

serum cholesterol levels ( $r=0.89$ ) and serum cholesterol levels and CHD incidence rates ( $r=0.81$ ) (Keys 1972). Followup after 10 years still supported these findings (Stamler 1979).

International migration studies are yet another type of cross-country comparison. The movement of population groups from less affluent to more affluent societies provides a special opportunity to evaluate changes in risk factors among persons sharing the same genetic and cultural background. Such observations have helped to dispel the view that atherosclerosis and CHD essentially represent an immutable aging process, with most of the variations representing the inherited population pattern, or that the cholesterol levels encountered in most people in the United States can be regarded as normal. They indicate that as populations move and show a rise in dietary fat and saturated fat intake, they move from areas with low incidence of CHD to high incidence. They also display concurrent elevations in serum cholesterol. For example, the Ni-Hon-San Study, initiated in 1965 with middle-aged men of Japanese ancestry residing in Japan, Honolulu, and the San Francisco Bay area, showed intakes of saturated fat to be about 7 percent, 12 percent, and 14 percent, respectively. Average dietary cholesterol intakes were 464, 545, and 533 mg/day, and mean body weights were 55, 63, and 66 kg for the respective populations. Compared with Japan, serum cholesterol was 12 percent higher in Hawaii and 21 percent higher in San Francisco, and CHD mortality was 1.7 times higher in Hawaii and 2.8 times higher in San Francisco (Kato et al. 1973; Marmot et al. 1975; Robertson, Kato, Gordon, et al. 1977; Robertson, Kato, Rhoads, et al. 1977; Worth et al. 1975).

*Within-Population Studies.* The existence of groups within populations who consume diets different from the rest of the population provides another opportunity to examine the relationship between diet, serum cholesterol, and CHD. For example, studies in the United States comparing serum cholesterol levels in communities of omnivores (consuming animal and vegetable products), vegans (consuming only vegetable products), and lacto-ovo vegetarians (consuming milk, egg, and vegetable products) showed that vegans, who habitually consume a low saturated fat and cholesterol-free diet, had mean serum cholesterol levels 29 percent lower than omnivores, and those of lacto-ovo vegetarians were 16 percent lower (Hardinge and Stare 1954). Seventh-day Adventists who consume lacto-ovo vegetarian diets have lower mean serum cholesterol levels than the general American population. A 6-year prospective study of 20,044 Seventh-day Adventists in California showed that CHD mortality rates among those 35 to 64 years of age and over age 65 were 72 percent lower and 50 percent lower, respectively, than rates found in the general population.

Among Seventh-day Adventists, risk for CHD in nonvegetarian males 35 to 64 years of age was threefold greater than in vegetarian males (Phillips, Lemon, and Kuzma 1978).

All these types of epidemiologic studies involve analysis of data for groups. Despite the strength and consistency of results of group comparisons across and within populations, it has been difficult in studies of individuals within a given population to demonstrate similar relationships of dietary fat with either the plasma cholesterol level or CHD. While studies of individuals have revealed strong relationships between plasma cholesterol and CHD, only weak associations of dietary factors with plasma cholesterol levels or CHD have been shown.

In the Puerto Rico Heart Study, for example, baseline serum cholesterol levels in the urban sample were positively related to percent of calories from protein, fat, and saturated fat, and serum cholesterol was negatively related to percent of calories from total carbohydrate and complex carbohydrate (Garcia-Palmieri et al. 1977). In the Honolulu Heart Study, baseline serum cholesterol was positively related to dietary cholesterol, animal protein, and saturated fat and to percent of calories from total protein, total fat, animal protein, and saturated fat; it was negatively associated with percent of calories from complex carbohydrate and total carbohydrate (Kato et al. 1973). Multivariate analysis controlling for age, relative weight, systolic blood pressure, serum cholesterol, and cigarette smoking showed CHD incidence after 6 years to be inversely related to alcohol, starch, and caloric intake per kilogram of body weight (Gordon et al. 1981). Followup of the Honolulu cohort after 10 years showed that percentage of calories from fat, saturated fat, and dietary cholesterol was related directly to CHD mortality, although percentage of calories from fat was inversely related to total mortality, cancer mortality, and stroke mortality (McGee et al. 1985).

The Western Electric Study examined diet, serum cholesterol, and other variables in 1,900 middle-aged men, who were examined at entry, 1 year later, and 20 years later. Changes in the intake of saturated fat and dietary cholesterol between entry and 1-year visits were positively related to change in the level of serum cholesterol. The dietary data collected at the first two visits were averaged to provide baseline estimates of intake for the followup study analysis. Results showed that the 19-year risk for death from CHD was inversely related to polyunsaturated fat intake and positively related to dietary cholesterol intake. These correlations persisted after adjustment for baseline serum cholesterol, body mass index, systolic pressure, cigarette smoking, monthly alcohol intake, and age (Shekelle et al. 1981). After 25 years of followup, dietary cholesterol was

still positively and independently related to risk for death from CHD (Shekelle and Stamler 1988).

The Ireland-Boston Heart Study reported within-population analyses showing that individuals who died of CHD had a higher intake of saturated fatty acids and cholesterol and a lower intake of polyunsaturated fatty acids. Mean total fat intake was higher (39.4 percent vs. 38.5 percent) in the group who died of CHD, but the difference was not statistically significant. Fiber intake was significantly lower among those who died of CHD (Kushi et al. 1985).

Although these epidemiologic studies have shown that diet, particularly the amount and type of fat in the diet, influences the level of plasma cholesterol, other studies of individuals within populations, such as Framingham, Tecumseh, and Evans County, have failed to find any association of diet with plasma cholesterol or CHD (Kannel and Gordon 1970; Nichols et al. 1976; Cassel 1971; Gordon et al. 1981).

Difficulties in establishing a consistent correlation between diet and plasma cholesterol in individuals within a given population (short of such extremes as comparing vegetarians with the general public) have been attributed to several factors. First, most methods used for measuring habitual dietary patterns in free-living populations have a high degree of technical error (Bingham 1982). Daily variability in dietary intakes of individuals is greater than the variability among individuals. Hence, methods that measure dietary intake only over 1 day, as was done in Puerto Rico (Garcia-Palmieri et al. 1980), Honolulu (Kato et al. 1973), and Tecumseh (Nichols et al. 1976), can result in considerable misclassification of individuals on the basis of long-term dietary patterns (Liu et al. 1978).

Intake of fat, especially saturated fat, and cholesterol tends to be uniformly high in Western industrialized countries. Under such circumstances, possible fallacies may arise (Rose 1985). If nearly everyone in a population is exposed to a causal agent such as smoking or high saturated fat intake, then the presence of disease in an individual will appear to be attributable to individual genetic and personal characteristics, and traditional case-control and cohort methods will fail to identify the causal agents. Under these circumstances, causal agents are better revealed by differences between populations or by contrasting changes within populations over time (Rose 1985).

Other problems arise from the variability and error in measurement of factors such as plasma cholesterol. These difficulties weaken considerably

any attempt to correlate diet with other CHD indices (Liu et al. 1978). Conversely, epidemiologic correlations based on group averages of populations, such as the international comparisons cited earlier, tend to overestimate the true effect (McGill, McMahn, and Wene 1981). Thus, the true contribution of diet to plasma cholesterol levels probably lies somewhere between the estimates obtained in comparisons between groups and between individuals within a group.

#### Animal Studies

Animal models extend the observations made in humans by providing opportunities to explore directly mechanisms by which dietary factors mediate the development, progression, and regression of atherosclerotic lesions. Such studies often cannot be done in humans because the disease develops slowly over a long period of time, and techniques to measure the severity of the disease carry risk and have technical limitations. The advantages and disadvantages of the use of various animal models in atherosclerosis research have been reviewed (Jokinen, Clarkson, and Prichard 1985). Because no single animal model can duplicate the range of human arterial lesions that develop over long periods of time, several animal species have been used, depending on the mechanism to be investigated. These species vary in the natural occurrence and sensitivity to induction of experimental atherosclerosis.

Hyperlipidemia, which leads to the development of atherosclerosis, is readily produced in rabbits, pigeons, chickens, turkeys, Japanese quail, pigs, and some nonhuman primates by feeding diets high in cholesterol and saturated fats. Dogs and rats have generally been considered to be resistant to both naturally occurring and experimentally induced atherosclerosis, although, even in these species, advanced atherosclerotic lesions have been produced by adding to the diet cholesterol and coconut oil (dogs) and cholesterol and cholic acid (rats). Of all the animal models, many breeds of pigs and several species of nonhuman primates tend to resemble humans most closely in lipoprotein patterns and the pathologic components of the lesion (Jokinen, Clarkson, and Prichard 1985).

For example, studies in miniature pigs fed hog chow supplemented with cholesterol and either lard or beef fat showed elevations in plasma cholesterol. Myocardial infarctions were observed, and the diet-induced atherosclerosis was very similar to the proliferative lesions of human atherosclerosis. As in humans, individual variability in response to diet was observed (Mahley 1979).

Nonhuman primates have several characteristics that make them valuable as animal models: They are phylogenetically close to human beings; they develop arterial lesions similar to those seen in humans; and dietary manipulation can produce hyperlipidemia that, in some species, resembles that of humans. Some nonhuman primates develop atherosclerosis in their natural habitat, but their lesions are minimal compared with monkeys that consume diets like humans consume in Western societies. Both human and nonhuman primates are variable in their response to dietary cholesterol and subsequent amount of atherosclerosis that develops. Atherogenic diets—high in saturated fatty acids and dietary cholesterol—have reportedly been associated with myocardial infarction in rhesus monkeys and cynomolgus monkeys (Jokinen, Clarkson, and Prichard 1985). Baboons are apparently relatively resistant to diet-induced hyperlipidemia in comparison with other nonhuman primates and rabbits (McGill, McMahn, Kruski, Kelley, et al. 1981), but they develop experimental atherosclerosis, which is positively associated with LDL cholesterol concentrations and inversely associated with HDL cholesterol concentrations (McGill, McMahn, Kruski, and Mott 1981).

Although much of the diet-induced atherosclerosis in animals has been achieved with extreme diets and is thus not directly applicable to humans, some studies illustrate the effects of more moderate diets. Rhesus monkeys fed diets resembling the typical American diet compared with those fed a “prudent” ration reduced in calories, cholesterol, fat, and saturated fat had much higher cholesterol levels and more frequent and more severe atherosclerotic lesions. The lesions seen in the animals fed the average American regimen resembled those seen in autopsy examination of the coronary arteries and aorta of young adult Americans (Wissler et al. 1983). Cholesterol feeding of rhesus monkeys—at levels that do not elevate plasma cholesterol above those achieved on a cholesterol-free diet—may also stimulate atherosclerosis (Armstrong, Megan, and Warner 1974).

Regression of diet-induced atherosclerosis by the reduction of serum cholesterol to normal levels has been demonstrated in pigs, dogs, fowl, and nonhuman primates (Vesselinovitch and Wissler 1978). Extensive investigation of lesion regression has been conducted in rhesus monkeys. Over a dozen studies in at least five centers found that lesions undergo substantial regression on cholesterol lowering regimens (Wissler and Vesselinovitch 1984; Malinow et al. 1983). Rhesus monkeys fed rations containing 25 percent peanut oil and 2 percent cholesterol or 25 percent coconut oil-butter fat and 2 percent cholesterol for 12 to 14 months developed severe

hyperlipidemia and aortic and coronary artery atherosclerosis typical of advanced atherosclerosis in humans (Vesselinovitch and Wissler 1978). A subsequent change to a 12- to 14-month diet in which calories, cholesterol, and fat were reduced to resemble levels recommended by the American Heart Association resulted in a prompt and sustained low serum cholesterol level and a substantial arrest and reversal of advanced aortic and coronary atherosclerosis. Similar evidence of regression was seen when cholestyramine was added either to the low-fat, low-cholesterol diet or to the atherogenic diet.

Regression of atherosclerosis has also been demonstrated in swine. Advanced atherosclerosis was produced by a combination of mechanical injury and a 4-month high-cholesterol, high-fat diet. Fourteen months after the animals were returned to their normal mash diet, significant regression had occurred (Fritz et al. 1976).

A new animal model for endogenous hypercholesterolemia has become available through the discovery of a strain of rabbits designated Watanabe heritable hyperlipidemic (WHHL). In these animals, severe hypercholesterolemia results from a single genetic defect, and fulminant atherosclerosis occurs despite the ingestion of a cholesterol-free diet. The WHHL rabbit has the same defect in the LDL receptor gene that occurs in persons with familial hypercholesterolemia (Goldstein, Kita, and Brown 1983).

#### Effects of Fatty Acids on Thrombosis

Because atherosclerosis is a multifactorial disease, diet may have effects on CHD that are not mediated through plasma cholesterol and lipoprotein levels. Arterial thrombosis is induced by vascular injury and the response of blood platelets. Dietary studies have shown that platelet reactivity is associated with the fatty acid composition of the diet.

Epidemiologic studies in France and Great Britain (Renaud 1987) have shown that clotting activity of platelets and their response to thrombin-induced aggregation were more closely related to the intake of saturated fatty acids than to serum cholesterol levels. Intervention studies also show that replacement of dietary saturated fat with polyunsaturated vegetable oils is associated with decreased platelet aggregation and clotting activity (Hornstra 1980; Renaud 1987). In animal studies, most saturated fatty acids were found to induce platelet aggregation and arterial thrombosis and to increase plasma cholesterol levels, whereas unsaturated fatty acids tended to reduce platelet aggregation and also tended to lower plasma cholesterol levels (Goodnight et al. 1982).

While long-chain saturated fatty acids tend to induce thrombosis in animal studies, long-chain unsaturated dietary fats are either neutral or antithrombotic. In rats, the most thrombogenic fatty acid is stearic acid (Renaud 1969) despite its apparent neutral effect on serum cholesterol (Keys 1967; Bonanome and Grundy 1988). One study in rats showed that palm oil (containing about 50 percent saturated fat) was similar to polyunsaturated vegetable oils in thrombotic tendency. The reasons for this anomaly are not clear but might be related to some other constituents in palm oil that counteract the thrombogenic properties of the saturated fatty acids (Hornstra and Lussenberg 1975). Oleic acid, the major dietary monounsaturated fatty acid, seems to have little or no effect on thrombosis (Goodnight et al. 1982). The mechanisms by which dietary fatty acids may affect thrombosis are poorly understood but may be related to prostaglandin metabolism (Goodnight et al. 1982).

Linoleic acid, the most common dietary polyunsaturated fatty acid, is the precursor of arachidonic acid and prostaglandins that regulate platelet aggregation and, accordingly, thrombogenesis. Prostacyclin ( $\text{PGI}_2$ ), for example, has been shown to be the most potent *in vivo* vasodilator and antiaggregatory agent in animals and in humans, and to inhibit white cell adherence to vessel walls, nylon fibers, and endothelial monolayers *in vitro* (Moncada 1982). Its effects are counterbalanced by another prostaglandin, thromboxane  $\text{A}_2$ , a powerful vasoconstrictor and platelet aggregator. It is theorized that arterial thrombosis may depend partly on the ratio between these two prostaglandins.

Linoleic acid is also incorporated directly into membrane phospholipids, thereby altering the structure and the function of the platelet membrane. This process affects the fluidity and, therefore, the permeability of the cells and influences processes including thrombus formation. Contrary to expectation, increasing the dietary intake of linoleic acid does not increase the synthesis of arachidonic acid in platelet membranes, perhaps because of competitive inhibition of certain enzymes. Increased dietary intake of linoleic acid, however, has been associated in humans with significant reduction in platelet aggregability (Hornstra et al. 1973; Jakubowski and Ardlie 1978).

**Fish Oils.** The consumption of fish and other marine animals may confer special benefits in reducing CHD mortality (Kromhout, Bosschieter, and Coulander 1985). The fatty acids in these species are rich in long-chain polyunsaturated fatty acids of the omega-3 series, particularly eicosapentaenoic acid and docosahexaenoic acid. Most polyunsaturated fatty acids commonly found in vegetables belong to the omega-6 series. The differ-

ences in chemical structure between omega-3 and omega-6 fatty acids affect several metabolic processes related to blood platelet function, thrombosis, and lipid metabolism that may relate to CHD.

Early observations in Greenland suggested that Eskimos who habitually consumed large quantities of fish and other marine animals had a low incidence of CHD despite a high fat and cholesterol intake (Kromann and Green 1980; Dyerberg and Jorgensen 1982). Similar observations have been made in other maritime communities (Kagawa et al. 1982; Yotakis 1981). Subsequent examinations of Greenland Eskimos showed that they have lower serum triglycerides and cholesterol levels and higher HDL levels than Danes consuming a Western-type diet. The blood of Eskimos also takes longer to clot. It has been hypothesized that the low incidence of atherosclerosis and thrombosis in Greenland Eskimos is partly attributable to the high proportion of omega-3 fatty acids in traditional Eskimo diets (Dyerberg and Jorgensen 1982).

A recent prospective study of Dutch men showed that 20-year mortality from CHD was reduced by 50 percent in men who consumed at least 1 oz of fish per day (Kromhout, Bosschieter, and Coulander 1985). Whether the benefit shown in this study can be attributed to omega-3 fatty acid intake or to some other factor associated with fish consumption is uncertain. Men who consumed low-fat fish derived the same benefit as those consuming higher fat varieties. The effect of fish consumption on CHD mortality has been examined in other large prospective studies. One found no relationship (Vollset, Heuch, and Bjelke 1985). In another, fish consumption at entry into the study was inversely associated with 25-year risk of CHD (Shekelle et al. 1985), and in the third study, CHD death rate was higher in the group that consumed no fish compared with the group that consumed fish (Curb and Reed 1985).

Early clinical experiments in which different sources of fat were given showed that fish oils were at least as effective as polyunsaturated vegetable oils in reducing serum cholesterol levels. More recently, fish oils have been studied in relation to their effects on lipoprotein metabolism and other CHD parameters. Clinical studies in normal volunteers and patients with hypertriglyceridemia who were fed diets enriched in omega-3 fatty acids generally showed variable reductions in total cholesterol and LDL cholesterol. In some cases, LDL increased; HDL levels were either unchanged or increased (Phillipson et al. 1985; von Lossonczy et al. 1978). The most consistent and striking effect of fish oil on lipoprotein metabolism has been a reduction in triglyceride and VLDL levels, an effect not observed with vegetable oils (von Lossonczy et al. 1978; Saynor, Verol, and Gillott 1984; Harris and Connor 1980; Nestel et al. 1984).



Most experimental studies have used rather large amounts of fish (200 to 300 g/day) or fish oil (more than 20 g/day). One study sought to determine the effects of more moderate fatty fish consumption. One hundred male volunteers each consumed 3 oz or more of fatty fish at least twice a week for 3 months and little or no fatty fish for another 3 months. Mean plasma triglyceride concentration decreased significantly, by nearly 7 percent, on the fish diet. There were no significant changes in plasma total cholesterol, HDL, or LDL (Fehily et al. 1983).

Another line of investigation involves studies on the effects of fish oils on the vessel wall. A 6-week study in seven healthy men indicated that diets supplemented with 18 g of fish oil per day may have anti-inflammatory properties that could diminish infiltration of lipids in the vessel wall in response to tissue injury (Lee et al. 1985).

In another study, the effect of cod liver oil on the development and progression of atherosclerosis in a hyperlipidemic swine model was assessed. All animals were fed an atherogenic diet, 7 were given a cod liver oil supplement, and 11 controls did not receive the supplement. Significantly less disease was seen in coronary arteries from the animals fed cod liver oil despite severe hyperlipidemia. Differences in the extent of coronary atherosclerosis were not related to differences in plasma lipid levels. Prostaglandin synthesis from arachidonic acid was markedly reduced in the oil-fed group (Weiner et al. 1986).

### **Role of Other Dietary Factors in CHD**

#### **Obesity**

Obesity is associated with many important CHD risk factors such as hypertension, low levels of HDL, elevated plasma glucose levels, high blood cholesterol, and hypertriglyceridemia (see chapter on obesity) and hence increases the risk for CHD. Data from the Framingham Heart Study, in which 5,209 men and women were observed for 26 years for the development of CHD, showed that relative weight was a significant independent long-term predictor of CHD incidence, especially in women (Hubert et al. 1983). The association of weight with CHD incidence was most pronounced in those under age 50. Weight gain in adulthood conveyed an added risk. Total calorie consumption has been associated with CHD prevalence in international comparisons. However, studies within populations have shown that a greater caloric intake is associated with a reduced risk for CHD, but increased body weight is associated with increased CHD risk. This suggests that increased energy expenditure, which would tend to increase caloric requirements, may be related to reduced risk for CHD

(Gordon et al. 1981). Current evidence suggests that leanness and avoidance of weight gain before middle age are advisable goals in the prevention of CHD for most men and women (Hubert et al. 1983; Bray 1983). In addition, weight loss often improves the status of other risk factors such as diabetes and high blood pressure (see respective chapters).

#### Alcohol

The relationship between alcohol consumption and CHD is complex (Hulley and Dzvonik 1984). High alcohol intake has been associated with CHD deaths, as well as deaths from other causes (see chapter on alcohol), but some epidemiologic studies have shown an association between light to moderate alcohol intake and a decreased incidence of CHD (LaPorte, Cresanta, and Kuller 1980). In these studies, light intake is generally considered to be more than one drink per month but fewer than one per day and moderate intake is 1 to 3 oz per day. Numerous cross-sectional studies have shown positive correlations of alcohol intake with HDL cholesterol levels (Castelli et al. 1977), with the response related to doses of alcohol ranging from 0 to 3 oz per day (Ernst et al. 1980; Haskell, Camargo, and Williams 1984). Thus, it has been postulated that the decreased incidence of CHD in those who consume moderate amounts of alcohol might be attributable to an ethanol-induced increase in HDL cholesterol levels. Recent reports suggest, however, that moderate alcohol consumption induces compositional changes in HDL that are inconsistent with current understanding of the anti-atherogenic properties of HDL subfractions, because it increases HDL-3 levels but not those of the antiatherogenic HDL-2 subfractions (Haskell, Camargo, and Williams 1984). The significance of alcohol-induced changes in apoprotein fractions (Camargo et al. 1985) is also uncertain. Since heavy drinking has numerous adverse effects, including several on the cardiovascular system (Burch and Giles 1971), the use of alcohol, even in moderate quantities, for its possible beneficial effects on CHD is not recommended.

#### Carbohydrate

Major dietary carbohydrates include starch, fiber, and sugars. Customary diets containing 60 to 70 percent of calories from starch, such as those consumed in Asian countries, are associated with low plasma cholesterol levels and a low risk for CHD (Keys 1970). Such diets tend to be relatively high in fiber and very low in fat and thus have been widely advocated for the treatment of hypercholesterolemia. Epidemiologic studies cited previously have shown that intake of starch (Gordon et al. 1981) and intake of fiber (Kushi et al. 1985) were negatively related to CHD. Furthermore, the effect of starch did not appear to be an indirect effect of lowered fat intake. On the

other hand, total carbohydrate was inversely associated with HDL cholesterol—and positively associated with LDL cholesterol—in cross-sectional studies, but these correlations were very weak (U.S.–U.S.S.R. Steering Committee 1984). Some experimental studies have shown that hypertriglyceridemia can be induced with high-starch (70 percent of calories) diets, but the effect is temporary and appears to occur mainly after changing from a high-fat to a high-carbohydrate diet (Little, McGuire, and Derksen 1979; Ahrens 1986).

The water-soluble fiber fractions, as found in oat bran, guar gum, psyllium seeds, certain beans, and pectin, for example, have been shown to have hypocholesterolemic effects in humans (Jenkins et al. 1975; Kirby et al. 1981; Anderson et al. 1984). Addition of fiber to high-carbohydrate diets has been reported to prevent triglyceride elevation on high-carbohydrate diets (Anderson, Chen, and Sieling 1980). A high fiber intake is often associated with low-fat diets, and the net effect may provide additional benefits in cholesterol reduction.

The role of sugars in CHD is unclear. A high sucrose intake has been claimed to play a causal role in CHD (Yudkin and Roddy 1964), but there is little evidence to sustain this view. Although some animal studies have suggested that substitution of sucrose for other sources of calories increases atherogenesis, the major epidemiologic studies of diet and CHD risk have failed to identify an association with sucrose intake (Glinsmann, Irausquin, and Park 1986). Sucrose and fructose have been shown experimentally to promote hypertriglyceridemia in susceptible (carbohydrate-sensitive) individuals. Men appear to be more susceptible than premenopausal women, older persons more than younger persons, and hypertriglyceridemic persons more than normal triglyceridemic persons (Reiser et al. 1981; Coulston et al. 1987). Recommended treatment for patients with elevated plasma triglyceride and VLDL levels includes weight control, alcohol restriction, increased physical activity, and restriction of saturated fat and cholesterol. Substitution of carbohydrate for fat is favored; although increasing dietary carbohydrate may raise triglycerides, the response is usually transient and triglyceride levels (and VLDL) later decline (NIH 1983).

#### Protein

In animals, high protein levels accelerate the formation of atheromatous lesions. Casein appears to be more atherogenic than soy protein (Kritchevsky 1979). Recent studies on rabbits showed that LDL receptors were suppressed after feeding a cholesterol-free diet composed of carbohydrate and casein (Goldstein, Kita, and Brown 1983). The low levels of plasma

cholesterol observed among strictly vegetarian populations (West and Hayes 1968) may be attributable to the quantity and quality of protein. However, their diets also tend to be lower in saturated fat and cholesterol and higher in complex carbohydrate and fiber than diets of lacto-ovo vegetarian or nonvegetarian groups (Sacks et al. 1985; Sacks et al. 1975; Burslem et al. 1978). Studies involving the substitution of soy protein and other vegetable proteins for animal protein in the diets of hyperlipidemic patients have shown a marked reduction in serum cholesterol levels (Descovich et al. 1980; Sirtori, Gatti, and Mantero 1979) but only a small change in persons with normal plasma cholesterol levels (Forsythe, Green, and Anderson 1986). The mechanism for these effects has not been established.

### Coffee

Evidence relating coffee consumption to increases in serum total and LDL cholesterol levels or to CHD has been inconsistent. Recent reports from cross-sectional epidemiologic studies in Norway, Israel, and the United States have shown an independent, positive, linear association with serum cholesterol, nearly all of which can be accounted for by LDL cholesterol (Thelle, Arnesen, and Forde 1983; Kark et al. 1985; Williams et al. 1985). One study associates coffee drinking (five or more cups per day) with increased risk for CHD (LaCroix et al. 1986). The effect of coffee drinking on serum cholesterol has also been examined in controlled experiments. Coffee taken in amounts of six cups or more per day has been reported to increase serum cholesterol levels (Arnesen, Forde, and Thelle 1984). Decaffeinated coffee has also been reported to be associated with such elevations in some studies (Naismith et al. 1970), although not all (Mathias et al. 1985); in most studies, tea did not affect blood cholesterol levels (Prineas et al. 1980; Little et al. 1966; Kark et al. 1985). Such findings would appear to rule out caffeine as a causal factor (Klatsky et al. 1985). Other studies have found no association between coffee and cholesterol (Kovar, Fulwood, and Feinleib 1983) or different effects in men and women (Shirlow and Mathers 1983). Inconsistencies in the results of different studies have been attributed to confounding effects of cigarette smoking and diet as well as to variations in method of preparation. At present, the information regarding the relationship between coffee intake and blood cholesterol levels is insufficient to allow conclusions to be drawn.

### Vitamins and Minerals

The relationship of micronutrients (vitamins and minerals) to cardiovascular disease risk has been studied to a much lesser extent than the macronutrients, except in the case of sodium and hypertension (see chapter on high blood pressure). Although dietary patterns that promote high plasma cho-

lesterol levels would be expected to be different in micronutrient content from dietary patterns associated with low plasma cholesterol levels, there is at present no strong evidence linking vitamin and mineral intake to high plasma cholesterol levels or to CHD.

*Vitamin E.* Vitamin E was once widely advocated for prevention and treatment of CHD (Shute and Taub 1972). Early studies supporting these claims were marred by lack of controls and doubtful diagnosis of CHD, and subsequent studies have failed to confirm them (Hodges 1979).

*Vitamin C.* Vitamin C (ascorbic acid) deficiency results in scurvy, which is sometimes associated with cardiac abnormalities. Observations that high doses of ascorbic acid reduce serum cholesterol in cholesterol-fed rabbits and guinea pigs have led to the idea that high doses of vitamin C might reduce blood cholesterol levels in patients with elevated levels. To date, uncontrolled clinical trials have yielded conflicting results, and there is no convincing evidence that vitamin C is related to CHD (Hodges 1979; Anonymous 1984).

*Thiamin.* Thiamin deficiency leads to beriberi, and congestive heart failure is associated with the "wet" form of this disease. Cardiac impairment is generally completely reversible with appropriate administration of thiamin. Thiamin deficiency is uncommon in the United States today, largely because of effective food enrichment programs. Nevertheless, inadequate intakes are sometimes observed among persons with faulty dietary patterns or among hospitalized patients who have been ill for prolonged periods (Hodges 1979).

*Niacin.* Niacin (nicotinic acid) in pharmacologic (large) doses far in excess of its requirements for vitamin function exerts HDL-raising and lipid-lowering effects, principally in the VLDL fraction (Fredrickson and Levy 1972). The long-term followup of patients treated with niacin in the Coronary Drug Project (as mentioned in the section on Efficacy of Dietary Interventions in CHD) showed significant reduction in coronary and total mortality. In a recent study, nicotinic acid in combination with colestipol and a cholesterol-lowering diet slowed progression of coronary artery lesions in men who had undergone coronary bypass surgery (Blankenhorn et al. 1987). There is no evidence, however, that niacin ingested at physiologic levels exerts any protective effect against factors that elevate blood lipid levels.

*Calcium.* High serum cholesterol levels have been observed in calcium-deficient rats, and calcium-deficient rabbits and rats fed an atherogenic diet

significantly increased their serum cholesterol and triglyceride levels over control animals fed a stock ration. Supplementation of experimental diets with calcium reduced the plasma lipid levels to near or below the levels of the control group but also was associated with increased incidence of kidney and heart lesions (Mertz 1979). In humans, an uncontrolled study of 10 hyperlipidemic subjects showed that the addition of 800 mg of calcium (as calcium carbonate) daily over 1 year reduced blood cholesterol levels by 25 percent, and another uncontrolled study in older women showed that 750 mg of daily calcium supplementation reduced cholesterol levels 36 mg/dl from a mean 266 mg/dl (Mertz 1979). Such observations remain to be confirmed by controlled clinical trials. The possible role of calcium continues to be a subject of investigation (Renaud 1987).

*Magnesium.* Magnesium therapy may correct some cardiac arrhythmias, although it is uncertain whether magnesium deficiency causes them (Laban and Chorbon 1986). Magnesium and calcium may interact with dietary fat in the promotion of atherosclerotic lesions. In animals, the increased incidence of kidney and heart lesions associated with very high intake of calcium is reduced or eliminated by high levels of dietary magnesium. This protective effect, however, was evident only at very high dietary calcium levels (0.6 percent by weight) and only in the presence of elevated serum cholesterol (Mertz 1979).

*Copper.* Copper deficiency has been associated with cardiovascular damage and abnormalities in cholesterol metabolism in animals. In one human study, copper deficiency was shown to produce a rise in plasma cholesterol concentrations, perhaps because copper is a cofactor for enzymes involved in cholesterol synthesis and lipoprotein degradation (Klevay et al. 1984).

*Zinc.* Because dietary zinc increases the copper requirement (Sandstead et al. 1982), it has been postulated that a high ratio of zinc to copper in the modern American diet could be a risk factor for CHD (Klevay 1975). Long-term zinc supplementation in children, however, has not been associated with any detectable rise in plasma cholesterol levels (Mertz 1979). Although administration of high-dose zinc supplements has been reported to reduce blood levels of HDL cholesterol in human subjects (Hooper et al. 1980), more physiologic doses had no effect on blood lipid values (Crouse et al. 1984).

*Selenium.* In China, very low levels of dietary selenium have been associated with juvenile cardiomyopathy (Chen et al. 1980). Although a causal role has not been firmly established, epidemiologic studies have also suggested a role for selenium deficiency in CHD. Cardiovascular disease

mortality rates are significantly lower in areas of the United States with high selenium soils. In Sweden, the lowest death rate from cardiovascular diseases was reported in the city of Malmö, which has a higher selenium content of tap water than Stockholm or Gothenburg. Other studies, however, have failed to demonstrate any differences in selenium concentrations in serum and urine of patients with hypertension or in the coronary arteries of persons who died from myocardial infarction and atherosclerosis as compared with control groups (Thomson and Robinson 1980).

Human platelets contain more selenium than other human tissues, suggesting that selenium deficiency may affect thrombosis. Experimental selenium deficiency reduces platelet antioxidant activity, and this activity is restored by selenium supplementation (Levander 1982).

A low serum selenium concentration has been associated with increased clinical manifestations of CHD in a prospective study in Finland (Salonen et al. 1982), yet a subsequent longitudinal case control study in another Finnish population showed that levels of selenium in blood were highly correlated to blood levels of eicosapentaenoic acid. Because fish is a major source of selenium in the Finnish diet, it is difficult to distinguish the antiatherogenic effects of selenium from those of polyunsaturated fatty acids in these studies (Miettinen et al. 1983).

### **Efficacy of Dietary Intervention in CHD**

Clinical studies in free-living populations over long periods of time have been conducted to determine the potential of dietary change to influence blood cholesterol and CHD. In general, large-scale diet studies have achieved 10 to 15 percent blood cholesterol reductions (Rifkind et al. 1983), compared with about 25 percent in controlled metabolic ward studies, probably because of less rigorous adherence to the diet. For example, the *National Diet-Heart Study*, in which the experimental diets contained either 30 percent fat with 15 percent polyunsaturated fatty acids or 40 percent fat with 18 to 20 percent polyunsaturated fatty acids, showed that reductions in serum cholesterol were proportional to the degree of adherence to the diets and that excellent adherence produced an average serum cholesterol reduction of about 13 percent in free-living adults (National Diet-Heart Research Group 1968). The *Oslo Study* achieved 13 to 15 percent reductions (Hjermann et al. 1981).

The *Multiple Risk Factor Intervention Trial* (MRFIT) was a randomized primary prevention trial to test the effect of a multifactor intervention program on CHD mortality in 12,866 men in the upper 10 percent of risk on

account of their levels of cigarette smoking, blood cholesterol, and blood pressure. It resulted in a 5 percent reduction in blood cholesterol in the special care (diet and other intervention) group and 3 percent in the usual care group, suggesting that many people were making changes in their diets even in the absence of direct intervention (MRFIT Research Group 1982). The results of this study were further complicated because of the cholesterol raising effect of diuretics in the hypertensive group and because the men who stopped smoking were less successful in weight control than the men who continued to smoke. Greater reductions in cholesterol were achieved among MRFIT men with elevated cholesterol who were nonhypertensive and nonsmokers over the 6-year intervention trial (Dolecek et al. 1986).

The impact of dietary-induced cholesterol lowering on CHD incidence has also been assessed in several other clinical trials. They have generally reported some reduction in CHD incidence and, taken together, have shown a consistent relationship between degree of cholesterol lowering and CHD risk reduction (Mann and Marr 1981). However, the ability to draw definite conclusions from such trials is made difficult by problems such as small sample size, failure to randomize subjects into treatment and control groups, failure to mask treatment assignment (a pervasive and essentially insoluble problem in all large-scale diet studies), and inadequate followup (Cornfield and Mitchell 1969), as well as the type of problems cited above in the MRFIT.

*The Finnish Mental Hospital Study* was a trial conducted in two hospitals, one of which replaced whole milk and butter with a skim milk emulsion containing soy oil and a high polyunsaturated margarine while the other retained the usual diet. After 6 years, the diets were reversed, and the study continued an additional 6 years. The study involved the total hospital population in each site and encompassed 29,217 person-years of experience. Results showed that mean serum cholesterol values were reduced 12 to 18 percent and that death rates from all cardiovascular diseases for men and women were 39 percent and 14 percent lower, respectively, on the experimental diet. All-cause mortality for men was 12 percent lower on the experimental diet, but for women it was similar on both diets (Miettinen et al. 1972). The authors attribute the findings in women to an exceptionally low death rate experienced in one hospital during the control period following transfer of chronic cases to another hospital.

The dietary trial conducted in a *Veterans Administration domiciliary facility* in Los Angeles used a double-blind experimental design in which 846 middle-aged and older male participants were randomly assigned to either a control or a cholesterol-lowering diet group. Although the results



suggested that a diet low in saturated fats and cholesterol and high in polyunsaturated fats reduced coronary events, the experimental and control groups did not differ in overall mortality (Dayton et al. 1969). The excessive mortality rate from cancer observed at first in the intervention group has been reinterpreted, and subsequent analysis of the data and those of four similar trials has found no association of cholesterol-lowering diets with any increase in either cancer incidence or mortality rate (Ederer et al. 1971).

*The Oslo Study* was a primary prevention trial designed to test whether lowering serum lipids by dietary measures and smoking reduction would reduce incidence of new CHD in 1,232 high-risk participants studied over 5 years. The dietary intervention consisted of advice to substitute polyunsaturated fats for saturated fat, to increase intake of whole grain cereals, and to reduce energy intake (in cases of elevated triglyceride levels). At the completion of the trial, mean serum cholesterol levels were reduced 13 percent in the intervention group, and the combined incidence of myocardial infarction and sudden death was significantly reduced in the treated group by 47 percent compared with controls. Statistical analysis identified the predominant effect as the decrease in plasma total cholesterol by diet (Hjermann et al. 1981).

It is widely accepted that diet is a major cause of high blood cholesterol and high LDL levels and that these play a causal role in atherosclerosis. Evidence from animal-experimental studies has shown that reducing diet-induced hypercholesterolemia, whether by diet or other means, reverses the atherosclerotic process. The consistency of these studies supports the conclusion that blood cholesterol lowering *per se* rather than a specific action of the cholesterol-lowering agent produces the benefit. Hence, consideration of evidence from the clinical trials using drugs to lower cholesterol is relevant to assessment of the efficacy of dietary intervention to lower CHD risk.

*The Coronary Drug Project* assessed the long-term efficacy of five lipid-influencing drugs in 8,341 middle-aged men. Treatment with niacin significantly decreased nonfatal recurrent myocardial infarction but not coronary mortality during the treatment phase of the study (Canner et al. 1986). However, followup at 9 years beyond the study demonstrated that total mortality was reduced in the niacin-treated group.

*The Lipid Research Clinics Coronary Primary Prevention Trial* (LRC-CPPT) was a double-blind placebo-controlled clinical trial in high-risk middle-aged men to test the efficacy of lowering cholesterol levels for the

primary prevention of CHD. The LRC recruited 3,806 men with primary hypercholesterolemia, free of symptomatic CHD at entry, but at high risk for CHD due to elevated LDL cholesterol levels. The study participants were randomly assigned to two groups that were similar in baseline characteristics. The treatment group received the bile acid sequestrant cholestyramine, and the control group received a matched placebo. Although the LRC-CPPT was not designed as a dietary intervention trial, both groups followed a diet plan calculated to achieve a 3 to 5 percent reduction in plasma cholesterol. A net reduction in plasma cholesterol of 9 percent in the treatment group resulted in a 19 percent reduction in fatal and nonfatal myocardial infarctions. Corresponding reductions in angina pectoris, electrocardiographic abnormalities, and bypass surgery were also found in the treatment group (Lipid Research Clinics Program 1984a, 1984b).

The *Helsinki Heart Study* reported substantial benefit in reducing the incidence of CHD by drugs (Frick et al. 1987). The study was a randomized double-blind placebo-controlled primary prevention trial involving 4,081 middle-aged men in a 5-year followup. To qualify, participants had to have LDL plus VLDL cholesterol concentrations equal to or greater than 200 mg/dl. Treatment with gemfibrozil resulted in several changes in plasma lipids: modest (8 percent) reductions in total and LDL cholesterol, a more pronounced (35 percent) decrease in triglycerides, and a moderate (greater than 10 percent) increase in HDL cholesterol. At the end of 5 years, nonfatal myocardial infarction alone was reduced by 37 percent and CHD mortality alone by 26 percent. These results were obtained despite an incidence of CHD in the placebo group that was considerably lower than expected. Total mortality, however, was not significantly affected.

Another approach to assessing benefit of cholesterol lowering is to measure changes in atherosclerotic lesions. Early studies in nonhuman primates demonstrated regression of atherosclerotic lesions with cholesterol-lowering diets or with drugs (Armstrong, Warner, and Connor 1970; Wissler and Vesselinovitch 1984). The effect of cholesterol lowering on coronary arteries can now be assessed with serial angiograms in humans.

In the *Leiden Study*, 39 men with stable angina pectoris and advanced arteriosclerosis, as assessed by coronary angiography, were prescribed a vegetarian diet containing a polyunsaturated-to-saturated-fatty-acid ratio of 2, and dietary cholesterol of less than 100 mg/day. Mean serum cholesterol decreased 10 percent from a baseline value of 267 mg/dl. Since there was no control group, the effect of dietary intervention could not be assessed directly. However, angiographic examination performed after 24 months showed no progression of disease in the group that had maintained lower

values for the ratio of total cholesterol to HDL cholesterol throughout the trial or who significantly lowered their ratio of total cholesterol to HDL cholesterol (Arntzenius et al. 1985).

Another double-blind placebo-controlled trial, the *NHLBI Type II Coronary Intervention Study*, evaluated the efficacy of reduction in cholesterol levels induced by cholestyramine on progression of coronary artery disease. The rate of progression, defined angiographically, was compared in patients treated with cholestyramine plus diet with that of patients treated with placebo plus diet. When the relationship between coronary artery disease progression and lipid changes was examined independent of a specific treatment group, a significant inverse relationship was found between progression at 5 years and the combination of an increase in HDL and a decrease in LDL. These trends were observed in both the placebo-treated and the cholestyramine-treated group (Levy et al. 1984).

The *Cholesterol-Lowering Atherosclerosis Study (CLAS)* was a randomized placebo-controlled angiographic investigation of the ability of drugs (colestipol and niacin) and diet to reduce blood cholesterol levels and to cause regression of atherosclerosis in the coronary arteries. Participants were 162 men who had undergone coronary bypass surgery. The study reported 26 and 43 percent reductions in total blood cholesterol and LDL, respectively, in the treatment plus diet group compared with 4 and 5 percent reductions, respectively, in the placebo plus diet group. There was also a considerable increase in HDL and considerable decrease in triglycerides in the drug plus diet group. These changes were associated with significantly less progression of overall coronary disease in both the grafts and the native coronary arteries with some suggestive evidence of regression (Blankenhorn et al. 1987).

Despite some deficiencies in definition of lesions, control groups, and small numbers of patients, these coronary angiographic studies support the benefit of intervening with blood cholesterol reduction in the presence of established disease.

#### Aggregate Analysis of Clinical Trials of Blood Cholesterol Lowering

Many of the clinical trials of blood cholesterol lowering to prevent CHD have been hampered by small numbers and modest cholesterol lowering (Mann and Marr 1981; Oliver 1985). However, additional information has been obtained by evaluating them in aggregate.

Joint analysis of dietary trials has shown a linear relationship of cholesterol lowering to risk reduction, with a 1 to 1.5 percent reduction in relative risk

found for each 1 percent reduction in blood cholesterol (Hulley et al. 1981; Mann and Marr 1981). When the various drug studies are analyzed, the results are almost comparable, with a 2 percent reduction in risk resulting from a 1 percent reduction in cholesterol (Lipid Research Clinics Program 1984b). This relationship is close to that predicted from the results of prospective epidemiologic studies such as the Framingham study.

In the Helsinki Heart Study, a greater effect was observed: An 8 percent reduction in total cholesterol resulted in a 34 percent reduction in CHD incidence. This suggests that the moderate increase in HDL cholesterol and marked fall in triglycerides might also have contributed to the benefit (Frick et al. 1987).

Taken together, these clinical trials provide compelling evidence that lowering plasma cholesterol reduces CHD morbidity and mortality. However, the total mortality has generally not been reduced in these studies. A small increase in noncardiovascular deaths was observed in the Los Angeles Veterans Administration Trial, the Helsinki Mental Hospital Study, the WHO Clofibrate Trial, the LRC-CPPT (Oliver 1981; Lipid Research Clinics Program 1984a), and the Helsinki Heart Study (Frick et al. 1987). There is a lack of consistency in the various noncardiovascular causes of death in these studies; in some studies, more cancers have occurred, while in others, more accidental or violent deaths. In the drug trials, some of the observed mortality from various noncoronary causes may have been specific to the drug itself. One study has reported a significant reduction in total mortality. In the Coronary Drug Project, total mortality in the niacin-treated group was 11 percent lower than in the placebo group, a benefit that became evident during a 9-year followup after termination of the trial (Canner et al. 1986). This raises the possibility that the effect of cholesterol lowering on mortality takes longer to emerge than its impact on nonfatal heart attacks. The difficulties in showing an effect on total mortality may reflect the problem that no clinical trial to date has had a sample size sufficiently large to address this issue with adequate statistical power.

## **Implications for Public Health Policy**

### **Dietary Guidance**

#### **General Public**

High blood cholesterol is one of the three major modifiable risk factors for CHD. The principal nutritional factors identified with high blood cholesterol and the development of CHD are dietary fat, particularly saturated fatty

acids and cholesterol, and energy imbalance leading to obesity. Other dietary constituents, such as fiber or alcohol, may interact with these factors in ways that are not clearly understood.

The relationship of dietary fat and cholesterol to CHD is supported by extensive and consistent clinical, epidemiologic, metabolic, and animal evidence. These studies strongly indicate that the formation of atherosclerotic lesions in coronary arteries—contributing to the risk for CHD—is increased in proportion to levels of total and LDL cholesterol in blood, which, in turn, are increased by diets high in total and saturated fat but decreased by diets containing polyunsaturated and/or monounsaturated fat. International epidemiologic comparisons and migration studies have revealed strong associations of fat, especially saturated fat, intake to development of elevated blood cholesterol levels, atherosclerosis, and CHD. Evidence from studies within a given population has been less consistent but points in a similar direction. Dietary intervention trials in men with elevated blood cholesterol levels have demonstrated small but significant proportionate improvements such that each 1 percent reduction in total blood cholesterol is accompanied by about a 1.5 percent reduction in heart disease risk. Intervention to lower elevated blood cholesterol levels has been shown in both human and animal studies to reduce CHD risk and to slow lesion progression. Animal studies have shown lesion regression, and there is suggestive evidence from some clinical studies that this also occurs in humans.

Taken together, these studies provide strong support for recommendations for an overall considerable decrease in dietary fat intake by the general public from the present level of 37 percent of total caloric intake and decrease in saturated fat from the present level of about 13 percent of total caloric intake.

Although the effect of dietary cholesterol on blood cholesterol is somewhat weaker and more variable among individuals than that for dietary saturated fatty acids, a reduction in the amount of cholesterol consumed by the general public from present average levels of approximately 305 mg/day for women and 440 mg/day for men seems appropriate.

Obesity is associated with such CHD risk factors as elevated LDL and total blood cholesterol, lower HDL cholesterol, high blood pressure, and diabetes mellitus. It is also a significant independent predictor of CHD, especially in women and in persons under age 50. Thus, current evidence suggests that an overall decrease in the prevalence and severity of overweight in the population, through both a decrease in caloric intake and an

increase in caloric expenditure, is advisable on the basis of the relationship of obesity to heart disease risk.

Studies of animal protein, coffee, and sugar have shown variable associations with increased blood lipid levels, but present evidence of their relationship to CHD, if any, is too weak and insufficient to draw implications for changes in the consumption of these substances. Likewise, evidence from some studies that certain components of dietary fiber and omega-3 fatty acids from fish oils reduce blood cholesterol levels and heart disease risk is too preliminary to recommend changes in average intake of these substances. In addition, advice concerning vitamin and mineral supplements on the basis of their relationship to CHD is unwarranted.

### Special Populations

There is a need to identify those individuals with high cholesterol levels, who are therefore at greatest risk. For individuals whose high total and LDL cholesterol levels warrant treatment, the first line of intervention is diet therapy. The recently released National Cholesterol Education Program guidelines on the treatment of high blood cholesterol in adults recommend that intensive dietary treatment should generally be carried out for at least 6 months. As indicated in this Report, only after that period of time, and if the cholesterol level remains significantly high, should the addition of drugs to the dietary regimen be considered. Even then, continuation of diet therapy can reduce the need for drugs and thus their risk of side effects and cost. Furthermore, studies in persons with CHD suggest that diets low in fat, saturated fat, and cholesterol can retard the progression of the disease, including recurrent heart attacks, and perhaps induce regression of atherosclerotic lesions. Persons with such high blood cholesterol levels should receive dietary guidance by qualified health professionals.

Adults with total cholesterol levels of 240 mg/dl or above (whose LDL cholesterol levels are also significantly elevated), and those with total cholesterol levels of 200 to 239 mg/dl with CHD or two or more CHD risk factors should begin a program of supervised dietary treatment. The NCEP guidelines recommend starting dietary therapy with a step-one diet, in which the intake of total fat is less than 30 percent of calories, saturated fat is less than 10 percent of calories, and cholesterol is less than 300 mg/day. If after 3 months on this diet cholesterol lowering is insufficient, the person should progress to a step-two diet, in which saturated fat is further reduced to less than 7 percent of total calories and cholesterol intake is further reduced to less than 200 mg/day.

Although in epidemiologic studies light to moderate alcohol consumption is associated with reduced heart disease risk, a cause-and-effect relationship has not been proved. Since heavy drinking has numerous adverse health consequences (see chapters on maternal and child nutrition and on alcohol), including several on the cardiovascular system, the use, even in moderate quantities, of alcohol for its possible beneficial effects on CHD is not recommended.

### **Nutrition Programs and Services**

#### **Food Labels**

Evidence related to the role of dietary factors in CHD supports the need for manufacturers to increase the number of food labels with their total fat, fatty acids, and cholesterol content.

#### **Food Services**

Evidence related to the role of dietary factors in CHD suggests that the public would benefit from increased availability of foods low in fat, saturated fat, and cholesterol in food service programs. The need is critical for the one in four persons with cholesterol levels that put them at appreciably high risk for CHD.

#### **Food Products**

Evidence related to the role of dietary factors in CHD suggests that food manufacturers should increase availability of foods and food products that are low in fat, saturated fat, and cholesterol.

#### **Special Populations**

Persons with high blood cholesterol and their food preparers should be given access to counseling by qualified health professionals and assistance in the development of diets low in fat, saturated fat, and cholesterol as well as in the appropriate balance of caloric intake and expenditure. Education and training opportunities for health professionals should be expanded to meet this need.

### **Research and Surveillance**

Research and surveillance issues of special priority related to the role of diet in CHD should include investigations into:

- The identification and management of individuals with high blood cholesterol in the general population.
- The most effective educational and dietary intervention strategies to reduce blood lipid levels and heart disease risk.
- Improved methods for assessing American dietary patterns in relation to CHD risk.
- Refinement of current dietary recommendations, including evaluation of other potentially efficacious dietary regimens, evaluation of dietary fiber, and optimal intakes of omega-3 and omega-6 fatty acids to prevent CHD.
- The mechanisms by which alterations in dietary fatty acids affect atherogenesis and the risk for CHD, including degree of saturation, chain length, and fatty acid series.
- Clarification of the role of dietary cholesterol in atherogenesis, including variability in response, effects on cholesterol metabolism in both fasting and postprandial states, and interactions of postprandial lipoproteins and lipoprotein remnants with cells of the arterial wall.



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