Pathogenesis of hyperlipoproteinemia

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In the past 25 years, great advances have been made in our understanding of lipoprotein metabolism and of the causation of hyperlipidemia. These advances have been due in part to the study of patients with unusual defects in lipoprotein metabolism. Follow-up investigations into the specific metabolic defects in these patients have revealed qualitative abnormalities in the structure and function of apolipoproteins, the lipolytic system, and cell-surface receptors for lipoproteins. The development of isotopic tracer techniques, particularly multicompartmental analysis, has facilitated the elucidation of quantitative defects of lipoprotein transport responsible for other dyslipoproteinemias. In the last few years, it has been possible to integrate these discoveries and to create a more cohesive picture of the complex system of plasma lipid transport and of the abnormalities that can occur within it.

Definition of hyperlipidemia

Except for severe hypertriglyceridemia, an elevation of plasma lipids rarely produces immediate harmful effects. The danger of prolonged hyperlipidemia is accelerated atherosclerosis. For this reason, hyperlipidemia can reasonably be defined as lipid concentrations that enhance atherogenesis. What then are these concentrations? Some investigators believe that the correlation between plasma cholesterol and atherogenesis is linear over the whole range of cholesterol concentrations; while this may be true, several epidemiological studies suggest that the risk for coronary heart disease (CHD) begins to increase sharply at cholesterol levels above 200 mg/dl (1). If such a threshold for CHD risk does exist, hypercholesterolemia can be defined as a concentration above this level. Although a large fraction of the American public would be hypercholesterolemic by this definition (2), many epidemiologists believe that this "mass hypercholesterolemia" is largely responsible for the high prevalence of atherosclerotic disease in the Western world (3). In recent years there has been increasing acceptance of this viewpoint, although a group of investigators still maintain that the term hypercholesterolemia should be restricted to levels in the upper 5% of the population distribution. The latter approach however ignores the relationship between cholesterol levels and risk for atherosclerotic disease.

A link between plasma triglyceride (TG) levels and development of atherosclerosis has been difficult to demonstrate. Some workers, such as Carlson (4, 5), claim that TG levels are closely related to risk for CHD even within the so-called "normal" range. Other investigators, exemplified by Hully et al. (6), deny a causative relationship. The disagreement is largely semantic. Most epidemiological studies (6) have shown that plasma TG levels are positively correlated with risk for CHD. However, TG concentrations lose their predictive value when data are subjected to multifactorial analysis where other risk factors are taken into consideration. The truth is that the mechanisms responsible for accelerated atherosclerosis in patients with hypertriglyceridemia are unknown. Furthermore, the presence or absence of elevated TG levels may be more predictive of CHD than the degree of elevation. Regardless of the nature of the relationship, the fact remains that hypertriglyceridemia is present in a disproportionate portion of patients with CHD.

Etiology of hyperlipidemia

Three factors—nutrition, genetics, and metabolic (secondary) diseases—can raise plasma lipid concentrations. Another factor, aging, may do the same (2, 7). The importance of nutrition has been a continuing debate. How this debate is resolved will be of great importance because it will influence recommendations about possible dietary prevention of CHD. Epidemiologists traditionally have favored the dietary causation of "mass hypercholesterolemia", while clinical investigators and basic scientists have emphasized the role of genetic factors. There is mounting evidence that both are right; dietary factors can cause unusual rises in lipid levels in individuals who are genetically susceptible. Furthermore, secondary forms of hyperlipidemia are more common

Abbreviations: CHD, coronary heart disease; TG, triglyceride; LPL, lipoprotein lipase; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HTGL, hepatic triglyceride lipase; FH, familial hypercholesterolemia; HLP, hyperlipoproteinemia.

than generally recognized, and they too can be subject to dietary influences.

Mechanisms of hyperlipidemia

To discuss the mechanisms of hyperlipidemia, the basic pathways of lipoprotein metabolism must be reviewed first. Most forms of hyperlipidemia are associated with lipoproteins containing one of the two forms of apolipoprotein B (apoB), B-48 or B-100. The latter is the larger of the two molecules. Kane, Hardman, and Paulus (8) demonstrated that chylomicrons of intestinal origin contain apoB-48, while lipoproteins of hepatic origin possess apoB-100. Circulating chylomicrons also have other apolipoproteins, the apoC's, apoE's, apoA-I, and apoA-IV. TG of chylomicrons undergoes lipolysis through the action of lipoprotein lipase (LPL) in peripheral capillaries. LPL appears to be activated by apoC-II (9). After lipolysis is almost complete, chylomicron remnants are released into the circulation and are cleared rapidly by the liver. Hepatic uptake occurs at high velocity (10); although uptake may be saturable, it appears to be mediated by cell-surface receptors. These receptors may recognize apoB-48; however, they appear to interact primarily with apoE and hence have been called apoE receptors (11).

The liver secretes TG-rich particles called very low density lipoproteins (VLDL). Stalenhoef et al. (12) have shown recently that very large VLDL containing apoB-100 behave as chylomicrons; that is to say, they are cleared rapidly from the circulation, possibly being removed by hepatic apoE receptors. Other and presumably smaller VLDL are degraded by lipolysis to longer-lived VLDL remnants (**Fig. 1**). These remnants can have two fates: they can be removed by the liver or be converted to low density lipoproteins (LDL). In experimental animals (11, 13), and almost certainly in humans, VLDL remnants of this type are cleared by hepatic cell-surface receptors that recognize apoB-100. However, uptake of VLDL remnants appears to be accelerated by the presence of apoE, and hence the receptors have been called B/E receptors (11) or B-100/E receptors (14). The steps in conversion of VLDL remnants to LDL are not well understood. Havel (14) has postulated that the liver is required for this conversion; if so, hepatic triglyceride lipase (HTGL) may hydrolyze the remaining core TG as well as the excess surface-coat phospholipids of the remnant.

The fate of plasma LDL has been elucidated by the work of Brown, Dana, and Goldstein (15), Goldstein and Brown (16), and others (17, 18). LDL binds to specific cell-surface receptors that in fact are B-100/E receptors. These receptors are present on many cell types; however, Dietschy, Turley, and Spady (19) among others (20, 21) have demonstrated in experimental

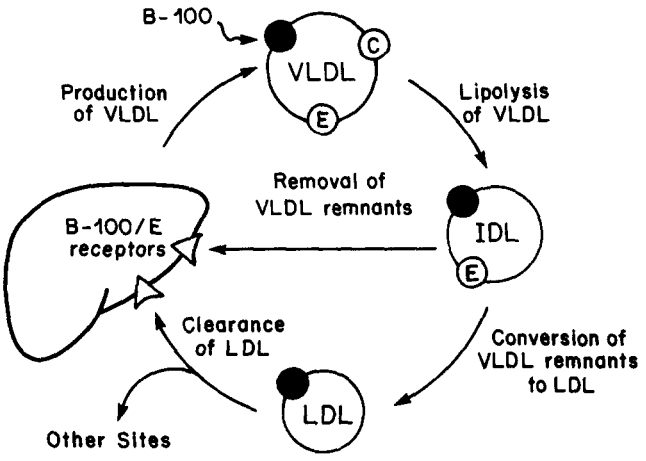

Fig. 1. Major steps in the metabolism of lipoproteins containing apoB-100. Production of VLDL-apoB-100 is by the liver. Lipolysis of VLDL-TG occurs via lipoprotein lipase (LPL). The resultant VLDL remnants, or intermediate density lipoproteins (IDL), can have two fates. They can be cleared by the liver via apoB-100/E receptors or be converted to LDL. LDL likewise can be removed by the same receptors, either in the liver or extrahepatic tissues.

animals that the liver is the major site of LDL clearance. Circumstantial evidence has been presented by Starzl et al. (22), in a hypercholesterolemic child who was genetically devoid of LDL receptors and who underwent liver transplant, that the liver also is the major organ of LDL removal in humans; following transplantation of a normal liver, LDL levels fell to near the normal range. While B-100/E receptors remove most of plasma LDL, a nonreceptor pathway, presumably nonspecific pinocytosis, extracts between 10 and 15% of the circulating LDL pool each day (23).

Defects in any of the pathways outlined in Fig. 1 can produce hyperlipoproteinemia. These defects can consist of either an overproduction of a lipoprotein or a decrease in its catabolism. The concentration of a lipoprotein species depends on the balance between its input and clearance. In the steady state, the input and output are constant. When an increase in the input of lipoproteins occurs, compensatory adjustments may mitigate the rise in concentrations. In some cases, compensation is almost complete, and the increase in level is minimal. In others, adjustments are moderately successful, and the rise in concentration is mild; but in still others, compensation is poor and marked hyperlipidemia develops. This variability in catabolic response calls forth the concept of a "latent defect" in clearance, i.e., a defect that becomes apparent only when input of lipoproteins is abnormally high. Finally, some patients have a frank clearance defect, and they have hyperlipidemia even without enhanced influx of lipoproteins. It must be noted that a clearance defect can be of two types: one present at a tissue site, such as a decrease in a lipase or a receptor,

or another in the lipoprotein particle itself that causes it to interact poorly with a lipase or receptor.

LDL clearance defects

The most striking and probably the most common cause of a decrease in clearance of LDL is a reduction in activity of LDL (B-100/E) receptors. The discovery of the LDL receptor by Goldstein and Brown (15, 16) opened a new era in the study of lipoprotein metabolism. A deficiency of LDL receptors was first discovered in patients with familial hypercholesterolemia (FH). Patients with the homozygous form of this disease have inherited two defective genes for the synthesis of receptors, one from each parent. Recent studies by Tolleshaug et al. (24) have uncovered multiple inherited defects in the primary structure of LDL receptors; all of these result in poor or absent binding to LDL. Patients with homozygous FH usually have cholesterol levels in the range of 800 to 1000 mg/dl, and they develop atherosclerotic disease very early in life.

The mechanism for severe hypercholesterolemia in homozygous FH initially was assumed to be the result exclusively of decreased clearance of LDL. However, isotope kinetic studies in homozygotes have shown that production of LDL also is increased markedly (23). Furthermore, some of these studies suggested that the excessive input of LDL was due to "direct" secretion of LDL, i.e., independent of VLDL (24). This finding appeared consistent with the idea that FH homozygotes have a deregulation of hepatic synthesis of apoB-100, increased formation of LDL within hepatocytes, and direct secretion of LDL into plasma (25). These processes however have been cast into doubt by recent studies in the WHHL rabbit, an animal which is almost devoid of LDL receptors like homozygous FH. Bilheimer, Watanabe, and Kita (26) observed that WHHL rabbits have overproduction of LDL, as well as defective clearance, just as do FH homozygotes. Despite this, Kita et al. (27) could not demonstrate direct secretion of LDL in these rabbits, nor could they show an excessive synthesis or secretion of any apoB-containing lipoproteins. For this reason, the scheme shown in **Fig. 2** was proposed to explain defective clearance and overproduction of LDL in both the WHHL rabbit and FH homozygotes. This scheme indicates that an absence of B-100/E receptors prevents the hepatic uptake of both LDL and VLDL remnants; the latter allows for all VLDL to be converted to LDL which is measured as overproduction of LDL. Since the absence of receptors prevents uptake of LDL, only the nonreceptor pathway is available for LDL clearance.

The dual defect in LDL metabolism caused by a low activity of LDL receptors has implications beyond homozygous FH (Fig. 2). For example, patients with heterozygous FH have inherited a defective gene for synthesis of LDL receptors from only one parent, and they consequently have only half the normal number of receptors. These patients also have both overproduction and defective clearance of LDL (26, 28), although neither are present to the degree found in homozygotes.

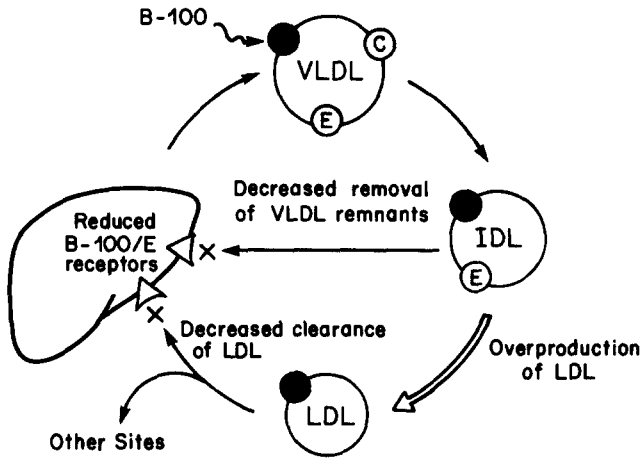

Fig. 2. Effects of a deficiency (or reduction) of apoB-100/E receptors on lipoprotein metabolism. First, hepatic clearance of VLDL remnants (IDL) is reduced, and consequently, more IDL is converted to LDL; and second, clearance of LDL is reduced. The net result is an increase in LDL concentrations.

Still other patients have mild-to-moderate hypercholesterolemia without recognizable FH. What is the mechanism for their elevated LDL level? Some of them could have structural defects in the LDL receptor that reduce but do not obliterate binding to LDL. In others, genetic defects of a different type might suppress the synthesis of normal LDL receptors. Those of the latter type could be unusually sensitive to dietary factors that within themselves may suppress the formation of LDL receptors. Dietary cholesterol in particular must reduce receptor production. If the liver receives large amounts of cholesterol from the diet, less will be required from circulating LDL, and synthesis of receptors will be suppressed. Data from studies of LDL turnover in humans are consistent with the concept (29, 30). The mechanism by which saturated fatty acids raise the LDL level is less well understood; however, the observation of Shepherd et al. (31) that these acids retard the clearance of LDL is suggestive of a reduction in activity of LDL receptors.

Are LDL receptors important for controlling LDL levels in humans who do not have an inherent defect in their function? Tissue culture studies suggest that LDL receptors are saturated at relatively low concentrations. Does this not mean that the nonreceptor pathway for LDL clearance should predominate in vivo? Isotope kinetic studies by Kesaniemi, Witztum, and Steinbrecher (32) imply not. Most of LDL clearance in normal

humans seemingly occurs via LDL receptors (32). However, the activity of receptors can vary. LDL levels usually rise with age; this change undoubtedly is due in part to a reduction in clearance of LDL, and as Miller (7) postulates, there probably is a decline in receptor activity with aging. However, Kesaniemi and Grundy (33) have shown that production rates of LDL also vary and affect LDL levels; but as shown in Fig. 2, higher production rates of LDL may simply be a reflection of lower activity of LDL receptors.

Another cause of high LDL levels could be an abnormality in the primary structure of apoB-100 that imparts a poor affinity for the LDL receptor. ApoB is a large and complex molecule, and while variations in its amino acid sequence have not been identified, they nonetheless must exist. If so, they could interfere with the normal binding of LDL to its receptor and thus cause a rise in LDL levels.

Defects in lipolysis

Two factors can be responsible for defective lipolysis of plasma TG, a reduction in the availability of LPL and an abnormality in the lipoproteins themselves rendering them a poor substrate for the enzyme. With regard to the former, rare patients have a congenital absence of LPL (34). Such patients, who are homozygous for LPL deficiency, have marked elevations of TG-rich lipoproteins, especially chylomicrons. VLDL levels generally are not increased proportionately. This pattern of high chylomicron levels and normal VLDL is called type 1 hyperlipoproteinemia (HLP). Why are VLDL levels not increased in proportion to chylomicrons? There are two possibilities: first, the synthesis of VLDL likely is relatively low in most type 1 patients; but perhaps more important, many newly secreted VLDL may be the size of chylomicra and thus are mistakenly called chylomicrons. The finding that the chylomicron fraction of patients with defective lipolysis contains appreciable quantities of apoB-100 is compatible with the hepatic secretion of some very large VLDL (12).

If complete deficiency of LPL results in severe chylomicronemia, are there partial deficiencies responsible for milder hypertriglyceridemia? Of interest, heterozygotes for LPL deficiency usually have normal plasma TG levels, although they may have a mild clearance defect for chylomicrons (35). Several reports nonetheless claim that some patients with elevated plasma TG have abnormalities in LPL, either quantitative or qualitative (36–38). These reports are highly suggestive that reduced activity of LPL can raise plasma TG, but the existence of definitive abnormalities in LPL function is difficult to prove in the intact patient. A portion of hypertriglyceridemic patients apparently have a reduction in heparin-releasable LPL, while others have a decrease in LPL in adipose tissue. Unfortunately, it is difficult to relate these defects to changes in the in vivo activity of LPL, and more studies are needed to determine to what extent abnormalities in the metabolism of LPL, without complete absence of the enzyme, contribute to hypertriglyceridemia.

Another cause of hypertriglyceridemia can be a defect in composition of apoproteins of TG-rich lipoproteins. This cause is best illustrated by patients who have a congenital absence of apoC-II (39), the apoprotein required for activation of LPL (9). In this condition, marked hypertriglyceridemia occurs. It has been suggested that a partial deficiency of apoC-II likewise can raise TG levels (40–42), but this mechanism for hypertriglyceridemia is questionable. Nor has it been shown that abnormalities in other apoproteins, such as apoC-III or apoE, affect the interaction of lipoproteins with LPL in vivo. The size of TG-rich particles could be another important factor determining lipolytic rates. Chylomicrons seemingly are much better substrates for LPL than are the smaller VLDL. Within the VLDL fraction, size too may be important. Large VLDL may undergo rapid lipolysis and be cleared quickly from the circulation, possibly by chylomicron remnant receptors (12). The TG of smaller VLDL apparently is hydrolyzed less rapidly. Consequently, if there is an increased input of small VLDL, sluggish lipolysis of their TG could raise TG levels.

Remnant removal defects

An important advance in recent years is the recognition that apoE plays a crucial role in the removal of remnants of TG-rich lipoproteins. The chylomicron remnant receptor may recognize apoE, whether it is on remnants of chylomicrons or large VLDL. ApoE also appears to promote removal of smaller VLDL remnants via the LDL receptor. There are three major isoforms of apoE including E-3, E-4, and E-2 (43), and all isoforms do not have the same affinity for receptors. ApoE-3 binds tightest to the receptor, E-4 next, and E-2 least. Every person inherits two genes for apoE and thus six genotypes are possible: E-3/3, E-3/4, E-3/2, E-4/4, E-4/2, and E-2/2. People with the E-2/2 genotype tend to accumulate remnants because of sluggish removal. In the absence of other defects in lipoprotein metabolism, however, the E-2/2 pattern rarely causes frank hyperlipidemia, i.e., it remains a latent defect (44).

Overproduction of lipoproteins

There is increasing evidence that overproduction of lipoproteins, particularly of VLDL, contributes significantly to several forms of hyperlipidemia. This evidence has been forthcoming from isotope kinetic studies that trace the input and exit of apoB-containing lipoproteins.

Since the number of apoB molecules per lipoprotein particle is constant (45), quantification of apoB kinetics should accurately follow the metabolism of lipoprotein particles.

Increased secretion of VLDL can be either primary or secondary. The causes of primary lipoprotein overproduction are unknown. Whether excessive synthesis of apoB without a concomitant overproduction of VLDL-TG can lead to increased secretion of VLDL particles remains to be determined. Causes of secondary lipoprotein overproduction are obesity with a high caloric intake (46, 47), diabetes mellitus (48), and probably the nephrotic syndrome. High carbohydrate diets and excess alcohol intake can stimulate synthesis of VLDL-TG (49, 50), but these stimuli may merely expand the size of VLDL particles with extra TG and not increase the number of particles secreted (49).

Overproduction of VLDL seemingly is associated with a high absolute conversion of VLDL to LDL, i.e., it causes overproduction of LDL (47, 48). Theoretically, hypersecretion of VLDL might raise levels of both VLDL and LDL. Overproduction of VLDL however does not always induce hyperlipidemia (**Fig. 3A**). Lipoprotein overproduction without hyperlipidemia has been reported in obese patients (47), in patients with adult-onset diabetes (48), and in some patients with premature coronary heart disease (51). Protection from development of hyperlipidemia in overproducers appears to be afforded by a compensatory increase in clearance rates of lipoproteins. For example, most patients who have overproduction of VLDL and increased absolute conversion of VLDL to LDL also have enhanced clearance rates of LDL (52). The reason for accelerated clearance of LDL is unclear. In overproducers of VLDL, LDL frequently are "polydisperse" or heterogeneous in size (52, 53). Some of these particles could have an unusually high affinity for the LDL receptor.

On the other hand, many patients with VLDL overproduction do, in fact, have hyperlipidemia. If overproduction of VLDL-apoB is associated with excessive synthesis of VLDL-TG, the result will be endogenous hypertriglyceridemia, or type 4 HLP (38). However, in most instances in which hyperlipidemia is associated with overproduction of VLDL, there seemingly is a concomitant defect in clearance of one or another lipoprotein species (Fig. 3B). For example, the type 4 phenotype also can be the result of the combination of overproduction of VLDL and a lipolytic defect for plasma TG (38). The latter may be mild, i.e., a latent defect, so that hypertriglyceridemia would not be present in absence of overproduction. When the lipolytic defect is more severe, both VLDL and chylomicrons will be elevated (type 5 HLP). We have shown recently that type 5 HLP usually is the result of a dual defect in TG metabolism, defective clearance of TG-rich lipoproteins plus overproduction of VLDL-TG (54). The latter abnormality can be primary or secondary; indeed many type 5 patients have either diabetes mellitus or obesity (or both) as causes of their overproduction.

When hypersecretion of VLDL is combined with the apoE-2/2 genotype, a marked increase in VLDL remnants, or beta-VLDL, occurs (55); this pattern, which is

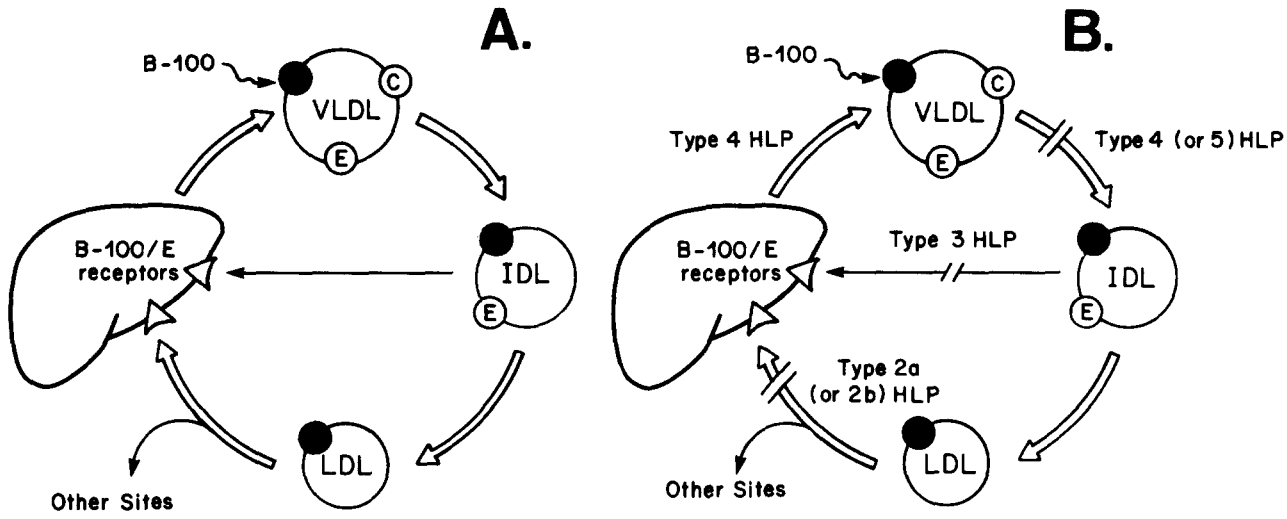

Fig. 3. Metabolic consequences of overproduction of VLDL. A. Some patients have overproduction of VLDL without developing hyperlipidemia. They have a high flux rate of VLDL, IDL, and LDL but, because of efficient clearance mechanisms, the concentrations of these lipoproteins are not increased. B. Other patients with overproduction have defective clearance of one or more lipoproteins. Simultaneous overproduction of VLDL-apoB and VLDL-TG can cause type 4 HLP. Defective lipolysis can yield either types 4 or 5 HLP. The E-2/2 genotype delays clearance of VLDL remnants causing type 3 HLP. Finally, a defective clearance of LDL can produce either hyperapobetalipoproteinemia or type 2 HLP.

called type 3 HLP, is a good example of how a latent catabolic defect can accentuate hyperlipidemia in a patient with overproduction of VLDL. Without overproduction, the E-2/2 genotype imparts ony trivial increments in remnant lipoproteins, but when input of VLDL is excessive, remnants accumulate to a striking degree.

Finally, a high secretion of VLDL can cause elevated levels of LDL. Usually, however, LDL levels do not rise to abnormally high levels despite enhanced conversion of VLDL to LDL. As mentioned before, the LDL particles associated with overproduction of VLDL are abnormal, and they tend to be cleared rapidly from the circulation. On the other hand, if secretion of VLDL is extremely high, causing massive conversion of VLDL to LDL, the plasma LDL will be elevated (52). Furthermore, if a concomitant defect in clearance of LDL is present, LDL levels also will be high. An elevated LDL can occur in two forms, hyperapobetalipoproteinemia and type 2 HLP. Hyperapobetalipoproteinemia was defined by Sniderman et al. (56, 57) as an increase in LDL-apoB levels with a normal concentration of plasma LDL-cholesterol. This relationship can exist because the apoB-to-cholesterol ratio in LDL is abnormally high in the presence of VLDL hypersecretion. A rise in the number of LDL particles, therefore, will cause an abnormally high level of LDL-apoB while LDL-cholesterol remains in the normal range. Thus, hyperapobetalipoproteinemia usually is the result of a mild defect in clearance of LDL linked with overproduction of VLDL. A more severe defect in LDL clearance leads to elevations in LDL-cholesterol as well as in LDL-apoB and hence to type 2 HLP.

The combination of overproduction of VLDL and one or more catabolic defects for various lipoprotein species explains how multiple lipoprotein phenotypes can occur within a single family. This phenomenon was designated *familial combined hyperlipidemia* by Goldstein et al. (58, 59), and families with this condition were noted to have a variety of lipoprotein abnormalities types 2a, 2b, 4, and 5 HLP. Since this first description, additional variants have been recognized as belonging to the lipoprotein overproduction disorder, namely, type 3 HLP (55), hyperapobetalipoproteinemia (56, 57), and a normolipidemic variant (51, 52, 60). Furthermore, these multiple variants can occur whether the overproduction is on a primary or secondary basis. One of the challenges for future study of this disorder is to understand the molecular basis for overproduction of apoB-100 lipoproteins by the liver.

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