A high concentration of plasma cholesterol has been recognized as one of the principal risk factors in the development of coronary, peripheral, and, possibly, cerebral arteriosclerosis in man. Studies in experimental animals have shown a direct relationship between hypercholesterolemia and the accumulation of cholesterol in the arterial wall. It is usually assumed that cholesterol in blood plasma is transferred to the arterial wall as such or as part of a lipoprotein complex. Indeed, free or complexed beta-lipoprotein or apoprotein has been demonstrated in atheromatous plaques and fatty streaks (1-6). It is not known, however, whether the presence of lipoprotein in a diseased artery causes plaque formation or results from increased arterial permeability due to the disease. The finding that cholesterol can enter the normal aortic wall as a constituent of lipoprotein, primarily beta-lipoprotein (7, 8), suggests the possibility of a causal relationship.

Various mechanisms proposed to explain the accumulation of lipids in the arterial wall have been summarized recently (9). Many of them include a high concentration of plasma cholesterol or a high concentration of low-density (beta) lipoproteins as a necessary condition for atherogenesis. More recently, clinical and epidemiological evidence (10-12) has implicated elevated plasma triglycerides or pre-beta-lipoproteins as an additional risk factor for clinical atherosclerosis. The mechanism by which the pre-beta-lipoproteins act as atherogenic agents is not clear, since they are probably too large (250–750 Å) (13) to penetrate into the arterial intima (14-16). I wish to propose a mechanism of atherogenesis that attributes key roles not only to beta-lipoproteins but also to very low-density or pre-beta-lipoproteins (Sₗ > 20-400) and to chylomicrons (Sₗ > 400).

The proposal is partly based on the demonstration that, as a result of lipolysis in vitro or in vivo, pre-beta-lipoproteins are converted to beta-lipoproteins (17-23) and that chylomicrons are degraded to relatively small cholesterol-rich remnants (24, 25). Although these conversions may occur in post-heparin plasma in vitro, it is likely that under physiological conditions very low-density lipoproteins and chylomicrons are degraded while they are adsorbed to, or engulfed by, vascular endothelium (15, 16). It has been repeatedly demonstrated (26) that lipoprotein lipase, the enzyme which catalyzes these degradations, is localized in capillary endothelium, adipose cells, myocardium, and skeletal muscle cells. Lipoprotein lipase may also be present in arteries, particularly in the larger ones (27-29), and in endothelial cells covering atheromatous plaques (28). A focal increase in lipase activity in arterial lesions has been observed in rabbits susceptible to cholesterol-induced atherosclerosis (28). The presence of lipoprotein lipase in the arterial wall suggests that the concentrations of triglyceride-poor, cholesterol-rich beta-lipoproteins at the blood-artery interface may greatly exceed the concentrations in the circulating blood.

Lipoprotein Interactions with Heparin and Lipoprotein Lipase.—Before outlining a possible sequence of events that might explain the focal accumulation of beta-lipoprotein at the surface of the arterial wall, two apparently unrelated actions
of heparin should be discussed. (1) Intravenously
injected heparin releases lipoprotein lipase from
tissue sites into the bloodstream (28, 30). (2) In
the presence of calcium ions and at physiological
salt concentrations, heparin causes aggregation of
chylomicrons and pre-beta-lipoproteins. (Calcium-
heparin beta-lipoprotein complexes also form, but
at physiological salt concentrations they are less
tight than are the corresponding pre-beta-lipopro-
tein or chylomicron complexes [31-33]. At lower
ionic strengths, beta-lipoprotein forms insoluble
complexes with heparin and calcium ions [31, 32].
Thus beta-lipoproteins may attach to the arterial
surface more loosely but in the manner described
for chylomicrons and pre-beta-lipoproteins.) The
aggregation of lipoproteins is most easily explained
by a binding and cross-linking effect of heparin
(31); heparin also binds to lipoprotein lipase (34).
Thus it is likely that heparin or heparinlike material
can act as a bridge linking chylomicrons, pre-beta-
lipoproteins, beta-lipoproteins, and lipoprotein li-
pase to the arterial surface (6). Injected heparin
might release lipoprotein lipase and lipoproteins by
competing for binding sites at the vascular surface.

If we assume that heparin or heparinlike material
exists on the intimal surface in different surface
concentrations at different sites, the following
sequence of events could lead to focal cholesterol
deposition in the arterial intima. Triglyceride-rich
and cholesterol-containing pre-beta-lipoproteins
and chylomicrons of the plasma are adsorbed at
arterial foci in proportion to the local concentra-
tions of sulfated polysaccharides at the endothelial
surface. While adsorbed, the large complexes are
subjected to lipolysis, whereby cholesterol-rich
beta-lipoprotein or chylomicron remnants are
formed. Because the cross-linking effect of heparin
and calcium at physiological salt concentrations is
weaker for beta-lipoprotein than it is for chylomi-
crons or pre-beta-lipoproteins (32, 33), much of the
beta-lipoprotein is released into the bloodstream.
However, some of the cholesterol-rich degradation
products may stay bound to the intimal surface long
enough to be incorporated into the arterial intima
by pinocytosis, filtration, free diffusion, or some
presently undefined mechanisms.

The lipolytic process at the intimal surface not
only maintains a very high concentration of
cholesterol-rich lipoproteins at the blood-artery
interface but also supplies fatty acid anions which
may facilitate cholesterol or lipoprotein transport
across the arterial barrier (35). The fatty acids, at
the pH of plasma, are present primarily in the form
of soaps, which solubilize and disperse crystalline
cholesterol. Moreover, soaps disrupt cell mem-
branes, and the presence of a high soap concentra-
tion while beta-lipoprotein is adsorbed at the cell
surface may create conditions favorable to chole-
sterol or lipoprotein transport into the intima.

These mechanisms do not necessarily replace
current views on the importance of high serum
beta-lipoprotein concentrations in blood plasma.
The lipoprotein lipase mechanism could well act in
combination with any or all of the various mechanisms
proposed to explain atherogenesis. However, if for
the sake of argument the lipoprotein lipase
mechanism were viewed as the major mechanism
responsible for cholesterol deposition in the arterial
wall, the correlation between plasma cholesterol
concentration and atherogenesis would no longer
indicate a cause and effect relationship.

Hyper-beta-lipoproteinemia and Atherogenesis
Resulting from a Lipolytic Process.—In the blood
plasma of man the major part of the cholesterol is
carried by beta- and pre-beta-lipoproteins. It has
been proposed (21) that most, if not all, of the
plasma beta-lipoprotein is derived from the pre-
beta-lipoproteins, presumably as a result of lipopro-
tein lipase activity at the capillary endothelial
surface. Patients with highly active lipoprotein
lipase probably rapidly convert the circulating pre-
beta-lipoproteins to beta-lipoprotein, leading to
relatively low plasma pre-beta-lipoprotein and high
plasma beta-lipoprotein levels. Indeed, reciprocal
changes in the concentration of serum beta- and
pre-beta-lipoproteins have been shown to occur in the
plasma of patients undergoing weight reduction
or treatment with Atromid-S (36). Both treatments
are known to affect lipoprotein lipase activities in various
tissues (28, 37).

If the atherogenic process depends primarily on
the concentration of cholesterol-rich lipoproteins at the
surface of the arterial wall, then the development
of atheromatous lesions should be rapid under
various conditions. A very high concentration of
beta-lipoprotein in the circulating blood, for ex-
ample, would imply that a high concentration of
these lipoproteins also exists at the arterial surface.
Thus, the well-known frequent, early manifestation
of arteriosclerosis in patients with type II hyperli-
poproteinemia (38) is readily understandable.

The large majority of people suffering from
arteriosclerosis do not show extremely high serum
cholesterol concentrations. Epidemiological and
clinical studies have emphasized a correlation
between atherosclerosis and moderate elevations of
plasma cholesterol levels, triglyceride levels, or both (12). It is quite possible that for this type of hyperlipidemic person the mechanism of atherosclerosis is not causally related to the plasma cholesterol concentration but is a direct result of the degradation of pre-beta-lipoproteins and chylomicrons at the arterial surface. Thus various conditions—highly active lipoprotein lipase in the arterial endothelium, high concentrations of substrate (pre-beta-lipoprotein or chylomicrons), and the extent of binding of the cholesterol-rich degradation products (beta-lipoproteins or chylomicron remnants) to the arterial surface by heparin or heparin-like materials—might promote atherogenesis as a result of this reaction.

Patients with broad beta disease (type III hyperlipoproteinemia) show evidence of premature atherosclerosis (38), and the predominant plasma lipoprotein present in these patients probably is a degradation product of chylomicrons (39, 40). Although chylomicrons usually are not considered to be atherogenic, this conclusion is based on the relative absence of premature atherosclerosis in patients with hyperchylomicronemia or type I hyperlipoproteinemia (38). However, since these patients suffer from a deficiency of post-heparin lipoprotein lipase, they do not convert these chylomicrons efficiently to atherogenic remnants. In contrast, for a normal person on a diet high in cholesterol and fat, chylomicrons are degraded at the endothelial surfaces of the vascular system throughout most of the day.

If the degradation of triglyceride-rich lipoproteins at the endothelial surfaces of capillaries and arteries is regulated by the same metabolic factors, then, when the degradation proceeds rapidly at both sites, the beta-lipoprotein concentration in the circulating blood should be high and the arterial deposition of cholesterol should be rapid. According to this viewpoint, the high concentration of serum beta-lipoprotein is not the cause of atherosclerosis but is the result of the same enzymatic reaction that accelerates the deposition of lipid in the arterial intima.

Implications for Diagnosis and Treatment.—Although the rapid conversion of pre-beta-lipoproteins and chylomicrons to their end products may tend to increase the concentration of cholesterol-rich material, the latter is also controlled by the rate at which the beta-lipoprotein fraction is removed from the circulation. There may be individuals who have relatively high production rates of beta-lipoproteins from pre-beta-lipoproteins and high rates of atherogenesis but who have normal beta-lipoprotein concentrations in the circulating plasma due to active beta-lipoprotein removal mechanisms. Thus the use of serum lipoprotein concentrations as indexes of atherogenesis may need reevaluation if the lipoprotein lipase mechanism is a major factor in the pathogenesis of atherosclerosis. Moreover, the customary use of fasting blood samples for the measurement of plasma lipids and lipoproteins may need reconsideration if chylomicrons have atherogenic properties.

The proposal has certain implications for the treatment of atherosclerosis. If arterial lipoprotein lipase is a link in the atherogenic process, it might be beneficial if lipoprotein lipase activity in the arterial wall were reduced. Although lipase inhibitors should be investigated, the chylomicronemia resulting from such inhibitors has undesirable side effects. A treatment that would release the arterial lipase into the bloodstream, such as the administration of heparin, would be more rational. After injection of heparin the triglyceride-rich lipoproteins are still degraded to smaller fragments, but the fragments are formed in the bulk of the bloodstream away from the arterial wall and away from the potential site of atherogenesis. Beneficial effects of heparin on clinical atherosclerosis have been reported by several investigators (41-43), but clinical evidence of this type must be interpreted cautiously. However, if the beneficial effects of heparin are related to the release of lipoprotein lipase from the arterial surface and the subsequent reduction in the surface concentration of beta-lipoprotein, then the effect should be more pronounced at a stage of atherogenesis when cholesterol deposition is the predominant event, i.e., in the early stages of atherosclerosis. Such an effect would be difficult to demonstrate in patients, but it has been demonstrated in some experiments with animals.

More than 20 years ago Graham et al. (44) observed that the administration of heparin caused a shift in the lipoprotein pattern in the plasma of rabbits fed a high-cholesterol diet; moreover, the chronic administration of heparin retarded the development of fatty deposits in the arterial wall. Horlick and Duff (45), in a particularly well-controlled experiment, showed retardation of atherogenesis by heparin in cholesterol-fed rabbits, although total serum cholesterol was not affected by the heparin treatment. Constantinides and co-workers (46-48), Besterman (49), and Murata (50) observed antiatherogenic effects of...
heparin and sulfated polysaccharides in rabbits. Meng and Davis (51) also found a reduction in lipid deposits in rabbit aorta and liver after treatment with heparin, but the effects were not large. Retardation of atheromatosis by heparin in the iliac arteries of cholesterol-fed rabbits after endarterectomy has also been observed (52, 53). These observations do not prove that the antiatherogenic effects were related to the release of lipoprotein lipase. Heparin could also influence atherogenesis by diminishing platelet stickiness or blood coagulability.

In contrast, other workers were not able to demonstrate beneficial effects of heparin treatment in rabbits (54, 55) or chickens (58, 57). There are several possible explanations for these discrepancies. First, it is likely that the lipoprotein lipase released by heparin injection is replaced by lipase synthesized in situ or derived from adipocytes or muscle cells (26, 30, 58). Thus, in heparin therapy a dose schedule of heparin that minimizes the surface concentration of lipoprotein lipase in the large arteries, particularly when plasma triglyceride concentrations are high, should be determined. Second, most of the experiments were carried out on rabbits or chicks with very high serum cholesterol concentrations. Recent work has demonstrated that high serum cholesterol concentrations inhibit lipoprotein lipase activity in vitro (59), and, possibly in some of the experiments the interaction of pre-beta-lipoproteins or chylomicrons with arterial lipoprotein lipase was inhibited. Under these circumstances the presence of beta-lipoprotein in the circulating blood would be the primary atherogenic stimulus, and the administration of heparin would have little or no effect.

Previous work with heparin and other sulfated mucopolysaccharides in intact animals and in man has emphasized the shift in plasma lipoprotein patterns rather than the possible effects on the arterial surface. Future workers should consider the lipolytic reaction at the arterial surface and the effects of activators and inhibitors on this reaction.

Several of the smaller proteins found in pre-beta-lipoproteins, alpha-lipoproteins, and chylomicrons (60) have an activating or an inhibiting effect on lipoprotein lipase in vitro (61-66). It is likely that these proteins regulate the lipolytic degradation of triglyceride-rich lipoproteins at the capillary endothelial surface. In view of the foregoing comments, it is possible that the concentration of these inhibiting and activating proteins might influence the atherogenic process.

The present discussion has pointed to a possible atherogenic effect of the lipoprotein lipase reaction. Evidence has been presented to support the hypothesis that atherogenesis may result from the liberation of cholesterol-rich fragments in proximity to the arterial endothelium when pre-beta-lipoproteins or chylomicrons are degraded by arterial lipoprotein lipase. High local concentrations of cholesterol-rich lipoproteins resulting from surface lipolysis and the release of potentially injurious fatty acids would enhance the uptake of cholesterol by the arterial intima. Therefore, high concentrations of plasma beta-lipoproteins in some patients with atherosclerosis might be the consequence of an atherogenic lipolytic process rather than the cause of atherosclerosis.

**References**


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ATHEROSCLEROSIS AND LIPOPROTEIN LIPASE


A Proposal Linking Atherogenesis to the Interaction of Endothelial Lipoprotein Lipase with
Triglyceride-Rich Lipoproteins
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