MEDICAL GRAND ROUNDS

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FAMILIAL HYPERCHOLESTEROLEMIA AND OTHER DISORDERS OF LIPOPROTEIN METABOLISM

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The hyperlipoproteinemias are disturbances of lipid transport that result from abnormalities in the synthesis or degradation of plasma lipoproteins. The clinical importance of the elevated plasma lipoprotein level derives from the ability of plasma lipoproteins to cause two life-threatening diseases: atherosclerosis and pancreatitis. Some hyperlipoproteinemias are the direct result of primary defects in the metabolism of lipoprotein particles. Other hyperlipoproteinemias are secondary, i.e., the elevated plasma lipoprotein level occurs as part of a constellation of abnormalities caused by an underlying disorder in a related metabolic system, such as thyroid hormone deficiency or insulin deficiency. The primary hyperlipoproteinemias can be further divided into two broad categories: 1) single-gene disorders that are transmitted by simple dominant or recessive mechanisms and 2) multifactorial disorders with complex inheritance patterns in which multiple variant genes interact with environmental factors to produce varying degrees of hyperlipoproteinemia in scattered members of a family.

PHYSIOLOGIC ROLE OF LIPOPROTEINS IN LIPID TRANSPORT

The lipoproteins are globular particles of high molecular weight that serve to transport nonpolar lipids (primarily triglycerides and cholesteryl esters) through the plasma. A general model for the structure of a lipoprotein particle is shown in Fig. 100-1. Each lipoprotein particle contains a nonpolar core in which many molecules of hydrophobic lipid are packed together to form an oil droplet. This hydrophobic core, which accounts for most of the mass of the particle, consists of triglycerides and cholesteryl esters in varying proportions. Surrounding the core is a polar surface coat composed predominantly of phospholipids that stabilize the lipoprotein particle so that it can remain in solution in the plasma. In addition to phospholipids, the polar coat contains small amounts of

unesterified cholesterol. Each lipoprotein particle also contains specific protein molecules (termed apoproteins) that are partly exposed at the surface. The apoprotein binds to specific enzymes or transport proteins, thus directing the lipoprotein to its sites of metabolism.

Table 100-I describes the characteristics of the five major classes of lipoproteins that normally circulate in human plasma. Each of these five lipoprotein classes differs from one another in the composition of the nonpolar lipids in the core, in the composition of its apoproteins, and in density, size, and electrophoretic mobility.

Lipid Transport: The Exogenous Pathway

Figure 100-2 shows the pathways by which lipoproteins transport lipids in human plasma. The largest amounts of lipoproteins are involved in the transport of dietary fat, which amounts to more than 100 gm of triglyceride and about 1 gm of cholesterol per day. Within intestinal epithelial cells, dietary triglycerides and cholesterol are incorporated into large lipoprotein particles called chylomicrons. The chylomicrons are secreted into the intestinal lymph and circulate to the capillaries of adipose tissue and skeletal muscle where they adhere to binding sites on the capillary walls. While bound to this endothelial surface, the chylomicrons are exposed to the enzyme lipoprotein lipase which hydrolyzes the triglycerides of the chylomicrons and releases free fatty acids and monoglycerides. The fatty acids pass through the endothelial cells and enter the underlying adipocytes or muscle cells where they are either reesterified to triglycerides or oxidized.

After its core triglycerides have been removed by the action of lipoprotein lipase, the remainder of the chylomicron dissociates from the capillary endothelium and reenters the circulation. It has now been transformed into a particle that

is relatively poor in triglyceride and relatively enriched in cholesteryl esters. It has also undergone an exchange of apoproteins with other plasma lipoproteins. The net result is the conversion of the chylomicron to a remnant particle that is enriched in cholesteryl esters and apoproteins B, C-III, and E. This chylomicron remnant travels to the liver where it is taken up with great efficiency. The overall result of the chylomicron transport process is to deliver dietary triglyceride to adipose tissue and to deliver dietary cholesterol to the liver.

Some of the cholesterol that reaches the liver in the chylomicron remnants is converted to bile acids which are excreted into the intestine to act as detergents, facilitating the absorption of dietary fat. In addition, the liver excretes some unesterified cholesterol into the intestine through the bile duct. The liver also distributes cholesterol to the other parenchymal cells of the body (discussed below).

Lipid Transport: The Endogenous Pathway

Triglyceride synthesis in the liver is enhanced when the diet contains excess carbohydrates. The liver converts the carbohydrate to fatty acids, esterifies the fatty acids with glycerol to form triglycerides, and secretes the triglyceride into the bloodstream in the core of very low density lipoproteins (VLDL). The VLDL particles are relatively large, contain 5 to 10 times more triglycerides than cholesteryl esters, and contain apoproteins that are similar to those of chylomicrons (Table 100-I).

The VLDL particles are transported to tissue capillaries where they interact with the same lipoprotein lipase enzyme that catabolizes chylomicrons. The core triglycerides of the VLDL are hydrolyzed and the fatty acids are used for triglyceride synthesis within adipose tissue. The remnants generated from the action of lipoprotein lipase on VLDL are similar to those formed from chylomicrons. However,

in man, most of the VLDL remnants are not catabolized by the liver, as are the chylomicron remnants. Rather, the VLDL remnants undergo a further transformation in which nearly all of the residual triglycerides are removed and replaced with cholesteryl esters. During this conversion, all of the apoproteins are removed from the particle with the exception of apoprotein B. The result is the transformation of the VLDL remnant particle into the cholesterol-rich lipoprotein low density lipoprotein (LDL). The core of LDL is composed almost entirely of cholesteryl esters, and the surface coat contains only one apoprotein, apoprotein B. About three-fourths of the total cholesterol that is present in normal human plasma is contained within LDL particles.

The function of LDL is to supply cholesterol to extrahepatic parenchymal cells, such as adrenal cortical cells, lymphocytes, muscle cells, renal cells, etc. These cells are thought to synthesize an LDL receptor that is localized on the cell surface. LDL that binds to this receptor is taken up and digested by the cells within lysosomes. The cholesteryl esters of LDL are hydrolyzed by a lysosomal cholesteryl esterase (acid lipase) and the liberated cholesterol is used both for membrane synthesis and as a precursor for steroid hormone synthesis. Recent evidence suggests that this LDL receptor pathway serves as the major route for the degradation of LDL in the human body.

In addition to its degradation by the LDL pathway in extrahepatic parenchymal cells, some of the LDL is degraded by a scavenger cell system that consists of phagocytic cells located primarily in the reticuloendothelial system. In contrast to the receptor-mediated pathway for LDL degradation, the scavenger cell pathway functions not to supply cholesterol to cells but to degrade LDL when the lipoprotein reaches high concentrations in plasma.

As the membranes of parenchymal cells and scavenger cells undergo turnover and as cells die and are renewed, unesterified cholesterol is released into the plasma where it binds initially to high density lipoprotein (HDL). This unesterified

cholesterol is then coupled to a fatty acid in an esterification reaction catalyzed by the plasma enzyme lecithin:cholesterol acyltransferase (LCAT). The cholesteryl esters that are formed on the surface of HDL are transferred to VLDL and eventually appear in LDL. This establishes a cycle by which LDL delivers cholesterol to extrahepatic cells and by which cholesterol is returned to LDL from extrahepatic cells via the intermediary of HDL. Some of the cholesterol released from extrahepatic tissues is transported to the liver for excretion in the bile. The mechanism by which the liver takes up this cholesterol is unknown, but it is possible that hepatic LDL receptors are involved.

DIAGNOSIS OF HYPERLIPOPROTEINEMIA

A variety of diseases cause elevations in the concentrations of one or more lipoprotein classes in plasma. In general, these abnormalities are detected by the finding of an elevated concentration of triglycerides or cholesterol in fasting plasma, a condition called hyperlipidemia. The absolute and relative values for the plasma cholesterol and triglyceride levels give a great deal of information regarding the nature of the lipoprotein particle that is present in increased amounts. An isolated elevation in the level of plasma triglycerides indicates that the concentrations of chylomicrons, VLDL, and/or remnants are increased. On the other hand, an isolated elevation of plasma cholesterol nearly always indicates that the concentration of LDL is increased. Frequently, both triglycerides and cholesterol are elevated. Such a combined abnormality may be produced by a marked elevation in chylomicrons or VLDL in which case the ratio of triglyceride to cholesterol in plasma will be greater than 5:1. Alternatively, there may be an elevation of both VLDL and LDL in which case the triglyceride:cholesterol ratio in plasma is less than 5:1.

The definition of hyperlipoproteinemia is somewhat arbitrary because plasma lipid and lipoprotein levels show a bell-shaped distribution in the population,

without any clear separation between normal and abnormal values. Since lipoprotein concentrations are subject to strong influences from diet and other environmental factors, standards must be established for each different population. What is usually done is to set arbitrary statistical limits of normal concentrations based on the examination of a large number of healthy-appearing subjects of different ages. The cut-off limit that is usually used is the approximate upper 10% to 5% of values found in apparently healthy individuals (i.e., the 90th to 95th percentile values). However, it must be emphasized that a vast amount of epidemiologic data gathered from highly industrialized and more agrarian cultures indicate that lipid and lipoprotein concentrations that are "normal" in a statistical sense are not necessarily healthy. As a working rule, clinically significant hyperlipoproteinemia is considered to be present in any individual below the age of 20 years whose total plasma cholesterol level exceeds 200 mg/dl or whose triglyceride level exceeds 140 mg/dl. In individuals above the age of 20, significant hyperlipoproteinemia exists whenever the plasma cholesterol level exceeds 240 mg/dl or the triglyceride level exceeds 200 mg/dl.

The various combinations of elevated lipoproteins that occur in disease states have been divided into six lipoprotein types or patterns. These are summarized in Table 100-II. As shown in Table 100-III, each of the lipoprotein types can be caused by several different genetic diseases; conversely, each genetic disease can produce more than one lipoprotein type. In addition, each of the abnormal lipoprotein types can occur as a secondary consequence of another metabolic disease (Table 100-IV). Hence, each lipoprotein type should be thought of as a shorthand notation to describe an abnormal lipoprotein pattern in plasma, and not as a designation of a specific disease state.

Ordinarily, the simple measurement of plasma lipid levels, coupled with a clinical assessment of the patient, will be sufficient to classify the patient as

to the type of lipoprotein abnormality (Table 100-II). Occasionally, paper electrophoresis of the plasma may be helpful in defining which lipoprotein is elevated. Such electrophoresis is useful either when an elevation in remnant particles is suspected (type 3 lipoprotein pattern giving a "broad beta" band on electrophoresis) or when chylomicronemia is expected (type 1 pattern). Recently, a great deal of interest has been generated in the measurement of HDL levels, since high levels of this lipoprotein class are statistically associated with a decreased risk of myocardial infarction (see Chapter 250). The level of HDL can be estimated in clinical laboratories using standardized lipoprotein separation techniques. However, the value of HDL measurement for predicting the occurrence of myocardial infarction in the individual patient has not been established.

PRIMARY HYPERLIPOPROTEINEMIAS RESULTING FROM SINGLE GENE MUTATIONS

Familial Lipoprotein Lipase Deficiency

This is a rare autosomal recessive disorder due to the absence or marked reduction in the activity of the enzyme lipoprotein lipase. This deficiency leads to a metabolic block in the metabolism of chylomicrons, causing these lipoproteins to accumulate to massive levels in plasma.

Clinical Features. The disease usually presents in infancy or childhood with recurrent attacks of abdominal pain. These attacks result from pancreatitis that occurs as a consequence of the massive elevation of chylomicrons in plasma. Affected individuals intermittently develop eruptive xanthomas, which are small yellowish papules, frequently surrounded by an erythematous base, that appear predominantly on the buttocks and other pressure sensitive surfaces. The xanthomas are caused by the deposition of large amounts of chylomicron-triglycerides in cutaneous histiocytes. Triglycerides are also deposited at widespread sites in phagocytes of the reticuloendothelial system, producing hepatomegaly, splenomegaly, and foam-cell infiltration of the bone marrow. When the level of chylomicrons in the blood is massively elevated (i.e., plasma triglyceride level greater than 3000 mg/dl), the blood appears pale and creamy and is said to be lipemic. When viewed with the ophthalmoscope, the retina appears extremely pale, and the retinal vessels are white, producing the classic appearance of lipemia retinalis. Despite the massive elevation of triglycerides in the bloodstream, accelerated atherosclerosis does not occur in patients with this disorder.

Pathogenesis. Affected individuals are homozygous for a mutation that prevents normal expression of lipoprotein lipase activity. The parents are obligate heterozygotes for this defect, but they are clinically normal. As a result of the deficiency of lipoprotein lipase, chylomicrons cannot be metabolized

normally, and the level of chylomicrons in the blood rises to extremely high levels after a fat meal. In normal individuals chylomicrons disappear from the blood after a 12 hour fast. However, in affected patients high levels of chylomicrons are found in the plasma even after several days of fasting or ingestion of a fat-free diet.

The circulating chylomicrons inflame the pancreas when they pass through its capillaries. Within the lumen, the chylomicrons are exposed to small amounts of pancreatic lipase that leaks from the tissue. Partial hydrolysis of the triglycerides and phospholipids of the chylomicron produces toxic products, including fatty acids and lysolecithin that break down tissue membranes and cause further leakage of lipase from the pancreatic acinar cells. This produces a vicious cycle that eventually causes fulminant pancreatitis.

Diagnosis. The diagnosis of familial lipoprotein lipase deficiency is suggested by the finding of lipemic plasma in a young individual who has been fasting for at least 12 hours. This lipemic plasma, when collected in the presence of EDTA, has a characteristic appearance after it has incubated overnight in a refrigerator at $4^{\circ}C$. A white layer of cream (which consists of chylomicrons) appears at the top of the tube. The infranatant layer beneath the cream layer is clear. The diagnosis of familial lipoprotein lipase deficiency is supported by the finding of a type 1 pattern on lipoprotein electrophoresis. It is confirmed by the demonstration that lipoprotein lipase levels in plasma fail to show the normal increase following the intravenous infusion of heparin. In normal individuals, intravenous heparin releases lipoprotein lipase from its binding sites within the capillary endothelium, and increased amounts of enzyme can then be assayed in the plasma.

Treatment. All of the symptoms and signs of the disease recede when the patient is placed on a fat-free diet. Every attempt should be made to maintain

the fasting plasma triglyceride level below 1000 mg/dl in order to prevent pancreatitis. It has been found empirically that the chronic fat intake in affected adults must be less than 20 gm per day in order to prevent symptomatic hyperlipemia. Since medium chain triglycerides are not normally incorporated into chylomicrons, they have been employed to help achieve normal caloric intake. The diet should be supplemented with fat-soluble vitamins.

Familial Dysbetalipoproteinemia

This is an inherited disorder in which the plasma concentrations of cholesterol and triglycerides are both elevated due to the accumulation in plasma of remnant-like particles derived from the partial catabolism of VLDL. Also called familial type 3 hyperlipidemia, this disorder is transmitted by a single-gene mechanism, but its expression appears to require the presence of contributory environmental and/or genetic factors (discussed below).

Clinical Features. Affected individuals do not characteristically manifest hyperlipidemia or any of the other clinical features of the disease until after the age of 20 years. In addition to the dysbetalipoproteinemia (discussed below), a unique clinical feature of this disorder is the occurrence of two types of cutaneous xanthomas. These are: xanthoma striata palmaris, which appear as orange or yellow discolorations of the palmar and digital creases, and tuberous or tuberoeruptive xanthomas, which are bulbous cutaneous xanthomas that may vary from pea to lemon-sized. These tuberous xanthomas are characteristically located over the elbows and knees. Xanthelasmas of the eyelids also occur, but these are not unique to this disorder (see section on Familial Hypercholesterolemia).

Severe and fulminant atherosclerosis involving the coronary arteries, the internal carotids, and the abdominal aorta and its branches is also a prominent

feature of the disorder. The clinical sequelae include the occurrence of premature myocardial infarctions, strokes, intermittent claudication, and gangrene of the lower extremities. Patients who develop clinical manifestations of dysbetalipoproteinemia are often found to have hypothyroidism, obesity, or diabetes mellitus.

Pathogenesis. The hyperlipidemia is caused by the accumulation of relatively large lipoprotein particles that contain both triglycerides and cholesteryl esters. These particles resemble the remnants that are normally produced from the catabolism of VLDL through the action of lipoprotein lipase. In normal subjects these remnant particles are rapidly taken up by the liver, and hence they are barely detectable in plasma. In patients with familial dysbetalipoproteinemia, the uptake of VLDL remnants by the liver is blocked, and these lipoproteins accumulate to high levels in plasma and deposit in tissues, producing xanthomas and atherosclerosis.

The mutation responsible for this disease appears to involve the gene that encodes the structure of apoprotein E, a protein that is normally found in VLDL and its remants and that is thought to play a role in the uptake of VLDL remnants by the liver. Apoprotein E is actually a complex of proteins that can be resolved by isoelectric focusing into three components, which are designated E-I, E-II, and E-III. Patients with familial dysbetalipoproteinemia are homozygous for a mutant gene that prevents the expression of the E-III component. Thus, affected individuals show a complete deficiency of E-III in their plasma.

Both parents of an E-III deficient subject and half of his or her first-degree relatives have a 50% deficiency of E-III, suggesting that they have one normal allele and one mutant allele at the genetic locus that specifies the E-III apoprotein. Inasmuch as the occurrence of familial dysbetalipoproteinemia requires a complete E-III deficiency, the disease would be expected to behave as a simple autosomal recessive trait. However, several factors act to make the inheritance

pattern atypical for an autosomal recessive disease. First, the frequency of the heterozygous state of E-III deficiency among the general population is extremely high, involving 12% of asymptomatic individuals. Moreover, about 1% of unselected asymptomatic individuals are homozygous for the E-III deficiency, yet most of these latter subjects have normal lipid levels. Only about 1 in 100 individuals with complete E-III deficiency express the familial dysbetalipoproteinemia syndrome. Thus, a situation exists in which all patients with symptomatic familial dysbetalipoproteinemia have homozygous E-III deficiency, but most patients with homozygous E-III deficiency never develop clinical signs of familial dysbetalipoproteinemia. Probably no more than 1 in 10,000 people among the general population show the typical clinical features of familial dysbetalipoproteinemia.

The high frequency of the heterozygous state for E-III deficiency gives rise to pedigrees in which symptomatic familial dysbetalipoproteinemia occurs in several generations of the same family. Such a pseudodominant inheritance pattern is caused by the fact that an individual homozygous for E-III deficiency has a 12% chance of marrying a heterozygote. In such a mating, half the children will have homozygous E-III deficiency, and thus a recessive trait will occur in a parent and a child. This situation is extremely rare in other recessive syndromes in which the heterozygous state is less common.

The nature of the factors that produce symptomatic dysbetalipoproteinemia in only a minority of patients with homozygous E-III deficiency are not known. The disease is markedly exacerbated by hypothyroidism, and many patients with E-III deficiency who develop symptomatic dysbetalipoproteinemia are found to have occult hypothyrodism. Other factors that predispose to the expression of the disease in an E-III deficient individual include obesity and the independent inheritance of diabetes mellitus or multiple lipoprotein-type hyperlipidemia.

Diagnosis. The diagnosis is suggested by the finding of palmar or tuberous xanthomas in a patient with elevated plasma levels of both cholesterol and triglyceride. Approximately 80% of symptomatic patients will exhibit these xanthomas. The diagnosis is also suggested when a moderate elevation in the plasma concentration of both cholesterol and triglyceride occurs in such a way that the absolute concentrations of cholesterol and triglyceride are nearly equal (e.g., the plasma cholesterol and triglyceride level are both about 300 mg/dl). This finding does not always hold true, and it is especially unreliable when the disease is in severe exacerbation, in which case the plasma triglyceride level tends to rise much higher than the cholesterol level.

The diagnosis is supported by the finding of a so-called "broad beta" band on lipoprotein electrophoresis (type 3 pattern). This appearance results from the presence of the remnant particles which migrate between β and pre-β lipoproteins and cause a distinctive smear of this region of the electrophoretogram. The diagnosis can be firmly established in specialized laboratories by two procedures. First, the plasma can be subjected to ultracentrifugation and the chemical composition of the VLDL fraction can be measured. In affected patients, the VLDL fraction will contain the abnormal remnant praticles and thus it will have a relatively high ratio of cholesterol to triglyceride. Second, the diagnosis can be confirmed by the finding of a complete deficiency of apoprotein E-III on isoelectric focusing of the proteins extracted from the remnant particles.

Treatment. A vigorous search for occult hypothyroidism should be made, including measurement of plasma thyroid stimulating hormone levels. If any evidence of hypothyroidism exists, a trial of L-thyroxine should be instituted. Patients who have hypothyroidism show a dramatic lowering of lipid levels when this condition is treated. In addition, attempts should be made to control obesity and diabetes mellitus through diet and insulin treatment as indicated.

If these measures are not successful, patients with familial dysbetalipoproteinemia should be treated with clofibrate. Affected patients with this disease usually show a dramatic and sustained reduction in plasma lipid levels when treated with this drug.

Familial Hypercholesterolemia

This common autosomal dominant disorder affects approximately 1 in 500 persons in the general population. Heterozygotes manifest a 2 to 3-fold elevation in the concentration of total plasma cholesterol which is attributable to an elevation in the plasma level of LDL. Rare cases of the homozygous form of this disease have been described in which 6 to 8-fold elevations in plasma LDL-cholesterol levels occur.

Clinical Features. Heterozygotes with familial hypercholesterolemia can often be diagnosed at birth because their umbilical cord blood contains a 2 to 3-fold increased concentration of LDL-cholesterol. The elevated levels of LDL in plasma persist throughout life, but symptoms do not typically develop until the third to fourth decade. The most important clinical feature is the occurrence of premature and accelerated coronary atherosIcerosis. Myocardial infarctions begin to occur in male subjects in the third decade and show a peak incidence in the fourth and fifth decades. By the age of 60, approximately 85% of affected males will have experienced a myocardial infarction. In females the incidence of myocardial infarction is also extremely elevated, but the mean age of onset is delayed by 10 years as compared with males. Heterozygotes constitute about 5% of all patients who have a myocardial infarction.

Xanthomas of the tendons constitute the second major clinical manifestation of the heterozygous state for familial hypercholesterolemia. These xanthomas are nodular swellings that typically involve the Achilles tendon and various tendons

about the knee, elbow, and dorsum of the hand. They are formed by the deposition of LDL-derived cholesteryl esters in the interstitial spaces and within tissue macrophages that become so swollen with lipid droplets that they resemble foam cells. Cholesterol also deposits about the soft tissue of the eyelid producing xanthelasma and within the cornea producing arcus corneae. Whereas tendon xanthomas are essentially diagnostic of familial hypercholesterolemia, xanthelasma and arcus corneae are not so specific. The latter abnormalities also occur in many adults with normal plasma lipid levels. The incidence of tendon xanthomas in familial hypercholesterolemia increases with age, but no more than 75% of affected heterozygotes display this sign.

Approximately 1 in 1 million persons in the general population inherits two copies of the familial hypercholesterolemia gene and is a homozygote for this disorder. These individuals have marked elevations in the plasma level of LDL from birth, the plasma cholesterol level usually being 6 to 8-fold above normal. A unique type of planar cutaneous xanthoma is often present at birth and always develops within the first six years of life. These characteristic xanthomas are raised yellow plaque-like lesions that occur at points of cutaneous trauma, such as over the knees, elbows, and buttocks. Moreover, they almost always occur in the interdigital webs of the hands, particularly between the thumb and index finger. Tendon xanthomas, arcus corneae, and xanthelasma also occur in homozygotes, as they do in heterozygotes.

Coronary artery atherosclerosis frequently has its clinical onset in homozygotes before the age of 10. A myocardial infarction as early as 18 months of age has been recorded. In addition to coronary atherosclerosis with its accompanying angina pectoris and myocardial infarctions, homozygotes frequently develop cholesterol deposition in the aortic valve producing symptomatic aortic stenosis. Homozygotes usually succumb to the complications of myocardial infarction before the age of 20.

In contrast to the disorders causing hypertriglyceridemia, in familial hypercholesterolemia obesity and diabetes mellitus do not occur with increased frequency. A slender body habitus is the general rule.

Pathogenesis. The primary defect resides in the gene for the LDL receptor. Three types of mutant alleles at this locus have been described. The most common mutant allele, designated receptor-negative or R^{b^o}, specifies a gene product that is nonfunctional. The second most common mutant allele, designated receptor-defective or R^{b-}, produces a receptor that has 1 to 10% of normal LDL binding activity. The third type of mutant allele, designated R^{b^+,i^o}, produces a receptor that binds LDL normally but is unable to transport the receptor-bound lipoprotein into the cell. This very rare allele produces the so-called internalization defect.

Phenotypic homozygotes possess two mutant alleles at the LDL receptor locus, and hence their cells show a total or near total inability to bind or take up LDL. Heterozygotes have one normal allele and one of the three mutant alleles at the LDL receptor locus, and hence their cells are able to bind and take up LDL at one-half the normal rate.

Because of the reduction in LDL receptor activity, LDL catabolism is blocked and the level of LDL in plasma rises in a manner that is inversely proportional to the reduction in LDL receptors. In addition to the impaired catabolism of LDL, in homozygotes an increased production of LDL has also been noted. This enhanced production has been attributed to the lack of an LDL receptor on liver cells such that the liver fails to sense the adequacy of the plasma LDL level with consequent overproduction of LDL. In contrast to normal individuals in whom all plasma LDL appears to be derived from VLDL, in FH homozygotes a large fraction of circulating LDL is secreted directly from the liver into the plasma. This overproduction of LDL, together with its reduced catabolism, contributes to the high LDL levels in affected patients.

In homozygotes the LDL level rises 6 to 8-fold above normal, and in heterozygotes the level rises 2 to 3-fold above normal before a steady state is obtained. In both types of subjects, the elevated LDL level causes an increase in the uptake of LDL by scavenger cells, and LDL accumulates in these macrophage-like cells at various sites in the body, such as in tendons producing xanthomas.

The accelerated coronary atheroslcerosis in this disease also results from the high LDL levels, which lead to an enhanced infiltration of LDL into the artery wall following episodes of endothelial damage. The large amounts of LDL that penetrate into the artery wall present a load of lipoproteins that is greater than can be cleared from the interstitial space by the scavenger cells, and atherosclerosis ultimately results. Evidence also indicates that the high LDL levels may act on platelets to accelerate their aggregation at sites of endothelial injury, thereby enhancing the growth of the atherosclerotic plaque (see Chapter 250).

Diagnosis. The diagnosis of heterozygous familial hypercholesterolemia is suggested by the finding of an isolated elevation of plasma cholesterol, with a normal concentration of plasma triglycerides. In nearly all cases, such an isolated elevation in plasma cholesterol will be due to an isolated elevation in the plasma concentration of LDL (type 2a pattern). However, most individuals in the general population with type 2a hyperlipoproteinemia do not have familial hypercholesterolemia. The majority of such patients have a form of polygenic hypercholesterolemia that puts them on the upper end of the bell-shaped curve for the general population (see section of Polygenic Hypercholesterolemia). Type 2a hyperlipoproteinemia is also caused by the disease multiple lipoprotein-type hyperlipidemia (discussed below). In addition, a variety of metabolic disorders, including hypothyroidism and nephrotic syndrome, can cause type 2a hyperlipoproteinemia (Table 100-IV).

Among individuals who have a type 2a lipoprotein pattern, those with heterozygous familial hypercholesterolemia can be distinguished from those with polygenic hypercholesterolemia and multiple lipoprotein-type hyperlipidemia on several grounds. First, in familial hypercholestermia the plasma cholesterol level tends to be higher. A plasma cholesterol level in the range of 350 to 400 mg/dl is much more suggestive of heterozygous familial hypercholestermia than the other disorders. However, many patients with heterozygous familial hypercholestermia have cholesterol levels of 285-350 mg/dl, a range in which the other disorders cannot be ruled out. Second, the occurrence of tendon xanthomas virtually establishes the diagnosis of familial hypercholesterolemia since such xanthomas do not typically occur in patients with other forms of hyperlipidemia. In cases where the diagnosis is in doubt, other family members should be surveyed. In familial hypercholesterolemia the penetrance of the gene is extremely high with 50% of first-degree relatives showing an elevated plasma cholesterol level. Hypercholesterolemia is particularly informative when it occurs in children since hypercholesterolemia in childhood is characteristic of familial hypercholesterolemia but not of any of the other aforementioned disorders.

Approximately 10% of heterozygotes with familial hypercholestermia have an elevation in the plasma triglyceride level in addition to the raised cholesterol level (type 2b pattern). In these cases, the disease is difficult to differentiate from mutiple lipoprotein-type hyperlipidemia. The finding of a tendon xanthoma or a hypercholesterolemic child in the family would favor the diagnosis of heterozygous familial hypercholesterolemia.

The diagnosis of homozygous familial hypercholestermia ordinarily affords no problem, providing that the physician is familar with this rare entity. Most of these patients present to dermatologists in childhood because of the obvious cutaneous xanthomas. Occasionally, the presentation is delayed until the onset

of angina pectoris or until the child suffers a syncopal episode owing to the xanthomatous aortic stenosis. The finding of a cholesterol level greater than 600 mg/dl with a normal triglyceride level in a nonjaundiced child is highly suggestive of the diagnosis. Both parents should have moderately elevated cholesterol levels and other features of heterozygous familial hypercholesterolemia.

In specialized laboratories the diagnosis of both heterozygotes and homozygotes familial hypercholesterolemia can be made by direct measurement of the number of LDL receptors on cultured skin fibroblasts or freshly isolated blood lymphocytes. Homozygous familial hypercholesterolemia has been diagnosed *in utero* by the finding of an absence of LDL receptors on cultured amniotic fluid cells.

Treatment. Inasmuch as the atherosclerosis in this disorder is a consequence of the long-standing elevation in plasma LDL levels, every effort should be made to lower the plasma LDL level into the normal range. Patients should be placed on a diet that is low in cholesterol, low in saturated fats, and high in polyunsaturated fats. This generally means the avoidance of milk, butter, cheese, chocolate, shellfish, and fatty meats and the addition of liquid cooking oils such as corn oil and safflower oil. With such a diet, heterozygotes usually show a 10-15% drop in plasma cholesterol level.

Bile acid binding resins, such as cholestyramine, should be added to the regimen when dietary therapy fails to lower the cholesterol levels to the normal range. These resins trap the bile acids that are secreted by the liver into the intestine and carry them into the feces. Since the body responds to bile acid depletion by converting additional cholesterol into bile acids, the initial result is a dramatic loss of cholesterol from the body. However, affected subjects respond to bile acid depletion by developing enhanced cholesterol synthesis in the liver, and this compensatory response ultimately limits the long-term success of this therapy. With the combination of diet and bile acid binding resins, the

extent of reduction in plasma cholesterol level that is usually achieved in heterozygotes is in the range of 25%. The addition of nicotinic acid may help to block the compensatory increase in hepatic cholesterol synthesis, thus allowing a further lowering of the cholesterol levels. A major side effect of bile acid binding resins consists of gastrointestinal bloating, cramps, and constipation. The major side effect of nicotinic acid is hepatotoxicity; it also produces flushing and headaches in most patients. Several other agents, such as probucol, are sometimes used for the treatment of familial hypercholesterolemia. Their efficacy has not been demonstrated.

Affected heterozygotes will often show a moderate-to-marked lowering of plasma cholesterol level in response to the creation of an intestinal anastomosis that bypasses the ileum. This operation has the same functional effect as bile acid binding resins, i.e., it causes a loss of bile acids in the stool. In certain patients in whom drug therapy is not tolerated the performance of an ileal bypass may be indicated.

Homozygotes are much more resistant than heterozygotes to all forms of treatment. In general, combination therapy consisting of diet, a bile acid binding resin, and nicotinic acid has little effect. Ileal bypass is uniformly ineffective in homozygotes. Several children have responded to the performance of a portacaval anastomosis. However, this procedure is still considered to be experimental. The use of a continuous-flow blood cell to perform plasma exchanges at monthly intervals is one treatment that will lower the cholesterol in all homozygotes. After each plasma exchange, the plasma cholesterol level drops to about 300 mg/dl and then gradually rises over the ensuing 4 weeks to the pretreatment level of 600 to 900 mg/dl. When facilities for carrying out this procedure on a monthly basis are available, plasma exchange is the treatment of choice for familial hypercholesterolemia homozygotes.

Familial Hypertriglyceridemia

This is a common autosomal dominant disorder in which the concentration of VLDL is elevated in the plasma, causing hypertriglyceridemia.

Clinical Features. Affected individuals do not usually express hypertriglyceridemia until puberty or early adulthood. Thereafter, the fasting plasma triglyceride level tends to be moderately elevated in the range of 200 to 500 mg/dl (type 4 lipoprotein pattern). The typical affected patient exhibits a clinical triad consisting of obesity, hyperglycemia, and hyperinsulinemia. In addition, hypertension and hyperuricemia are frequent.

The incidence of atherosclerosis is increased in patients with familial hypertriglyceridemia. In one study affected patients constituted 6% of all patients with myocardial infarction. However, it has not been established that the hypertriglyceridemia *per se* accounts for the increased atherosclerosis. As discussed above, many patients with this disease have diabetes, obesity, and hypertension. Each of these features by itself may predispose to atherosclerosis. Xanthomas are not a characteristic feature of familial hypertriglyceridemia.

Affected patients who ordinarily have mild to moderate hypertriglyceridemia can develop a severe exacerbation when exposed to a variety of precipitating factors. These include: poorly-controlled diabetes, excessive consumption of alcohol, ingestion of birth control pills containing estrogen, and the development of hypothyroidism. In response to any one of these stimuli, the plasma triglyceride level in affected patients can rise to values well in excess of 1000 mg/dl. Under these conditions, large triglyceride-laden particles with the characteristics of chylomicrons appear in plasma. During these exacerbations, such patients develop *mixed hyperlipemia* - i.e., they show an elevation in the concentration of both VLDL and chylomicrons (type 5 lipoprotein pattern). Whenever the concentration

of chylomicrons rises to high levels, patients are predisposed to the formation of eruptive xanthomas and the development of pancreatitis. With treatment of the exacerbating condition, the chylomicron-like particles disappear from plasma, and the patient returns to his basal condition in which the concentration of triglycerides is moderately elevated.

In certain families with familial hypertriglyceridemia, some of the patients exhibit a severe mixed hyperlipemia even in the absence of known exacerbating factors. This is the so-called "familial type 5 hyperlipidemia". Other affected individuals in the same family may have only the mild form of the disease with moderate hypertriglyceridemia and no hyperchylomicronemia (type 4 pattern).

Pathogenesis. The disease is transmitted within families as an autosomal dominant trait, implying a mutation in a single gene. However, the nature of the mutant gene and the mechanism by which it produces hypertriglyceridemia have not been identified. It is likely that this disorder is genetically heterogeneous in that patients from different families may have different mutations accounting for the hypertriglyceridemia phenotype.

Metabolic studies show that some affected patients have an elevated production rate for VLDL, especially when they ingest diets that are high in carbohydrate. However, many of these patients suffer from obesity and diabetes mellitus. Other individuals with obesity and diabetes mellitus, who have normal plasma VLDL levels, also overproduce VLDL. The latter observation has led to the suggestion that patients with familial hypertriglyceridemia have an underlying defect in their ability to catabolize the triglycerides of VLDL. When VLDL production rates become elevated due to obesity or diabetes these patients are unable to increase the catabolism of VLDL proportionately and hypertriglyceridemia results. However, lipoprotein lipase activity in plasma following the administration of heparin is generally normal in these patients. No abnormalities of lipoprotein structure have thus far been identified.

The reason for the increased prevalence of diabetes and obesity in this syndrome is believed to be fortuitous, owing to the fact that both of these conditions tend to increase VLDL production and hence to exacerbate hypertriglyceridemia. Thus, in family studies, one can find relatives who have diabetes without hypertriglyceridemia and relatives who have hypertriglyceridemia without diabetes, indicating that the two diseases are inherited by independent mechanisms. When an individual inherits both the gene(s) for diabetes and the gene for hypertriglyceridemia, the hypertriglyceridemia is much more severe and such a person is more apt to come to medical attention. Similarly, an individual with familial hypertriglyceridemia who has a normal weight will usually have mild hypertriglyceridemia and will be less likely to come to medical attention. However, if such an individual becomes obese, the hypertriglyceridemia will worsen and a diagnosis is more likely to be made.

Diagnosis. The finding of a moderate elevation in plasma triglyceride level, together with a normal cholesterol level, raises the possibility of familial hypertriglyceridemia. In most patients, the plasma will be clear to somewhat cloudy on inspection. Chylomicrons will not typically be found at the top of the plasma after it has been placed in a refrigerator overnight. Electrophoresis of the plasma will show an increase in the pre-β fraction (type 4 lipoprotein pattern). As mentioned above, an occasional patient will exhibit severe hypertriglyceridemia with an elevation in chylomicrons and VLDL. In this case, the plasma will show a cream layer on top (chylomicrons) and a cloudy infranatant layer (VLDL) after overnight storage in the refrigerator (type 5 lipoprotein pattern).

Given an individual who has an elevation in VLDL levels with or without an elevation in chylomicrons, no simple test currently exists to determine whether this subject has familial hypertriglyceridemia or hypertriglyceridemia due to

some other genetic or acquired cause, such as multiple lipoprotein-type hyperlipidemia or sporadic hypertriglyceridemia. In a typical case of familial hypertriglyceridemia, 50% of the first-degree relatives will show hypertriglyceridemia and no relatives with isolated hypercholesterolemia should be found. Measurement of plasma lipid levels in children is not usually of diagnostic value inasmuch as the disease does not typically manifest until the time of puberty.

Treatment. Attempts should be made to control all of the exacerbating conditions. In particular, the diet should be restricted in calories until the patient loses weight. The dietary content of saturated fat should also be restricted. Alcohol and oral contraceptives should be avoided. Diabetes mellitus, if present, should be controlled. Thyroid function should be checked and hypothyroidism should be treated vigorously. If the above measures fail, patients frequently respond to the administration of clofibrate, a drug whose mechanism of action is unknown.

Multiple Lipoprotein-type Hyperlipidemia

This common disorder, which is also called familial combined hyperlipidemia, is inherited as an autosomal dominant trait. Affected individuals in a single family characteristically show one of three different lipoprotein patterns: hypercholesterolemia (type 2a), hypertriglyceridemia (type 4), or both hypercholesterolemia and hypertriglyceridemia (type 2b).

Clinical Features. Hyperlipidemia is not ordinarily present in affected patients in childhood. Elevations in the plasma cholesterol and/or triglyceride level begin to appear at puberty and continue throughout life. The lipid elevations tend to be mild and tend to change from time to time so that affected individuals may have a mildly elevated cholesterol level at one examination and/or a mildly

elevated triglyceride level at another time. Xanthomas are not a feature of this condition. However, premature atherosclerosis occurs, and the incidence of myocardial infarction in middle age is elevated in affected women as well as men. Thus, patients usually exhibit a strong family history of premature coronary artery disease. Patients with this disorder constitute about 10% of all patients who have a myocaridal infarction. The frequency of obesity, hyperuricemia, and glucose intolerance is increased in affected individuals, especially those with hypertriglyceridemia. However, this association is not so striking as the one found with familial hypertriglyceridemia.

Pathogenesis. The disease is transmitted within families as an autosomal dominant trait, implying a mutation in a single gene. Family studies show that about half of the first-degree relatives of an affected individual also have hyperlipidemia. However, blood lipid levels are highly variable among affected individuals in the same family as well as in the same individual at different times. About one-third of hyperlipidemic relatives will have hypercholesterolemia (type 2a lipoprotein pattern), one-third will have hypertriglyceridemia (type 4), and one-third will have both hypercholesterolemia and hypertriglyceridemia (type 2b). In most affected relatives the plasma lipid levels tend to be just above the 95th percentile for the population and to dip into the normal range intermittently.

While the extent of the genetic heterogeneity and the nature of the precise biochemical mechanism underlying the disease are not known, it has been postulated that affected individuals have an elevated secretion rate for VLDL from the liver. Depending on the interplay of factors governing the efficiency of conversion of VLDL to LDL and the efficiency of catabolism of LDL, this overproduction of VLDL may manifest itself alternatively as an elevation in plasma VLDL levels (hypertriglyceridemia), an elevation in LDL levels (hypercholesterolemia), or both. The hyperlipidemia in patients with hypertriglyceridemia is worsened by diabetes, alcoholism, and hypothyroidism.

Diagnosis. No clinical or laboratory methods exist by which to determine at one point in time whether an individual with hyperlipidemia has the multiple lipoprotein-type disorder. The 2a, 2b, and 4 lipoprotein patterns can each occur in patients with several other diseases (see Tables 100-III and 100-IV). However, this disorder should be suspected in any individual whose hyperlipoproteinemia is mild and whose lipoprotein type changes with time. The diagnosis is supported by the finding of multiple abnormal lipoprotein types among the individual's relatives. The diagnosis can be ruled out by the finding of tendon xanthomas in the patient or in his relatives or by the finding of hypercholesterolemia in a relative under the age of 10 years.

Treatment. Therapy should be directed at the predominant lipid that is elevated at a given time in a given individual. General measures such as weight reduction, restriction of dietary saturated fat and cholesterol, and avoidance of alcohol and oral contraceptives are useful. In addition, when the triglyceride level is elevated with or without hypercholesterolemia, affected individuals may respond to clofibrate. When the cholesterol level alone is elevated, a response to a bile acid binding resin may be achieved. However, in some individuals the lowering of cholesterol levels with such a drug is accompanied by an increase in triglyceride levels that tends to negate its beneficial effects.

PRIMARY HYPERLIPOPROTEINEMIAS OF UNKNOWN ETIOLOGY

Polygenic Hypercholesterolemia

By definition, 5% of individuals in the general population have LDL-cholesterol levels that exceed the 95th percentile and therefore have hypercholesterolemia (type 2a or type 2b lipoprotein patterns). On the average, among every 20 such hypercholesterolemic persons, one person will have the heterozygous form of

familial hypercholesterolemia and two will have multiple lipoprotein-type hyperlipidemia. The remaining 17 will have a form of hypercholesterolemia, designated polygenic hypercholesterolemia, that owes its origin not to a single mutant gene but rather to a complex interaction of multiple genetic and environmental factors that determines the LDL-cholesterol level in every individual. Most of the factors that place an individual in the upper part of the bell-shaped curve for cholesterol levels are not known. It is likely that subtle genetic differences exist among people with regard to many processes governing cholesterol metabolism. For example, among normal people there may be genetic polymorphisms in the proteins that govern the rates of intestinal cholesterol absorption, bile acid synthesis, cholesterol synthesis, and LDL synthesis or catabolism. Particular unfavorable combinations of these mildly altered proteins, coupled with an environmental challenge, such as a diet high in cholesterol or saturated fat, may raise the plasma cholesterol level in certain individuals.

Clinically, there are several ways to distinguish polygenic hypercholesterolemia from familial hypercholesterolemia and multiple lipoprotein-type hyperlipidemia: 1) family studies (hyperlipidemia is present in no more than 10% of first-degree relatives in polygenic hypercholesterolemia in contrast to 50% in the other two disorders); and 2) examination for tendon xanthomas (absent in both polygenic hypercholesterolemia and multiple lipoprotein-type hyperlipidemia but present in about 75% of adult heterozygotes with familial hypercholesterolemia).

Certain patients with polygenic hypercholesterolemia respond well to dietary restriction of saturated fat and cholesterol. Other patients require drug therapy in order to achieve a significant lowering of plasma cholesterol levels. Clofibrate is sometimes effective in this latter group. Cholestyramine may also be used.

Sporadic Hypertriglyceridemia

In addition to the forms of primary hypertriglyceridemia that show familial aggregation, endogenous hypertriglyceridemia with or without hyperchylomicronemia is sometimes seen in individuals whose relatives do not manifest hyperlipidemia. For purposes of classification, this form of hypertriglyceridemia is called sporadic hypertriglyceridemia. Affected patients comprise a heterogeneous group. Some of them would undoubtedly be classified under one of the genetic disorders described above if a larger number of relatives were available for lipid measurements. Other than for an absence of hyperlipidemic relatives, patients with sporadic hypertriglyceridemia cannot be distinguished clinically from patients with the single-gene forms of primary hypertriglyceridemia. Inasmuch as patients with sporadic hypertriglyceridemia may develop hyperchylomicronemia and pancreatitis, they should be treated with diet and drugs as described above for familial hypertriglyceridemia.

Familial Hyperalphalipoproteinemia

This disorder is characterized by elevated plasma levels of HDL, which is also called alpha-lipoprotein. The plasma levels of LDL, VLDL, and triglycerides are normal. The elevated HDL causes a slight elevation in the total plasma cholesterol level. Although a selective elevation in plasma HDL-cholesterol can be observed in individuals after exposure to cholorinated hydrocarbon pesticides, in alcoholism, and after administration of exogenous estrogen, most cases of hyperalphalipoproteinemia have a genetic basis. In some cases, hyperalphalipoproteinemia is inherited as an autosomal dominant trait, while in others a multifactorial or polygenic basis is suspected.

Individual subjects with familial hyperalphalipoproteinemia show no distinctive clinical findings other than a selective increase in the plasma level of HDL-

cholesterol. Statistical studies of families with this disorder suggest that the hyperalphalipoproteinemia is associated with a slightly increased longevity and an apparent protection against myocardial infarction. The mechanism for the quantitative increase in plasma HDL levels in this disorder remains to be determined.

SECONDARY HYPERLIPOPROTEINEMIAS

A variety of clinical disorders produce secondary hyperlipoproteinemias. These are summarized in Table 100-IV and discussed in detail in Chapter 7 in the 8th edition of Diseases of Metabolism (see references). The three most frequently encountered forms of secondary hyperlipoproteinemia occur in association with diabetes mellitus, consumption of alcohol, and ingestion of oral contraceptives. These three situations are discussed below.

Diabetes Mellitus

Three distinct patterns of hypertriglyceridemia occur in patients with diabetes mellitus. Classical "diabetic hyperlipemia" consists of a massive elevation in the plasma triglyceride level that occurs in patients who have suffered from insulin deficiency or insulin resistance for many weeks or months. Such insulin-deprived patients develop a progressive increase in concentration of plasma VLDL and eventually of chylomicrons as well. Triglyceride levels as high as 25,000 mg/dl are seen. Eruptive xanthomas and lipemia retinalis are common, and hepatomegaly can occur secondary to fatty infiltration. Ketosis is frequently present, but severe acidosis does not characteristically occur. It should be emphasized that this form of massive hyperlipemia is only seen in patients who have been in a state of partial insulin deficiency for several weeks. Patients with total insulin deficiency develop acute diabetic ketoacidosis before they

have sufficient time to develop massive hyperlipemia. Patients with classical diabetic hyperlipemia usually respond to a fat-free diet and to the administration of insulin.

The second type of hypertriglyceridemia that occurs in diabetics is that associated with acute ketoacidosis. On admission to the hospital, such patients frequently exhibit a mild hyperlipidemia with elevations of VLDL but not chylomicrons. The triglyceride level is below 500 mg/dl and quickly returns to normal with control of the diabetes.

The third type of hypertriglyceridemia in diabetics is a mild to moderate elevation in plasma VLDL that persists even when patients appear to be adequately treated for their diabetes. This chronic type of triglyceride elevation generally occurs in patients who are obese. Inasmuch as most patients with well-controlled diabetes have normal plasma triglyceride levels, the occasional patient with persistent hypertriglyceridemia is likely to have an underlying familial hyperlipoproteinemic disorder. Indeed, family studies indicate that many of these patients have inherited the trait for familial hypertriglyceridemia in a pattern independent of the inheritance of diabetes mellitus (discussed above).

The insulin deficiency or insulin resistance of diabetes produces a high VLDL level by two mechanisms. With acute insulin deprivation there is an increase in VLDL secretion from the liver as a secondary response to the increased mobilization of free fatty acids from adipose tissue. As the state of insulin deprivation becomes prolonged, the rate of removal of VLDL and chylomicrons from the circulation declines because lipoprotein lipase activity becomes diminished.

Alcohol Consumption

In any individual the daily consumption of large amounts of ethanol can produce a mild and clinically asymptomatic elevation in the plasma triglyceride level due to an elevation in VLDL. However, a subgroup of individuals exists in whom ethanol ingestion regularly produces massive and clinically significant hyperlipemia with elevations in both VLDL and chylomicrons (type 5 lipoprotein pattern). In most of these severely affected individuals, the VLDL level remains mildly elevated (type 4 lipoprotein pattern) even when they are in a basal state after recovery from alcoholic hyperlipemia. This suggests that these individuals may have a form of familial hypertriglyceridemia or multiple lipoprotein-type hyperlipidemia that is exacerbated and converted to a type 5 pattern by the ethanol ingestion.

Ethanol elevates the plasma triglyceride level primarily because it inhibits fatty acid oxidation and enhances fatty acid synthesis in the liver. The excess fatty acids are esterified to triglyceride. Some of this excess triglyceride accumulates in the liver, producing the characteristic enlarged fatty liver of alcoholics. The remainder of the newly formed triglyceride is excreted into plasma, resulting in an increased secretion of VLDL. In those individuals who develop massive alcoholic hyperlipemia, there appears to be a partial defect in the catabolism of these VLDL particles. As the concentration of VLDL increases, the lipoprotein begins to compete with chylomicrons for hydrolysis by lipoprotein lipase, and the plasma concentration of chylomicrons also rises.

In severe alcoholic hyperlipemia, eruptive xanthomas and lipemia retinalis are frequently present. The most serious complication is pancreatitis, which is frequently life-threatening. Pancreatitis may be difficult to diagnose since elevated triglyceride levels can interfere with the estimation of serum amylase. There is no solid evidence to indicate that pancreatitis itself can cause hyperlipemia, but rather the hyperlipemia is the cause of the pancreatitis.

Plasma from patients with alcoholic hyperlipemia is creamy in appearance. If a blood sample is drawn in EDTA and the plasma placed in the refrigerator at $4^{o}C$ overnight, the chylomicrons will float to the top of the tube and the infranatant layer will be turbid, owing to the combined elevation of VLDL and chylomicrons (type 5 pattern).

Oral Contraceptives

The ingestion of estrogen-containing birth control pills is regularly associated with an increase in the VLDL secretion rate from the liver. In most women the catabolism of VLDL also increases so that the overall increase in plasma triglyceride level is only modest. However, in women who have an underlying genetic disorder (such as familial hypertriglyceridemia or multiple lipoprotein-type hyperlipidemia), the plasma VLDL-triglyceride level can increase to massive degrees and hyperchylomicronemia can appear when estrogen-containing medications are taken. These women generally have mild to moderate hypertriglyceridemia prior to the institution of oral contraceptive therapy, and they presumably are unable to increase their VLDL catabolism in response to the stimulation of VLDL production. As the plasma VLDL concentration rises, the elevated VLDL prevents the normal catabolism of chylomicrons by lipoprotein lipase, and secondary hyperchylomicronemia ensues. When the latter develops, severe pancreatitis can occur.

In addition to the adverse effects on triglyceride metabolism, ingestion of oral contraceptives has been implicated as a risk factor in promoting thromboembolic disease in young women, especially those with pre-existing hypercholesterolemia. Thus, it is important to measure the plasma cholesterol and triglyceride levels prior to the institution of birth control therapy. The finding of hyperlipidemia should be a contraindication to the use of these drugs.

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TABLE 100-I

Characteristics of the Major Classes of Lipoproteins in Human Plasma

LIPOPROTEIN CLASS	MAJOR CORE LIPIDS	MAJOR APOPROTEINS	DENSITY (g/ml)	DIAMETER (Å)	ELECTROPHORETIC MOBILITY
Chylomicrons	Dietary triglycerides	A-I, A-II, B, C-I, C-II, C-III	< 1.006	800-5000	Remains at origin
VLDL	Endogenous triglycerides	B, C-I, C-II, C-III, E	< 1.006	300-800	pre-β
Remnants	Cholesteryl esters, triglycerides	B, C-III, E	<1.019	250-350	slow pre-β
LDL	Cholesteryl esters	B	1.019-1.063	180-280	β
HDL	Cholesteryl esters	A-I, A-II	1.063-1.210	50-120	α

TABLE 100-II

Patterns of Lipoprotein Elevation in Plasma

(Lipoprotein Types)

Lipoprotein Pattern	Major Elevation In Plasma	
	Lipoprotein	Lipid
Type 1	Chylomicrons	Triglycerides
Type 2a	LDL	Cholesterol
Type 2b	LDL and VLDL	Cholesterol and triglycerides
Type 3	Remnants	Triglycerides and cholesterol
Type 4	VLDL	Triglycerides
Type 5	VLDL and chylomicrons	Triglycerides and cholesterol

TABLE 100-III

Characteristics of the Primary Hyperlipoproteinemias Resulting from Single Gene Mutations

Genetic Disorder	Primary Biochemical Defect	Plasma Lipoprotein Elevation	Lipoprotein Pattern	Typical Clinical Findings			Lipoprotein Pattern in Affected Relatives
				Xanthomas	Pancreatitis	Premature Atherosclerosis	
Familial Lipoprotein Lipase Deficiency	Deficiency of lipoprotein lipase	Chylomicrons	1	Eruptive	+		1
Familial Dysbeta-lipoproteinemia	Deficiency of apoprotein E-III of VLDL	Remnants	3	Xanthelasma; tuberous; palmar creases		+	3 or 4
Familial Hyper-cholesterolemia	Deficiency of LDL receptor	LDL	2a (rarely 2b)	Xanthelasma; tendon		+	2a (rarely 2b)
Familial Hyper-triglyceridemia	Unknown	VLDL (rarely Chylomicrons)	4 (rarely 5)	(Eruptive)	(+)	+	4 (rarely 5)
Multiple Lipoprotein-type Hyperlipidemia (Familial Combined Hyperlipidemia)	Unknown	LDL and VLDL	2a, 2b, or 4 (rarely 5)			+	2a, 2b, or 4 (rarely 5)

TABLE 100-IV

Clinical Disorders Associated with Secondary Hyperlipoproteinemia

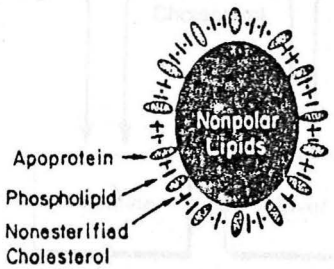
Underlying Disorder	Plasma Lipoprotein Elevation				Lipoprotein Type	Proposed Mechanism for Hyperlipoproteinemia	Associated Abnormality of Carbohydrate Metabolism
	Chylo-microns	Remnants	VLDL	LDL			
ENDOCRINE AND METABOLIC							
Diabetes Mellitus	+		+++		4 (rarely 5)	Increased secretion of VLDL. Decreased catabolism of VLDL and chylomicrons due to reduced lipoprotein lipase activity	Insulin deficiency or resistance
von Gierke's Disease (Glycogenosis, Type I)	+		+++		4 (rarely 5)	Increased secretion of VLDL. Decreased catabolism of VLDL and chylomicrons due to reduced lipoprotein lipase activity	Hypoglycemia with decreased insulin secretion
Lipodystrophies (congenital and acquired forms)			++		4	Increased secretion of VLDL	Insulin resistance
Cushing's Syndrome			+	++	2a or 2b	Increased secretion of VLDL with conversion to LDL	Insulin resistance
Sexual Ateliotic Dwarfism (isolated growth hormone deficiency)			++	++	2b	Increased secretion of VLDL with conversion to LDL	Insulin deficiency or resistance
Acromegaly			+		4	Increased secretion of VLDL	Insulin resistance
Hypothyroidism		+		+++	2a (rarely 3)	Decreased catabolism of LDL and remnants	

Anorexia Nervosa			++	2a	Reduced biliary excretion of cholesterol and bile acids	
Werner's Syndrome			++	2a	Unknown	Insulin resistance
Acute Intermittent Porphyria			++	2a	Unknown	
DRUG-INDUCED						
Alcohol	+	+++		4 (rarely 5)	Increased secretion of VLDL in individuals genetically predisposed to hypertriglyceridemia	
Oral Contraceptives	+	+++		4 (rarely 5)	Increased secretion of VLDL in individuals genetically predisposed to hypertriglyceridemia	Insulin resistance
Glucogenic Corticosteroids		+	++	2a or 2b	Increased secretion of VLDL with conversion to LDL	Insulin resistance
RENAL						
Uremia		+++		4	Decreased catabolism of VLDL due to reduced lipoprotein lipase activity	Insulin resistance
Nephrotic Syndrome		++	+++	2a or 2b	Increased secretion of VLDL. Direct secretion of LDL from liver. Decreased catabolism of VLDL and LDL	
HEPATIC						
Primary Biliary Cirrhosis and Extrahepatic Biliary Obstruction				↑ Cholesterol ↑ Phospholipids ↑ Lipoprotein X	Diversion of biliary cholesterol and phospholipids into bloodstream	

Acute Hepatitis (non-fulminant)			+++	4	Decreased hepatic secretion of lecithin:cholesterol acyltransferase (LCAT)
Hepatoma			++	2a	Lack of feedback inhibition of hepatic cholesterol synthesis by dietary cholesterol
IMMUNOLOGIC					
Systemic Lupus Erythematosis	++			1	Presence of IgG or IgM that binds heparin, thereby decreasing activity of lipoprotein lipase
Monoclonal Gammopathies (myeloma, macroglobulinemia, lymphoma)		++	++	3 or 4	Presence of IgG or IgM that forms immune complex with remnants and/or VLDL, thereby decreasing their catabolism
STRESS-INDUCED					
Emotional stress, acute myocardial infarction, extensive burns, acute gram-negative sepsis			++	4	Increased secretion and decreased catabolism of VLDL

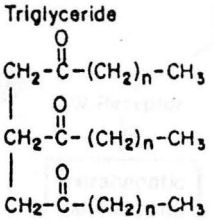
FIGURE 1

A. TYPICAL LIPOPROTEIN PARTICLE



B. NONPOLAR LIPIDS

Triglyceride



Cholesteryl Ester

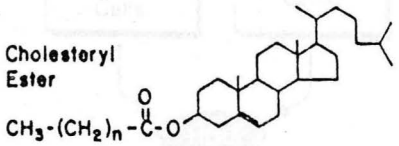
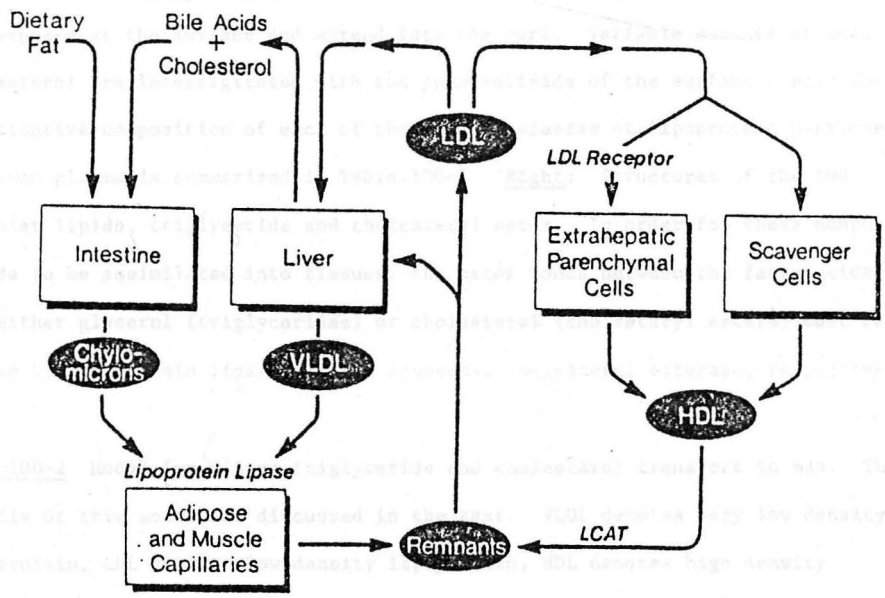


FIGURE 2


Dietary Fat
Bile Acids + Cholesterol
LDL
LDL Receptor
Intestine
Liver
Extrahepatic Parenchymal Cells
Scavenger Cells
Chylo-microns
VLDL
HDL
Lipoprotein Lipase
Adipose and Muscle Capillaries
Remnants
LCAT

LEGENDS TO FIGURES

Fig. 100-1 Left: Diagrammatic representation of the structure of a typical plasma lipoprotein particle. The core of the spherical lipoprotein particle is composed of two nonpolar lipids, triglyceride and cholesteryl ester, which are present in different lipoproteins in varying amounts. The nonpolar core is surrounded by a surface coat composed primarily of phospholipids. Apoproteins are exposed at the surface and extend into the core. Variable amounts of unesterified cholesterol are interdigitated with the phospholipids of the surface coat. The quantitative composition of each of the 5 major classes of lipoprotein particles in human plasma is summarized in Table 100-I. Right: Structures of the two nonpolar lipids, triglyceride and cholesteryl ester. In order for these nonpolar lipids to be assimilated into tissues, the ester bonds between the fatty acids and either glycerol (triglycerides) or cholesterol (cholesteryl esters) must be broken by lipoprotein lipase and the lysosomal cholesterol esterase, respectively.

Fig. 100-2 Model for plasma triglyceride and cholesterol transport in man. The details of this model are discussed in the text. VLDL denotes very low density lipoprotein, LDL denotes low density lipoprotein, HDL denotes high density lipoprotein, LCAT denotes lecithin:cholesterol acyltransferase.