion of apo A-I from the liver and/or the intestine, and that saturates stimulate apo A-I secretion more than polyunsaturates. Monounsaturates seem to be similar to saturates in their effect on apo A-I secretion. Re-
placing fatty acids with carbohydrates will result in a decrease in apo A-I secretion and also may result in increased fractional clearance of apo A-I, both of which will lead to lower plasma levels of this protein. Altered levels of apo A-I will result, under most conditions, in altered plasma concentrations of HDL cholesterol. (The relationship of apo A-I to HDL cholesterol is described in detail in Chapter 14.)

**Effects of Fatty Acids on Triacylglycerol Concentrations.** In general, saturated fatty acids increase plasma triacylglycerol levels moderately whereas polyunsaturated fatty acids reduce them to a similar degree. Exceptions to the moderate effects of fatty acids on plasma triacylglycerol are those effects observed when large amounts of ω3 fatty acids (4 to 8 g/day) are consumed (Harris et al., 1990). This class of fatty acids includes α-linolenic acid (18:3), eicosapentaenoic acid (EPA; 20:5), and docosahexaenoic acid (DHA; 22:6). Soybean and canola oils are good sources of ω-linolenic acid, and EPA and DHA are found mainly in the fat tissue of cold-water fish. Consumption of large quantities of salmon oil was shown to significantly reduce the secretion of VLDL from liver in normal and hypertriglyceridemic humans. Omega-3 fatty acids also reduce postprandial triacylglycerol levels. EPA and DHA can increase the intracellular degradation of nascent apo B in cultured liver cells. Capsules of concentrated ω3 fatty acids have been used to treat patients with severe hypertriglyceridemia.

**Effects of Fatty Acids on Lp(a) Levels.** Lp(a) is a subclass of LDL that contains apo(a) in addition to apo B. Some, but not all, epidemiological studies have indicated increased risk for ASCVD as Lp(a) increases. Although some studies have suggested that greater than 90% of the variability in Lp(a) levels appears to be genetically determined, recent studies have found that increases in plasma Lp(a) levels occur in normal and dyslipidemic individuals when saturated fatty acids are decreased in the diet, with either replacement of dietary calories by carbohydrate or monounsaturated fat (Ginsberg et al., 1998). Lp(a) concentrations were not altered by changes in dietary saturated fats or cholesterol in several previous studies (Berglund, 1995). In contrast, Lp(a) levels did rise in the majority of studies in which trans fatty acids were increased (Mensink and Katan, 1990; Nestel et al., 1992; Lichtenstein et al., 1993). Further studies will be needed to investigate and confirm the mechanisms underlying these effects of fatty acids on Lp(a) concentrations in plasma.

**Dietary Cholesterol**

The role of dietary cholesterol in the development of both hypercholesterolemia and atherosclerosis has been the focus of many investigations over the past century. The studies by Ignatowski (1908) and later by Anitschkow and Chalatow (1913) indicated the importance of dietary cholesterol, and their work in rabbits has been supported by many studies in other animal models and by human dietary and epidemiological investigations (Stamler and Shekelle, 1988). However, although many continue to support the view that dietary cholesterol is the major atherogenic nutrient in the diet, other investigators have come to opposite conclusions after reviewing numerous human feeding studies. This controversy has been evident in the changing prominence of dietary cholesterol in the American Heart Association (AHA) Diet Statements published every several years (Chait et al., 1993; Grundy et al., 1989).

One reason for this controversy is that experimental animals may not be appropriate models. Clearly, humans do not respond to dietary cholesterol with the marked increases in plasma cholesterol observed in rabbits. Even rodent species, which are resistant to atherosclerosis, respond to dietary cholesterol and fat with larger increases in lipid levels than do humans. Another problem with the animal studies is that the amounts of cholesterol fed in most early studies were much beyond the highest intakes reported in humans. More recently, however, diets with modest increases in cholesterol content have been shown to significantly increase plasma cholesterol in nonhuman primates, with concomitant development of atherosclerosis.

Many studies of the effects of dietary cholesterol on plasma cholesterol levels in humans have been published during the past
several decades. However, many were of poor quality, with little control over nutrient intake other than cholesterol. Several excellent studies deserve review. First, as always, the classic studies of Keys et al. (1965) and Hegsted et al. (1965) provided us with regression coefficients for the effects of dietary cholesterol on plasma total cholesterol levels. These coefficients suggested that for each 100 mg of dietary cholesterol added per day, plasma cholesterol would rise between 3 mg/100 mL (Keys et al., 1965) and 6 mg/100 mL (Hegsted et al., 1965). Hegsted et al. (1993), in a later review of more experiments, lowered their estimate of the effect of dietary cholesterol to be in line with that of Keys et al. (1965). Ginsberg carried out two very well controlled studies in healthy young men (1994b) and women (1995). Dietary cholesterol ranged from about 125 mg/day to 750 mg/day and was added to a National Cholesterol Education Program (NCEP) Step I diet. Several levels of cholesterol were fed, allowing for regression analysis of the results, as shown in Figure 41-2. For each addition of 1 egg (about 200 mg of cholesterol), LDL cholesterol increased about 3 to 4 mg/100 mL. This change was statistically significant, but obviously modest, particularly in the setting of baseline LDL cholesterol levels of about 100 mg/100 mL. The changes observed amounted to about 60% of the original estimate of response reported by Keys et al. (1965). HDL cholesterol tended to increase in the men and significantly increased in the women (1 mg/100 mL for each egg added to the diet) (Ginsberg et al., 1994b, 1995).

Human metabolic studies of the effects of dietary cholesterol on lipoprotein production and degradation have added to our knowledge of the mechanism underlying effects on plasma levels. Dietary cholesterol does not seem, within the range of typical intakes, to affect VLDL production by the liver, but increased secretion of LDL directly into the circulation has been observed in a small group of subjects fed very high levels of cholesterol. Several studies of 3-hydroxy-3-methylglutaryl (HMG) CoA reductase inhibitors, which reduce endogenous cholesterol synthesis, have demonstrated reduced secretion of VLDL in vivo. Thus, the effects of dietary cholesterol on VLDL assembly and secretion remain incompletely characterized.

A number of studies have focused on the effects of dietary cholesterol on LDL metabo-

lism. Ginsberg et al. (1981) determined LDL apo B turnover in 5 healthy men on diets containing 300 and 1200 mg of cholesterol/day. Both diets contained 40% of calories as fat, with a P:S ratio of 0.4. The three-fold increase in dietary cholesterol had no effect on LDL production or fractional clearance, and LDL cholesterol levels did not change. In a similar study by Packard et al. (1983), an eight-fold increase in dietary cholesterol (1800 mg/day compared with 200 mg/day) on top of a diet containing 40% of calories as fat, with a P:S ratio of 0.2, increased plasma cholesterol levels, and this was associated with both increased LDL production and decreased fractional removal of LDL. The differences in results in these two studies may have been related to the greater absolute cholesterol load or lower P:S ratio in the study by Packard et al. (1983).

Dietary Carbohydrates

Dietary recommendations to lower total fat intake include increasing dietary carbohydrate intake, because favorable plasma lipid and lipoprotein levels have been reported for populations and individuals whose habitual diet is high in carbohydrates. However, there is concern over reports of a decrease in HDL cholesterol and an elevation of plasma triacylglycerols with high carbohydrate consumption. Populations who eat high-carbohydrate diets have low plasma HDL cholesterol levels and low CHD rates. Plasma triacylglycerol levels are not significantly elevated in these populations, possibly because obesity is rare. Another issue currently being studied is whether it is advisable to recommend high-carbohydrate diets to individuals with insulin resistance and diabetes (Garg et al., 1994), who may have high plasma triacylglycerol and low HDL cholesterol levels. The concern is that high-carbohydrate diets may exacerbate the risk for heart disease. In a well-controlled multicenter study (Lefevre et al., 1997), small differences in plasma HDL cholesterol and triacylglycerol levels were observed in men and women fed diets higher in carbohydrate or higher in monounsaturated fatty acids; the diet higher in carbohydrate (lower in monounsaturated fatty acids) was associated with slightly lower HDL cholesterol and slight higher triacylglycerol levels.

Dietary Fiber

Studies have shown that only watersoluble fiber plays a role in lipoprotein metabolism in humans. The soluble fiber content of oat, barley, guar gum, beans, and psyllium seeds is of interest in relation of CAD. A meta-analysis of 20 studies (Ripsin et al., 1992) found that intake of oat products reduces serum cholesterol levels. The lipid-lowering effect was dose-related and was most significant in individuals with the highest initial cholesterol levels. A daily intake of approximately 3 g of soluble fiber from oats has been reported to reduce serum cholesterol levels by 5.6 mg/100 mL (Davidson, 1991). The hypcholesterolemic effects of oats depend on the bran which contains β-glucan, a watersoluble fiber. Controlled trials with psyllium have shown that a daily intake of 5.1 to 10.4 g of psyllium can lower total cholesterol levels by 8.1% to 14.8% and LDL cholesterol levels by 5.7% to 20.2% within 6 to 16 weeks and is tolerated well (Anderson et al., 1988; Levin et al., 1990; Sprecher et al., 1993). Although they have other beneficial effects, insoluble fibers in wheat and vegetables do not appear to reduce serum cholesterol levels. The mechanisms by which dietary fiber affects plasma lipid levels have not been established, but the major hypotheses are summarized in Chapter 8.

Dietary Protein

In the 1950s, population studies indicated that people who ate large amounts of soy protein had lower rates of atherosclerosis. Soy protein has been shown to lower serum cholesterol levels in animals and in hypercholesterolemic individuals when compared with casein and beef proteins. In a meta-analysis of 38 studies, which included data from 730 human subjects, Anderson et al. (1995) reported a 12.9% reduction in LDL cholesterol, a 2.4% rise in HDL, and a 10.5% reduction in triacylglycerols when the average intake of soy protein was 20 g per day. Of the studies included in this meta-analysis, 21 used isolated soy protein, 14 studies used textured soy protein, and 3 studies
used a combination of the two types of protein. Four of the studies were in children and thirty-four were in adults. The mechanism underlying these responses to soy protein is not clear. Soy protein may affect cholesterol absorption, bile acid absorption, the insulin-glucagon ratio, serum thyroxine levels, and hepatic LDL receptor activity. It is also believed that the soy isoflavone termed genistein, a molecule that resembles estradiol, may play a role in cholesterol metabolism.

Proteins differ in amino acid composition, and this may affect cardiovascular risk. A chronic dietary supplement of L-arginine in animals has been shown to decrease platelet aggregation and the adhesiveness of the aortic endothelium for monocytes, to prevent the intimal thickening of coronary arteries; and to reverse endothelial dysfunction. These effects appear to be due to the metabolism of L-arginine to nitric oxide, whose many biological roles recently have been reviewed (Loscalzo, 1995). L-Arginine also has been shown to improve endothelial dysfunction of both coronary microvasculature and epicardial coronary arteries in cardiac transplant recipients. Platelet aggregation in hypercholesterolemic individuals is also reduced by L-arginine supplements. These findings are intriguing because L-arginine availability should not be rate limiting for nitric oxide synthesis under most dietary conditions. Arginine, which is generally higher in plant proteins, appears to have a hypocholesterolemic effect, whereas lysine and methionine, amino acids generally higher in animal proteins, appear to raise plasma cholesterol concentrations.

Energy

The states of overweight (body mass index greater than 25 kg/m²) or obesity (body mass index greater than 30 kg/m²) are the result of caloric intake in excess of energy expenditure. The association between obesity and an increased risk for cardiovascular disease is well established for both women and men (Donahue et al., 1987; Manson et al., 1990). Within a given range of body mass index, abdominal obesity also is a significant and independent predictor of coronary heart disease and is associated with insulin resistance, hypertension, and hyperlipidemia. Even levels of body fat that are average for the American population, and not labeled as overweight, increase the risk of elevated plasma lipid concentrations, glucose intolerance, and high blood pressure. The leanest individuals have a lower risk of CHD than those with average degrees of adiposity, suggesting that weight reduction may also benefit individuals who are not overtly overweight. A meta-analysis of 70 studies indicated that weight reduction was associated with significant decreases in total, LDL, and VLDL cholesterol levels, decreases in plasma triglyceride concentration, and increases in HDL cholesterol level (Dattilo and Kris-Etherton, 1992).

Alcohol

Epidemiological studies have shown a reverse trend between low to moderate alcohol consumption (less than 40 g/day of pure ethanol for men and less than 30 g/day for women) and coronary heart disease in both men and women (Kannel, 1988). This protective effect has been associated with an increased concentration of plasma HDL cholesterol as well as increased levels of HDL apoproteins A-I, A-II, and A-IV. Among the major subclasses of HDL, HDL₄ and HDL₅ are both increased by alcohol consumption. Reduced platelet aggregation and blood coagulation and increased fibrinolytic activity are all associated with alcohol consumption; these may be looked upon as possible additional underlying mechanisms for the cardioprotective effect of alcohol. These observations have led some physicians to recommend daily consumption of moderate amounts of alcohol; this translates into 1 5-ounce glass of wine, 12 ounces of beer, or 1.5 ounces of distilled spirits per day for women and no more than twice that for men.

This recommendation continues to be controversial because the data on alcohol are difficult to assess for lack of enough controlled human studies and because of a lack of clarity in the description of “moderate” and “heavy” drinking in relation to the pathophysiology of atherosclerosis. Excessive ethanol consumption can result in alcoholic cardiomyopathy. In addition, regular alcohol con-
Consumption raises blood pressure and contributes significantly to the prevalence of hypertension (Beilin and Puddey, 1993). Finally, although moderate drinking appears to have benefits, including an inverse correlation with CHD risk, any possible benefits must be balanced against risks. The risks include stroke, motor vehicle accidents, cancer, birth defects, and dangerous interactions with drugs. In addition, when people do not adhere to recommendations for low to moderate intake, both social and health problems will increase.

A potential metabolic risk derives from the observation that alcohol, given in moderate amounts, increases hepatic synthesis of VLDL. Similar responses are not seen with isocaloric intake of supplemental calories in the form of either carbohydrates or fats. Plasma triacylglycerol levels can be elevated for several hours up to several days in fasting individuals after alcohol ingestion (Ginsberg et al., 1974). HDL cholesterol levels, as noted, are increased modestly by alcohol, so the alcohol-induced hypertriglyceridemia is the exception to the rule that higher triacylglycerols are associated with lower HDL cholesterol levels. Low or subnormal levels of LDL cholesterol have been consistently found in chronic alcoholics. One possible explanation is that VLDL is less readily converted to LDL in alcoholics. Alternatively, excessive alcohol intake is usually associated with malnutrition and weight loss, and these may result in lower LDL levels.

**DIET, BLOOD LIPIDS, AND ATHEROSCLEROSIS**

**Dietary Lipids**

The 20th century has seen the continuous growth of a base of information supporting a significant role for diet in the atherogenic process. Following the groundbreaking studies in rabbits by Ignatowski (1908) and Antschkow and Chalatow (1919), scientists were able to observe and record the "natural" experiment associated with World War II in which the incidence of CHD fell in occupied countries (Malmros, 1980). The similar patterns of association between increases in dietary fat intake and CAD seen in Japanese men migrating to Hawaii and the mainland United States (Kato et al., 1973) and in all Americans between 1950 and 1970 provided strong evidence for the link between diet and heart disease. At the same time, Keys et al. (1966), utilizing epidemiological approaches to support their clinical diet studies, reported the Seven Countries study that showed remarkable relationships between dietary saturated fatty acid intake and heart disease mortality.

Cohort studies such as the Ireland-Boston Heart Study and the Western Electric Study have added further support for hypotheses linking dietary saturated fatty acid and/or cholesterol to CAD. A detailed review of these data is provided in the Diet and Health report of the National Research Council (1989) and the Surgeon General's Report (U. S. Department of Health and Human Services, 1988). Probably the most convincing data derive from the clinical trials that have been carried out using only dietary interventions. In the early study of Dayton et al. (1968), higher amounts of polyunsaturates in the diet were associated with lower CHD events in an elderly population. The Finnish Mental Hospital Study (Miettinen et al., 1983) demonstrated reduced CHD in men and women receiving lower dietary saturated fat and cholesterol. More recently, the Oslo Heart Study (Hjemann et al., 1986) found that men given diets high in polyunsaturated and low in saturated fatty acids had fewer fatal and nonfatal CHD events. Both the Lifestyle Heart Trial (Ornish et al., 1990) and the STARS trial (Watts et al., 1992) showed less progression or even regression of coronary atherosclerosis in men treated with lower fat and cholesterol diets. The STARS trial also demonstrated fewer CHD events in the treated group compared with untreated men.

Overall, the link between dietary saturated fatty acids and CAD is clear and convincing. Similar, but less convincing, data are available for dietary cholesterol. The association between these dietary factors and atherosclerosis is almost certainly based on their effects on plasma lipid and lipoproteins, but
separate effects on thrombogenic factors must be considered as well (Miller, 1995).

**Antioxidants**

The concept that oxidatively modified LDL is proatherogenic and exists in vivo is supported by a growing body of data. Supplementation of diets with nutrients that can act as antioxidants (e.g., ascorbic acid, \( \alpha \)-tocopherol, and \( \beta \)-carotene) has been shown to inhibit the progression of atherosclerosis in animals. At present, clinical trial data are not sufficient to make recommendations regarding the use of antioxidant supplements to reduce the risk of CAD in humans (Jha et al., 1995).

A significant inverse relationship was found between plasma vitamin C and CAD in epidemiological studies (Gey et al., 1987). Ascorbate concentrations were also found to be lower in the aortas of people with atherosclerosis, diabetes, and CAD compared with unaffected control subjects. Ascorbate levels were also lower in smokers than in nonsmokers. It has been hypothesized that low concentrations of ascorbate in the arterial wall may predispose LDL to oxidation and that the greater levels of oxidized LDL promote atherogenesis.

\( \alpha \)-tocopherol is the predominant lipophilic antioxidant in plasma membranes and tissue and is the most abundant antioxidant in LDL. On average there are 6 molecules of \( \alpha \)-tocopherol per LDL particle; they can function as antioxidants by trapping free radicals. Low plasma levels of \( \alpha \)-tocopherol were inversely correlated with CAD in a cross-sectional study and with angina pectoris in a case-control study (Gey et al., 1991; Riemersma et al., 1991). In prospective studies (Stampfer et al., 1992b), \( \alpha \)-tocopherol supplementation appeared to reduce the risk of coronary events in both men and women. In a randomized placebo-controlled study in men, the LDL oxidation kinetics in a group supplemented with 800 IU of \( \alpha \)-tocopherol were similar to those in the group that received combined supplementation with 1.0 g of ascorbate, 30 mg of \( \beta \)-carotene, and 800 IU of \( \alpha \)-tocopherol; there was a 40% decrease in the LDL oxidation rate after 3 months of \( \alpha \)-tocopherol or combined supplementation.

Beta-carotene has been shown to be a powerful antioxidant. It is carried predominantly in the LDL particle. The antioxidant effects of \( \beta \)-carotene are most potent at low partial pressures of oxygen. Beta-carotene has been shown to inhibit oxidation of LDL and Lp(a) (Jialal et al., 1991). Smokers have lower LDL \( \beta \)-carotene levels relative to nonsmokers. The Physicians’ Health Study, however, did not demonstrate benefit from \( \beta \)-carotene supplementation (Hennekens et al., 1996).

Completed randomized trials suggest that none of these antioxidants beneficially affect total mortality or mortality from cardiovascular disease (Hennekens et al., 1996; Omenn et al., 1996). The epidemiological data, however, suggest that high intakes of vitamin E from diet or supplementation that are sustained for 2 or more years are associated with a reduced risk for fatal or nonfatal cardiovascular disease. Use of \( \beta \)-carotene or vitamin C was less clearly associated with a reduced risk. (The antioxidant and other known functions of vitamin C, vitamin E, and \( \beta \)-carotene are discussed in Chapters 23, 24, and 26.)

**Nutrient Intake Deficiency Associated with Homocysteinemia**

Elevated levels of total homocysteine in the blood stream have been associated with an increased risk of cardiovascular disease (van Poppel et al., 1994). Recent clinical studies have linked moderate hyperhomocysteinemia to peripheral vascular, cerebrovascular, and coronary heart disease. A prospective study of male physicians indicated that plasma total homocysteine concentrations of 17 \( \mu \)mol/L or 12% above the upper limit of normal, were associated with a three- to fourfold increase in the risk of acute myocardial infarction (Stampfer et al., 1992a). A high plasma homocysteine concentration and low levels of folate and vitamin B\(_6\), through their role in homocysteine metabolism, were also associated with an increased risk of extracranial carotid artery stenosis. The effect of homocysteine is independent of the established risk factors such as hyperlipidemia and hypertension. An elevated homocysteine level may reflect inadequate availability of folate, vitamin B\(_6\), or vitamin B\(_12\). Supplementation with these vitamins, particu
larly folic acid, may normalize plasma homocysteine levels. (See Chapters 11 and 21 for further discussions of homocysteine and B vitamins.)

Iron

Iron overload on the myocardium as a potential risk for coronary heart disease was indicated in animal experiments in which iron overload increased myocardial damage caused by anoxia and reperfusion. A role for iron in promoting oxidation of LDL cholesterol and atherosclerosis has been proposed, but convincing data are lacking. A prospective study in Finland (Salonen et al., 1992) showed a two-fold increase in acute myocardial infarction among men with serum ferritin levels above 200 μg/L. In contrast, a study with American physicians (Stampfer et al., 1993) and a cohort study of Icelandic men and women (Jonsson et al., 1991) showed no association between serum levels of ferritin or iron and the risk of myocardial infarction. Serum total iron-binding capacity was inversely correlated with the risk of myocardial infarction (Jonsson et al., 1991). Increased risk for myocardial infarction has also been directly correlated with high serum iron concentrations (Morrison et al., 1994) but not associated with serum transferrin saturation levels (Sempos et al., 1994). In summary, the data presently available for a link between iron and CHD are inconsistent and do not justify changes in food fortification policy or dietary recommendations. (For more information about iron, see Chapter 31.)

Selenium

Selenium is an integral part of the antioxidant enzyme glutathione peroxidase and has been studied in relation to CHD. A reduced plasma selenium level has been associated with an increased risk of cardiovascular disease and death in some studies (Salonen et al., 1982). Other studies, however, did not show this association (Salonen, 1987). Whereas high intake levels of selenium may not be protective, a low intake of selenium could be a risk factor. However, in a cross-sectional study of random population samples of apparently healthy mid-

dle-aged men in four European countries, selenium levels did not correlate with the reported rates of CHD (Riemiesma et al., 1990). (More information about selenium can be found in Chapter 34.)

Chromium

Trials in humans showed that chromium elevated serum HDL and lowered total serum cholesterol levels (Anonymous, 1983; Roebuck et al., 1991). Men receiving β-adrenergic blocking agents (commonly used antihypertensive drugs that tend to lower HDL cholesterol) were given three daily doses of 200 μg of chromium or a placebo for 8 weeks; men treated with chromium had an increase in serum HDL cholesterol levels of 5.8 mg/100 mL. In this randomized, double-blind, placebo-controlled study, no significant changes were seen in LDL or triacylglycerol levels (Roebuck et al., 1991). In a study of 28 moderately obese, non-insulin-dependent diabetics, supplements of chromium picolinate for 2 months lowered plasma triacylglycerol levels by 17% (Lee and Reasner, 1994). In the American population, chromium intake from self-selected meals can be as low as 25 μg/day. (Chromium and its nutritional significance are discussed in Chapter 36.)

DIETARY TREATMENT OF HYPERCHOLESTEROLEMIA

It is clear that efforts to optimize plasma lipid and lipoprotein levels and reduce the risk for CHD should start with diet modification. In general, diet modification should focus on

1. Reducing the intake of saturated fatty acids.
2. Reducing caloric intake in excess of energy requirements, and
3. Reducing the intake of dietary cholesterol.

Lowering intake of saturated fat and cholesterol should clearly be the most important focus of any nutritional treatment for hypercholesterolemia. For most people with elevated plasma cholesterol levels, dietary changes aimed at lowering saturated fat and