Nutrition, Lipids, and Cardiovascular Disease
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The evolving epidemic of cardiovascular disease in many newly industrialized societies will bankrupt their health care systems and reduce the available resources for other health priorities. Therefore, the prevention of this epidemic, or at least slowing the increase, is of the highest priority. The development of coronary heart disease (CHD) is an example of a common source epidemic due to increased consumption of saturated fat and cholesterol, low intakes of polyunsaturated fat, and increasing obesity. Hypertension, cigarette smoking, and diabetes mellitus contribute to risk of disease. The prevention of atherosclerosis beginning in young adults is of paramount importance. Careful monitoring of the evolving epidemic of CHD, including noninvasive evaluation of atherosclerosis, is important. A high-risk approach is very successful but expensive.

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INTRODUCTION

Many newly industrialized countries are experiencing an evolving epidemic of cardiovascular disease (CVD). The greater life expectancy and changes in diet and exercise habits have resulted in a higher prevalence of obesity, elevated blood cholesterol levels, hypertension and diabetes. Further, the increasing prevalence of cigarette smoking has led, in a relatively short period of time, to a rising incidence and mortality due to CVD. Many of these countries are still dealing with major public health concerns of malnutrition, infectious diseases, and environmental hazards (sanitation) as well as the growing epidemic of HIV.

In the United States, the evolution of the CVD epidemic took perhaps 50 or more years, while in many of these other countries, the time period has been compressed to 10 to 15 years. Growing pressures on the health system for expensive resources to treat CVD and its complications have to compete with the continuing health problems related to poverty: malnutrition, high infant and childhood mortality, poor sanitation, and infectious diseases. The failure to prevent and control the evolving epidemics of CVD will have a severe and negative impact on the utilization of health resources and the economic well-being of newly industrialized countries.

CVD is preventable; however, unfortunately, the application of known preventive approaches in most countries is inadequate. The emphasis has been on treatments of clinical CVD such as coronary bypass surgery and angioplasty, expensive drug therapies for treating hyperlipidemia, diabetes, hypertension, and congestive heart failure (CHF), hospitalization for complications of CVD, CHF, and growing disability from coronary heart disease (CHD), stroke, and peripheral vascular disease.

Atherosclerosis and its clinical complications does not occur at high prevalence in the absence of population average total cholesterol levels of over about 160 mg/dL, low prevalence of cigarette smoking, hypertension, and diabetes. The primary determinants of risk factor levels are diet, too many calories in relation to caloric expenditure (physical activity), high specific chain length, saturated fatty acids and dietary cholesterol, lower intake of omega-3 and -6 long-chain polyunsaturated fats, and increased intake of sodium chloride usually from processed foods that raise blood pressure.

The level of low-density lipoprotein (LDL), or specifically the level of apolipoprotein B (ApoB) and number of LDL particles are the primary determinants of the development of atherosclerosis. Research is attempting to determine the sequence of pathophysiological changes that result in the accumulation of LDL and subsequently modified LDL in the intimal layer of large and medium-size arteries, endothelial dysfunction, inflammatory responses to the growing “atheromatous” lesions, changes in the characteristics of the atheroma that result in fissure and hemorrhages in the plaque, thrombosis leading to
myocardial infarction, sudden death, and unstable angina pectoris.

Atherosclerotic disease begins in childhood. The incubation period from the development of atherosclerosis in the coronary arteries to clinical disease is very long.\(^6,7\) The clinical manifestation, myocardial infarction or sudden death, from “normal” health to clinical event can be very brief, especially for sudden CHD death. However, the underlying disease, atherosclerosis, which causes the likelihood of sudden CHD death or myocardial infarction, has evolved over a long period of time. By the time CHD incidence and mortality in a country has substantially increased, the prevalence of atherosclerotic disease will be very high, even in young people, and a major epidemic of clinical CVD is very likely. The focus of the prevention of clinical CVD must therefore be on atherosclerosis and not just on clinical disease. Focus only on the identification and treatment of clinical cardiovascular events or reaching just the high-risk segment of the population with elevated risk factors will be very costly and unlikely to be successful in reducing the increasing burden and cost of CVD in a community, but will obviously benefit the high-risk population(s).

The costs of treating CVD are astounding. In the United States, it was estimated that the cost of treating CVD cost $259 billion in 1993. The treatment costs will bankrupt the health systems of most developing countries.\(^8\)

Most clinical CHD events occur among individuals at moderate risk.\(^9,10\) A high-risk prevention strategy becomes increasingly important as the population mean level of LDL and other risk factors rises. The high-risk prevention strategy to prevent atherosclerosis and its complications usually requires extensive dietary modifications and pharmacological therapy (e.g., statins).

**THE CVD EPIDEMIC**

The epidemic of atherosclerotic disease is a good example of a “common source epidemic.”\(^11,12\) The dietary intake of cholesterol and saturated fats of specific chain lengths are the primary determinants of the development of atherosclerosis. In a seminal paper in 1978, Henry Blackburn noted that “nutritional influences account for the mass hyperlipidemia and atherosclerosis.”\(^13\) He noted that “mass hyperlipidemia in a population is the primary determinant of mass atherosclerosis which was manifest as premature and increasing CVD incidence, death and disability.” His views at that time are still prevalent today: “the changes in the national dietary goals and cultures and personal eating patterns are the best approaches for the prevention of the mass atherosclerosis.” This demands a major public health effort.

In the absence of elevated LDL or a diet high in saturated fat and cholesterol or other risk factors such as cigarette smoking, elevated blood pressure, or diabetes, the risks of CHD are small.\(^14\) A study of Yanomamo Indians in Brazil noted mean cholesterol of 123 mg/dL for men and 114 mg/dL for women and triglyceride levels of 120 mg/dL for men and 110 mg/dL for women.\(^15\)

The diet in the Yanomamo population was largely vegetarian, low in fat and cholesterol, and high in fiber, and the physical activity levels of the people were high. Interestingly, within these populations there was a direct linear relationship between the amount of cholesterol in the diet and plasma cholesterol level \(R = 0.898\). There are populations, such as in some of the Asian countries, in which the prevalence of cigarette smoking is very high and consistently high and the risks of CHD remain low because of the low LDL levels, even though the risk of stroke, left ventricular hypertrophy, CHF, and renal failure may be very high.\(^16\)

Zimmet et al.\(^17\) studied a population “in transition”: the coastal and highland Melanesian people in Papua, New Guinea.\(^17\) These populations originally had low blood cholesterol levels. Modernization of the lifestyle in New Guinea occurred after World War II, with the greatest changes occurring in the 1980s and 1990s. An increasing frequency of CHD began to be reported in these populations at that time. Low serum cholesterol levels were no longer found. The prevalence of hypercholesterolemia over 200 ranged from 16% in rural highlanders to 56% in the urban coastal subjects. The rural populations with a relatively traditional lifestyle had the lowest levels of obesity, non-insulin-dependent diabetes mellitus, and hypercholesterolemia, while the urban populations suffered from a high prevalence of obesity, diabetes, and hypercholesterolemia.

By 1991, cholesterol levels had substantially increased and were much higher than those found in 1977. The prevalence of diabetes was also increasing, directly related to changes in lifestyle as measured by a modernity index. Other studies of the Pacific Island countries by Zimmet and others have document similar striking changes in cholesterol levels with changes in diet, which included increased saturated fat and cholesterol. Previous studies in these populations also failed to show any increase in LDL with increasing age, but recent studies have clearly documented this. Diet surveys revealed energy intake in excess of requirements, with higher fat and dietary cholesterol intake.

Increases in the prevalence of obesity usually accompany increases in saturated fat and cholesterol. The
increase in body weight, especially in young adult life, is an important determinant of higher LDL, even in childhood, and the increase in LDL from young to older ages. Obesity is also a major determinant of the risk of diabetes. On average, diabetics have 2 to 3 times the risk of CHD at any level of LDL. 

Central obesity or increasing visceral fat is associated with increasing insulin resistance and diabetes. The abnormalities of fatty acid metabolism increase fat deposition in the liver and muscle associated with insulin resistance, and obesity further contributes to changes in lipoprotein patterns with increasing numbers of LDL particles, higher very-low-density-lipoprotein (VLDL) triglycerides, and decreases in LDL particles and in HDL particles and size. This increasing number of particles and smaller particles may contribute above and beyond the total LDL to the evolving development of atherosclerosis and risk of heart attack.

The Bogalusa Heart Study is a long-term epidemiological study of the early natural history of atherosclerosis in children and young adults from a semi-rural, biracial (65% white, 35% black) community in Bogalusa, Louisiana, USA. LDL levels increased with age from 5 to 10 and from 19 to 26, were higher in whites than in blacks, and were similar in boys and girls. There have been two follow-up studies to evaluate the relationship between risk factors and atherosclerosis in the Bogalusa Heart Study. A pathology study follow-up attempted to obtain autopsy material on individuals who had been in the study who had subsequently died, usually from a traumatic event. These were early lesions, but there was a strong association between atherosclerosis in the aorta and total cholesterol and LDL levels measured in childhood, and an inverse relationship with the ratio of LDL/HDL. Higher levels of LDL were related, but not as strongly, to atherosclerosis in the coronary arteries. There was also a strong association between triglycerides and VLDL cholesterol with atherosclerosis in the coronary arteries, and an inverse association with HDL. Measures of body mass were positively associated with atherosclerosis in both the coronary and aortic arteries. They have also used ultrasound of the carotid arteries, to measure carotid intimal medial thickness. A sample of 518 black and white subjects who were previously enrolled in the Bogalusa Heart Study, and now were at a mean age of 32, was evaluated. In multivariate analysis, systolic blood pressure, race, age, and LDL were related to common carotid intimal medial thickness. The mean intimal medial thickness increased with the combination of multiple risk factors.

The Pathobiological Determinants of Atherosclerosis in Youths (PDAY) Study evaluated postmortem specimens of victims of violent death between the ages of 15 and 34. The extent of atherosclerosis was related to risk factors cigarette smoking, postmortem blood cholesterol levels, and estimations of antemortem blood pressure and obesity. The prevalence of severe atherosclerosis lesions, even at this younger age, was greater in men than in women. There was an increase in the extent of atherosclerosis from ages 15 to 19 and 30 to 34. It was estimated that 28% of the autopsied individuals had a non-HDL over 160 mg/dL (including LDL, intermediate-density lipoprotein [IDL], and VLDL). Non-HDL was significantly related to atherosclerosis in the coronary arteries and in the aorta. Obesity (BMI > 30 kg/m²) was also strongly related to atherosclerosis in both the coronary arteries and in the aorta.

The Special Turku Coronary Risk Factor Intervention Project for children (STRIP) study evaluated whether dietary changes in children could reduce their blood cholesterol after age 7. Healthy 7-month-old infants (N = 1062) were randomized into an intervention and a control group (N = 540). Individualized dietary counseling of parents aimed at a low-saturated fat and low-cholesterol diet from the age of 7 months markedly lowered total and non-HDL levels and apolipoprotein concentrations up to the age of 5 years. The intervention group received twice a year dietary and lifestyle counseling given by a team of physicians and dieticians. A diet of 10% to 15% of energy from protein, 30% fat, less than 10% from saturated fat, and 55% to 60% of energy from carbohydrates was given. Baseline adjusted mean and serum total and non-HDL and ApoB concentrations

Table 1. Key Guidelines for Public Health and Preventive Medicine Programs

- Must reach the population(s) at risk
- Two types of programs: public health (lower risk) and preventive medicine (higher risk)
- Usually must be based on results of clinical trials
- Need well-designed effectiveness studies
- Identify determinants of disease incidence
- Lower education and income groups usually at higher risk of morbidity and mortality due to risk factor levels and adherence to therapies
- Changing lifestyles are a major determinant of “new epidemics” and often begin in the better educated and migrate downward
- Public health, preventive medicine for entire populations
- Do no harm
- Individual public health programs for chronic disease may be costly; community, environmental approaches are often necessary
- Presumption that doing “good” and having good results are one and the same is wrong
- Public health, preventive medicine must have a close link to medicine and human biology
were lower in the intervention boys than the control boys throughout the 7 years. Boys also had lower triglyceride levels. For girls, cholesterol was also lower in the intervention compared with the control group, but the differences were not statistically significant.

A follow-up of 356,220 men from the Multiple Risk Factor Intervention Trial (MRFIT) screened age 35 to 57 has provided substantial information regarding the risk of CHD death in relationship to serum cholesterol levels over the entire range of serum cholesterol and in combination with other risk factors.29 The relationship between serum cholesterol and risk of coronary artery disease was linear and graded from serum cholesterol levels of 167 or higher. The relative risk was greatest in the youngest age group (35 to 39 years of age) compared with the oldest age group (55–57) in the trial at entry. However, the absolute risk, or the difference between high and low cholesterol, was greatest in the oldest age group. The MRFIT follow-up documented that the regression coefficients for risk of CHD death by level of blood cholesterol were similar for white, black, Hispanic and Asian groups.30,31 There were absolute differences in risk by cholesterol level related to other risk factor levels, such as blood pressure, smoking, and history of diabetes. There was no evidence from this large sample in MRFIT that the association between higher cholesterol levels and risk of CHD death varies by ethnic groups.

The follow-up to the MRFIT cohort and several long-term follow-up cohorts from studies in Chicago documented that both men and women with reduced risk factors were at very low risk of CHD. For example, in the MRFIT very low risk men with serum cholesterol under 182 mg%, blood pressure under 120/80, who were non-smokers and nondiabetic at entry and had no previous heart attack, there were 12 year death rates that were lower by 80% for CHD, 79% for stroke, 86% for all CVD, 30% for cancer, 21% for all other causes, and 53% for all causes combined. Their longevity was estimated to be at least 9 years greater than that in non-low risk men.32

The basic problem in these studies was that only a very low percentage of adult men in the United States met these low risk criteria: only 11,098 out of a cohort of 361,662 men age 35 to 57. Therefore, the primary emphasis must be to reduce the prevalence of these elevated risk factors within the population in order to substantially reduce the epidemic of CVD.

Increased risk of CHD with rising blood cholesterol levels are also found in populations in which the risk of coronary artery disease is much lower because of traditionally lower serum cholesterol and other risk factors. The Chinese Multiple Provincial Cohort Study evaluated 30,121 Chinese adults ages 35 to 64 at baseline in 1992–1993 and followed them until 2002.33 A total of 191 CHD events occurred in the Chinese cohort. The 10-year CHD event rate was low, 1.5% for men and 0.6% for women, while in the Framingham Heart Study, the corresponding rates were 8% for men and 2.8% for women. Prevalence of elevated cholesterol was much lower in the Chinese population. Only 31% had a blood cholesterol over 200, as opposed to 62% in the Framingham Heart Study among men. There was a linear increase in risk by total cholesterol level in the Chinese population present in both men and women. The absolute risk at any cholesterol level was much higher in the Framingham study than in the Chinese population. Multivariate model prediction from the Framingham study was much lower in the Chinese population, but the risk was linearly related to the Framingham Risk Factor Score.

A recent large case-control study of cardiovascular risk factors has further documented the similarities of the risk factors for CVD across many populations.34 The Interheart Study evaluated the risk factors in patients with CHD and controls in 52 countries, divided into 15,152 cases and 14,820 controls. The study noted that 80% of the global burden of CVD occurs in low income populations. The odds ratios increased for key risk factors and were consistent across populations: the ApoB/A ratio for the South American sample 5th versus 1st quartile was 3.87 (CI = 3.39–4.42) and 2.97 (CI = 1.85–4.23), respectively. This ratio accounted for 54% of the attributable risk of heart attack. Similar recent analysis from the British Regional Heart Study estimated that 52% of increased risk of CHD was due to elevated blood cholesterol levels. Furthermore, in that study, smoking, elevated cholesterol, and blood pressure accounted for 91% of attributable risk of CHD.35

The Mediterranean or French paradox, the low coronary death rate in spite of higher intakes of dietary cholesterol and saturated fat and higher blood cholesterol levels, has created a great deal of interest regarding the relationship between diet, cholesterol level, and risk of coronary artery disease.36 France is a country with low CHD incidence and mortality. The energy supplied by fat was 36% in Toulouse in 1985–1986, but more recently was found to be 39%.36 The intake of cholesterol and saturated fat is similar in Finland and France, but Finland had higher CHD death rates and incidence than France. The consumption of vegetables and vegetable oils containing mono- and polyunsaturated fatty acids is greater in France than in Finland. The cholesterol/saturated fat index was developed as a measure of the amount of cholesterol and saturated fat in the diet, and then the relationship was studied in 40 countries. France had a cholesterol/saturated fat index of 24/1000 calories and a CHD mortality rate of 198/100,000, while Finland had a cholesterol/saturated fat index of 26/1000 and a CHD
mortality rate of 1031/100,000. It is important to note that in the French population, levels of blood cholesterol remain a strong predictor of CHD.

Renaud and Lorgeri believe that the French paradox may be due to the high consumption of wine in that country. Interestingly, the consumption of wine in France is greater than in many countries but also differs in consumption patterns: consumption is consistent across the week, whereas in many other countries, heavy consumption, or binge drinking, occurs around the weekends.

The second possibility relates to the oxidative modification of the LDL hypothesis. Oxidized LDL may be an important determinant in the development of atherosclerotic plaques. Flavonoids are found in many plants, fruits, and vegetables, and may inhibit LDL oxidation. There are large amounts of flavonoids in red wine. There has been some suggestion that the consumption of red wine with meals reduces lipid peroxidation. Flavonoids, as noted, are high in specific fruits and vegetables, and it has been thought that the combination of higher fruit and vegetable intake and wine consumption (especially all week long) may be associated with the reduction in LDL oxidation and reduction in risk of CHD.36,38

The lower rates in France are also found in parts of Italy, Greece, and Spain. Interestingly, a recent analysis of the changing trends in mortality in these countries has documented that the CHD death rates in the United States are gradually falling and that in some areas in the United States, the CHD mortality rates, especially in the younger age groups (35–44 years of age) have actually reached similar to those in France. Likewise, CHD mortality has dropped dramatically in Finland with substantial changes such as reduction of saturated fat and cholesterol in the diet, control of hypertension, and decreased cigarette smoking, so that the levels are now approaching those of southern European countries.38–41

There is no evidence that the prevalence of atherosclerosis is lower in southern Europe (France). Therefore, it is impossible to determine whether the decreased risk of CHD is a function of the lower prevalence of atherosclerosis or the lower risk of heart attack given similar extent of atherosclerosis. Another interesting issue is the distribution of lipoprotein particles, especially the effect of both alcohol intakes and higher polyunsaturated fat, alpha linolenic acids, or monounsaturated fat (olive oil). It is possible that the diet and alcohol modulate LDL and HDL particle distribution. We and others have showed that the distribution of LDL and HDL particles and size are important determinants of risk of CHD.

We are evaluating a similar interesting potential paradox. In post-World War II Japan, there has been a substantial increase in cholesterol, saturated fat, and total fat in the diet, a greater increase in body weight (especially in men), very high prevalence of cigarette smoking, and a continued high prevalence of hypertension. However, levels of LDL remained roughly the same. In spite of the increase in these risk factors, there has been little evidence of any substantial increase in CHD mortality or incidence in the post-World War II birth cohorts in Japan. This cannot be explained by genetic differences between Japan and US populations because Japanese migrants to Hawaii exhibit, within a very short time, substantial increases in CHD incidence and mortality that begin to rival those of the US Caucasian populations.42

We have been evaluating the extent of atherosclerosis in a population sample in men age 45 to 49 years in Japan, a similar population of Japanese living in Hawaii, and populations of blacks and whites living in Pittsburgh, Pennsylvania. We have evaluated the extent of atherosclerosis using measures of carotid intimal medial thickness and coronary artery calcium, which has been shown to be an excellent surrogate for the extent of coronary atherosclerosis (i.e. the amount of plaque), but not necessarily for the extent of coronary stenosis. The preliminary results from this study have shown that the Japanese in Japan have less coronary artery calcium, and less carotid intimal medial thickness than the age-matched US, primarily Caucasian, population. The Japanese have a higher prevalence of alcohol intake rivaling France, fish omega-3 fatty acid, and possibly antioxidated flavonoids and have lower BMIs.

In the Healthy Women Study in Pittsburgh, PA, we evaluated the relationship of risk factors measured premenopausally when women were approximately 46 years of age and the development of coronary artery calcium, a measure of coronary atherosclerosis, at ages 62 to 70 (approximately 12 to 20 years after menopause). Risk factors measured premenopausally predicted the extent of high coronary artery calcium (≥100 Agatston units). LDL was 101 mg/dL for women with 0 coronary artery calcium (premenopausal) and 122 mg/dL for those with coronary artery calcium 100 Agatston units or above. We also showed that higher intake of cholesterol and saturated fat (as a percentage of calories) and keys score measured from one 24-hour recall premenopausally was associated with the presence of coronary artery calcium, approximately 15 years later, after menopause. These results are consistent with a long incubation period for atherosclerosis. The prevention of elevated risk factors at as early an age as possible is therefore very important.43

Genetic factors or “host susceptibility” are important in determining response to environmental exposures such as dietary saturated fat and cholesterol.44–46 These important genetic determinants have the greatest impact
on extremes of the distribution of lipoprotein levels and probably on the development of atherosclerosis given a specific lipoprotein level. Racial difference in the prevalence of important genes related to lipoprotein metabolism can also affect the population level of risk factors; for example, the higher HDL and low triglycerides among blacks associated with variation in hepatic lipase genes, or the low LDL among blacks associated with genes related to the LDL receptor. However, the effect of differences in lifestyles in general swaps the host susceptibility to the population risk of CHD. Genetic attributes may also affect the magnitude of response to both diet and drug therapies.

INTERVENTIONS

CHD, stroke, and total mortality have declined dramatically in the United States and in many other countries over the past 20 to 30 years. This decline in mortality has been attributed to both the changes in cardiovascular risk factors and improved medical treatment. It has been difficult to monitor the trends in CHD incidence because of the changing criteria for the diagnosis of myocardial infarction. There has been a very substantial decline in first-event sudden cardiac death, which probably represents an indirect estimate of changing incidence. The decline in sudden deaths has especially been precipitous in younger age groups.

In the United States and in other countries, there has been an extraordinary decline in the mean serum cholesterol levels, which are related to changes in diet and especially decreases in the consumption of saturated fat and cholesterol. Mean serum cholesterol level in 1960–1962 for both sexes was 222 mg/dL, and in the most recent data from 1999–2002 was 203 mg/dL. Declines have been similar and substantial for both men and women, blacks and whites. Data from the Mexican-American population has been available since 1976–1980. The mean total cholesterol was 209 mg/dL for both men and women in 1976–1980 and 205 mg/dL for men and 198 mg/dL for women in 1999–2002.

From 1980–1994, The Nurses’ Health Study followed approximately 86,000 women who were between 35 and 59 years of age and had no previous CVD or cancer. Diet and lifestyle variables were assessed at baseline and then updated. The study has reported a 31% decline from 1980–1982 to 1992–1994. During this time, there has been a precipitous decline (41%) in cigarette smoking, substantial improvement in the diet, decreases in trans-fatty acids as a percent of total energy, an increase in the ratio of polyunsaturated to saturated fats, an increase in cereal fiber, an increase in marine omega-3 fatty acid intake, increases in folate, and a substantial improvement in the diet score.

It is generally estimated that about half of the decline in mortality due to CHD is due to the reduction in risk factors. A recent detailed analysis in the United Kingdom suggested that most of the decline in CHD was due to a reduction in risk factors. The largest component of risk factor reduction was cigarette smoking (34% reduction and 54% of life years gained); control of blood pressure (7.5% decline and 28% of life years gained); and cholesterol (5.6% reduction and 22.5% life years gained). These improvements in life expectancy have occurred in spite of substantial increases in obesity, decreased physical activity, and increased prevalence of diabetes. It is likely, however, that over time the increase in obesity and diabetes will blunt or even reverse the decline in CHD.

The original recommended diet of under 10% saturated fats in the diet has been shown to have relatively small overall effects on reducing blood cholesterol levels, primarily because of the substantial decline in the amount of saturated fat and cholesterol in the traditional diets in the United States, Canada, and many countries in Europe (a 2% to 3% reduction in blood cholesterol).

The more recent “therapeutic diet” from the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATPIII) in 2002 recommended a reduction of saturated fat to less than 7%, polyunsaturated fat to less than 10%, monounsaturated fat to less than 20%, total fat to around 20% to 35%, carbohydrates to 50% to 60%, an increase in fiber to 20 to 30 g, and dietary cholesterol to less than 200 mg/d. Dietary recommendations now also include an effort to reduce total calories and increase energy expenditure to prevent or treat obesity. The effects of this more aggressive dietary interventions as done by well-trained nutritionists and behavioral scientists are somewhat more substantial, perhaps a 10% to 15% reduction in LDL. However, long-term adherence to recommended dietary changes in the general population are extremely different and often unsuccessful.

More aggressive approaches to diet have therefore been proposed. Stamler et al. have tried to estimate the effects of dietary modification in reducing blood cholesterol level. Thus, decreasing saturated to less than 7% and dietary cholesterol to less than 80 mg/1000 kcals would probably result in about a 22% reduction: increasing polyunsaturated fat to 9% resulted in a 4 mg/dL reduction; increasing fiber to 125 g resulted in a 10 mg/dL reduction, for a total of 42 mg/dL reduction in blood cholesterol or about 21%. Stamler and others have proposed adding higher levels of fiber, especially viscous fiber, of 5 to 10 g/d to reduce cholesterol levels a further 3% to 5%, and recent interest in increasing plant sterols and stanols and esters about 2 g/d would have about a 6% to 15% reduction. Thus, adherence to this diet could...
reduce total cholesterol by 20% to 30%. Such dietary modifications should primarily be done under the supervision of nutritionists and behavioral scientists who can work with patients or participants to both maximize the quality and adherence to the diet.53

The Ornish Lifestyle Heart Program showed benefit in surrogate measures of CHD in secondary prevention (patients who already had heart disease) using an intensive intervention that included less than 10% of total fats, less than 2% saturated fat, essentially a vegetarian diet, smoking cessation, stress management, and moderate exercise.54 Jenkins et al.55 recently reported that using a so-called portfolio diet, a much more intensive diet, including the addition of 23 g of soluble fiber, 51 g of soy, 33 g of almonds, and 2.4 g of plant sterols could reduce LDL levels comparable to those obtained with moderate doses of lipid-lowering statin drugs: Lovastatin causes a 32% reduction and the portfolio diet 29%.

Such approaches are not inexpensive and are restricted primarily to individuals who have relatively high LDL levels (>130 mg/dL) and clinical CHD. They are therapeutic approaches rather than a public health approach for reducing LDL. For higher-risk individuals, these diets are a first step prior to the utilization of lipid-lowering drug therapies.

There has been some continued controversy about the percentage of total fat and refined carbohydrates in the diet. Of particular concern has been the potential increase in triglyceride levels associated with a very low-fat, high-carbohydrate diet. In general, there is an increase in blood triglyceride levels with such a diet that does not include caloric reduction and decreases in body weight. However, with the inclusion of a reduction in calories and body weight, triglyceride increases are relatively modest. There is little or no evidence that reducing total fat alone without changing the composition of the diet (e.g., the amount of saturated and polyunsaturated fats) has any effect on LDL or CHD morbidity and mortality. Similarly, although weight gain is associated with an increase in blood cholesterol level and is probably a major factor accounting for the increase in cholesterol level with age, as previously noted, changes in body weight without changing dietary composition probably have little effect on total LDL or number of LDL particles, but will change the distribution of LDL particles to perhaps a less-atherogenic LDL particle distribution.

The difficulties of maintaining adherence to dietary recommendations (i.e., preventive therapies) has been a major stumbling block in diet clinical trials of cholesterol lowering and risk of heart attack.56 The National Diet Heart Feasibility trials in the 1960s concluded that a large diet heart trial in the United States would probably not be feasible because of the sample size required and the extent of adherence that might not be possible in free-living populations.56

The MRFIT included interventions not only in diet but in smoking and blood pressure as well in high-risk men to try and partially compensate for the large sample sizes required in a purely diet trial.57 Unfortunately, maintaining adherence to dietary change in these high-risk men was difficult throughout the trial and the extent of lipid-lowering was not nearly large enough to demonstrate any major benefit on cardiovascular outcomes. The only clinical trial that has demonstrated major effects on cardiovascular outcome was the Oslo Diet Heart Trial, which demonstrated over time a substantial reduction in CHD incidence and mortality.58 The trial had the advantage of a population with very high total cholesterol (around 328 mg/dL) as a starting point and very high intakes of saturated fat and cholesterol. Thus, it was possible to both substantially reduce the total cholesterol levels in the intervention compared with the control group and to successfully modify the very high saturated fat and cholesterol intake. The reduction of CHD risk was similar to recent drug trials using statins. The reduction in risk also occurred within a short time period after the beginning of the trial, suggesting that the effects of interventions such as diet or drugs are related primarily to lipid lowering. The modeling of lipid lowering and the reduction in CHD risk suggests that probably at least a 20% to 30% reduction in LDL levels in the intervention group compared with the controls is necessary to reduce the incidence of CHD in higher-risk individuals or those who have clinical CVD (i.e., secondary prevention).59,60 Except in small, selected samples, this degree of reduction in LDL is very hard to maintain with dietary intervention alone.61

The Women’s Healthy Lifestyle Project was a clinical trial among women with average risk factors going through menopause. The goal of the trial was to prevent weight gain and the reduction of waist circumference (intra-abdominal fat) through menopause with a low saturated fat and cholesterol diet instead of the usual dietary recommendations.52 The progression of carotid intimal medial thickness was less in the intervention compared with the health education group.63 The trial was unique in that it focused on preventing the increase in risk factors pre- to postmenopause and not on lowering established risk factors or reversing atherosclerosis.63

There is evidence from secondary prevention trials that increased intake of omega-3 fatty acids reduces the risk of cardiovascular deaths.64 The effect is greatest in reducing the number of sudden CHD deaths. However, it is also possible that increased intake of omega-3 fatty acids may also have a positive effect in reducing the extent of atherosclerosis or thrombosis.65,66 Populations such as those in Japan have very high intake of omega-3.
fatty acid from fish, and a lower risk of CHD in spite of a high prevalence of cigarette smoking, hypertension, and increasing LDL levels.

It is clear that the increasing the intake of EPA and DHA results in increases in the omega-3 fatty acids in tissue or in cellular lipids and circulating lipids, along with the simultaneous reduction of the omega-6 fatty acids. These changes are most noticed in cell membrane-bound phospholipids and play an important role in eicosanoid formation, including prostaglandins, leukotrienes, and thromboxanes.67,68 These changes may have a positive effect on platelet aggregation and thrombosis, and may be one of the major factors in the lower rates of CHD found in some of the Mediterranean countries and in populations with very high consumption of omega-3 fatty acids from fish.69,70

Many vegetable oils are also greatly enriched in omega-6 fatty acids, mainly linoleic acid, in corn, sunflower, and soybean oils. Some plant foods contain n-3 polyunsaturated fatty acids such as alpha-linoleic acid. High amounts of alpha-linoleic acid is found in flaxseeds and walnuts. The Lyon Diet Heart Study randomized 605 French patients with coronary disease to either a diet rich in fruits, vegetables, nuts, and alpha-linoleic acid-rich margarine or a usual Western diet.71 After 4 years, the intervention group had significantly reduced cardiovascular events, although other risk factors were comparable in the two populations.71 Similarly, the Indo-Mediterranean Diet Heart Study randomized 1000 patients with coronary artery disease to a diet rich in whole grains, fruits, vegetables, walnuts, and almonds with a substantial increase in alpha-linoleic acid. After 2 years, total cardiovascular events were significantly lower in the intervention group than in the controls.72

The typical American diet has provided 1 to 3 g of alpha-linoleic acid per day, but only about 0.10 to 0.15 g of EPA and DHA. The American diet is very high in n-6 polyunsaturated fatty acids (about 12–15 g/d). The ratio of n-6 to n-3 fatty acids currently in the diet is about 8:1. There is some recommendation that this ratio should now be reduced to perhaps as low as 4:1 or even lower.68

A recent report from the American Heart Association included a detailed evaluation of the health benefits of omega-3 fatty acids. Their committee concluded that patients without documented CHD should eat a variety of fish (preferably oil fish), oils, and foods rich in alpha-linoleic acid, such as flaxseed, canola, and soybean oils, and nuts such as walnuts. Those patients with CHD should consume on average at least 1 g of EPA or DHA per day, preferably from oily fish, but supplements can also be used. For patients needing to lower blood triglyceride levels, 2 to 4 g of EPA or DHA per day should be provided as capsules, but this should be done under a physician’s guidance.69

One interesting approach has been to try and change the sources of oils in the diet at the population level: an environmental change. The multi-ethnic island nation of Mauritius in the Indian Ocean experienced rapid industrialization. The mortality from CHD and diabetes also increased rapidly, exceeding that of most Western countries. In 1987, the government of Mauritius instituted a National Noncommunicable Diseases Intervention Program after a baseline survey had demonstrated substantial elevated cardiovascular risk.73 The 5-year program demonstrated substantial reductions in hypertension, triglyceride levels, and blood cholesterol levels, but increases in obesity and slight increase in diabetes, which were very similar to the experience in the United States. The government limited the content of palm oil in cooking oil used almost exclusively in Mauritius. Palm oil, very high in saturated fatty acids, was the major component of the oil, approximately 75% to 100%. The government instituted a program to switch from palm to soy oil, so that by 1992 almost the entire cooking oil content was soybean oil. Soybean oil is 56% polyunsaturated fat. The content in the oil changed from 37% saturated fat and 20% polyunsaturated fat to 14% saturated fat and 56% polyunsaturated fat. Analysis of the fatty acid content of serum samples showed a dramatic increase in both men and women in polyunsaturated fats and decreases in saturated fat. There was a substantial change in blood cholesterol level, decreasing by about 15% in Mauritius during the 5 years from 1987–1992.74 There has also been a substantial decrease in CHD incidence within this population.73,74 The governmental environmental approach offers an excellent method to reducing population blood cholesterol levels.

In Beijing, China, on the other hand, there has been a substantial increase in the death rate from CHD, especially in the younger age groups.75 For example, between 1984 and 1999 there has been a 111% increase in CHD mortality in the younger age group (35–44 years of age). It has been estimated that the increase in CHD mortality of about 77% could be attributed to the rise in blood cholesterol levels, about 19% to diabetes, 4% to increasing BMI, and only about 1% to the small changes in cigarette smoking. There was a 5-fold increase in the consumption of red meat, eggs, and oils between 1978 and 1992, and declines in fruit and vegetable consumption. The rapid rise in CHD in this population is also consistent with studies from eastern Europe, where, again, lifestyle and diet changes resulted in a rapid increase in CHD mortality.

**DISCUSSION**

The growing epidemic of CHD in evolving industrial societies will substantially increase the utilization of
health care services to treat a rising incidence of disabilities associated with CVD. The increasing cost and need for health care services will drain health care resources needed to deal with the prevalent problems of malnutrition, sanitation, infectious diseases, and high infant mortality. The increased prevalence of CHD has been noted first among the upper and better-educated components of these societies, who are likely to be in a position to demand more of the health care dollars be used for cardiovascular care, including the availability of the best technology for diagnostic and surgical therapies and costly drug therapies. These medical therapies will have a very positive impact in reducing the morbidity and disability associated with CVD at a substantial cost. The ever-increasing incidence of CHD will rapidly spread into the lower-income populations, where financial resources may not be available for adequate medical care. The burden on economic resources of the country will become substantial and is likely to bankrupt the healthcare system. Prevention is the key to controlling the growing epidemics of CHD.76

In 1998 as part of the 4th International Conference on Preventive Cardiology in Montreal, Quebec, the cardiovascular specialty societies stated a call-to-action to try to prevent cardiovascular epidemics. It was noted that governmental activities are clearly needed to stem the growing epidemic of CVD. The knowledge base that has been gained for preventive cardiology over the past 50 years can be implemented to substantially reduce the risk of CHD. As noted, by the time the incidence of CHD is rising in these populations, the extent of atherosclerotic disease is substantial, given the incubation period between developing atherosclerosis and incident CHD. Thus, waiting for the development of high rates of CHD in a population will be unsuccessful in stemming the evolving epidemic of atherosclerotic disease.77

Recommendations that have been proposed at the governmental level include increasing taxation in an effort to control the availability of tobacco and modification of the available food sources (e.g., the successful efforts in Mauritius to change the distribution of food oils). In the United States, for example, the decline in saturated fat has been fairly substantial since the 1960s, and now has dropped further from 13% in 1971–1974 to 11% through the year 2000.4 The decline in the saturated fat in the American diet has occurred because of changes in food processing driven by changing consumer selection. There is little evidence that dietary therapy within physicians’ offices are of any substantial value in reducing blood cholesterol levels. Individual dietary interventions for substantial reductions in LDL level should be done by trained dieticians, which is expensive and therefore probably needs to be restricted to higher-risk populations.78,79

The major initial emphasis at the national level in the reduction of CHD and CVD should be modification of the available foods with an emphasis on specific oils, increasing emphasis on poly- and monounsaturated fats to replace saturated fats and trans fatty acids, increasing lower-fat dairy products, decreasing cholesterol in the diet, reducing salt in processed foods, emphasizing the importance of increasing physical activity, encouraging caloric reduction to prevent weight gain and obesity, and reducing the amount of meat and highly saturated baked goods in the diet.4

Monitoring of the potential epidemic of CHD within a country is of extreme importance. Good vital statistics should be a high priority. Monitoring of CHD mortality (especially sudden CHD deaths) and perhaps incidence of CHD in well-defined populations of younger age groups rather than attempting to change a whole region or country analysis may be of value.

New technologies to measure the extent of atherosclerosis in vivo are now available and require relatively modest sample sizes to determine the extent of atherosclerosis. These may be particularly valuable in determining an evolving epidemic of atherosclerosis in a population, especially in younger and middle ages.80,81 Monitoring of traditional risk factors is also of high priority, especially blood lipoproteins, obesity, cigarette smoking, and blood pressure. As noted, the obesity epidemic could threaten prior successes in reducing CHD mortality.12

There is a great deal of interest in measuring a variety of “new” risk factors. However, these contribute markedly little to the overall burden of CVD in any population. Control of the major risk factors—blood lipoproteins, obesity, cigarette smoking, and blood pressure—will have the greatest impact in reducing the burden of CVD. Prevention of rises in risk factors and the prevalence of atherosclerosis must be the highest priority. Failure to stem the epidemic of CHD incidence will almost certainly bankrupt the health care systems in many developing countries and drive resources away from other important health problems.

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