Review of Literature
Historical Remarks: -

The vast array of fat types in the diet coupled with the growing realization that the type of dietary fat consumed may have importance consequences in the body, suggests that recommendations about dietary fat consumption must be consider fat type as well as fat amount.

In the past, dietary fat got bad press. There was a deeply rooted belief that they were basically unhealthy, were useful at best as energy store for hard times, and had one purpose only—to keep the body supplied with fuel and energy. This view is not completely wrong; about 80% of the ingested fat, and the saturated and unsaturated fatty acids it contains, is stored in special cells and burnt up as required. However, there is more to fats than that. Some fats and fatty acids have specific physiologic roles to play.

In 1918; Aron, first proposed that fat may be essential for normal growth and development of animals. Butter apart from its caloric value, was deemed to have an important nutritional value because of the presence of certain lipid molecules. The nutritional importance of specific lipid molecules in fat was first revealed through the pioneering work of George and Mildred Burr in the late 1920s. Evans and Burr in 1927 subsequently demonstrated that a deficiency of fat severely affected both growth and reproduction of experimental animals, despite addition of certain nutritionally essential fat soluble vitamins A, D, and E to the diet. The authors suggested that fat contained a new essential substance and was considered to be a new ‘vitamin’; because the previous vitamin found was called vitamin ‘E’, the new essential active substance was given the name vitamin ‘F’.

The work of Burr and Burr in 1929 first showed the nutritional importance of specific lipid in fat, and observed that, when weanling rats fed a fat-free diet, showed impaired growth, scaly skin, tail necrosis, and increased mortality, conditions that were reversed by feeding “linoleic acid” (C18:2n-6). In his further work, the same authors described impaired fertility, augmented water consumption, and diminished urine production as additional symptoms of a deficiency of either “linoleic acid (LA) or α-linolenic acid [ALA] (C18:3n-3), and concluded that both polyunsaturated fatty acids (PUFAs) was able to provide the missing factor. It was the era of the discovery of essential nutritional
factors. The term “essential fatty acids” (EFA) was coined by Burr and Burr for those fatty acids (FA) not synthesized in mammals and for which deficiencies could be reversed by dietary addition.

In vegetable and animal oils and fats, the occurrences of vitamins ‘F’ and ‘E’ are invariably linked to one another; the higher the concentration of PUFAs, the higher the contents of vitamin ‘E’. The known reason of this association is that vitamin ‘E’ functions specifically as an antioxidant for PUFAs. It protects the labile double bonds in PUFAs from oxidization.

Strangely enough, even though they discovered almost simultaneously, the fate of the 2 vitamins took different courses. Whereas vitamin ‘E’ soon became an accepted factor for human health, the term vitamin ‘F’ disappeared into oblivion. The medical profession doubted that essential fatty acids had any relevance to human health and the view that certain fatty acids could be the essential components of the human diet never captured the minds of the broader public.

Arachidonic acid [AA] (C20:4n-6) a n-6 fatty acid (LA) derived eicosanoid, was determined to be an essential fatty acid in 1938. It was found to be approximately three times as effective as LA (n-6) in reliving essential fatty acid deficiency (EFAD) symptoms. LA (n-6) was subsequently found to under go biotransformation to AA (n-6); thus LA (n-6) was judged to be the primary unsaturated fatty acid required in the diet of animals. Although, various researchers were able to generate essential fatty acid deficiency (EFAD) in different species by feeding EFA-deficient diets. Infants fed a milk-based formula diet lacking EFA showed severe skin symptoms that were alleviated by addition of C18:2n-6 ie. LA.

In human adults, EFA-deficiency was subsequently described as a consequence of parental nutrition in which fat-free solutions containing only glucose, amino acids, electrolytes and micronutrients were continuously infused. The resulting rash and low plasma concentrations of polyunsaturated fatty acids (PUFA) were reversed by infusion of intravenous emulsions containing LA (n-6). Holman et al. (1982) reported the first example of deficiency symptoms attributed to ALA (C18:3n-3) deficiency in a 6 year-old girl maintained parenterally for 5 months on a safflower-oil-based emulsion rich in LA (n-6). Deficiency symptoms, including neuropathy and low serum concentrations of ALA.
(n-3), were corrected by changing the parenteral nutrition recipe to include soybean oil emulsion rich in n-3 fatty acids was demonstrated by Holman RT et al. 1982. Neuringer et al. in 1984 demonstrated ALA (n-3) deficiency in the offspring of rhesus monkeys showing a loss in visual activity. ALA (n-3) deficiency was also described by Bjerve K.S. et al. 1989 in nine patients who had received 0.02 to 0.09% of calories as n-3 fatty acids via gastric tube feeding over a period of 2.5 to 12 years. The scaly dermatitis and depressed concentrations of n-3 fatty acids in plasma and erythrocytes of the patients were reversed by supplementation with ALA (n-3) [Petar J. H. Jones & Stanley Kubow, Historical Introduction: Modern Nutrition in Health & Diseases; 9th edition, page No. 67 -90].

It was not until the 1960s, that it was discovered how closely the metabolisms of essential fatty acids and eicosanoids are related. It is known today that some of the highly unsaturated fatty acids serve as the precursors of prostaglandins, thromboxanes, and leukotrienes – all highly potent, short-lived molecules with greatly diverse activities. This function of some long-chain fatty acids seemed to be of little relevance to human health until the work of Dyerberg, Bang, and Hjorne in Eskimos sparked an entire field of research into the health effect of n-3 long-chain poly-unsaturated fatty acids (Long-chain PUFAs, [LCPUFA or LCP]). In there epidemiologic studies of Eskimos living in Greenland, these 3 Danish scientists showed that this population group had one-eighth the risk of dying from cardiovascular disease that Eskimos who emigrated to Denmark had. The plausible explanation of the phenomenon was that the traditional diet of Greenland Eskimos is rich in two n-3 long-chain PUFAs: eicosapentaenoic acid [EPA] (20:5n-3) and docosahexaenoic acid [DHA] (22:6n-3), which gives rise to eicosanoids of anti-thrombotic potential. This pioneering work stimulated research worldwide, with the result that the potential role and mechanism of action of highly unsaturated fatty acids in prevention and therapy has become a major area of international research (The American Journal of Clinical Nutrition; [Suppl.], Vol:71; No.1(s), page-169s-1175s; January 2000).
**Introductory remarks**

Low-fat foods are common nowadays, and for very good reasons. People on diets to lose weight have discovered that they can satisfy their appetite with fewer calories by eating protein and carbohydrate instead of fat. Losing weight not only makes a person look good, it can reduce the danger of getting heart disease, diabetes and cancer (1).

Dietary fat by itself, not just the body fat it produces, is a health hazard. A recent study has shown that reducing dietary fat from 36% of total calories to 26% of total calories can significantly lower blood pressure within 8 weeks (2). It has long been known that saturated fat in the diet can increase the risk of heart disease from atherosclerosis (fatty plaques on blood vessel walls) by raising blood cholesterol. But unsaturated fat is more likely to form free radicals by lipid peroxidation, which can lead to cancer and may accelerate aging. Therefore, both saturated and unsaturated fat have health hazards.

For many years nutritionists have recommended substituting mono-unsaturated and poly-unsaturated fats for saturated fats, but a more recent recommendation is to substitute protein and carbohydrate calories for fat calories (3). Fats (especially animal fats) are the primary vehicle by which pesticides enter the body. Some people might conclude that it would be a good idea to eliminate all fat from the diet. But eliminating all fat is not a good idea.

**Role of fats in diet**

Human body needs fats to function properly. Nearly half of the dry weight of the brain is fat, and a quarter of this is cholesterol. Cholesterol is an essential part of sex hormones, bile acids, D vitamins and steroid hormones from the cortex of the adrenal gland -- among other important substances. Cholesterol does not need to be eaten, however, because the liver and other tissues can manufacture cholesterol from saturated fats. But too many saturated fats result in excessively high blood levels of cholesterol that can end up being deposited in atherosclerotic plaques on blood vessels, leading to cardiovascular disease. High blood cholesterol also depresses the immune system and thereby increases the incidence of cancer (4). Excessive blood cholesterol is more often caused by eating too many saturated fats than by eating cholesterol itself.
The term blood cholesterol is actually a reference to HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein) and VLDL (Very Low-Density Lipoprotein). "Lipo" means "lipid", a general term that refers to all biological fats and oils. HDL has been called "good cholesterol" because it can pick-up excess fats and carry them back to the liver. LDL (and especially VLDL) has been called "bad cholesterol" because it can become so overloaded with fats that the fats are dropped on blood vessel walls rather than carried to the cells where they are needed. LDL could also be called "good", because LDL supplies cells with fats needed for structure and function. In fact, LDL is the main carrier of oil-soluble substances (like Vitamin E) to body cells. LDL-cholesterol is just HDL-cholesterol with a larger load of surrounding fat. Exercise creates HDL from LDL by removing fat from LDL for use as energy.

Studies in the United States and Northern Europe have established that the incidence of coronary heart disease mortality is nearly two-and-a-half times higher for people with the highest 25% of blood cholesterol compared with people with the lowest 25%. Yet the coronary heart disease mortality for the same cholesterol levels is only one-third as great in Japan or the Mediterranean. A person in west Scotland having the same blood cholesterol levels as a person in Catalonia, Spain is 8-times more likely to die of coronary heart disease. So although cholesterol is a factor in coronary mortality, it is not the only factor. Oxidation of LDL is what causes cholesterol to be deposited in plaque on blood vessel walls.

The vulnerability of LDL cholesterol to oxidation depends on both the amount of antioxidants in the blood and on the type of fatty acid in the LDL. Fruits, vegetables and supplements (especially Vitamin E with Vitamin C) will reduce LDL oxidation. The dietary fat that is most vulnerable to oxidation is linoleic acid. High blood levels of homocysteine thiolactone cause LDL to aggregate. Oxidized, aggregated LDL is readily attacked by macrophages to form atherosclerotic plaques on blood vessel walls.

Aside from cholesterol, most other fat in the body is constructed from what is known as fatty acids. A fatty acid is a long straight chain of carbon atoms (studded with hydrogen atoms) that has an acid group (carboxylic acid) at one end (the water-soluble end). The rest of the fatty acid is oil-soluble, with a methyl group at the other end. Fatty acids in the
body usually exist unattached to any other molecule (free fatty acids), attached to glycerol in groups of three (triglycerides), or attached to phosphatidic acid molecules (phospholipids).

Fatty acids differ from one another not only by the number of carbons in their chain, but by the number of double-bonds between the carbon atoms. Fatty acids with only single-bonds are called saturated because they are "saturated" with as many hydrogen atoms as they can carry. Fatty acids with only one double-bond are called mono-unsaturated. And fatty acids with more than one double-bond are called poly-unsaturated.

Polyunsaturated fats have often been recommended to reduce coronary heart disease (9). But all saturated fats do not have the same effect on cholesterol synthesis in the liver. Only the saturated fats of chain-length 12, 14 and 16 (lauric acid, myristic acid and palmitic acid) have been shown to elevate blood cholesterol. Of these, myristic acid (high in coconut and palm oil) elevates cholesterol the most (10). Stearic acid (18-carbon, saturated) has been shown to lower cholesterol by 21% — even more than oleic acid (18-carbon, mono-unsaturated), which lowers LDL by 15% (11).
Methyl LAURIC ACID Carboxyl Oil-Soluble 12 carbons Water-Soluble OMEGA (\(\omega\)) END DELTA (\(\Delta\)) END

Methyl MYRISTIC ACID Carboxyl Oil-Soluble 14 carbons Water-Soluble OMEGA (\(\omega\)) END DELTA (\(\Delta\)) END

Methyl PALMITIC ACID Carboxyl Oil-Soluble 16 carbons Water-Soluble OMEGA (\(\omega\)) END DELTA (\(\Delta\)) END

Methyl STEARIC ACID Carboxyl Oil-Soluble 18 carbons Water-Soluble OMEGA (\(\omega\)) END DELTA (\(\Delta\)) END
Polyunsaturated fatty acids can be a health hazard because carbon-carbon double bonds can lead to free-radical formation and reactions with oxygen to form unstable lipid peroxide compounds containing the same unstable oxygen-oxygen bond found in hydrogen peroxide. Lipid peroxidation and free radicals can cause cancer and may accelerate aging. High rates of lung cancer among women in China have been associated with lipid-peroxidized oils in fumes from cooking polyunsaturated vegetable oils in a wok (12). Hot oil in open air is subject to much lipid peroxidation. Fast-food restaurants that fry foods in the same oil all day serve lots of lipid peroxides to their customers.

Polyunsaturated "cis" fatty acids can be beneficial in cell membranes by preventing the tight packing of fatty acids in membranes -- thereby making the membranes more "fluid." Membrane fluidity is important for optimal function of most cells in the body. But membrane fluidity is especially important on portions of cells that act as receptors for hormones or neurotransmitters. The typical North American eats three times as much saturated fat as unsaturated fat, yet animal experiments show that insulin receptor responsiveness is substantially improved when dietary unsaturated fat is greater than saturated fat (13). With aging, however, cell membrane fluidity declines in part because of increasing amount of cholesterol in the membranes, but more importantly because of free-radical oxidation (14). Antioxidants that protect cell membranes, like Vitamin E, are extremely valuable in opposing membrane oxidation.

Fatty acid double-bonds come in two configurations known as cis (carbon chains on the same side of a double-bond) and trans (carbon chains on the opposite side of a double-bond). Most of the double-bonds made by biological systems have the cis configuration. It is the cis configuration of unsaturated fatty acids that prevents tight packing of fatty acids in membranes, and hence increases membrane fluidity.

Saturated fats (like butter or lard) and fatty acids with trans double-bonds (like margarine) tend to be solids at room temperature, whereas natural fatty acids with cis double-bonds (like vegetable oils) tend to be liquids. By artificially hydrogenating vegetable oils, the food processing industry reduces the number of double bonds and causes the formation of trans fatty acids. Hydrogenation results in margarines that are more solid and results in peanut butter that does not have an oil that separates. But when
trans fatty acids are incorporated into cell membranes, the membrane fluidity is reduced and the cells do not function as well. Not all trans fatty acids in the diet are due to food processing. For example, natural butter is 5% trans fat.

The chemistry of essential fatty acids

<table>
<thead>
<tr>
<th>NAMES AND CHEMICAL DESCRIPTIONS OF SOME COMMON FATTY ACIDS</th>
<th>LIPID CHAIN LENGTH</th>
<th># DOUBLE BONDS</th>
<th>OMEGA # POSITION</th>
<th>SCIENTIFIC NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMON NAME</td>
<td>(# of carbons)</td>
<td>BONDS (double bond position)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lauric Acid</td>
<td>12</td>
<td>0</td>
<td>none</td>
<td>dodecanoic acid</td>
</tr>
<tr>
<td>Myristic Acid</td>
<td>14</td>
<td>0</td>
<td>none</td>
<td>tetradecanoic acid</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>16</td>
<td>0</td>
<td>none</td>
<td>hexadecanoic acid</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>18</td>
<td>0</td>
<td>none</td>
<td>octadecanoic acid</td>
</tr>
<tr>
<td>Oleic Acid</td>
<td>18</td>
<td>1</td>
<td>omega-9</td>
<td>9-octadecenoic acid</td>
</tr>
<tr>
<td>Linoleic Acid</td>
<td>18</td>
<td>2</td>
<td>omega-6</td>
<td>9,12-octadecadienoic acid</td>
</tr>
<tr>
<td>Conjugated Linoleic Acid (CLA)</td>
<td>18</td>
<td>2</td>
<td>omega-6</td>
<td>9,11-octadecadienoic acid(*)</td>
</tr>
<tr>
<td>Alpha-Linolenic Acid</td>
<td>18</td>
<td>3</td>
<td>omega-3</td>
<td>9,12,15-octadecatrienoic acid</td>
</tr>
<tr>
<td>Gamma-Linolenic Acid (GLA)</td>
<td>18</td>
<td>3</td>
<td>omega-6</td>
<td>6,9,12-octadecatrienoic acid</td>
</tr>
<tr>
<td>Dihomo-Gamma-Linolenic Acid (DGLA)</td>
<td>20</td>
<td>3</td>
<td>omega-6</td>
<td>8,11,14-eicosatrienoic acid</td>
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<tr>
<td>Arachidonic Acid</td>
<td>20</td>
<td>4</td>
<td>omega-6</td>
<td>5,8,11,14-eicosatetraenoic acid</td>
</tr>
<tr>
<td>Eicosapentaenoic Acid (EPA)</td>
<td>20</td>
<td>5</td>
<td>omega-3</td>
<td>5,8,11,14,17-eicosapentaenoic acid</td>
</tr>
<tr>
<td>Docosahexaenoic Acid (DHA)</td>
<td>22</td>
<td>6</td>
<td>omega-3</td>
<td>4,7,10,13,16,19-docosahexaenoic acid</td>
</tr>
</tbody>
</table>

(*) Some 10,12 CLA also occurs, but the 9,11 form greatly predominates in ruminant foods.

The human body can manufacture most of the fats it needs, including cholesterol, saturated fatty acids and unsaturated fatty acids. But there are two fatty acids which cannot be manufactured in the body, and which must be obtained from dietary sources: linoleic acid and alpha-linolenic acid. These are the essential fatty acids. Linoleic acid is an 18-carbon chain with 2 double bonds, whereas alpha-linolenic acid is an 18-carbon chain with 3 double bonds. The position of double bonds in a fatty acid is critical to function, and this is especially true of double bonds close to the methyl end. For long-chain fatty acids, the body's enzymes cannot add double bonds near the methyl end.

The carbon on the methyl group is called the omega carbon because it is the last carbon in the chain and because omega is the last letter of the Greek alphabet. Because the
closest double bond to the methyl group in linoleic acid is 6 carbon atoms away from the methyl, linoleic acid is called an omega-6 fatty acid (ω-6 FA). For alpha-linolenic acid, the double bond closest to the methyl group is only 3 carbons away, so it is an omega-3 fatty acid (ω-3 FA). ω-3 FA and ω-6 FA are also known as n-3 and n-6 FA respectively by many researchers. The carbon next to the carboxylic acid is called the alpha (α) carbon because alpha is the first letter of the Greek alphabet. But to confuse matters, the acid end of a fatty acid is called the delta end.

The configuration (geometry) at the double bond can be either cis (adjacent hydrogen atoms on the same side of the molecule) or trans (adjacent atoms on the opposite side). Unsaturated fatty acids in the trans configuration are more linear, more rigid and have a higher melting point. The distinctiveness of cis & trans fatty acids merit unique names: cis-9-octadecanoic acid is oleic acid, whereas trans-9-octadecanoic acid is elaidic acid.
The body cannot make an omega-3 or omega-6 fatty acid because human metabolism cannot add a double-bond to a fatty acid that is more than 9 carbons away from the delta end. For the same reason, the body cannot convert an omega-3 to an omega-6 fatty acid, or vice-versa. But the body can make omega-9 fatty acids. And the body can add more double-bonds closer to the delta end of omega-3 and omega-6 fatty acids.

Two distinct families of essential fatty acids exist in the human body: the omega-3 family and omega-6 family. The omega-3 family comes from alpha-linolenic acid, and the omega-6 family comes from linoleic acid. Each family is the result of increasing chain length and of forming double-bonds from one of these two essential fatty acids. The two families compete for the same enzymes for forming double bonds (desaturase enzymes) and enzymes for lengthening the carbon chain (elongase enzymes). Elongase enzymes always add carbon atoms (in pairs) to the delta end of the fatty acid.
Linoleic Acid and Alpha-Linolenic Acid compete for the same Δ-6-desaturase enzyme, but this enzyme has a much greater preference for Alpha-Linolenic Acid. The enzymes Lipoxygenase and Cyclo-oxygenase compete for DGLA, EPA or Arachidonic Acid. The winner of the competition will depend on the chemical environment in the cell, which will be different in different tissues and body organs. DGLA cannot be converted to Lipoxins or Leukotrienes, and is only poorly converted to Thromboxanes. Lipoxins are only produced from Arachidonic Acid. [Diagram modified from #96]

[The official name of cyclo-oxygenase is "PGH (endoperoxide) synthetase", but the name cyclo-oxygenase is much more frequently used. It has also been called "the world's most important enzyme" because of the billions of dollars that are spent annually to block its action.]

Forming a double-bond at the 9th carbon of linoleic acid results in gamma-linolenic acid (GLA). Like alpha-linolenic acid, gamma-linolenic acid has 3 double-bonds. But gamma-linolenic acid is an omega-6, whereas alpha-linolenic is an omega-3 fatty acid. The words "alpha" and "gamma" in this case have no chemical meaning. The confusing terms "alpha-linolenic" and "gamma-linolenic" are common names, not scientific names, and are meaningless in the context of current scientific naming conventions.
Another important product of linoleic acid is arachidonic acid. Arachidonic acid is a 20-carbon omega-6 fatty acid with 4 double-bonds. Arachidonic acid, in turn, gives rise to a whole group of 20-carbon, biologically-important substances known as the eicosanoids (eicosa- is Greek for "20"), including prostaglandins, thromboxanes, lipoxins and leukotrienes — which affect immunity, inflammation and blood clotting (among other actions).
Noteworthy members of the omega-3 family of fatty acids manufactured from alpha-linolenic acid are EicosaPentaenoic Acid (EPA) and DocasaHexaenoic Acid (DHA). A pentaenoic acid has 5 double-bonds. A hexaenoic acid has 6 double-bonds. EPA is a 20-carbon chain fatty acid, whereas DHA is a 22-carbon chain fatty acid. Like arachidonic acid, EPA gives rise to its own class of eicosanoids. The EPA-generated eicosanoids are in the omega-3 family, as distinct from the omega-6 eicosanoids derived from arachidonic acid.

Essential fatty acids in the diet
The primary source of omega-6 fatty acid in the diet is linoleic acid from the oils of seeds and grains. Sunflower, safflower and corn oil are particularly rich sources of linoleic acid, which is at the root of the omega-6 fatty-acid family. Evening primrose oil and borage oil are high not only in linoleic acid, but the omega-6 derivative gamma-linolenic
Acid (GLA). Avocado is 15-20% oil — mainly monosaturated, but also high in linoleic acid. (Avocado has the highest fat content and the highest fiber content — soluble as well as insoluble — of any fruit.)

**FAT CONSTITUENTS AS % OF TOTAL FAT FOR SELECTED FOODS**

<table>
<thead>
<tr>
<th>FOOD</th>
<th>PALMITIC (C-16:0)</th>
<th>STEARIC (C-18:0)</th>
<th>OLEIC (C-18:1)</th>
<th>LINOLEIC (C-18:2)</th>
<th>ALPHA-LINOLINIC (C-18:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perilla Oil</td>
<td>6</td>
<td>2</td>
<td>17</td>
<td>15</td>
<td>61</td>
</tr>
<tr>
<td>Flaxseed (Linseed) Oil</td>
<td>3</td>
<td>7</td>
<td>21</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>Menhaden Herring Oil (1)</td>
<td>4</td>
<td>4</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Canola Oil</td>
<td>5</td>
<td>2</td>
<td>53</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Walnut Oil</td>
<td>7</td>
<td>2</td>
<td>15</td>
<td>60</td>
<td>10</td>
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<tr>
<td>Soybean Oil</td>
<td>11</td>
<td>4</td>
<td>23</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>Butter (2) Milkfat</td>
<td>25</td>
<td>11</td>
<td>26</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Beef Fat</td>
<td>29</td>
<td>20</td>
<td>42</td>
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<tr>
<td>Palm Oil</td>
<td>45</td>
<td>5</td>
<td>38</td>
<td>10</td>
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<tr>
<td>Olive Oil</td>
<td>14</td>
<td>3</td>
<td>71</td>
<td>10</td>
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<tr>
<td>Corn Oil</td>
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<tr>
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<td>4</td>
<td>24</td>
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<tr>
<td>Borage Oil (3)</td>
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<tr>
<td>Evening Primrose Oil (4)</td>
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<td>1</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Safflower Seed Oil</td>
<td>7</td>
<td>7</td>
<td>15</td>
<td>75</td>
<td>0</td>
</tr>
</tbody>
</table>

[NOTE: C-18:3 means a fatty acid with an 18-carbon chain and 3 double-bonds]

(1) Menhaden Herring Oil is 11% EPA and 9% DHA
(2) 30% of Butter is saturated fat of chain length less than 16 (butyric acid, C-4:0 has a "buttery" flavor)
(3) Borage Oil is 24% Gamma-Linolenic Acid (GLA)
(4) Evening Primrose Oil is 10% Gamma-Linolenic Acid (GLA)

Omega-3 fatty acids, on the other hand, are more frequently found in green leaves. The leaves and seeds of the perilla plant (widely eaten in Japan, Korea and India) are the richest plant source of alpha-linolenic acid, although linseed oil is also a rich source. Fish oil contains very little alpha-linolenic acid, but is rich in the omega-3 derivatives EPA and DHA. Fish are at the top of a food chain based on phytoplankton (algae) that manufactures large amounts of EPA and DHA. Nonetheless, fish can be high in toxic methylmercury.

It has been estimated that thousands of years ago the diet of human hunter-gatherers consisted of approximately equal parts of omega-3 and omega-6 essential fatty acids (15). Since the beginning of agriculture ten thousand years ago there has been a steady increase in omega-6 at the expense of omega-3 fat in the human diet. This process accelerated about 50 years ago as cattle began to be fed increasingly on grains rather than grass.
Recommendations by nutritionists to eat margarine rather than butter (polyunsaturated rather than saturated fats) only increased the trend toward omega-6 consumption. Currently, the ratio of omega-6 to omega-3 fatty acids in the American diet is 7-to-1 or more. There are good reasons to believe that this imbalanced essential fatty acid ratio has led to increased cancer, heart disease, allergies, diabetes and other afflictions. Much of the reason for this lies in the membranes of our cells.

**Essential fatty acids in cell membranes**

Phospholipids (PL) and cholesterol are the principal components of nearly all cell membranes. The backbone of a phospholipid is the same glycerol molecule that forms the backbone of triglycerides. But instead of 3 fatty acids attached to glycerol, a phospholipid consists of 2 fatty acids, a phosphate group and an alcohol. The most common alcohols are derived from serine, ethanolamine, choline and inositol. Thus, the most common phospholipids are phosphatidylcholine, phosphatidylethanolamine, phosphatidylinerine, and phosphatidylinositol. Phosphatidylcholine is also known as lecithin. "Commercial lecithin" (which is used as an emulsifying agent in food processing) is a mixture of phospholipids from eggs, soybeans, nuts, etc., with phosphatidylcholine as the major ingredient.
**Phospholipids in Cell Membranes:**

Different cells have different quantities of phospholipid in their membranes. Gray matter in the brain is nearly 70% phospholipid, whereas brain white matter is less than half phospholipid because of high concentrations of glycolipid (sugar-fat). There is much variation in the amounts and kinds of phospholipid in membranes. Brain gray matter is 30% phosphatidylcholine whereas brain white matter is 10% phosphatidylcholine. The inner layer of neuron membranes primarily contain phosphatidylethanolamine & phosphatidylserine, whereas in the outer layer phosphatidylcholine & sphingomyelin predominate.

Mitochondrial and endoplasmic reticulum membranes are both 40% phosphatidylcholine. But mitochondrial membranes are also 35% phosphatidylethanolamine, whereas endoplasmic reticulum membrane is about 17% phosphatidylethanolamine.

Cells also vary considerably in the kinds of fatty acids attached to phosphatidic acid. In gray matter cell membranes, the fatty acids in the middle position of phospholipids are composed of carbon chains that are longer and more unsaturated than fatty acids found in the membrane phospholipids of most other cells. Fatty acids that are long and highly unsaturated increase membrane fluidity and functionality, which is why DHA and
arachidonic acid are highly concentrated in the phospholipids of neuron synapses. Unsaturated fatty acids are also important for membrane activity at the site of hormone receptors. Insulin resistance in adult-onset diabetes is associated with fewer membrane long-chain unsaturated fatty acids due to impaired desaturase and elongase enzyme function (16).

The alcohol portion of a phospholipid protrudes away from the membrane, whereas the two fatty acids jut into the membrane. The middle fatty acid (in the second position) is usually unsaturated (like DHA or arachidonic acid) whereas the end fatty acid (in the first position) is usually saturated (like stearic acid). Each of the 3 groups attached to the glycerol backbone has a special enzyme that can separate the group from the backbone. Phospholipase A₁ enzyme attacks the attachment of the first fatty acid, Phospholipase A₂ attacks the attachment of the middle fatty acid and Phospholipase D attacks the alcohol attachment. Phospholipase C — which is a major toxin secreted by bacteria — releases 1,2-DiAcylGlycerol (DAG) along with a phosphoryl base.

Phospholipase Enzymes in Cell Membranes
Frequently the unsaturated fatty acid stored in the second position of a cell membrane will be arachidonic acid, EPA or DHA (especially in the neurons). The release of arachidonic acid or EPA from cell membranes by Phospholipase A₂ allows the enzymes lipoxygenase and cyclooxygenase to form biologically active eicosanoids like prostaglandins (PGZs, first isolated in prostate gland), thromboxanes (TXZs, first isolated in thrombocytes) and leucotrienes (LTZs, first isolated in leucocytes). These eicosanoids can be compared to hormones, except that unlike hormones they are destroyed by local enzymes within seconds or minutes after formation. This limits the activities of eicosanoids to the area where they were released.

Having cell membranes contain fatty acids that can form the hormone-like eicosanoids gives the body the capacity to produce quick, localized action in almost any tissue or organ. The most general need for rapid, local action is the response to trauma. Therefore, eicosanoids are most often concerned with clotting, inflammation and the initiation of immune defense.

Some membrane phospholipids, such as the phosphatidylinositol, function to convert activity at cell surface G-protein-coupled receptors into intracellular signals. Hydrolysis by phospholipase C and phospholipase D produce the second messengers (intracellular messengers) DiAcylGlycerol (DAG) [which stimulates Protein Kinase C (PKC)] and Inositol triPhosphate (IP₃) [which causes intracellular release of calcium]. Activated PKC concentrates in the plasma membrane where it phosphorylates membrane proteins of receptors and ion-channels to inhibit their function (negative feedback). Nuclear Factor kB (NFkB) activated by PKC binds to DNA promoters & enhancers of inflammatory cytokines, among other genes. IP₃ binds to the endoplasmic reticulum, releasing calcium stored in that location. DAG can be further hydrolysed by Phospholipase A₂ to release more arachidonic acid. Ethanol increases Phospholipase A₂ activity, increasing oxidative stress.
Hydrolysis of Phospholipids

Three categories of Phospholipase A₂ (PLA₂) are recognized: secretory PLA₂ (sPLA₂), cytoplasmic PLA₂ (cPLA₂) and Ca²⁺-independent PLA₂ (iPLA₂). The cPLA₂ is activated by Ca²⁺ to a much greater extent than sPLA₂. Whereas sPLA₂ is more prominent in inflammatory disease, cPLA₂ is more associated with oxidative free radical damage. The cPLA₂ shows a marked preference for hydrolyzing oxidized arachidonic acid in cell membranes, which may be important for membrane maintenance when sufficient ATP is available to synthesize and insert fresh arachidonic acid into membranes. Arachidonic acid is a particularly common constituent of brain neuron membranes and the massive release of arachidonic acid in cerebral cortex ischemia/reperfusion plays a significant role in exacerbating ischemic/reperfusion damage. The activity of cPLA₂ on inner mitochondrial membranes can also be exacerbated under conditions of high oxidative stress.

There are three series of the prostaglandin and thromboxane eicosanoids: one derived from DGLA (series 1), one derived from arachidonic acid (series 2) and one derived from EPA (series 3). The series number indicates the number of double-bonds in the prostaglandin or thromboxane. Series 1 prostaglandins are not as common in the body as series 2 or 3 -- in part because DGLA is not plentiful in many tissues. Series 2 predominates over series 3 for at least three reasons: (1) arachidonic acid is more readily released from cell membranes than EPA. (2) arachidonic acid reacts far more avidly with
cyclo-oxygenase enzyme than does EPA and (3) contemporary Western diets contain large amount of linoleic acid, which results in large amounts of arachidonic acid in cell membranes. The predominance of arachidonic acid eicosanoids over EPA-eicosanoids due to excessively high dietary omega-6 (compared to omega-3) is at the root of many modern health problems, only some of which are concerned with the immune system.
Series-2 Eicosanoids (from Arachidonic Acid)

Different enzymes in different tissues will determine which eicosanoids will be produced in largest quantity. For example, **PGI₂** is produced by the enzyme **prostacyclin synthetase**, whereas **TXA₂** is produced by the enzyme **thromboxane synthetase** (an enzyme which is blocked by the chemical imidazole). If an isomerase enzyme is available, the **TXA₂** will be converted to **TXB₂** (which causes blood vessel constriction and platelet aggregation). **TXB₂** is the main product of Arachidonic Acid metabolism in platelets whereas **PGI₂** is the main product of Arachidonic Acid metabolism in the endothelial cells of blood vessels. If EicosaPentanoic Acid (EPA) is converted rather than Arachidonic Acid, then the primary product of EPA metabolism in the platelets will be **TXB₂** and the primary product of EPA metabolism in the blood vessel wall cells will be **PGI₃**. **PGI₃** is as potent in opposing platelet aggregation as **PGI₂**. But **TXB₂** is a weaker platelet aggregator than **TXB₂**. Therefore, increasing EPA (omega-3) and decreasing Arachidonic Acid (omega-6) is an alternative to aspirin for reducing the danger of excessive blood clotting, which could lead to heart attack.
Cyclooxygenases (COXs) can be divided into COX-1 (present at constant levels in most cells & tissues) and COX-2 (normally absent from most cells, but rapidly rising to high levels in response to growth factors, cytokines, hypoxia, toxins and other stimuli). COX-1 is regarded as a "housekeeping" enzyme responsible for such functions as maintaining gastrointestinal mucosal integrity and regulation of kidney blood flow. COX-2 expression in response to inflammation & mitogens may lead to cancer. COX-2 enhances the formation of prostaglandins that mediate pain & inflammation. The attempts to create drugs that specifically inhibit COX-2 without inhibiting COX-1 (which can result in
Lipogenase enzyme creates hydroperoxides from polyunsaturated fatty acids by an insertion of molecular oxygen. Both arachidonic acid (omega-6) and EPA (omega-3) can be acted-on by lipoxygenase enzyme, rather than by cyclooxygenase -- resulting in leucotrienes (LTZs) rather than the prostaglandins (PGZs) & thromboxanes (TXZs) produced by cyclooxygenase. Lipoxygenase produces series 4 leucotrienes from arachidonic acid or series 5 leucotrienes from EicosaPentoic Acid (EPA). Lipoxygenase is primarily found in granulocytes. HydroxyPeroxyEicosaTetraEnoates (HPETEs) are reactive hydroperoxides which can contribute to cellular damage in atherosclerosis [THE JOURNAL OF CLINICAL INVESTIGATION 111(8): 1107-1113(2003)]. HPETEs like other organic hydroperoxides (ROOH) can lead to lipid peroxidation by Fenton-like reactions.

**Arachidonic Acid conversion to Leukotrienes via HPETEs**

![Diagram of Arachidonic Acid conversion to Leukotrienes via HPETEs]

Arachidonic acid oxidized in the membranes of neurons which has been subsequently liberated by phospholipase results in enzymatic products known as isoeicosanoids because they are isomers of normal eicosanoids. Isoprostanes (isomers of...
cyclooxygenase-derived prostaglandins) and particularly F2-isoprostanes (isomers of prostaglandin F\textsubscript{2alpha}) have attracted special interest because they are chemically stable and can be sensitively measured using mass spectrometry. F2-isoprostanes have been used to quantify lipid peroxidation in atherosclerotic plaques, in the brains of Alzheimer's Disease patients and in the urine of smokers & myocardial infarction patients. Analogous F-ring oxidized isomers of DHA breakdown products known as F4-neuroprostanes have been isolated in elevated quantity in both cerebrospinal fluid and brain tissue of Alzheimer's Disease patients [CELLULAR AND MOLECULAR LIFE SCIENCES 59:808-820 (2002)].

**Fats for immunity:**

One very general way of classifying immunity is to distinguish between acquired immunity and innate immunity. Both systems make use of phagocytes (cells that "eat" foreign substances) and antibodies (Y-shaped chains of proteins known as immunoglobulins). Acquired immunity is seen when the immune system has identified a foreign protein as being an antigen. For innate immunity, however, there is a generalized reaction against tissue trauma and infectious agents that could as easily be described as inflammation as immunity. The swelling of inflammation is associated with immunoglobulin-E (IgE) and with an increased blood vessel permeability which allows Natural Killer cells, macrophages and neutrophils to leave the blood stream, migrate to the injured area and engulf the invaders. Although innate immune defense is not very specific, it is rapid. By contrast, the immune cells (lymphocytes) and immunoglobulins (IgM and IgG) of acquired immunity are slower to develop, but can be very powerful and very specific against antigens.

The eicosanoids produced from arachidonic acid cause a stronger inflammatory response than the eicosanoids from EPA or DGLA. The arachidonic acid products Leukotrienes B4 (LTB\textsubscript{4}) and Prostaglandin E2 (PGE\textsubscript{2}) are powerful promoters of inflammation. LTB\textsubscript{4} is only formed in granulocytes subject to stimuli favoring action by 5-lipoxygenase activating protein [ARCHIVES OF BIOCHEMISTRY AND PHYSICS 356(1):71-76 (1998)]. Both PGE\textsubscript{2} & LTB\textsubscript{4} increases tissue swelling (edema) by making the vascular endothelium leakier. LTB\textsubscript{4} stimulates superoxide production by neutrophils,
activates Natural Killer cells and powerfully attracts inflammatory leukocytes. PGE\(_2\) increases sensitivity to pain, raises temperature and increases the formation of the allergic antibody Immunoglobulin E (IgE) (17). Aspirin irreversibly blocks the enzyme cyclo-oxygenase, which prevents arachidonic acid from being converted to prostaglandin -- thereby limiting inflammation and pain. Gamma-tocopherol (the major form of Vitamin E in food, in contrast to alpha-tocopherol, which is the major form of Vitamin E in supplement pills) also blocks cyclo-oxygenase and reduces proinflammatory PGE\(_2\) & LTB\(_4\) formation [FASEB JOURNAL 17:816-822 (2003)].

Elevated body temperature, increased sensitivity to pain, inflammation and allergic reactions are important body defense mechanisms. Inflammation reduces the spread of infection. Elevated body temperature can kill bacteria and viruses. Increased sensitivity to pain reduces movement of injured body parts, preventing injury from getting worse. But when taken to an extreme, inflammatory reactions can result in auto-immune disease, septic shock, asthma and even fatal anaphylactic shock. Chronic inflammation of the pancreas, colon and other organs increase the risk of cancer in those organs. The increasing incidence of allergies and seasonal asthmas in modern society has been attributed to increased levels of the arachidonic acid eicosanoid LTB\(_4\) due to excessively high dietary omega-6 intake relative to omega-3 (18).

Gamma-Linolenic Acid (GLA) has been shown to be effective against the inflammation of rheumatoid arthritis in a number of studies. Although one might expect that GLA could lead to the formation of arachidonic acid's pro-inflammatory eicosanoids, there is instead a production of the anti-inflammatory prostaglandin PGE\(_1\) of the 1-series (19, 20). It may be that rheumatoid arthritis patients suffer from impaired function of desaturase enzymes, preventing arachidonic acid formation. In ulcerative colitis, an inflammatory condition in which desaturase enzymes are normal, both omega-3 oils from fish and perilla have been used for treatment (21).

Feeding laboratory animals diets rich in omega-3 fatty acids (linseed or fish oil) reduces Natural Killer cell and cytotoxic T-lymphocyte activity (22), but stimulates the more antigen-specific immunoglobulins IgM and IgG [*17]. Innate immune response, although closely tied to inflammation can be separated from inflammation to some extent. One
experiment showed that both fish oil and safflower oil reduced the secretion of Interleukin-6 (a cytokine that activates lymphocyte immune-cells and increases antibody production), but that only fish oil inhibited the secretion of Tumor Necrosis Factor alpha (a cytokine that increases fever, shock and blood vessel permeability) \(^{(23)}\).

As a first-line defense against infection, the inflammatory/innate-immunity response can sometimes mean the difference between life and death. Adding fish oil (which contains both DHA and EPA) to the diet of rats increased the likelihood that the rats would die when subjected to bacterial infection \(^{(24)}\). Mixtures of DHA and EPA strongly reduce Natural Killer and Lymphocyte Activated cells \(^{(25)}\). But immune suppression appears to be more due to EPA than to DHA \(^{(22)}\). In fact, when total fat intake is low, DHA shows no inhibition of immune system function, even though about 9% of DHA is converted back to EPA \(^{(26)}\). The omega-6 to omega-3 proportions may also determine immune suppression. An experiment, using a mixture of safflower oil and fish oil showed no immunosuppressive effect in rats when the omega-6 to omega-3 ratio was approximately 2-to-1 \(^{(23)}\).

Cells of the immune system (like T-Cells, B-Cells and Macrophages) have membranes that are particularly rich in long-chain unsaturated fatty acids (such as arachidonic acid or EPA). For this reason (and also because of their mobility and functions) immune system cells are more vulnerable to free-radical oxidation than other cells. The nutrients that most profoundly improve immune function are vitamin C, vitamin E, selenium, glutathione and zinc \(^{(27)}\). All of these nutrients are antioxidants, although zinc's effects are more due to direct actions on immune cell function than due to its anti-oxidant properties \(^{(28)}\). Vitamin E opposes some, but not all of the increased lipid peroxidation and immune suppression seen in essential fatty acid supplementation \(^{(29)}\). Vitamin E promotes immune function by reducing PGE\(_2\) synthesis and thus increasing T-cell proliferation, IL-2 production and antibody production, while reducing IL-6 production. By scavenging the hydroperoxide necessary for COX activity, Vitamin E opposes the increase in PGE\(_2\) formation that is typically seen in aging. PGE\(_2\) is known to suppress lymphocyte proliferation, to suppress synthesis of chemical factors (lymphokines)
influencing the immune system and to contribute to the auto-immune diseases that increase with aging (30).

**Fats against cancer:**

High fat diets are well-known to be associated with certain kinds of cancers, including breast cancer, in particular (31). Although butterfat stimulates breast cancer when compared with a fat-free diet, safflower oil margarine (linoleic acid, an omega-6) has been shown to induce breast cancer much more strongly (6). Linoleic acid is the fat that most frequently is associated with cancer, whereas omega-3 fatty acids like DHA and perilla-oil suppress cancer (32, 33). It has been theorized that linoleic acid causes cancer by chronic overproduction of the inflammatory arachidonic acid eicosanoids, which stimulate the proliferation of mutated cells (6).

\[ PGE_2 \] resulting from COX-2 enzyme is found in high levels in colorectal carcinomas where the prostaglandin promotes growth through transactivation of epithelial growth factor receptor signalling. \[ PGE_2 \] also induces expression of Vascular Endothelial Growth Factor (VEGF) in colon cancer cells, resulting in the neoangiogenesis (new blood vessels) required by growing tumors [JOURNAL OF CLINICAL INVESTIGATION; Williams,CS; 105(11):1589-1594 (2000)]. Nitric oxide is a regulator of COX-2 expression in the colon, and the phytochemical curcumin (an inhibitor of inducible nitric oxide synthetase found in curry) has been shown to reduce pre-cancerous colon lesions by 45% [CARCINOGENESIS; Rao,CV; 20(4):641-644 (1999)].

Although too much linoleic acid can increase the risk of cancer, a form of linoleic acid in which the double-bonds are closer together -- known as Conjugated Linoleic Acid (CLA) -- actually reduces cancer risk. CLA has been shown to significantly inhibit prostate cancer proliferation (34) and breast cancer formation (35) in experimental animals. Large quantities of CLA are not needed since the maximum anti-cancer effect is seen when CLA is no more than 1% of calories. There is controversy over whether CLA is an anti-oxidant. Some researchers who believe that CLA is not an anti-oxidant believe that CLA's effects are due to its blockage of arachidonic acid formation (36, 37). CLA has also been shown to reduce atherosclerosis in rabbits (38). The best dietary sources of
CLA are the food products of ruminant animals (ie, animals that "ruminate" their food by chewing a cud, like cows or deer), such as beef, milk, yoghurt and cheese.

Fats against diabetes and the effects of alcoholism
Insulin stimulates the delta-6-desaturase enzyme. Therefore, this enzyme's activity is much reduced in diabetes. Reduced delta-6-desaturase activity affects the omega-6 products significantly more than the omega-3 products (39). Although excessive arachidonic acid is associated with many modern illnesses, diabetics suffer from the effects of too little arachidonic acid. Arachidonic acid is essential for leucocyte (white blood cell) function. Reduced leucocyte function makes diabetics more vulnerable to infection (40).

Arachidonic acid deficiency in diabetics also reduces the activity of the "sodium pump", slowing nerve conduction velocity and ultimately leading to neuropathy (diseased nerves) (41). Insulin is the best treatment for these arachidonic acid deficiency conditions, but gamma-linolenic acid (GLA) also restores function. GLA bypasses the delta-6-desaturase step in arachidonic acid synthesis. Evening primrose oil is the most effective omega-6 treatment for diabetic neuropathy, despite the fact that borage oil has more GLA. Although fish oil can be somewhat beneficial when used alone, fish oil can detract from the effectiveness of evening primrose oil when they are used in combination (42).

Alcoholics suffer from disturbances of fat metabolism, notably in the liver. The liver is the most active site of delta-6-desaturase activity in the body. In fact, many (if not most) cells in the body have no delta-6-desaturase enzymes and are dependent upon the liver for omega-3/omega-6 desaturase/elongase products. Neuropathy and other conditions resulting from desaturase dysfunction in alcoholics are benefitted by both evening primrose oil and fish oil in combination (43). Arachidonic acid deficiency is the most serious problem for alcoholics, however, so evening primrose oil seems to be the best therapy (44).

Fats for brain:
DHA and arachidonic acid are the predominant essential fatty acids in the human brain. Neurons cannot synthesize arachidonic acid, but astrocytes and cerebral epithelial cells
have enzymes that can. The ability of enzymes to produce the omega-6 and omega-3 family of products of linoleic and alpha-linolenic acid declines with age. One experiment showed that desaturase enzyme function in old rats was only 44% of the desaturase function in young rats (39). This decline in desaturase activity has provided a rationale for supplementation with GLA (bypassing the delta-6-desaturase enzyme), and for supplementation with the omega-3 products EPA and DHA. Fatty acids in human gray matter phosphatidylethanolamine is roughly 25% DHA, 25% stearic acid, 14% arachidonic and 12% oleic acid. In the outer segments of retina photo-receptors of the eye, DHA accounts for more than 50% of the fatty acid content, probably because of the high membrane fluidity required for sensitivity to light.

In the last third of pregnancy, and in the first four months after birth, rapid brain growth in the human infant requires large amounts of omega-3 and omega-6 essential fatty acids. Human milk contains (in total fatty acids by weight) 12% linoleic acid, 0.5% alpha-linolenic acid, 0.6% arachidonic acid and 0.3% DHA [*45]. Infant formulas frequently have not contained arachidonic acid or DHA. One study showed that by (or just before) age 8, children who had been breast-fed as infants had an 8.3-point IQ advantage over children who had received formula (46). The study corrected for the education and social class of the mother.

Support for the idea that DHA is critical for brain development came from an experiment which studied the effects of adding DHA (in the form of fish oil) to infant formula. At both 16 and 30 weeks of age the breast-fed and supplement-formula-fed infants showed significantly better visual acuity than the placebo-formula-fed infants (47). Arachidonic acid supplementation is also needed because DHA supplementation given alone lowers arachidonic acid levels (48) and because arachidonic acid is essential for growth (49, 50). The lipoxygenase eicosanoids of arachidonic acid contribute to the ability of Nerve Growth Factor (NGF) to increase neurite outgrowth (51). Deficiency of arachidonic acid during brain development is less reversible than deficiency of DHA (6). Evidently an infant's desaturase and elongase enzymes are not fully developed because no amount of alpha-linolenic acid supplement can provide enough DHA for neural development (52).
More recent reviews have firmly recommended the inclusion of arachidonic acid and DHA in the formula of premature babies (53).

It seems reasonable to wonder if dietary fat or fat supplements affect the mental function of adults. Experiments on rats indicate that manipulation of dietary fats can alter the fatty acid composition of brain-cell membranes -- with effects on behavior. A diet high in saturated fat was shown to "impair a wide range of learning and memory functions" (54). Soybean oil has more alpha-linolenic acid than sunflower oil. Soybean-fed rats have shown significantly better learning and less sensitivity to pain than safflower-fed rats (55). Recent experiments testing relative concentrations of linoleic acid to alpha-linolenic acid in the range of from 3-to-1 to 6-to-1 verified that a 4-to-1 ratio is optimal for spatial learning and pain tolerance in rats (56).

The influence of essential fatty acid supplement on brain membrane content declines with maturity, however. Adult cell membrane content of DHA and arachidonic acid is only slowly altered by diet or supplement. If dietary intake of essential fatty acid is low, the body will sacrifice essential fatty acid content of cell membranes outside the brain before neurons are affected. A study of elderly men, however, showed greater cognitive impairment among those with a history of high dietary linoleic acid compared with controls, whereas those with high fish consumption showed reduced cognitive decline (57). One experiment showed promotion of neuron growth by DHA and inhibition by arachidonic acid (58). But an experiment on adult mice showed that excessively high supplements of DHA without arachidonic acid supplementation can impair physical and cognitive performance (59). Arachidonic acid may facilitate LTP-type learning in the hippocampus of the brain (51).

An experiment studying maze-learning in rats demonstrated that, after training, the rats showed less cholesterol and more membrane fluidity in the hippocampal and cortical regions of the brain (60). Adult mice fed fish oil for 12 months showed more brain DHA, less brain arachidonic acid, more synaptic membrane fluidity and higher maze-learning ability (61). Rats fed perilla oil showed 30% more hippocampal neuron synaptic vesicle density and improved learning compared to rats fed safflower oil (62).
Measurements of fatty acid content of brain cell (neuron) membranes show decreased DHA with aging. Since DHA is particularly concentrated in synaptic membranes, lowered DHA levels may contribute to declining brain function. DHA is also reduced when the brains of rats are experimentally exposed to high oxygen levels — suggesting that free-radical oxidation is causing the depletion in both cases. Vitamin E treatment protected the rats from neuron damage from the oxygen. This suggests that Vitamin E may be important for prevention of neurodegeneration in humans (63).

Arachidonic acid can be released from cell membranes exposed to neurotransmitters, neuromodulators and neurohormones. The release of arachidonic acid can directly modify neuron excitability by binding with hydrophobic binding sites of ion channels or can be metabolized to eicosanoids that ineract with neuronal eicosanoid receptors to have a second messenger effect.

Arachidonic acid is known to worsen brain damage during stroke and other conditions of oxygen depletion. Although Vitamin E reduces the toxic effects of arachidonic acid in hypoxic conditions, N-Acetyl-Cysteine (NAC, a nutrient which increases glutathione synthesis) completely blocks the arachidonic acid toxicity. Because NAC is not an effective anti-oxidant against superoxide, the arachidonic acid toxicity must be due to lipid peroxidation (51).

Since the 1950s it has been believed that schizophrenia is caused by brain disturbances involving the neurotransmitter dopamine. Recently it has been observed that many schizophrenics have reduced levels of DHA and arachidonic acid -- and a sizable proportion of these patients do not flush red on 200 mg doses of niacin. DHA is known to be highly concentrated in synapses, suggesting that reduced sensitivity to dopamine due to low levels of DHA and arachidonic acid in dopamine receptors may be a more fundamental cause of schizophrenia than dopamine deficiency (64).

As brain cell membranes age, the ratio of cholesterol to phospholipid increases and membrane fluidity decreases. A similar effect is seen in brains, which are becoming tolerant to ethyl alcohol (beverage alcohol). Experiments exposing rats to ethyl alcohol showed tissue depletion of DHA and arachidonic acid, particularly in the liver (65, 66).
Phosphatidylethanolamine in the cerebral cortex gray matter of the brains of alcoholics show lower levels of DHA and arachidonic acid (67). Methionine (or S-adenosylmethionine, SAM) has reversed the DHA and arachidonic acid depletion in the liver following alcohol treatment of rats (66). Oxidized DHA and arachidonic acid enzyme products (isoprostanes and neuroprostanes) are both markedly elevated in the cerebrospinal fluid of Alzheimer's Disease patients as compared to age-matched controls. Lipid peroxidation would be an expected consequence of inflammatory processes associated with Alzheimer's disease, but could also be indicative of oxidation as a cause of the disease.

**Fats for the heart:**

The low death rate from coronary heart disease among Greenland Eskimos led scientists to suspect that high fish consumption might be protective. A 20-year study of 852 middle-age Dutch men showed that coronary artery disease was more than 50% lower among the men who consumed at least 30 grams of fish per week, when compared with men who did not eat fish (68). A 30-year study of over 2,100 Chicago men showed a 62% risk of coronary heart disease and 56% risk of sudden myocardial infarction for men who ate at least 35 grams of fish daily, compared to those who ate none (69).

**Series 3** prostaglandins & thromboxanes inhibit the release of arachidonic acid from phospholipids and thus reduce formation of **series 2** prostaglandins & thromboxanes. PGI₃ is as potent an anti-aggregator as PGI₂, whereas TXA₃ is a weaker platelet aggregator than TXA₂ -- so the series 3 products result in a less net clotting. TXA₂ causes potent vasoconstriction.

Oxidative stress is known to contribute to atherosclerosis, but it is usually attributed to oxidation of LDL-cholesterol, causing it to adhere to artery walls. Some oxidative effect is also due to vascular smooth muscle cell proliferation induced by arachidonic acid derived eicosanoids functioning as transcription factors. The arachidonic acid lipoxygenase metabolites 12-HPETE and 15-HPETE act as mitogens by increasing AP-1 (Activator Protein-1) transcription factor activity [JOURNAL OF BIOLOGICAL CHEMISTRY; Rao,GN; 271(44):27760-27764 (1996)].
Fish oil has been shown to lower LDL-cholesterol by about 13% (70), to lower blood pressure (71), and to dramatically lower blood triglycerides (72, 73).

### INCIDENCE OF INDUCED HEART ARRHYTHMIA IN EXPERIMENTAL ANIMALS

<table>
<thead>
<tr>
<th>DIETARY FAT</th>
<th>RAT [78]</th>
<th>MONKEY [79]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEEP FAT (Saturated)</td>
<td>44%</td>
<td>45%</td>
</tr>
<tr>
<td>OLIVE OIL (Mono-Saturated)</td>
<td>36%</td>
<td>not used</td>
</tr>
<tr>
<td>SUNFLOWER SEED OIL (Omega-6)</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>FISH OIL (Omega-3)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

The effect on triglycerides, in particular, appears to be due to EPA and DHA, because flaxseed (i.e., linseed oil, which is over 50% alpha-linolenic acid) did not lower triglycerides. More careful analysis has established that DHA alone has no effect on blood triglycerides, but that EPA alone is capable of lowering blood triglycerides by about 30% (74). Purified DHA was shown to lower blood pressure and reduce blood viscosity. The evidence indicated that DHA increases red blood cell membrane fluidity, thereby increasing the deformability of the blood cells so that they can move through capillaries more easily and thus lower blood viscosity and blood pressure (75).

A high fasting blood insulin concentration has been determined to be an independent risk factor for ischemic heart disease (76). The fatty acid content of muscle membranes is critical in determining insulin sensitivity. A high-fat diet can increase insulin resistance, but both dietary omega-3 and omega-6 fatty acids can increase membrane fluidity and thereby improve insulin sensitivity (77).

The protective effect of fish oil against cardiac arrhythmias (irregular heartbeats) has been strikingly illustrated by two similar experiments, one performed on rats (78) and the other on marmoset monkeys (79). Middle-aged animals were fed sheep fat (saturated fat), sunflower seed oil (omega-6) or fish oil (omega-3) for 12 weeks (for rats) or for 24-30 months (for monkeys). With both rats and monkeys arrhythmia was produced in over
40% of the animals fed sheep fat, roughly 10% of the animals fed safflower oil and in none of the animals who were fed fish oil.

Phosphatidylethanolamine from monkey heart tissue showed 5 times more (over 25% total) DHA in the fish-oil fed monkeys than in the other two groups. EPA accounted for over 6% of the fatty acid phosphatidylethanolamine of fish-oil fed monkeys, and was undetectable in the other two groups. A similar experiment on rats using purified DHA and purified EPA, rather than fish-oil, indicated that DHA is responsible for most of the anti-arrhythmic effect (80). It is the DHA release from membrane breakdown, rather than DHA in the bloodstream, which is protective (81). Moreover, DHA in the membrane increases the efficiency of the heart cyclic-AMP (a cell messenger molecule) (82).

Although most fish oils are high in EPA and DHA, there are some fish oils which are not. Flounder, swordfish and sole are particularly low in EPA and DHA. Fish oils having the highest levels of EPA and DHA include mackerel, herring and salmon. Some fish, such as cod and haddock, store most of their fat in the liver, therefore the liver oils of these fish should be taken rather than the fillet.

Increased fish oil consumption, however, is associated with increased lipid peroxidation in heart, liver and lung tissue -- moreso than in the brain (83). Again, Vitamin E has been recommended for those who have a high fish oil consumption to reduce lipid peroxidation (84). In some cases, consumption of fish can harmful due to high levels of mercury. Lipid peroxidation of LDL cholesterol is believed to initiate arterial wall injury and facilitate the formation of atherosclerotic foam cells. Leucocytes & endothelial cells may contribute to atherosclerosis through inflammation induced by 5-lipoxygenase ;[PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (USA) 100(3):1238-1248 (2003)].

Getting the best fat nutrition:

In the face of all the data, there remains the question "What omega-3 and omega-6 fatty acids should be included in the diet, and in what quantities & proportions?" One standard, which is not of much use, in this case is the amount of essential fatty acid intake below, which a deficiency disease occurs. It is very difficult to produce a deficiency disease of
essential fatty acid in normal adults, even in the poorest of diets. The important question is "What levels of essential fatty acids provide optimum health?" This question still results in considerable controversy among nutritionists.

Deficiency disease results from diets where linoleic acid is less than 1% of total calories. Governmental agencies of various nations (including the World Health Organization) recommend an omega-6 intake of 1-3% of total calories, increased to 3-6% during pregnancy and lactation. Since deficiency disease symptoms have not been unquestionably demonstrated for the omega-3 fatty acids (DHA, EPA and alpha-linolenic acid) there is controversy about how much to recommend or whether to recommend omega-3 supplementation at all (85). Ironically, the avidity with which enzymes preferentially utilize omega-3 fatty acids could misleadingly make it appear that omega-6 is more essential. When stated, omega-3 recommendations are often given in relation to omega-6 intake, due to the enzyme competition between the two fatty acid families.

The same enzymes that produce the omega-6 products from linoleic acid also operate to produce the omega-3 products from alpha-linolenic acid. The competition for these enzymes by omega-6 and omega-3 fatty acids is unequal, however. Alpha-linolenic acid at 0.5% of calories can suppress arachidonic acid production to the same degree as linoleic acid at 7% of calories can suppress DHA production. Nonetheless, a 14-to-1 ratio of omega-6 to omega-3 is not necessarily optimal.

A 4-to-1 ratio has been cited as optimal in a brain function experiment (56), whereas another experiment showed 2-to-1 is the best ratio for immune function (23). A 5-to-1 ratio has been recommended on the basis of the ratio of omega-6 to omega-3 in human milk. But 5-to-1 is probably just a reflection of the dietary intake of contemporary mothers. The content of DHA and EPA in human milk has been increased experimentally by giving fish oil supplements to lactating women (86).

Some advocates of "a return to natural levels" of fatty acid intake recommend dietary ratios of 1-to-1. Up until about 200 years ago, the human diet contained much higher levels of omega-3 fatty acids. The meat of wild animals that forage for food is rich in EPA, unlike the meat of domesticated animals that have been fattened with grains. High
levels of dietary omega-6 vegetable oils are a modern phenomenon. EPA competes with arachidonic acid for the cyclo-oxygenase enzyme, reducing the production of thromboxane A2, the most powerful platelet aggregating agent known. Some people feel that restoration of the historic omega-3/omega-6 ratios is a more "natural" way of preventing heart attack than using aspirin to irreversibly inactivate cyclo-oxygenase (15). Aspirin, even in normal therapeutic doses, can produce dizziness, migraine headaches, depression, anxiety, and stomach irritation or stomach bleeding (87).

The high levels of omega-6 fatty acids in modern diets may even adversely affect omega-3 utilization by cellular mechanisms that reduce desaturase formation (88). Rats on a perilla oil diet which results in omega-6 to omega-3 ratios of approximately 1-to-4 showed the longest life spans. Eskimos have low heart and autoimmune disease on a fish oil diet that gives a 1-to-3 ratio (6). Concern that the anti-clotting effect of fish oil might lead to increased incidence of stroke are apparently unfounded, since stroke is primarily the result of high blood pressure and weakened blood vessels.

It would seem prudent to reduce fat intake of nonessential fats to as low a quantity as possible, so long as absorption of oil-soluble vitamins is not impaired. Dietary fat could mainly consist of essential fats. The value of EPA or DHA to prevent serious heart problems should be enough to encourage anyone to take an amount of these nutrients up to 1% of total calories. For a person on a 2,500 calorie daily diet, this would mean 5 to 7.5 grams of essential fatty acids per day with perhaps 500 mg each of EPA and DHA. But too much EPA and DHA can be harmful. When fish oil supplies up to 12% of calories, both the brain and the liver show arachidonic acid deficiencies (48). The same effect would probably be seen with excessive amounts of other omega-3 supplements, like linseed or perilla oil.

It would be nice to have a single essential fatty acid formulation that optimizes benefits to the heart, the brain and the immune system for people of all ages, but this is probably unrealistic. Since DHA is responsible for most of the omega-3 benefits to the brain and the omega-3 prevention of heart arrhythmia -- while avoiding most of the immune-system depression due to EPA -- omega-3 formulations that are higher in DHA rather than EPA should be preferred. For people who dislike fish oil, especially young people with healthy
immune systems and functioning desaturase enzymes, perilla oil or linseed oil may be adequate to obtain a better balance between omega-6 and omega-3. Nonetheless, only about a fifth of alpha-linolenic acid is normally converted to DHA and EPA, partially because the body more readily burns unsaturated fats for energy than saturated fats (6).

But for the very elderly, immune function might be the paramount consideration. Biomarkers of immune function were shown to be a very good predictor of the 2-year survival of 102 elderly people between the ages of 86 and 92 (89). A normally mild disease can be fatal to a person with a weakened immune system. One lifespan study on rats showed reduced lifespan on rats fed fish oil (90), possibly due to immune suppression by EPA. But rats are unlike humans in that they rarely die of cardiovascular disease and they have a lower capacity to synthesize the protective eicosanoid Prostacyclin (PC13) from EPA. Other experiments, on mice, have shown extended lifespan with fish-oil. Fish oil even increased the life-extending benefits of calorie restriction on the mice (91).

GLA supplements like evening primrose oil, or borage oil, might seem undesirable for normal people because of the danger that they would increase arachidonic acid. But studies have shown an increase in membrane DGLA and series 1 eicosanoids, with beneficial anti-inflammatory consequences (92). GLA can also lower blood pressure (93).

To minimize lipid peroxidation, essential fatty acid supplements should be taken with no less than 500 mg of Vitamin E per day. Both gamma and alpha forms of tocopherol should be included (94) for effectiveness. Vitamin E is an antioxidant which strongly prevents membrane peroxidation. The combination of Vitamin E and omega-3 fatty acid can reduce cancer risk while protecting heart cell membranes, brain cell membranes, immune-cell membranes and the receptor membranes that allow hormones to act. Vitamin E can protect essential fatty acids from lipid peroxidation in capsules and in the bloodstream, as well as in cell membranes. But for smokers, vitamin E may not be adequate to reduce oxidation of fish oil in LDL-cholesterol, and some medical authorities have cautioned against too much fish oil consumption by smokers (95).
Ideally, essential fatty acids and Vitamin E should be formulated together in an air-tight capsule. Vitamin C helps maintain the antioxidant capabilities of Vitamin E. Boosting glutathione levels with N-acetyl-cysteine (NAC) and the use of other antioxidant nutrients can further protect against lipid peroxidation of essential fats. Glutathione not only regenerates both Vitamin E and Vitamin C that has been oxidized, it prevents formation of deadly hydroxyl free-radicals.

Conclusion

Optimum dietary benefit from fat for most people would come from a program of reduced total fat, reduced saturated and unessential fat, and increased proportions of omega-3 (relative to omega-6) essential fats. High omega-3 oil like perilla oil might be a simple remedy for young people and the best remedy for smokers. But as most people age, they will benefit most from CLA, GLA, and DHA supplementation combined with antioxidants (especially vitamin E) to protect these polyunsaturated essential fats from oxidation.

Fats are an important component of membranes in our hearts, brains, immune cells and most of the other tissues of our bodies. Since we need these fats, it is important to ensure that we have the right kind of fats that we have enough of them and that we protect them with antioxidants.
Review of Status of Fatty Acids in Human inflammatory diseases
**Dietary modification of inflammation with lipids:**

The n-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in high proportions in oily fish and fish oils. The n-3 PUFA are structurally and functionally distinct from the n-6 PUFA. Typically, human inflammatory cells contain high proportions of the n-6 PUFA arachidonic acid and low proportions of n-3 PUFA. The significance of this difference is that arachidonic acid is the precursor of 2-series prostaglandins and 4-series leukotrienes, which are highly active mediators of inflammation. Feeding fish oil results in partial replacement of arachidonic acid in inflammatory cell membranes by EPA. This change leads to decreased production of arachidonic acid-derived mediators. This response alone is a potentially beneficial anti-inflammatory effect of n-3 PUFA. However, n-3 PUFA have a number of other effects which might occur downstream of altered eicosanoid production or might be independent of this activity. For example, animal and human studies have shown that dietary fish oil results in suppressed production of pro-inflammatory cytokines and can decrease adhesion molecule expression. These effects occur at the level of altered gene expression. This action might come about through antagonism of the effects of arachidonic acid-derived mediators or through more direct actions on the intracellular signalling pathways which lead to activation of transcription factors such as nuclear factor kappa B (NFB). Recent studies have shown that n-3 PUFA can down regulate the activity of the nuclear transcription factor NFB. Fish oil feeding has been shown to ameliorate the symptoms in some animal models of chronic inflammatory disease and to protect against the effects of endotoxin and similar inflammatory challenges. Clinical studies have reported that oral fish oil supplementation has beneficial effects in rheumatoid arthritis and among some patients with asthma, supporting the idea that the n-3 PUFA in fish oil are anti-inflammatory. There are indications that inclusion of n-3 PUFA in enteral and parenteral formulas might be beneficial to patients in intensive care or post-surgery.

**Current status of omega-3 fatty acids supplementation in treatment of hypertriglycerideremia:**

There is strong scientific evidence from human trials that omega-3 fatty acids from fish or omega-3 fatty acids supplements (EPA + DHA) significantly reduce blood triglyceride
levels (97-102). Benefits appear to be dose-dependent, with effects at doses as low as 2 grams of omega-3 fatty acids per day. Higher doses have greater effects, and 4 grams per day can lower triglyceride levels by 25-40%. Effects appear to be additive with HMG-CoA reductase inhibitor ("statin") drugs such as simvastatin (103), pravastatin (104; 105), and atorvastatin (106). The effects of omega-3 fatty acids on hypertriglyceridemia are similar in patients with or without diabetes (101), and in those with kidney disease receiving dialysis. It is not clear how omega-3 fatty acids therapy compares to other agents used for hypertriglyceridemia, such as fibrates (like gemfibrozil or fenofibrate) or niacin/nicotinic acid. Omega-3 fatty acids supplements also appear to cause small improvements in high-density lipoprotein ("good cholesterol") by 1-3%. However, increases (worsening) in low-density lipoprotein levels (LDL/"bad cholesterol") by 5-10% are also observed. Therefore, for individuals with high blood levels of total cholesterol or low-density lipoprotein, significant improvements will likely not be seen, and a different treatment should be selected. It is not clear if alpha-linolenic acid significantly affects triglyceride levels, and there is conflicting evidence in this area. The American Heart Association, in its 2003 recommendations, reports that supplementation with 2-4 grams of EPA + DHA each day can lower triglycerides by 20-40% (107). Because of the risk of bleeding from omega-3 fatty acids (particularly at doses greater than 3 grams per day), a physician should be consulted prior to starting treatment with supplements. C-Reactive Protein (CRP) levels: The data on omega-3 fatty acids and CRP is mixed (108, 109). While omega-3 fatty acids from both plants (ALA) and fish (EPA+DHA) have been shown to reduce CRP in some studies, others have failed to show an effect. There is growing evidence that reducing CRP is beneficial towards favorable cardiovascular outcomes, although additional research is pending in this area. Although statin drugs, weight reduction, smoking cessation, and COX-2 inhibitors all appear to reduce CRP, the evidence regarding omega-3 fatty acids remains equivocal.

Current status of omega-3 fatty acids supplementation in secondary cardiovascular disease prevention

Several well-conducted randomized controlled trials report that in people with a history of heart attack, regular consumption of oily fish (200-400 grams of fish each week equal to 500-800mg of daily omega-3 fatty acids) or omega-3 fatty acids/omega-3 supplements
(containing 850-1800mg of EPA + DHA) reduces the risk of non-fatal heart attack, fatal heart attack, sudden death, and all-cause mortality (death due to any cause) (107; 110-115). Most patients in these studies were also using conventional heart drugs, suggesting that the benefits of omega-3 fatty acids may add to the effects of other therapies. Benefits have been reported after 3 months of use, and after up to 3.5 years of follow-up. Benefits of supplements may not occur in populations that already consume large amounts of dietary fish (116). Multiple mechanisms have been proposed for the beneficial effects of omega-3 fatty acids. These include reduced triglyceride levels, reduced inflammation, slightly lowered blood pressure, reduced blood clotting, reduced tendency of the heart to develop abnormal rhythms, and diminished buildup of atherosclerotic plaques in arteries of the heart. Experiments suggest that omega-3 fatty acids may reduce platelet derived growth factor (PDGF), decrease platelet aggregation, inhibit the expression of vascular adhesion molecules, and stimulate relaxation of endothelial cells in the walls of blood vessels (117). The American Heart Association, in its 2003 recommendations, suggests that people with known coronary heart disease take in approximately 1 gram of EPA and DHA (combined) each day (107). This may be obtained from eating fish, or from omega-3 fatty acids capsule supplements. Because of the risk of bleeding from omega-3 fatty acids (particularly at doses greater than 3 grams per day), a physician should be consulted prior to starting treatment with supplements.

**Current status of omega-3 fatty acids supplementation in treatment of high blood pressure**

Multiple human trials report small reductions in blood pressure with intake of omega-3 fatty acids (118-124). Reductions of 2-5 mmHg have been observed, and benefits may be greater in those with higher blood pressures. Effects appear to be dose-responsive (higher doses have greater effects) (119). DHA may have greater benefits than EPA (125). However, intakes of greater than 3 grams of omega-3 fatty acids per day may be necessary to obtain clinically relevant effects, and at this dose level, there is an increased risk of bleeding. Therefore, a physician should be consulted prior to starting treatment with supplements. Other approaches are known to have greater effects on blood pressure, such as salt reduction, weight loss, exercise or antihypertensive drug therapy. Therefore,
although omega-3 fatty acids do appear to have effects in this area, their role in the management of high blood pressure is limited.

**Current status of omega-3 fatty acids supplementation in primary cardiovascular disease prevention**

Several large studies of populations ("epidemiologic" studies) report a significantly lower rate of death from heart disease in men and women who regularly eat fish (126-135). Other epidemiologic research reports no such benefits (136-138). It is not clear if reported benefits only occur in certain groups of people, such as those at risk of developing heart disease. Overall, the evidence suggests benefits of regular consumption of omega-3 fatty acids (139-141). However, well-designed randomized controlled trials which classify people by their risk of developing heart disease are necessary before a firm conclusion can be drawn (142). The American Heart Association, in its 2003 recommendations, suggests that all adults eat fish at least two times per week (107). In particular, fatty fish are recommended, including mackerel, lake trout, herring, sardines, albacore tuna, and salmon.

**Current status of omega-3 fatty acids supplementation in treatment of Rheumatoid arthritis**

Multiple randomized controlled trials report improvements in morning stiffness and joint tenderness with the regular intake of omega-3 fatty acids supplements for up to three months (143-157). Benefits have been reported as additive with anti-inflammatory medications such as NSAIDs (like ibuprofen or aspirin). However, because of weaknesses in study designs and reporting, better research is necessary before a strong favorable recommendation can be made. Effects beyond three months of treatment have not been well evaluated. Ingestion of omega-3 fatty acids relieved several clinical parameters used in the present study. However, patients showed a more precocious and accentuated improvement when omega-3 fatty acids supplements were used in combination with olive oil. (158)

**Current status of omega-3 fatty acids supplementation in protection from cyclosporine toxicity in organ transplant patients**

There are multiple studies of heart transplant and kidney transplant patients taking cyclosporine (Neoral), who were administered omega-3 fatty acids supplements. The
majority of trials report improvements in kidney function (glomerular filtration rate, serum creatinine) (159-168), and less hypertension (high blood pressure) (159; 169; 170) compared to patients not taking omega-3 fatty acids. Although several recent studies report no benefits on kidney function (171-175), the weight of scientific evidence favors the beneficial effects of omega-3 fatty acids. No changes have been found in rates of rejection or graft survival.

**Current status of omega-3 fatty acids supplementation in secondary cardiovascular disease prevention**

Several randomized controlled trials have examined the effects of alpha-linolenic acid in people with a history of heart attack. Although some studies suggest benefits (114; 135; 176; 176), others do not (177-179). Weaknesses in some of this research make results difficult to interpret, such as the use of other foods that may also be beneficial. Additional research is necessary before a conclusion can be drawn in this area.

**Current status of omega-3 fatty acids supplementation in primary cardiovascular disease prevention**

Several large studies of populations ("epidemiologic" studies) report a significantly reduced risk of fatal or non-fatal heart attack in men and women who regularly consume foods high in #945;linolenic acid (135;180;181). Other epidemiologic research reports no such benefits (138;179). Although the existing research is compelling, weaknesses in this research make results difficult to interpret, such as the use of other foods that may also be beneficial, or effects of risk factors for heart disease such as smoking. Additional research is necessary before a conclusion can be drawn in this area. The American Heart Association, in its 2003 recommendations, suggests that in addition to eating fish at least two times per week, all adults should consume plant-derived sources of omega-3 fatty acids, such as tofu/soybeans, walnuts, flaxseed oil, and canola oil (107).

**Current status of omega-3 fatty acids supplementation in stroke prevention**

Several large studies of populations ("epidemiologic" studies) have examined the effects of omega-3 fatty acid intake on stroke risk. Some studies suggest benefits (182-184), while others do not (176; 185-187). Effects are likely on ischemic or thrombotic stroke risk, and very large intakes of omega-3 fatty acids ("Eskimo" amounts) may actually increase the risk of hemorrhagic (bleeding) stroke (188). At this time, it is unclear if there...
are benefits in people with or without a history of stroke, or if effects of omega-3 fatty acids are comparable to other treatment strategies. Multiple mechanisms have been proposed for the beneficial effects of omega-3 fatty acids. These include reduced triglyceride levels, reduced inflammation, slightly lowered blood pressure, reduced blood clotting, and diminished buildup of atherosclerotic plaques in blood vessels. Experiments suggest that omega-3 fatty acids may reduce platelet derived growth factor (PDGF), decrease platelet aggregation, inhibit the expression of vascular adhesion molecules, and stimulate relaxation of endothelial cells in the walls of blood vessels (117).

Current status of omega-3 fatty acids supplementation in treatment of atherosclerosis

Some research reports that regular intake of fish or omega-3 fatty acids supplements reduces the risk of developing atherosclerotic plaques in the arteries of the heart (189;190), while other research reports no effects (191). Additional evidence is necessary before a firm conclusion can be drawn in this area.

Current status of omega-3 fatty acids supplementation in prevention of restenosis after coronary angioplasty (PTCA)

Several randomized controlled trials have evaluated whether omega-3 fatty acid intake reduces blockage of arteries in the heart following balloon angioplasty (percutaneous transluminal coronary angioplasty/PTCA). Some research has reported small significant benefits (192; 193), while other investigations have not found benefits (194-196). The evidence in this area remains inconclusive.

Current status of omega-3 fatty acids supplementation in prevention of graft failure after heart bypass surgery

There is limited study of the use of omega-3 fatty acids in patients after undergoing coronary artery bypass grafting (CABG). Initial research suggests possible small benefits in reducing blood clot formation in vein grafts (197; 198). Additional evidence is necessary before a firm conclusion can be drawn in this area.

Current status of omega-3 fatty acids supplementation in treatment of angina pectoris

Preliminary studies report reductions in angina associated with omega-3 fatty acids intake (199; 200). Better research is necessary before a firm conclusion can be drawn.
Current status of omega-3 fatty acids supplementation in treatment of cardiac arrhythmias (abnormal heart rhythms)

There is promising evidence that omega-3 fatty acids may decrease the risk of cardiac arrhythmias (201-203). This is one proposed mechanism behind the reduced number of heart attacks in people who regularly ingest omega-3 fatty acids or EPA + DHA. Additional research is needed in this area specifically before a firm conclusion can be reached.

Current status of omega-3 fatty acids supplementation in cancer prevention

Several population (epidemiologic) studies report that dietary omega-3 fatty acids or omega-3 fatty acids may reduce the risk of developing breast, colon or prostate cancer (204-210). Randomized controlled trials are necessary before a clear conclusion can be drawn.

Current status of omega-3 fatty acids supplementation in treatment of colon cancer

Omega-3 fatty acids are commonly taken by cancer patients (211). Although preliminary studies report that growth of colon cancer cells may be reduced by taking omega-3 fatty acids, effects on survival or remission have not been measured adequately.

Current status of omega-3 fatty acids supplementation in infant eye/brain development

It has been suggested that fatty acids, particularly DHA, may be important for normal neurologic development. Fatty acids are added to some infant formulas. Several studies have examined the effects of DHA on development of vision in preterm infants (212-218). Short-term benefits have been reported compared to formulas without DHA, although these benefits may not be meaningful in the long-term. Well-designed research is necessary before a clear conclusion can be reached.

Current status of omega-3 fatty acids supplementation in treatment of ulcerative colitis

It has been suggested that effects of omega-3 fatty acids on inflammation may be beneficial in patients with ulcerative colitis when added to standard therapy, and several studies have been conducted in this area (219-230). Although results have been promising, the majority of trials are small and not well designed. Therefore, better research is necessary before a clear conclusion can be drawn.
Current status of omega-3 fatty acids supplementation in treatment of Crohn's disease

It has been suggested that effects of omega-3 fatty acids on inflammation may be beneficial in patients with Crohn's disease when added to standard therapy, and several studies have been conducted in this area (221; 231-233). Results are conflicting, and no clear conclusion can be drawn at this time.

Current status of omega-3 fatty acids supplementation in treatment of IgA nephropathy

There are conflicting results from several trials in this area (234-240).

Current status of omega-3 fatty acids supplementation in treatment of nephrotic syndrome

There is not enough reliable evidence to form a clear conclusion in this area (241; 242).

Current status of omega-3 fatty acids supplementation in treatment of lupus erythematosus

There is not enough reliable evidence to form a clear conclusion in this area (243-245).

Current status of omega-3 fatty acids supplementation in treatment of psoriasis

Several studies in this area do not provide enough reliable evidence to form a clear conclusion (246-257).

Current status of omega-3 fatty acids supplementation in treatment of eczema

Several studies of EPA for eczema do not provide enough reliable evidence to form a clear conclusion (258-260).

Current status of omega-3 fatty acids supplementation in treatment of asthma

Several studies in this area do not provide enough reliable evidence to form a clear conclusion, with some studies reporting no effects (261-263), and others finding benefits. Because most studies have been small without clear descriptions of design or results, the results cannot be considered conclusive.
Osteoarthritis
And
Role of Fatty Acids in the Therapy
Osteoarthritis is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints. Cartilage is a protein substance that serves as a "cushion" between the bones of the joints. Osteoarthritis is also known as degenerative arthritis. Among the over 100 different types of arthritis conditions, osteoarthritis is the most common, affecting over 20 million people in the United States. Osteoarthritis occurs more frequently as we age. Before age 45, osteoarthritis occurs more frequently in males. After age 55 years, it occurs more frequently in females. In the United States, all races appear equally affected. A higher incidence of osteoarthritis exists in the Japanese population, while South African blacks, East Indians and Southern Chinese have lower rates.

Osteoarthritis commonly affects the hands, feet, spine, and large weight-bearing joints, such as the hips and knees. Most cases of osteoarthritis have no known cause and are referred to as primary osteoarthritis. When the cause of the osteoarthritis is known, the condition is referred to as secondary osteoarthritis.

What causes osteoarthritis?

Primary osteoarthritis is mostly related to aging. With aging, the water content of the cartilage increases and the protein makeup of cartilage degenerates. Repetitive use of the joints over the years irritates and inflames the cartilage, causing joint pain and swelling. Eventually, cartilage begins to degenerate by flaking or forming tiny crevasses. In advanced cases, there is a total loss of the cartilage cushion between the bones of the joints. Loss of cartilage cushion causes friction between the bones, leading to pain and limitation of joint mobility. Inflammation of the cartilage can also stimulate new bone outgrowths (spurs) to form around the joints. Osteoarthritis occasionally can be found in multiple members of the same family, implying an heredity (genetic) basis for this condition.
Secondary osteoarthritis is caused by another disease or condition. Conditions that can lead to secondary osteoarthritis include obesity, repeated trauma or surgery to the joint structures, abnormal joints at birth (congenital abnormalities), gout, diabetes, and other hormone disorders.

Obesity causes osteoarthritis by increasing the mechanical stress on the cartilage. In fact, next to aging, obesity is the most powerful risk factor for osteoarthritis of the knees. The early development of osteoarthritis of the knees among weight lifters is believed to be in part due to their high body weight. Repeated trauma to joint tissues (ligaments, bones and cartilage) is believed to lead to early osteoarthritis of the knees in soccer players. Interestingly, recent studies have not found an increased risk of osteoarthritis in long-distance runners.

Crystal deposits in the cartilage can cause cartilage degeneration, and osteoarthritis. Uric acid crystals cause arthritis in gout, while calcium pyrophosphate crystals cause arthritis in pseudogout.

Some people are born with abnormally formed joints (congenital abnormalities) that are vulnerable to mechanical wear, causing early degeneration and loss of joint cartilage. Osteoarthritis of the hip joints is commonly related to design abnormalities of these joints that had been present since birth.
Hormone disturbances, such as diabetes and growth hormone disorders, are also associated with early cartilage wear and secondary osteoarthritis.

**What are symptoms of osteoarthritis?**

Osteoarthritis is a disease of the joints. Unlike many other forms of arthritis that are systemic illnesses, such as rheumatoid arthritis and systemic lupus, osteoarthritis does not affect other organs of the body. The most common symptom of osteoarthritis is pain in the affected joint(s) after repetitive use. Joint pain is usually worse later in the day. There can be swelling, warmth, and creaking of the affected joints. Pain and stiffness of the joints can also occur after long periods of inactivity, for example, sitting in a theater. In severe osteoarthritis, complete loss of cartilage cushion causes friction between bones, causing pain at rest or pain with limited motion.

Symptoms of osteoarthritis vary greatly from patient to patient. Some patients can be debilitated by their symptoms. On the other hand, others may have remarkably few symptoms in spite of dramatic degeneration of the joints apparent on x-rays. Symptoms also can be intermittent. It is not unusual for patients with osteoarthritis of the hands and knees to have years of pain-free intervals between symptoms.

Osteoarthritis of the knees is often associated with obesity or a history of repeated injury and/or joint surgery. Progressive cartilage degeneration of the knee joints can lead to deformity and outward curvature of the knees referred to as "bow legged." Patients with osteoarthritis of the weight bearing joints (like the knees) can develop a limp. The limping can worsen as more cartilage degenerates. In some patients, the pain, limping, and joint dysfunction may not respond to medications or other conservative measures. Therefore, severe osteoarthritis of the knees is one of the most common reasons for total knee replacement surgical procedures in the United States.

Osteoarthritis of the spine causes pain in the neck or low back. Bony spurs that form along the arthritic spine can irritate spinal nerves, causing severe pain, numbness, and tingling of the affected parts of the body.
Osteoarthritis causes the formation of hard bony enlargements of the small joints of the fingers. Classic bony enlargement of the small joint at the end of the fingers is called a Heberden's node, named after a very famous British doctor. The bony deformity is a result of the bone spurs from the osteoarthritis in that joint. Another common bony knob (node) occurs at the middle joint of the fingers in many patients with osteoarthritis and is called a Bouchard's node. Dr. Bouchard was a famous French doctor who also studied arthritis patients in the late 1800s. The Heberden's and Bouchard's nodes may not be painful, but they are often associated with limitation of motion of the joint. The characteristic appearances of these finger nodes can be helpful in diagnosing osteoarthritis. Osteoarthritis of the joint at the base of the big toes leads to the formation of a bunion. Osteoarthritis of the fingers and the toes may have a genetic basis, and can be found in numerous women members of some families.

Diagnosis:

There is no blood test for the diagnosis of osteoarthritis. Blood tests are performed to exclude diseases that can cause secondary osteoarthritis, as well as to exclude other arthritis conditions that can mimic osteoarthritis.

X-rays of the affected joints can suggest osteoarthritis. The common x-ray findings of osteoarthritis include loss of joint cartilage, narrowing of the joint space between adjacent bones, and bone spur formation. Simple x-ray testing can be very helpful to exclude other causes of pain in a particular joint as well as assist the decision-making as to when surgical intervention should be considered.

Arthrocentesis is often performed in the doctor's office. During arthrocentesis, a sterile needle is used to remove joint fluid for analysis. Joint fluid analysis is useful in excluding gout, infection, and other causes of arthritis. Removal of joint fluid and injection of corticosteroids into the joints during arthrocentesis can help relieve pain, swelling, and inflammation.

Arthroscopy is a surgical technique whereby a doctor inserts a viewing tube into the joint space. Abnormalities of and damage to the cartilage and ligaments can be detected and
sometimes repaired through the arthroscope. If successful, patients can recover from the
arthroscopic surgery much more quickly than from open joint surgery.

Finally, a careful analysis of the location, duration, and character of the joint symptoms
and the appearance of the joints helps the doctor in diagnosing osteoarthritis. Bony
enlargement of the joints from spur formations is characteristic of osteoarthritis.
Therefore, Heberden's nodes, Bouchard's nodes, and bunions of the feet can help the
doctor make a diagnosis of osteoarthritis

**Treatment**

Aside from weight reduction and avoiding activities that exert excessive stress on the
joint cartilage, there is no specific treatment to halt cartilage degeneration or to repair
damaged cartilage in osteoarthritis. The goal of treatment in osteoarthritis is to reduce
joint pain and inflammation while improving and maintaining joint function. Some
patients with osteoarthritis have minimal or no pain, and may not need treatment. Others
may benefit from conservative measures such as rest, exercise, weight reduction, physical
and occupational therapy, and mechanical support devices. These measures are
particularly important when large, weight-bearing joints are involved, such as the hips or
knees. In fact, even modest weight reduction can help to decrease symptoms of
osteoarthritis of the large joints, such as the knees and hips. Medications are used to
complement the physical measures described above. Medication may be used topically,
taken orally, or injected into the joints to decrease joint inflammation and pain. When
conservative measures fail to control pain and improve joint function, surgery can be
considered.

Resting sore joints decreases stress on the joints, and relieves pain and swelling. Patients
are asked to simply decrease the intensity and/or frequency of the activities that
consistently cause joint pain.

Exercise usually does not aggravate osteoarthritis when performed at levels that do not
cause joint pain. Exercise is helpful in osteoarthritis in several ways. First, it strengthens
the muscular support around the joints. It also prevents the joints from "freezing up" and
improves and maintains joint mobility. Finally, it helps with weight reduction and promotes endurance. Applying local heat before and cold packs after exercise can help relieve pain and inflammation. Swimming is particularly suited for patients with osteoarthritis because it allows patients to exercise with minimal impact stress to the joints. Other popular exercises include walking, stationary cycling, and light weight training.

Physical therapists can provide support devices, such as splints, canes, walkers, and braces. These devices can be helpful in reducing stress on the joints. Occupational therapists can assess daily activities and determine additional devices that may help patients at work or home. Finger splints can support individual joints of the fingers. Paraffin wax dips, warm water soaks, and nighttime cotton gloves can help ease hand symptoms. Spine symptoms can improve with a neck collar, lumbar corset, or a firm mattress, depending on what areas are involved.

In many patients with osteoarthritis, mild pain relievers such as aspirin and acetaminophen (Tylenol) may be sufficient treatment. Studies have shown that acetaminophen given in adequate doses can often be equally as effective as prescription anti-inflammatory medications in relieving pain in osteoarthritis of the knees. Since acetaminophen has fewer gastrointestinal side effects than NSAIDS, especially among the elderly patients, acetaminophen is generally the preferred initial drug given to patients with osteoarthritis. Medicine to relax muscles in spasm might also be given temporarily. Pain-relieving creams applied to the skin over the joints can provide relief of minor arthritis pain. Examples include capsaicin (Arthricare, Zostrix), salycin (Aspercreme), methyl salicylate (Bengay, Icy Hot), and menthol (Flexall).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that are used to reduce pain and inflammation in the joints. Examples of NSAIDs include aspirin (Ecotrin), ibuprofen (Motrin), nabumetone (Relafen), and naproxen (Naprosyn). It is sometimes possible to use NSAIDs for a while and then discontinue them for periods of time without recurrent symptoms, thereby decreasing side effect risks.
The most common side effects of NSAIDs involve gastrointestinal distress, such as stomach upset, cramping diarrhea, ulcer and even bleeding. The risk of these and other side effects increases in the elderly. Newer NSAIDs called Cox-2 Inhibitors have been designed that have less toxicity to the stomach and bowels. Because osteoarthritis symptoms vary and can be intermittent, these medicines might be given only when joint pains occur or prior to activities that have traditionally brought on symptoms.

Recently, the food supplements glucosamine and chondroitin have been shown to relieve symptoms of pain and stiffness for some persons with osteoarthritis. These supplements are available in pharmacies and health food stores without a prescription, although there is no certainty about the purity of the products or the dose of the active ingredients because they are not monitored by the FDA. The National Institutes of Health is studying glucosamine and chondroitin in the treatment of osteoarthritis and this research will clarify many issues regarding dosing, safety, and effectiveness of these products for osteoarthritis. Patients taking blood-thinners should be careful taking chondroitin as it can increase the blood-thinning and cause excessive bleeding. Fish oil supplements have been shown to have some anti-inflammation properties and increasing the dietary fish intake and/or fish oil capsules (omega 3 capsules) can sometimes reduce inflammation of arthritis.

While oral cortisone is generally not used in treating osteoarthritis, when injected directly into the inflamed joints, it can rapidly decrease pain and restore function. Since repetitive cortisone injections can be harmful to the tissue and bones, they are reserved for patients with more pronounced symptoms.

For persisting pain of severe osteoarthritis of the knee that does not respond to weight reduction, exercise or medications, a series of injections of hyaluronic acid (Synvisc, Hyalgan) into the joint can sometimes be helpful, especially if surgery is not being considered. These products seem to work by temporarily restoring the thickness of the joint fluid, allowing better joint lubrication and impact capability, and perhaps by directly affecting pain receptors.

Surgery is generally reserved for those patients with osteoarthritis that is particularly severe and unresponsive to the conservative treatments. Arthroscopy, discussed above,
can be helpful when cartilage tears are suspected. Osteotomy is a bone removal procedure that can help realign some of the deformity in selected patients, usually those with knee disease. In some cases, severely degenerated joints are best treated by fusion (arthrodesis) or replacement with an artificial joint (arthroplasty). Total hip and total knee replacements are now commonly performed in community hospitals throughout the United States. These can bring dramatic pain relief and improved function.

**What does the future hold for osteoarthritis?**

In the future, medications may be available which protect the cartilage from the deteriorating consequences of osteoarthritis. New treatments, including an anti-inflammatory lotion, diclofenac (Pennsaid) are being studied for the relief of the pain of osteoarthritis. Recently, surgical innovation has led to a technique for the repair of isolated splits of cartilage (fissures) of the knee. In this procedure, a patient's own cartilage is actually grown in the laboratory, then inserted into the fissure area and sealed over with a "patch" of the patient's own bone covering the tissue. While this is not a procedure for the cartilage damage of osteoarthritis, it does open the door for future cartilage research. These and other developing areas hold promise for new approaches to an old problem.

Investigators at the National Institutes of Health are currently looking into whether or not taking glucosamine or chondroitin could actually improve or protect the quality of the cartilage in joints affected by osteoarthritis.

Research scientists have found that doxycycline, a tetracycline drug, has been shown to slow the progression of cartilage degeneration in the knees of patients with osteoarthritis. More studies are needed to determine the significance of this early, but interesting, work.

**Osteoarthritis at a Glance**

- Osteoarthritis is a joint inflammation that results from cartilage degeneration.
- Osteoarthritis can be caused by aging, heredity, and injury from trauma or disease.
- The most common symptom of osteoarthritis is pain in the affected joint(s) after repetitive use.
- There is no blood test for the diagnosis of osteoarthritis.
- The goal of treatment in osteoarthritis is to reduce joint pain and inflammation while improving and maintaining joint function.

Arthritis is a disease of epidemic proportions, but it has been around for so many centuries that it is considered by most people as a part of growing old or a consequence of physical injury. Arthritis is in fact a far more complex disease than is generally known. For instance, Dorland's Medical Dictionary describes 27 different types of arthritis, and that does not include such diverse conditions as systemic lupus erythematosus, scleroderma, fibromyalgia, and numerous other conditions which some authorities consider to be types of arthritis (264). One authority states that there are approximately 100 causes for arthritis (265).

Arthritis is thought to affect more than 50 million Americans, and is generally accepted to be the leading cause of movement limitation and disability. It deserves and receives a great deal of research and medical attention. There are hundreds of drugs, procedures, and medical aids and devices directed at coping with the many manifestations of the disease. Given this degree of complexity, certainly no one agent alone could ever be expected to manage or cure "arthritis" in its entirety. New agents take their place in the spectrum and make a contribution.

Herbal remedies are among the most popular alternative therapies used by individuals with arthritis. Scientific evidence suggests that the following herbs are most effective for treating OA:

**Glucosamine and Chondroitin**

Glucosamine and chondroitin are compounds that occur naturally in human cartilage. For use in supplements, they are derived from bovine and calf cartilage. They have been widely used in Europe for more than a decade and have also recently gained popularity in
the United States. Both compounds have been shown to inhibit inflammation in laboratory experiments. To evaluate the long-term effectiveness and possible toxic effects of these substances, the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH) has funded a large clinical trial comparing glucosamine, chondroitin, and a combination of the two agents, to placebo. The study is projected to be complete by March 2005.

Several reviews of clinical trials examining either glucosamine or chondroitin for OA concluded that these agents showed a number of benefits

- Devil's claw (*Harpagophytum procumbens*)
- Willow bark (*Salix* spp.)
- Stinging nettle (*Urtica dioica*)
- A combination of aspen (*Populus tremula*), ash (*Fraxinus excelsior*), and goldenrod (*Solidago virgaurea*)
- An Ayurvedic herbal mixture containing extracts of ashwagandha (*Withania somnifera*), boswellia (*Boswellia serrata*), and turmeric (*Curcuma longa*)
- A combination of willow bark (*Salix* spp.), black cohosh (*Cimicifuga racemosa*), sarsaparilla (*Smilax* spp.), guaiacum (*Guaiacum officinale*) resin, and poplar bark (*Populus tremuloides*)

Other herbs that have shown promise in the treatment of OA include:

**Capsaicin (*Capsicum frutescens*)**

Capsaicin is the main component in hot chili peppers (also known as cayenne). Applied to the surface of the skin, it is believed to deplete stores of a substance that contributes to inflammation and pain in arthritis. Several studies have shown that capsaicin cream provided much better pain relief than a placebo but no improvement in joint swelling, grip strength, or function for people with OA. Pain reduction generally begins 3 to 7 days after applying the capsaicin cream to the skin.
Avocado/Soybean extracts

Laboratory studies suggest that avocado/soybean extracts stimulate the growth of collagen (the principal protein of the skin, tendons, cartilage, and bone) in cartilage cells. In a study of 164 people with OA of the knee or hip, researchers found that participants who received avocado/soybean extracts for 6 months experienced the following improvements with few or no side effects:

- Reduction in pain and disability
- Increase in mobility
- Reduced need for NSAIDs

Cat's claw (*Uncaria tomentosa*)

In a study of 45 people with OA of the knee, those who received cat's claw reported a significant reduction in knee pain compared to those who received placebo.

Ginger (*Zingiber officinale*)

Ginger extract has long been used in traditional medical practices (such as Ayurvedic and Chinese) to decrease inflammation. Although there have been a few case reports of the benefit of ginger for OA in medical literature, one recent trial found that the herb was no more effective than ibuprofen or placebo in reducing symptoms of OA.

Kava kava (*Piper methysticum*)

Kava has traditionally been used as a pain reliever, but few scientific studies have evaluated kava for this purpose.

S-adenosylmethionine (SAMe)
Laboratory and animal studies suggest that SAMe may reduce pain and inflammation, but researchers are not clear how this works. Clinical trials with humans (although generally small in size and of short duration) have also shown favorable results for SAMe when used to relieve OA symptoms.

In several short-term studies (ranging from 4 to 12 weeks), SAMe supplements (1200 mg/day) compared favorably to NSAIDs in adults with knee, hip, or spine osteoarthritis in the following ways:

- Diminished morning stiffness
- Decreased pain
- Reduced swelling
- Improved range of motion
- Increased walking pace

In an extensive review of studies conducted with SAMe (collectively representing over 20,000 people), including trials of longer duration (namely, 2 years), the supplement was associated with the following benefits:

- Improved symptoms
- Few side effects
- No negative influences on cartilage production (unlike NSAIDs)
- Reduced risk for relapse

**Vitamin D**

Vitamin D is essential to bone and cartilage health. Studies evaluating vitamin D use for OA have found the following:

- Vitamin D prevents breakdown of cartilage
• Lower intake of vitamin D may be linked to greater risk of hip OA in older women and OA-related joint changes (visible on X-rays) in both men and women.

**Antioxidants**

Antioxidants appear to significantly ease oxidative stress and inflammation caused by free radicals and may therefore slow the progression of OA. Free radicals can be produced in the joints and have been implicated in many degenerative changes in the aging body, including destruction of cartilage and connective tissue. Antioxidants appear to offset the damage caused by free radicals. Although further evidence is needed to substantiate these claims, studies of groups of people observed over time suggest that the following antioxidants may help to reduce the symptoms of OA:

- Vitamin A and beta-carotene
- Vitamin C
- Vitamin E

In addition, more extensive research on vitamin E revealed that people with OA experienced a significant reduction in pain after taking 600 mg of vitamin E per day, compared with those who received placebo. Those who took 600 mg of vitamin E three times a day experienced significantly less pain than those who took the NSAID diclofenac.

**Niacinamide:**

In one preliminary study, 72 patients with OA were randomly assigned to receive niacinamide, a form of vitamin B₃ or placebo. Participants in the niacinamide group experienced a 30% improvement in symptoms compared to a 10% worsening of symptoms experienced by those in the placebo group. People taking niacinamide reported the following:

- Improved joint mobility
- Reduced need for anti-inflammatory medications
The study authors speculate that niacinamide may aid cartilage repair and suggest that it may be used safely with NSAIDs to reduce inflammation. Further research is needed to fully understand how niacinamide benefits people with OA and to determine whether the results apply to all people with the condition. It does appear, however, that niacinamide must be used for at least 3 weeks before the benefits described are seen. Experts also suggest that long-term use (1 to 3 years) may slow the progression of the disease.

**Omega-3 Fatty Acids:**

Omega-3 fatty acids are found in coldwater fatty fish (such as salmon, mackerel, and herring), flaxseed, rapeseed and walnuts. Research regarding the use of omega-3 fatty acid supplements for inflammatory joint conditions has focused almost entirely on rheumatoid arthritis. Based on laboratory studies, however, many researchers suggest that diets rich in omega-3 fatty acids (and low in omega-6 fatty acids) may benefit people with other inflammatory disorders, such as OA. In fact, several laboratory studies of cartilage-containing cells have found that omega-3 fatty acids decrease inflammation and reduce the activity of enzymes that break down cartilage.

Another potential source of omega-3 fatty acids is the New Zealand green lipped mussel (*Perna canaliculus*), used for centuries by the Maori people for good health. In a trial involving 38 people with OA, nearly 40% of those who received *P. canaliculus* extracts experienced the following:

- Decreased joint stiffness and pain
- Increased grip strength
- Enhanced walking pace

It is also important to note, however, that 10% of participants experienced a temporary worsening of symptoms when first taking the supplement. In addition, it is better to use lipid extracts of *P. canaliculus* rather than powder as there is less chance of an allergic reaction. *P. canaliculus* should be avoided by people who are allergic to seafood. Fatty acid imbalances are commonly seen in patients with chronic inflammatory conditions such as arthritis. While there can be many causes of inflammation, the final common
mediators of cellular inflammation and cellular invasion are always chemical. These chemotactic mediators include cytokines, leukotrienes, and eicosanoids, whose production is greatly impacted by levels of fatty acids in the body.

Examination of patients with cartilage degradation in osteoarthritis has linked increased severity of lesions with a higher proportion of arachidonic acid, an omega-6 fatty acid which shifts production toward more inflammatory prostaglandins, leukotrienes, and thromboxanes (266). In fact, two of these local hormones, prostaglandins E2 and leukotriene B4, are considered the primary mediators of inflammation in arthritis, modulated not only by fatty acid balance but by other factors such as treatment with mud pack therapy or consumption of ginger 267-269).

Changes in the Western diet during this century have resulted in increasing consumption of omega-6 oils, including arachidonic acid, with decreasing consumption of omega-3 oils. The net result of this dietary change has been a dramatic imbalance in fatty acid metabolism—causing a shift in production toward more pro-inflammatory eicosanoid hormones. These arachidonic acid metabolites play an integral role in the pathophysiology of osteoarthritis (270).

The Essential and Metabolic Fatty Acids Analysis can identify high levels of archidonic acid and other fatty acid imbalances promoting a heightened inflammatory response in arthritis, atherosclerosis, eczema, irritable bowel disease, and many other disorders.

**Recent theories on the genesis of osteoarthritis:**

Osteoarthritis is traditionally seen as a disease of articular cartilage, with erosion of this tissue being one of the main features. However, it is increasingly recognised that the changes in other musculoskeletal tissues, e.g. bone and muscle, are not easily explained as secondary changes but may be part of the primary disease process. Epidemiological
studies have suggested a systemic aetiology (271; 272) and indicated that the recognised link with obesity is not solely one of overloading a joint but could have a metabolic component (273). This is supported by studies showing patients with generalised OA have raised serum cholesterol levels (274) and that this is an independent risk factor (274). This is supported by unpublished observations from a study which found a preponderance of individuals in Aberdeen undergoing total hip arthroplasty for OA who were overweight and had a total serum cholesterol of greater than 5 mmol L⁻¹ (the Scottish Intercollegiate Guidelines Network threshold for considering lipid-lowering intervention for prevention of coronary heart disease) is shown in Fig A. Essential fatty acids are known to affect calcium transport, with implications for osteoporosis (275), and a recent study showed that the serum lipid profile was related to bone mass (276). Studies have also shown that femoral head cancellous bone contains twice the amount of fat per unit volume of tissue as OP bone (Fig. B) and has elevated levels of (n-6) fatty acids, especially arachidonic acid (Fig. C) (277).

One of the hypothesis is that generalised OA is a metabolic disorder in which systemic factors induce changes in skeletal tissues by modifying the formation and biosynthetic activity of cells derived from mesenchymal precursors (278). In this case, the erosion of articular cartilage would be mechanically driven, but the disease itself would not. However, this is only a small part of the disease process. This hypothesis can also offer explanations for the changes in bone, even at sites remote from joints (279; 280), in other tissues such as muscle (281; 282), and for the link with obesity. What is becoming clear, however, is that searching for changes among the articular cartilage matrix proteins is not likely to yield significant insight into the disorder except in rare cases.

Osteoarthritic changes in juxta-articular bone are well described with sclerosis of the subchondral bone, the formation of so-called ‘cysts’ within it, and the development of osteophytes. This involvement of the bone is universally recognised, though it is largely believed to be a secondary consequence of the disease. More recently, alterations have been found in the bone matrix and in osteoblast behaviour, which are difficult to explain as secondary changes. There is a reduced mineralisation in the femoral head (283–285), increased formation of woven bone and evidence for enhanced osteoclastic activity (286). Patients with OA changes evident on hip radiographs were found to have a higher than
average bone mineral density not only in the hip but also in the distal radius, vertebrae and calcaneus (287). Increased mineralisation and greater levels of growth factors were found in the iliac crest of patients with OA of the hand (279). These matrix changes are reflected in cellular changes and it has been shown that osteoblasts from patients with OA proliferate in vitro more rapidly than normal and express different levels of markers (288;289).

**Fig A.** Total serum cholesterol and body mass index in a random selection of patients presenting for a total hip replacement in Aberdeen with the WHO definitions of overweight and obese and the Scottish Intercollegiate Guidelines Network threshold for intervention for hyperlipidaemia. An indication of the expected normal range is shown shaded.
Fig B. Total lipid content in cancellous bone (including marrow) of the hip expressed as mass per unit volume of bone tissue. Despite the increased porosity of osteoporotic bone it contains only half the fat content of bone from patients with OA.
Fig C. Fatty acid contents of lipids extracted from the OA and OP bones showed different profiles in the two diseases. Of particular note is the two-fold higher level of arachidonic acid in OA, in the light of its role as a precursor for the pro-inflammatory PGE2. (*P<0.05, **P<0.01, ***P<0.001)

While chronic pain often necessitates medical therapy, particularly in extreme cases, an integrative approach that combines simple dietary modifications, regular exercise, and nutritional supplements can dramatically improve quality of life and reduce the requirement for non-steroidal anti-inflammatory drugs (NSAIDs) to control pain.

Unfortunately, physicians rarely recommend alternative therapies to patients, either because they are unaware of their potential benefits, or for fear of criticism from their colleagues and peers.

**Diet and Arthritis:**

The “inflammatory cascade” begins with a fatty acid called arachidonic acid (AA). AA is cycled through the COX enzymes to form a family of eicosanoids. Eicosanoids include prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), which are small fatty acid metabolites that have hormone-like activities critical to maintaining normal physiologic functions.

In addition, these fatty acid metabolites are mobilized when the body is confronted with an acute injury. When AA is the substrate for the COX enzyme, the PGs, TXs, and LTs that are produced are quite pro-inflammatory (Fig. 1).
If the long-chain fatty acid at the top of the inflammatory cascade is a different fatty acid such as the omega-3 fatty acids found in fish—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—then the subsequent eicosanoids that are produced are not harmful and actually reduce inflammation. The epidemiological data from the Greenland Eskimos sparked interest in the potential benefits of the omega-3 fatty acids 25 years ago and at this point, numerous scientific studies have affirmed their benefit (290-292).

Research has shown that certain foods, such as fatty cuts of meat, organ meats and egg yolks provide arachidonic acid to the body. Therefore, it would be beneficial to reduce the consumption of these foods.

If one then increases the intake of foods rich in the omega-3 fatty acids (fish, some seeds and nuts), the omega-3 fatty acids displace AA as the primary substrate for the COX enzymes. This leads to the production of a species of eicosanoids that are far less pro-inflammatory than AA.

In addition to cutting back on foods that are high in AA, I also recommend avoiding foods containing partially hydrogenated oils. Partially hydrogenated vegetable oils, which contain trans fatty acids, actually promote inflammation to an even greater degree than...
AA. Additionally, trans fatty acids have been shown to be more prone to initiating atherosclerosis than the saturated fats found in meats (293-295).

In addition to increasing the consumption of fish, nuts and seeds (all high in omega-3 fatty acids), it’s a good idea to reduce intake of sugars, starches, and other carbohydrates that break down into simple sugars, and trigger excess production of insulin, a powerful promoter of inflammation (296).

Many people find that these simple dietary modifications often reduce the severity of pain enough to make exercise possible again—and exercise has been shown to aid in reducing chronic pain suffered by people with inflammatory arthritis (297).

Role of Dehydroepiandrosterone (DHEA) in arthritis and other chronic inflammatory conditions:

Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal glands. One well-studied application of DHEA is its role in reducing pain and inflammation in people with Systemic Lupus Erythematosis (SLE) (298).

DHEA seems to be helpful in a number of other chronic inflammatory diseases as well, including Crohn’s disease, rheumatoid arthritis and inflammatory arthritis (299). This adrenal steroid seems to improve the patient’s subjective measure of disease activity such as pain and fatigue. How it does this is still not clear, but it appears that DHEA is involved in directly reducing inflammatory cytokines, independent of the COX pathway. There is even a recent report in the literature where DHEA administration has prevented the development of osteoarthritis in animals (300).

DHEA is typical of many dietary supplements, in that it provides a broad range of beneficial effects with few, if any, adverse effects—in contrast to pharmaceuticals with narrow ranges of benefits and long lists of side effects.

In addition to its profound anti-inflammatory properties, clinical trials with DHEA indicate that it may also be an effective treatment for osteoporosis in both men and women (301,302). Dosages in the clinical trials have varied from a low of 25 mg to a
high of 100 mg. Women should be aware that if they take too much DHEA they may grow a few facial hairs, or experience an episode of acne. However, these side effects are easily and rapidly reversed once the dosage is lowered.

**Role of Essential Fatty Acids in osteoarthritis:**

**EPA/DHA**

More than 25 years ago, epidemiological data on Greenland Eskimos triggered a spate of research into the role of essential fatty acids contained in fish oils. Today, the benefits of eating fish rich in omega-3 fatty acids are well established.

Additionally, a large body of research suggests that consuming fish oil capsules can aid in reducing the symptoms of systemic lupus (303) and rheumatoid arthritis (304). Supplementing with the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) also works in much the same way as the dietary modifications discussed at the outset of this article.

The EPA and DHA contained in fish oils compete favorably with AA, and are processed by COX enzymes. The family of eicosanoids produced from omega-3 fatty acids are far less inflammatory than those produced by AA, which is an omega-6 fatty acid. Supplementing with fish oil capsules should be considered in addition to the dietary changes suggested above.

**Gamma-linolenic acid (GLA):**

Generally it is recommended that patients opt for monounsaturated fatty acids (such as olive, canola, walnut, grapeseed and macadamia nut oils) as their primary edible oils. Additionally, it is recommended to avoid most of the polyunsaturated fatty acids found in the American diet, such as corn, sunflower and soybean oils, which are rich in omega-6 fatty acids. The one exception is supplementation with the botanical lipid, GLA.

GLA (gamma-linolenic acid) is an omega-6 fatty that possesses significant therapeutic properties. GLA has been shown to reduce the pain and inflammation of systemic inflammatory diseases most notably, rheumatoid arthritis (305). GLA works in much the
same way as the omega-3 fatty acids, replacing the arachidonic acid utilized by the COX enzymes. In doing so, GLA supports the production of anti-inflammatory eicosanoids and cytokines.

Supplementing with a combination of omega-3 fatty acids and omega-6 fatty acids (from GLA) prevents the accumulation of arachidonic acid in the blood, and helps to reduce the pain associated with inflammation (306). One group from Surrey, England, suggests that combing antioxidants and fatty acids will ameliorate the symptoms of inflammatory systemic illnesses, based upon the growing body of scientific literature (307).
Rheumatoid arthritis
and
Role of fatty acids in the treatment of rheumatoid arthritis
Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. Rheumatoid arthritis can also cause inflammation of the tissue around the joints, as well as other organs in the body. Autoimmune diseases are illnesses, which occur when the body tissues are mistakenly attacked by its own immune system. The immune system is a complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with these diseases have antibodies in their blood which target their own body tissues, where they can be associated with inflammation. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease.

While rheumatoid arthritis is a chronic illness, meaning it can last for years, patients may experience long periods without symptoms. Typically, however, rheumatoid arthritis is a progressive illness that has the potential to cause joint destruction and functional disability.

In some patients with rheumatoid arthritis, chronic inflammation leads to the destruction of the cartilage, bone and ligaments causing deformity of the joints. Damage to the joints can occur early in the disease and be progressive. Moreover, studies have shown that the progressive damage to the joints does not necessarily correlate with the degree of pain, stiffness, or swelling present in the joints.

Rheumatoid arthritis is a common rheumatic disease, affecting more than two million people in the United States. The disease is three times more common in women as in men. It afflicts people of all races equally. The disease can begin at any age, but most often starts after age forty and before sixty. In some families, multiple members can be affected, suggesting a genetic basis for the disorder.

What causes rheumatoid arthritis?

The cause of rheumatoid arthritis is unknown. Even though infectious agents such as viruses, bacteria, and fungi have long been suspected, none has been proven as the cause. The cause of rheumatoid arthritis is a very active area of worldwide research. Some scientists believe that the tendency to develop rheumatoid arthritis may be genetically inherited. It is suspected that certain infections or factors in the environment might trigger
the immune system to attack the body's own tissues, resulting in inflammation in various organs of the body such as the lungs or eyes.

Regardless of the exact trigger, the result is an immune system that is geared up to promote inflammation in the joints and occasionally other tissues of the body. Immune cells, called lymphocytes, are activated and chemical messengers (cytokines, such as tumor necrosis factor/TNF and interleukin-1/IL-1) are expressed in the inflamed areas.

Environmental factors also seem to play some role in the cause of rheumatoid arthritis. Recently, scientists have reported that smoking tobacco increases the risk of developing rheumatoid arthritis.

What are the symptoms of rheumatoid arthritis?

The symptoms of rheumatoid arthritis come and go, depending on the degree of tissue inflammation. When body tissues are inflamed, the disease is active. When tissue inflammation subsides, the disease is inactive (in remission). Remissions can occur spontaneously or with treatment, and can last weeks, months or years. During remissions, symptoms of the disease disappear, and patients generally feel well. When the disease becomes active again (relapse), symptoms return. The return of disease activity and symptoms is called a flare. The course of rheumatoid arthritis varies from patient to patient, and periods of flares and remissions are typical.

When the disease is active, symptoms can include fatigue, lack of appetite, low-grade fever, muscle and joint aches, and stiffness. Muscle and joint stiffness are usually most notable in the morning and after periods of inactivity. Arthritis is common during disease flares. During flares, joints frequently become red, swollen, painful and tender. This occurs because the lining tissue of the joint (synovium) becomes inflamed, resulting in the production of excessive joint fluid (synovial fluid). The synovium also thickens with inflammation (synovitis).

In rheumatoid arthritis, multiple joints are usually inflamed in a symmetrical pattern (both sides of the body affected). The small joints of both the hands and wrists are often involved. Simple tasks of daily living, such as turning door knobs and opening jars can
become difficult during flares. The small joints of the feet are also commonly involved. Occasionally, only one joint is inflamed. When only one joint is involved, the arthritis can mimic the joint inflammation caused by other forms of arthritis such as gout or joint infection. Chronic inflammation can cause damage to body tissues, cartilage and bone. This leads to a loss of cartilage and erosion and weakness of the bones as well as the muscles, resulting in joint deformity, destruction, and loss of function. Rarely, rheumatoid arthritis can even affect the joint that is responsible for the tightening our vocal cords to change the tone of our voice, the cricoarytenoid joint. When this joint is inflamed, it can cause hoarseness of voice.

Since rheumatoid arthritis is a systemic disease, its inflammation can affect organs and areas of the body other than the joints. Inflammation of the glands of the eyes and mouth can cause dryness of these areas and is referred to as Sjogren's syndrome. Rheumatoid inflammation of the lung lining (pleuritis) causes chest pain with deep breathing or coughing. The lung tissue itself can also become inflamed and sometimes nodules of inflammation (rheumatoid nodules) develop within the lungs. Inflammation around the heart (pericarditis) can cause a chest pain that typically changes in intensity when lying down or leaning forward. The rheumatoid disease can reduce the number of red blood cells (anemia), and white blood cells. Decreased white cells can be associated with an enlarged spleen (referred to as Felty's syndrome) and can increase the risk of infections. Firm lumps under the skin (rheumatoid nodules) can occur around the elbows and fingers where there is frequent pressure. Even though these nodules usually do not cause symptoms, occasionally they can become infected. A rare, serious complication, usually with long-standing rheumatoid disease, is blood vessel inflammation (vasculitis). Vasculitis can impair blood supply to tissues and lead to tissue death. This is most often initially visible as tiny black areas around the nail beds or as leg ulcers.

The distribution of joint inflammation is important to the doctor in making a diagnosis. In rheumatoid arthritis, the small joints of the hands, wrists, feet and knees are typically inflamed in a symmetrical distribution (affecting both sides of the body). When only one or two joints are inflamed, the diagnosis of rheumatoid arthritis becomes more difficult.
The doctor may then perform other tests to exclude arthritis due to infection or gout. The detection of rheumatoid nodules (described above), most often around the elbows and fingers, can suggest the diagnosis.

Abnormal blood antibodies can be found in patients with rheumatoid arthritis. A blood antibody called "rheumatoid factor" can be found in 80% of patients. Citrulline antibody (also referred to as anti-citrulline antibody, anti-cyclic citrullinated peptide antibody, and anti-CCP) is present in most patients with rheumatoid arthritis. It is used in the diagnosis of rheumatoid arthritis when evaluating patients with unexplained joint inflammation. A test for citrulline antibodies is most helpful in looking for the cause of previously undiagnosed inflammatory arthritis when the traditional blood test for rheumatoid arthritis, rheumatoid factor, is not present. Citrulline antibodies have been felt to represent the earlier stages of rheumatoid arthritis in this setting. Another antibody called "the antinuclear antibody" (ANA) is also frequently found in patients with rheumatoid arthritis.

A blood test called the sedimentation rate is a measure of how fast red blood cells fall to the bottom of a test tube. The sedimentation rate is used as a crude measure of the inflammation of the joints. The sedimentation rate is usually faster during disease flares, and slower during remissions. Another blood test that is used to measure the degree of inflammation present in the body is the C-reactive protein. The rheumatoid factor, ANA, sedimentation rate, and C-reactive protein tests can also be abnormal in other systemic autoimmune conditions. Therefore, abnormalities in these blood tests alone are not sufficient for a firm diagnosis of rheumatoid arthritis.

Joint x-rays may be normal or only show swelling of soft tissues early in the disease. As the disease progresses x-rays can show bony erosions typical of rheumatoid arthritis in the joints. Joint x-rays can also be helpful in monitoring the progression of disease and joint damage over time. Bone scanning, a radioactive test procedure, can demonstrate the inflamed joints.

Analysis of the joint fluid, in the laboratory, can help to exclude other causes of arthritis, such as infection and gout. Arthrocentesis can also be helpful in relieving joint swelling.
and pain. Occasionally, cortisone medications are injected into the joint during the arthrocentesis in order to rapidly relieve joint inflammation and further reduce symptoms.

**How is rheumatoid arthritis treated?**

There is no known cure for rheumatoid arthritis. To date, the goal of treatment in rheumatoid arthritis is to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Early medical intervention has been shown to be important in improving outcomes. Aggressive management can improve function, stop damage to joints as seen on x-rays, and prevent work disability. Optimal treatment for the disease involves a combination of medications, rest, joint strengthening exercises, joint protection, and patient (and family) education. Treatment is customized according to many factors such as disease activity, types of joints involved, general health, age, and patient occupation. Treatment is most successful when there is close cooperation between the doctor, patient, and family members.

Two classes of medications are used in treating rheumatoid arthritis: fast-acting "first-line drugs," and slow-acting "second-line drugs (also referred to as Disease-Modifying Antirheumatic Drugs or DMARDs)." The first-line drugs, such as aspirin and cortisone (corticosteroids), are used to reduce pain and inflammation. The slow-acting second-line drugs, such as gold, methotrexate and hydroxychloroquine, promote disease remission and prevent progressive joint destruction, but they are not anti-inflammatory agents.

The degree of destructiveness of rheumatoid arthritis varies from patient to patient. Patients with uncommon, less destructive forms of the disease or disease that has quieted after years of activity ("burned out" rheumatoid arthritis) can be managed with rest, pain and anti-inflammatory medications alone. In general, however, patients improve function and minimize disability and joint destruction when treated earlier with second-line drugs (disease-modifying antirheumatic drugs), even within months of the diagnosis. Most patients require more aggressive second-line drugs, such as methotrexate, in addition to anti-inflammatory agents. Sometimes these second-line drugs are used in combination. In some patients with severe joint deformity, surgery may be necessary.

"First-line" Drugs:
Acetylsalicylate (Aspirin), naproxen, ibuprofen, and etodolac are examples of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are medications that can reduce tissue inflammation, pain and swelling. NSAIDs are not cortisone. Aspirin, in doses higher than that used in treating headaches and fever, is an effective anti-inflammatory medication for rheumatoid arthritis. Aspirin has been used for joint problems since the ancient Egyptian era. The newer NSAIDs are just as effective as aspirin in reducing inflammation and pain, and require fewer dosages per day. Patients' responses to different NSAID medications vary. Therefore, it is not unusual for a doctor to try several NSAID drugs in order to identify the most effective agent with the fewest side effects. The most common side effects of aspirin and other NSAIDs include stomach upset, abdominal pain, ulcers, and even gastrointestinal bleeding. In order to reduce stomach side effects, NSAIDs are usually taken with food. Additional medications are frequently recommended to protect the stomach from the ulcer effects of NSAIDs. These medications include antacids, sucralfate, proton-pump inhibitors, and misoprostol.

Corticosteroid medications can be given orally or injected directly into tissues and joints. They are more potent than NSAIDs in reducing inflammation, and in restoring joint mobility and function. Corticosteroids are useful for short periods during severe flares of disease activity, or when the disease is not responding to NSAIDs. However, corticosteroids can have serious side effects, especially when given in high doses for long periods of time. These side effects include weight gain, facial puffiness, thinning of the skin and bone, easy bruising, cataracts, risk of infection, muscle wasting, and destruction of large joints, such as the hips. Corticosteroids also carry some increased risk of contracting infections. These side effects can be partially avoided by gradually tapering the doses of corticosteroids as the patient achieves improvement of the disease. Abruptly discontinuing corticosteroids can lead to flares of the disease or other symptoms of corticosteroid withdrawal, and is discouraged. Thinning of the bones due to osteoporosis may be prevented by calcium and vitamin D supplements. For further information on corticosteroids, please read the article on prednisone.

"Second-line" or "Slow-acting" Drugs (Disease-modifying Anti-rheumatic Drugs or DMARDs):
While "first-line" medications (NSAIDs and corticosteroids) can relieve joint inflammation and pain, they do not necessarily prevent joint destruction or deformity. Rheumatoid arthritis requires medications other than NSAIDs and corticosteroids to stop progressive damage to cartilage, bone, and adjacent soft tissues. The medications needed for ideal management of the disease are also referred to as Disease-modifying Antirheumatic Drugs or DMARDs. They come in a variety of forms and are listed below. These "second-line" or "slow-acting" medicines may take weeks to months to become effective. They are used for long periods of time, even years, at varying doses. If effective, DMARDs can promote remission, thereby retarding the progression of joint destruction and deformity. Sometimes a number of second-line medications are used together as combination therapy. As with the first-line medications, the doctor may need to use different second-line medications before treatment is optimal.

Recent research suggests that patients who respond to a DMARD with control of the rheumatoid disease may actually decrease the known risk (small, but real) of lymphoma that exists from simply having rheumatoid arthritis.

Hydroxychloroquine is related to quinine, and is also used in the treatment of malaria. It is used over long periods for the treatment of rheumatoid arthritis. Possible side effects include upset stomach, skin rashes, muscle weakness, and vision changes. Even though vision changes are rare, patients taking Plaquenil should be monitored by an eye doctor (ophthalmologist).

Sulfasalazine (Azulfidine) is an oral medication traditionally used in the treatment of mild to moderately severe inflammatory bowel diseases, such as ulcerative colitis and Crohn's colitis. Azulfidine is used to treat rheumatoid arthritis in combination with antiinflammatory medications. Azulfidine is generally well tolerated. Common side effects include rash and upset stomach. Because Azulfidine is made up of sulfa and salicylate compounds, it should be avoided by patients with known sulfa allergies.

Methotrexate has gained popularity among doctors as an initial second-line drug because of both its effectiveness and relatively infrequent side effects. It also has an advantage in dose flexibility (dosages can be adjusted according to needs). Methotrexate is an immune suppression drug. It can affect the bone marrow and the liver, even rarely causing
cirrhosis. All patients taking methotrexate require regular blood test monitoring of blood counts and liver function blood tests.

Gold salts have been used to treat rheumatoid arthritis throughout most of the past century. Gold thioglucose and gold thiomalate are given by injection, initially on a weekly basis for months to years. Oral gold, auranofin was introduced in the 1980's. Side effects of gold (oral and injectable) include skin rash, mouth sores, kidney damage with leakage of protein in the urine, and bone marrow damage with anemia and low white cell count. Patients receiving gold treatment are regularly monitored with blood and urine tests. Oral gold can cause diarrhea. These gold drugs have lost such favor that many companies no longer manufacture them.

D-penicillamine can be helpful in selected patients with progressive forms of rheumatoid arthritis. Side effects are similar to those of gold. They include fever, chills, mouth sores, a metallic taste in the mouth, skin rash, kidney and bone marrow damage, stomach upset, and easy bruising. Patients on this medication require routine blood and urine tests. D-penicillamine can rarely cause symptoms of other autoimmune diseases.

Immunosuppressive medicines are powerful medications that suppress the body's immune system. A number of immunosuppressive drugs are used to treat rheumatoid arthritis. They include methotrexate (Rheumatrex, Trexall) as described above, azathioprin, cyclophosphamide, chlorambucil, and cyclosporine. Because of potentially serious side effects, immunosuppressive medicines are generally reserved for patients with very aggressive disease, or those with serious complications of rheumatoid inflammation, such as blood vessel inflammation (vasculitis). The exception is methotrexate, which is not frequently associated with serious side effects and can be carefully monitored with blood testing. Methotrexate has become a preferred second-line medication as a result.

Immunosuppressive medications can depress bone marrow function and cause anemia, a low white cell count and low platelets counts. A low white count can increase the risk of infections, while a low platelet count can increase the risk of bleeding. Methotrexate can also lead to liver cirrhosis and allergic reactions in the lung. Cyclosporin can cause
kidney damage and high blood pressure. Because of potentially serious side effects, immunosuppressive medications are used in low doses, usually in combination with anti-inflammatory agents.

**Newer Treatments:**

Newer "second-line" drugs for the treatment of rheumatoid arthritis include leflunomide (Arava), and the "biologic" medications etanercept (Enbrel), infliximab (Remicade), anakinra (Kineret), and adalimumab (Humira).

Leflunomide (Arava) is available to relieve the symptoms and halt the progression of the disease. It seems to work by blocking the action of an important enzyme that has a role in immune activation. Arava can cause liver disease, diarrhea, hair loss, and/or rash in some patients. It should not be taken just before or during pregnancy because of possible birth defects.

Other medications that represent a novel approach to the treatment of rheumatoid arthritis and are the products of modern biotechnology. These are referred to as the biologic medications or biological response modifiers. In comparison with traditional DMARDs, the biologic medications have a much more rapid onset of action and can have powerful effects on stopping progressive joint damage.

Etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira) are biologic medications. These medications intercept a protein in the joints (tumor necrosis factor, or TNF) that causes inflammation before it can act on its natural receptor to "switch on" inflammation. This effectively blocks the TNF inflammation messenger from calling out to the cells of inflammation. Symptoms can be significantly, and often rapidly, improved in patients using these drugs. Etanercept (Enbrel) must be injected subcutaneously once or twice a week. Infliximab (Remicade) is given by infusion directly into a vein (intravenously). Adalimumab (Humira) is injected subcutaneously either every other week or weekly. Each of these medications will be evaluated by doctors in practice to determine what role they may have in treating various stages of rheumatoid arthritis. Recent studies demonstrate that biological response modifiers also prevent the progressive joint destruction of rheumatoid arthritis. They are currently recommended for use after other medications have not been effective. The biological response modifiers
(TNF-inhibitors) are expensive treatments. They are also frequently used in combination with methotrexate and other DMARDs. Furthermore, it should be noted that the TNF-blocking biologies all are more effective when combined with methotrexate.

Anakinra (Kineret) is another biologic treatment that is used to treat moderate to severe rheumatoid arthritis. Anakinra (Kineret) works by binding to a cell messenger protein (IL-1, a proinflammation cytokine). Anakinra (Kineret) is injected under the skin daily. Anakinra (Kineret) can be used alone or with other DMARDs. The response rate of anakinra (Kineret) does not seem to be as high as with other biologic medications.

While biologic medications are often combined with traditional DMARDs in the treatment of rheumatoid arthritis, they are generally not used with other biologic medications because of unacceptable risk for serious infections.

**Other Treatments:**

There is no special diet for rheumatoid arthritis. Fish oil may have anti-inflammatory effects, but so far this has only been shown in laboratory experiments studying inflammatory cells. Likewise, the benefits of cartilage preparations remain unproven. Symptomatic pain relief can often be achieved with oral acetaminophen (Tylenol) or over-the-counter topical preparations, which are rubbed into the skin. Antibiotics, in particular the tetracycline drug minocycline (Minocin), have been tried for rheumatoid arthritis recently in clinical trials. Early results have demonstrated mild to moderate improvement in the symptoms of arthritis. Minocycline has been shown to impede important mediator enzymes of tissue destruction, called metalloproteinases, in the laboratory as well as in humans.

The areas of the body, other than the joints, that are affected by rheumatoid inflammation are treated individually. Sjogren's syndrome (described above, see symptoms) can be helped by artificial tears and humidifying rooms of the home or office. Regular eye check-ups and early antibiotic treatment for infection of the eyes are important. Inflammation of the tendons (tendinitis), bursae (bursitis) and rheumatoid nodules can be injected with cortisone. Inflammation of the lining of the heart and/or lungs may require high doses of oral cortisone.
Proper, regular exercise is important in maintaining joint mobility, and in strengthening the muscles around the joints. Swimming is particularly helpful because it allows exercise with minimal stress on the joints. Physical and occupational therapists are trained to provide specific exercise instructions and can offer splinting supports. For example, wrist and finger splints can be helpful in reducing inflammation and maintaining joint alignment. Devices, such as canes, toilet seat raisers, and jar grippers can assist daily living. Heat and cold applications are modalities that can ease symptoms before and after exercise.

Surgery may be recommended to restore joint mobility or repair damaged joints. Doctors who specialize in joint surgery are orthopedic surgeons. The types of joint surgery range from arthroscopy to partial and complete replacement of the joint. Arthroscopy is a surgical technique whereby a doctor inserts a tube-like instrument into the joint to see and repair abnormal tissues.

"Total joint replacement" is a surgical procedure whereby a destroyed joint is replaced with artificial materials. For example, the small joints of the hand can be replaced with plastic material. Large joints, such as the hips or knees, are replaced with metals.

Finally, minimizing emotional stress can help improve the overall health of the patient with rheumatoid arthritis. Support and extracurricular groups afford patients time to discuss their problems with others and learn more about their illness.

**Future Treatments:**

Scientists throughout the world are studying many promising areas of new treatment approaches for rheumatoid arthritis. These areas include treatments that block the action of the special inflammation factors, such as tumor necrosis factor (TNF-alpha) and interleukin-1 (IL-1), as described above. Many other drugs are being developed that act against certain critical white blood cells involved in rheumatoid inflammation. Also, new NSAIDs with mechanisms of action which are different from current drugs are on the horizon.
Rituxan (rituximab) is an antibody that is used to treat lymphoma, cancer of the lymph nodes. Research has suggested that it may be effective in treating autoimmune diseases like rheumatoid arthritis because it depletes B-cells, which are important cells of inflammation and in producing antibodies. Preliminary studies have shown that Rituxan was also found to be beneficial in treating severe rheumatoid arthritis complicated by blood vessel inflammation (vasculitis) and cryoglobulinemia.

Abatacept is a recently developed biologic medication that blocks T-cell activation. Abatacept is currently being studied and showing preliminary results indicating benefit in treating patients who have failed TNF-blocking biologic medications.

Studies involving various types of the connective tissue collagen are in progress and show encouraging signs of reducing rheumatoid disease activity. Finally, genetic research and engineering is likely to bring forth many new avenues of earlier diagnosis and accurate treatment in the near future. Gene profiling, also known as gene array analysis, is being identified as a helpful method of defining which people will respond to which medications. Studies are underway that are using gene array analysis to determine which patients will be at more risk for more aggressive disease. This is all occurring because of technology improvements. We are at the threshold of tremendous improvements in the way rheumatoid arthritis is managed.

Recent antibody research has found that the presence of citrulline antibodies in the blood (see above in diagnosis) has been associated with a greater tendency toward more destructive forms of rheumatoid arthritis.

Rheumatoid Arthritis At A Glance

- Rheumatoid arthritis is an autoimmune disease that can cause chronic inflammation of the joints and other areas of the body.

- Rheumatoid arthritis can affect persons of all ages.

- The cause of rheumatoid arthritis is not known.

- Rheumatoid arthritis is a chronic disease, characterized by periods of disease flares and remissions.
- In rheumatoid arthritis, multiple joints are usually, but not always, affected in a symmetrical pattern.

- Chronic inflammation of rheumatoid arthritis can cause permanent joint destruction and deformity.

- Damage to joints can occur early and does not correlate with symptoms.

- The "rheumatoid factor" is an antibody blood test that can be found in 80% of patients with rheumatoid arthritis.

- There is no known cure for rheumatoid arthritis.

- The treatment of rheumatoid arthritis optimally involves a combination of patient education, rest and exercise, joint protection, medications, and occasionally surgery.

- Early treatment of rheumatoid arthritis results in better outcomes.

Supplementation with long-chain n-3 polyunsaturated fatty acids (PUFA) in rheumatoid arthritis:

Rheumatoid arthritis (RA) is a debilitating disease and is associated with increased risk of cardiovascular disease and osteoporosis. Poor nutrient status in RA patients has been reported and some drug therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed to alleviate RA symptoms, may increase the requirement for some nutrients and reduce their absorption. Supplementation with long-chain n-3 polyunsaturated fatty acids (PUFA) consistently demonstrates an improvement in symptoms and a reduction in NSAID usage. Evidence relating to other fatty acids, antioxidants, zinc, iron, folate, other B vitamins, calcium, vitamin D and fluoride are also considered. The present evidence suggests that RA patients should consume a balanced diet rich in long-chain n-3 PUFA and antioxidants. More randomized long-term studies
are needed to provide evidence for the benefits of specific nutritional supplementation and to determine optimum intake, particularly for n-3 PUFA and antioxidants.

Role of fish oils in the treatment of rheumatoid arthritis:

Fish oils are a rich source of omega-3 long chain polyunsaturated fatty acids (n-3 LC PUFA). The specific fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are homologues of the n-6 fatty acid, arachidonic acid (AA). This chemistry provides for antagonism by n-3 LC PUFA of AA metabolism to pro-inflammatory and pro-thrombotic n-6 eicosanoids, as well as production of less active n-3 eicosanoids. In addition, n-3 LC PUFA can suppress production of pro-inflammatory cytokines and cartilage degradative enzymes. In accordance with the biochemical effects, beneficial anti-inflammatory effects of dietary fish oils have been demonstrated in randomised, double-blind, placebo-controlled trials in rheumatoid arthritis (RA). Also, fish oils have protective clinical effects in occlusive cardiovascular disease, for which patients with RA are at increased risk. Implementation of the clinical use of anti-inflammatory fish oil doses has been poor. Since fish oils do not provide industry with the opportunities for substantial profit associated with patented prescription items, they have not received the marketing inputs that underpin the adoption of usual pharmacotherapies. Accordingly, many prescribers remain ignorant of their biochemistry, therapeutic effects, formulations, principles of application and complementary dietary modifications. Evidence is presented that increased uptake of this approach can be achieved using bulk fish oils. This approach has been used with good compliance in RA patients. In addition, an index of n-3 nutrition can be used to provide helpful feedback messages to patients and to monitor the attainment of target levels. Collectively, these issues highlight the challenges in advancing the use of fish oil amid the complexities of modern management of RA, with its emphasis on combination chemotherapy applied early.
Hepatitis
And
Role of essential fatty acids in hepatitis
Hepatitis means inflammation of the liver. Many illnesses and conditions can cause inflammation of the liver, for example, drugs, alcohol, chemicals and autoimmune diseases. Many viruses, for example, the virus of mononucleosis and the cytomegalovirus can inflame the liver. Most viruses, however, do not primarily attack the liver; the liver is just one of several organs that the viruses affect. When doctors speak of viral hepatitis, they usually are referring to hepatitis caused by a few specific viruses that primarily attack the liver. There are several hepatitis viruses; they have been named types A, B, C, D, E, F (not confirmed), and G. As our knowledge of hepatitis viruses grows, it is likely that this alphabetical list will become longer. The most common hepatitis viruses are types A, B, and C.

The liver is located in the upper right hand side of the abdomen, mostly behind the rib cage. The liver of an adult normally weighs close to three pounds. The liver performs the following vital functions:

1. The liver helps purify the blood by changing harmful chemicals into harmless ones. The source of these chemicals can be external, such as medications or alcohol, or internal, such as ammonia or bilirubin. Typically, these harmful chemicals are broken down into smaller chemicals or attached to other chemicals that then are eliminated from the body in the urine or stool.

2. The liver produces many important substances, especially proteins that are necessary for good health. For example, it produces albumin, the protein building block of the body, as well as the proteins that cause blood to clot properly.

3. The liver stores many sugars, fats and vitamins until they are needed elsewhere in the body.

4. The liver builds smaller chemicals into larger, more complicated chemicals that are needed elsewhere in the body. An example of this type of function is the manufacture of cholesterol.
When the liver is inflamed, it does not perform these functions well, which brings about many of the symptoms, signs, and problems associated with hepatitis.

**What are the common types of viral hepatitis?**

**Hepatitis A:**

Viral hepatitis A (HAV) accounts for about 150,000 of the 500,000-600,000 new cases of viral hepatitis that occur each year in the United States. The hepatitis caused by HAV is an acute illness (acute viral hepatitis) that never becomes chronic. At one time, hepatitis A was referred to as "infectious hepatitis" because it could be spread from person to person like other viral infections. Infection with hepatitis A virus can be spread through the ingestion of food or water, especially where unsanitary conditions allow water or food to become contaminated by human waste containing hepatitis A (the fecal-oral mode of transmission). Hepatitis A typically is spread among household members and close contacts through the passage of oral secretions (intimate kissing) or stool (poor hand washing). It also is common to have infection spread to customers in restaurants and among children and workers in day care centers if hand washing and sanitary precautions are not observed.

**Hepatitis B:**

There are 200,000-300,000 new cases of viral hepatitis B (HBV) infection each year in the United States. Type B hepatitis was at one time referred to as "serum hepatitis," because it was thought that the only way hepatitis B virus (HBV) could spread was through blood or serum (the liquid portion of blood) containing the virus. It is now known that hepatitis B can spread by sexual contact, the transfer of blood or serum through shared needles in drug abusers, accidental needle sticks with needles contaminated with infected blood, blood transfusions, hemodialysis, and by infected mothers to their newborns. The infection also can be spread by tattooing, body piercing, and sharing razors and toothbrushes (if there is contamination with infected blood). About 6-10% of patients with hepatitis B develop chronic HBV infection (infection lasting at least six months and often years to decades) and can infect others as long as they remain infected. Patients with chronic hepatitis B infection also are at risk of...
developing cirrhosis, liver failure and liver cancer. It is estimated that there are 1.2 million people in the United States and 200-300 million people world-wide who suffer with chronic hepatitis B infection.

**Hepatitis C:**

There are about 150,000 new cases of hepatitis C each year. Type C hepatitis was previously referred to as "non-A, non-B hepatitis," because the causative virus had not been identified, but it was known to be neither hepatitis A nor hepatitis B. The hepatitis C virus (HCV) usually is spread by shared needles among drug abusers, blood transfusion, hemodialysis, and needle sticks. Approximately 90% of transfusion-associated hepatitis is caused by hepatitis C. Transmission of the virus by sexual contact has been reported, but is considered rare. An estimated 50-70% of patients with acute hepatitis C infection develop chronic HCV infection. Patients with chronic hepatitis C infection can continue to infect others. Patients with chronic hepatitis C infection are at risk for developing cirrhosis, liver failure, and liver cancer. It is estimated that there are about 3.5 million people with chronic hepatitis C infection in the United States.

**Types D, E, F, and G Hepatitis:**

There also are viral hepatitis types D, E, F (not confirmed yet), and G. The most important of these at present is the hepatitis D virus (HDV), also known as the delta virus or agent. It is a small virus that requires concomitant infection with hepatitis B to survive. HDV cannot survive on its own because it requires a protein that the hepatitis B virus makes (the envelope protein, also called surface antigen) to enable it to infect liver cells. The ways in which hepatitis D is spread are by shared needles among drug abusers, contaminated blood, and by sexual contact, essentially the same ways as for hepatitis B.

Patients who already have chronic hepatitis B infection can acquire delta virus infection at the same time as they acquire the hepatitis B infection or, alternatively, on top of a chronic hepatitis B infection. Patients with chronic hepatitis due to hepatitis B and hepatitis D viruses develop cirrhosis (severe liver scarring) rapidly. Moreover, the combination of delta and B virus infection is very difficult to treat.
Who is at risk for viral hepatitis?

People who are most at risk for developing viral hepatitis are workers in the health care professions, people with multiple sexual partners, intravenous drug users, and hemophiliacs who receive blood clotting factors. Blood transfusion, once a common means of spreading viral hepatitis, now is a rare cause of hepatitis. Viral hepatitis is generally thought to be as much as ten times more common among lower socioeconomic and poorly educated individuals. About one third of all cases of hepatitis come from an unknown or unidentifiable source. This means that you don't have to be in a high risk group in order to be infected with a hepatitis virus.

What are the symptoms and signs of viral hepatitis?

The period of time between exposure to hepatitis and the onset of the illness is called the incubation period. The incubation period varies depending on the specific hepatitis virus. Hepatitis A has an incubation period of about 15-45 days; hepatitis B from 45-160 days, and hepatitis C from 2 weeks to 6 months.

Many patients infected with hepatitis A, B, and C have few or no symptoms of illness. For those who do develop symptoms of viral hepatitis, the most common are flu-like symptoms including:

- Loss of appetite
- Nausea
- Vomiting
- Fever
- Weakness
- Tiredness
- Aching in the abdomen

Less common symptoms include:
• Dark urine
• Light-colored stools
• Fever
• Jaundice (a yellow appearance to the skin and white portion of the eyes)

What is the prognosis of viral hepatitis?

The prognosis of viral hepatitis for most patients is good. Symptoms of viral hepatitis such as fatigue, poor appetite, nausea, and jaundice usually subside in several weeks to months, without any specific treatment. In fact, virtually all patients with acute infection with hepatitis A and most adults (greater than 95%) with acute hepatitis B recover completely. Complete recovery from viral hepatitis means

1. The hepatitis virus has been completely eliminated from the liver by the body's immune system
2. The inflammation in the liver subsides,
3. The patient develops immunity to future infection with the same virus, and
4. The patient cannot transmit the infection to others.

Unfortunately, not all patients with viral hepatitis infections recover completely. Five percent of patients with acute hepatitis B infection and 80% of patients with acute hepatitis C infection develop chronic hepatitis.

Acute viral hepatitis needs no specific treatment. Patients who develop chronic infection have chronic viral hepatitis and often need treatment to prevent further liver damage.

What is acute fulminant hepatitis?

Rarely, individuals with acute infections with hepatitis A and hepatitis B develop severe inflammation, and the liver fails (acute fulminant hepatitis). These patients are extremely ill with the symptoms of acute hepatitis already described and the additional problems of
confusion or coma (due to the liver’s failure to detoxify chemicals) and bruising or bleeding (due to a lack of blood clotting factors). In fact, up to 80% of people with acute fulminant hepatitis can die within days to weeks; therefore, it is fortunate that acute fulminant hepatitis is rare. For example, less than 0.5% of adults with acute infection with hepatitis B will develop acute fulminant hepatitis.

What is chronic viral hepatitis?

Patients infected with hepatitis B and hepatitis C can develop chronic hepatitis. Doctors define chronic hepatitis as hepatitis that lasts longer than 6 months. In chronic hepatitis, the viruses live and multiply in the liver for years or decades. For unknown reasons, these patients’ immune systems are unable to eradicate the viruses. The viruses cause chronic inflammation of the liver. Chronic hepatitis can lead to the development over time of extensive liver scarring (cirrhosis), liver failure, and liver cancer. Liver failure from chronic hepatitis C infection is the most common reason for liver transplantation in the United States. Patients with chronic viral hepatitis can transmit the infection to others.

How is viral hepatitis diagnosed?

Diagnosis of viral hepatitis is based on symptoms, physical findings as well as blood tests for liver enzymes, viral antibodies, and viral genetic materials.

Symptoms and physical findings

Diagnosis of acute viral hepatitis often is easy, but diagnosis of chronic hepatitis can be difficult. When a patient reports symptoms of fatigue, nausea, abdominal pain, darkening of urine, and then develops jaundice, the diagnosis of acute viral hepatitis is likely and can be confirmed by blood tests. On the other hand, patients with chronic hepatitis due to hepatitis B and hepatitis C often have no symptoms or only mild nonspecific symptoms such as chronic fatigue. Typically, these patients do not have jaundice until the liver damage is far advanced. Therefore, these patients can remain undiagnosed for years to decades.
**Blood tests**

There are three types of blood tests for evaluating patients with hepatitis: liver enzymes, antibodies to the hepatitis viruses, and viral proteins or genetic material (viral DNA or RNA).

**Liver enzymes.** Among the most sensitive and widely used blood tests for evaluating patients with hepatitis are the liver enzymes, called aminotransferases. They include aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT). These enzymes normally are contained within liver cells. If the liver is injured (as in viral hepatitis), the liver cells spill the enzymes into the blood, raising the enzyme levels in the blood and signaling that the liver is damaged.

The normal range of values for AST is from 5 to 40 units per liter of serum (the liquid part of the blood). The normal range of values for ALT is from 7 to 56 units per liter of serum. Patients with acute viral hepatitis (for example, due to hepatitis A or hepatitis B) can develop very high AST and ALT levels (sometimes in the thousands of units per liter range). These high AST and ALT levels will become normal in several weeks or months as the patients recover completely from their acute hepatitis. In contrast, patients with chronic hepatitis B and hepatitis C infection typically have only mildly elevated AST and ALT levels, but these abnormalities can last years or decades. Since most patients with chronic hepatitis are asymptomatic (no jaundice or nausea), their mildly abnormal liver enzymes are often unexpectedly encountered on routine blood screening tests during yearly physicals or insurance physicals.

Elevated blood levels of AST and ALT only means that the liver is inflamed, and elevations can be caused by many agents other than hepatitis viruses, such as medications, alcohol, bacteria, fungus, etc. In order to prove that a hepatitis virus is responsible for the elevations, blood must be tested for antibodies to each of the hepatitis viruses as well as for their genetic material.

**Viral antibodies.** Antibodies are proteins produced by white blood cells that attack invaders such as bacteria and viruses. Antibodies against the hepatitis A, B, and C viruses usually can be detected in the blood within weeks of infection, and the antibodies remain
detectable in the blood for decades thereafter. Blood tests for the antibodies can be helpful in diagnosing both acute and chronic viral hepatitis.

In acute viral hepatitis, antibodies not only help to eradicate the virus, but they also protect the patient from future infections by the same virus, that is the patient develops immunity. In chronic hepatitis, however, antibodies and the rest of the immune system are unable to eradicate the virus. The viruses continue to multiply and are released from the liver cells into the blood where their presence can be determined by measuring the viral proteins and genetic material. Therefore in chronic hepatitis, both antibodies to the viruses and viral proteins and genetic material can be detected in the blood.

Examples of tests for viral antibodies are:

- Anti-HAV (hepatitis A antibody)
- Antibody to hepatitis B core, an antibody directed against the inner core (nucleus) of the virus (core antigen)
- Antibody to hepatitis B surface, an antibody directed against the outer surface envelope of the virus (surface antigen)
- Antibody to hepatitis B e, an antibody directed against the genetic material of the virus (e antigen)
- Hepatitis C antibody—antibody against the C virus

**Viral proteins and genetic material.** Examples of tests for viral proteins and genetic material are:

- Hepatitis B surface antigen
- Hepatitis B DNA
- Hepatitis B e antigen
- Hepatitis C RNA
Other tests. Obstruction of the bile ducts, from either gallstones or cancer, occasionally can mimic acute viral hepatitis. Ultrasound testing can be used to exclude the possibility of gallstones or cancer.

How is viral hepatitis treated?

Treatment of acute viral hepatitis and chronic viral hepatitis are different. Treatment of acute viral hepatitis involves relieving symptoms and maintaining adequate intake of fluids. Treatment of chronic viral hepatitis involves medications to eradicate the virus and taking measures to prevent further liver damage.

Acute hepatitis

In patients with acute viral hepatitis, the initial treatment consists of relieving the symptoms of nausea, vomiting and abdominal pain. Careful attention should be given to medications, which can have adverse effects in patients with abnormal liver function. Only those medications that are considered necessary should be administered since the impaired liver is not able to eliminate drugs normally, and drugs may accumulate in the blood and reach toxic levels. In addition, sedatives and “tranquilizers” are avoided because they may accentuate the effects of liver failure on the brain and cause lethargy and coma. The patient must abstain from drinking alcohol since alcohol is toxic to the liver. It occasionally is necessary to provide intravenous fluids to prevent dehydration caused by vomiting. Patients with severe nausea and/or vomiting may need to be hospitalized for treatment and intravenous fluids.

Chronic hepatitis

Treatment of chronic infection with hepatitis B and hepatitis C usually involves medication or combinations of medications to eradicate the virus. Doctors believe that in properly selected patients, successful eradication of the viruses can stop progressive damage to the liver and prevent the development of cirrhosis, liver failure, and liver cancer. Alcohol aggravates liver damage in chronic hepatitis, and can cause more rapid progression to cirrhosis. Therefore, patients with chronic hepatitis should stop...
drinking alcohol. Smoking cigarettes also can aggravate liver disease and should be stopped.

Medications for chronic hepatitis C infection include:

- Injectable interferon
- Oral ribavirin

Medications for chronic hepatitis B infection include:

- Injectable interferon
- Oral lamivudine (Epivir)
- Oral adefovir (Hepsera)
- Oral entecavir (Baraclude)

Decisions regarding treatment of chronic hepatitis can be complex, and should be directed by gastroenterologists or hepatologists (doctors specially trained in treating diseases of the liver) for several reasons including:

1. The diagnosis of chronic viral hepatitis may not be straightforward. Sometimes a liver biopsy may have to be performed for confirmation of liver damage. Doctors experienced in managing chronic liver diseases must weigh the risk of liver biopsy against the potential benefits of the biopsy.

2. Not all patients with chronic viral hepatitis are candidates for treatment. Some patients need no treatment (since some patients with chronic hepatitis B and C do not develop progressive liver damage or liver cancer).

3. Medications for chronic infection with hepatitis B and hepatitis C are not always effective. Prolonged treatment (6 months to years) often is necessary. Even with prolonged treatment, rates of successful treatment (defined as complete and lasting eradication of the virus) often are low (usually less than 80% and often around 50%).
4. Some of the medications such as interferon and ribavirin can have serious side effects, and doses may have to be reduced.

5. There are several different strains of hepatitis C viruses with differing susceptibilities to medications. For example, hepatitis C type 3 is more likely to respond to interferon injections and ribavirin than type 1. Certain hepatitis B strains are resistant to lamivudine but respond to adefovir or entecavir.

**Role of essential fatty acids in hepatitis**

It is theorized that the HCV virus has as some part of its structure a lipid or fat envelope. Essential fatty acids such as omega 3 and omega 6 may play an important role in altering the stability of this lipid envelope by either increasing or decreasing cellular membrane fluidity. It is theorized that the disruption or uncoating of the lipid envelope would make HCV more susceptible to destruction by the host’s immune system.

Sophisticated, yet relatively inexpensive, blood tests are now available for identifying levels of approximately 30 fatty acids. Omega 3 and omega 6 fatty acids, monounsaturated, saturated and trans fatty acids can all be tested through blood analysis.

The importance of these fats in health and disease is well proven. Essential fatty acids, and other fatty acids, are important constituents of all cellular membranes. Over 30 different structural fatty acids are known to exist. Healthy cellular membranes allow for several important physiological functions including: the free exchange of waste products, nutrients and electrolytes in and out of the cell, structural stability of the cellular membranes and the reception of cellular messengers for cell-to-cell communication and recognition.

Essential fatty acids are direct precursors forming eicosanoids, which in turn form prostaglandins. The eicosanoids and prostaglandins (which include PG1, PG2 and PG3) allow for proper balance of inflammatory and anti-inflammatory reactions in the body. HCV is usually associated with excessive inflammatory reactions in the liver that result in liver cell damage and forward the progression and damage induced by the virus. Virus transformed cells tend to accumulate excessive oleic acid (an omega 9 fatty acid found in
high concentrations in olive oil) (East Mediterr Health J. 2003 Jan-Mar;9(1-2):61-9). The accumulation of oleic acid relative to stearic acid (an important lipid) causes an increase in cellular metabolic rate associated with a higher capacity of cellular divisions, in other words, it speeds up replication of HCV-infected cells. Polyunsaturated fatty acids suppress the development of acute hepatitis and prolong survival in females, regardless of whether they are of the n-6 or n-3 type, which are associated with altered gene expressions (J Nutr Biochem. 2004 May;15(5):273-80). Dietary supplementation with essential fatty acids and polyunsaturated lecithin may improve biochemical and histological parameters in liver disease.
Dyslipidemia
And
Role of fatty acids in Dyslipidemia
Disorders of lipoprotein metabolism, in conjunction with the prevalence of high-fat diets, obesity, and physical inactivity, have resulted in an epidemic of atherosclerotic disease in the United States and other developed countries. The interaction of common genetic and acquired disorders of lipoproteins with these adverse environmental factors leads to the premature development of atherosclerosis. In the United States, mortality from coronary artery disease (CAD), particularly in persons younger than 60 years, has been declining since 1970; however, atherosclerotic cardiovascular disease remains the most common cause of death among both men and women.

Formerly, hyperlipidemia was defined as elevation of a lipoprotein level in the population. The recognition that a low level of high-density lipoprotein (HDL) and the presence of small, dense low-density lipoprotein (LDL) are clinically important in the pathophysiology of lipid disorders has led to the use of the term dyslipidemia to describe a range of disorders that include both abnormally high and low lipoprotein levels, as well as disorders in the composition of these particles. Dyslipidemias are clinically important, principally because of their contribution to atherogenesis. Pancreatitis and fatty liver disease are less common but clinically significant manifestations of lipid disorders.
Lipoprotein Physiology:

Lipoprotein Composition and Metabolism:

Lipoproteins are spherical macromolecular complexes of lipid and protein (see Figure E).

Fig E: Macromolecular complex of lipoprotein.

Lipoproteins transport water-insoluble triglyceride and cholesterol through the bloodstream. All apo B-containing lipoproteins have a structure similar to that shown for very low density lipoproteins (VLDL). The core is composed of triglyceride and cholesteryl ester, whereas the monolayer surface is composed of phospholipid, unesterified cholesterol, and protein in the form of apolipoproteins. VLDL contains apolipoproteins B-100, C-I, C-II, and E. Low-density lipoprotein (LDL), which transports most of the cholesterol found in blood, contains primarily apo B-100.

Clinically important lipids in the blood include cholesterol (both unesterified and esterified) and triglyceride (molecules consisting of three fatty acids attached to a glycerol backbone). Cholesterol has three primary functions: it plays a role in the
structure of cell membranes, in the synthesis of steroid hormones, and in the formation of bile acids. The major functions of triglyceride are energy storage (in fat) and energy use (by muscle). Because fat cannot readily dissolve in plasma, cholesterol and triglyceride are made miscible by incorporation into lipoproteins (e.g., very low density lipoprotein [VLDL], LDL, and HDL). Apolipoproteins are the protein component of lipoproteins; they aid in the lipid transport and delivery process in three ways: they serve as structural elements, as ligands for receptors, and as regulatory cofactors (table A)

(Table A)

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I</td>
<td>Structural protein of HDL; activates lecithin-cholesterol acyltransferase</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>Structural protein of HDL</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>Structural protein of chylomicron</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>Structural protein of VLDL, IDL, and LDL; ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo C-II</td>
<td>Activator of LPL</td>
</tr>
<tr>
<td>Apo C-III</td>
<td>Potential inhibitor of apo C-II and apo E functions</td>
</tr>
<tr>
<td>Apo E</td>
<td>Ligand for chylomicron remnant receptor and LDL receptor</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>Function unknown; antagonizes plasminogen</td>
</tr>
</tbody>
</table>

HDL—high-density lipoprotein IDL—intermediate-density lipoprotein LDL—low-density lipoprotein LPL—lipoprotein lipase VLDL—very low density lipoprotein

Lipoprotein Structure and Classification:

A mature lipoprotein particle is a sphere consisting of a central core of lipids (triglyceride and cholesteryl ester) surrounded by a monolayer surface of phospholipid, unesterified cholesterol, and apolipoproteins (see Figure-F). Operationally, the lipoproteins can be described on the basis of their size and buoyancy characteristics (figure F).
Chylomicron

Chylomicrons are the largest of the lipoprotein particles. The major structural protein is apolipoprotein B-48 (apo B-48). The bulk (~80%) of the lipid core consists of triglyceride. Synthesized and secreted from the intestine, chylomicrons transport exogenous cholesterol, fatty acids, and fat-soluble vitamins absorbed from digested food [see Exogenous Pathway, below].

VLDL

This triglyceride-rich particle (~80% of the lipid core consists of triglyceride) is synthesized in the liver, delivers triglyceride to the periphery, and is the precursor for intermediate-density lipoproteins (IDLs) and LDL. The major structural protein of this lipoprotein is apo B-100 [see Endogenous Pathway, below].

IDL

The remnant of VLDL is of IDL density. It is formed after triglyceride in VLDL is hydrolyzed by lipoprotein lipase. The core is roughly 50% triglyceride and 50% cholesteryl ester. Approximately half of the body's IDL particles are cleared from the plasma into the liver; the other half are further processed to form LDL [see Endogenous Pathway, below].

Fig F: Characteristics of lipoproteins.
Pathway, below]. In clinical practice, assessment of LDL levels includes the determination of cholesterol in both IDL and LDL fractions.

**LDL**

This lipoprotein results from the hepatic processing of VLDL remnants. The core is rich in cholesteryl ester and accounts for the majority of cholesterol circulating in the blood. LDL plays a major role in the development of atherosclerosis [see LDL Catabolism, below].

**HDL**

HDL forms from the unesterified cholesterol and phospholipid removed from peripheral tissues and the surface of triglyceride-rich proteins [see Function and Regulation of HDL, below]. The major structural protein is apo A-I; the core is predominantly cholesteryl ester. HDL mediates the return of lipoprotein and tissue cholesterol to the liver for excretion in the process referred to as reverse cholesterol transport. Another of its functions is to shuttle apo E and apo C-II to and from chylomicrons and VLDL.

**Lipoprotein Assembly and Catabolism**

**Exogenous Pathway**

After a meal, intestinal cells absorb fatty acids and cholesterol, esterify them into triglyceride and cholesteryl ester, and incorporate them into the core of chylomicrons (308). Triglyceride greatly predominates over cholesterol ester in the chylomicron core. The chylomicrons are secreted into plasma, where apo C-II on the chylomicron surface activates endothelial-bound lipoprotein lipase (LPL). LPL in turn hydrolyzes the chylomicron's core triglyceride and releases free fatty acids, which are taken up by adipose tissue for storage and by muscle for energy. During lipolysis, the chylomicron decreases in size, and some surface components are transferred to HDL; the remaining particle is the chylomicron remnant particle. This chylomicron remnant next acquires apo E from HDL and is subsequently taken up by the liver after binding to sites that recognize apo E. It is then degraded, thereby delivering dietary cholesterol to the liver.
Endogenous Pathway

The liver secretes triglyceride-rich VLDL into plasma, where they too acquire apo C-II from HDL. As with chylomicrons, VLDL interacts with LPL on the capillary endothelium, and the core triglyceride is hydrolyzed to provide fatty acids to adipose and muscle tissues (308). About half of the catabolized VLDL remnants (IDL density) are taken up by hepatic receptors that bind to apo E for degradation; the other half—apo B-100 particles, depleted of triglyceride relative to cholesteryl ester—are converted by the liver to cholesteryl ester-rich LDL. As IDL is converted to LDL, apo E becomes detached, leaving only one apolipoprotein, apo B-100. Each particle in this cascade from VLDL to LDL contains one molecule of apo B-100.

In the metabolism of both chylomicrons and VLDL, apo C-II permits the hydrolysis of triglyceride by lipoprotein lipase, and apo E prompts hepatic uptake of remnants. A major difference in the metabolism of these particles is that chylomicrons contain a truncated form of apo B (i.e., apo B-48), whereas VLDL contains the complete form (i.e., apo B-100). Another difference is that chylomicron remnants are degraded after they are absorbed by the liver, whereas many of the VLDL remnants are most likely processed in the hepatic sinusoids to become LDL.

Regulation of Lipoprotein Metabolism

There are four major clinically significant physiologic steps in the lipoprotein cascade from VLDL to LDL—namely, VLDL assembly, hydrolysis by LPL, remnant catabolism, and LDL catabolism (see Figure G) (308, 309). Defects at any step in the cascade can lead to hyperlipidemia. These defects can be genetic or acquired (i.e., secondary to disease or the effects of drugs) or the result of an interaction of genetic and acquired factors.
The apolipoprotein B-100 (apo B-100) cascade. VLDL is secreted from the liver with one apo B on the surface and triglyceride and cholesteryl ester in the core. Core triglyceride is hydrolyzed by lipoprotein lipase and becomes a remnant lipoprotein that is recognized by the liver—in part, by apo E. The remnant lipoprotein is further processed to form LDL, which has a cholesterol-rich core and an intact apo B on its surface. The LDL particle can be removed by peripheral or hepatic LDL receptors. As the VLDL core is hydrolyzed, the unesterified cholesterol and phospholipid are transferred to HDL by phospholipid transfer protein to become the cholesteryl ester of HDL. (CE—cholesteryl ester; HL—hepatic lipase; LPL—lipoprotein lipase; PLTP—phospholipid transfer protein; TG—triglyceride)

**Fig G: Lipoprotein cascade from VLDL to LDL.**

**Lipoprotein Assembly:**

Apo B-100 is synthesized constitutively in the endoplasmic reticulum of the hepatocyte, and much of it is degraded in the endoplasmic reticulum. Triglyceride is added to the surviving apo B that will be secreted as VLDL. It is transported to the Golgi complex, where it acquires additional core lipid, forming the nascent VLDL particle. This particle is secreted into plasma, where it acquires apolipoproteins (e.g., apo C-II and apo E) from HDL (308).

Abnormalities in VLDL secretion can occur in two genetic forms of hyperlipidemia: familial hypertriglyceridemia (FHTG) and familial combined hyperlipidemia (FCHL).
FHTG is characterized by the overproduction of triglyceride contained within a normal number of VLDL particles; this results in each particle's having an excessive amount of triglyceride. In FCHL, an excessive amount of apo B-100 is secreted into VLDL or LDL particles; these particles tend to be smaller than normal (310).

The metabolic syndrome, which is a common condition in the general population, is a component of most cases of FCHL and also contributes to the residual dyslipidemia seen in patients with type 2 diabetes mellitus who have been treated with insulin or insulin secretagogues. The molecular basis of the hepatic triglyceride or apo B oversecretion in these disorders is unknown.

A deficiency in lipoproteins containing apo B is referred to as hypobetalipoproteinemia; an absence of apo B is termed abetalipoproteinemia. Abetalipoproteinemia may occur because of a defect involving both apo B genes that prevents the production of apo B. It also may occur in individuals who are homozygous for mutations in the microsomal triglyceride transport protein, which is critical for apo B transport in the endoplasmic reticulum. Homozygous hypobetalipoproteinemia and abetalipoproteinemia lead to deficiencies in fat-soluble vitamins because each of these conditions results in a shortage of apo B-containing lipoproteins, which are needed to transport fat-soluble vitamins. Hypobetalipoproteinemia, which is characterized by apo B levels of 50% normal, can be caused by a defect in a single apo B gene (311).

**Lipoprotein(a):** Lipoprotein(a) [Lp(a)] is a specific class of lipoprotein particles that are synthesized in the liver and that have a lipid composition similar to that of LDL. Lp(a) differs from LDL by the presence of apolipoprotein(a) [apo(a)], a protein whose structure is homologous to plasminogen (312). The apo(a) protein is bound by a disulfide linkage to apo B-100 to form Lp(a). High levels of Lp(a) are both prothrombotic and atherogenic (312). Levels of Lp(a) in plasma are almost completely determined by genetic variation in the \( Lp(a) \) gene.
Lipoprotein Catabolism:

Lipoprotein lipase-mediated triglyceride removal: LPL is synthesized in adipose tissue and muscle and then transported to the luminal surface of the endothelial lining of the adjacent capillary, where it acts on triglyceride-rich lipoproteins. The fatty acids that are released during the processing of triglyceride-rich particles (i.e., chylomicrons and VLDL) can be used for energy by muscle, or they can be reesterified into triglyceride and stored in adipocytes for later use (313). Apo C-II, the LPL activator, is carried on the triglyceride-rich lipoproteins chylomicrons and VLDL.

Genetic defects that result in impaired lipoprotein lipase synthesis or function are rare autosomal recessive causes of hyperlipidemia. Usually, these mutations present in neonates or infants as severe hypertriglyceridemia. Heterozygote parents of these children often have mild hypertriglyceridemia. Acquired defects of LPL, such as untreated diabetes or uremia, are more common causes of hyperlipidemia. When an acquired defect of LPL is associated with a disorder characterized by excessive input of VLDL, marked hypertriglyceridemia can ensue. The coexistence of two or more disorders that independently increase the level of triglycerides in plasma (e.g., FHTG or FCHL coexistent with untreated diabetes) can lead to marked hypertriglyceridemia (313).

Remnant catabolism: Both chylomicron and VLDL remnants acquire apo E from HDL before they can bind to hepatic receptors for either uptake and degradation or further processing to LDL. Three alleles of the APOE gene (i.e., APOE*E2, APOE*E3, and APOE*E4) result in six possible combinations. The APOE*E4 allele product has the greatest affinity for hepatic receptors, followed by the APOE*E3 allele product; the APOE2 allele product has markedly reduced receptor affinity.

Individuals who are homozygous for the APOE*E2 allele (E2/E2) have marked impairment of hepatic remnant lipoprotein uptake, which results in the accumulation of these remnants in the plasma and in very low levels or the absence of LDL. Interestingly, individuals with E2/E2 typically have either normal or low cholesterol levels because of the paucity of LDL particles characteristic of this disorder (314). If, however, an individual who is homozygous for the APOE*E2 allele (E2/E2) has a defect—either
inherited or acquired—that causes excessive input of VLDL, then excessive accumulation of VLDL remnants and hyperlipidemia occur. This results in remnant removal disease. Because chylomicron and VLDL remnants contain roughly equal amounts of triglyceride and cholesterol, the hyperlipidemia of remnant removal disease is characterized by both hypercholesterolemia and hypertriglyceridemia (314).

**LDL catabolism:**

The final step at which a defect in lipoprotein metabolism can occur is in LDL catabolism. Apo B-100 on the surface of LDL binds to its receptor on the cell surface; LDL is then absorbed into the cell, where it is catabolized [see figure H] After hydrolysis of the core lipids, unesterified cholesterol is used by cells for synthesis of membranes, bile acids, and steroid hormones and for various regulatory actions that prevent overaccumulation of cholesterol within the cell. The vast majority of LDL particles in plasma are taken up by the liver by means of the LDL receptor.

![Figure H](image)

*LDL is absorbed by cells through the LDL receptor. This receptor recognizes apo B-100, the apolipoprotein on the surface of LDL. Once internalized, the lipoprotein is catabolized, releasing cholesterol and amino acids. The free cholesterol is converted to*
cholesteryl oleate by the enzyme acyl-coenzyme A: cholesterol acyltransferase (ACAT). The LDL receptor is recycled back to the cell surface.

Fig H: Steps for LDL catabolism.

Mutations of the LDL receptor (as found in familial hypercholesterolemia [FH]) or, less commonly, mutations in the apo B-100 molecule (as found in familial defective apo B-100) lead to an impairment in the interaction of LDL with its receptor; this can result in elevated LDL levels. LDL levels also can be influenced by dietary factors. For example, dietary cholesterol delivered to the liver by chylomicron remnants can suppress hepatic LDL receptors, leading to impaired LDL removal from plasma. Dietary saturated fats also may reduce LDL receptor activity and may increase LDL production. Hypothyroidism can also be associated with defective LDL receptor-mediated cholesterol removal (315).

Function and Regulation of HDL:

The major HDL apolipoproteins are apo A-I and apo A-II, which are formed in the liver and small intestine (316). Apo A-I is secreted with phospholipid in a disklike structure called nascent HDL. Most of the apolipoproteins and phospholipid destined to become nascent HDL are initially secreted on the surface of chylomicrons and VLDL. After LPL hydrolyzes triglyceride in chylomicrons and VLDL, the core lipid content in these lipoprotein particles becomes smaller, and redundancies of unesterified cholesterol and phospholipid occur in the surface layer. These redundant surface components are transferred to HDL by phospholipid transfer protein. Nascent HDL particles also pick up excess unesterified cholesterol and phospholipid from peripheral tissues via the transporter ABCA1. This HDL cholesterol then undergoes esterification by the plasma enzyme lecithin-cholesterol acyltransferase (LCAT). LCAT is activated by apo A-I on the HDL surface to esterify free cholesterol into cholesteryl ester, causing it to move into the core. In this process, the particle becomes the larger, more buoyant HDL₃ particle and progresses to the even larger HDL₂ particle (316, 317). At some point, apo A-II may be added to the HDL₂ particle, which then is directed to deliver cholesteryl ester to the liver by cholesteryl ester transfer protein (CETP). Hepatic lipase activity on the liver surface
hydrolyzes the phospholipid and triglyceride in the HDL\textsubscript{2} particle, promoting the decrease in size and density to HDL\textsubscript{3} and then to even smaller HDL particles (317). Recycling of some of the apo A-I causes the process to repeat itself see Figure I.

**Fig I.** The circular pathway of HDL formation and degradation

*The circular pathway of HDL formation and degradation. HDL begins as an apo A-I phospholipid complex. Unesterified cholesterol and phospholipid are added to the nascent HDL via adenosine triphosphate-binding cassette transporter A-1 and phospholipid transfer protein to begin the formation of the smaller HDL\textsubscript{3} particle. LCAT transfers a fatty acid from phospholipid to unesterified cholesterol to cholesteryl ester, which moves to the HDL core. In this process, the HDL particle becomes the larger, more buoyant HDL\textsubscript{3} particle and progresses to the even larger HDL\textsubscript{2} particle. Cholesteryl ester transfer protein contributes to the transfer of cholesteryl ester from HDL\textsubscript{2} to the liver and various lipoproteins; with this loss of cholesteryl ester, the HDL particle shrinks in size. Hepatic lipase hydrolyzes the phospholipid and triglyceride in the*
HDL₂ particle, promoting the decrease in size and density to HDL₃ and then to even smaller HDL particles, including apo A-I. Recycling of some of the apo A-I causes the process to repeat itself. The role of apo A-II in this process in humans is not clear. (ABCA1—ATP-binding cassette transporter A1; CETP—cholesteryl ester transfer protein; LCAT—lecithin-cholesterol acyltransferase; LPL—lipoprotein lipase; PL—phospholipid; PLTP—phospholipid transfer protein; SR-BI—scavenger receptor BI; UC—unesterified cholesterol)

Abnormally high or low levels of HDL cholesterol may be caused, rarely, by genetic defects. Elevations in the HDL cholesterol level may result from genetic hyperalphalipoproteinemia or CETP deficiency. Markedly reduced HDL cholesterol levels may be caused by apo A-I structural mutation; homozygosity for mutations in ABCA1 (318), leading to Tangier disease; or homozygosity for mutations in the enzyme LCAT, leading to LCAT deficiency and fish-eye disease. Factors associated with an increase in HDL levels include female sex, aerobic exercise, weight reduction, high-fat diets, and certain drugs (e.g., alcohol, estrogens, fibrates, and nicotinic acid) [see Table 2]. Factors associated with a decrease in HDL levels include male sex, central obesity, cigarette smoking, low-fat diets, hypertriglyceridemia, uremia, being heterozygous for Tangier disease, and certain drugs (e.g., androgens, progestins, and some antihypertensive agents) [see Table-B]. Low HDL particle number is commonly associated with increased triglyceride levels, as seen in the metabolic syndrome.
Table B: Effects of Selected Drugs on Lipoprotein Levels.

<table>
<thead>
<tr>
<th>Drug</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol*</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Estrogens, estradiol*</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Androgens, testosterone</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Progestins</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Glucocorticoids*</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Cyclosporines</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Tacrolimus</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Thiazide diuretics*</td>
<td>+</td>
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<td>-</td>
</tr>
<tr>
<td>Beta blockers*</td>
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<td>-</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline*</td>
<td>Possible+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Protease inhibitors*</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valproate and related drugs</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Isotretinoin*</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Can cause severe hypertriglyceridemia and chylomicronemia syndrome in patients with a familial form of hypertriglyceridemia or type 2 diabetes mellitus.

Function of Hepatic Lipase:

Hepatic lipase is synthesized in the hepatocyte, binds to endothelial surfaces in the liver sinusoids, and acts on lipoproteins (317). After triglyceride-rich VLDL particles exchange triglyceride for the cholesteryl ester in LDL and HDL, hepatic lipase can hydrolyze the phospholipid and triglyceride in LDL and HDL (see Figure J).
Fig. 1: Dyslipidemia in the metabolic syndrome.

Triglyceride-rich VLDL exchanges triglyceride for the cholesteryl ester in LDL and HDL particles. This change in lipoprotein composition is initiated by cholesteryl ester transfer protein. Hepatic lipase hydrolyzes the triglyceride and phospholipid in large LDL and HDL particles, decreasing the size of each particle. (CE—cholesteryl ester; TG—triglyceride; CETP—cholesterol ester transfer protein).

This process leads to the formation of small, dense LDL and converts HDL₂ to HDL₃. This process may be driven by the presence of excessive levels of triglyceride-rich VLDL in the presence of normal hepatic lipase activity or by increases in the level of hepatic lipase. Factors such as male sex and the accumulation of intra-abdominal fat predispose to increased hepatic lipase levels and are associated with an increase in small, dense LDL levels and a decrease in HDL₂ levels. Increased hepatic lipase activity is an important factor in the dyslipidemia of the metabolic syndrome (317, 319). Hepatic lipase also may facilitate hepatic recognition and uptake of chylomicron and VLDL remnant lipoproteins.

Clinical Manifestations of Dyslipidemia:

The main clinical consequences of hyperlipidemia are premature atherosclerosis; pancreatitis, which is usually associated with the chylomicronemia syndrome; and nonalcoholic fatty liver disease. Atherosclerosis is most clearly associated with elevated
levels of LDL cholesterol and reduced levels of HDL cholesterol. In both pancreatitis and fatty liver disease, the underlying lipid disorder is hypertriglyceridemia.

**Dyslipidemia in Atherosclerosis:**

There is consensus that elevated plasma LDL levels and reduced HDL levels are associated with an increased risk of atherosclerosis. The role of hypertriglyceridemia as a cardiovascular risk factor is more complex. Hypertriglyceridemia may be a marker for other lipoprotein abnormalities (e.g., increased levels of small, dense LDL particles; low levels of HDL; or remnant accumulation) that are part of the dyslipidemic pattern associated with FCHL, type 2 diabetes mellitus, and the metabolic syndrome. In these settings, hypertriglyceridemia is a predictor of increased premature cardiovascular risk. However, other forms of hypertriglyceridemia may not be associated with premature cardiovascular disease [see *Familial Hypertriglyceridemia*, below]. The precise mechanisms whereby increased levels of LDL result in increased atherosclerotic risk are unclear. Very high levels of large, buoyant LDL particles, such as occur in FH and familial defective apo B-100, as well as the presence of more moderate numbers of small, dense LDL particles, are associated with an increased risk of cardiovascular disease.

Accumulating evidence suggests that LDL needs to be modified before it becomes atherogenic (320). Oxidation of LDL may increase its atherogenicity. Oxidized LDL has many biologic properties that may cause it to become atherogenic. The atherogenicity of small, dense LDL particles may result from the ability of LDL to enter the arterial intima, where it is retained by matrix molecules and undergoes oxidation more readily than larger, more buoyant LDL particles. The antiatherogenic properties of HDL are probably related to its role in reverse cholesterol transport, and HDL may have anti-inflammatory and antioxidant effects.

**Dyslipidemia in the Chylomicronemia Syndrome:**

Pancreatitis is associated with chylomicronemia, usually with elevated levels of VLDL. The mechanism by which chylomicronemia causes pancreatitis is unclear. Pancreatitis is believed to be caused by the release of free fatty acids and lysolecithin from...
chylomicrons in excess of their binding capacity in the capillaries of the pancreas by pancreatic lipase.

The chylomicronemia syndrome occasionally occurs when LPL is defective as a result of genetic variation in the enzyme or its cofactor, apo C-II. Much more commonly, chylomicronemia is caused by the coexistence of a genetic form of hypertriglyceridemia combined with an acquired disorder of plasma triglyceride metabolism, the most common being untreated diabetes. Other conditions may be implicated (e.g., hypothyroidism and nephrotic syndrome), as may the use of drugs that raise triglyceride levels.

The chylomicronemia syndrome is associated with abdominal pain, eruptive xanthomas, and transient memory loss. Eruptive xanthomas occur most frequently on the buttocks and the extensor surfaces of the upper limb. A reversible loss of memory, particularly for recent events, and peripheral neuropathy, which sometimes mimics the carpal tunnel syndrome, also may occur. The retinal vessels occasionally demonstrate lipemia retinalis. If the chylomicronemia syndrome is not corrected, it may lead to acute pancreatitis. Acute pancreatitis can be fatal and is often recurrent until low triglyceride levels are maintained. The risk of pancreatitis caused by severe hypertriglyceridemia markedly increases with triglyceride levels over 2,000 mg/dl.

**Dyslipidemia in Nonalcoholic Fatty Liver Disease:**

Fatty liver disease seems to occur in both genetic and acquired hypertriglyceridemia. It usually is caused by the synthesis of hepatic triglyceride in amounts that are excessive relative to the amount of apo B that is synthesized; this leads to accumulation of triglyceride in the liver, rather than the hepatic secretion of VLDL triglyceride. Fatty liver disease also may occur in heterozygous familial hypobetalipoproteinemia because of the decreased synthesis of hepatic apo B associated with this disorder. Alcoholic fatty liver disease also occurs with increased hepatic triglyceride synthesis in the face of impaired apo B synthesis (321). Fatty liver disease has been associated with the metabolic syndrome (319), which is related to central obesity, insulin resistance, and hypertriglyceridemia.
Any severe form of hypertriglyceridemia with defective VLDL catabolism also can be associated with fatty liver and hepato splenomegaly. In fact, familial LPL deficiency—a form of hypertriglyceridemia caused entirely by an extrahepatic defect in triglyceride hydrolysis—is commonly associated with fatty liver disease; in this setting, fatty liver disease regresses rapidly with restriction of dietary fat. In some patients, fatty liver disease progresses to steatohepatitis that is associated with fibrosis and necrosis; the reasons for such a progression are not clear. Perhaps a second insult is needed for these patients to develop nonalcoholic steatohepatitis and then progress to cirrhosis.

**Approach to the Patient with Abnormal Lipid Levels:**

**Patients with Isolated Elevation of LDL Cholesterol Levels:**

A patient's cholesterol level is said to be "above desirable" in an individual with low atherosclerotic risk if the LDL cholesterol level exceeds 130 mg/dl. High LDL levels are those above 190 mg/dl. The patient's triglyceride level is by definition normal (322), and the HDL cholesterol level is variable but is often normal. The lipid disorders in these patients are usually discovered through routine cholesterol screening. Although some observers question the cost-effectiveness of screening men and women older than 20 years, the high prevalence of elevated LDL cholesterol in the United States warrants population screening, as recommended by the National Cholesterol Education Program (NCEP) and other authorities.

Severely elevated cholesterol levels are an indication of FH. The ability to diagnose FH is valuable because affected individuals will require drug therapy from a relatively young age [see Familial Hypercholesterolemia, below].

Isolated hypercholesterolemia may be present intermittently in patients with FCHL. A family history that is strongly positive for premature cardiovascular disease, or the presence of any of the other criteria for FCHL, should provide clues to the diagnosis of this disorder. Not all cases of mild isolated hypercholesterolemia are indicative of FH or FCHL; such cases may result from interactions of acquired and environmental factors,
particularly dietary factors, with unknown genetic factors that confer susceptibility to hypercholesterolemia.

Most current treatment guidelines are based primarily on LDL cholesterol levels, because reduction of LDL has been shown to reduce cardiovascular disease by as much as 50% (323). Reduction in the consumption of dietary saturated fat and cholesterol usually leads to a modest reduction in LDL cholesterol levels; such a reduction depends in part on the baseline diet [see CE:IV Diet and Exercise]. Lifestyle changes, including diet and weight loss, will suffice in some individuals for reducing LDL cholesterol levels to an acceptable range. However, this approach is unlikely to suffice in patients with familial forms of dyslipidemia, such as FH or FCHL.

In patients with familial forms of the disease or in patients for whom lifestyle measures alone fail to bring LDL cholesterol levels within guideline goals, cholesterol-lowering drugs should be added to the treatment regimen [see Drug Therapy in Dyslipidemia, below]. Diet therapy can reduce LDL cholesterol levels an additional 5% to 15% beyond reductions achieved with drugs (324). Diet therapy can therefore lead to a reduction in the dosages of required drugs and should be used in combination with drug therapy. The major class of drugs used to reduce LDL cholesterol is the statins. However, bile acid-binding resins and drugs that block cholesterol absorption are of value in patients who do not respond adequately to statins alone, and they can be used in combination with statins and other drugs.

Patients with Isolated Elevation of Triglyceride Levels:

An isolated elevation in triglyceride levels may be caused by a primary disorder of lipid metabolism (e.g., FHTG or FCHL); it may arise secondary to the use of therapeutic drugs; or it may be a component of the metabolic syndrome or type 2 diabetes mellitus. Unlike with cholesterol levels, it has been difficult to determine the level of triglyceride at which the risk of CAD increases or decreases. It is valuable to ascertain the cause of the hypertriglyceridemia, because the therapeutic approaches may differ.

For example, it is important to distinguish FHTG, which confers no risk of premature CAD, from FCHL, which is associated with a high incidence of premature atherosclerosis.
(324). However, it can be difficult to distinguish these disorders when FCHL is associated with hypertriglyceridemia. A positive personal or family history of premature atherosclerosis suggests FCHL. In addition, patients with FCHL frequently have nonlipid cardiovascular risk factors (i.e., central obesity, hypertension, insulin resistance, impaired glucose tolerance, increased levels of plasminogen activator inhibitor-1, (PAI-1) and increased levels of circulating inflammatory markers). Hypertriglyceridemia present in FCHL indicates the presence of increased numbers of small, dense LDL particles and confers an increased risk of premature cardiovascular disease (319). Similarly, hypertriglyceridemia associated with type 2 diabetes mellitus and the metabolic syndrome is an important cardiovascular risk factor. Other cardiovascular risk factors are usually present in patients with type 2 diabetes mellitus, the metabolic syndrome or FCHL. Therefore, the therapeutic strategy must consider factors beyond the lipid disorder.

Patients with FHTG do not appear to be at significantly increased risk for developing premature CAD. However, they are at increased risk for developing the chylomicronemia syndrome when secondary forms of hypertriglyceridemia are present, such as the hypertriglyceridemia caused by the use of triglyceride-raising drugs. The chylomicronemia syndrome occurs in FCHL in combination with other causes of hypertriglyceridemia as well. In patients with pancreatitis caused by hypertriglyceridemia, triglyceride levels are above 2,000 mg/dl and can be much higher. It is recommended that plasma triglyceride levels be maintained below 2,000 mg/dl to prevent recurrent acute pancreatitis. A safe goal would be a level of less than 1,000 mg/dl.

Patients with Elevations in Cholesterol and Triglyceride Levels:

Patients with elevations in the levels of both total plasma cholesterol and triglyceride fall into three categories. In the first category, there is an elevation in VLDL and in LDL, as seen in FCHL. In the second category, there is an elevation in VLDL remnants and chylomicron remnants, as in remnant removal disease. The third category consists of patients with very high triglyceride levels in whom the increase in total cholesterol is a result of the cholesterol in VLDL and chylomicrons.
In patients with FCHL, an increase in triglycerides and in LDL cholesterol is often seen. These patients have elevated apo B levels and small, dense LDL particles. Therapy for these individuals often requires several drugs, one aimed at lowering the triglyceride level and one aimed at reducing the amount of small, dense LDL particles [see Drug Therapy in Dyslipidemia, below].

In patients with remnant removal disease, the levels of plasma cholesterol and triglyceride are often equal. It is important to consider remnant removal disease in these circumstances. Therapy in this case is related to decreasing hepatic lipoprotein secretion with statins, fibrates, or niacin.

In patients with severe hypertriglyceridemia, the increase in total plasma cholesterol is a result of the cholesterol in VLDL and chylomicrons. Fibrates are often the drug of choice. However, it is very important to determine the etiology of the severe hypertriglyceridemia and remove any offending drug (see Table-B) or treat any secondary cause for the hypertriglyceridemia.

**Patients with Low HDL Cholesterol Levels:**

Many if not most patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels. Therefore, the management of low HDL cholesterol levels should be considered in the context of the management of the underlying disorder (e.g., FCHL or type 2 diabetes mellitus) [see Patients with Isolated Elevation of Triglyceride Levels, above]. Isolated low HDL cholesterol levels of 20 to 30 mg/dl without concomitant hypertriglyceridemia or other changes in lipid and lipoprotein levels are rare, but such low levels are a risk factor for cardiovascular disease (316). In the past, these reductions in HDL levels were often not identified; the screening strategies that were employed were based on the assessment of total cholesterol levels, and total cholesterol levels often are not elevated in patients with isolated reductions in HDL. Specific measurement of HDL cholesterol is required to identify these patients. The treatment of the rare patients with isolated low levels of HDL cholesterol remains somewhat controversial. There are no currently available drugs that effectively increase HDL cholesterol levels only (325). Gemfibrozil, a fibrate that decreases VLDL triglyceride
levels, also raises HDL cholesterol levels. Many studies of fibrate therapy for atherosclerosis have been inconclusive. However, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated a reduction in cardiovascular events (326). Nicotinic acid, which acts at many metabolic sites, also raises HDL cholesterol. It decreased cardiovascular death in the Coronary Drug Project of the 1970s (327). Few other studies have evaluated the effect of niacin on atherosclerotic events.

Patients with Atherosclerosis and Normal Lipid Levels:

On rare occasions, a middle-aged patient with established atherosclerosis is seen to have no detectable lipid or lipoprotein abnormality. In addition to the standard lipid profile, measurement of apo B and Lp(a) will often reveal subtle lipoprotein abnormalities, such as increased numbers of small, dense LDL particles in these patients. Assessment of nonlipoprotein risk factors (e.g., homocysteine and inflammatory markers such as C-reactive protein [CRP]) also may be of value in assessing cardiovascular risk factors. Although the levels of some of these risk factors can be reduced by various strategies (e.g., homocysteine by folate therapy), the use of statins in all categories of high-risk individuals, particularly those who have established vascular disease, has been shown to be of benefit, even if lipid levels are apparently normal.

Genetic Disorders of Lipoprotein Metabolism:

Primary disorders of lipoprotein metabolism are those that arise from genetic defects in the metabolic pathways of lipoproteins (i.e., familial disorders caused by increased hepatic secretion of lipoproteins or by catabolic defects). The disorders that cause increased lipoprotein secretion are the metabolic syndrome, familial combined hyperlipidemia, type 2 diabetes mellitus, and FHTG; elevations of Lp(a) can also cause increased lipoprotein secretion. Disorders of LDL catabolism are FH and familial defective apo B-100. Remnant removal disease is a defect in remnant catabolism.

Metabolic Syndrome:
The metabolic syndrome consists of a central distribution of adiposity or visceral obesity; insulin resistance; elevations in plasma free fatty acid levels; impaired glucose tolerance; hypertension; dyslipidemia; and an abnormal procoagulant state. Many features of this syndrome are known to predispose men and women to premature CAD (319).

**Etiology and Risk Factors:**

An accumulation of visceral rather than subcutaneous fat has been observed in individuals with the central body fat distribution characteristic of the metabolic syndrome. Men have more visceral fat than premenopausal women, even when matched for body mass index. It has been suggested that these differences in visceral fat and the associated changes in lipoproteins and blood pressure could account, in part, for the difference in risk of premature CAD between men and premenopausal women (328, 329). Increased visceral fat is associated with insulin resistance, hyperinsulinemia, low plasma adiponectin, and elevations in plasma free fatty acid levels (330). It has been suggested that the accumulation of visceral fat precedes and causes insulin resistance and the resultant hyperinsulinemia, because insulin sensitivity increases and free fatty acid levels fall when visceral fat is decreased after caloric restriction (331).

The levels of insulin, glucose, triglyceride, HDL cholesterol, blood pressure, PAI-1, and other inflammatory markers are increased above the mean normal in patients with the metabolic syndrome. Although these variables are usually shifted to high levels, some of these variables are in the high-normal range in some affected individuals. HDL levels tend to be lower than mean normal. Genetic and environmental factors appear to affect the distribution of these variables in both normal persons and those with the metabolic syndrome. Because the metabolic syndrome is associated with multiple cardiovascular risk factors, individuals with the metabolic syndrome are at increased risk for CAD. Whether all individuals who meet the NCEP guidelines for the metabolic syndrome (332) are at increased risk for premature CAD is unknown. However, type 2 diabetes mellitus and FCHL are specific disorders of which the metabolic syndrome is a component (319). These two disorders account for at least 40% to 50% of premature CAD and need to be considered in the context of the metabolic syndrome.
The risk of abdominal fat patterning, dyslipidemia, impaired glucose metabolism, and hypertension—the sentinel symptoms of the metabolic syndrome—increases with age (333). Central obesity associated with the metabolic syndrome may be evident in young adults after completion of adolescent growth; however, it is more typical for central obesity and insulin resistance to manifest in midlife. Whereas elevations in LDL cholesterol levels may not predict the onset of atherosclerosis in the elderly, central obesity, hypertension, and insulin resistance are risk factors for atherosclerosis, and their prevalence increases with age (333-337), possibly because of the metabolic syndrome.

Pathophysiology:

Although the association of central obesity and insulin resistance with dyslipidemia is well established, the underlying cause remains unclear. One mechanism that would explain the association of central obesity and insulin resistance with dyslipidemia is an increase in portal vein long-chain free fatty acids. Such an increase would inhibit hepatic apo B from undergoing degradation in the endoplasmic reticulum and would increase the likelihood of apo B undergoing hepatic secretion as triglyceride-containing lipoproteins. This would account for the increased levels of triglyceride and the increased number of VLDL and LDL particles seen in patients in insulin-resistant states (338). Another effect of long-chain free fatty acids is to increase hepatic lipase on the surface of hepatic cells. Hepatic lipase hydrolyzes triglyceride and phospholipid in LDL and HDL, decreasing the size of each particle [see Figure 6] (319). However, CETP also contributes to this lipoprotein remodeling process, whether hepatic lipase or CETP has the predominant effect on the size and density of LDL and HDL particles depends on the triglyceride content of VLDL and the secretion rate of VLDL. The differences in LDL particle size and HDL₂ levels between men and premenopausal women can largely be accounted for by differences in visceral fat in men and women.

Diagnosis:

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) has suggested five clinical variables as diagnostic criteria for the metabolic syndrome: (1) increased waist circumference, (2) increased triglyceride level, (3) decreased HDL.
cholesterol level, (4) increased blood pressure, and (5) elevated level of fasting plasma glucose [see Table 3] (322). A diagnosis of the metabolic syndrome is made when three or more of these clinical variables are present. When these five variables were assessed in a survey of 8,814 adult men and women, approximately 24% of those surveyed met the diagnostic criteria for diagnosis of the metabolic syndrome (339-340). The World Health Organization (WHO) also has criteria for the metabolic syndrome. An attempt to harmonize the two sets of criteria is in progress.

Visceral obesity and insulin resistance are major contributors to the dyslipidemia associated with the metabolic syndrome. The following lipid abnormalities are associated with the metabolic syndrome: increased levels of triglyceride; increased numbers of small, dense LDL particles; increased apo B levels; and decreased levels of HDL cholesterol. However, in normal, randomly selected populations, isolated visceral obesity and insulin resistance were associated with only a slight increase in triglyceride levels and only a slight decrease in HDL cholesterol levels (330). In contrast, visceral obesity and insulin resistance can contribute to a more severe dyslipidemia, such as that associated with type 2 diabetes mellitus and FCHL (319).

The dyslipidemia of the metabolic syndrome can be diagnosed by demonstrating mild to moderate increases in plasma triglyceride and apo B levels, decreased levels of HDL cholesterol, and normal levels of LDL. Although the LDL level is normal in patients with this disorder, the number of LDL particles is generally increased; the predominant form is small, dense LDL particles, which are cholesterol poor relative to large, buoyant LDL particles. The presence of small, dense LDL particles can be determined by direct measurement of LDL size or density. The routine measurement of plasma apo B levels in clinical practice is not necessary for the diagnosis of this disorder; however, measurement of plasma apo B levels can indicate the presence of increased numbers of small, dense LDL particles. Similarly, total HDL levels reflect changes in the HDL$_2$ levels, indicating that HDL subfractions do not need to be measured (341).

**Treatment:**
Aerobic exercise and a diet low in saturated fat are indicated as therapy for most people with the metabolic syndrome. If the metabolic syndrome is severe or FCHL or type 2 diabetes mellitus is present, more aggressive therapy is indicated.

**Familial Combined Hyperlipidemia:**

FCHL is an autosomal dominant disorder that accounts for up to half of the familial causes of CAD (342); it was first described in families of survivors of myocardial infarction (343-345). FCHL is characterized by elevations in triglyceride or cholesterol levels, or both, in affected relatives. In addition to increases in triglyceride and cholesterol levels, patients with FCHL characteristically have elevations in apo B levels and increased numbers of small, dense LDL particles (346).

Genetic linkage analysis suggests that the inheritance of the lipid phenotype in FCHL involves separate gene effects (347) for the elevation in apo B levels (348) and the increased numbers of small, dense LDL particles that are present in FCHL families. Further evidence for genetic heterogeneity comes from studies that found that in one third of individuals with FCHL, the activity level of LPL in postheparin plasma was reduced by half (349). Visceral obesity and insulin resistance contribute to the dyslipidemia seen in FCHL but cannot account for the elevation in apo B levels (350).

In the Familial Atherosclerosis Treatment Study (FATS), intensive lipid-lowering therapy with nicotinic acid or lovastatin in combination with colestipol led to decreased hepatic lipase activity; decreased numbers of small, dense LDL particles; and elevated levels of HDL₂ cholesterol, with subsequent regression of CAD, as evidenced by angiography (351). Intensive lipid lowering resulted in subsequent regression of atherosclerosis, particularly in individuals with small, dense LDL particles who had FCHL or who had elevated Lp(a) levels at baseline.

An aggressive approach to modify reversible cardiovascular risk factors should be undertaken in individuals affected by this disorder. Diet therapy and therapeutic lifestyle modification that includes physical activity should be undertaken together with lipid-lowering drug therapy *(see Drug Therapy in Dyslipidemia, below)* (325), and management of other cardiovascular risk factors. Which lipid-lowering drug to use
depends to some extent on whether the primary lipid manifestation is hypercholesterolemia, hypertriglyceridemia, or combined elevations of cholesterol and triglyceride. If hypercholesterolemia is the primary manifestation, the approach should be the same as that for the hypercholesterolemic patient (see Patients with Isolated Elevation of LDL Cholesterol Levels, above). If hypertriglyceridemia is the major abnormality, the initial approach might be that used for patients with isolated hypertriglyceridemia. However, most patients will have elevations in both triglyceride and LDL levels and will require combination therapy; regimens may combine a statin and niacin, fibrate, or ezetimibe (see Drug Therapy in Dyslipidemia, below).

Type 2 Diabetes Mellitus:

Patients undergoing treatment of type 2 diabetes mellitus characteristically have visceral obesity and insulin resistance. A defect in insulin secretion is present in insulin-resistant individuals who develop hyperglycemia. First-degree relatives of individuals with type 2 diabetes mellitus may be centrally obese and insulin resistant or may experience decreased insulin secretion in response to glucose; first-degree relatives who are both centrally obese and who have a defect in insulin secretion invariably develop type 2 diabetes mellitus. Although the genes contributing to central obesity, insulin resistance, and defective insulin secretion are mostly unknown, type 2 diabetes mellitus is a classic example of an oligogenic disorder. Determining all of the genes involved will require careful phenotypic characterization of subsets of individuals with type 2 diabetes mellitus.

The dyslipidemia of untreated diabetes mellitus and hyperglycemia is discussed later in this chapter under acquired disorders (see Endocrine Disorders That Cause Dyslipidemia, below). The dyslipidemia of treated type 2 diabetes mellitus is similar to that of the metabolic syndrome and FCHL; it is characterized by a mild increase in triglyceride levels, decreased HDL\(_2\) cholesterol levels, and increased numbers of small, dense LDL particles. Treatment entails diet therapy, increased physical activity, and lipid-lowering drug therapy (see Drug Therapy in Dyslipidemia, below) (352).

Familial Hypertriglyceridemia:
FHTG is a common inherited disorder, thought to be autosomal dominant, that affects about 1% of the population. FHTG is characterized by an increase in triglyceride synthesis resulting in VLDL particles enriched with triglyceride secreted in normal numbers. Affected people have elevated VLDL levels but low levels of LDL and HDL and are generally asymptomatic unless severe hypertriglyceridemia (i.e., chylomicronemia syndrome) develops. FHTG does not appear to be associated with an increase in the risk of premature CAD (324).

A diagnosis is made by family history and examination of fasting lipoprotein profiles of the patient and relatives. The triglyceride level ranges from 250 to 1,000 mg/dl in approximately one half of first-degree relatives; a strong family history of premature CAD usually is lacking; and elevated LDL levels should not be present.

Patients with FHTG should lose weight if necessary, exercise regularly, and reduce their intake of saturated fatty acids and cholesterol. Alcohol, exogenous estrogens, and other drugs that increase VLDL levels might need to be restricted. Diabetes, if present, should be well controlled. Hypertriglyceridemia in patients with FHTG often responds to these measures. If triglyceride levels exceed 500 mg/dl after 6 months of nonpharmacologic therapy, drug therapy with a fibrate should be considered (326); at levels above 1,000 mg/dl, drug therapy should be instituted.

Fibrates are the drugs of choice to reduce elevated triglyceride levels in patients with familial hypertriglyceridemia (see Drug Therapy in Dyslipidemia, below). In familial combined hyperlipidemia, niacin can be very useful. Niacin has several additional beneficial effects on blood lipids—it increases HDL cholesterol levels; it reduces levels of small, dense LDL particles; and it may reduce Lp(a) levels. Despite having a less dramatic effect on triglycerides than fibrates, statins have been shown to be of value in high-risk patients with moderate hypertriglyceridemia and increased levels of small, dense LDL particles, such as occur in patients with type 2 diabetes mellitus and FCHL.

Familial Hypercholesterolemia:

FH is an autosomal dominant disorder caused by a mutation in the gene encoding the LDL receptor protein. The extremely rare homozygote with FH has two mutant alleles at
the LDL receptor locus, leaving the person with an absolute or nearly absolute inability to clear LDL from the circulation by the LDL receptor (315). Heterozygotes with FH possess one normal allele, giving them approximately one half of the normal receptor activity. Because the LDL receptor contributes to VLDL remnant clearance from the plasma, a deficiency of LDL receptors may lead to some accumulation of remnant lipoproteins. High concentrations of LDL result in nonreceptor-mediated uptake of LDL by the extracellular matrix, including that of the arterial wall, which leads to the formation of xanthomas and atherosclerosis. The heterozygous form of this disorder has a prevalence of about one in 500 people, making it one of the more common genetic diseases (315).

**Diagnosis:**

Hypercholesterolemia can be detected at birth in umbilical cord blood. If FH is not detected at birth, various associated conditions may suggest the diagnosis later in life. Tendon xanthomas are a highly specific sign of FH; typically, they begin to appear by 20 years of age and may be present in up to 70% of older patients. Occasionally, xanthomas are seen on the patellar tendon. Because xanthomas are subtle, careful examination of the dorsal hand tendons and Achilles tendon is required for their detection. Xanthelasma (cutaneous xanthomas on the palpebra) and corneal arcus are common in patients with FH after 30 years of age; however, they also occur in normocholesterolemic persons. Early corneal arcus is seen superiorly and inferiorly in the eyes and later becomes totally circumferential.

CAD develops early, with symptoms often manifesting in men in the fourth or fifth decade. Approximately 5% of all cases of premature MI occur in patients with heterozygous FH (315). Before the development of statin therapy, at least 50% of men with heterozygous FH experienced MI by 60 years of age; in women, symptoms tend to develop about 10 years later. The total cholesterol level in heterozygous patients generally ranges from 350 to 550 mg/dl. The triglyceride level may be mildly elevated, and the HDL cholesterol level is reduced in about 10% of heterozygotes. LDL receptor function can be measured only in special laboratories.
Heterozygous FH should be suspected when severe hypercholesterolemia from elevated LDL is detected. If tendon xanthomas are present, the diagnosis is virtually certain. If tendon xanthomas are absent, secondary causes of hypercholesterolemia (e.g., hypothyroidism) should be sought, but the diagnosis of familial hypercholesterolemia is not excluded. A comprehensive family history should reveal a strong history of premature CAD and hypercholesterolemia without hypertriglyceridemia; the disorder affects approximately one half of first-degree relatives. The presence of hypercholesterolemia and tendon xanthomas in a parent or sibling is virtually diagnostic, as is hypercholesterolemia in a child in the family. Careful screening of family members is mandatory, because 50% of first-degree relatives will be affected and will require aggressive lipid-lowering therapy (325, 353).

Treatment:

Management of FH requires both dietary intervention and drug therapy. The goal of therapy is to lower the LDL cholesterol level to less than 130 mg/dl, or even lower if the patient exhibits CAD. In patients with heterozygous FH, effective treatment is possible with combinations of statins, intestinally active drugs, and nicotinic acid. Because LDL cholesterol levels tend to be very high, combination therapy with two drugs is often required, and three drugs may be necessary [see Drug Therapy in Dyslipidemia; below]. Although diet therapy alone is not sufficient for patients with heterozygous FH, reducing saturated fatty acid and cholesterol intake will lower LDL levels and reduce the amount of medication required. This is particularly important in children and adolescents before initiation of drug therapy. Tendon xanthomas have been shown to regress when LDL levels are maintained in a desirable range. Aggressive reduction of LDL cholesterol in men and women who have heterozygous FH may cause a regression of coronary atherosclerosis.

Familial Defective Apolipoprotein B-100:

A mutation in apo B-100 that inhibits its binding to the LDL receptor is another genetic cause of elevations in the LDL level. The prevalence of this disorder is unknown but is estimated to be 5% to 10% that of FH. LDL receptor structure and function are normal. A
full-length apo B-100 molecule is produced with a single amino acid substitution; this results in apo B that binds poorly to LDL receptors, leading to LDL accumulation in the plasma.

Affected individuals are clinically indistinguishable from patients with heterozygous FH: they may present with severe hypercholesterolemia, tendon xanthomas, and premature atherosclerosis. Treatment with statins appears to lower LDL cholesterol levels in patients with this disorder. Specialized tests available only in selected research laboratories are required to distinguish affected people with defective apo B from those with defective LDL receptors.

**Increased Levels of Lipoprotein(a):**

Lp(a) is a specific class of lipoprotein particles synthesized in the liver (312). An important component of Lp(a) is apo(a), which has a structure homologous with plasminogen, a key protein in the coagulation cascade. Plasma concentrations of Lp(a) vary markedly among individuals, ranging from undetectable to 200 mg/dl. Lp(a) plasma concentration is strongly controlled by genetic factors.

Most epidemiologic studies suggest that Lp(a) is a risk factor for CAD and stroke. If Lp(a) is atherogenic, it may be because of its LDL-like properties: Lp(a) has been shown to undergo endothelial uptake and oxidative modification and to promote foam cell formation. Because Lp(a) has a high degree of homology with plasminogen, it may play a role in thrombosis by interfering with the binding of plasminogen to fibrin. Elevated Lp(a) levels appear to increase the atherogenicity of other cardiovascular risk factors, with earlier onset of cardiovascular events.

Data suggest that reducing LDL cholesterol levels in patients with high levels of Lp(a) may be an effective strategy to slow the progression of atherosclerosis and to prevent coronary events. The Lp(a) level itself can be reduced with high-dose niacin, estrogen, or tamoxifen, as well as with LDL apheresis. Insufficient data exist regarding the efficacy of lowering the Lp(a) level per se to inhibit atherosclerosis or to prevent coronary events (312).
Remnant Removal Disease:

Remnant removal disease, also called type III hyperlipoproteinemia, dysbetalipoproteinemia, and broad-beta disease, is defined as the presence of VLDL particles that migrate in the beta position on electrophoresis (normal VLDL particles migrate in the pre-beta location). Beta-VLDL particles are chylomicron and VLDL remnants.

Remnant removal disease is caused in part by a mutation in the APOE gene (314) [see Regulation of Lipoprotein Catabolism, above]; this mutation leads to an impairment in the hepatic uptake of apo E-containing lipoproteins and stops the conversion of VLDL and IDL to LDL. Without the presence of additional genetic, hormonal, or environmental factors, remnants do not accumulate to a degree sufficient to cause hyperlipidemia, because they are cleared by hepatic receptors that also bind, with less avidity, to apo B-48 and apo B-100. Remnant removal disease results when an apo E defect (almost always the E2/E2 genotype) occurs in conjunction with a second genetic or acquired defect that causes either overproduction of VLDL (such as occurs with FCHL) or a reduction in LDL receptor activity (such as occurs in heterozygous FH or hypothyroidism). The E2/E2 genotype is found in 1% of the white population and in virtually all persons with remnant removal disease.

Diagnosis:

Persons with remnant removal disease have elevations in both cholesterol and triglyceride levels and are likely to develop premature CAD. For reasons that are not understood, these patients are at particularly increased risk for peripheral vascular disease. Hyperlipidemia usually does not develop before adulthood. Palmar xanthomas (xanthoma striata palmaris)—orange-yellow discolorations of the palmar creases—are pathognomonic for genetic remnant removal disease, but they are not always present. Palmar xanthomas may be difficult to see and should be carefully sought using good lighting. Tuboeruptive xanthomas are occasionally found at pressure sites, particularly the elbows, buttocks, and knees.
The diagnosis of remnant removal disease should be suspected in a person with elevated total cholesterol and triglyceride levels, elevated VLDL and IDL cholesterol levels, and reduced LDL and HDL cholesterol levels. Cholesterol and triglyceride levels range from 300 to 1,000 mg/dl and are roughly equal, except during an acute exacerbation, at which time hypertriglyceridemia tends to predominate. Beta-migrating VLDL is present on electrophoresis, although this test is seldom used today. Ultracentrifugation demonstrates that the ratio of VLDL cholesterol to total plasma triglyceride is greater than 0.3. Definitive diagnosis is made by detecting the E2/E2 phenotype by isoelectric focusing of plasma lipoproteins or the genotype by gene analysis.

Treatment:

Generally, therapy for remnant removal disease is the same as that for other forms of hypertriglyceridemia. A low-fat diet, weight loss, and exercise can have a major effect on lipid levels. Fibrates, statins, and nicotinic acid have been used successfully in this disorder. However, drugs that increase triglyceride levels, such as bile acid–binding resins, must be avoided.

Rare Disorders:

Severe hypertriglyceridemia can present in childhood as a result of LPL deficiency or, extremely rarely, as apo C-II deficiency. These patients are at risk for acute pancreatitis with severe hypertriglyceridemia and must be treated with moderate to severe dietary-fat restriction until plasma triglyceride levels are below 1,000 to 2,000 mg/dl.

Homozygous FH is extremely rare and leads to severe hypercholesterolemia, atherosclerosis, and death, often in the first two decades of life. Patients with homozygous FH may benefit from LDL apheresis. At the other extreme, the absence of apo B-containing lipoproteins can result from defects in the synthesis of apo B (e.g., homozygous hypobetalipoproteinemia) or from defects in the transport of apo B into the
hepatic endoplasmic reticulum. Individuals with very low apo B levels are not at risk for atherosclerosis.

The absence of HDL can occur in persons with homozygosity for defects in the cholesterol and phospholipid transporter ABCA-1. The heterozygous state is an uncommon cause of isolated low-HDL cholesterolemia (i.e., hypoalphalipoproteinemia).

Miscellaneous Common Dyslipidemias:

Polygenic hypercholesterolemia was once thought to be common. Polygenic hypercholesterolemia is a term used to refer to the occurrence of mild elevations in LDL cholesterol in the apparent absence of a familial form of dyslipidemia or of dyslipidemia of secondary cause. This category of dyslipidemia continues to shrink as LDL variants such as Lp(a) and small, dense LDL particles are discovered.

Mild to moderate hypertriglyceridemia may occur in the presence of modest defects in LPL. Typically, it presents as an increase in VLDL levels in conjunction with a decrease in HDL cholesterol levels. It is seen in the obligate heterozygote parents of children with LPL deficiency. This defect may predispose to premature CAD.

Secondary Disorders of Lipoprotein Metabolism:

Secondary dyslipoproteinemias are caused by acquired defects in lipoprotein metabolism that result in hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia; the HDL level may or may not be low. Secondary hypertriglyceridemia in conjunction with a common genetic form of hypertriglyceridemia may be severe enough to cause chylomicronemia with pancreatitis. Dyslipoproteinemia may also be caused by selected medications.

Endocrine Disorders that Cause Dyslipidemia:

Untreated Hyperglycemia:
Untreated hyperglycemia in patients with diabetes mellitus causes an increase in VLDL synthesis, a reduction in VLDL catabolism with an accompanying reduction in LPL activity, or both. These abnormalities result in hypertriglyceridemia and a reduction in the level of HDL. The LDL level usually is normal. Fasting chylomicronemia occurs when there is a coexisting primary form of hypertriglyceridemia. VLDL and chylomicrons compete to interact with LPL, and both lipoproteins may accumulate. A low HDL level results from impaired lipolysis of triglyceride-rich lipoproteins, which supply lipid components for HDL development. These defects occur in both untreated type 1 and untreated type 2 diabetes mellitus. Lipid levels should approach normal with comprehensive treatment of diabetes; if they fail to do so, additional causes should be sought [see Genetic Disorders of Lipoprotein Metabolism, above]. In diabetic patients with persistent moderate to severe hypertriglyceridemia, a fibric acid is suitable because it reduces the secretion of VLDL and enhances the activity of LPL. Nicotinic acid may be used, but with care, particularly in patients with type 2 diabetes mellitus, because it may exacerbate hyperglycemia (354). Statins are effective in reducing coronary events in diabetic patients (352).

Hypothyroidism:

Hypothyroidism may cause a severe elevation of LDL levels because of reduced LDL receptor activity; in addition, it frequently causes hypertriglyceridemia and an associated reduction in the HDL level as a result of reduced LPL activity. Remnants of chylomicrons and VLDL may also accumulate and unmask remnant removal disease. The dyslipoproteinemia that occurs with hypothyroidism is corrected by thyroid hormone replacement.

Dyslipidemia Secondary to Estrogen and Progestin Therapy:

Oral contraceptives that contain a combination of estrogen and progestin can have variable effects on lipoproteins, depending on the specific combination used. Estrogen
tends to raise VLDL and HDL levels and lower LDL levels. Progestins tend to lower VLDL and HDL levels and raise LDL levels, but the effect varies considerably. Postmenopausal estrogen replacement therapy lowers LDL levels and raises HDL levels; the addition of progesterone to protect the uterus lessens these effects but does not eliminate them (355). Estrogen may increase triglycerides to severe levels in women who have an underlying primary triglyceride disorder, leading to pancreatitis; therefore, triglyceride levels should be closely monitored in these patients (313). Oral combination therapy with estrogen and progesterone was associated with a mild increase in CAD (350) in the Women's Health Initiative Study. In this randomized study of 16,608 women, use of oral hormone replacement therapy also was associated with an excess rate of breast cancer. In women who have undergone hysterectomies, estrogen therapy has been shown to increase the risk of stroke [see Managing Dyslipidemia in Women, below] (356). These studies have led to a decrease in the use of postmenopausal hormone replacement therapy.

Renal Disorders that Cause Dyslipidemia:

Nephrotic Syndrome:

The nephritic syndrome causes enhanced hepatic secretion of apo B-100-containing lipoproteins (i.e., VLDL) in response to the loss of albumin and other proteins in the urine. Hepatic synthesis of cholesterol is also increased. The LDL level is typically elevated, and it may be severely elevated. The VLDL level elevation may be associated with a reduction in the HDL level as lipolysis becomes impaired (357). Patients with the nephritic syndrome are at increased risk for CAD, and the lipid disorder should be treated aggressively. Dietary change, weight loss, and exercise may improve lipoprotein levels, but pharmacologic therapy is necessary to achieve desirable lipoprotein levels. Nicotinic acid should be effective in the treatment of this disorder because it inhibits
hepatic secretion of apo B-100-containing lipoproteins; however, it has not been studied extensively for this use. The statins are useful in lowering LDL cholesterol levels in patients with the nephritic syndrome. Combination drug therapy with statins, nicotinic acid, fibrates, or ezetimibe may be necessary for the reduction of LDL cholesterol and triglyceride levels [see Drug Therapy in Dyslipidemia, below]. Studies are needed to evaluate the effects of various drug combinations on cardiovascular outcomes.

**Chronic Renal Failure:**

Chronic renal failure produces hypertriglyceridemia as a result of a decrease in LPL and hepatic triglyceride lipase (357). Triglyceride levels typically range from 150 to 750 mg/dl, and the HDL level is usually low; the risk of CAD is increased. Dietary measures should be initiated while drug treatment is being considered. Gemfibrozil, a drug that enhances LPL activity, has been shown to be effective in lowering triglyceride levels in patients with renal insufficiency (358). Gemfibrozil is preferred over other fibrates (e.g., fenofibrate and clofibrate) in this setting because gemfibrozil is partly cleared by the liver; as such, it carries a lower risk of drug-induced myopathy than do fibrates that are cleared by the kidneys. Nonetheless, because gemfibrozil is partially excreted renally, the drug should be administered in the lowest effective dose. Nicotinic acid and statins have been less well studied in this condition. Combination therapy with nicotinic acid, statins, or gemfibrozil may be necessary to attain the therapeutic goal.

**Gastrointestinal Disorders that Cause Dyslipidemia:**

Primary biliary cirrhosis is the most significant gastrointestinal cause of dyslipidemia. In the early stages of primary biliary cirrhosis, when some hepatocellular function remains, mild elevations of VLDL and LDL levels occur because of elevations in the levels of remnant lipoproteins and HDL. Terminal liver disease with cirrhosis results in severe elevation in cholesterol levels because of increased production of lipoprotein X—an abnormal lipoprotein particle containing albumin and other plasma components that is rich in free cholesterol and phospholipid. Treatment of this terminal disorder requires liver transplantation.

**Other Causes of Secondary Dyslipidemia:**
Many commonly used drugs have adverse effects on lipoproteins [see Table 2]. Discontinuance of the drug often will improve lipid levels. An increase in VLDL, LDL, and HDL cholesterol levels can result from the use of drugs for the prevention of rejection after organ transplantation. Pravastatin is the drug of choice for lowering LDL levels because of its unique catabolic pathways. Immunosuppressive agents such as cyclosporine compete with atorvastatin and simvastatin for the cytochrome P-450 3A4 system. The use of antifungal agents also can interfere with the metabolism of these statins. The predominant dyslipidemia that is seen in patients with AIDS is similar to the dyslipidemia that occurs in patients with the metabolic syndrome; mild hypertriglyceridemia is common, and low HDL cholesterol is seen in some patients (359). In others, extreme hypertriglyceridemia can result from the use of HIV drugs, and the resultant hypertriglyceridemia may be associated with pancreatitis. The etiology of dyslipidemia in AIDS is complex: excessive free fatty acid mobilization is seen, along with the development of lipodystrophy and insulin resistance. In addition, AIDS patients typically use dyslipidemia-causing drugs. The specific therapy in each patient needs to be individualized.

**Prevention and Treatment of Coronary Artery Disease:**

**Primary Prevention:**

The treatment of lipid disorders in individuals who do not have clinical evidence of CAD is considered primary prevention. Primary prevention is based on the assumption that modification of lipid risk factors will alter the natural history of the untreated condition—the so-called lipid hypothesis. An association between cholesterol and CAD has been known since the early 1950s; however, it was not until the publication of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in 1984 that there were data to support the lipid hypothesis.

The LRC-CPPT enrolled almost 4,000 men with moderate hypercholesterolemia; patients were followed for 7 years. The treatment group was prescribed cholestyramine, which resulted in LDL cholesterol levels being 12.6% lower than those of the control subjects, who were given placebo. The cholestyramine group had a 19% reduction in CAD deaths and nonfatal myocardial infarcts ($P < 0.05$), although no decrease in total mortality was
observed (360). Further analysis demonstrated that the extent of benefit depended upon the achieved reduction in serum cholesterol (reflecting drug compliance). Use of a proportional hazards model indicated that a 25% decrease in total cholesterol or a 35% decrease in LDL cholesterol would be expected to decrease the risk of a CAD event by 50% (361).

The Helsinki Heart Study used the fibrate gemfibrozil to treat dyslipidemic men without CAD. After 6 years of follow-up, a 34% reduction in CAD events was seen in the treatment group, compared with the group receiving placebo (362). Again, no decrease in CAD mortality was demonstrated.

In both the Helsinki Heart Study and the LRC-CPPT, the sample size was calculated on the power to detect CAD events, not on fatal outcomes alone. As such, the lack of an effect on mortality was not surprising, but an increase (not statistically significant) in noncoronary death in the treatment groups of both these studies was troublesome (360-362) and confounded the recommendations for primary preventive therapy in hypercholesterolemic patients. These concerns were not completely addressed until 1995, when results of the West of Scotland Coronary Prevention Study (WOSCOPS) were published (363).

The WOSCOPS trial evaluated the effect of 5 years of treatment with pravastatin on the incidence of nonfatal myocardial infarction (MI) and CAD deaths in 6,595 men. The men were middle-aged (45 to 64 years of age) and moderately hypercholesterolemic (LDL cholesterol level above 155 mg/dl). The treatment group manifested a 20% reduction in total cholesterol, a 26% reduction in LDL cholesterol, a 12% decrease in triglycerides, and a 5% increase in HDL cholesterol, as compared with the control group. On the basis of intention-to-treat principles, these changes were associated with a 31% risk reduction in nonfatal MI or CAD deaths ($P < 0.001$), a 32% risk reduction in all cardiovascular deaths ($P = 0.033$), and a 22% risk reduction in total mortality ($P = 0.051$). In addition, coronary interventions (i.e., angiography, angioplasty, and coronary artery bypass surgery) were reduced 31% to 37% ($P < 0.01$).
The reduction in clinical events began within 6 months of randomization and were independent of other risk factors, such as diabetes, smoking, blood pressure, family history of CAD, and the ratio of total cholesterol to HDL cholesterol (364). Although there was no risk reduction without a decrease in LDL cholesterol, a decrease in LDL cholesterol of approximately 24% was adequate to see the full benefit of treatment. The treatment effect was proportionately the same regardless of baseline lipid levels and the reduction in LDL cholesterol. As such, LDL reduction alone did not account for all the benefits of treatment with pravastatin (365). Importantly, there was no increase in noncoronary deaths, which was reported in earlier primary preventive trials.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was the first large primary intervention trial to study the effects of cholesterol lowering in individuals with average cholesterol levels (366). That is, the mean total and LDL cholesterol levels were nearer the average value for the general population (221 mg/dl and 150 mg/dl, respectively). In addition, it was the first large study to include women (997 of a total of 6,605 patients). Lovastatin was the treatment agent in this randomized, placebo-controlled trial. LDL cholesterol reduction was 25%, and follow-up was 5 years. The total absolute benefit was 2%, meaning that 50 patients had to be treated for 5 years to prevent one event. The treatment group had a 28% reduction in cardiovascular hospitalizations, a 23% decrease in angioplasty, and a 32% reduction in coronary bypass surgery. An analysis of the cost-effectiveness of lovastatin treatment demonstrated a 27% (or $524 per patient) reduction in cardiovascular health care costs for the lovastatin group, as compared with the group that received placebo (367).

Persons with average cholesterol levels were also evaluated in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm {ASCOT-LLA} (368). Nearly 20,000 hypertensive patients were randomized to one of two antihypertensive regimens. The lipid-lowering arm of this study randomized 10,305 patients with total cholesterol levels of 251 mg/dl or lower to treatment with atorvastatin or placebo. The study was halted early because a significant benefit was observed in the treatment group. Median follow-up was 3.3 years. The study did not demonstrate statistically significant reductions in
cardiovascular or all-cause mortality; however, significant reductions were seen in total coronary events, total cardiovascular events and procedures, and stroke (368).

The effect of atorvastatin (10 mg/day) on primary prevention of cardiovascular disease in diabetic patients was examined in the Collaborative Atorvastatin Diabetes Study [CARDS] (352). CARDS randomized almost 3,000 diabetic patients with LDL levels of 160 mg/dl or lower, triglyceride levels of 600 mg/dl or lower, and at least one of the following: retinopathy, albuminuria, smoking habit, or hypertension. The trial was stopped 2 years early because predetermined criteria had been met. The atorvastatin group demonstrated a 36% reduction in coronary events, a 31% reduction in coronary revascularization procedures, a 48% decrease in stroke, and a 27% reduction in all-cause deaths, as compared with the placebo group.

These studies support lipid-lowering therapy as primary prevention for patients with high LDL and average LDL values. There are virtually no data on primary prevention in patients with other lipid abnormalities, such as isolated low HDL cholesterol levels or elevated triglyceride levels.

Secondary Prevention:

Lipid-lowering therapy in patients with documented CAD is considered secondary prevention. Lipid levels have a significant influence on CAD death rates in those with and without CAD; however, the impact is significantly greater in patients with established CAD (369).

Several trials have investigated the effect of aggressive lifestyle intervention in patients with CAD. The Saint Thomas Atherosclerosis Regression Study (STARS) randomized men with CAD and total cholesterol levels above 232 mg/dl to conventional care or a low-fat, low-cholesterol diet. Despite relatively modest changes in lipid levels (the intervention group had an LDL cholesterol average of 162 mg/dl), the progression of CAD decreased and the rate of regression increased in the intervention group. Angina symptoms also improved (370).
The effects of a Mediterranean diet (increased a-linoleic acid) were compared with those of a prudent Western diet in the Lyon Diet Heart Study (371). All study participants had had a first MI. Those consuming the Mediterranean diet had lower rates of primary (death and MI) and secondary (unstable angina, stroke, heart failure) end points than those on the prudent Western diet at 27 months. This effect persisted after 4 years of follow-up. The group on the Mediterranean diet had a rate of combined primary and secondary end points of 2.59 events per 100 patients per year, compared with 9.03 events per 100 patients per year in the group on the prudent diet (372).

A variety of pharmacologic agents have been used alone and in combination in secondary prevention trials. Some trials have used angiographic end points in assessing progression or regression of CAD, whereas others have used clinical end points. The Familial Atherosclerosis Treatment Study (FATS) examined the effect of several lipid-reducing regimens in men with elevated apo B levels. The two most aggressive regimens (nicotinic acid-colestipol and lovastatin-colestipol) were equally effective; both regimens were associated with delayed progression (21% and 25%, respectively, versus 46% in the placebo-colestipol group) and an increased likelihood of regression of coronary artery stenoses (32% and 39%, respectively, versus 11% in the placebo-colestipol group). Clinical end points (death, MI, worsening angina, and revascularization) were also reduced in the more aggressively treated groups (4.2% and 6.5%, respectively, versus 19% in the placebo-colestipol group) (351). This was the first major study to document the regression of CAD with aggressive lipid-lowering therapy. A subsequent analysis of these patients correlated the change in CAD severity with therapy-induced changes in LDL buoyancy and hepatic lipase activity (373).

The Scandinavian Simvastatin Survival Study (4S) evaluated 4,444 patients with known CAD and moderate to severe hyper-cholesterolemia at baseline [total cholesterol concentration ranging from 212 to 309 mg/dl] (374). Patients were randomized to a regimen of diet plus simvastatin or diet plus placebo. At 5.4 years, there was a significant reduction in total mortality (8% on simvastatin versus 12% on placebo), major coronary events (19% versus 28%), CAD deaths (42% reduction), and cerebrovascular events
The reduction in cardiovascular events correlated with total cholesterol and LDL cholesterol levels and with changes from baseline (375).

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial randomized approximately 9,000 men and women with a history of recent MI or unstable angina to receive either placebo or pravastatin (376). The study was stopped prematurely at 60 months because of a significant benefit associated with pravastatin therapy. CAD death was reduced in the treatment arm of the study (6.4% versus 8.3%), as were total mortality (11% versus 14%), stroke (20% relative decrease), need for bypass surgery (8.9% versus 11.3%), and MI (7.4% versus 10.1%). The benefit was primarily related to changes in lipid levels and was seen in all predefined subgroups. The greatest reduction in coronary events was seen in those patients thought to be at highest risk, as assessed by concomitant risk factors (377).

The Cholesterol and Recurrent Events (CARE) trial evaluated 4,159 patients with relatively low lipid levels. The average total cholesterol level was 209 mg/dl, and the average LDL cholesterol level was 139 mg/dl. Treatment with pravastatin over 5 years resulted in significant reductions in coronary death or nonfatal myocardial infarction (10.2% versus 13.2% for placebo), need for revascularization (14.1% versus 18.8%), and frequency of stroke (2.6% versus 3.8%) (378). However, in contrast to the results seen with 4S and LIPID, the absolute or percentage reductions in LDL had little relationship to coronary events (379). The benefits were seen only in patients with LDL levels above 125 mg/dl (379).

The Heart Protection Study enrolled over 20,000 persons with a history of cardiovascular disease (coronary, cerebrovascular, or peripheral vascular disease), diabetes, or treated hypertension (380). As such, it was a mixture of primary and secondary intervention. One third of the individuals had baseline LDL cholesterol levels below 116 mg/dl, and 25% had initial LDL levels ranging from 116 to 135 mg/dl. Participants were randomized to receive simvastatin or placebo. After an average follow-up of 5.5 years, the lipid-lowering group showed a 24% reduction in major cardiovascular events, an 18% reduction in cardiovascular deaths, and a 13% reduction in all-cause mortality, as compared with the placebo group. The percentage reductions in events were similar in all
three tertiles of baseline LDL cholesterol levels and in patients with LDL cholesterol levels below 100 mg/dl at baseline. These results differ from those reported in the CARE study, but they are consistent with results from the 4S and LIPID trials. The results of the Heart Protection Study also suggest that there may not be a threshold beyond which increased LDL-lowering therapy ceases to improve outcome, at least in patients at high risk for recurrent coronary events.

Aggressive LDL-lowering therapy appears to be more effective than standard lipid-lowering treatment. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial compared standard LDL-lowering treatment (pravastatin, 40 mg daily) with intensive LDL-lowering treatment (atorvastatin, 80 mg daily) in more than 4,000 patients recently hospitalized with an acute coronary syndrome (381). The average follow-up was 24 months. The median LDL cholesterol level achieved with atorvastatin was 62 mg/dl, compared with 96 mg/dl in the group treated with pravastatin. The primary composite end point was death from any cause, MI, unstable angina not requiring hospitalization, coronary revascularization, and stroke. The rate of reaching the primary end point was 22.4% in the atorvastatin group and 26.3% in the pravastatin group. The benefit of aggressive therapy with atorvastatin was apparent as early as 30 days after initiating therapy and was consistent over time.

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial also compared moderate LDL-lowering therapy (pravastatin, 40 mg daily) with more intensive LDL-lowering therapy (atorvastatin, 80 mg daily) (382) The study used coronary intravascular ultrasound, a sensitive means of measuring plaque volume, as a baseline measurement and primary end point. The median percentage change in atheroma volume was -0.4% in the atorvastatin group, compared with +2.7% in the pravastatin group. This finding correlated with mean LDL cholesterol levels of 79 mg/dl in the atorvastatin group and 110 mg/dl in the pravastatin group. These results gave further support to the view that aggressive LDL-lowering therapy is superior to standard LDL-lowering therapy.

Few studies have examined the benefit of raising HDL cholesterol levels in the secondary prevention of CAD. The VA-HIT trial enrolled 2,531 patients with known CAD and with
LDL cholesterol levels below 140 mg/dl, HDL cholesterol levels of 40 mg/dl or above, and triglyceride levels of 300 mg/dl or below (326). The patients were randomized to receive gemfibrozil or placebo. The subsequent mean HDL cholesterol level in the gemfibrozil group was 6% higher than that in the placebo group, and the mean triglyceride level in the gemfibrozil group was 31% lower. The mean LDL cholesterol levels were 113 mg/dl in both groups. The combined primary end point of cardiac death and nonfatal myocardial infarction was 17% in the gemfibrozil group and 22% in the placebo group (relative risk reduction, 22%). The beneficial effect of gemfibrozil did not become apparent until 2 years after randomization.

Combination therapy using a statin to lower LDL cholesterol levels and niacin to raise HDL cholesterol levels has been shown to provide increased cardioprotection. In one study, patients were randomized to one of four groups: simvastatin plus niacin, vitamins, simvastatin-niacin plus antioxidants, or placebos. At entry, the HDL cholesterol level was below 35 mg/dl, and the LDL cholesterol level was below 145 mg/dl. The mean LDL and HDL cholesterol levels were unaltered in the antioxidant and placebo groups but were changed significantly in the simvastatin plus niacin groups (mean LDL cholesterol level reduced by 42% and mean HDL cholesterol level raised by 26%). At 3 years, the reduction of clinical events in the simvastatin and niacin groups was greater than that which is usually reported in studies of statins alone (relative risk, 0.1 to 0.4 compared with placebo), suggesting that a benefit may be associated with the elevation of HDL cholesterol levels. The antioxidants provided no additional benefit and may even have attenuated the benefits of combination therapy (383).

Risk Stratification:

CAD risk factors seldom occur in isolation, and the risk associated with each varies widely in combination with other risk factors. The variability in risk prompted the NCEP ATP III to standardize guidelines for risk assessment of CAD. Over time, the guidelines were revised to recommend more aggressive lipid-lowering targets as a means of reducing CAD risk. This evolution in guidelines is the result of consistently emerging data that extend our understanding of dyslipidemia, associated risk factors and their relationship to CAD, and the utility of new therapeutic options.
The ATP guidelines focus primarily on LDL cholesterol levels as the major lipid risk factor. More recently, low HDL levels have become a factor in risk assessment. In ATPIII, the metabolic syndrome was added as a risk factor in an attempt to assess risk for CAD in centrally obese patients who have modest elevations in triglyceride levels, low HDL cholesterol levels, and small, dense LDL particles, as well as type 2 diabetes mellitus or FCHL. In an effort to better identify those at highest risk for CAD events, the NCEP recognizes several CAD equivalents. They include diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease and multiple risk factors that confer a 10-year risk of CAD greater than 20% (322). The presence of these CAD equivalents requires a level of therapeutic aggressiveness equal to that recommended for patients with established CAD.

The American College of Physicians (ACP) has adopted a somewhat less aggressive recommendation for treatment of individuals with type 1 diabetes mellitus. The ACP reserves the use of statins for patients with type 2 diabetes and other CAD risk factors (384). The ATPIII guidelines do not differentiate between the risk of CAD in patients with type 1 diabetes and that in patients with type 2 diabetes. An argument can be made that the CAD risk is greater in type 2 diabetes and that treatment guidelines should differentiate between these entities.

The ATPIII guidelines use the Framingham scoring system for estimating the 10-year risk of CAD. Some studies indicate that the Framingham score overestimates risk in Japanese-American and Hispanic men, Native-American women, and some European and Asian populations (385-387). It also has been suggested that the Framingham score weights age too heavily as a risk factor. The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study, which is the only prospective study to assess statin therapy in men and women older than 70 years, demonstrated that statin therapy was of no benefit in those without preexisting atherosclerosis (388). Any age bias present in the Framingham scoring system is eliminated when the system is used to predict risk in nonelderly patients.

A multicenter, international study confirmed the validity of risk stratification. In this study of over 15,000 patients with acute MI from 52 countries, over 90% of the
population-attributable risk could be accounted for by nine potentially modifiable risk factors (9389). Most of the risk is accounted for by an elevated apo B to apo A1 ratio, smoking, hypertension and diabetes. These risk factors were more important in younger than in older individuals. As such, principles of cardiovascular disease prevention are similar worldwide and have the potential to have a major impact.

Drug Therapy in Dyslipidemia:

Drugs Used to Lower LDL Cholesterol Levels:

Several classes of drugs lead to a reduction in LDL cholesterol levels [see table 4] (323). Before the introduction of statins in the mid-1980s, the major drugs used for this purpose were the bile-acid sequestrants and niacin. The introduction of statins, with their powerful effects on LDL cholesterol, their tolerability, and their relative lack of toxicity, provided a significant advance in the management of patients with hypercholesterolemia. The introduction of intestinally active drugs has provided additional approaches both for monotherapy—especially for individuals who are unable to tolerate statins—and, more particularly, for combination therapy.

Statins:

Several statins are now available, and new ones continue to be introduced. To date, statins have been highly effective in clinical trials in reducing clinical events, including stroke. Although some of the benefits of statins have been attributed to the so-called pleotropic effects of this class of drugs, the extent of reduction in LDL cholesterol levels nonetheless appears to be the major determinant of risk reduction.

Intestinally active compounds:

Bile-acid sequestrants were among the earliest drugs to become available for the treatment of hypercholesterolemia, and they were the first class of drugs to demonstrate that the reduction of LDL cholesterol was associated with reduced risk of CAD; however, their use was limited by their very poor tolerability and their modest effect in reducing LDL cholesterol. Moreover, triglyceride levels tend to increase with their use in patients with high baseline plasma triglyceride levels. The introduction of a more tolerable bile-
acid sequestrant, colesevelam, resulted in improved compliance with this class of drugs, especially when used in combination therapy in patients with very high LDL cholesterol levels (e.g., for patients with FH).

Unlike bile-acid sequestrants, the intestinally active drug ezetimibe directly inhibits cholesterol absorption. Although clinical data are limited, it appears ezetimibe is able to reduce LDL cholesterol by approximately 20%, whether used as monotherapy or in combination with other lipid-lowering agents (390). In addition, ezetimibe does not cause an increase in plasma triglyceride levels, as occurs with bile-acid sequestrants. Ezetimibe has not yet been reported in clinical trials with cardiovascular end points.

Drugs Used Primarily to Lower Triglyceride Levels:

The preferred drugs for treatment of hypertriglyceridemia are the fibrates and niacin. Niacin is the best drug currently available for raising HDL cholesterol levels. It also produces modest reductions in LDL and reduces apo B levels, but because it worsens insulin sensitivity, its use in patients with type 2 diabetes mellitus is limited. Fibrates are the drugs of choice for patients with marked hypertriglyceridemia, for whom the primary goal of therapy is the prevention of pancreatitis and other features of the chylomicronemia syndrome. They also are of use in hypertriglyceridemic states (e.g., the familial forms of hypertriglyceridemia and in some patients with diabetic dyslipidemia), especially when triglyceride levels are more than mildly elevated. Fibrates also have a modestly beneficial effect on HDL cholesterol levels. Both fibrates and niacin are useful in combination therapy, primarily with statins.

Omega-3 fatty acids (e.g., those found in marine oils) have been used for the treatment of hypertriglyceridemia, especially when other modalities of therapy have failed to reduce markedly elevated levels of triglycerides.

Combination Therapy:
Combinations of drugs often need to be used when both LDL cholesterol and triglyceride levels are elevated. Combination therapy also is of use when monotherapy, especially with statins, fails in achieving target lipid and lipoprotein levels, especially LDL cholesterol levels. Commonly used combinations include statins and fibrates—although little is known of their additive benefit in reducing clinical events—and statins and niacin. Statins and bile-acid sequestrants also are a useful combination, and the use of the new cholesterol absorption inhibitors with other classes of drugs, particularly statins, is likely to be of value. In some cases, triple therapy (e.g., statins, niacin, and an intestinally active agent) is required.

Special Issues in the Management of Dyslipidemia:

Screening for Hypercholesterolemia in Children:

Numerous autopsy studies demonstrate that coronary atherosclerosis begins in childhood and adolescence and that lipoprotein levels are consistently associated with the extent of such atherosclerosis. Children in families with FH and early CAD have higher cholesterol levels, and childhood cholesterol levels are significant predictors of adult levels. However, a significant proportion of children and adolescents who have mildly elevated cholesterol level will not as adults develop cholesterol levels high enough to warrant intervention; screening all children for high cholesterol would risk labeling many young people as diseased. All children older than 2 years would benefit from a diet that is low in saturated fat; this goal should be a part of any population strategy for controlling epidemic atherosclerosis. However, the safety and efficacy of long-term drug therapy have not been established in this age group, and treatment must be approached cautiously.

Considering these and other issues, the recommendations of the NCEP's Expert Panel on Blood Cholesterol Levels in Children and Adolescents seem appropriate (391). Physicians should advise patients younger than 55 years who have a known CAD or a
lipid disorder that their children or grandchildren should undergo regular cholesterol testing, and patients with a genetically well-defined lipid disorder should obtain appropriate genetic counseling. Physicians who care for patients younger than 20 years who have markedly elevated LDL levels should exhaust all lifestyle interventions before considering medications. If such measures are ineffective, resins should be used, and referral to a specialty clinic should be considered.

Treatment of young adults with elevated cholesterol levels is controversial. The strategy of matching the intensity of intervention with the level of risk of atherosclerosis has been proposed, but for young adults, a short-term (e.g., 10-year) risk assessment may be inadequate for estimating the potential benefit of cholesterol lowering. It is incorrect to argue that all treatment can be safely deferred to later life or until the occurrence of an atherosclerotic event. Population-level prevention and lifestyle interventions should still be favored for young adults, but advances in technology that better enable the identification of asymptomatic patients (of any age) who should take steps to reduce risk are greatly needed. Such advances may make it possible to reliably identify or quantify vulnerable plaques; markers of inflammation; or noninvasive measurements of endothelial dysfunction.

Managing Dyslipidemia in Women:

Before menopause, women have a lower incidence of CAD than men of the same age. Although rare, CAD does occur in premenopausal women, usually in association with multiple genetic and environmental risk factors, such as in patients with familial forms of dyslipidemia or in diabetic patients who smoke cigarettes.

After menopause, some women develop the metabolic syndrome, characterized by visceral obesity, insulin resistance, hypertension and dyslipidemia (328). There is some evidence that estrogen replacement therapy can reverse these findings. However, the Women's Health Initiative Study demonstrated that combined oral estrogen and progesterone did not protect women from CAD and that it in fact had adverse effects (392). The estrogen-alone component of the Women's Health Initiative Study indicated
Managing Dyslipidemia in Older Patients:

Age is the most significant risk factor for the development of atherosclerosis. CAD is currently a major cause of disability and mortality in older populations; however, the relative risk associated with any single coronary risk factor decreases with age because of the comorbid conditions and noncardiovascular mortality that affect an aging population. One implication of the complex relationships between risk factors and comorbid conditions in the pathogenesis of coronary-related events in the elderly is represented by the multiple effects of treatment of single risk factors, such as the decrease in LDL cholesterol levels and inflammation markers yielded by statins. A growing body of evidence from clinical trials indicates that statin therapy is effective in the elderly; lipid-lowering therapy is probably indicated in this population in persons who are at high risk for atherosclerosis or who have preexisting atherosclerosis (380, 388). Primary intervention with drug therapy in persons not at high atherosclerotic risk is controversial. In the PROSPER trial of persons older than 70 years, no benefit was seen with statin therapy in those who did not have preexisting clinical atherosclerosis. Indeed, there was a suggestion of increased gastrointestinal cancer with statin therapy in these elderly patients (388). Attention to other concomitant diseases and the nutritional state, as well as to capabilities of the elderly, are important considerations in the management of older patients with dyslipidemia (393).

Role of essential fatty acids in Dyslipidemia:

Plant-derived alpha-linolenic acid has been studied in a limited number of investigations. So far, some epidemiologic and a few mechanistic studies suggest a potential of protection from cardiovascular disease, but this potential remains to be proven in intervention studies. In contrast, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are prevalent in fish and fish oils, have been studied in thousands of investigations. A consistent body of evidence has been elaborated in various types of investigations, ultimately demonstrating reduction in total mortality, cardiovascular
mortality, and morbidity by ingestion of roughly 1 g/d of EPA plus DHA. Current guidelines, however, do not discern between the omega-3 fatty acids mentioned; in fact, most even do not differentiate polyunsaturated fatty acids at all. Unfortunately, this complicates efficient implementation of an effective means of prophylaxis of atherosclerosis (394).

Hyperlipoproteinemia is a key factor in development of atherosclerosis, whereas regression of atherosclerosis mostly depends on decreasing the plasma level of total and LDL-cholesterol. Many studies have reported the hypocholesterolemic effect of linolenic acid.

**TYPES OF POLYUNSATURATED FATTY ACIDS (PUFA):** Linoleic and alpha-linolenic acids are essential fatty acids. The main sources of linoleic acid are vegetable seeds and of alpha-linolenic acid-green parts of plants. alpha-linolenic acid is converted to eicosapentaenoic and docosahexaenoic acid. Linoleic acid is converted into arachidonic acid competing with eicosapentaenoic acid in the starting point for synthesis of eicosanoids, which are strong regulators of cell functions and as such, very important in physiology and pathophysiology of cardiovascular system. Eicosanoids derived from eicosapentaneoic acid have different biological properties in regard to those derived from arachidonic acid, i.e. their global effects result in decreased vasoconstriction, platelet aggregation and leukocyte toxicity.

**ROLE AND SIGNIFICANT OF PUFA:**

The n-6 to n-3 ratio of polyunsaturated fatty acids in the food is very important, and an optimal ratio 4 to 1 in diet is a major issue. Traditional western diets present absolute or relative deficiency of n-3 polyunsaturated fatty acids, and a ratio 15-20 to 1. In our diet fish and fish oil are sources of eicosapentaenoic and docosahexaenoic acid. Refined and processed vegetable oils change the nature of polyunsaturated fatty acids and obtained derivates have atherogenic properties (395).

When considering dietary fat quantity, there are two main factors to consider, impact on body weight and plasma lipoprotein profiles. Data supporting a major role of dietary fat quantity in determining body weight are weak and may be confounded by differences in
energy density, dietary fiber, and dietary protein. With respect to plasma lipoprotein profiles, relatively consistent evidence indicates that under isoweight conditions, decreasing the total fat content of the diet causes an increase in triglyceride and decrease in high-density lipoprotein (HDL) cholesterol levels. When considering dietary fat quality, current evidence suggests that saturated fatty acids tend to increase low-density lipoprotein (LDL) cholesterol levels, whereas monounsaturated and polyunsaturated fatty acids tend to decrease LDL cholesterol levels. Long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:6n-3), are associated with decreased triglyceride levels in hypertriglyceridemic patients and decreased risk of developing coronary heart disease (CHD). Dietary trans-fatty acids are associated with increased LDL cholesterol levels (396). Hence, a diet low in saturated and trans-fatty acids, with adequate amounts of monounsaturated and polyunsaturated fatty acids, especially long-chain omega-3 fatty acids, would be recommended to reduce the risk of developing CHD. Additionally, the current data suggest it is necessary to go beyond dietary fat, regardless of whether the emphasis is on quantity or quality, and consider lifestyle. This would include encouraging abstinence from smoking, habitual physical activity, avoidance of weight gain with age, and responsible limited alcohol intake (one drink for females and two drinks for males per day).

It has long been recognized from epidemiological studies that Greenland Eskimos have substantially reduced rates of acute myocardial infarction (MI) compared with Western controls. From these epidemiological observations, the benefits of fatty fish consumption have been explored in cell culture and animal studies, as well as randomized controlled trials investigating the cardioprotective effects of omega-3 fatty acids. Dietary omega-3 fatty acids seem to stabilize the myocardium electrically, resulting in reduced susceptibility to ventricular arrhythmias, thereby reducing the risk of sudden death. These fatty acids also have potent anti-inflammatory effects, and may also be antithrombotic and anti-atherogenic. Furthermore, the recent GISSI-Prevention study of 11 324 patients showed a marked decrease in risk of sudden cardiac death as well as a reduction in all-cause mortality in the group taking a highly purified form of omega-3 fatty acids, despite the use of other secondary prevention drugs, including beta-blockers and lipid-lowering
therapy. The use of omega-3 fatty acids should be considered as part of a comprehensive secondary prevention strategy post-myocardial infarction.

Disorder of blood lipids plays an important role in atherosclerosis progress in patients ongoing chronic haemodialysis (PCHD). These patients have specific features of blood lipids with increment of triglycerides and decrement of HDL-cholesterol. Phenotype of lipid disorder in PCHD is mostly type IV according to Fredrickson (30%), and IIA and IIB phenotypes are less frequent. About 9% of lipid disorders in PCHD are isolated increase of Lp(a). Main reason of hypertriglyceridemia in PCHD is attenuated metabolism of VLDL-cholesterol because of lipoprotein lipasis inhibition. There are changes in lipoproteins quality, specially changes in LDL particle have atherogenic potential. Renal dyslipidemia treatment must be vigorous in the early stages of renal insufficiency. Treatment can be dietary measures (specially omega-3-fatty acids), statins, gemfibrozil, intravenous L-carnitin and bicarbonate given per os. Haemodialysis modifications such as highflux haemodialysis, low molecular weight heparin, vitamin E coated dialyzers and LDL-apheresis in extreme cases have important role in renal dyslipidemia treatment (397).

Of all known dietary factors, long-chain omega-3 fatty acids may be the most protective against death from coronary heart disease. New evidence has confirmed and refined the cardioprotective role of these fatty acids. RECENT FINDINGS: Omega-3 fatty acid supplementation reduces the risk of sudden cardiac death and death from any cause within 4 months in post-myocardial infarction patients. Evidence continues to accrue for benefits in the primary prevention of coronary heart disease and stroke, and an anti-arrhythmogenic mechanism is emerging as the most likely explanation. Current evidence suggests that individuals with coronary artery disease may reduce their risk of sudden cardiac death by increasing their intake of long-chain omega-3 fatty acids by approximately 1 g per day (398).

Fatty acids are an important source of energy which can have an influence on serum lipids. Omega-3 and omega-6 fatty acids, both polyunsaturated fatty acids, have been advocated as replacement for saturated fat. Omega-3 fatty acids, derived from fish and certain green plants, lower serum triglycerides, but they have also been shown to have a
direct effect on myocardial contractility, blood pressure, platelet function, coagulation factors, cell-mediated immunity and markers of inflammation. Recently available clinical trial data, including those using the concentrated omega-3 fatty acid preparation Omacor, indicate that omega-3 fatty acids are valuable in preventing sudden death following myocardial infarction. Studies indicate that omega-3 fatty acids are just as effective as, or have a benefit superior to, statins in secondary prevention. Omacor is also useful in the treatment of hypertriglyceridaemia, both as monotherapy and in combination with statins (399).

For many years, clinical and animal studies on polyunsaturated n-3 fatty acids (PUFAs), especially those from marine oil, eicosapentaenoic acid (20:5, n-3) and docosahexaenoic acid (22:6, n-3), have reported the impact of their beneficial effects on both health and diseases. Among other things, they regulate lipid levels, cardiovascular and immune functions as well as insulin action. Polyunsaturated fatty acids are vital components of the phospholipids of membrane cells and serve as important mediators of the nuclear events governing the specific gene expression involved in lipid and glucose metabolism and adipogenesis. Besides, dietary n-3 PUFAs seem to play an important protecting role against the adverse symptoms of the Plurimetabolic syndrome. This review highlights some recent advances in the understanding of metabolic and molecular mechanisms concerning the effect of dietary PUFAs (fish oil) and focuses on the prevention and/or improvement of dyslipidemia, insulin resistance, impaired glucose homeostasis, diabetes and obesity in experimental animal models, with some extension to humans(400).

Essential polyunsaturated fatty acids (PUFAs), linoleic acid n6 (LA) and linolenic acid (ALA) n3 obtained from the diet are precursors of the long-chain polyunsaturated fatty acids (Lc-PUFAs) arachidonic acid (AA) and docosahexaenoic acid (DHA) respectively. Consumption of PUFAs is related with a better neurological and cognitive development in newborns. It has been demonstrated that consumption of n-6 and n-3 PUFAs decreases blood triglycerides by increasing fatty acid oxidation through activation of PPARalpha or by reducing the activation of SREBP-1 inhibiting lipogenesis. Dietary PUFAs activate PPARalpha and PPARgamma increasing lipid oxidation, and decreasing insulin resistance leading in a reduction of hepatic steatosis. Beneficial effects of PUFAs have been observed in humans and in animals models of diabetes, obesity, cancer, and
cardiovascular diseases. It is important to promote the consumption of PUFAs. Main food sources of PUFAs n-6 are corn, soy and safflower oil, and for PUFAs n-3 are fish, soy, canola oil and, flaxseed. Finally FAO/WHO recommends an optimal daily intake of n6/n3 of 5-10:1 (401).

Dietary triglycerides containing predominately poly-unsaturated fatty acids (PUFAs) are known to reduce plasma total and low density lipoprotein (LDL) cholesterol concentrations relative to triglycerides containing predominately saturated fatty acids(402).
Flax seed oil
Flax as an ancient crop:

Flax has been grown since the beginnings of civilization, and people all over the world have celebrated its usefulness throughout the ages. Cultivated flax, *L. usitatissimum*, is of two types: one is grown for the seed and the other for fibre production. In North America, it is primarily the oilseed varieties, which are produced commercially. Records show that the human race has eaten this seed since early times.

About 3,000 B.C. Flax is cultivated in Babylon. Burial chambers depict flax cultivation and clothing from flax fibers.

About 650 B.C. Hippocrates writes about using flax for the relief of abdominal pains. In the same era, Theophrastus recommends the use of flax mucilage as a cough remedy.

About 1st Century A.D. Tacitus praises the virtues of flax.

About 8th Century A.D. Charlemagne considered flax so important for the health of his subjects that he passed laws and regulations requiring its consumption.

About 15th Century A.D. Hildegard von Bingen used flax meal in hot compresses for the treatment of both external and internal ailments

Chemistry: -

LA is an n-6 FA, cis-configuration containing 18 carbon atoms and two double bonds. LA is designated as 18:2n-6. On the other hand, ALA is an n-3 FA, all-cis polyunsaturated fatty acid containing 18 carbon atoms and three double bonds. It is designated as 18:3n-3.

Pharmacokinetic: -

LA and ALA-laden triglycerides are absorbed from the small intestine aided by bile salts. During this process, there is some deacylation of the fatty acids of the triglycerides. Reacylation takes place within the mucosal cells of the small intestine, and the LA and ALA-laden triglycerides enter the lymph system in the form of chylomicrons. LA and ALA-laden chylomicrons are transported from the lymph into the blood, where LA and ALA is then carried in various lipid particles to the various cells of the body.

LA and ALA then metabolically undergoing desaturation and elongation converted to arachidonic acid (AA), and EPA and DHA respectively. AA; & EPA, DHA are the
respective long-chain derivatives of LA and ALA respectively. In tissues further metabolism of the AA; and EPA, DHA. Supplementation of n-3 fatty acids can decrease the formation of interconversion products from n-6 fatty acids and vice versa.

A large metabolic fate of the n-6 and n-3 fatty acids is their metabolism in tissues by cyclooxygenases and lipooxygenasein pathway to biologically active products of great physiological and therapeutic significance.

**Mechanism of action:**
Unlike many other pharmacological agents, which have one or few well-defined mechanisms of action, the activity of N-6 and n-6 PUFAs is multifaceted. The hypolipidemic effect of n-6 and n-3 fatty acids may result from a combination of inhibition of intestinal cholesterol absorption, altered cholesterol biotransformation, modification of the clearance of lipoproteins from circulation, and possibly a stimulatory effect on hepatic bile secretion.

Prevention of rapid intracellular calcium accumulation following ischemia and electrophysiological stabilization of myocardial cells, modulation of other cellular second messengers and facilitation of recovery of mitochondrial energy metabolism (are some of the effects which underline the cardioprotective role of n-3 fatty acids. Although multiple mechanisms have been proposed, none has been fully validated. The sequence of effects is also not clear.

Arachidonic acid-derived eicosanoids are proinflammatory and regulated the function of immune system cells. ALA-derived EPA and DHA, following incorporation into cellular membrane lipids, compete with AA for metabolism by the cyclooxygenase and lipooxygenase pathways. This leads to a variety of anti-inflammatory and immunomodulatory effects documented in various in vitro, ex vivo and in vivo studies. There may be inhibition of neutrophil chemotaxis and adherence to vessel wall, reduce lymphocyte activation and expression of adhesion molecules reduce expression of interleukin-2 (IL-2) receptors on lymphocytes and curtailed production of pro-inflammatory cytokines like prostaglandin-E2 (PGE-2), thromboxane-B2 (TxB-2), leukotrine B-4 (LTB-4), IL-2, IL-6, tumor necrosis factor-α (TNF-α), and platelet-activating factor (PAF). The modulation of signal transduction and/or gene expression within inflammatory and immune cells may also contribute to these effects. However, not
all studies have been positive with respect to the anti-inflammatory or immuno-regulatory activity of PUFAs. There may well be other mechanisms of action.

**Doses:** Doses recommendation for n-6 and n-3 PUFAs is difficult. The Eskimo diet is estimated to contain 5.4 gm of n-3 fatty acids per day (*The extra pharmacopeia, 1996*), but this level of dietary intake is unlikely in other communities. Hence the question of pharmacological supplementation arises and such supplementation may be acceptable even to subjects who cannot take fish because of cultural or other reasons.

Clinical trials have been conducted with a wide variety of preparations (from animal as well as plat sources) and a range of doses. Doses have also varied with indications. In general however, studies that have explored dose-dependence indicate that a dose 2 gm daily in divided form is the minimum necessary for desirable changes in lipid profile. A few studies have reported beneficial effects even at lower doses than this. Higher doses may have more pronounced effects but may also increase LDL-cholesterol, causes excessive oxidative stress and may be associated with a higher incidence of gastrointestinal adverse drug reactions, limiting patient compliance.

Administration of LA and ALA with food helps to reduce nausea and eructations. To optimize clinical benefits, appropriate dietary modifications should be encouraged concurrently with the use of EFAs.

**INDICATIONS AND USAGE**
Flaxseed and flaxseed oil may be indicated in hyperlipidemia, to decrease platelet aggregation, to lower blood pressure, to help prevent heart attacks and stroke, and to ameliorate some of the symptoms of arthritis. There is a suggestion that it may be helpful in some cancers. Claims that it can be useful in the treatment of anxiety, benign prostatic hyperplasia, constipation, vaginitis and weight loss are unsubstantiated.

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**
Women who are pregnant should not use supplemental flaxseed oil or flaxseed because of the theoretical possibility that these lignan-containing substances might induce menstruation.
PRECAUTIONS
Infants, young children and nursing mothers should avoid supplemental flaxseed oil. Because of possible antithrombotic activity, those with hemophilia and those taking warfarin should be cautious about the use of supplemental flaxseed oil or flaxseed. Flaxseed oil intake should be halted in those having surgical procedures.

ADVERSE REACTIONS
Flaxseed oil may cause mild gastrointestinal symptoms, such as diarrhea.

INTERACTIONS

DRUGS
Interactions may occur between flaxseed oil-ALA and its metabolites and warfarin, aspirin and NSAIDs. Such interactions, if they were to occur, might be manifested by nosebleeds and increased susceptibility to bruising. If this does occur, consideration should be given to lowering or stopping intake.