Implications of long-chain fatty acid studies

All of us need fat in our diet. We need fat as a source of energy and to supply us with essential fatty acids and fat-soluble vitamins, as well as for culinary reasons. Approximately 30–40% of our energy intake is derived from fat, most of which consists of triglycerides containing fatty acids with 16 and 18 carbon atoms. In the gastrointestinal tract, the dietary triglycerides are hydrolyzed into monoglycerides, free fatty acids and glycerol before absorption in the intestine. Following reesterification within the intestinal cells, the long-chain triglycerides are incorporated in the chylomicrons and secreted into the blood via the lymphatic system. Depending on the length of the carbon skeleton, and on the number and the geometry of the double bonds, the different long-chain fatty acids show different physiological properties. Although this presentation concerns the effects of variations of the type and amount of long-chain fatty acids in the diet, the physiological effects of a change of dietary fat quality will also depend on several other factors, including, e.g., the content of antioxidants in the diet, genetic predisposition and, possibly, gender.

One of the main reasons for our interest in dietary fat quality is the association between the amount and type of dietary fat on the one hand and morbidity and mortality in specific diseases, especially coronary heart disease, on the other. The Seven Countries Study showed a strong association between the dietary energy percent derived from saturated fat and coronary heart disease mortality among middle-aged men from different countries (1).

A high saturated fat intake is correlated to elevated serum cholesterol concentrations (2,3). This may be one major cause for the direct relationship between saturated fat in the diet and coronary heart disease. In a recent meta analysis compiled of 27 dietary studies, Mensink and Katan (4) described the effect on the serum lipoprotein composition of substituting dietary fat for carbohydrates. Shifting to saturated fat from carbohydrates increased the total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations, while these concentrations were reduced after substitution of unsaturated fat for carbohydrates. The reduction was more pronounced after polysaturated than after monounsaturated fatty acids. A substitution of dietary fat for carbohydrates, irrespective of the degree of saturation, caused increased high-density lipoprotein (HDL) cholesterol and reduced triglyceride levels.

It has long been known that major cholesterol elevating fatty acids are the saturated fatty acids with 12, 14 and 16 carbon atoms. Keys and co-workers (2) showed that stearic acid with 18 carbon atoms did not seem to elevate the serum cholesterol concentration compared with carbohydrates or oleic acid. Studies during the last years, especially by Grundy and co-workers (5) in Dallas, have verified that stearic acid seems to be neutral with regard to serum cholesterol levels compared to carbohydrates, with an effect on total serum cholesterol levels comparable with that of oleic acid. A recent comparison between a diet rich in stearic acid and a diet rich in linoleic acid, however, showed that stearic acid caused clearly higher total cholesterol and LDL-cholesterol concentrations, and lower HDL-cholesterol, than linoleic acid in healthy subjects (6). The diets were identical except that 8% of the dietary fat was either stearic acid or linoleic acid.

Myristic acid with 14 carbon atoms has repeatedly been shown to be the fatty acid that seems to have the most pronounced cholesterol-elevating properties, while palmitic acid increases the serum cholesterol concentrations to a somewhat lower extent (3,4). Also lauric acid with 12 carbon atoms increases the serum and LDL-cholesterol concentrations com-
Table 2
Relationships (definite or probable) between dietary fat and development of atherosclerotic cardiovascular disease

<table>
<thead>
<tr>
<th>Dietary fat (quality, quantity)</th>
<th>Lipoprotein disorders</th>
<th>Hypertension</th>
<th>Peripheral insulin resistance</th>
<th>Glucose intolerance</th>
<th>Blood coagulation disorders</th>
<th>Oxidative stress</th>
<th>Impaired vasodilatation</th>
<th>Atherosclerosis</th>
<th>Thrombosis</th>
<th>Coronary heart disease</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>b</td>
<td>c</td>
<td>s</td>
<td>i</td>
<td>t</td>
<td>y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pared with oleic acid, although the effects seem to be somewhat less pronounced than those by a similar amount of palmitic acid (7).

*trans* Isomers of oleic acid are formed during hydrogenation of linoleic or ω-linolenic acids in the rumen of the cow or in the hardening factories of the industry. *trans* Fatty acids were for a long period of time considered to be neutral with regard to effects on the serum cholesterol concentrations. Recent studies by Katan and co-workers (6,8), however, have demonstrated that *trans* fatty acids, at least *trans* fatty acids with 18 carbon atoms and 1 double bond (elaidic acid), have properties which seem to be more similar to those of the saturated fatty acids than to the corresponding fatty acid with 18 carbon atoms and 1 double bond in *cis* configuration, oleic acid. Although *trans* fatty acids clearly may increase the serum cholesterol levels, the LDL cholesterol elevation caused by elaidic acid seems to be less pronounced than that expected from a similar amount of cholesterol elevating fatty acids with 12–16 carbon atoms (6). The cholesterol-elevating effect of elaidic acid seems to be dose-dependent, as is the lowering effect on HDL cholesterol. In addition, an increased content of *trans* fatty acids in the diet seems to be associated with an increase of lipoprotein(a), another potentially atherogenic lipoprotein fraction (9,10). The estimated effects on serum cholesterol levels of the different dietary long-chain fatty acids is summarized in Table 1.

The immediate cause of acute coronary heart disease and sudden death is usually a thrombus formed at the endothelial surface of a ruptured atherosclerotic plaque or an episode of malignant cardiac arrhythmia. The risk factor pattern appears to be partly different for the development of the atherosclerotic lesion as such and for the formation of a thrombus and probably also for initiation of cardiac arrhythmias. Although there are clear indications from experimental studies in animal models that long-chain saturated fatty acids, including stearate, are more thrombogenic than *e.g.*, linoleic acid (11,12), it has been hard to demonstrate similar differences *in vivo*. Experimental research, clinical studies and epidemiology tell us, however, that an antithrombogenic effect may be achieved by increasing the amount of n-3 fatty acids in the diet (13). The long-chain, polyunsaturated fatty acids of the n-6 (arachidonic) and n-3 (eicosapentaenoic) series are precursors of the eicosanoids. An increased relative content of eicosapentaenoic acid, compared with arachidonic acid, will decrease the tendency for platelet aggregation due to an effect on the balance between the proaggregatory thromboxanes and the prostacyclins, which have vasodilatory effects and reduce platelet aggregability. In addition there are several other functions of the n-3 fatty acids that may affect the cardiovascular system and contribute to a reduced tendency for thrombus formation (13). Experimental studies in animals have indicated that the substitution of n-6, as well as n-3, fatty acids for saturated fat in the diet seems to reduce the frequency of episodes of cardiac arrhythmia.

Addition of n-3 fatty acids in the diet of subjects with mild hypertension has been associated with moderately reduced blood pressure levels in several studies. It has been shown by Bonna et al. (14) in Tromsø that the reduction of blood pressure took place only in subjects with a low content of n-3 fatty acids in the serum phospholipids, indicating a low dietary intake of n-3 fatty acids. In the subjects, who had a content of n-3 fatty acids in the phospholipids above the median of the group, no effects were achieved by increasing the amount of dietary n-3 fatty acids. This demonstrates that, with regard to the effect on blood pressure, there seems to be an optimal relation between dietary n-3 and n-6 fatty acids that may be relevant also for many other physiological functions.

Recent, and highly interesting, studies (15–17) have indicated that the dietary fat quality also may be critical with regard to the risk to develop peripheral insulin insensitivity. Insulin resistance is thought to be one, and maybe the major, cause behind the development of different metabolic disorders, such as glucose intolerance and noninsulin-dependent diabetes mellitus, essential hypertension, hypertriglyceridaemia and impaired fibrinolysis (18). Storlien and co-workers could show that rats fed a high-fat diet developed insulin resistance compared with rats fed an ordinary carbohydrate-rich chow diet. The impairment of insulin sensitivity could be avoided by substituting limited amounts of n-3 fatty acids for saturated fatty acids or n-6 fatty acids in the high-fat diet (15,16). They could also show that the insulin sensitivity in the rats was directly related to the amount of n-3 fatty acids in the skeletal mus-
Table 3

A reduction of the dietary fat intake—with reduction primarily of the saturated (hard) fat is desirable to:

- Lower the energy intake—reduce obesity and its complications
- Reduce risk for atherosclerotic cardiovascular disease
- Reduce risk for development of and complications to diabetes mellitus
- Reduce risk for common cancers
- Increase nutrient density (especially at low energy levels) and give room for other nutrients in other types of foods, e.g., fruits and vegetables

Table 4

Major sources of saturated fatty acids in the Swedish diet—1988 (Ref. 20)

<table>
<thead>
<tr>
<th>Food group</th>
<th>Total saturated fat</th>
<th>12:0 + 14:0 + 16:0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/day</td>
<td>g/day</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Cereals</td>
<td>3.7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>6</td>
</tr>
<tr>
<td>Meat, meat products</td>
<td>8.7</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>16</td>
</tr>
<tr>
<td>Fish</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>Milk, cheese, cream</td>
<td>18.9</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>35</td>
</tr>
<tr>
<td>Butter</td>
<td>7.8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>5.1</td>
<td>15</td>
</tr>
<tr>
<td>Margarine, oil</td>
<td>9.1</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>17</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Potatoes, fruits,</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>vegetables</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Other foods</td>
<td>3.8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 5

Practical advice regarding fatty food

- If you are overweight or have a high-fat intake (e.g., dairy products, margarines, meat products), use more low-fat products.
- Choose soft fats when suitable (including fat fish).
- Limit fried products; throw away fat after pan-frying.
References


**Vitamin B-1 used to lower LDL cholesterol**

Large doses of vitamin B-1 lower low-density lipoprotein (LDL) cholesterol levels among elderly men more cost effectively than do four commonly prescribed drugs, according to an Ohio State University study cited in the Nov. 18, 1993, issue of *The Journal of Commerce*.

In the two-year study of 234 patients at a Veterans Administration hospital, university researchers compared the performance of nicotinic acid, commonly known as niacin or vitamin B-1, with four cholesterol-lowering drugs. Results showed that nicotinic acid was the most cost-effective in reducing total cholesterol levels as well as LDL levels.

The drug lovastatin, sold under the brand name Mevacor, caused a larger drop in LDL levels but was more expensive. Other drugs in the study included gemfibrozil, sold under the brand name Lopid; cholestyramine, sold under the brand name Questran; and probucol, sold under the brand name LorcABCDEFGHIJ.

The researchers found vitamin B-1 to be effective at doses of 1,250 milligrams, which is at least ten times the amount used in vitamin supplements.

Meanwhile, a review of clinical trials with garlic indicates the equivalent of one-half to a clove of garlic a day lowered serum cholesterol levels 17 to 29 points—about 9%—in persons with borderline-high and high cholesterol levels. Stephen Warshafsky of the New York Medical College in Valhalla, who conducted the review, credited alliin contained in the garlic as responsible for the effect.

Warshafsky recommended that more studies should be conducted to look specifically at LDL, rather than total, cholesterol. The review was published in the Oct. 1, 1993, issue of the *Annals of Internal Medicine*.  

**Greek study links margarine and CHD**

Researchers in Greece, studying the relationship between diet and coronary heart disease (CHD), concluded that using margarine as the principal cooking fat was associated with an increased risk of CHD.

A report on the study was prepared by Anastasia Tzonou and colleagues and published in the November issue of *Epidemiology*. Subjects for the study were 329 patients with electrocardiographically confirmed coronary infarction or a positive coronary arteriogram, or both, who were admitted to an Athens hospital during a 16-month period, and 570 controls admitted to the same hospital for minor conditions unrelated to nutrition, according to a summary in the Nov. 15, 1993, issue of *Food Chemical News*.

The scientists noted that “striking ecologic correlations between saturated fat intake and occurrence of CHD and the exceptionally low incidence of this disease in the Greek population, which has traditionally consumed high quantities of olive oil, represents powerful evidence for an important effect of fat composition on risk of CHD.” However, they pointed out, their study results showing increased risk among regular users of margarine for cooking suggested “a possible explanation for the failure to see protective effects of monounsaturated and polyunsaturated fats.”

Writing an editorial in the same issue of *Epidemiology*, Matthew Longnecker of the UCLA School of Public Health, noted, “The widespread recommendations to decrease the intake of saturated fatty acids may have worked at cross purposes by increasing trans fatty acid intake.” He added, “One can only hope that research will resolve this question, so that future dietary recommendations and food processing practices reduce rather than raise the risk of our leading cause of death.”

**Fat cravings are linked to brain chemicals**

Brain chemicals that stimulate appetites for fat or carbohydrates may
explain abnormal eating patterns in persons who are obese, anorexic or bulimic, a researcher from Rockefeller University told attendees at the Society for Neuroscience's annual meeting in November.

Sarah F. Liebowitz noted that at least two chemicals in the brain—neuropeptide Y and galanin—may affect eating patterns. Injected into the brains of rats, neuropeptide Y increased the rats' appetite for carbohydrates, while galanin caused overeating of fat, she reported, according to articles in the Nov. 22, 1993, issue of Food Chemical News and the Nov. 13, 1993, issue of Science News.

"Animals that naturally prefer fat have high levels of galanin, and the gene that controls production of galanin is overactive in these subjects. In contrast, animals with a stronger appetite for carbohydrate showed an overproduction of neuropeptide Y in the brain, but normal amounts of galanin," Liebowitz reported.

Scientists can slow production of these messengers by suppressing the genes that control output, Liebowitz and colleagues said at the meeting. Her research team gave rats small pieces of a specific "antisense" genetic material each day for four days. This interfered with the brain cell's ability to make neuropeptide Y. As a result, the rats ate only about one-third their normal carbohydrate and fat calories.

Liebowitz predicted that her studies may lead to new ways to treat eating disorders in humans. Other researchers, however, cautioned that there may be many neuropeptides that affect food intake and that the solution may be very complex, Science News reported.

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**Low-cholesterol diets can cut food costs**

A low-fat, low-cholesterol diet can cost less than a typical diet consumed by persons living in the United States, according to researchers at the Mary Imogene Bassett Hospital Research Institute and Pennsylvania State University.

Presenting findings at the American Health Associations annual meeting in Atlanta in November, Thomas A. Pearson, director of the Mary Imogene Bassett Hospital Research Institute, said a low-fat, low-cholesterol diet actually costs about 75 cents per person per day less than a typical diet. Also, the more effective a diet is in reducing cholesterol levels, the less it costs, according to meeting highlights summarized in the Nov. 22, 1993, issue of Food Chemical News.

Pearson said an ongoing study is monitoring the eating habits of 291 patients with high blood cholesterol in 16 rural medical practices. Diet information came from interviews both before and six months after dietary counseling.

"We felt the perception of high cost was a major barrier preventing many people from adopting healthier eating habits. But, since a cholesterol-lowering diet can actually be less expensive, the cost factor should be an incentive instead," Pearson said.

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**High-fat diet increases risk of lung cancer**

High-fat diets increase the risk of lung cancer even for nonsmokers, according to a National Cancer Institute (NCI) study published in the Dec. 1, 1993, issue of the Journal of the National Cancer Institute.

The study compared the diets of 429 nonsmoking women who had lung cancer with the diets of 1,021 nonsmoking women without lung cancer. All the subjects lived in Missouri and were about the same age.

Results showed that those who obtained 15% or more of their calories from saturated fat were about six times more likely to develop lung cancer than those who obtained 10% or less of their calories from saturated fat.

Michael C.R. Alavanja, an NCI researcher, said the study found that those with diets containing the lowest amount of saturated fat and the highest amount of fruits, vegetables, beans and peas were the least likely to develop lung cancer.

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**Cancer-inhibiting carotenoids studied**

A research group headed by Sukeyoku Nishina at Kyoto (Japan) Medical University has reported studies showing that natural carotenoids exhibit strong cancer-inhibiting properties in mice.

Carotenoid studied were α-carotenoïd, fucoxanthin and peridinin. Mice were dosed with a carcinogen, with some also being given α-carotene. Mice that did not receive the carotenone were reported as average 4.1 tumors; mice that received the carotenone averaged 1.3 tumors.

In skin cancer tests, mice that did not receive carotenoids averaged 5.5 tumors; mice that received fucoxanthin average 4.5 and mice that received peridinin averaged 1.0, Nishina said in a paper during an October 1993 meeting of the Japan Cancer Society.

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**Nutrition brief**

Approximately 160 persons attended a Japan Oil Chemists' Society seminar on "Nutritional Aspects of the Biochemistry of Oils and Fats" held Oct. 22, 1993, in Tokyo, Japan. Some of the topics and speakers included: dietary fats and oils in Japan, Shuichi Kimura of Showa Women's College; nutritional evaluation of oils and fats, Keisuke Tsuji of the National Institute of Health and Nutrition; oleic acid, Masumi Kimoto of Tokushima University; polyunsaturated fatty acids, Ikue Ikeda, Kyushu University; marine oils, Kenshiro Fujimoto of Tohoku University; and membrane lipid peroxidation, Teruo Miyazawa, also of Tohoku University.