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FOREWORD

The American public has been made widely conscious that saturated fat and cholesterol may have something to do with mortality rates from heart disease.

Dietary fat has economic as well as nutritional and medical importance. Much emphasis has been placed upon the possible ill effects of excess fat per se, or of excess intake of certain types of fat. Some investigations have implicated dietary fats or faulty fat metabolism as factors in elevated concentration of cholesterol and other lipids in blood plasma and in the development of atherosclerosis and its complications, and have suggested that the American people should reduce their consumption of fat, particularly the proportion of saturated fat. Such changes in fat consumption alter the relative distribution of the other major food components—carbohydrate and protein—within the diet and can be justified only on sound evidence that the net results are likely to be beneficial to the population as a whole.

Fats are valuable food substances in their own right, and are usually by-products of protein resources and, to a large extent, determine the economy of protein production. Agriculture and the fat-processing industries are looking to nutrition scientists, biochemists, and physicians for the answer to the question, "How much and what kind of fat is compatible with human health?" Agriculture and the food industry can adapt their production to the best interests of the public if they know what those interests are.

A report, The Role of Dietary Fat in Human Health, was first published in 1958 by the Food and Nutrition Board as NAS-NRC Publication 575, based on a report submitted by a Committee on Fats established in 1956. A new committee was appointed in 1961 to consider revision of Publication 575 in the light of new information on blood lipids, tissue fats, and changes in dietary patterns. The report was reprinted with minor changes in 1962 and a new revision is issued herewith. The committee comprised Drs. C. S. Davidson, Chairman, E. H. Ahrens, Jr., D. S. Fredrickson, W. S. Hartroft, R. T. Holman, C. S. Lieber,

J. F. Mead, O. N. Miller, and T. B. Van Itallie. Dr. Fred Mattson and Dr. M. K. Horwitt aided the committee.

The Board is grateful for the committee's efforts in a very difficult assignment.

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CONTENTS

FAT IN THE NATIONAL DIET

The diet of the American consumer is varied, and in most households, according to our present knowledge, it is nutritionally sound (56, 192). The increases in dietary levels of some of the nutrients in food-consumption surveys conducted between 1936 and 1955 were achieved in part by a greater consumption of meat and milk.

According to the 1955 survey, fat accounted for 44 percent of the calories in the food that families used. In 1948, it accounted for 42 percent, and in 1936, 38 percent of the calories. Adjustment for discarded food would cause a decrease of perhaps 1 or 2 percent. Thus, in this 20-year period, a trend toward a higher proportion of the calorie intake as fat was evident (192).

About 40 percent of the fat in the American diet comes from fats purchased as such—margarine, shortening, salad and cooking oils, and butter—and much of this is consumed as ingredients of bakery products and other foods. About 60 percent of the fat in the American diet is supplied by such foods as meats (35 percent), dairy products excluding butter (15 percent), and nuts and cereals (10 percent) (191).

The extent to which fat contributes to the caloric value of selected foods is shown by the following approximations. In whole milk, fat contributes about 50 percent of the calories; in cheddar cheese, 70 percent; and in eggs, 65 percent. Fat accounts for 65 percent of the calories in broiled hamburger, 80 percent in cooked frankfurters, 40 percent in canned pink salmon, and 30 percent in chipped beef. In a rib roast of beef, fat furnishes over 82 percent of the calories when both lean and fat are eaten but only 50 percent when the separable fat is discarded.

In 1963, the total fat of foods marketed in the United States provided 145 grams of fat per person per day (190). Of this total, saturated fatty acids accounted for 37 percent, oleic acid for 40 percent, and linoleic acid for 12 percent. For 30 years, there has been practically no change in the quantity of saturated fatty acids in marketed foods, but the polyunsaturated fatty acid content has increased. The ratio of polyunsaturated (linoleic) to

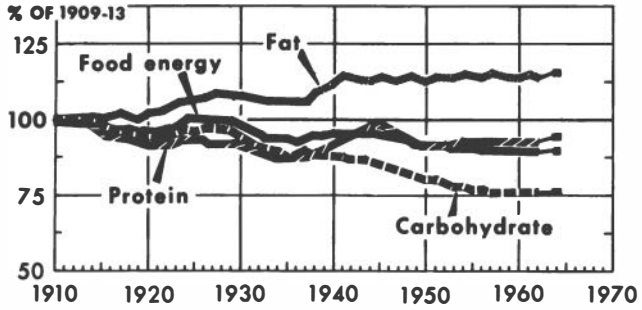

Figure 1. Trends in per capita civilian consumption of basic food nutrients. Data for 1964 shown by end points. (5-year moving average.)

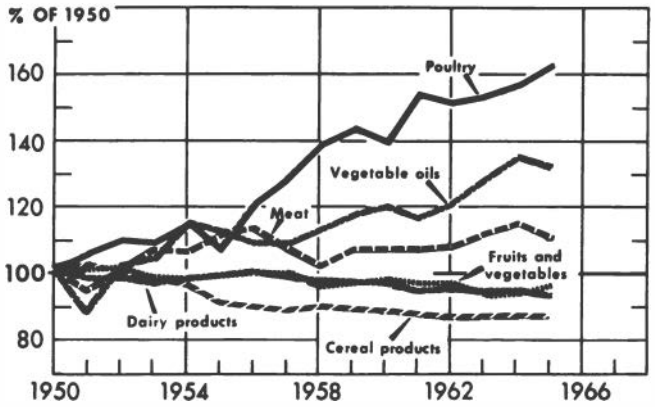

Figure 2. Trends in per capita food consumption of selected foodstuffs combined in terms of constant retail prices. Preliminary data for 1965 shown by end points. (Data on fruits and vegetables exclude melons, soup, and baby foods.)

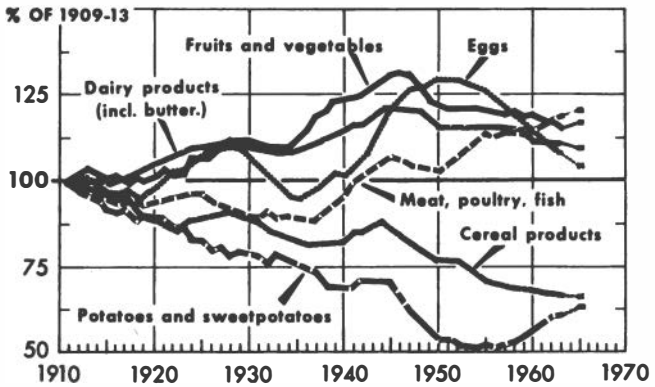

Figure 3. Trends in per capita civilian consumption of selected foodstuffs, using constant retail prices as index weights. Data for 1965 shown by end points. (5-year moving averages centered.)

Figures 1, 2, and 3 from U.S. Department of Agriculture

saturated fatty acids has progressively increased from 0.23 in 1936 to 0.33 in 1963. Increased use of salad and cooking oils—notably soybean, corn, and cottonseed oils—and of poultry has contributed to the increase in linoleic acid (191).

Some indication of the trends in food consumption in the United States is shown in Figures 1, 2, and 3.

CHEMISTRY OF FOOD FATS

Most separated natural fats are made up of about 98 to 99 percent triglycerides, of which 92 to 95 percent is fatty acid and the remainder glycerol. The remaining 1 or 2 percent of separated natural fats includes traces of monoglycerides, diglycerides, free fatty acids, phospholipids, and unsaponifiable matter containing sterols.

Fatty Acid and Glyceride Structures

Most fats are mixtures of triglycerides containing four or five major fatty acids and many more minor, or trace, constituents. In butterfat, at least 60 different fatty acids have been identified. The individual glyceride molecules in most food fats contain both saturated and unsaturated fatty acids. Fully saturated glycerides are a rarity in natural fats, appearing in only a few, such as beef tallow and coconut oil. Thus "saturated" and "unsaturated" are not truly definitive terms when applied to food fats.

In foods for human consumption, myristic, palmitic, and stearic acids are the most abundant of the saturated fatty acids. Of the unsaturated acids, oleic acid with one double bond is the most abundant, and of the polyunsaturated acids, linoleic acid is the most abundant and constitutes a high percentage of the commonly used vegetable oils. Several of the polyunsaturated acids cannot be synthesized in the animal body and must be provided in the diet. These have been termed "essential fatty acids" and are mainly represented by linoleic acid. Linolenic acid, which may partially relieve some of the evidence of essential fatty acid deficiency in experimental animals but which is not an essential fatty acid in the strict sense, occurs in several seed fats, such as linseed and soybean oils. Arachidonic acid does not occur in vegetable oils in appreciable amounts, but is synthesized from linoleic acid in the animal body and comprises about 1 percent of most animal fats. In the naturally occurring polyunsaturated fatty acids, the double bonds are not conjugated (contiguous), but

are almost always separated by a methylene group. In addition, the configuration is of the cis type in which the hydrogens are on the same side of the chain and a 120° bend is introduced into the chain itself. Fatty acids containing trans bonds, in which the hydrogens are on opposite sides, are found in small amounts in natural fats and in greater amounts after processing involving catalytic hydrogenation (98).

Fatty Acid Composition of Fats

The fatty acid composition of common food fats is extremely variable (Table 1). The unqualified terms "animal fat" and "vegetable fat" do not indicate fatty acid composition or nutritional value. Cow's milk, in contrast to human milk, contains appreciable quantities of fatty acids with fewer than ten carbon atoms (55). The linoleic acid content of human milk fat is usually considerably higher than that of butterfat.

Many animal fats, such as beef and mutton tallow, are relatively rich in saturated fatty acids, but some fats of animal origin, such as poultry fat and fish oils (94), have a high degree of unsaturation. The fatty acid composition of nonruminant animal fat is markedly influenced by diet. It has long been known that linoleic acid may vary from a low percentage to as much as one third of the fatty acids in pork fat, depending on the feed of the pig (52).

The fatty acid composition of egg yolk from commercially available eggs is relatively saturated, owing to the low-fat rations used in feeding the laying hen. A considerable shift in fatty acid pattern can be effected, however, by incorporating unsaturated fat in the rations.

Unprocessed vegetable fats are generally liquid at ordinary temperatures because of their high percentage of unsaturated fatty acids. Especially abundant in these fats are oleic and linoleic acids. Oleic acid may make up four fifths of the fatty acid content of olive oil. In corn, peanut, cottonseed, safflower, and soybean oils—used for cooking, salads, margarines, and shortenings—12 to 25 percent of the fatty acids are saturated, wheareas 21 to 53 percent may be linoleic acid. Even among the vegetable fats, however, there are exceptions. Coconut oil is one of the most saturated (about 90 percent) of the food fats.

The intake of essential fatty acids in the American diet is mostly from vegetable sources. Chicken fat and the fats of other

TABLE 1
TYPICAL MAJOR FATTY ACID ANALYSES OF SOME FATS OF ANIMAL AND PLANT ORIGIN[a]

	SATURATED								UNSATURATED					
	4-8	Capric 10.0	Lauric 12.0	Myristic 14.0	Palmitic 16.0	Stearic 18.0	Arachidic 20.0	Behemic 22.0	Palmitoleic 16.1	Oleic 18.1	Linoleic 18.2	Linolenic 18.3	Arachidonic 20.4	Other Polyenoic Acids
ANIMAL														
Lard				1.5	27.0	13.5			3.0	43.5	10.5	0.5		
Chicken			2.0	7.0	25.0	6.0			8.0	36.0	14.0			
Egg					25.0	10.0				50.0	10.0	2.0	3.0	
Beef				3.0	29.0	21.0	0.5		3.0	41.0	2.0	0.5	0.5	
Butter	5.5	3.0	3.5	12.0	28.0	13.0			3.0	28.5	1.0			
Human Milk		1.5	7.0	8.5	21.0	7.0	1.0		2.5	36.0	7.0	1.0	0.5	
Menhaden				9.0	19.0	5.5			16.0					48.5
VEGETABLE														
Corn					12.5	2.5	0.5			29.0	55.0	0.5		
Peanut					11.5	3.0	1.5	2.5		53.0	26.0			
Cottonseed				1.0	26.0	3.0			1.0	17.5	51.5			
Soybean					11.5	4.0				24.5	53.0	7.0		
Olive					13.0	2.5			1.0	74.0	9.0	0.5		
Coconut	7.0	6.0	49.5	19.5	8.5	2.0				6.0	1.5			

[a] Composition is given in weight percentages of the component fatty acids (rounded to nearest 0.5) as determined by gas chromatography. The number of carbon atoms: number of double bonds are indicated under the common name of the fatty acid. These data were derived from a variety of sources. They are representative determinations, rather than averages, and considerable variation is to be expected in individual samples from other sources.

poultry may contain as much as 25 percent linoleic acid, but these fats are not used extensively. Fish oils are rich in polyunsaturated fatty acids but are poor sources of the essential fatty acids, arachidonic and linoleic acids being minor components (188).

Monoglycerides and Diglycerides

In addition to the triglycerides, glycerol esters of the fatty acids in which one or two of the hydroxyl groups remain unesterified may be encountered in food fats. Trace amounts on the mono- and diglycerides and of free fatty acids are present in natural fats. Within the body, these lipids are found during digestion and absorption (2) and are present in the circulating lipids of the plasma (31). The fat used to provide the physical character desired in shortening for such baked goods as cakes may contain 5 to 20 percent of added mono- and diglycerides.

Phospholipids

Phospholipids form a group of complex lipids having in common in their molecules a phosphate radical, an esterified fatty acid, and usually a nitrogenous base. Lecithin, or phosphatidyl choline, is the most widely distributed of the phospholipids. Raw vegetable oils, such as corn oil, contain traces of lecithin, and many animal lipids, notably egg yolk and liver (but not depot fats), are rich in this phospholipid.

Assessing the role of food phospholipids in human health is complicated because of the diverse chemical nature of this group of lipids. The complex mixture of the phospholipids in common food products is illustrated by the phospholipids of egg yolk. A typical analysis of egg yolk reveals 72.8 moles percent phosphatidyl choline, 14.8 phosphatidyl ethanolamine, 5.8 sphingomyelin, 2.1 lysophosphatidyl ethanolamine, and 0.9 mole percent plasmalogen, 0.6 inositol phospholipid, and 0.2 phosphatidyl amino acids (170). Phospholipid is one third of the lipid of egg yolk; one egg contributes approximately 2 gm of phospholipid to the diet.

Invisible fat of both plant and animal tissues contains appreciable amounts of phospholipid, but the visible separated fats are generally poor in these lipids, except when lecithin has been deliberately added to take advantage of its emulsifying and

antioxidant properties. The amount of phospholipid associated with the glycerides of seeds is usually small, and expression, purification, and refining of the oil remove most of this amount. In animal tissues, important amounts of phospholipid are found in liver and other edible parts, but the phospholipid concentration in most adipose tissues is low. In the preparation of separated fat, such as lard or butter, much of the phospholipid is removed. Unsaponifiable constituents also are decreased during preparation of visible fats.

Unsaponifiable Constituents

The small amount of unsaponifiable matter in food fats consists of sterols, fatty alcohols, hydrocarbons, pigments, glycerol ethers, and various other compounds. One of the principal differences between animal and vegetable fats is the nature of the sterols present. Cholesterol, found almost exclusively in animal tissue, differs from phytosterols (plant sterols) in that phytosterols have more highly branched side chains and may have a second double bond in the nucleus. Cholesterol occurs in all animal fats. It is a normal constituent of every animal tissue and a major component of brain and nerve tissues. Whole eggs contain about 0.5 percent cholesterol on a fresh weight basis (all in yolks). Butter, organ meats, and shellfish contain between 0.2 and 0.3 percent, and meats and animal fat contain less than 0.1 percent cholesterol.

Hydrogenation

The process of hydrogenation converts oils from a liquid to a plastic state, a property necessary for margarines and shortenings. The process also imparts increased stability. This is of particular importance for soybean oil in which the presence of up to 10 percent linolenic acid renders it very susceptible to oxidation. Hydrogenation reduces linolenic acid to a level at which oxidative rancidity is not a problem.

If hydrogenation were complete, a fully saturated hard fat of simple composition would result. Such a fat would be unacceptable as a food item. The partial hydrogenation process that is employed results in four types of chemical change.

1. The main change is a conversion of some of the polyunsaturated fatty acids to monounsaturated fatty acids, as indicated by lowering of the iodine value. The extent of this conversion depends on the hydrogenation conditions selected. The melting point of the fat is raised but, as employed, this process results in the formation of only small amounts of additional saturated fatty acids.

2. The double bond may shift position along the carbon chain, producing isomeric acids. These new unsaturated acids have the same iodine number, but may differ from the original in melting point.

3. The predominantly occurring cis configuration may change to the trans configuration. This isomerization also leaves the iodine number unchanged, but leads to a significant rise in the melting point. For example, oleic acid melts at 13°C and is liquid at room temperatures; its trans isomer melts at 44°C and thus is solid at room temperatures.

4. During hydrogenation of linoleic, linolenic, or arachidonic acids, double bonds may become conjugated, in which system they are no longer separated by a methylene group. These conjugated systems are relatively rare in natural food fats and the amount of conjugated acids found in hydrogenated fats is quite small.

It is apparent that the complexity of the chemical composition of fats is increased by partial hydrogenation. To a great extent, these changes can be controlled by varying the processing conditions.

Trans fatty acids are not, strictly speaking, unnatural. They occur in measurable amounts in the depot fats of ruminants (86), apparently arising through the activity of rumen bacteria. Nevertheless, these trans isomers of unsaturated fatty acids are only minor constituents of natural fats. Summer butterfat may contain 9 or 10 percent trans acids (40), and human milk fat may contain 5 or 6 percent. Amounts of several percent have been reported in human depot fat. In the latter two instances, the trans acids may be derived from the diet.

Margarines and shortenings with a wide range of fatty acid composition and increased levels of polyunsaturated fatty acids have been made available. These fats have a range in unsaturation between those of olive and cottonseed oils, but they are solid. Their higher melting points are due to a slight increase in saturated fatty acids and to the presence of trans acids. The derived

properties of the margarines or shortenings are obtained by the proper blending of partially hydrogenated, lightly hydrogenated, or unhydrogenated oils. Trans acids may account for from 15 to 40 percent of the total. A portion of the polyunsaturated acids escaping hydrogenation are converted to isomeric acids.

Polyunsaturated fatty acids that have undergone any of the four chemical changes resulting from the partial hydrogenation process lose their essential fatty acid activity; indeed, these acids may be preferentially converted to monounsaturated acids by hydrogenation. Whereas highly hydrogenated types of margarines and shortenings are comparable to natural fats of similar firmness as sources of essential fatty acids, the newer products, although indistinguishable as far as appearance is concerned, contain much higher levels of essential acids. All of these types of margarines and shortenings are equally well utilized as energy sources. Trans and positional isomers of the natural fatty acids appear to be metabolized by the body with the same ease as the more common cis forms (146). Neither of the trans isomers of oleic and linoleic acid has essential fatty acid activity. Evidence of interference with the activity of cis linoleic acid is conflicting (96, 140).

Cooking

Common methods of cooking have no appreciable effect on the essential fatty acids in such foods as beef, lamb, poultry, and pork (34). Similarly, the fatty acid makeup of lard (33) is not altered in baked products. Changes have been observed in heated corn oil used in deep fat frying. It is possible that the polyunsaturated fatty acids that make up a high percentage of such oils, under conditions of elevated temperature in the presence of air, can absorb oxygen to form peroxide or polymer products which, in large amounts, may prove to be toxic. However, under the usual conditions of commercial use, such products are not formed in appreciable amounts (44, 145), and the nutritive value, measured by growth rate of animals, is not altered.

Rancid fat has a toxic effect upon rats on a low-fat diet, the toxic agent apparently being peroxidized fatty acids or their esters (160) rather than aldehydes or low polymers.

FAT METABOLISM

A discussion of the changes that the various fat components undergo in the body is pertinent to a consideration of the role of fat in health and disease.

Digestion and Absorption

A small amount of fat-splitting may take place in the stomach, but most of the digestion of food fat is carried on in the intestine through the action of intestinal and pancreatic enzymes and of bile.

The main path of fat digestion progresses from triglycerides to 1,2-diglycerides, to 2-monoglycerides, and finally to free fatty acids and glycerol, perhaps after isomerization to the 1-monoglyceride (159).

During digestion, an exchange of free fatty acids with glyceride fatty acids occurs. Furthermore, some synthesis of triglycerides from the mono- and diglycerides takes place simultaneously with hydrolysis of the fat (2). Thus the earlier stages of fat digestion are reversible processes and modify the makeup of ingested food fat. There is some selectivity in reincorporation of liberated fatty acids into the glyceride molecule in the intestine. For example, butyric acid fed at the same time as long-chain glycerides is not incorporated into the glycerides, whereas longer chain acids are readily interchanged (24).

Thus, in the intestinal lumen, the action of pancreatic lipase on ingested fat results in a complex mixture of tri-, di-, and monoglycerides and fatty acids. In addition, the entry of bile into the duodenum contributes important amounts of bile salts and lecithin, the latter quickly undergoing hydrolysis to lysolecithin. Both of these classes of compounds are essential to solubilization of the lipids in the intestinal contents, which form a two-phase system—an oil phase containing almost all the tri- and diglycerides, and a water-clear micellar solution of monoglycerides, bile salts, lysolecithin, and soaps. All present evidence is consistent with the view that absorption takes place from the

micellar phase into the mucosal lining of the intestine. In this manner, extremely small aggregates of monoglycerides and fatty acids are transferred through the brush border of the intestinal mucosa and are then re-esterified to triglycerides within the mucosal cell. In turn, through further lypolysis, the micellar phase is continually replenished from the oil phase. Thus, it is doubtful that significant amounts of tri- and diglycerides are absorbed as such. The mechanism of absorption of sterols, lysolecithin, and the fat-soluble vitamins remains to be elucidated.

Absorption of fatty acids takes place mainly in the upper small intestine, and the absorbed long-chain fatty acids (with more than 12 carbon atoms), after re-esterification to triglycerides, are transported through the intestinal lymphatics into the thoracic duct, thence into the great veins in the neck in the form of chylomicrons. These chylomicrons appear in the blood stream 3 to 6 hr after a fatty meal. Cholesterol is largely re-esterified in the mucosal cell and is incorporated into the chylomicron along with the triglycerides. By contrast, bile acids and fatty acids of chain length shorter than 12 carbon atoms pass into the portal circulation rather than the intestinal lymphatics; they are transported directly to the liver, probably bound to albumin and to the nonparticulate lipoproteins.

Under normal circumstances, fat absorption is 95 to 100 percent for most food fats. More than 50 percent of dietary cholesterol is absorbed, but the percentage is reduced in the presence of plant sterols.

In addition to absorption of dietary fat, reabsorption of the lipids contributed by the bile takes place. The bile acids recirculate from the portal vein blood through the liver into the bile and intestinal tract and back to the liver several times each day. Cholesterol and lecithin in the bile are also largely reabsorbed. The enterohepatic circulation of bile acids and cholesterol regulates the endogenous synthesis of cholesterol and the conversion of cholesterol to bile acids, exemplifying a negative feedback control system.

Plasma Lipids and Their Transport

The transport of fatty acids through the extracellular fluid is in the range of 200 to 300 gm per day. The bulk of the fatty acids in net transit is in either glycerides or free fatty acids.

The transport of such large quantities of water-insoluble material in the plasma and lymph occurs in complexes stabilized by specific proteins as well as more polar lipids such as phospholipids. The transport systems may be divided into: the albumin-free fatty acid complex; high-density lipoproteins (HDL) or α-lipoproteins; low-density lipoproteins (LDL) or β-lipoproteins; and glyceride-rich lipoproteins or larger aggregates called particles. Glyceride arising endogenously from synthesis in the liver is found in very LDL of α_2 or pre-β electrophoretic mobility. When the glyceride is of exogenous origin it is mainly in particles called chylomicrons (46).

Free Fatty Acids

The free fatty acids make up only a small proportion of the total fatty acids in plasma. Their concentration normally ranges from 0.2 to 0.7 meq per liter. Tightly bound to their albumin carrier, they nevertheless join and leave this carrier easily at cell surfaces. Their plasma turnover is extremely rapid, permitting the equivalent of several thousand calories per day to be transported in this form (58).

Lipoproteins

In the fasting state, most of the plasma lipid is present in the α- and β-lipoproteins. In apparently healthy American adults, this comprises total lipids varying as widely as from 400 to 1,000 mg per 100 ml of plasma that may include 120 to 350 mg of cholesterol, 150 to 380 mg of phospholipid, and 25 to 150 mg of triglyceride (59). Consideration of age and sex is required in evaluating the significance of plasma lipid concentrations, and what is usual cannot be considered necessarily normal. Approximately 45 percent of the fasting plasma fatty acid content is in phospholipids, 35 percent in glycerides, 15 percent, relatively more unsaturated, in cholesterol esters, and 5 percent as free fatty acids.

α-Lipoproteins

In the postabsorptive state, roughly one fourth of the plasma cholesterol by weight and one half of the phospholipids are combined with a specific globulin designated A or α-apolipoprotein. The composition of these resultant macromolecules is fairly constant,

and they have hydrated densities between 1.06 and 1.2. When isolated between these density limits in the ultracentrifuge, they are called HDL. When they are identified or isolated by electrophoresis, these lipoproteins are called α-lipoproteins from their characteristic mobility.

HDL concentrations do not change greatly with age. They are significantly lower in men than in women (29, 67, 100, 130, 157, 173) and in men can be elevated by giving estrogens (51). HDL concentrations have been reported to be low in patients with coronary artery disease (15, 100, 173), but neither predictive value nor an etiologic role in atherosclerosis has been assigned them.

It has recently been reported (128) that α-lipoproteins are not only present as HDL but are also part of the very low-density complexes involved in the transport of endogenous glyceride. It is possible, then, that α-lipoproteins take part in the transport of glyceride but this is not proved. From patients with Tangier disease (61) it is known that severe deficiency of the A apoprotein is associated with marked tissue storage of cholesterol esters, and this protein may have some special function in transporting cholesterol.

β- and Pre-β-lipoproteins

Although the protein in LDL is considered to be homogeneously the B apoprotein, some minor antigenic variations among humans, which are genetically determined, have been suggested (23). From observations of patients with abetalipoproteinemia (174), it appears that when significant amounts of glyceride are synthesized by the liver, there is probably a requirement for the β-lipoprotein (or at least the B apolipoprotein) to mobilize the glyceride from the cells. As already noted, the triglyceride plus B lipoproteins is joined by α-lipoproteins to form "very low density" lipoproteins that have an electrophoretic mobility between the β- and α-lipoproteins (hence, the terms pre-β on paper (127) and α_2-lipoproteins on starch) (120). When the amounts of endogenous glyceride become large enough, there is aggregation into bigger molecules or particles, which scatter light. On paper electrophoresis in a buffer containing albumin (127), these endogenous particles trail from the pre-β region to the origin (126).

The origin of the component lipids and special proteins and the sites of assembly of the lipoprotein molecules remain to be precisely defined. It seems most likely that the liver synthesizes much of

the cholesterol (63, 76) and most of the phospholipid and triglyceride found in plasma lipoproteins. The apoproteins A and B are also probably synthesized mainly in the liver (139, 168), although the intestines (171) and other tissues may also have this capacity. The ability of the liver for lipoprotein synthesis will obviously be dependent on the flow to it of precursors such as amino acids, carbohydrates, and adipose tissue fatty acids. Thus many processes, remote from the liver, can grossly affect the plasma lipoproteins. For example, with malabsorption there is severe decrease in plasma concentrations of LDL and HDL.

In the American population, α- and β-lipoprotein concentrations nearly double in the first few weeks of age, then rise very slowly up to about age 20-25 years. Then the β-lipoproteins almost invariably rise more sharply with age during at least the third, fourth, and fifth decades in both sexes (67). The pre-β-lipoproteins also tend to be more commonly detectable after the third decade; this latter group of lipoproteins is very common in men who have had a myocardial infarction (18), although no prospective study of such an association has been made.

From the foregoing, it can be seen that the disordering of metabolism or transport of the several lipids found in plasma involves generally increase in concentrations of LDL and decrease in those of HDL. It is also apparent that in hyperlipidemia, with increased cholesterol or glycerides or both, there will also be an increase in one or more classes of LDL. The apparent value of measurements of both lipids and these lipoproteins in attempts to predict vulnerability to atherosclerosis arises from these associations.

Particles (Chylomicrons)

As already noted, when glycerides are present in high concentration they tend to form particulate emulsions (46). These are stabilized by phospholipids in combination with cholesterol and perhaps small amounts of protein. They scatter visible light and produce lactescence in blood. Such particles isolated from extracellular fluid may be as large as 1,500 mμ in diameter, although it is uncertain whether they achieve such size in vivo.

The physiological particle is the chylomicron formed during fat absorption. This package of glyceride is carried up the thoracic duct into the blood stream and is rapidly removed by many tissues, including muscle and adipose tissue. The role of the liver in this process is still uncertain. Within the tissues,

the glycerides are hydrolyzed and the fatty acids appear in phospholipids and other glycerides. Some of the fatty acids reappear quickly in plasma, both as esterified lipids containing lipoproteins and as free fatty acids.

In heart and adipose tissue, although not in liver tissue, the enzymes responsible for hydrolysis of particulate glycerides include lipoprotein lipase. This enzyme catalyzes hydrolysis of glyceride and is activated in plasma by heparin or other sulfated polysaccharides.

The particles of glyceride arising endogenously (pre-β-lipoproteins) may also be handled by the same mechanisms utilized for clearing exogenous glycerides. This is not yet known, however, it appears that most examples of endogenous hyperlipemia (hyperglyceridemia with lactescent plasma) are not associated with low activity of postheparin lipases (mainly lipoprotein lipase) (60).

Lipid Synthesis and Utilization

The metabolism of lipids cannot be considered independently of other metabolic processes. Phospholipids, cholesterol, and triglycerides are intricately linked in a highly complex network of reactions. Both cholesterol and the fatty acids are synthesized enzymatically in the body from the same fundamental unit, acetylcoenzyme A. Enzymatic syntheses of phospholipids and triglycerides also progress through common intermediates. Because of the close interlinking of these metabolic reactions, it is necessary to consider lipid metabolism in the broad sense in connection with nutrition or with pathological conditions.

Fatty Acids and Glycerides

Most tissues in the body not only participate in the synthesis of fat but also have the ability to oxidize fats completely and rapidly. A high percentage of the energy used by heart muscle is derived from free fatty acids. The biosynthesis of fatty acids from carbohydrate and amino acids and their oxidation are accomplished through reversible reactions involving acetate and coenzyme A.

Fatty acids may also be interconverted in the body through stepwise alteration of the chain length by addition or removal of two-carbon fragments and by introduction or removal of double bonds. Most mammals, including man, are able to

introduce one double bond into stearic acid to make oleic acid, but cannot continue the desaturation to yield linoleic acid. Given a dietary source of linoleic acid, the body can synthesize arachidonic acid, but cannot do so from a saturated fat, oleic acid, or the basic reactions of fat synthesis. Thus, fat derived largely by synthesis from carbohydrate is more saturated and more firm than that derived from dietary fat, due to the low rate of conversion of the newly formed monoenoic acids to more unsaturated acids.

Arachidonic acid is the principal polyunsaturated fatty acid that the animal synthesizes from linoleic acid. When linolenic acid is fed, even more highly unsaturated and longer chain acids are formed (194, 202). It is possible that vitamin B_6 is required for conversion of linoleic acid into arachidonic acid (206).

Mammary tissue is able to synthesize both fatty acids and cholesterol from nonfat precursors. Thus, milk fat can arise through biosynthesis from acetate in the mammary gland as well as in other tissues, such as liver. On low fat or fat-free regimens, milk fat is synthesized by the mammary gland. On a high-fat diet, however, a large portion of the fatty acids in human milk may come from dietary fat via the plasma lipids, and the fatty acid composition of human milk can be highly variable (99).

Phospholipids

Human plasma phospholipids are nearly all choline-containing lipids. Lecithin (phosphatidyl choline) greatly predominates, with sphingomyelin accounting for an appreciable fraction (164). Phosphatidyl serine and phosphatidyl ethanolamine comprise only a small fraction of the total phospholipids in plasma (164), but are much more prominent among tissue phospholipids.

The phospholipids, like the glycerides, contain a variety of fatty acids, but they have a proportionately higher content of polyunsaturated fatty acids. They are important structural constituents of the membranes of cells and their organelles and are essential components of some enzyme systems. They probably perform an essential function in transport of lipids, because their emulsifying properties serve to solubilize other fats and to stabilize both the lipoprotein and particulate systems in extracellular fluid.

The liver appears to be the chief organ for synthesis as well as degradation of the phospholipids of plasma. Pathways for biosynthesis of phospholipids have been clarified by work with isolated

enzyme systems (107, 108, 119, 198). Cytidine coenzymes have been shown to be essential in this synthesis. In the enzymatic synthesis of lecithin, for example, the coenzyme cytidine diphosphate choline is an important intermediate in converting 1,2-diglyceride to phospholipid.

Fat Storage

Most of the energy stored in the body is in the form of triglyceride. This caloric reserve is maintained mainly in adipose tissue cells and may derive directly from the fatty acids in food or it may arise from the conversion of glucose or certain amino acids into fatty acids. Adipose tissue is capable of removing fatty acids from circulation for triglyceride synthesis, and can also manufacture fat from blood glucose. Thus, the adipose cell can store, synthesize, and release fatty acids, depending on the requirements of the body.

The rate at which triglyceride is manufactured within the fat cell depends primarily on the state of energy balance of the organism at the time. Excess dietary calories, whether from fat, carbohydrate, or protein, are stored as fat; when energy expenditure exceeds intake the fat stores help make up the deficit. Under normal circumstances, the process of lipogenesis from carbohydrate continues even though the individual is in energy equilibrium. This simply means that an appreciable proportion of dietary carbohydrate and, indirectly, some protein are converted to fat prior to utilization.

The rate at which the fat cells release free fatty acids into the circulation is usually inversely related to the rate of carbohydrate utilization. In the fasting state, in uncontrolled diabetes, and in response to such hormones as somatotrophin and epinephrine, the adipose tissue releases fatty acids at increased rates. The fat depots not only are the major supply of storage energy but also provide a large proportion of the fuel used by the body under normal metabolic conditions.

Cholesterol Metabolism

Cholesterol is manufactured in the body, principally in the liver (50, 51), and circulates in the plasma as a component of lipoproteins.

In healthy individuals, the body tends to maintain plasma cholesterol concentration by compensating for dietary intake through adjustment of synthesis and also through degradation and excretion of cholesterol and its products (71, 129, 161).

Isotope studies have demonstrated that cholesterol can be synthesized from acetylcoenzyme A by a series of reactions involving the successive formation of such intermediates as mevalonic acid, squalene, and lanosterol (166).

The rate of endogenous cholesterol synthesis is variable and has been estimated to range between 0.5 and 2 gm per day (74, 135).

The ring structure of cholesterol is not readily degraded in the body. The principal catabolic pathway for cholesterol is conversion to bile acids by the liver. Some intact cholesterol leaves the body by excretion into the bile and by direct loss through the intestinal wall and feces.

The quantities of cholesterol and bile acids that enter the small intestine in bile are variable. The quantity of cholesterol *per se* secreted with bile into the intestine may reach 50 percent of that synthesized each day in the body; however, much of this amount may be reabsorbed in the presence of fat and bile acids (180). The bile acids are continually reabsorbed through an enterohepatic cycle with only a small fraction of the circulating pool being lost each day in the feces. The quantity excreted daily approximates the amount of bile acids produced from cholesterol in the liver (17).

In man, the bile acids produced in the liver are cholic acid and chenodeoxycholic acid. These acids are converted to other forms prior to excretion in the feces. Cholesterol is excreted in the feces as such or is changed in the intestine to products such as coprosterol and coprostanone.

The chemical similarity of cholesterol and steroid hormones suggests a metabolic interrelationship of these compounds. Whether biosynthesis of the steroid hormones of the adrenals, testes, ovaries, and corpus luteum proceeds by way of cholesterol still is not certain. The endocrine tissues that produce these hormones do synthesize cholesterol from acetate and, at least in the case of the adrenal cortex, can convert cholesterol into steroid hormones (175). Proof that cholesterol is an obligatory intermediate is still lacking.

Lipotropic Factors

Lipotropic factors are nutrients whose absence from the diet leads to excess deposition of liver fat. The most important of these factors are: the base choline, a constituent of some phospholipids (vide); the essential amino acid, methionine, which enables the body to synthesize choline; and vitamin B_{12}, perhaps the most important of the three.

On a diet deficient in the lipotropic factors, rats accumulate excessive amounts of liver fat. Choline deficiency results in increased hepatic-fat synthesis (207), decreased release of lipoproteins from the liver (162, 182), and possibly decreased hepatic-fat oxidation (13). It is not known which mechanism is primarily responsible for the hepatic-fat accumulation. If the accumulation of hepatic fat becomes sufficiently great, the cells rupture and coalesce into fatty cysts. Eventually cirrhosis may occur. In the kidney, also, abnormal accumulation of lipid induces cellular destruction. Here, however, the sequence of events leads to interference with blood supply of the fatty swollen tubules and culminates in the hemorrhagic renal syndrome of choline deficiency.

Inositol also has some lipotropic activity. Fatty livers may develop, however, in animals on low-protein diets even when dietary fat is at a minimum and adequate choline is present (179). Such fatty livers can be prevented by certain amino acids, notably threonine. Fatty livers also have been observed when lysine in the diet is low. It is not yet clear to what degree these results in animals are related to human liver disease.

NUTRITIONAL ROLE OF FOOD FATS

Energy and Storage

Fat is the most concentrated energy source in the diet. One gram of fat provides approximately 9 calories, compared with 4 calories from 1 gm of protein or carbohydrate. Fat is the only form of energy that the body can store in quantity. For this purpose, both carbohydrate and protein are converted to fat. Adipose tissue insulates the body from rapid changes in environmental temperature and cushions organs and the body as a whole against external forces.

Palatability of Diets

Dietary fat has a palatability role difficult to measure but important to proper nutrition. An appreciable content of fat is requisite to a diet generally acceptable in our society. Observations of fat-craving are quite common among peoples deprived of their accustomed intake of fat. Satiety from fats in the diet may be in part traceable to the slower emptying of the stomach when a high-fat meal has been ingested. Many of the substances responsible for the flavors and aromas of foods are dissolved in fat and associated with the fat in the diet. The distinctiveness and attractiveness of a foodstuff often can be attributed to desirable flavor and texture qualities provided by the fatty constituents.

Nutrient Carriers

Fats in the diet act as carriers of certain nonfat nutrients. Some fats, such as butterfat and the fats of marine animals, eggs, and margarine (through fortification), provide important amounts of vitamins A and D. Many fats contain vitamin E and some are sources of vitamin K.

Essential Fatty Acids

The essentiality of certain polyunsaturated fatty acids in the diet was demonstrated first in experiments with rats (27). The essential fatty acids are required by animals for growth, reproduction, membrane integrity, and the proper utilization and metabolism of fat. Linoleic and arachidonic acids will cure essential fatty acid deficiency, but linolenic acid and its related polyunsaturated acids are not fully effective (147).

The amount of dietary linoleate required by experimental animals to prevent deficiency symptoms and for maintenance of the usual pattern of polyunsaturated acids has been determined to lie between 1 and 2 percent of total calories for rats (98) and swine (36). At lower levels of dietary linoleate, the content of linoleate and arachidonate of tissue and plasma lipids decreases, and eicosotrienoic acid increases.

Infantile eczema (32) may sometimes be an expression of essential fatty acid deficiency (83) and the linoleate requirement of infants has been estimated to be between 1 and 3 percent of total calories. Human milk normally is at least three times richer in essential fatty acids than cow's milk.

Dietary cholesterol affects essential fatty acid deficiency in the rat (163) and the polyunsaturated acid pattern in the tissues. As essential fatty acids account for a substantial proportion of the fatty acids of cholesterol esters and phospholipids in plasma lipoproteins and of mitochondrial lipoproteins, these acids presumably may have critical roles in membrane structures and in transport processes.

ATHEROSCLEROSIS (ARTERIOSCLEROSIS)

The Nature of Atherosclerosis

Atherosclerosis is a disease that first involves the arterial intima. The early lesions consist of fatty changes in the arterial walls that may result in formation of atheromas. Advanced lesions of atheroma are composed of fibrous masses of lipid, collagen, hyalin, and fibrin, in which areas of recent and old hemorrhage abound in a vascularized tissue framework (204). Deposits of iron, cholesterol (both in free form and as esters), triglycerides, phospholipids, ceroid pigment, and calcium salts are prominent. The elastic elements in the intimal tissue are frayed or absent, and the medial layer may be replaced by sclerotic tissue. The latter changes appear to be secondary.

Large atheromatous plaques in the aorta are more common in the abdominal portion than in the thoracic portion. They occur most frequently around orifices of branches and, accordingly, are more numerous in the posterior wall. Lesions are often less advanced in coronary arteries than in more distal arteries. The left coronary artery is more frequently affected than the right coronary artery.

With ulceration of lesions, formation of a clot attached to the vessel wall (mural thrombosis) develops which, if it occurs in a coronary artery, may lead to occlusion and often fatal infarction. Occlusive thrombosis in coronary arteries occurs, however, more frequently than can be accounted for by ulceration.

The precise morphologic counterpart of human atherosclerosis has not been produced in any experimental animal. In some experimental animals with lesions induced by cholesterol feeding, abnormal deposits of cholesterol are found not only in blood vessels but also to varying extent in liver, spleen, lung, kidney, and tongue (143). Such visceral deposits are absent in atherosclerosis of man.

Much experimental work centering on cardiovascular disease has dealt with atheroma and has not included its complications, such as thrombosis. Yet the factors that initiate atheroma may

not necessarily be identical with those responsible for its fatal complications. Myocardial infarction with formation of mural thrombi has been induced in rats on a drastically altered dietary regimen (89).

Numerous hypotheses regarding the initiation of atheromatous lesions have been considered. Among these are: vascular injury, trauma or inflammation; abnormal lipid synthesis in the arterial tissue; abnormal plasma lipids; thrombus formation; degenerative change in the protein of the elastic membranes, media, or intimal tissue; prolonged hypertension; and abnormal activities of certain hormones. Thus, both chemical and mechanical factors have been postulated as causes of this cardiovascular disease. Many workers have pointed out that the variable focal distribution of atherosclerosis in the arterial system implies that some local factor or factors operate in initiation and development of the disease.

Any hypothesis centering on an atherogenic toxin in the diet as the cause of atherosclerosis must recognize that atherosclerosis is not a disease of modern man, but has been recognized in its present form for several thousand years (122) and in people existing on widely different diets.

The abnormal lipid hypothesis regarding the development of atheroma pictures atherosclerosis as originating in some disorder of lipid metabolism affecting the arterial wall either directly or indirectly and implicating dietary fats and changes in plasma lipids in the pathogenesis. The fact that iron deposits, red blood cells, and fibrous tissue or fibrin as well as lipids are found even in early lesions is sometimes forgotten.

Another method of learning about early lesions and their progression is the study of infants, children, and young adults. Only a few studies in children under the age of 15 years have been made, but they are noteworthy because the stage of the lesion can be dated more accurately than in the adult. Fatty streaks have been reported in coronary arteries and aortas at early ages—even a few days after birth. Lipid streaks and even early hyalinization in coronary arteries of infants and juveniles have been reported (155); completely uninvolved coronary arteries were found only in fetuses. Studies (57) of hearts and aortas of young American soldiers in Korea demonstrated that fatal coronary occlusion could occur between 18 and 21 years of age and, in cases of young soldiers killed in battle, advanced coronary lesions were frequently observed. Thus, lesions regarded as preatheromatous were found at an early age, and advanced lesions were found even in the late teens.

Intensified study, with contemporary techniques, of these lesions in children would help to elucidate the true natural history of atheroma. The fact that lesions may have formed by the end of the pediatric period indicates that attention also should be focussed on the diet and other factors in this age group. Epidemiologic factors related to atheroma, such as hypertension and smoking, are not prevalent in children and lesions might be more susceptible to reversal than those in the adult where calcification and fibrosis are present.

Experimental Production of Atherosclerosis

Knowledge concerning experimental atherosclerosis, from the standpoint of the pathologic anatomist, has been strengthened during the past decade by at least two major advances—investigations have been conducted on many species other than the chick and rabbit, and electron microscopy has permitted visualization and positive identification of structures in the arterial wall.

Morphologic studies of cholesterol-induced atheroma have been reported in many species—rabbit and chick (10, 39, 47, 106), dog (181), rat (54, 90, 205), mouse (42), guinea pig (7), hamster (68), domestic pig (169), monkey (41, 138, 186, 187), susceptible strain of pigeon (134), duck (106), and prairie gopher (9).

From these studies and others, the following points have emerged:

1. Lipid in some form is a prominent feature of lesions in whatever artery (coronary, aorta, etc.) they develop. There is a disagreement, however, as to whether it appears before any other demonstrable change; whether it initially appears as triglyceride (or free fatty acid), cholesterol, or cholesterol esters (at later stages all forms are present); or whether it enters the arterial wall directly, is carried by macrophages (foam cells), or enters by both methods. Some investigators (65) think the lipid may be synthesized in situ by myogenic foam cells in the subintima and inner portion of the media. Ceroid has been found in all models when searched for, as well as in man (87, 88).

2. The foam cell is present in lesions induced in all species. It is much more prominent in some, such as the rabbit, than in others, such as the monkey. The presence of the foam cell is regarded by many as the most important cytologic response of the arterial wall to atherogenic stimuli. A smaller but important body of opinion regards the reaction and modification of smooth muscle cells as an equally fundamental response (210).

3. From studies of early lesions and other approaches (injection of thrombi with resultant pulmonary arterial atheroma) (48), intimal deposition of fibrin, platelets, and, in some instances, red blood cells is regarded as the primary and cardinal event by supporters of the thrombogenic theory of pathogenesis of atheroma. Lipid and foam cells are considered to be secondary subsequent additions to the lesion as the thrombus becomes organized and converted to a plaque. Changes occurring more deeply within the wall (intima and media) also are considered secondary to the initial thrombotic event. Most supporters of this hypothesis agree that the fibroblasts are derived from intimal endothelial cells, although certain forms of reticuloendothelial cells in the circulating blood have been considered possible precursors of fibroblasts (8).

4. Edema and abnormal accumulation of mucopolysaccharides (151) have been considered as initiating pathogenic events, but evidence in support of either concept is still inadequate.

5. In all species studied, lesions consisting of foam cells and lipid, and with some proliferation of intimal cells and usually of smooth muscle cells as well (altered or not), can be readily produced. Fibrosis, hyalinization, calcification (egg-shelling), ulceration, and thrombosis are not consistently encountered. All of these features have been reported only in rabbits (39), although most of them have been seen in rats (90).

6. Some evidence suggests that dietary factors enhance blood coagulation and thus the formation of thrombi (see page 29) and that they may be different from those affecting atherogenesis.

Relation of Lipids in Normal and Atherosclerotic Arteries to Plasma Lipids

Evidence has accumulated indicating that an exchange between plasma lipids and lipids in atherosclerotic arteries exists in man. The deposition of ^{14}C-labeled dietary cholesterol in the atheromatous aorta, although slow, does occur (167). Plasma cholesterol, likewise, exchanges with arterial-wall cholesterol, although the rate is slower than in any other tissue except brain tissue (21, 35, 121). In normal intima, equilibration with plasma cholesterol probably occurs eventually (35), but the presence of atherosclerosis appears to delay the rate of reaching equilibrium. The factors that influence this rate are not known.

On ordinary diets, the fatty acid composition of the arterial-wall lipids is similar to that in plasma (22, 25, 154, 184, 189). When polyunsaturated fat is substituted for saturated fat in the diet, the degree of unsaturation of the plasma lipids gradually rises and, ultimately, similar changes occur in the arterial wall. When normal aortic intima or media are compared with fatty deposits in the aorta, the only lipid class that showed changes in fatty acid composition were cholesteryl esters (154).

The lipid composition in several areas of the aorta in patients with atherosclerosis has been reported (183). Both early and advanced plaques were found to have significantly less linoleic acid and more oleic acid in the cholesteryl ester fraction than plasma from the same individuals.

An increase of lipid with age, both in the coronary arteries and in the aorta, has been found in subjects who died of causes unrelated to occlusive coronary disease and was accounted for by the deposition of cholesterol and cholesteryl esters (200). In contrast, in subjects who died from coronary heart disease, 60 percent more cholesteryl ester and 80 percent more cholesterol was found in their coronary arteries (201). No significant increase in triglycerides or phospholipids was found in the latter group, however, there was an increase in ash content of the coronary arteries of the coronary-occlusion group.

These studies of atherosclerotic arteries do not support any cause-and-effect hypothesis relating diet to coronary artery disease or to atherosclerosis in general, but do provide evidence of a relationship, although not perfect, between plasma lipids and those in atherosclerotic plaques.

Plasma Triglycerides, Obesity, Diabetes, and Atherosclerosis

A large portion of plasma lipid is in the form of triglyceride, particularly after a meal. Patients with known coronary artery disease frequently have high plasma triglyceride concentrations (5, 6, 30, 176), and some investigators consider the correlation between increased triglyceride concentration and coronary artery disease to be better than the correlation with plasma cholesterol concentration. Elevated plasma triglyceride concentration was found to be the most characteristic blood lipid change after myocardial infarction, in the age group between

33 and 50 years (6, 30). The plasma triglycerides are mainly carried in the low-density lipoproteins, so that these recent reports confirm earlier data (66) that indicated that the concentration of those lipoproteins rich in triglycerides (density 1.006-1.019) correlated more closely with the presence of coronary heart disease than did that of the cholesterol-rich lipoprotein (density 1.019-1.063).

There is much evidence to suggest that obesity predisposes to coronary heart disease (203). The Framingham study, however, has revealed only a small risk for obesity alone unless it was very marked or associated with high plasma cholesterol (105). Triglycerides in the plasma were not reported from the Framingham study. In other investigations, weight reduction of obese subjects, even to normal weights, did not correlate importantly with the plasma cholesterol concentration (28, 149).

Atherosclerosis is common in individuals with diabetes, and in diabetes the plasma cholesterol and triglyceride concentrations are often increased. The concentration of the triglyceride is a well-recognized index of adequacy of control of the disease. Obesity is commonly seen in maturity-onset diabetes and the frequency of atherosclerotic complications in this situation is particularly high. These observations suggest that the metabolic defect or defects leading to diabetes and to high plasma cholesterol and triglyceride concentrations, as well as obesity, may be important in the pathogenesis of the atherosclerosis. It may be significant that levels of plasma triglycerides can be reduced in diabetics, overweight nondiabetic adults, patients with coronary artery disease, and most patients with hyperlipemia in a fasting state by the ingestion of diets reduced in calories and carbohydrates and relatively rich in fats, particularly polyunsaturated fats.

High-carbohydrate diets, especially in populations that enjoy a sufficiency (if not an excess) of calories, promote lipogenesis which facilitates the manufacture of saturated fats and increases their plasma concentration. Plasma triglyceride concentration also can be lowered by weight reduction. Similarly, increased physical activity results in a reduction of plasma triglyceride concentration, presumably by means of the negative calorie balance.

It is not known whether these plasma lipid changes are causally related to atherosclerosis. The plasma cholesterol concentration is still the most likely to correlate with coronary heart disease, perhaps, in part, because it has been studied much longer than the plasma triglycerides. Nevertheless,

recommendations for dietary alterations designed to reduce plasma lipids or prevent rises should take into consideration the possible relationship of triglycerides and atherogenesis and the fact that plasma triglyceride and cholesterol concentrations respond to dietary manipulations somewhat differently.

Vitamin E and Lipid Metabolism

Vitamin E, or tocopherol, functions as a biological antioxidant (97); that is, it retards the undesirable oxidative rancidification of polyunsaturated fatty acids in tissues. One means of inducing tocopherol deficiency has been to overtax tissue supplies of the vitamin by feeding large amounts of highly unsaturated oils without tocopherol (97). Diets rich in polyunsaturated fatty acids must, therefore, contain and be protected by sufficient tocopherol or other biological antioxidants (185).

In clinical studies, tocopherol deficiency has resulted from disorders of lipid absorption such as cystic fibrosis of the pancreas (72), chronic pancreatitis (25), sprue, or protein deficiency (45).

Although the primary products of lipid autoxidation are difficult to demonstrate in tissues, lipid polymers called ceroid or lipofuscins are relatively easy to demonstrate in human atheromatous lesions, in the smooth muscle of patients with cystic fibrosis of the pancreas (72), and in chronic pancreatitis in adults (26). In animals deprived of vitamin E, ceroid pigment is found in many tissues.

Plant oils that have high amounts of linoleic and linolenic acids usually have high levels of total tocopherol (85). The proportion of α-tocopherol in the total tocopherols may vary greatly, and some tocopherol may be lost during refining, storage, and cooking.

The utilization and storage of both vitamin A and carotene are affected by the amount of tocopherol supplied (150).

Effects of Fats on Blood Coagulation and Thrombosis

Despite much research, relationships between dietary or blood fats, blood clotting, and atherosclerosis remain uncertain (165). Most studies of this problem have dealt with effects of fats on coagulation mechanisms. It is well established that one or

perhaps several phospholipids are among the factors accelerating the first stage of clotting, but no implications with respect to atherosclerosis can be drawn from this information. In experimental models simulating the human artery, platelets are essential for thrombus formation. Moreover, diet may affect platelet metabolism (153). After ingestion of some types of fat, blood fibrinolysis may be inhibited but without any relationship to the degree of unsaturation of the fats (80). Exercise in conjunction with a fatty meal decreases this antifibrinolytic activity (79). Thromboembolic phenomena in hospitalized patients (84) were found to be higher in those fed butter and margarine than in those fed vegetable oil with their meals. As a group, patients with ischemic heart disease show increased coagulability by *in vitro* clotting tests (141). *In vitro* tests purporting to show increased coagulability are difficult to interpret at best and are not necessarily correlated with the key clinical problem—that of thrombosis (137).

Alcohol, Blood Lipids, and Atherosclerosis

Some clinicians have the impression that chronic alcoholic patients have less arteriosclerosis than nonalcoholic subjects; some believe that alcohol predisposes to atherosclerosis. There are no clinical studies that conclusively support either of these concepts. In experimental animals, alcohol has been found variously to favor (73), protect against (49), or have no significant effect on (156, 158) atherosclerosis produced by experimental means.

The carbon atoms of alcohol have been traced to a variety of body constituents, including lipids and glycogen, but most of the alcohol is oxidized in the body to carbon dioxide (199). Alcohol has been found to spare body fat (14), but whether or not it spares protein is questionable (152). When carbohydrates are replaced by alcohol (36 percent of the total calories), fatty infiltration of the liver develops in both man and rats despite ingestion of an otherwise adequate diet (133). Alcohol can increase hepatic fatty acid synthesis, but whether this or other mechanisms are responsible for the production of the fatty livers common in alcoholics is still controversial (43, 131).

On short-term alcohol administration (6-8 hr), a rise in circulating triglycerides without change in cholesterol has been reported (104). On more prolonged alcohol administration, plasma

triglycerides increased during the first 8-10 days, but returned to normal thereafter (133). Alcoholics usually have either normal plasma lipids or various degrees of mild hyperlipemia, and the transient effect of alcohol suggests that the variable degree of lipemia of alcoholics may depend on the duration of the alcohol intake. The mechanism of this moderate alcoholic hyperlipemia has not yet been elucidated; it does not appear to be due solely to an increase in total caloric intake because a similar effect could not be reproduced by the administration of isocaloric amounts of fat or carbohydrate (104). On rare occasions, gross lipemia (up to 10 gm percent plasma glycerides) with marked lactescence has been observed in alcoholics. This is usually accompanied by symptoms associated with liver insufficiency (209). The excessive hyperlipemia could be due to the potentiating effect of alcohol on lipoprotein lipase deficiency (136) or to an associated pancreatitis (4).

In addition to its effect on circulating glycerides, alcohol also increases plasma cholesterol in both man (78, 133) and rats (49, 73, 158). Similar effects have been described for circulating phospholipids (133, 158).

In man, acute administration of alcohol results in immediate short-time fall of circulating free fatty acids (FFA) (132). More prolonged alcohol administration, however, produces no deviation from normal plasma FFA concentration, but very large doses of alcohol (40 oz of 86 proof per day) increase FFA concentration (133).

PLASMA CHOLESTEROL LEVELS AS RELATED TO DIET AND HEART DISEASE

As has been indicated, cholesterol is a prominent constituent of atheromas. Experimental atherosclerosis was first induced by feeding rabbits rather large amounts of cholesterol (10). These studies were discounted for many years since cholesterol is a foreign food substance of the vegetarian rabbit. However, many investigators have found that certain disease states in which the plasma cholesterol is elevated (diabetes, familiar hypercholesterolemia, etc.) are associated with an increased susceptibility to atherosclerosis and ischemic heart disease (64, 106, 109). Briefly stated, the evidence implicating plasma cholesterol levels in the causation of ischemic heart disease is as follows:

1. Those populations in which coronary disease is an important cause of death have substantially higher plasma cholesterol levels than those in which this disease is rare (106). Thus, in the United States where coronary disease is a leading cause of death, the average plasma cholesterol level in middle-aged men is approximately 220-230 mg percent; whereas in Guatemala, among the Bantu of Africa and in similar groups, the average level is approximately 180 mg percent, or perhaps lower.

2. Within population groups such as in the United States, those with elevated plasma cholesterol levels have a greater risk of developing the disease. This has been most clearly shown in the Framingham study (105). In this population, the risk of developing coronary disease appears to be directly related to the plasma cholesterol, other things being equal.

It is important to recognize that the data indicate no safe level of plasma cholesterol, but rather that each increment in the plasma cholesterol level above the lower levels encountered in the study appears to be associated with an increased risk. The same type of evidence is available from studies of patients who have had coronary disease. The average level is well above the levels in those who do not have evidence of the disease. However, it should be apparent that high levels of plasma cholesterol are not diagnostic of coronary disease. Some people with levels

below the average in the United States do develop the disease and high levels do not inevitably result in a coronary attack.

3. In all experimental animals in which elevated plasma cholesterol levels have been produced by various means, atheromatous lesions develop.

Such evidence does not prove that an elevated level of plasma cholesterol is the cause of atherosclerosis or of coronary disease. The elevated plasma cholesterol might be simply associated with the disease or with some other causal factor. For example, it has been claimed that elevated plasma triglycerides are more characteristic of patients with coronary disease than is a high plasma cholesterol (6). Since both the triglycerides and the cholesterol are carried in the various lipoprotein fraction, these two lipid fractions are associated and the significance of this conclusion is as yet unknown. It had been previously suggested (66) that the low-density lipoproteins, richer in triglycerides than cholesterol, were more closely associated with coronary disease. However, no epidemiologic studies are yet available to suggest that plasma triglycerides are a more likely causal factor than plasma cholesterol.

Proof that a high plasma cholesterol level is causative of coronary disease in man can probably only come from experimental manipulation of the plasma cholesterol level in a sizable group of men and the demonstration that such treatment will lessen the incidence of the disease. Such evidence is not yet available, although some (11) is at least suggestive that this may be true. It becomes of great interest, therefore, to develop feasible methods of lowering the plasma cholesterol. Manipulation of the diet is a possibility and the role of the several dietary and pharmacological factors that may influence plasma cholesterol is discussed below.

Effect of Dietary Cholesterol on Plasma Cholesterol Level

The various animal species in which the effects of dietary cholesterol have been studied respond in widely different fashion. Some species, such as the rabbit and chicken, are very sensitive, and moderate increases in the level of cholesterol in the diet cause pronounced raises in the amount of the plasma. Other species, such as the rat and the dog, show little response to dietary cholesterol alone (110).

Early studies in man suggested that dietary cholesterol was of little importance since fairly large doses of cholesterol produced little change in the plasma level (117). It now appears that as the food cholesterol is increased from 0 to perhaps 0.8 gm per day, other things being equal, the plasma cholesterol progressively increases, but further increases in intake provoke relatively little further increase in the plasma level (19, 20, 37, 38, 92, 112). The situation is complicated, however, by evidence that the dietary source of the cholesterol—the form of the dietary cholesterol—may be important. Some natural sources of cholesterol may produce more substantial increases in the plasma than does crystalline cholesterol. Thus, the intake of cholesterol must be considered in devising diets that lower cholesterol levels, but more substantial changes in the plasma cholesterol may be produced by manipulation of the dietary fat.

Effect of Kind of Dietary Fat on Plasma Cholesterol Level

The observations (81) that substitution of unsaturated vegetable oils for animal fats in the diet produced a substantial lowering of the plasma cholesterol level have been confirmed by many investigators. It would appear obvious that a sustained change in the level of plasma cholesterol must reflect either a change in the rate of synthesis in the body or its degradation and excretion if the cholesterol content of the diet is not modified. The dietary fat might also affect the distribution of cholesterol within the vascular and cellular compartments of the body.

Although there is general agreement that unsaturated vegetable oils tend to lower the plasma cholesterol levels while diets high in the ordinary saturated animal fats have the opposite effect, there is as yet no agreement upon fatty acid components presumed to be effective in raising or lowering the plasma cholesterol level. One group of investigators (3) concluded that the plasma cholesterol level induced by a dietary fat was related to the degree of unsaturation of the fat, thus implying that oleic acid was about half as effective as linoleic acid. Another group (115) concluded that the monounsaturated acids have no effect. Rather, they have concluded (116) that the plasma cholesterol is a function of the total saturated fatty acid and the polyunsaturated acid content of the dietary fat, the saturated fatty acids being approximately twice as active in elevating the plasma cholesterol as the

polyunsaturated acids are in lowering it. From more recent work (92, 112), it appears that the saturated fatty acids are not all equally active in elevating plasma cholesterol. Others (91) have also concluded that the chain length of the saturated fatty acids may be important in determining their effect. Various other parameters of fat composition (82, 101, 118) have been suggested as a means of predicting the effect of the dietary fat. Contrary to expectations (53, 144), hydrogenation of some vegetable oils was not found to influence their effect upon plasma cholesterol.

It appears impossible at this time to arrive at any consensus of opinion as to the most important factors in dietary fats that control plasma cholesterol levels or upon the mechanism of action. This does not, however, modify the conclusion that large and sustained decreases in the circulating cholesterol can be easily induced by substitution of highly unsaturated vegetable oils in the diet in place of most of the saturated fats ordinarily present in the American diet.

Effect of Dietary Carbohydrate on Plasma Cholesterol Level

Those populations that experience little atherosclerosis generally consume diets that are not only low in fat but also high in starch and other forms of complex carbohydrates. It appears to be characteristic that, as the societies become more affluent, the consumption of both fat and sugar increases. It has been suggested that high sugar intakes may be a causal factor in the development of atherosclerotic heart disease (36, 208). Little evidence is available to support this contention. In the few carefully controlled studies that have been reported (77, 114, 142), substitution of various complex forms of carbohydrate for sugar has resulted in only moderate lowering of the level of cholesterol in the plasma, much less than can be achieved by modification of the dietary fat.

Since the consumption of animal fats and of sugar is highly correlated in most countries, epidemiologic data are not helpful in distinguishing between the possible effects of these two dietary factors.

Although, as discussed elsewhere, the consumption of very low-fat high-carbohydrate diets may induce hyperglyceridemia, this condition does not appear to be characteristic of populations consuming low-fat diets (11).

Pharmacological Control of Plasma Cholesterol

Plasma cholesterol concentration can be influenced by changing cholesterol degradation and excretion, its biosynthesis, or its distribution in the vascular and cellular compartments of the body. Several pharmacological agents that influence plasma cholesterol concentration are noted below.

The oral administration of neomycin induces a reduction in plasma cholesterol concentration and a considerable increase in the fecal excretion of bile acids (69). These findings were interpreted to suggest that "neomycin lowers plasma cholesterol levels primarily by an increase in fecal excretion of sterols and bile acids." Presumably, neomycin is effective, at least in part, by inducing a change in the intestinal flora which alters the structure of sterols and bile acids and thus changes their absorption. Cholesterol synthesis and degradation probably are increased during neomycin administration, but whether the regimen effects an over-all loss of cholesterol from the body is uncertain.

When the enterohepatic circulation of the bile acids is interrupted by cannulation of the bile duct and the formation of an external fistula, a greatly increased synthesis of bile acids from cholesterol occurs (193). This and other work suggests that feedback mechanisms regulate bile acid formation and, simultaneously, the degradation of cholesterol.

Oral administration of cholestyramine, an insoluble anion exchange resin that will bind bile acids *in vitro* and in the intestinal tract, has been observed to decrease the plasma cholesterol in man by about 20 percent (range: 6-38 percent in 26 patients) (16). The largest decreases usually occurred in those patients with the highest initial cholesterol concentrations. Although side effects (impairment of fat and fat-soluble vitamin absorption) have not been a problem, further work is needed to establish the effectiveness and safety of this drug.

Large doses of nicotinic acid by mouth also will lower the blood cholesterol concentration in many individuals (69). The mechanism for this is not understood, but it appears probable that nicotinic acid in some way interferes with the hepatic synthesis of lipids, particularly cholesterol. Nicotinic acid is presently being used in the treatment of hypercholesterolemia, but whether it has any effect on atherosclerosis, either in prevention or treatment, is unknown.

Epidemiologic and Other Population Studies of Diet, Plasma Lipids, and Heart Disease

Studies of populations by epidemiologic methods, in which, for example, differences in diet are correlated with the incidence of coronary heart disease, do not in themselves prove cause and effect. Nevertheless, if carefully done, they provide much collateral and confirming evidence about the setting in which this disease occurs, and often such studies act as stimuli to further research. Many epidemiologic studies concerning the relationships between diet, plasma lipids and atherosclerosis have been done. Some of these are poorly controlled, and in others the data are, for other reasons, inconclusive. A few of the more thought-provoking or better controlled studies are noted here.

People who live on extremely low fat intakes have been investigated in many parts of the world. In one such study, 440 Koreans were eating approximately 7 percent of their 2,900 calories as fat. Although they were ingesting only about half as much linoleic acid as in the usual American diet, their adipose tissue had almost twice as much linoleic acid as is found in Americans (125).

The occurrence rate of coronary artery disease in most oriental countries is though to be very much lower than in Western countries. This has been reasonably well documented for the Japanese and for the Koreans and has been associated with low plasma lipid, especially cholesterol, concentrations. Several studies have emerged from these observations. In one, a group of Korean soldiers who had been eating their low-fat army diet were attached to U.S. Army units. Within a few weeks, the change to the American diet, with nearly half the calories coming from fat, was associated with a considerable increase in concentration of plasma lipids in the Korean soldiers. Other environmental factors also changed, but the probability remains that the diet was the most important factor (124).

It has been pointed out that Japanese men between the ages of 40 and 49, all with a common ancestry but presently living in three different environments—Kyushu, Hawaii, or Los Angeles—had a greatly different incidence of coronary heart disease. As expected, it was very low in Kyushu, higher in Hawaii, and higher still in Los Angeles. These differences were parallel to average plasma cholesterol concentrations which were proportional to the percentage of calories from fat in the diet. The intake of

polyunsaturated fatty acids in Japan was said to be much the same as in Hawaii and in the continental United States (109).

Additional evidence that race is not the important factor in influencing plasma cholesterol concentration comes from a study in Hawaii of the plasma cholesterol concentration among adult Honolulu men who were of Caucasian, Chinese, Philippine, Japanese, and Hawaiian extraction. The results of the study were consistent with the view that race is of negligible influence upon the plasma cholesterol concentration, but that environmental factors are influential (1). Further inspection of the literature substantiates the concept that race is not important.

Studies among the Bantu of South Africa have, for many years, established that their habitual diet is very low in fat, that the plasma cholesterol concentration tends to be lower than in most Western countries, particularly after the age of 40, and that severe atherosclerosis and coronary artery disease are less common among the Bantu, for example, than among Europeans and Indians living in the same area but with different dietary (and other) habits. Moreover, Bantu living in cities and eating food more like that of a European, with a higher fat content, do have a considerably higher plasma cholesterol concentration (93, 195, 196, 197).

A careful study of the disease patterns in autopsied individuals in Central Africa and Albany, New York, demonstrated a striking difference in the occurrence rate of myocardial infarction. This disease is almost nonexistent among the Africans studied, even in the older age groups, and is relatively common among the New Yorkers studied. The study was carefully corrected for age (70, 123). The African parts of this study were done in Ibadan, Nigeria, where the fat content of the diet is low and most of it is polyunsaturated, and in East Africa where various pastoral tribes live mostly on milk, blood, or meat; that is, a high saturated-fat diet. Thus, the differences in myocardial infarction rate could not be related to quantity or quality of dietary fat. Other environmental factors presumably are effective.

The Masai, another pastoral tribe, who live almost entirely on milk and blood, also have a high saturated-fat intake. Nevertheless, their blood cholesterol concentrations are relatively low and, as far as can be determined, atherosclerosis and coronary heart disease are infrequent.

The Samburu people of nothern Kenya have a particularly low plasma cholesterol concentration (mean for males: 166 mg/100 ml) despite a diet usually made up of milk, meat when it is available,

and small quantities of vegetables. In fact, when milk is plentiful, a warrier may drink 10 liters a day. The habitual diet is, thus, high in fat, most of which is saturated. Moreover, this group of people shows no increase in total cholesterol concentration with age. They are generally very active physically (177). Another tribe, living largely on camel milk rather than cow's milk had a considerably higher plasma cholesterol concentration (178).

In general, then, pastoral tribes like these have a moderately low or very low plasma cholesterol concentration and probably a low incidence of coronary heart disease despite their high, usually animal, fat intake. These studies in Africa, where diet is so completely different for different areas, yet where plasma lipids are similar and atherosclerosis presumably low in frequency, point out clearly that environmental factors other than diet are undoubtedly influential; physical exercise may be the most important of these.

Population studies are by no means confined to those done abroad. Many longitudinal diet and serum lipid studies have been done in the United States.

In a study of 280 Minnesota businessmen, aged 45 to 55, only the plasma cholesterol concentration proved to be statistically significant in predicting risk of future coronary artery disease (109). Although overweight, overfatness, and elevated blood pressure were associated with greater risk, their predicting value was far below that for plasma cholesterol. These findings are much the same as those of the Framingham study.

Further evidence that the plasma cholesterol concentration has value in predicting risk of clinically manifest heart disease is indicated by the U.S. Public Health Service prospective study in Framingham, Massachusetts (105). This study showed that incidence of new coronary disease in a group of men in early middle age, followed over an 8-year period, was more than four times as great among those with plasma cholesterol concentrations of 240 mg/100 ml or above as among men in a similar age category with cholesterol concentrations lower than 220 mg/100 ml. The risk of developing new heart disease was compounded by such additional factors as obesity, hypertension, and heavy cigarette smoking.

Extensive experience with the effects on plasma cholesterol concentration of a diet rich in polyunsaturated fatty acids is provided by the Diet and Coronary Heart Disease Study begun in New York City early in 1957 and still continuing (103). This

regimen was associated with reduction in plasma cholesterol concentrations in many of the subjects, particularly those with the highest initial values. An analysis was made of the prevalence of heart attacks in the subjects who received this polyunsaturated-fatty-acid-rich regimen, and the results for the men aged 40 to 59 were compared with the incidence rates reported from the Framingham study in which the subjects continued to eat their usual diet, containing a high proportion of saturated fat. The rate of new coronary events per 1,000 men in New York was 3.4 as against 14.5 per 1,000 in Framingham. Thus, the ratio of actual to expected events in the New York study proved to be remarkably low. Problems involved in comparing the data from the New York and Framingham studies must be pointed out, however. For example, the New York subjects displayed a high degree of health consciousness, and differed sociologically and ethnically from the Framingham subjects. Moreover, the Framingham report was based on a different method of accumulation of persons-years of experience. The absence of a suitable control group makes it difficult to interpret the results obtained in the New York study. A somewhat different answer follows from a small study in London (172). Here 31 patients with a recent myocardial infarction and 49 with angina were followed for 2 years while they consumed their usual diet or substituted olive oil or corn oil for much of their saturated fat. The plasma cholesterol concentrations were unchanged except for those who took the corn oil, in whom it was reduced. Fresh myocardial infarctions, however, were not reduced by either the olive oil or corn oil substitutions. In fact, if anything, the risk of a new infarction was increased in those taking the corn oil.

The possibility, however, that the cholesterol-lowering diet may have had a favorable influence on morbidity and mortality from coronary heart disease underlines the urgent need for obtaining a more definitive answer. A controlled study of the immense size necessary to provide reliable answers to the questions posed will be extremely difficult.

To test the feasibility of such large-scale field trials, a "National Diet-Heart Study," supported by the National Heart Institute, has been conducted in several large cities in the United States. Some 1,500 healthy male volunteers, aged 45 to 54, and their families have been entered in the study after being carefully examined medically, with particular emphasis on the cardiovascular system. These families followed diets that were changed from the usual American diet to be lower in saturated

and higher in unsaturated fat. Careful follow-up is being continued with biochemical studies as well as medical evaluations. The results of the feasibility study will at least give an indication as to whether a large field trial can or should be undertaken.

These worldwide population and epidemiologic studies, thus, do not decide the problems of dietary fats, blood lipids, and atherosclerosis. Diets very low and, conversely, those high in fat are compatible with low plasma cholesterol concentrations. Even diets high in saturated fats are associated with low cholesterol, in spite of the careful clinical and metabolic studies in this country that seem to show the opposite. Undoubtedly, other environmental conditions must be taken into account, especially energy expenditure (physical exercise). Genetic influences, although unlikely, are not so far excluded.

SUMMATION AND RECOMMENDATIONS

Fats are the most concentrated energy sources in man's diet. They provide the essential fatty acids and important amounts of vitamins A, D, and E, facilitate their absorption, and contribute to palatability and satiety. Most Americans obtain about 40 percent of their calories from fat, more of which, in recent years, has been from oils than from solid fats.

In the conversion of a vegetable oil to a solid fat, partial hydrogenation leads to formation of isomers of the unsaturated fatty acids and decreases the essential fatty acid content. No obviously harmful nutritional effects of such processing have been demonstrated, although further studies of the effects of these or other possible changes caused by processing are needed.

A large amount of information has accumulated relating dietary fats to the etiology of human atherosclerosis and its complications, particularly coronary artery disease. As yet, the causes and course of development of atheroma and its relation to coronary heart disease in man are imperfectly known. Disorders of fat transport or metabolism or both certainly participate, but are not the only factors. Heredity is involved in individual susceptibility. Disorders of blood flow and blood clotting are implicated in atheroma formation in addition to contributing to the fatal complications of the disease.

Evidence to support the concept that increased plasma concentrations of cholesterol are atherogenic is considerable but not conclusive. The type and quantity of dietary fat and the amount of cholesterol eaten influence the cholesterol concentration in the blood. Fats high in saturated fatty acids support a somewhat higher plasma cholesterol concentration than do those richer in polyunsaturated fatty acids. Many, but not all, population studies indicate that diets high in fat, among other nutrients, are correlated with higher concentrations of plasma cholesterol and with increased prevalence of cardiovascular disease. However, proof of a causal relationship is lacking. In the majority of the adult population the concentration of plasma cholesterol can usually be reduced by increase in the quantity of polyunsaturated fat in

the diet at the expense of saturated fat. That this degree of reduction in plasma cholesterol is beneficial is still uncertain.

Increased plasma triglyceride concentrations, not necessarily dependent upon the plasma cholesterol, have recently been related to atherosclerosis. Triglycerides in the plasma do not respond to dietary changes in a manner identical with that of cholesterol. In some individuals, replacement of dietary fat with carbohydrate causes plasma triglycerides to rise while cholesterol falls. Caloric excess, regardless of the form, may elevate plasma triglyceride as well as cholesterol concentrations.

Thus, in spite of the large amount of information accumulated in recent years about atherosclerosis and its pathogenesis, many gaps in knowledge remain. Results of recent studies, while valuable and thought provoking, do not provide sufficient data for firm recommendations for radical dietary changes.

The attractiveness and availability of rich or fatty foods, however, place the American consumer in danger of overnutrition and dietary imbalance. The Food and Nutrition Board considers that, for many Americans, moderate reduction in total fat intake and some substitution of polyunsaturated for saturated fat may be indicated. The degree to which this is done must be judged on an individual basis and, in adjustment of the diet, other changes in caloric and nutrient intake must be taken into consideration.

The food industry, communication media, and official regulatory agencies, meanwhile, can be powerful constructive forces: (a) in prevention of obesity by making known the importance of exercise and the restriction of calories after adult years are attained; (b) by restraining exaggerated claims that particular foods or classes of foods are necessary daily in large quantities for health; and (c) by clearly labeling the composition of packaged foods and those promoted in advertising.

Until we learn more about which fats are desirable nutritionally, the Board recommends that the American consumer should partake of the foods that make up a varied, adequate, and not overly rich diet and maintain a normal body weight by judicious control of caloric intake and by daily exercise.

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