Hypertriglyceridemia is associated with increased risk of coronary heart disease (CHD) (1–5), and it is an integral component of the overlapping syndromes of familial combined hyperlipidemia, insulin resistance syndrome, atherogenic lipoprotein profile, and hyperapoliproteinemia (6). More than one mechanism may be involved in the increased risk of CHD associated with increased serum triglycerides:

- Triglyceride-rich lipoproteins (TGRLs) may participate directly in atherogenesis, particularly when they have undergone attack by oxygen free radicals (7).
- TGRLs may decrease circulating concentrations of HDL-cholesterol by attracting cholesteryl ester out of HDL in a process mediated by cholesteryl ester transfer protein (CETP). Furthermore, cholesteryl ester, which might otherwise undergo uptake by the hepatic scavenger receptor BI receptor and thus complete reverse cholesterol transport, can be redirected into chylomicrons and VLDL by CETP. From chylomicrons and VLDL in the circulation, the triglycerides can enter chylomicron remnants and LDL (derived from chylomicrons and VLDL, respectively), both of which are atherogenic (8).
- Increased circulating concentrations of TGRLs are also intimately associated with the formation of small, dense LDL (9). This small, cholesterol-depleted LDL subspecies is particularly atherogenic and is the cause of the increase in serum apolipoprotein B (apo B) in hyperapoliproteinemia, which is disproportionately greater than the increase in LDL-cholesterol (10).

The most common reason for an increase in circulating triglycerides is increased hepatic secretion of VLDL (11–14). This is usually attributable to an increased flux of nonesterified fatty acids to the liver, as, for example, in obesity and insulin resistance. Even in such circumstances, however, increased VLDL secretion does not necessarily lead to hypertriglyceridemia (15). Hypertriglyceridemia is avoided if there is efficient clearance of TGRLs from the circulation (16, 17), a clearance that is largely determined by the activity of lipoprotein lipase (11, 18). Severe defects in triglyceride clearance from the circulation, such as that in familial lipoprotein lipase deficiency, are rare. By contrast, minor defects are almost invariably present when hypertriglyceridemia is evident, for example, in the insulin resistance syndrome or familial combined hyperlipidemia. Heterozygous lipoprotein lipase mutations are relatively common (19), and the enzyme is insulin-dependent (11, 18). Many patients with hypertriglyceridemia, however, are not heterozygous for a lipoprotein lipase mutation, and evidence is incomplete that the more common types of insulin resistance extend beyond defects in glucose uptake to, for example, down-regulation of lipoprotein lipase (20). Thus, a gap has existed in our knowledge about the link between VLDL overproduction and its diminished catabolism in commonly occurring hypertriglyceridemia. It seems likely that the recently discovered apolipoprotein A5 (apo A5), the subject of the report by O'Brien et al. (21) in this issue of Clinical Chemistry, may contribute to the explanation.

Apo A5 is part of the important regulatory gene cluster on chromosome 11, which has been recognized for many years and contains the genes for apo A1, apo C3, and apo A4 (22). Polymorphisms in this cluster have previously been linked to both CHD and hypertriglyceridemia (22–26). The comparatively late discovery of apo A5 reflects its low concentrations in the circulation. The other apolipoproteins were discovered by separation of the proteins after delipidation of plasma lipoproteins—initially classified as apolipoprotein A if present in α-lipoproteins (HDL), apolipoprotein B if in β-lipoproteins (LDL), and apolipoprotein C if in pre-β-lipoprotein (VLDL) (27). Following further protein purification, sequencing, and genomic studies, these were reclassified and the major apolipoproteins affecting lipoprotein metabolism, apolipoproteins A1, A2, A4, B100, B48, C1, C2, C3, and E, were identified (28). With the exception of apo B, which remains bound to VLDL and chylomicrons, their clearance from the circulation, apolipoproteins exchange between the lipoproteins. HDL acts as circulating reservoir for apolipoproteins C2 and C3, which are transferred to the surface of newly secreted chylomicrons and VLDL. As these undergo lipolysis in the circulation as a result of the activity of lipoprotein lipase located principally on the capillary endothelium of adipose tissue and skeletal muscle, their triglyceride core becomes progressively smaller and the C apolipoproteins along with other excess surface components are released to rejoin HDL.

Apolipoprotein A5 was finally identified following the discovery of an open-reading frame in the gene cluster for apolipoproteins A1-C3-A4, which did not correspond to any known apolipoprotein (29). Its genetic sequence was found to be expressed principally in liver, particularly in regenerating liver (30). In apo A5-knockout mice, triglycerides increased fourfold (30, 31), and expression of the human A5 genetic sequence in transgenic mice decreased serum triglyceride concentrations by 50–70% (32). Fascinatingly, this decrease in serum triglyceride concentrations was associated with diminished VLDL production and increased VLDL catabolism (33). Thus, for the first time, a single gene could affect the two processes involved in common hypertriglyceridemias.

The report of O'Brien et al. (21) is the first attempt to provide precise information about the plasma concentra-
tion of apo A5 in humans. Presumably, apo A5 directly affects intracellular VLDL assembly or secretion within the liver. Its low expression in adipose tissue and skeletal muscle implies that the albeit low circulating concentrations of apo A5 directly decrease lipoprotein lipase activity there. O’Brien et al. (21) also provide evidence that apo A5 is located not only on VLDL, but also on HDL, so that transfer from HDL to VLDL and back, similar to the transfer of apo C2 and C3, is likely. Apo C2 is an activator of lipoprotein lipase. Indeed, the rare autosomal recessive deficiency of apo C2 can lead to a decrease in lipoprotein lipase deficiency as profound as that in familial lipoprotein lipase deficiency (34, 35). Apo C3, on the other hand, is an inhibitor of lipoprotein lipase (32). Apo A5 now joins these as a metabolic regulator of triglyceride clearance, but one that uniquely also influences VLDL secretion.

Two major questions are raised by the report of O’Brien et al. (21). Firstly, how does apo A5 down-regulate lipoprotein lipase when its concentration is so much lower than the concentrations of apo C2 and apo C3? Does it synergize or compete with these directly, or does it influence lipoprotein lipase synthesis or its migration and attachment to the capillary endothelium? Secondly, if apo A5 has a marked influence on serum triglycerides, why is there such a weak relationship between its circulating concentration and the circulating concentration of triglycerides? As O’Brien et al. suggest, this may be because the concentrations of apo C2 and apo C3 must also be considered in the relationship. In addition, the serum concentration may not directly reflect the degree of influence of apo A5 expression on hepatic VLDL production. Finding the answers to these questions and determining the contribution of genetic and nutritional influences to the variation in apo A5 expression and thus to hypertriglyceridemia will be fascinating, particularly because the peroxisome proliferator-activated (PPAR) response element of the apo A5 gene means that its expression can be modified with PPARα agonists (36).

References
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