THE FIRST LINE for therapy of hyperlipidemia is diet modification. One approach to dietary treatment of hyperlipidemia is the "one-diet" concept, according to which a single diet can be used for treatment of all forms of hyperlipidemia. This approach was advocated by the American Heart Association in its dietary recommendations for treatment of hyperlipidemia in adults. The foundation of the American Heart Association's recommendation is the low-fat diet. A diet low in total fat intake was suggested for all forms of hyperlipidemia, and the recommendation called for a progressive reduction in fat intake. In other words, a marked reduction in fat intake was not prescribed from the beginning of therapy but instead was to be achieved in a progressive, stepwise fashion. The "one-diet" concept for treatment of hyperlipidemia has the advantage of simplicity, but for physicians or therapeutic dieticians who have a good understanding of the different forms of hyperlipidemia, use of the same diet in all patients may not be necessary or even desirable. In this article, therefore, consideration will be given to the various categories of hyperlipidemia and how dietary therapy may be used to maximal benefit in each case.

The low-fat diet is attractive because epidemiologic data indicate that rates of coronary heart disease (CHD) are relatively low in populations that habitually consume such diets. For example, in Japan and China and in other parts of the orient, the diet is relatively low in total fat and prevalence of CHD is low. Furthermore, plasma cholesterol levels are low in these populations, which could contribute to the low prevalence of CHD. These observations suggest that low-fat diets are responsible for low concentrations of plasma cholesterol; indeed, metabolic-ward investigations demonstrate that low-fat diets can reduce plasma cholesterol compared with diets rich in total fat and saturated fatty acids. Nevertheless, this finding does not mean that low-fat diets are the only means of attaining a reduced level of cholesterol.

For instance, substitution of polyunsaturated fatty acids for saturated fatty acids in the diet is known to reduce the plasma cholesterol level. This reduction occurs mainly in low-density lipoproteins (LDLs). Thus use of diets high in polyunsaturated fatty acids might be an alternative approach to the prevention of CHD. Unfortunately, there is no strong epidemiologic evidence that diets high in polyunsaturated actually will prevent CHD. No large populations have ever consumed large quantities of polyunsaturated fatty acids with proven benefit or safety. The lack of epidemiologic data supporting the safety of polyunsaturates has led many investigators to recommend that high intakes of polyunsaturates, e.g., greater than 10% of total calories, be avoided. This recommendation is supported by possible long-term adverse effects of polyunsaturated fatty acids. For instance, in humans high intakes of polyunsaturates will lower the plasma high-density lipoproteins (HDLs) and may predispose to gallstones in some patients. In addition, in laboratory animals polyunsaturates can suppress the immune...
system\textsuperscript{8} and promote the development of tumors.\textsuperscript{9} Therefore it seems unwise to recommend that a significant reduction in dietary saturated fatty acids be restored exclusively by polyunsaturated fatty acids in the diet.

Yet another source of calories is monounsaturated fatty acids, of which oleic acid is the major constituent. Monounsaturated fatty acids have been consumed in large quantities, in the form of olive oil, in the Mediterranean region for centuries with apparent safety. Furthermore, in this region, rates of CHD are relatively low, as are levels of plasma cholesterol.\textsuperscript{10} Recent studies in our laboratory have demonstrated that monounsaturated fatty acids are as effective as polyunsaturated fatty acids\textsuperscript{11} and carbohydrates\textsuperscript{12} in lowering the level of LDL. And in contrast to polyunsaturates and carbohydrates, monounsaturates do not lower the HDL concentration. Thus, on the basic of epidemiologic studies and metabolic-ward investigations, diets high in monounsaturated fatty acids appear to be as protective against CHD as those low in total fat (i.e., high in carbohydrates).

Most nutritional studies suggest that saturated fatty acids are the major factor raising the plasma concentrations of total cholesterol and LDL. When saturated fatty acids are replaced by any other major nutrient — carbohydrates, polyunsaturated fatty acids, or monounsaturated fatty acids — levels of total cholesterol and LDL cholesterol fall. Therefore, the primary aim in prevention of CHD is to decrease intakes of saturates, and it seemingly matters little which nutrients are used in their place. The choice of nutrients thus will depend on other considerations (e.g., other possible harmful effects, preference, and cost).

Another dietary factor affecting the plasma cholesterol is dietary cholesterol. In many subjects, an increase in the dietary intake of cholesterol will raise the plasma cholesterol level.\textsuperscript{11} Most of this rise occurs in the LDL fraction. However, the effects of dietary cholesterol are variable. Some individuals show little increase, while others demonstrate a marked response. A rise in LDL concentrations, however, is not the only effect of dietary cholesterol. Some investigators have suggested that ingestion of cholesterol in the diet may give rise to atherogenic postprandial lipoproteins that enhance risk for CHD even when fasting levels of cholesterol are unchanged.\textsuperscript{12} Results of several epidemiologic studies indicate that dietary cholesterol is an "independent" risk factor for CHD, i.e., that the effect of dietary cholesterol on CHD rates is greater than can be explained by the rise in fasting levels of total cholesterol. This is consistent with the concept that dietary cholesterol has effects on the rate of atherogenesis in ways other than by raising levels of LDL cholesterol.

One other factor — an excessive intake of total calories — can have adverse effects on the plasma lipoproteins. Obesity is associated with an increased production of very low-density lipoprotein (VLDL) triglycerides\textsuperscript{13} and VLDL apolipoprotein B (apo B)\textsuperscript{14, 15}; this overproduction gives rise to elevated plasma triglycerides and sometimes cholesterol. Furthermore, obesity reduces the HDL level.\textsuperscript{16} Thus high caloric intakes associated with obesity can be considered another dietary factor contributing to abnormal levels of lipoprotein.

With these general concepts of the effects of dietary constituents on plasma lipoproteins in mind, we can turn our attention to the different forms of hyperlipidemia and how diet can be used in their management.

Familial hypercholesterolemia. This condition is characterized by a deficiency in specific, cell-surface receptors for LDL.\textsuperscript{17} Normally, individuals inherit one gene encoding for LDL receptors from each parent, and both genes actively induce the formation of receptors. One person in 500 inherits a defective and nonfunctional gene for the LDL receptor. When this occurs, the individual synthesizes only half the normal number of receptors, and clearance of LDL from the circulation consequently is reduced. As a result, plasma concentrations of LDL are approximately twice normal, and the patient is said to have heterozygous familial hypercholesterolemia.\textsuperscript{17} Patients with heterozygous familial hypercholesterolemia frequently have tendon xanthomas, and they are prone to develop CHD prematurely. Affected men often develop CHD in their 30s and 40s, women with familial hypercholesterolemia commonly develop CHD in their 50s and 60s. Familial hypercholesterolemia is inherited as an autosomal dominant trait. Rarely (one in a million people), a defective gene is inherited from both parents, and the result is homozygous familial hypercholesterolemia. Patients with homozygous familial hypercholesterolemia have no functioning LDL receptors, and their cholesterol levels are about four times normal. Severe atherosclerotic disease frequently occurs when they are teenagers.

Patients with homozygous familial hypercholesterolemia are essentially unresponsive to modification of diet.\textsuperscript{18} This is because cholesterol-lowering diets act mainly by increasing LDL receptors, so that in the absence of receptors alteration of the diet has little effect. In contrast, patients with heterozygous familial hypercholesterolemia usually respond to dietary changes.\textsuperscript{19} Diets rich in saturated fatty acids and cho-
Cholesterol suppress the activity of LDL receptors; therefore, these constituents should be removed from the diet to the extent possible. The means elimination of eggs and fats rich in saturated acids. The richest sources of the latter are products containing butter fat, coconut oil, and palm oil. Meat fat (pork and beef) also have saturated fatty acids, but these fats seemingly are less hypercholesterolemic than butter fat.

The saturated fatty acids should be reduced to below 10% of total calories and preferably below 7% in patients with heterozygous familial hypercholesterolemia. Cholesterol intake should be less than 200 mg/day. Saturated fatty acids can be replaced by monounsaturated fatty acids, carbohydrates, or polyunsaturated fatty acids, but for the reasons indicated above, polyunsaturates should be kept to below 10% of total calories. Weight reduction also will reduce concentrations of LDL in obese patients with heterozygous familial hypercholesterolemia. Unfortunately, modification of the diet will not normalize LDL levels in most patients with heterozygous familial hypercholesterolemia, and the aim of therapy is to achieve a normalization. Therefore, maximal dietary therapy should be used in these patients, but complementary drug therapy will be needed in most patients. One effective drug regimen is a bile acid sequestrant combined with nicotinic acid, but a more promising combination is a bile acid sequestrant and an inhibitor of HMG CoA reductase (e.g., lovastatin, still an investigational drug in the United States).

Primary (nonfamilial) hypercholesterolemia. The recent Consensus Conference on Cholesterol defined hypercholesterolemia as a cholesterol level exceeding 240 mg/dl. A cholesterol level of 240 mg/dl essentially doubles the risk for CHD (compared with 200 mg/dl) and when the level reaches 300 mg/dl, the risk is doubled again. Cholesterol concentrations in the range of 240 to 300 mg/dl can be called primary hypercholesterolemia, provided the LDL cholesterol level exceeds 160 mg/dl. Only a small percentage of patients in this category will have heterozygous familial hypercholesterolemia. The remaining majority might be said to have "nonfamilial" hypercholesterolemia, although genetic factors probably contribute to elevations of cholesterol concentrations in most of these patients. Another term that has been used for the condition is "polygenic" hypercholesterolemia because several genes affecting LDL metabolism may act together to raise the LDL concentrations to an abnormally high range. Most patients with primary hypercholesterolemia (other than familial hypercholesterolemia probably have a metabolic suppression of LDL receptor activity and do not have a specific structural defect in the genes encoding for LDL receptors. The abnormalities underlying this "metabolic suppression" have not been determined.

In many patients with nonfamilial primary hypercholesterolemia, dietary factors probably contribute to raising the LDL concentration. For example, diets high in saturated fats, cholesterol, and total calories may raise the LDL concentration to the hypercholesterolemic range in individuals who otherwise would not have cholesterol levels exceeding 240 mg/dl. Still, many people on the same "cholesterol-raising" diet will not develop frank hypercholesterolemia, and hence genetic factors undoubtedly play a significant role in development of primary hypercholesterolemia. These genetic factors may cause a person to be "hyperresponsive" to dietary saturated fatty acids and cholesterol. Nonetheless, dietary therapy can be extremely valuable in treatment of primary hypercholesterolemia, particularly in patients of the latter type.

In most patients with cholesterol concentrations in the range of 240 to 300 mg/dl, a prolonged trial with diet modification is justified. Many patients cannot acquire new dietary habits within a few days or weeks, and often 6 months to 1 year are required for a complete change. For the patient with cholesterol levels in this range, therefore, the physician should not resort to medications prematurely. As a first step in dietary therapy, the intake of total fat should be reduced to 30% of calories, saturated fatty acids to less than 10% and dietary cholesterol to less than 200 mg/day. If the response to diet is adequate, i.e., if the LDL cholesterol level falls to 140 mg/dl or less, there is no need to alter the diet further. On the other hand, if the response is considered inadequate, a further reduction in intakes of saturated fatty acids and cholesterol can be tried. Many patients should demonstrate an adequate response to dietary therapy, and drugs will not be needed.

Even if the response is "inadequate," drugs may not be required. The risk for CHD associated with an inadequate response to diet must be considered in the light of possible risk of drug therapy. Therefore a dietary "failure" does not necessarily require a prescription for drugs. The patient's overall risk status must be taken into consideration. Factors that favor use of drugs include (1) persistent marked hypercholesterolemia, (2) male gender, (3) other coronary risk factors (e.g., smoking, hypertension, diabetes mellitus, low HDL levels), (4) manifest angina pectoris or CHD, and (5) a strong family history of CHD. The best drug to use in conjunction with diet in the treatment of primary hypercholesterolemia is probably a bile acid
In the future, HMG CoA reductase inhibitors may be indicated for this purpose, or for high-risk patients, even the combination of sequestrants and reductase inhibitors.

**Dietary hypercholesterolemia.** Cholesterol concentrations in the range of 200 to 240 mg/dl impart an increased risk for CHD compared with levels below 200 mg/dl. In populations at high risk, a high proportion have cholesterol concentrations in this range, which appears to be a major factor in the high rates of CHD among Americans. Since many people naturally have cholesterol concentrations below 200 mg/dl, a level above 200 mg/dl may be partially the result of genetic factors; but for most Americans, diet plays an important role in raising the LDL concentrations, which justifies the term “dietary” hypercholesterolemia. Again, dietary saturated fatty acids and cholesterol suppress the activity of LDL receptors, and an excess of total calories induces overproduction of lipoproteins. Both mechanisms lead to higher concentrations of LDL.

For people without manifest CHD, dietary modification is the only management required for “dietary” hypercholesterolemia. A decrease in saturated fatty acids and cholesterol to less than 10% of calories and less than 300 mg/day, respectively, should be sufficient for most people. Overweight individuals should attempt to achieve a desirable body weight. Drug therapy is rarely indicated for patients with cholesterol concentrations in the range of 200 to 240 mg/dl.

**Familial combined hyperlipidemia.** This form of hyperlipidemia has been reported to occur in approximately 10% of patients with CHD. It may occur in about 1% of the whole population. The condition is characterized by multiple lipoprotein phenotypes within a single family. Some patients have an increase in LDL alone, others have an increase in VLDL alone, and still others have increases in both of these lipoproteins. Rarely, patients in this category have an elevation of chylomicrons in addition to raised VLDL levels. The diagnosis of familial combined hyperlipidemia can be made in an individual patient only by the finding of multiple lipoprotein patterns within a single family. Affected patients appear to be at increased risk for CHD regardless of their lipoprotein phenotype. The mechanisms underlying this condition have not been fully elucidated. An overproduction of lipoproteins containing apo B appears to be an underlying cause in many patients. However, in other patients who appear to have this condition, a defective lipolysis of VLDL-triglycerides or a decreased activity of LDL receptors may be the major mechanism.

Because of the complexity of familial combined hyperlipidemia, a simple recommendation about diet is difficult. However, many affected patients are obese, and weight reduction can produce a marked decrease in circulating lipids in these patients. A decreased intake of saturated fatty acids and cholesterol certainly seems prudent, but their benefit in this disorder has not been proved. For patients with hypertriglyceridemia, diets high in carbohydrates and alcohol should be avoided, and a diet rich in monounsaturated fatty acids may be preferable. Administration of large amounts of fish oils to patients will cause a lowering of the plasma triglycerides, but they may cause a concomitant increase in the LDL cholesterol level. Therefore the utility for fish oils in the treatment of familial combined hyperlipidemia remains in doubt, and for this reason the use of fish oils for therapy cannot be advocated.

If diet fails to control LDL levels in patients with familial combined hyperlipidemia, it may be necessary to resort to drugs. Nicotinic acid is one drug that may be effective. The use of a fibric acid derivative in combination with lovastatin also appears to hold promise.

**Familial hypertriglyceridemia.** In some families, an elevation of plasma triglycerides is inherited as a monogenic disorder. This condition usually is manifest by an increase in plasma VLDL alone, and plasma triglycerides are in the range of 250 to 500 mg/dl. Occasionally, plasma triglycerides are as high as 1000 mg/dl, but when this occurs chylomicrons usually are present (see below). The cholesterol levels in affected patients frequently are below 240 mg/dl, unless the triglyceride concentrations are considerably greater than 500 mg/dl. The risk for CHD in patients with familial hypertriglyceridemia is not markedly increased, but the best way to assess the risk in these patients is not known. One way may be to use the standard risk factors — total cholesterol and HDL cholesterol, or the total cholesterol/HDL cholesterol ratio. The level of plasma apo B also is being investigated as a predictor of risk.

The causes of familial hypertriglyceridemia are not entirely clear. Some patients may have an isolated overproduction of VLDL triglycerides with a normal production of VLDL apo B, similar to that which occurs in individuals on diets rich in carbohydrates or alcohol. Other patients appear to have a defective clearance of triglyceride-rich lipoproteins, possibly because of a deficiency of lipoprotein lipase.

If a patient with familial hypertriglyceridemia is judged not to be at increased risk for CHD according to the standard risk factors, specific therapy for mild
hypertriglyceridemia is not indicated. Such patients can be advised to avoid excessive intakes of carbohydrates and alcohol, and a diet rich in monounsaturated fatty acids can be suggested. If the patient is overweight, a reduction in weight can be recommended. Drug therapy of hyperlipidemia is not required. If there is an increase in cholesterol concentration, a major reduction in HDL cholesterol, or established CHD, the patient can be treated as if he or she had familial combined hyperlipidemia.

**Primary hyperchylomiconemia.** This condition, which is accompanied by severe hypertriglyceridemia, can occur in two forms. Very rare patients have a congenital absence of lipoprotein lipase, with severe hypertriglyceridemia and chylomicronemia in the presence of a relatively normal concentration of VLDL. This disorder has been called type 1 hyperlipoproteinemia or “fat-induced” hyperlipidemia. In the second disorder, both chylomicrons and VLDL are increased, a condition called type 5 hyperlipoproteinemia.

A congenital absence of lipoprotein lipase (type 1 hyperlipoproteinemia) is characterized by severe chylomicronemia, eruptive skin xanthomas, lipemia retinalis, acute pancreatitis, and an absence of atherosclerotic disease. These clinical manifestations of severe hypertriglyceridemia usually occur in infancy or childhood. The primary purpose of therapy is to prevent pancreatitis. This can be accomplished by reducing intake of total fat to less than 10% of total calories, which will reduce the formation of chylomicrons. Drug therapy is of no value.

Type 5 hyperlipoproteinemia is characterized by an increase in both chylomicrons and VLDL, eruptive skin xanthomas, bouts of acute pancreatitis, and frequently premature atherosclerotic disease. It occurs most often in adults and usually is caused by a combination of overproduction of VLDL and a defective lipolysis of triglyceride-rich lipoproteins. Again, the primary aim of therapy is to prevent acute pancreatitis. Toward this aim, a reduction in intake of total fat is indicated, and an attempt should be made to reduce the intake to less than 15% of total calories. However, many patients with type 5 hyperlipoproteinemia will respond to drugs — fibric acids or nicotinic acid — and one of these drugs should be tried in addition to greatly reducing the fat intake.

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