Most patients with diabetes die from macrovascular complications. Little is known about the pathogenesis of diabetic vascular disease, but recent advances in molecular genetics and oxidation chemistry provide clues to the mystery of diabetes and atherosclerosis. Genetic variants of well-known proteins such as lipoprotein lipase and apolipoprotein E are common. These proteins are suitable candidates for mediating diabetic vascular risk because their variants can produce hypertriglyceridemia, a risk factor for atherosclerosis in diabetes. However, mutations could have different effects on lipoprotein flux across arteries depending on whether expression is dominant in the vascular space or the vascular wall. Lipoproteins retained in the arterial wall are subject to oxidative modification, which could be dependent on glycoxidation, the enzyme myeloperoxidase, or reactive nitrogen species derived from nitric oxide. Accelerated vascular disease in diabetes is likely the result of complex interactions between metabolic derangements such as hyperglycemia, mutations in genes controlling lipid metabolism, and antioxidant defense mechanisms.


Surely it was time someone invented a new plot, or that the author came out from the bushes.

—Virginia Woolf, 1941

By the time those words were written, the association between diabetes, blood lipids, and premature atherosclerosis had been recognized. More than half a century later, the mechanisms explaining this association are still unknown. So far, the mystery of diabetes and atherosclerosis has been dominated by character development: lipoproteins, the principal characters, have been described in detail. From our perspective, the new plot is determining how genes cause diabetic dyslipidemia and exactly how lipoproteins trigger vascular wall dysfunction. The authors of the mystery, glucose and insulin, have long been out from the bushes, but how these mediators interact with specific gene products to accelerate macrovascular disease is only beginning to be understood.

Not everyone with diabetes develops premature vascular disease. Over the time frame of prospective studies, the vast majority of individuals with elevated LDL cholesterol, an established cardiac risk factor, do not develop clinically evident atherosclerosis (1). Likewise, diabetes increases atherosclerotic risk but does not predestine heart disease. Why then do some patients with good glycemic control suffer premature myocardial infarctions, peripheral vascular disease, and strokes while others with fairly poor control escape severe macrovascular complications?

Diabetic vascular injury is probably not uniformly caused by a single offender such as hyperglycemia. Recent studies of experimental atherosclerosis support this concept; hyperglycemia accelerates diet-induced atherosclerosis in inbred BALB/c mice but not in genetically distinct C57BL/6 mice (2). Diabetic vascular disease also does not appear to be physiologically unique; diabetic patients with coronary disease benefit from lipid lowering with hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (3), which suggests that diabetic vascular lesions, like those in nondiabetic subjects, are stabilized by lipid lowering. Instead, the phenotypic variations seen in clinical practice probably reflect interactions between metabolic derangements (hyperglycemia, insulin resistance, circulating insulin, elevated free fatty acids, and others), diet, and variants in individual genes controlling lipid metabolism, vascular wall biology, and lipoprotein modification.

There are several comprehensive, sensible reviews that provide background information regarding diabetes and atherosclerosis (4–7). In this perspective, we take a more focused approach to address the role of candidate genes and oxidized lipoproteins in the pathogenesis of diabetic vascular disease.

CANDIDATE GENES AFFECTING LIPID METABOLISM AND THE VASCULAR WALL

Lipoprotein lipase. Lipoprotein lipase (LPL) is rate-limiting for removal of triglycerides from the circulation and critical for the generation of HDL particles. Highest expression is found in heart, adipose tissue, and skeletal muscle (8,9), but
arterial wall macrophages also express the enzyme. In adipose tissue and muscle, the enzyme is transported from parenchymal cells across endothelial cells by unknown mechanisms and binds to glycosaminoglycans at the luminal side of the capillary endothelium. From this site, it hydrolyzes triglycerides, releasing free fatty acids for uptake by tissues.

LPL is insulin sensitive and is known to be altered in diabetes. The dyslipidemia seen in many diabetic patients, high triglycerides and low HDL cholesterol, is associated with low LPL activity (6). In insulin-deficient animals, LPL activity can be increased, attenuating dyslipidemia (10,11). Heterozygous LPL deficiency in patients with NIDDM can cause extreme hypertriglyceridemia (12). Underlying defects in LPL could exacerbate dyslipidemia in diabetes and promote vascular damage.

The exact role of LPL in atherosclerosis is unknown. Homozygous LPL deficiency can present with chylomicronemia, a serious metabolic disturbance associated with pancreatitis. Early studies suggested that individuals with this condition were not at increased risk for atherosclerosis (13), but this concept has been recently challenged (14). Unlike homozygous LPL deficiency, which is rare, heterozygous LPL deficiency is common. Dozens of coding region mutations and two promoter mutations that decrease LPL enzyme activity have been described (15). A surprisingly high 3–7% of individuals in population-based studies have heterozygous LPL deficiency (16), and some LPL mutations may increase the risk for vascular disease (17). Detailed population-based studies in diabetic patients are unavailable, but if the frequency of heterozygous LPL deficiency in diabetic individuals is similar to that in the general population, this disorder could represent an extremely common predisposing factor for dyslipidemia.

Triglyceride-rich lipoproteins, especially remnants, are probably atherogenic. Such particles are present in human atherosclerotic lesions (18). Low levels of HDL cholesterol may impair reverse cholesterol transport. Both abnormalities occur with heterozygous LPL deficiency, and this genetic condition has striking effects on postprandial lipid metabolism (19). Pharmacological induction of LPL activity lowers triglycerides and decreases experimental atherosclerosis in rats (20). These data suggest that LPL activity in the vascular compartment is beneficial.

The weight of evidence suggests that LPL activity is antiatherogenic, but the protein itself could have different effects. It is expressed in macrophages in human atherosclerotic lesions (21), and macrophage LPL expression is positively associated with atherosclerotic susceptibility in inbred mice (22). LPL promotes retention of LDL particles by subendothelial matrix (23), perhaps by binding to the NH2-terminus of apolipoprotein (apo) B (24). Such retention might increase the likelihood of modification of particles leading to foam cell formation (25). If LPL-mediated retention of atherogenic particles in the vessel wall is important, decreases in LPL protein mass associated with some types of heterozygous LPL deficiency would decrease atherosclerosis.

Thus, LPL enzyme activity in plasma probably decreases vascular risk, but LPL protein mass in the vascular wall could increase risk (Fig. 1). Each property might be independently affected by glucose, insulin, and fatty acids. Animal models will help determine the effects of LPL on atherosclerosis. LPL-knockout mice are now available. Homozygotes die with extreme hypertriglyceridemia, but heterozygotes are viable and fertile (26). Experimental diabetes exacerbates dyslipidemia in the heterozygotes (27) and results in the production of potentially atherogenic remnant particles (C.F.S., unpublished observation). Studies of experimental atherosclerosis with these mice and mice in which LPL has been altered in specific cell types such as macrophages will help resolve the role of this candidate gene in diabetic atherosclerosis.

LPL may also have indirect but important effects on vascular risk by directing fuels to specific tissues. The regulation of LPL expression in skeletal muscle and adipose tissue is usually reciprocal. In the insulin resistance syndrome, muscle LPL is decreased and strongly correlated with insulin sensitivity (28). Decreased muscle LPL may promote abdominal obesity by directing the metabolism of fats away from muscle (a site of oxidation) and toward adipocytes for storage. Since abdominal fat enhances VLDL overproduction, probably through the provision of fatty acids for the stabilization of apo B and subsequent VLDL assembly (29), decreased muscle LPL may perpetuate the dyslipidemia of insulin resistance. Apo E. Apo E is found on the surface of all of the major classes of circulating lipoproteins. It is necessary for the normal clearance of chylomicron remnants, VLDL, and intermediate-density lipoprotein (IDL) and may participate in reverse cholesterol transport (Fig. 1). Apo E–knockout mice develop marked hyperlipidemia and extensive atherosclerosis on low-fat, low-cholesterol diets, which supports a crucial role for this protein in mediating vascular risk (30,31). Overexpression of apo E prevents dyslipidemia in mice with streptozocin-induced diabetes (32).

There are three common alleles for the apo E gene: e2, e3, and e4. The most common phenotypes are E2/E3 (considered normal), E4/E3, and E2/E3. The distribution of these pheno-
types is similar in diabetic and nondiabetic populations. In subjects with IDDM or NIDDM, the e4 allele is associated with coronary heart disease (33,34). Subjects with the e4 allele have higher levels of both LDL and triglycerides, the latter reflecting abnormal postprandial lipid metabolism in both diabetic and nondiabetic subjects (35,36).

Like LPL, apo E may affect vascular wall biology as well as circulating lipids (Fig. 1). Two independent groups have expressed apo E in the arterial wall of mice (37,38). In both models, arterial expression of apo E decreased atherosclerosis despite the fact that the transgenes had little effect on circulating lipids. These results could be explained by enhanced efflux of cholesterol from the vessel wall or by effects of apo E on the complex cell biology of the atheroma. The effect of diabetes on vascular wall apo E expression is unknown.

Apo CIII. Apo CIII is a small protein (79 amino acids) found in each class of lipoproteins. Overexpression of human apo CIII in transgenic mice produces hypertriglyceridemia (39), probably by displacing apo E from triglyceride-rich lipoproteins (40) and interfering with lipoprotein catabolism. These mice develop more diet-induced atherosclerosis than controls (41), suggesting that hypertriglyceridemia has a direct effect on the promotion of atherogenesis. Alternatively, apo CIII overexpression might also antagonize the effects of apo E at the vessel wall to promote atherosclerosis. Since apo CIII levels are elevated in patients with high triglycerides (42) and hypertriglyceridemia is the hallmark of diabetic dyslipidemia, apo CIII is a candidate gene for mediating vascular risk in diabetes.

Polymorphisms have been described in the apo CIII promoter, and certain haplotypes occur more frequently in individuals with triglycerides >1,000 mg/dl (43). Insulin suppresses apo CIII transcription (44) in transformed cells derived from human hepatocytes. However, variant sequences in the apo CIII promoter abolish the ability of physiological concentrations of insulin to suppress the activity of a reporter gene in apo CIII promoter/reporter constructs (45). These data suggest that discrete variations in the apo CIII gene could induce a form of insulin resistance, reflecting the inability of insulin to regulate an insulin-responsive gene. Similar mutations could explain certain types of diabetic dyslipidemia.

Cholesterol ester transfer protein. Cholesterol ester transfer protein (CETP) mediates the exchange of cholesterol esters in HDL particles for triglycerides in VLDL particles. It may be important for reverse cholesterol transport, the net movement of cholesterol from the arterial wall to the liver. Accordingly, high CETP activity might inhibit atherosclerosis by accelerating the removal of excess cholesterol from the arterial wall. However, CETP produces VLDL particles that are cholesteryl-ester enriched and ultimately decreases HDL levels (46), two potentially atherogenic lipoprotein changes observed commonly in diabetes. In IDDM subjects, CETP activity tends to be high (47), while in NIDDM, low CETP activity is observed (48).

Recent data suggest that these disparate changes in CETP activity are both proatherogenic. Hypertriglyceridemic mice expressing human CETP develop less diet-induced atherosclerosis than hypertriglyceridemic mice without human CETP (41). In mice with normal triglycerides, CETP promotes diet-induced atherosclerosis (49), the opposite effect. In diabetes, triglycerides may provide the critical clue. When triglycerides are high (as in NIDDM), CETP transfers cholesteryl esters to VLDL, but these particles may be cleared too rapidly to tilt the net flux of cholesterol toward the arterial wall; VLDL particles in hypertriglyceridemia are known to bind with high affinity to LDL receptors (50). In this setting, CETP activity would inhibit atherosclerosis by enhancing reverse cholesterol transport. However, when triglycerides are normal (as frequently occurs in IDDM), VLDL binds poorly to LDL receptors (51). These particles, cholesteryl-ester enriched by high CETP activity associated with IDDM and cleared less rapidly than particles from subjects with hypertriglyceridemia, would promote atherosclerosis. This hypothesis awaits testing in animal models of diabetes.

CETP polymorphisms are associated with macrovascular disease in NIDDM patients independent of lipid levels (52). These data raise the possibility that CETP expression in the arterial wall could affect atherosclerosis.

Fatty acid synthase. Fatty acid synthase (FAS), a large (~560-kDa) multifunctional cytoplasmic protein, is rate limiting for long-term fatty acid biosynthesis (53). Expression is high in intra-abdominal adipose tissue from humans (54). There is no direct evidence that increased FAS expression at this site increases portal free fatty acids, but such a mechanism could help explain insulin resistance associated with abdominal obesity (55). FAS expression is also high in liver (54). Hepatic de novo lipogenesis is not thought to be quantitatively important in humans; however, this process is induced by diet (56), and its contribution to lipid metabolism in obesity or diabetes is unknown. Even if the quantitative contribution of hepatic FAS to VLDL production is small in these conditions, FAS-produced fatty acids could reside in a distinct hepatic regulatory pool serving to stabilize apo B for VLDL assembly.

Dietary induction of FAS could reflect hormonal or nutrient effects. Insulin increases hepatic FAS, but this induction may require glucose (57). In fact, several nutrients affect hepatic FAS expression. Polysaturated, but not saturated, fatty acids suppress FAS (58), perhaps explaining the ability of diets rich in polysaturated fatty acids to lower LDL and protect primates against atherogenesis. Essential amino acids regulate FAS expression by altering levels of uncharged tRNA (transfer RNA not carrying its cognate amino acid); when amino acid levels are low, uncharged tRNA levels are high, causing FAS suppression (59). The high levels of amino acids that occur in insulin resistance (60) could have a permissive effect on FAS expression and promote dyslipidemia.

Glucose increases FAS expression, probably through a combination of increased transcription and enhanced mRNA stability (61). Since the total flux of glucose across the liver in NIDDM is substantially increased, glucose alone could increase the expression of FAS and other lipogenic enzymes and promote dyslipidemia. Sterols also regulate FAS expression, probably through a mechanism involving one of the sterol regulatory element-binding proteins controlling LDL receptor expression (62). Understanding mechanisms responsible for nutrient control of FAS in diabetes could provide new targets for the development of nutritional and pharmacological therapies for diabetic dyslipidemia.

CANDIDATE PROCESSES AFFECTING LIPOPROTEIN OXIDATION

In the general population, an elevated level of LDL is an important risk factor for atherosclerosis (63). LDL levels are usually normal in diabetic subjects (6), but these particles may be
modified to forms that promote atherogenesis (64,65). For example, nonenzymatic glycation may cause LDL to be rapidly internalized by macrophages (66,67). Macrophages are precursors of foam cells characteristic of early atherosclerotic lesions (68). Elevated glucose levels may favor the production of oxidized LDL, which is thought to play an important role in atherogenesis (64,65). Diabetic hypertriglyceridemia is associated with elevated concentrations of apo B100-containing lipoproteins other than LDL (6), and these lipoproteins may be susceptible to some of the same modifications seen with LDL.

**Oxidative modification of lipoproteins in atherosclerosis and diabetes.** Several lines of evidence implicate oxidatively damaged LDL in atherogenesis. Epitopes specific for lipid peroxidation products colocalize in vascular lesions with apo B100, the predominant protein of LDL (69,70). Lipoproteins with many characteristics of oxidative damage have been isolated from atheroma (71,72). Several chemically unrelated antioxidants, which are potent inhibitors of lipoprotein lipid peroxidation in vitro, retard atherogenesis in animal models of hypercholesterolemia (64). In vitro work shows that extensively oxidized LDL is rapidly taken up and degraded by cultured macrophages (73,74), suggesting a role for LDL oxidation in lipid accumulation by the arterial wall. Oxidized LDL is strongly cytotoxic (75), perhaps explaining why cellular necrosis is prominent in advanced atherosclerotic lesions.

Indirect evidence suggests that lipoprotein oxidation is enhanced in diabetes. First, nontargeted index changes of lipid oxidation are increased in diabetic subjects (65). Second, plasma lipoproteins isolated from diabetic rats have increased levels of oxidation products and are cytotoxic to cultured cells (76), suggesting that they may have been oxidatively modified in vivo. Both lipoprotein oxidation products and cytotoxicity are reduced by either antioxidants or insulin treatment. LDL oxidation in vitro is stimulated by glucose itself (77-79), and glycoxidation products have been detected in LDL isolated from diabetic patients (79,80). These observations raise the possibility that lipoprotein oxidation in diabetes can occur by different discrete pathways.

**PATHWAYS PROMOTING LDL OXIDATION**

**The glycoxidation pathway.** In diabetics, glycoxidation could be an important pathway for accelerated LDL oxidation (Fig. 2) (65,77-80). In its open-chain form, glucose possesses a reactive aldehydic moiety that reacts nonenzymatically with the lysine residues of proteins (81,82). The resulting Schiff base rearranges, which results in the formation of fructoseylsine, the Amadori product (81,82). Amadori product formation is greatly enhanced in diabetic subjects (65,83-85). The Amadori product of hemoglobin is HbA1c, an indicator of long-term glycemic control.

A protein with the Amadori product can be cross-linked through its reactive carbonyl group to other proteins and lipoproteins, forming a variety of advanced glycation end products (AGEs) (65,83-85). These reactions are poorly understood, but one important AGE is N1-(carboxymethyl)lysine (CML), formed by sequential glycation and oxidation reactions between reducing sugars and proteins (86). Another is pentosidin, formed during the cross-linking of protein lysine and arginine residues (87). Formation of CML is inhibited by metal chelators in vitro, which implicates free metal ions in AGE generation (88).

**FIG. 2. Pathways for the glycoxidation of proteins.** Glucose in its open-chain form possesses adjacent aldehyde and hydroxyl groups [RCH(OH)CHO]. The hydroxymaldehyde is in equilibrium with the enediol. Oxidation of the enediol yields a dicarbonyl sugar and partially reduced oxygen species like superoxide (O2·−), hydrogen peroide (H2O2), and hydroxyl radical (HO·). Glycated proteins may undergo an analogous set of reactions. Dicarbonyls covalently modify proteins and promote cross-linking reactions. Partially reduced oxygen species trigger the oxidation of proteins, lipids, and nucleic acids.

AGEs have been proposed to promote vascular disease (84,85,89). Potential mechanisms include the generation of oxidizing intermediates and dicarbonyl sugars, cross-linking of matrix-plasma components, and interactions with cell surface receptors that trigger the release of cytokines and other biologically active molecules.

Superoxide, hydrogen peroide, and hydroxyl radical, reactive oxygen species that could damage lipoproteins, are also formed during glucose autoxidation (65,77,78,90,91). Moreover, glucose autoxidation has been proposed to play a key role in protein oxidation and AGE formation (90,91). Glucose oxidation may take place directly in solution or after protein glycation has occurred, generating reactive carbonyl groups and toxic oxygen intermediates (65,88,90,91). Thus, a variety of glucose-dependent reactions might promote lipid and protein oxidation in the arterial wall (Fig. 2).

**The myeloperoxidase pathway.** Phagocytic white blood cells help destroy microorganisms and tumor cells. One enzyme used by these cells is myeloperoxidase, a secreted heme protein (92). Myeloperoxidase uses hydrogen peroide generated by activated neutrophils and monocytes to generate potent cytotoxins.

Active myeloperoxidase is a component of human atherosclerotic tissue (93). The enzyme colocalizes with macrophages in cellular regions of lesions and is closely associated with cholesterol crystals in extracellular lipid deposits. A similar pattern of immunostaining has been noted for protein-bound oxidized lipids in rabbit lesions (70), suggesting that myeloperoxidase may be a catalyst for LDL oxidation in vivo (Fig. 3).

Protein oxidation products generated by myeloperoxidase, including dityrosine and chlorotyrosine, can be detected by gas chromatography-mass spectrometry (94). They are present at increased levels in human atherosclerotic tissue and in LDL isolated from lesions (J.W.H., unpublished observations). Hypochlorous acid–modified proteins, unique products of myeloperoxidase, can be detected immunologically. They are abundant at all stages of the atherosclerotic process in
human subjects and in LDL isolated from lesions (95). These results indicate that reactive intermediates generated by myeloperoxidase catalyze oxidative reactions in the vascular wall and suggest that myeloperoxidase may play an important role in promoting atherosclerotic vascular disease.

Pathways for LDL oxidation such as phagocyte activation may be stimulated by hyperglycemia or other metabolic sequelae of the diabetic state (96). Indeed, hyperglycemia activates protein kinase C in the vascular wall, probably by stimulating de novo diacylglycerol synthesis (96,97). Protein kinase C activation stimulates myeloperoxidase secretion and oxidant generation by phagocytes (94,98,99). Moreover, plasma levels of free fatty acids are frequently elevated in diabetic subjects, and free fatty acids also trigger oxidant production by cultured phagocytes. By favoring phagocyte activation and the secretion of myeloperoxidase, hyperglycemia and free fatty acids may promote LDL oxidation and atherogenesis.

The reactive nitrogen pathway. NO generated by endothelial cells is a major regulator of vascular tone in muscular arteries; it also exerts other potent biological effects such as inhibition of platelet aggregation and of monocyte adhesion to endothelium (96,101).

NO is a relatively stable free radical that may contribute to lipoprotein oxidation by several different mechanisms (Fig. 4). NO reacts with superoxide to produce peroxynitrite, an extremely potent oxidant with hydroxyl radical–like properties (102). Chemically synthesized peroxynitrite promotes LDL nitration and lipid peroxidation, and LDL exposed to high concentrations of this oxidant is converted into a ligand for the macrophage scavenger receptor (103). Antibodies to nitrotyrosine, a product of protein oxidation by peroxynitrite, recognize epitopes in normal and atherosclerotic arterial wall (104). Recent studies demonstrate marked increases in the nitrotyrosine content of LDL isolated from human vascular lesions (J.W.H., unpublished observations), implicating reactive nitrogen species as one pathway for LDL oxidation in nondiabetic subjects.

In contrast, other studies suggest that NO protects LDL against oxidation (105–107). NO might suppress LDL oxidation by inhibiting heme-containing enzymes, scavenging superoxide, reacting with lipid radicals, or oxidizing important cellular enzymes involved in LDL oxidation. Inhibitor studies suggest that NO interferes with fatty streak formation in hypercholesterolemic rabbits (108). Acute hyperglycemia causes vasodilation in humans, suggesting that glucose might directly or indirectly trigger NO release (109,110). AGEs apparently react with NO or inhibit its actions (111), raising the possibility that hyperglycemia impairs the vasomotor response of the arterial wall. Aminoguanidine, which inhibits AGE formation in vitro, is effective in preventing diabetes-induced formation of AGEs in the vascular wall of rats (112). However, aminoguanidine also inhibits NO synthase (113), suggesting that increased NO production may account in part for accelerated AGE formation and vascular dysfunction in diabetic patients, possibly via increased generation of peroxynitrite or other reactive species.

The role of NO in diabetic atherosclerosis may thus reflect the balance between its pro- and antiatherogenic effects, and the availability of O$_2^-$ and AGEs may be critical in controlling this balance.

Other mechanisms for accelerated LDL oxidation. Other cellular mechanisms may oxidize LDL. Lipoygenase triggers LDL oxidation in vitro (114). Lipoygenase protein and mRNA colocalize with macrophages in atherosclerotic lesions (115). A stereospecific lipid oxidation product generated by lipoygenase was recently isolated from human atherosclerotic lesions (116).

Plasma antioxidant levels tend to be low in diabetes (117). Dietary intake of lipid-soluble antioxidants such as vitamin E is inversely associated with the risk of ischemic heart disease (64), and a recent clinical trial showed that supplemental vitamin E reduces the risk for acute coronary events in patients with established atherosclerotic disease (118).
Ascorbate is a scavenger of reactive intermediates in vitro, ascorbate levels are low in diabetes (117), and diabetic plasma is readily oxidized in vitro (119). Vitamin C improves endothelial-dependent vasodilation in diabetic patients (117). These results suggest that metabolic derangements such as hyperglycemia or insulin resistance hamper natural antioxidant mechanisms and increase the risk for LDL oxidation, vascular dysfunction, and atherosclerosis.

Variations in the susceptibility of LDL to oxidation may contribute to vascular damage. Small dense LDL particles, commonly seen in diabetic subjects, are particularly susceptible to oxidation (120,121). These particles also bind more avidly to proteoglycans, suggesting that they may be retained in the extracellular matrix of the arterial wall (25), a site vulnerable to oxidation.

Protein-bound AGEs can interact with specific cellular binding proteins (84,85). This interaction triggers oxidant generation by cultured endothelial cells, which could promote lipoprotein oxidation. Infusion of AGE-albumin into rats results in the appearance of lipid peroxidation products in normal tissues (25), indicating a site vulnerable to oxidative stress (86).

The effect of cholesterol lowering with statins effectively in diabetic subjects, and will such therapy influence elevation of high density lipoprotein cholesterol, and long-term treatment of genetic causes of dyslipidemia and oxidatively modified lipoproteins should help unravel the mystery of diabetes in diabetic subjects could provide answers. Is insulin therapy proatherogenic in humans with diabetes? Experiments studying the relative roles of insulin, insulin resistance, and glucose in the regulation of lipoproteins and the regulation of vascular wall gene expression will be critical. Are markers for specific oxidation pathways elevated in diabetic tissue? Detection of such markers would point toward specific redox pathways of potential importance in LDL oxidation. Could specific inhibitors of oxidative enzymes in the arterial wall decrease atherosclerosis in diabetic patients? Characterization of animals with inactivated genes implicated in specific reaction pathways will provide clues. The main characters have long been known, but the plot is clearly new. Future studies based on recent progress in the understanding of genetic causes of dyslipidemia and oxidatively modified lipoproteins should help unravel the mystery of diabetes and accelerated vascular disease.

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