LETTER REFERENCE 1

National Cholesterol Education Program

High Blood Cholesterol

Detection

Evaluation

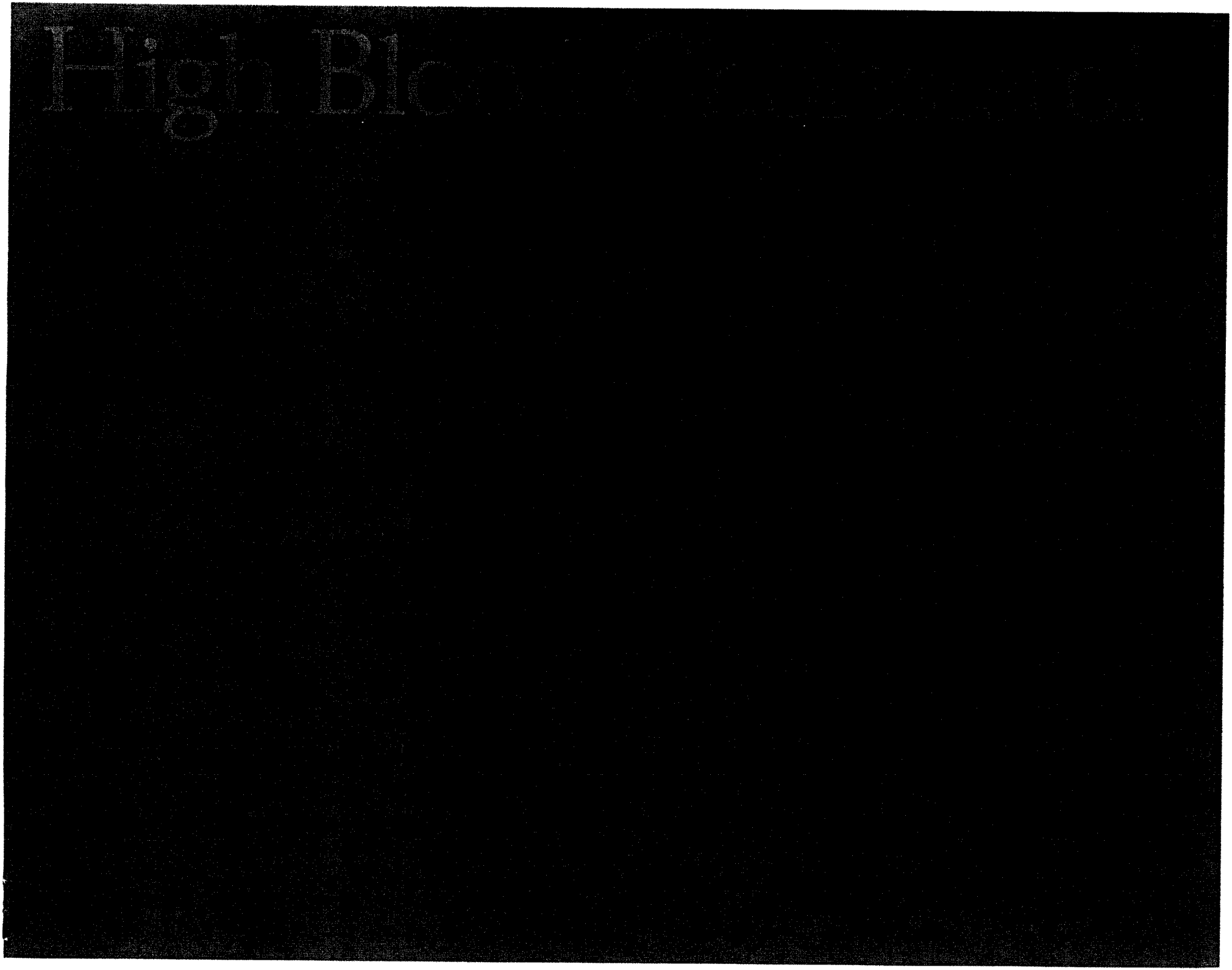
Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Final Report

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE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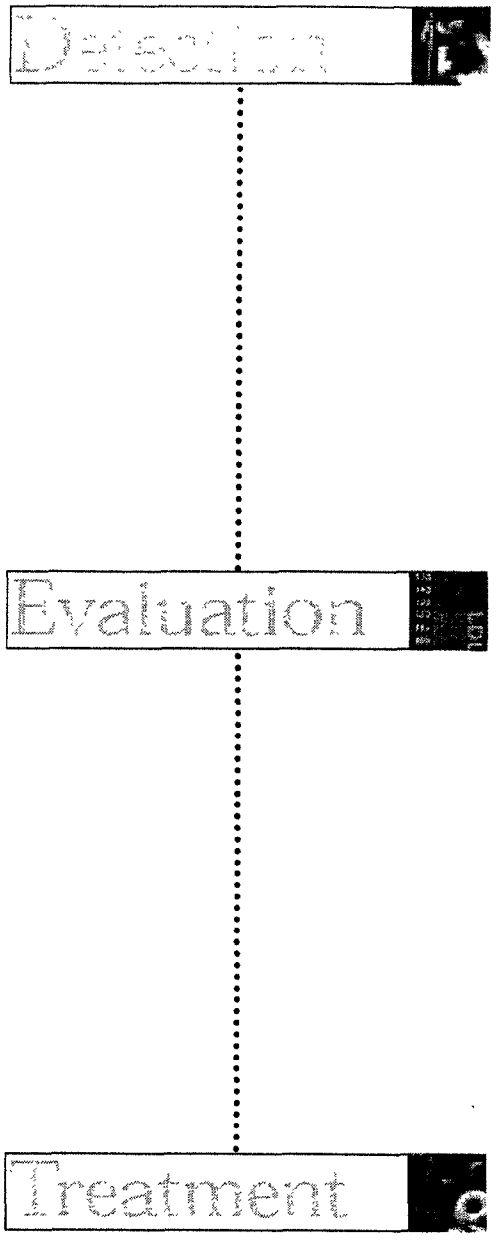

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

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National Heart, Lung, and Blood Institute

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Data show that plant-derived stanol/sterol esters at dosages of 2–3 g/day lower LDL-C levels by 6–15 percent with little or no change in HDL cholesterol or triglyceride levels.[707-713] The more recent among these studies indicate that maximal lowering of LDL cholesterol occurs at intakes of plant stanol/sterol esters of 2 g/day. LDL reductions also occur in individuals who have both hypercholesterolemia and type 2 diabetes[714] and in children with hypercholesterolemia.[715] A greater percent lowering of LDL occurs in older people than in younger people.[716] No studies have been conducted to determine the effect of plant stanols/sterols on CHD risk, although Law[716] has recently projected that their use should double the beneficial effect on CHD risk achieved by reducing dietary saturated fatty acids and cholesterol.

Plant sterols/stanols reduce absorption of dietary carotenoids, and decreased levels of plasma beta-carotene have been observed subsequent to consumption of margarines that contain either stanol ester or sterol ester.[706] Whether carotenoid decreases are deleterious is unknown, but prudence calls for adhering to current recommendations for intakes of fruits and vegetables with consumption of plant stanols/sterols.

Evidence statement: Daily intakes of 2–3 grams per day of plant stanol/sterol esters will reduce LDL cholesterol by 6–15 percent (A2, B1).

Recommendation: Plant stanol/sterol esters (2 g/day) are a therapeutic option to enhance LDL cholesterol lowering.

3) Soy protein

Soy protein included in a diet low in saturated fatty acids and cholesterol can lower levels of total cholesterol and LDL cholesterol in individuals with hypercholesterolemia. Recent reviews[717,718] gave particular weight to 16 well-controlled trials that reported intakes of saturated fatty acids and cholesterol. More than half of the studies used more than 40 g/day soy protein in some form. One report[719] indicated that 25 g/day soy protein in a diet low in saturated fatty acids and cholesterol lowers LDL cholesterol levels by about 5 percent.

The specific processing of the soybean determines the characteristics of soy protein, such as the content of isoflavones, fiber, and saponins. There is some evidence that an LDL-lowering effect is dependent upon isoflavone content[720] but conclusive data are lacking. Since there are inconsistent findings regarding both the dose and the potential benefit of soy protein, soy protein's major role in LDL-lowering may be to help reduce the intake of animal food products with their higher content of saturated fatty acids.

Evidence statement: High intakes of soy protein can cause small reductions in LDL cholesterol levels, especially when it replaces animal food products (A2, B2).

Recommendation: Food sources containing soy protein are acceptable as replacements for animal food products containing animal fats.

c. Other dietary factors that may reduce baseline risk for CHD

Epidemiological studies strongly suggest that other nutrient factors affect baseline risk for CHD. For example, in the Mediterranean region, where the diet is rich in fruits and vegetables, whole grains, ocean fish, and unsaturated fatty acids, the risk for CHD appears to be lower than predicted by the major risk factors. In contrast, in regions without this dietary pattern, such as Eastern Europe and Russia, CHD rates are higher than predicted by the prevalence of CHD risk factors. Such observational data provide a basis for a general recommendation for a dietary pattern that is consistent with a low baseline population risk. The Dietary Guidelines for Americans (2000),[241] were crafted to facilitate reduction in baseline risk for CHD (Table V.2–3).

In addition, nutritional research has focused on several specific factors that may have unique properties to reduce risk for CHD. The status of these emerging dietary factors are reviewed below and summarized in evidence statements.

1) n-3 (omega-3) polyunsaturated fatty acids

Polyunsaturated fatty acids of the n-3 (omega-3) type occur as alpha-linolenic acid (18:3), primarily in certain vegetable sources such as soybean, canola oil and

English walnuts, and in fish oils as eicosapentaenoic acid (EPA) (20:5) and docosahexaenoic acid (DHA) (22:6) *(marine n-3 fatty acids).*

Moderate fish consumption has been associated with reduced sudden cardiac death or reduced CHD mortality in several prospective cohort studies[721-723] but not in others.[724,725] One study found a trend toward increased relative risk of CHD death with marine n-3 fatty acids. A nested, case-control study found an inverse relationship between risk for sudden cardiac death and both reported intake of marine n-3 fatty acids and red blood cell n-3 fatty acid level.[726] Postulated mechanisms for the effects of marine n-3 fatty acids on CHD risk include favorable effects on cardiac rhythm, platelet aggregation, inflammatory responses, and serum triglyceride levels. High intakes of marine n-3 fatty acids reduce triglyceride levels;[727] this effect appears to be secondary to decreased VLDL production.[728] Generally, marine n-3 fatty acids have no effect on LDL cholesterol levels, but large doses have been shown to reciprocally increase LDL cholesterol levels in persons with hypertriglyceridemia.[729] Recent data indicate that some fish have a high mercury content and the toxic effects of mercury could attenuate protective effects of fish.[730,731]

Four clinical trials suggest that n-3 fatty acids from marine or plant sources reduce sudden death and overall death in populations with pre-existing cardiovascular disease. The DART trial[732] was a relatively large secondary prevention trial in which subjects advised to eat fatty fish had a 29 percent reduction in 2-year all-cause mortality compared with those not so advised, although myocardial infarction and coronary death were not specifically reduced. The Lyon Heart Trial[733] included increased intakes of alpha-linolenic acid as part of a "Mediterranean" diet. Compared to the control group, subjects consuming the Mediterranean diet had fewer coronary events. The authors attributed some of the benefit to higher intakes of n-3 fatty acids. In a small supplement trial, Singh et al.[734] treated patients with suspected acute myocardial infarction with fish oil capsules (EPA 1.08 g/day) or mustard oil (alpha-linolenic acid 2.9 g/day) or placebo. After one year, total cardiac events were significantly less in the groups on fish oil and mustard seed oil supplements. Further, the large placebo-controlled, but unblinded Italian GISSI Prevention trial[735] administered fish oil supplements containing n-3 fatty acids (1 g/day fish oil, n = 2836 subjects) and compared coronary outcomes to controls (n = 2828). The group receiving fish-oil supplements had a 14 percent reduction in total death and a 17 percent reduction in cardiovascular death. Other clinical trials are less suggestive of benefit from n-3 fatty acids. Angiographic data fail to show that marine n-3 fatty acids modify coronary lumen size.[736,737] Also, fish oil administration apparently does not prevent restenosis after coronary angioplasty.[738] Additional studies are underway to determine the effect of n-3 fatty acids on CHD risk in the U.S. population.[241]

Based on these findings, the Dietary Guidelines for Americans (2000)[241] noted that some fish, such as salmon, tuna, and mackerel, contain omega-3 fatty acids that are being studied to determine if they offer protection against heart disease. No quantitative recommendations for n-3 fatty acids were made for the general public.

Evidence statement: The mechanisms whereby n-3 fatty acids might reduce coronary events are unknown and may be multiple. Prospective data and clinical trial evidence in secondary CHD prevention suggest that higher intakes of n-3 fatty acids reduce risk for coronary events or coronary mortality (A2, C2).

Recommendation: Higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of the evidence is only moderate at present. ATP III supports the American Heart Association's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective n-3 fatty acids. However, a dietary recommendation for a specific amount of n-3 fatty acids is not being made (See Section VI for ATP III recommendations on n-3 supplements for reducing risk for CHD.)

Evidence statements: Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1).

Evidence statements: Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2).

Evidence statements: Evidence for an increase in total mortality due to an increased non CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).

Recommendations: Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

c. Other drugs

Probucol is no longer available in the United States and in most other countries. This drug has powerful antioxidant properties, which is theoretically beneficial. In one angiographic trial, probucol therapy failed to retard femoral atherogenesis; neither was a reduction in CHD risk observed. There is some current interest in reports that probucol reduced the restenosis rates following angioplasty.[883,884]

d. n-3 (omega) fatty acids

n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3–12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.

Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD (see Section V.3.c). Although this usage falls outside the realm of "cholesterol management," the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. The n-3 fatty acids can be derived from either foods (n-3 rich vegetable oils or fatty fish) or from fish-oil supplements. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

e. Hormone replacement therapy (HRT)

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature.[885-887] Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either

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