A high intake of saturated fatty acids and cholesterol is associated with a high incidence of occlusive arterial lesions involving both atherosclerosis and thrombosis. The evidence is based on epidemiological, experimental, and clinical studies. Such dietary habits increase serum low density lipoprotein cholesterol, a main risk factor for atherosclerosis. The mechanisms by which dietary saturated fatty acids are connected to arterial thrombogenesis are only partly known. Experimental and epidemiological studies also indicate an association between dietary saturated fatty acids and venous thrombosis; however, the chain of evidence lacks documentation from prospective clinical studies. When unsaturated fatty acids of the (n-9), (n-6), or (n-3) families replace saturated fatty acids in the diet, risk factors related to atherosclerosis may be reduced and the development of atherosclerosis inhibited. This potential is related both to the reduction of saturated fatty acids and, in varying degrees, to the individual unsaturated fatty acids. The very long-chain fatty acids of the (n-3) family and probably also linoleic acid of the (n-6) family have the potential to inhibit thrombogenesis. In this respect, the effect of the individual fatty acids seems even more important. To obtain an optimal dietary lipoprotein composition for the prevention of atherosclerosis and thrombosis, it is important to appreciate the metabolic and structural effects of the individual fatty acids. The interaction between the various dietary fatty acids and their effects on lipid biosynthesis is still only partly known. The present nutritional recommendations include a low intake of saturated fatty acids and cholesterol and a balanced content of the unsaturated fatty acids and represent a well-documented approach to the prevention of both processes. (Arteriosclerosis 10:149–163, March/April 1990)

Both atherosclerosis and thrombosis commonly produce occlusive vascular lesions in humans, which may lead to adverse clinical outcomes, such as stroke, myocardial infarction, or peripheral vascular disease. Since dietary lipids have been associated with the development of both processes, the present review was undertaken to analyze the evidence associating dietary lipids with the development of atherosclerosis, thrombosis, or both. The similarities and differences by which dietary fatty acids and cholesterol affect atherogenesis and thrombosis will be discussed, and data from epidemiologic, clinical, and experimental sources will be used. Finally, dietary recommendations based on our current state of knowledge will be presented.

The studies that initially suggested a relationship between nutrition and atherosclerosis in humans came from the Island of Java in 1916 when deLangen, a Dutch medical practitioner, suggested that the Javanese people had minimal atherosclerosis because their traditional diet contained little cholesterol and fat. When the Javanese were subsequently fed European diets rich in animal fat, their blood cholesterol level increased substantially. Animal studies reported from Russia and Germany showed that rabbits fed egg yolk or other diets rich in fat and cholesterol developed widespread atherosclerosis, a disease not ordinarily seen in that species, whose free-living diet is typically cholesterol-free and low in fat. More than 40 years later in 1959, Thomas and Hartroft fed diets rich in saturated fat and cholesterol containing cholic acid and thiouracil to rats and produced thrombosis and myocardial infarction in the absence of atherosclerosis. A year later, Gresham and Howard showed that by replacing butter with arachis oil in the original diet previously described by Thomas and Hartroft, it was possible to produce both atherosclerosis and thrombosis in the rat. These early studies suggested a direct relationship between nutrition and occlusive vascular lesions. In subsequent years there have evolved several lines of evidence that have related a high intake of dietary saturated fats and cholesterol to hyperlipemia and atherosclerotic cardiovascular disease. Conversely, a reduction in total fat consumption and the replacement of saturated fats...
Table 1. Major Families of Saturated and Unsaturated Fatty Acids

<table>
<thead>
<tr>
<th>Family designation</th>
<th>Parent fatty acid</th>
<th>Examples</th>
<th>Characteristic structure</th>
<th>Principal sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated</td>
<td>Acetic acid</td>
<td>C16:0</td>
<td>H₂C-RCOOH</td>
<td>Synthesis; from animal and vegetable fats</td>
</tr>
<tr>
<td>(n-9)</td>
<td>Oleic acid, 18:1 (n-9)</td>
<td>C20:3 (n-9)</td>
<td>H₂C-C-C-C-C-C-C-C-C=COOH</td>
<td>Synthesis from acetate; animal and vegetable fats</td>
</tr>
<tr>
<td>(n-6)</td>
<td>Linoleic acid, 18:2 (n-6)</td>
<td>C20:4 (n-6)</td>
<td>H₂C-C-C-C-C-C=COOH</td>
<td>Many vegetable oils</td>
</tr>
<tr>
<td>(n-3)</td>
<td>α-Linolenic acid, 18:3 (n-3)</td>
<td>C20:5 (n-3)</td>
<td>H₂C-C-C-C-C=COOH</td>
<td>Some vegetable oils (18:3); marine oils (20:5, 22:6)</td>
</tr>
</tbody>
</table>

The n number indicates the location of the first double bond counting from the methyl end of the fatty acid. An alternative nomenclature uses omega (ω) instead of n.

Table 2. Common Dietary Sources of Fatty Acids

<table>
<thead>
<tr>
<th>Type of fatty acid</th>
<th>Saturated</th>
<th>Monounsaturated</th>
<th>Linoleic</th>
<th>Arachidonic</th>
<th>α-Linolenic</th>
<th>Eicosapentaenoic, docosahexaenoic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly saturated cow milk fat</td>
<td>62</td>
<td>35</td>
<td>2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human milk fat</td>
<td>50</td>
<td>42</td>
<td>7</td>
<td>0.7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Beef tallow</td>
<td>48</td>
<td>47</td>
<td>4</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beef liver</td>
<td>39</td>
<td>44</td>
<td>10</td>
<td>6.0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Coconut oil</td>
<td>88</td>
<td>10</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocoa butter</td>
<td>60</td>
<td>37</td>
<td>3</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palm oil</td>
<td>48</td>
<td>43</td>
<td>9</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly monounsaturated olive oil</td>
<td>14</td>
<td>77</td>
<td>8</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken fat</td>
<td>33</td>
<td>49</td>
<td>17</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg yolk</td>
<td>37</td>
<td>48</td>
<td>13</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanut oil</td>
<td>29</td>
<td>51</td>
<td>19</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lard</td>
<td>36</td>
<td>53</td>
<td>10</td>
<td>0.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Predominantly (n-6) safflower oil</td>
<td>9</td>
<td>17</td>
<td>73</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn oil</td>
<td>13</td>
<td>29</td>
<td>57</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cottonseed oil</td>
<td>26</td>
<td>24</td>
<td>50</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunflower seed oil</td>
<td>10</td>
<td>34</td>
<td>56</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly (n-3) linseed oil</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>55.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon oil</td>
<td>26</td>
<td>59</td>
<td>1</td>
<td>1.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>19</td>
<td>54</td>
<td>2</td>
<td>1.0</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Mackerel oil</td>
<td>35</td>
<td>34</td>
<td>2</td>
<td>2.0</td>
<td>1.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Whale oil</td>
<td>19</td>
<td>68</td>
<td>1</td>
<td>4.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Both (n-6) and (n-3) soybean oil</td>
<td>15</td>
<td>27</td>
<td>51</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New rapeseed oil</td>
<td>8</td>
<td>64</td>
<td>20</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>English walnut oil</td>
<td>11</td>
<td>23</td>
<td>55</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Information is from references 26 and 126.

With unsaturated fats that are rich in fatty acids from the (n-9), (n-6), and particularly the (n-3) families may inhibit, or even reverse, pre-existing vascular lesions. The evidence relating diet to atherosclerosis and thrombosis is based on: 1) epidemiological studies, 2) animal experiments, 3) dietary intervention studies and drug trials, 4) studies based on the effects of diet on risk factors, and 5) cellular studies. For reference, the major families of dietary fatty acids are provided in Table 1, and their common dietary sources are outlined in Table 2.
Epidemiologic Relationships between Diet and Coronary Heart Disease

Beginning with a study1 that suggested a relationship between diet and coronary heart disease (CHD) published in 1916, a series of epidemiological studies,2-13 which included diverse populations from all over the world, has shown highly significant correlations between daily intake of saturated fats and cholesterol and mortality from CHD (Figure 1). When data from reports of national food consumption in 30 different countries were related to mortality rates from CHD in men ages 55 to 59 years, statistically significant positive correlations were found between the consumption of animal and dairy products and mortality (Table 3). The 15-year death rate in the Seven Countries Study showed that the mortality from CHD and all causes was negatively related to the energy percent from dietary monounsaturated fatty acids such as olive oil.14 In this analysis, death rates were unrelated to the intake of polyunsaturated fats in the diet.

Observations in Norway during the Second World War showed that reductions in postsurgical thrombosis and mortality from CHD were both related to a drastic reduction in the consumption of dietary saturated fatty acids due to wartime food shortages.15,16 However, it should be emphasized that during the same period the Norwegians also had a marked increase in the consumption of fish.17 More recently, a new dimension in the relationships between dietary fats and mortality from CHD was suggested by Dyerberg and coworkers,18 who noted that the Greenland Eskimos, who were eating a traditional diet low in saturated fatty acids, but high in cholesterol (0.79 g/day) and high in eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids of the (n-3) family, appeared to have a low incidence of CHD. A similar relationship has been reported in a coastal Japanese population.19

Table 3. Correlations between Mortality Rates from Coronary Heart Disease and Intake of Certain Dietary Nutrients

<table>
<thead>
<tr>
<th>Nutrient Intake</th>
<th>Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive correlations*</td>
<td></td>
</tr>
<tr>
<td>Animal protein</td>
<td>0.782</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.762</td>
</tr>
<tr>
<td>Meat</td>
<td>0.697</td>
</tr>
<tr>
<td>Total fat</td>
<td>0.676</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.666</td>
</tr>
<tr>
<td>Sugar</td>
<td>0.638</td>
</tr>
<tr>
<td>Total calories</td>
<td>0.633</td>
</tr>
<tr>
<td>Animal fat</td>
<td>0.632</td>
</tr>
<tr>
<td>No correlations†</td>
<td></td>
</tr>
<tr>
<td>Plant sterols</td>
<td>0.144</td>
</tr>
<tr>
<td>Fish</td>
<td>0.013</td>
</tr>
<tr>
<td>Vegetable fat</td>
<td>0.011</td>
</tr>
<tr>
<td>Vegetables</td>
<td>0.009</td>
</tr>
<tr>
<td>Negative correlations*</td>
<td></td>
</tr>
<tr>
<td>Starch</td>
<td>-0.464</td>
</tr>
<tr>
<td>Vegetable protein</td>
<td>-0.403</td>
</tr>
</tbody>
</table>

Data were derived from the national statistics about food consumption and deaths from 30 different countries in men ages 55 to 59 years (from reference 8).
*<p<0.05.
†Data available from only 29 countries.
‡p>0.05.
A recent worldwide epidemiological study has confirmed a negative correlation between fish consumption and mortality from CHD when adjustments were made for dietary cholesterol intake (Artaud-Wild SM, Connor WE, personal communication). However, there is conflicting evidence in the literature regarding the relationship between fish consumption and death from CHD in various population groups consuming a Western diet. In a study from the town of Zutphen in Holland, an inverse relation between the amount of fish eaten each week and the mortality from CHD was reported. The consumption of as little as 35 g of fish per day was associated with a 50% lower mortality than when no fish was consumed. This observation was confirmed in two studies, whereas no relation between fish consumption and deaths from CHD was observed in others.

In a recent study from Norway, the mortality of CHD was actually higher in a coastal-dwelling population who were consuming approximately three times more fish than an inland population. A recent study from Canada may indicate a similar pattern. In both these studies, the population groups with a high fish consumption also had a high intake of saturated fatty acids.

In summary, a series of epidemiological studies has established a direct relationship between the intake of dietary fatty acids and cholesterol and atherosclerotic vascular disease, whereas an inverse relation has been suggested for the dietary content of monounsaturated fatty acids. The possible relationships between dietary polyunsaturated fatty acids of the (n-3) and (n-6) families and cholesterol have not yet been firmly established. However, a high intake of (n-3) fatty acids in populations with a moderate to low consumption of dietary saturated fatty acids is definitely associated with a low incidence of CHD.

Diet in Experimental Atherosclerosis and Thrombosis

Experiments in a variety of animal species have shown that dietary factors may influence the development of atherosclerosis. When diets rich in saturated fatty acids and cholesterol were given to nonhuman primates, hypercholesterolemia and atherosclerotic lesions, which were occasionally complicated by gangrene or myocardial infarction occurred. Hypercholesterolemia and atherosclerosis may also be produced by feeding diets rich in saturated fatty acids and cholesterol to animal species that normally do not eat these foods. Conversely, regression of diet-induced atherosclerotic lesions has been produced in the rhesus monkey by a cholesterol-free diet.

Recent studies in swine have shown that the addition of cod-liver oil to a diet rich in saturated fat and cholesterol produced significantly less coronary atherosclerosis, despite the fact that severe hypercholesterolemia persisted in the animals fed the fish-oil diet. A similar effect has been reported in monkeys. However, in this study, fish oil replaced fatty acids in the diet, and the inhibition of aortic atherosclerosis was paralleled by a reduction of plasma total cholesterol from 800 to 400 mg/dl. In rabbits, the addition of a fish-oil supplement to the diet did not inhibit cholesterol-induced atherosclerosis, although serum cholesterol levels were higher than 1400 mg/dl in all animals.

In 1959, Thomas and Hartroft fed experimental diets to rats and produced thrombosis and myocardial infarction. Since that time, experiments with several different thrombosis models in animals have demonstrated an association between dietary fats and the development of thrombosis, which is unrelated to atherosclerosis. Each of these models has shown that diets rich in saturated fatty acids appear to be thrombogenic, with or without the addition of cholesterol. Polysaturated fatty acids of both the (n-6) and the (n-3) families counteracted the thrombogenic effect of the saturated fatty acids in some instances. However, in many of the studies, the possible beneficial effects of the polyunsaturated fatty acids have been difficult to evaluate, because the feeding of saturated fatty acids was often concomitantly reduced in the experimental animals. Similarly, many of the diets rich in saturated fatty acids also contained large amounts of other fatty acids, making the evaluation of the thrombogenic potential of the various fatty acids difficult.

Early studies showing an antithrombogenic effect of (n-3) fatty acids in rats used α-linolenic acid 18:2(n-3) as a substitute for dietary fatty acids, which was more effective than replacement with linoleic acid 18:2(n-6). Of special interest is the ability of the rat to elongate and desaturate α-linolenic acid to the highly unsaturated, very long-chain fatty acids of the (n-3) family. These fatty acids increased more than 10-fold in the platelet phospholipids of rats fed α-linolenic acid. Diets rich in cod-liver oil with a high content of EPA and DHA also showed antithrombogenic effects in the rat. When fish oil was used in similar experiments in different species of animals, the antithrombogenic effects were confirmed. The plasma, platelet, and/or tissue (n-3) fatty acids increased three- to 10-fold, with a parallel decrease in (n-6) polyunsaturated fatty acids, especially arachidonic acid. Many of the animal studies are unfortunately designed with a lipid content much higher than what is practical for human diets. Thus, species differences related to lipid metabolism, and experimental design in many animal studies reduces the relevance of such studies for the understanding of human thromboatherosclerosis.

Dietary Intervention Studies in Humans

All of the intervention studies performed to date in humans have attempted to determine whether a reduction in CHD can be produced by experimental manipulation of the diet. No distinction has been made as to whether thrombosis, atherosclerosis, or both have been altered. Since arterial thrombosis has been shown to be present in more than 90% of patients with acute myocardial infarction, the results of the intervention studies may reflect the effects of dietary changes on both atherosclerosis and thrombosis.

The early dietary intervention studies consistently showed that it was possible to significantly reduce the blood cholesterol concentration, one of the most important risk factors for the development of CHD. The
dietary changes in these trials included a reduction of saturated fatty acids and cholesterol and an increase in polyunsaturated fatty acids of the (n-6) family. Morbidity from CHD was regularly reduced; however, the data on mortality were inconclusive regarding the effect of the dietary intervention programs.

The large Multiple Risk Factor Intervention Trial (MRFIT) was designed to reduce simultaneously over a period of 6 years three major risk factors in middle-aged men who were at increased risk for CHD: elevated serum cholesterol, increased blood pressure, and excessive cigarette smoking. A significant reduction in risk factors was accomplished in the intervention group, but there was also a reduction, although less pronounced, in the control group. In both groups, the survivors had a greater reduction in serum cholesterol than did those participants who ultimately died from CHD. This suggests that a reduction in serum cholesterol by changes in the diet is associated with a lower mortality from CHD. However, the MRFIT Study was inconclusive in respect to overall mortality from CHD.

The primary prevention trial carried out by the Oslo Study Group51,52 lasted 8.5 years and included 1200 high risk men. This trial showed a reduction of total fat intake from 41% (controls) to 28% of calories and an assumed change in the polyunsaturated/saturated fat (P/S) ratio from 0.4 to approximately 0.7 (based on a 1-week dietary registration and a 4-day registration and weighing of the diet of subgroups) reduced CHD events, including CHD death and sudden death, by approximately 50% (Figure 2). The reduction in P/S ratio was caused mainly by reduction of saturated fatty acids. Approximately 75% of the beneficial effects observed in the Oslo Study appeared to be due to the changes in long-term dietary habits of the participants, whereas 25% were related to changes in smoking habits.53

Studies investigating the effects of dietary supplements of (n-3) polyunsaturated fatty acids on arterial disease in men, in which atherosclerosis and thrombosis represent the pathological substrates, are currently in progress. There have been several studies examining the possible beneficial effects of fish oil on the rate of restenosis after coronary artery angioplasty in patients taking aspirin. The cause of restenosis is unclear, but factors related both to thrombi and atheroma are involved.54,55 Two of the reports showed a reduction in the rate of restenosis, whereas a third study failed to show any effect.56,57,58

Several studies59-60 have examined the efficacy of drugs that lower plasma cholesterol or block platelet production of thromboxane A2, which were given in addition to diet modification, for the prevention of CHD. These studies may have some relevance for the evaluation of dietary intervention. Cholesterol-lowering drugs may reduce serum cholesterol even more efficiently than a reduction of dietary saturated fatty acid and cholesterol content. An increase of dietary (n-3) fatty acids reduces the platelet production of thromboxane A2, as does aspirin. However, it is obvious that the effects of drugs and diet may act by different mechanisms even if they have some actions in common. In the Lipid Research Clinics Coronary Primary Prevention Trial,59 cholesterol-tyramine was used to lower serum cholesterol concentration in men with hypercholesterolemia, and there was a significant reduction in CHD events. In several secondary and one primary prevention trial in which aspirin was administered to inhibit platelet aggregation, a significant reduction in nonfatal myocardial infarction and in death caused by acute myocardial infarction was found.60,61 However, another primary prevention trial52 failed to confirm a beneficial effect of aspirin therapy. Thus, the effect of drugs acting by mechanisms similar to those obtained by dietary intervention, on CHD seems to strengthen the indication for dietary changes.

In summary, the dietary intervention studies that are now available suggest that a reduction in the intake of dietary fatty acids and cholesterol may be beneficial in the prevention of atherosclerosis or thrombosis in humans. The amounts of polyunsaturated fatty acids of the (n-6) and (n-3) families in an optimal diet is not clear at present and will require additional controlled, prospective, randomized clinical trials. Dietary intervention studies have not yet explored the relationships, if any, between the intake of monounsaturated fatty acids and CHD. The evidence for a relation between CHD and diet still rests mainly on epidemiologic studies. The problems involved in designing and carrying through dietary intervention studies that may provide definitive answers may be so difficult that they will likely not be performed in the near future.

Figure 2. The cumulative incidence of coronary events (i.e., fatal and nonfatal myocardial infarction and sudden death) in men 40 to 49 years of age with increased risk factor level for coronary heart disease who participated in an Intervention program for 60 months and were followed up for an additional 42 months (the Oslo Study Diet and Antismoking Trial).
which in turn may further enhance the atherosclerotic process.

Risk factors for human atherosclerosis that may be influenced by diet are elevated levels of serum total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides, and reduced levels of high density lipoprotein (HDL) cholesterol. In contrast, the risk factors related to arterial thrombosis are not well defined. However, increased platelet vascular interactions, heightened activity of the coagulation system, or inhibition of fibrinolysis have been associated with an increased likelihood of thrombosis. Abnormalities in coagulation and fibrinolysis have generally been associated with venous thrombosis, whereas platelet and endothelial cell disturbances have been linked to the formation of arterial thrombi. The reduction in mortality from CHD and the parallel reduction in pulmonary emboli and venous thrombosis observed in the United States during the last decade, when taken in concert with the observations from Norway during the Second World War, may suggest common pathogenic factors for arterial and venous thrombosis. However, the nearly fourfold increase of phlebograms taken in the United States during the last 15 years may indicate that the decline in pulmonary emboli has been due to increased vigor in the treatment and diagnosis of venous thrombosis, not to dietary changes.

**Saturated Fats and Cholesterol**

A high intake of saturated fatty acids and cholesterol in the diet may lead to hypercholesterolemia, largely due to an increase of LDL. Hypercholesterolemia is defined as an LDL cholesterol level higher than 160 mg/dl. Palmitic and myristic acids (common saturated fatty acids in foods) appear to produce substantially more hypercholesterolemia than stearic acid, which has little, if any, effect upon serum cholesterol. However, the hypercholesterolemic potential of a given food may be calculated by use of the cholesterol/saturated fat index (CSI). CSI reflects the hypercholesterolemic and atherogenic potential of a given amount of food measured against another nutrient.

In a series of studies in nonhuman primates, hypercholesterolemia has been shown to induce monocytoid adherence, subendothelial migration, smooth muscle cell proliferation, and lipid accumulation in the vessel wall. After hypercholesterolemia had been present for several months, endothelial cells were found to be retracted and, in some instances, the appearance of mural thrombi was observed. These studies suggest that endothelial cell function is altered before obvious visible changes or frank desquamation of the endothelial cells occur. These changes in the vessel wall may thus be related to both atherosclerosis and thrombosis and, therefore, may represent a link between dietary lipids, hyperlipidemia, and vascular occlusive lesions leading to organ ischemia or infarction.

Hypercholesterolemia, induced by a high dietary intake of saturated fatty acids and cholesterol, has also been linked with processes that may be involved in thrombogenesis. In addition to the effects on endothelial cells discussed above, elevated levels of plasma LDL have been related to increased platelet coagulant activity, platelet aggregation, thromboxane A2 production, and shortened platelet survival in vivo. However, the results of the platelet function studies in patients with familial or secondary hypercholesterolemia have not been entirely consistent (for a review see references 87 and 88). Elevated blood cholesterol levels have also been associated with increases in prothrombin and coagulation factors VII and X. High fibrinogen levels have also been related to increases in serum cholesterol and to heightened cardiovascular risk. Of particular interest is the increased conversion of factor VII to its activated form (VIIa) in subjects with hyperlipidemia, particularly those with high levels of triglycerides.

Elevated factor VII coagulant activity has also been observed in diet-induced hypercholesterolemia in animals and in human subjects given a high fat diet. An association with postprandial lipemia has also been observed. In vitro the activated form of factor VII has a coagulant activity that is many times that of the nonactivated factor VII, and in prospective studies, the level of factor VII was an independent predictor of ischemic heart disease.

The mechanisms by which lipoproteins act on the concentration and activity of these clotting factors is not yet known. Others have suggested that the phospholipids on which the coagulation proteins usually act are made available by these lipoprotein molecules.

Reduced plasma fibrinolytic activity has also been observed in subjects with hyperlipidemia. The serum triglycerides and very low density lipoproteins (VLDL) seem to be the lipid fractions most closely associated with inhibitors of the fibrinolytic system. Moreover, recent studies have connected lipoprotein(a) (Lp[a]) with both a familial occurrence of CHD and impaired fibrinolytic activity through the relationship with plasminogen.

A high intake of saturated fatty acids in the diet could also affect thrombogenesis in a way unrelated to the effect on LDL concentrations. Renaud's group has reported a correlation between saturated fatty acids in the diet, the occurrence of eicosatrienoic acid 20:3(n-9) in platelet phospholipids, increased platelet aggregation induced by thrombin, and heightened platelet procoagulant activity. Eicosatrienoic acid is a fatty acid usually found in patients given an essentially fatty acid-free diet, but this acid appeared in small, but significant, amounts in the study population receiving a high amount of saturated fatty acids. Further studies established that eicosatrienoic acid potentiates the effects of platelet aggregating substances, probably via the formation of a lipoygenase product by platelets. In more recent dietary studies performed in rats, it was confirmed that feeding saturated fatty acids led to the appearance of eicosatrienoic acid in the platelet phospholipids. However, in the rat, addition of cholesterol and taurocholate to the diet was required to induce changes in platelet function and to shorten platelet survival. This and other dietary studies in rats indicate that dietary saturated fats...
may also produce an increase of oleic acid (18:1[n-9]) and di-homo-gamma-linolenic acid (20:3[n-6]) and a decrease of docosatetraenoic acid (22:4[n-6]) fatty acid in platelet lipids. These changes have been associated with an increased sensitivity of platelet aggregation to thrombin.\textsuperscript{114,115}

In a recent study\textsuperscript{116} rabbits were fed diets containing 20% fat composed of corn oil, cocoa butter, or milkfat with or without the addition of 0.2% cholesterol for 300 days. The animals that were given the saturated fatty acids had the highest concentrations of oleic acid (18:1[n-9]) and arachidonic acid (20:4[n-6]), with the latter fatty acid being particularly prominent in the animals fed milkfat. The observed fatty acid changes were not affected by the cholesterol supplement, and they were not associated with changes in adenosine 5'-diphosphate (ADP) or collagen-induced platelet aggregation. The potential of dairy fats to increase the arachidonic acid content in platelets, thus increasing the amount of substrate for thromboxane A\textsubscript{2} production, may be of significance for the thrombogenic effects of such dietary lipids.

In summary, high quantities of cholesterol and saturated fats in the diet may induce hypercholesterolemia, which is a significant risk factor for atherosclerosis. Hypercholesterolemia may also be associated with changes in coagulation factors and platelets, which favor thrombus formation. A diet rich in saturated fatty acids may also directly influence platelet and endothelial cell function by altering the fatty acid composition of these cells. These changes, representing long-term effects of such diets, may also be accompanied by the acute effects of post-prandial lipoproteins on coagulation and fibrinolytic activities, which favor thrombosis. Unfortunately, tests that will identify subjects who are at increased risk for arterial thrombosis as a consequence of a diet rich in saturated fatty acids or cholesterol are not yet available. We suggest that the primary bleeding time may be such a test, but we do not yet know the clinical significance of a shortened bleeding time. It must be emphasized that so far no prospective clinical study has established any relationship between hypercholesterolemia and venous thrombosis or pulmonary embolii.

Dietary Monounsaturated Fatty Acids

The low prevalence of CHD in the Mediterranean region of the world, where the consumption of olive oil and, thus, oleic acid (18:1[n-9]) is high, and a similar high intake of monounsaturated fatty acids among Greenland Eskimos, who also reportedly have a low incidence of CHD, may indicate a beneficial effect of these fatty acids on the development of CHD.\textsuperscript{14,117} Monounsaturated fatty acids have been considered neutral, i.e., neither raising nor lowering plasma lipids.\textsuperscript{78} Similarly, no thrombogenic or antithrombotic tendency has been associated with oleic acid in experimental studies.\textsuperscript{118} Recent studies\textsuperscript{119-122} with liquid formulas or mixed food diets containing 30% to 40% of calories as fat derived mainly from olive oil have shown a reduction of both total serum cholesterol and LDL cholesterol, whereas HDL cholesterol was usually unaffected. The LDL/HDL cholesterol ratio, an important risk factor for atherosclerosis, was significantly lower than the ratio produced by control diets rich in (n-6) polyunsaturated fatty acids or by diets with a low (20%) fat content.

Little data are currently available on the effects of dietary monounsaturated fatty acids on thrombogenesis. In healthy subjects given a low fat diet (28%) with 64% of total fatty acids as monounsaturated acids over a period of 8 weeks, the magnitude of platelet aggregation induced by collagen was reduced compared to the results of a similar diet rich in polyunsaturated (n-6) fatty acids.\textsuperscript{122} When platelets have been incubated with oleic acid in vitro or endothelial cells have been grown in culture with the medium enriched with oleic acid, neither thromboxane A\textsubscript{2} nor prostacyclin production has been significantly changed from that observed in cells from control cultures.\textsuperscript{46}

In summary, monounsaturated fatty acids, or more precisely oleic acid, may prove to be useful in decreasing the risk of atherosclerotic vascular disease. Further investigations into the possible relationships of dietary monounsaturated fatty acids and lipid metabolism and thrombosis are needed.

Dietary (n-6) Polyunsaturated Fatty Acids

The Seven Countries Study\textsuperscript{14} failed to demonstrate a correlation between increased dietary polyunsaturated fatty acids and reduced death rates from CHD. However, it has been known for more than 30 years that vegetable oils rich in (n-6) polyunsaturated fatty acids have a hypocholesterolemic effect in humans.\textsuperscript{8,123,124} It should be emphasized that in most studies that suggest such an effect of the (n-6) fatty acids, two variables have been changed at the same time: a reduction in saturated and an increase in polyunsaturated fatty acids.\textsuperscript{8} The magnitude of this effect has been related to the contents of polyunsaturated and saturated fatty acids as percents of total calories and the content of cholesterol in the diet.\textsuperscript{76,125,126} The predictive equations developed by Hegsted et al.\textsuperscript{78} and Keys et al.\textsuperscript{79,127} indicated that on a gram-for-gram basis, saturated fatty acids will raise cholesterol levels about twice as much as polyunsaturated fatty acids will lower them. In a series of studies, the average P/S ratio of the polyunsaturated diet was 4.6 versus 0.17 of the saturated diet. This difference was associated with an average total cholesterol decrease of 20%.\textsuperscript{120} The main effect of the polyunsaturated fatty acids was a lowering of the LDL cholesterol concentration.\textsuperscript{128} However, when a low fat diet (23% of calories) was given, an increase of the P/S ratio from 0.4 to 0.9 did not change the LDL or HDL concentrations.\textsuperscript{129}

These studies indicate that the P/S ratio, as such, should not be used as a predictor for the hypocholesterolemic or antiatherogenic effects of a given diet. The actual lipid content and fatty acid composition of the diets are of significance. We predict that future computer programs will more accurately predict the effect of a diet on the blood lipids of a given person.

The effect of polyunsaturated fats of the (n-6) family on the LDL and the HDL subfractions is related to the total fat
intake, the intake of saturated fatty acids, and the duration of the dietary intervention. Variable results reported in the literature may be explained in part by differences in the experimental conditions. Controlled metabolic studies indicate that a marked reduction in plasma HDL levels does not occur during polyunsaturated fatty acid feeding. However, when HDL concentrations were reduced, LDL concentrations had a similar or even greater reduction, leading to a constant LDL/HDL cholesterol ratio. The mechanisms involved in the hypolipidemic effect of the polyunsaturated (n-6) fatty acids have still not been completely clarified, although the effects on membrane composition and fluidity may be important.

The effects of the various (n-6) polyunsaturated fatty acids on thrombosis have been only partially elucidated. However, the discovery that 20:3(n-6) and 20:4(n-6) may serve as precursors for eicosanoids (Table 4), potent vasoactive and platelet reactive substances produced in platelets and endothelial cells, has focused attention on the potential role of these fatty acids in thrombus formation. Increased dietary intake of (n-6) polyunsaturated fatty acids, usually in the form of linoleic acid, is regularly followed by increased amounts of 18:2(n-6) in platelet phospholipids, with a concomitant decrease of arachidonic acid, which is regularly followed by increased amounts of 18:2(n-6) in platelet phospholipids, with a concomitant decrease of arachidonic acid.

The subsequent changes in platelet function seem to be, at least partly, related to the ratio of 18:2(n-6)/20:4(n-6) found in the platelet phospholipids. In most of the studies that have been performed in humans, dietary supplementation with (n-6) polyunsaturated fatty acid has been associated with a mild reduction in platelet aggregation induced by low concentrations of thrombin, prolonged platelet aggregation in the filter-grometer, and reduced platelet factor 3 activity. Stimulated thromboxane B2 (TXB2) production by platelets was significantly reduced in some studies, but in others, collagen-stimulated TXB2 production was similar to that found in controls.

The cutaneous bleeding time has not been prolonged in subjects with a high dietary intake of (n-6) polyunsaturated fatty acids, although measurements in subjects with a high consumption of (n-6) polyunsaturated fatty acids over prolonged periods of time have not been reported. Cultured endothelial cells grown in medium enriched with linoleic acid increase their content of 18:2(n-6), whereas arachidonic acid decreases it. These changes are paralleled by a reduced production of prostacyclin (PGI2) after stimulation of the cells with various agonists. A reduction of the daily urinary excretion of eicosanoids has been observed when the dietary linoleate level was increased from 3% to 6% of total calories. Cultured endothelial cells incubated with arachidonic or linoleic acids synthesize a lipoxigenase product, 13-hydroxylinoleic acid, which decreases platelet adhesion and may be a factor promoting thrombo-resistance of the vascular endothelium. A series of other products derived from (n-6) polyunsaturated fatty acid precursors are also synthesized by endothelial cells, but their functions have not yet been well characterized.

In conclusion, dietary fatty acids of the (n-6) family, principally linoleic acid, have effects on platelet and endothelial cell composition and function that may help to explain some of the antithrombogenic effects observed in experimental animal models of thrombosis. At present, however, the optimal amounts of these fatty acids in the human diet required to inhibit thrombosis is not known. Recent dietary intervention studies in humans may indicate that when a low saturated fatty acid diet (10%) is given, a moderate intake of polyunsaturated fatty acids (P/S ratio, 0.6 of 0.8) reduces both thrombin and ADP-induced platelet aggregation and platelet procoagulant activity to a greater extent than does a larger intake of polyunsaturated fatty acids (P/S ratio 1 to 3). The suppression of urinary eicosanoids by dietary linoleate may indicate reduced platelet/endothelial cell interaction; however, more detailed knowledge about the effects of the dietary (n-6) polyunsaturated fatty acids on the individual prostaglandins is needed to evaluate the significance of this observation. These studies may indi-
cate that there may be both a critical upper and lower limit for the content of dietary (n-6) polyunsaturated fatty acids in respect to a possible beneficial effect on thrombosis.\textsuperscript{148,149,150} These limits may need to be modified to account for the intake of the other dietary lipids, particularly saturated fatty acids.

### Dietary (n-3) Polyunsaturated Fatty Acids

The pioneering studies by Dyerberg and his co-workers\textsuperscript{18} and Bang et al.\textsuperscript{117} linking highly polyunsaturated (n-3) fatty acids in the diet to a low mortality from cardiovascular disease among the Greenland Eskimos, have stimulated further work to explore the mechanisms that might be involved in this relationship.\textsuperscript{26,128,151} The relationships between dietary lipids, atherosclerosis, and thrombosis are highlighted by the (n-3) polyunsaturated fatty acids, which affect both plasma lipid composition and platelet-endothelial cell interactions.

When eating their traditional diet, the Eskimos were found to have a significantly lower total cholesterol, LDL cholesterol, and VLDL cholesterol, and a higher HDL cholesterol than did Danes.\textsuperscript{152,153} The effect of a diet rich in fish oils on serum cholesterol concentrations has been known for many years.\textsuperscript{154} For example, in one study 22.5(n-3) and 22.6(n-3) fatty acids were six to seven times more effective than linoleic acid in lowering total serum cholesterol.\textsuperscript{155} Other studies have reported variable effects of a dietary supplement of (n-3) fatty acids on LDL concentrations in persons with normal blood lipids and in patients with hyperlipoproteinemia.\textsuperscript{156,157} A recent review\textsuperscript{158} on the effects of fish oils on plasma lipids and lipoprotein metabolism in humans concludes that when fish oils are fed and saturated fatty acid is constant, LDL cholesterol either does not change or may increase. HDL cholesterol has generally been reported to be unchanged after fish-oil feeding, although slightly increased levels (5% to 10%) have also been observed.\textsuperscript{158,159,161}

However, the most dramatic difference between dietary (n-6) and (n-3) fatty acids is the ability of the (n-3) fatty acids to lower plasma triglycerides and VLDL in both normolipidemic and hyperlipidemic subjects.\textsuperscript{151,159,160} The reduction of VLDL levels by (n-3) polyunsaturated fatty acids is the ability of the (n-3) fatty acids to lower plasma triglycerides and VLDL in both normolipidemic and hyperlipidemic subjects.\textsuperscript{151,159,160} The reduction of VLDL levels by (n-3) polyunsaturated fatty acids is produced largely by a suppression of hepatic triglyceride and VLDL production,\textsuperscript{162,163} although other mechanisms also may be involved.\textsuperscript{20} Thus, in a recent study it was suggested that a fish-oil diet inhibited or delayed the synthesis and/or secretion of chylomicrons from the gut.\textsuperscript{164} A reduction in chylomicrons could subsequently reduce the levels of the cholesterol-rich remnant particles that have been associated with atherosclerosis.\textsuperscript{152,165} Elevated plasma triglycerides were found to be an independent predictor for CHD in women in the Framingham Heart Study.\textsuperscript{167} Hypertriglyceridemia has also been defined as an independent risk factor in men.\textsuperscript{168,169} Although in other population studies, the plasma triglycerides have probably reflected the presence of certain atherogenic lipoproteins rather than being a direct cause of atherosclerotic disease.\textsuperscript{78,170} The hemostatic profile of the Greenland Eskimos was characterized by prolonged bleeding times and reduced platelet aggregation by collagen and ADP when comparisons were made to a European control population.\textsuperscript{171} These differences in platelet function were associated with increased concentrations of (n-3) polyunsaturated fatty acid and decreased arachidonic acid in the platelet phospholipids. As a consequence, the (n-3)-rich platelets were postulated to produce reduced amounts of TXA\textsubscript{2} with increased synthesis of poorly functional TXA\textsubscript{2} by the platelets. Similar changes were proposed for vascular endothelial cells, with a reduction in PGI\textsubscript{2} production but with synthesis of PGI\textsubscript{3}, which has been shown to retain biologic function.\textsuperscript{18} A recent examination of the urinary excretion of eicosanoid metabolites has now shown that in addition to production of PGI\textsubscript{3}, the Eskimos maintained normal or even increased synthesis of PGI\textsubscript{2}.\textsuperscript{172} These findings in Eskimos would suggest that the (n-3) fatty acids could reduce the propensity for thrombosis in man. Short- and long-term nutritional studies, both in healthy persons and in patients with hyperlipemias and cardiovascular diseases, have confirmed these observations in the Eskimos (for reviews see references 28, 128, and 151). However, only moderate effects on platelet function have been found in most of these studies, and these have been associated with rather large individual variations in the experimental data.

In addition to the effects of fish oil and (n-3) fatty acids on platelet and endothelial cell function mentioned above, diets rich in fish oils may reduce cellular production of leukotriene \(\text{B}_4\) with the appearance of leukotriene \(\text{B}_4\), leading to a subsequent reduction of inflammatory responses at the site of thrombus formation or vascular injury.\textsuperscript{173,174} Increased plasma levels of antithrombin III and tissue plasminogen activator, and decreased levels of fibrinolytic inhibitors, along with endothelial-dependent relaxation of coronary arteries in response to thrombin and ADP, have also been associated with dietary supplementation of (n-3) polyunsaturated fatty acids.\textsuperscript{175,176,177} Lastly, changes in the composition of erythrocyte membranes, with increased erythrocyte deformability and a decrease in whole blood viscosity ex vivo, have also been reported.\textsuperscript{178,179,180} Some of these changes may theoretically influence thrombus formation in man, although direct evidence of an antithrombotic effect in humans is lacking. A recent study including 2033 men who had recovered from myocardial infarction showed that subjects advised to eat fatty fish had a 29% reduction in 2-year all-cause mortality compared with those not so advised.\textsuperscript{181} The incidence of re-infarction plus death from CHD was not significantly affected.

In summary, research conducted over the last 10 years has established that dietary highly polyunsaturated (n-3) fatty acids from marine sources may influence both thrombosis and atherosclerosis. The mechanisms involved are still only partly understood, and the tests that might be used to measure or monitor the antithrombotic effects of fish oil have not been established. Finally, data are not yet available to indicate the dose or composition of fish or fish-oil concentrates needed to optimize a potential antithrombotic or antiatherosclerotic effect in humans.
Conclusions

Atherosclerosis and thrombosis are the two main processes involved in occlusive vascular diseases. The evidence that dietary fatty acids may influence these pathologic events is summarized below.

Epidemiological Evidence

The great majority of the reports in the literature have related a high intake of saturated fatty acids and cholesterol to increased mortality from CHD, including both atherosclerosis and thrombosis. In contrast, a high intake of the unsaturated dietary fatty acids from the (n-9), (n-6), and (n-3) families is associated with a lower mortality from CHD. The optimal dietary concentration of each of these groups of fatty acids needed to prevent or modify vascular disease are not yet known, but all epidemiological evidence indicates that a low intake of saturated fatty acids is beneficial.

Animal Model Evidence

In many animal species, the feeding of cholesterol and saturated fatty acids regularly induces atherosclerosis, whereas the substitution of polyunsaturated fatty acids of the (n-6) or the (n-3) families for saturated fatty acids reduces atherosclerosis. Saturated fatty acids appear to be thrombogenic when compared to the polyunsaturated fatty acids. The (n-3) fatty acids appear to be more antithrombotic than the dietary unsaturated fatty acids of the (n-6) series. The relevance of many animal dietary studies for the pathogenesis of human vascular disease is questionable.

Evidence from Intervention Studies

In general, the intervention studies have supported the analyses of the epidemiological data. However, they are all limited by the consequences of implementing dietary changes over a prolonged period of time in persons with a traditionally different diet. These studies suggest that a reduction of dietary, saturated fatty acids and cholesterol in persons with increased risk for developing CHD reduces the mortality from atherosclerotic and thrombotic cardiovascular disease. The intervention study that showed the most significant effect utilized a diet with a P/S ratio of approximately 0.7 and resulted in a reduced serum total cholesterol of about 10%. The overall mortality from CHD in these subjects was decreased by approximately 50%. 52,148

Evidence Related to Dietary Risk Factors for Atherosclerosis and Thrombosis

Saturated Fatty Acids and Cholesterol

A high intake of these dietary lipids results in increases of both total serum cholesterol and LDL cholesterol, two important risk factors for development of atherosclerosis. The association between high serum cholesterol levels and factors related to increased thrombotic tendency is questionable. Experimental studies indicate a positive correlation between saturated fatty acids and thrombosis.

Monounsaturated Fatty Acids

Monounsaturated fatty acids such as oleic acid reduce LDL cholesterol when replacing saturated fatty acids without changing HDL cholesterol. The subsequent reduction of the LDL/HDL cholesterol ratio may be associated with a reduced risk for atherosclerosis. Few studies are available to relate these fatty acids to a propensity for thrombosis.

(n-6) Polyunsaturated Fatty Acids

The inclusion of these fatty acids in the diet reduces total cholesterol and LDL cholesterol and thus may delay the development of atherosclerosis. The effects of (n-6) polyunsaturated fatty acids on HDL cholesterol remains controversial. However, the LDL/HDL cholesterol ratio is usually unchanged. The effects of these fatty acids on thrombogenesis may relate in part to effects on eicosanoid synthesis. Both low and high concentrations of linoleic acid in the diet may have adverse effects on thrombosis. Further studies on the effects of varying concentrations of this fatty acid on platelets, endothelial cells, and eicosanoid metabolism in humans are needed.

(n-3) Polyunsaturated Fatty Acids

The very long-chain fatty acids from marine sources reduce serum triglycerides and VLDL cholesterol without significant changes in the concentration of HDL cholesterol, and LDL cholesterol is unchanged or increased. Platelets, endothelial cells, and perhaps other factors involved in thrombus formation may be affected in an antithrombotic direction by the very long-chain (n-3) fatty acids. The optimal amounts of (n-3) fatty acids in the diet are not yet known. Because the conversion of α-linolenic acid to eicosapentaenoic and docosahexaenoic acids in humans is minimal, 182–184 the beneficial effects of (n-3) fatty acids obtained from plant sources are most likely limited. Long-term studies are needed to examine the potential of α-linolenic acid to produce physiologically significant levels of the long chain (n-3) fatty acids.

Prospectives

Given our present state of knowledge, the most important question on the relation of dietary lipids to occlusive arterial lesions is how the various unsaturated fatty acids should be incorporated into diets to achieve the possible anti-atherosclerotic and antithrombotic effects already obtained by reduction of saturated fatty acids and cholesterol. To do this, studies should be undertaken to:

1. Investigate the effect of dietary modifications, preferably in metabolic studies, on parameters in platelets, endothelial cells, coagulation, and fibrinolysis previously associated with increased venous thrombosis tendency.

2. Establish the significance of potential parameters, develop new tests for risk factors for arterial thrombosis, and investigate how these tests are influenced by the dietary modifications.

3. Study those animals which are close to the human species, examine the effects of (n-3) highly polyunsaturated and (n-9) monounsaturated fatty acids on the formation and regression of atherosclerosis and
thrombosis, and correlate the morphological events to changes in risk factors.

4. Initiate prospective clinical trials that are designed to evaluate the potential of, and the balance between, the various dietary fatty acids.

Until these data are obtained, clinicians should be advised to follow the dietary recommendations recently outlined by the National Cholesterol Education Program's expert panel,77 which also include a combined dietary/drug treatment program for patients with hyperiipopro-

Table 5. Dietary Guidelines for Prevention of Atherosclerosis and Thrombosis in Humans

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended intake</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>Less than 30% of total calories</td>
<td>Less than 10% of total calories</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ratio (n-6)/(n-3)=3/1]*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>Less than 10% of total calories</td>
<td>10% to 15% of total calories</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>50% to 60% of total calories</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>10% to 20% of total calories</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 300 mg/day</td>
<td></td>
</tr>
<tr>
<td>Total calories</td>
<td>To achieve and maintain normal weight</td>
<td></td>
</tr>
</tbody>
</table>

*The (n-3) fatty acids should come from marine sources.

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Index Terms: thrombosis • atherosclerosis • dietary fatty acids • cholesterol • prostaglandins • coronary heart disease