0031-6997/96/4802-0327$03.00/0
PHARMACOLOGICAL REVIEWS
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Vol. 48, No. 2
Printed in U.S.A.

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Actions of Heparin in the Atherosclerotic Process

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I. Introduction

Previous reviews of this subject (Engelberg, 1983, 1984, 1988, 1990) encompassed the relevant literature through 1988. Since then, much additional material has been published. The present article will present the new important evidence without repeating the earlier discussions, except in a few instances in which recent studies have clarified previously controversial areas.

The terms *heparin* and *heparin activity* have been and will be used interchangeably in this review. This should be clarified. Heparan sulfate proteoglycans (HSPGs) are widely distributed in all tissues and contain heparin moieties with heparin activity. The latter term includes the action of heparin per se or the heparin activity of HSPG. It is probable that the actions of low doses of exogenous heparin reflect and augment those of endogenous heparin activity.

II. Endogenous Plasma Heparin

Controversy existed previously about the presence of endogenous heparin in normal human plasma, although earlier studies (reviewed in Engelberg, 1983) showed that a plasma extract had heparin-like anticoagulant activity. However, some respected investigators stated they had not verified that heparin was present in the blood. Oddly, they overlooked the fact that it was protein-bound. In 1961, endogenous heparin was demonstrated in normal human plasma after tryptic proteolysis of the previously precipitated plasma proteins (Engelberg, 1961a). Plasma heparin levels were 1 to 2.4 mg/L.

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Abbreviations: HSPG, heparan sulfate proteoglycans; LPL, lipoprotein lipase; TG, triglyceride; HDL, high density lipoprotein; B-VLDL, B-very low density lipoprotein; SMC, smooth muscle cells; ANG, angiotensin; LDL, low-density lipoprotein; NO, nitric oxide; EC, endothelial cell; IL, interleukin; ET, endothelin; PDGF, platelet-derived growth factor; FR, oxygen free radicals; HUVEC, human umbilical vein EC; TNF, tumor necrosis factor; MCP-1, monocyte chemotactic factor; PAF, platelet activating factor; VCAM-1, a cell adhesion molecule, DNA, deoxyribonucleic acid; OXLDL, oxidized low-density lipoproteins; NF-kB, nuclear factor-kB; MPO, myeloperoxidase, myeloperoxidase-hydrogen peroxide-halides; IP_3, inositol triphosphate; HSV-1, Herpes simplex virus-1; AGE, advanced glycosylation end products; HCT, homocysteine; CMV, cytomegalovirus; IFN-G, interferon gamma; VSMC, vascular smooth muscle cell; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteases; DSPG, dermatan sulfate proteoglycans; TGF-B, transforming growth factor-beta; EGF, epidermal growth factor; HB-EGF, heparin binding EGF; ACE, angiotensin-converting enzyme; ECM, extracellular matrix; b-FGF, basic fibroblast growth factor; PAI-1, plasminogen activator inhibitor; TF, tissue factor; TFPI, TF pathway inhibitor; GAG, glycosaminoglycans; CS, chondroitin sulfates.

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Conclusive evidence about this question has been presented recently (Cavari et al., 1992). After exhaustive proteolysis, an endogenous anticoagulantly active substance was isolated from normal human plasma and identified as authentic heparin. It was inactivated by heparinase 1 and 2, but not by chondroitin or heparan sulfate lyases. The level of plasma heparin was very close to that reported years before (Engelberg, 1961a). In another very recent study, endogenous plasma heparin activity was demonstrated again in normal human plasma in somewhat larger quantities [0.54 mg/100 mL plasma (±0.17)], after very extensive proteolysis using sequentially papain, trypsin, chymotrypsin, collagenase and pepsin. The peak molecular mass was 7000, and the anticoagulant activity of the extracted material was 70 IU/mg (Volpi et al., 1995). Thus there is no justification for any further doubt about the normal presence of endogenous heparin in human blood.

Plasma heparin levels correlated inversely, but not highly significantly, with the serum cholesterol and Sf 0–12 lipoproteins. However, the inverse correlation with the triglyceride-rich Sf 12–400 lipoproteins was highly significant ($p < 0.01$) (tables 1 and 2, Engelberg, 1961b). In retrospect, it would have been desirable to compare heparin levels in normal individuals with those in patients with known coronary disease. The value of such a comparison was not appreciated at that time (35 years ago). However, approximately half of the 260 patients whose plasma heparin levels were analyzed had coronary heart disease. Unfortunately, there have not been any other reports of studies of serum lipids and their correlation with plasma heparin levels. It would be valuable for such investigations to be repeated by others. Confirmation of the earlier results (Engelberg, 1961b) would establish that a relative deficiency of endogenous heparin activity is a major factor contributing to lipid abnormalities important in atherogenesis.

III. Lipoprotein Lipase

Endogenous circulating heparin also relates to lipoprotein lipase (LPL) activity. It is well known that after heparin injection, LPL is mobilized from the vascular endothelial surface into the blood, and that LPL is the major enzymatic activity involved in the hydrolysis and removal of triglycerides from the bloodstream. It is less appreciated that plasma LPL activity has been demonstrated without the previous injection of heparin in some individuals. Studies in 482 nonfasting private patients (Engelberg, 1958) showed that endogenous plasma LPL activity was present in 18% of normal people, and it was inversely and significantly related to the triglyceride-rich Sf 12–400 lipoproteins. The circulating LPL enzymatic activity probably reflects the amount of enzyme bound at the vascular endothelial surface, where most triglyceride lipolysis occurs, and/or possibly the level of plasma endogenous heparin, or both. The presence of LPL activity in normal human plasma without the injection of heparin and its increase after a fat-containing meal recently has been confirmed (Karpe et al., 1992). This increase was considerably more in normal individuals than in patients with known coronary heart disease. Reduced LPL activity is also a contributing cause of lower levels of high density lipoproteins and the consequent increased susceptibility to coronary atherosclerosis (Durrington, 1993).

There are other significant recent observations about LPL activity, lipoprotein metabolism and atherogenesis. The postprandial metabolism of triglyceride-rich lipoproteins is severely defective in hypertriglyceridemia (Karpe et al., 1993). Postprandial lipemia is greater in patients with coronary artery disease. The magnitude of the triglyceride (TG) response after a fat load was a better indicator of the disease than was the fasting TG level (Nikkila et al., 1994). In 61 male patients with severe coronary atherosclerosis, as opposed to 40 angiographically normal matched control subjects, the maximal TG increase and the magnitude of postprandial lipemia was higher after a standardized fat meal. A single postprandial TG at 6 and 8 hours was highly discriminatory ($p < 0.001$) (Patsch et al., 1992). The study suggested that TG metabolism is a critical determinant of cholesterol metabolic routing, and that the negative association between high density lipoprotein (HDL) cholesterol blood levels and coronary artery disease actually originates in plasma TG in the postprandial state. The authors called HDL cholesterol the 'memory box' of TG metabolism. Prospective studies have established that hypertriglyceridemia can precede the onset of coronary atherosclerosis (Galton et al., 1994). Post-prandial TG metabolism has recently been reviewed (Cohn, 1994). The sons of patients with early coronary heart disease had prolonged postprandial lipemia significantly different at 8 to 12 hours after a fat meal than the sons of normal individuals (Uiterwaal et al., 1994), indicating that decreased LPL activity is a familial risk factor for coronary disease. Octogenarians had a significantly ($p < 0.0001$) decreased level of postprandial lipemia as compared with younger controls (Weintraub et al., 1992). The authors noted that the greater part of our lives is in the postprandial, not in the fasting state; thus vessel walls are exposed to postprandial lipoproteins most of the time.

There is mounting evidence that increased triglyceride levels are a vascular risk factor (Stein and Gotto, 1992; Patsch, 1994). Polyunsaturated fatty acids increased the clearance rate of chylomicron and triglyceride-rich lipoprotein remnants (Demacker et al., 1991), validating earlier studies that showed that lipoproteins containing polyunsaturated fatty acids were a better substrate for LPL activity (Engelberg, 1966). The long-term administration of a compound that increases LPL activity inhibited coronary artery atherosclerosis in rats with experimentally produced disease (Tsutsumi et al., 1993). Overexpression of human LPL in transgenic non-

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diabetic and diabetic mice increased resistance to diet-induced hypercholesterolemia and hypertriglyceridemia and also elevated HDL_2 (Shimada et al., 1993, 1994).

Missense mutations of LPL impair triglyceride tolerance and are associated with multiple lipoprotein abnormalities and increased triglycerides (Miesenbock et al., 1993; Wilson et al., 1990). Polymorphisms at the LPL gene locus are significantly ($p < 0.001$) increased in patients with coronary artery disease (Thorn et al., 1990), and with variability in plasma lipids (Mitchell et al., 1994). Over 40 different LPL gene mutations have been described with complete deficiency of LPL activity (Gagne et al., 1994). LPL gene mutations that only partially decrease LPL activity interact with environmental factors, like pregnancy, to induce hypertriglyceridemia (Hayden et al., 1994). LPL gene polymorphisms are associated with decreased levels of HDL cholesterol (Gerdes et al., 1995; Pimstone et al., 1995).

Much earlier evidence suggested that endogenous heparin plays an essential role in LPL function (reviewed in Engelberg, 1984, 1988, 1990). Conclusive proof was published recently when it was demonstrated that LPL was totally inactive if its binding to heparin was prevented by mutational changes in the enzyme (Auverx et al., 1989; Beg et al., 1990). Thus, heparin is an obligatory component of LPL function. There are five heparin-binding sites in the amino terminal domain of LPL (Hata et al., 1993). Decreased heparin activity would impair LPL function and result in elevated serum levels of triglyceride-bearing lipoproteins and the resultant lower levels of HDLs, both important factors in atherogenesis. Many years ago, it was stated "the overall data suggest that lipemia clearing factor (LPL) may exist normally in plasma in low concentrations depending on available heparin supply" (Anfinsen et al., 1952).

There are additional significant observations about the actions of heparin in relation to LPL. In cultured chick adipocytes, exogenous heparin decreased LPL degradation from 76 to 21% of the synthetic rate (Cupp et al., 1987). In mouse adipocytes, heparin totally arrested LPL intracellular degradation and increased the quantitative secretion of the mature form of the enzyme (Vannier and Ailhaud, 1989). Heparin decreased LPL binding to rat adipocytes and increased the release of newly synthesized LPL (Sasaki et al., 1993a). The reduction of endogenous heparin activity by heparinase markedly lowered the transport of LPL from its tissue synthetic sites to the luminal EC surface (Saxena et al., 1991). Heparin also induces the expression of hepatic triglyceride lipase (Busch et al., 1989), which, together with apolipoprotein E, is involved in the hepatic clearance of chylomicron and B-very low density lipoprotein (B-VLDL) remnant particles from the blood (Weintraub et al., 1987; Ji et al., 1994). Approximately 80 to 90% of apolipoprotein E remnant binding is mediated by interaction with HSPG. Heparinase treatment of liver cells almost totally abolishes hepatic clearance of remnant particles (Ji et al., 1994). Intravenously injected heparinase in mice inhibited the clearance of chylomicrons, their remnants and B-VLDL from the blood (Ji et al., 1995). The authors suggested that facilitating the binding of VLDL, LDL, and lipoprotein-a to endothelial cell surface HSPG resulted in catabolism of the lipoproteins. This is additional evidence of the function of endogenous heparin activity in the removal of triglycerides from the bloodstream.

There is a recently described action of LPL in arterial tissue that may play a role in foam cell formation and atherogenesis. The alpha-2 macroglobulin receptor/low density receptor-related protein is a large integral membrane glycoprotein present on a variety of cell types such as hepatocytes, macrophages, fibroblasts and smooth muscle cells (SMC). It binds and endocytoses alpha-2 macroglobulin/proteinase complexes, low density lipoproteins (LDL), and apolipoprotein E-enriched B-VLDL (Larnkjaer et al., 1995 and references therein). LPL is a ligand for this receptor and enhances the binding of lipoprotein particles to it, thus possibly playing an important role in foam cell formation. Heparin blocks LPL binding to the receptor that is the only lipoprotein receptor expressed on SMC in atherosclerotic lesions in vivo. This indicates another way heparin can beneficially affect atherogenesis.

IV. Lipoprotein and Fibrinogen Uptake by Arterial Walls

The sequence of very early prelesional arterial wall events induced by hypercholesterolemia has recently been reviewed (Simionescu and Simionescu, 1993). These changes occur before monocyte migration into the vessel wall with resultant foam cell and fatty streak formation. They start with the enhanced transport of excess plasma lipoproteins by transcytosis into the intima, followed by the intimal accumulation of oxidatively modified and reassembled lipoproteins, which cause endothelial dysfunctions and the production of chemoattractants and adhesion molecules instrumental in monocyte attachment and migration into the subendothelium. The outer glycocalyx coat of the vascular endothelium, which is the initial target of various adverse events, contains glycoproteins, HSPG (which contain heparin moieties) and sialoconjugates. It has a net negative charge caused by sialic acids and anionic molecules with heparin activity (Simionescu and Simionescu, 1986).

Neuraminidase pretreatment, which affects only sialic acid, increases LDL internalization by aortic endothelial cells (EC) four-fold. Pretreatment with cationized ferritin, which neutralizes both sialic acid and the anionic heparin negative charge, increases LDL uptake 20-fold (Gorog and Pearson, 1984). Diminution of EC negative charge also increases granulocyte adhesion and fibrinogen uptake by arterial walls (Gorog and Born, 1982a). Thinning of the arterial endothelial glycocalyx

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with a resultant decrease in negative charge and an increase in LDL uptake in response to hypercholesterolemia has been demonstrated in aortic bovine aortic EC (Sprague et al., 1988). Protamine, a cation, binds to endothelial anionic charges and decreases anionic charge-charge repulsion (Swanson and Kern, 1994). The important role of negative charge imparted by proteoglycans (PG) in the glycocalyx and extracellular matrix in the restriction of diffusive transport from the blood has recently been reviewed (Garcia and Schaphorst, 1995).

It is well known that exogenous heparin has high binding affinity for both arterial and venous endothelial cells and remains on the cell surface for up to 1 week (reviewed in Engelberg, 1984, 1988). Thus, it corrects the harmful effects of a reduction of endogenous glycocalyx heparin activity on the uptake of LDL and fibrinogen by the artery wall.

V. Hypoxia

Many investigations have confirmed the numerous atherosclerosis-increasing effects of hypoxia (reviewed in Engelberg, 1984, 1988, 1990). More recent studies have shown that hypoxia enhances endothelial-derived contracting factors (Luscher et al., 1992), invokes proliferation of vascular smooth muscle cells (Butler et al., 1991; Barker et al., 1993), increases xanthine oxidase activity (Wiezorek et al., 1994), initiates free radical reactions in the arterial wall (Crawford and Blankenhorn, 1991), is an initial lesion in atherosclerosis after thrombosis of the vasa vasorum (Martin et al., 1991), markedly decreases the synthesis of heparan sulfate by bovine aortic and pulmonary artery EC (Karlinsky et al., 1992), elicits arterial contraction via inhibition of the basal synthesis of NO (Muramatsu et al., 1992) and the stimulation of endothelin (ET) production (Levin, 1995), decreases the calcium buffering capacity of mitochondria (Siesjo, 1994) and induces the expression of interleukin (IL)-1 in human cultured EC and in mouse aortic tissue in vivo (Shreenievas et al., 1992). It is pertinent that foam cells, formed early in atherogenesis, increase oxygen demand (Björnhedin and Bondgers, 1987), and that mitochondria play an important role in intracellular calcium signaling (Jouaville et al., 1995). Hypoxia up-regulates genes that encode erythropoietin, platelet-derived growth factor (PDGF)-B, ET, IL-1 ornithine decarboxylase and vascular endothelial growth factor (Goldberg and Schneider, 1994).

The impairment of tissue oxygen supply by high serum triglyceride levels is an important area that has been overlooked. The evidence and the mechanisms involved have been discussed fully (Engelberg, 1983 and references therein). Because of its importance, the subject briefly will be summarized here. High fat feedings reduced the oxygen supply to hamster brain tissue. Surface films have been observed on red blood cells after fat feeding and on the aortic intima after several days of perfusion by lipemic serum. Fat films affect gas exchange. Fats combine with oxygen and affect its diffusion constant. The diffusion of oxygen through blood plasma is decreased by increasing concentrations of plasma lipoproteins even over normal physiologic ranges. High fat meals cause aggregation and rouleaux formation of erythrocytes and so interfere with the full availability of the red blood cell surface for oxygen transfer. A shift to the left of the oxyhemoglobin dissociation curve was noted in patients with high serum triglycerides; this became normal after dietary lowering of the elevated lipids. A decrease in subcutaneous oxygen tension was found in human subjects after a high fat meal. It quickly became normal after a small dose of intravenous heparin, which lowered the elevated serum triglycerides.

The higher serum triglyceride levels associated with decreased endogenous heparin activity in man (Engelberg, 1961b), or with the increase in VLDL after the acute inhibition of LPL in monkeys (Goldberg et al., 1988), would impair oxygen diffusion from the blood to the tissues and so contribute to the many harmful and pro-atherogenic effects of hypoxia. The lowering of serum triglycerides by exogenous heparin via the enhancement of LPL activity would improve tissue oxygen supply.

VI. Oxygen Free Radicals

There is an enormous literature on the harmful effects of free oxygen radicals (FR). Only those that apply to atherosclerosis will be mentioned here. Their role in the atherosclerotic process has been reviewed (Engelberg, 1990; Halliwell, 1989, 1991). FR caused human umbilical vein EC (HUVEC) dysfunction (Dreher, 1995), possibly via disturbance of the normal balance of xanthine dehydrogenase to xanthine oxidase: the balance changes from 2:1 to 1:2. This conversion can result from the action of neutrophil elastase, tumor necrosis factor (TNF), or complement factor 5a (Ward, 1991). LDL-platelet interaction under oxidation stress induces macrophage foam cell formation (Aviram, 1995). FR stimulate neutrophil, monocyte, and platelet adherence to the endothelium thus enhancing inflammatory reactions. They are second-messengers for the expression of an important monocyte chemotactic factor (MCP-1). FR mediate the activation of phospholipase A_2 (Zor et al., 1993), which is involved in the inflammatory process. The evidence that FR have an important role in many of the pathophysiologic vascular responses to hyperlipidemia has been summarized (Baas and Berk, 1995). FR are involved in EC synthesis of platelet activating factor (PAF) and VCAM-1, a cell adhesion molecule widely expressed in atherosclerotic lesions (Mariu et al., 1993); also, FR inhibit plasma acetylhydrolase, which catabolizes PAF, a potent pro-inflammatory factor (Ambrosio et al., 1994) (vide infra). Antioxidant therapy significantly decreased the development of intimal thickening

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after aortic injury in rabbits (Freyschuss et al., 1993) and protected rabbit aortic rings against the detrimental effects of FR on NO (Abrahamson et al., 1992). FR stimulate rat aortic smooth muscle cell growth (Rao and Berk, 1992) and play a role in the microvascular injury caused by IgG immune complex deposition (Ward, 1991). Mitochondrial deoxyribonucleic acid (DNA) is very susceptible to damage by oxygen FR because of its very high use of cellular oxygen, and so has a much bigger rate of harmful mutations than nuclear DNA (Tritschler and Medori, 1993). Elevated homocysteine blood levels contribute to arterial intimal-medial wall thickening (Malinow et al., 1993), and copper-catalyzed FR generation from homocysteine injures aortic EC (Starkebaum and Harlan, 1986). Hypertriglyceridemia triggers FR production by leukocytes (Aranjo, 1995) and monocytes (Hiramatsu and Arimori, 1988). Activated complement increases FR release by arterial EC (Friedl et al., 1989). FR accelerate the formation of harmful advanced glycosylation end products (Cameron and Cotter, 1995). Some viruses stimulate the generation of FR by infected cells (Maeda and Akaike, 1991).

FR contribute to the oxidation of LDL. There is much evidence that oxidized low-density lipoproteins (OXLDL), much more than native LDL, have a major role in atherogenesis (reviewed in Witztun and Steinberg, 1991; Berliner and Haberland, 1993). OXLDL adversely affect all types of arterial wall cells involved in the atherosclerotic process. They increase the expression and release of ET from human endothelium (Boulanger et al., 1992). Oxidative modification of LDL occurs primarily in the arterial intima (Witztun, 1994). The author recommended that the prevention of LDL oxidation should be a primary goal of therapy.

FR are apparently widely used messengers in the activation of nuclear factor-kB (NF-kB), which can rapidly induce the expression of genes involved in inflammatory, immune and acute phase responses (Schrack et al., 1991). NF-kB is a very widespread intracellular messenger which, because its action does not require new protein synthesis, embodies an efficient system for rapidly transducing extracellular signals into specific patterns of gene expression in the nucleus (Lenardo and Baltimore, 1989). The evidence that NF-kB activation in EC is involved in the initiation of the atherosclerotic process has been reviewed (Collins, 1993).

The generation of FR often is determined by the availability of iron and copper catalysts (Halliwell, 1989). Most FR injury is iron-related (Herbert et al., 1994 and references therein). Transition metals play a role at several points of the lipid peroxidation of LDL in addition to the initial stages (Yu, 1994). Iron loading of EC augments oxidant damage (Balla et al., 1990). In the blood, iron and copper are protein-bound and unavailable as free ions. However, human aortic atherosclerotic lesions contained iron and copper in catalytic form that may have been released from binding proteins by macrophage actions. Lesion extracts stimulated lipid peroxidation, which was inhibited by iron chelation (Smith et al., 1992).

Despite much evidence, it has not been fully appreciated that heparin activity inhibits FR effects (Yu, 1994). The earlier work has been reviewed (Engelberg, 1984, 1988, 1990). In summary:

- heparin decreased FR release by activated neutrophils and, as detected by luminol chemiluminescence, mitigates FR effects in vivo;
- it alleviated FR production by radiation, and significantly decreased hydrogen ion accumulation in and its release by reperfused ischemic muscle preparations;
- heparinase pretreatment markedly increased FR release by EC;
- small amounts of heparin enhanced the antioxidant activity of superoxide dismutase. HSPG tether antioxidant superoxide dismutase to cell surfaces and so contribute to the inhibition of FR tissue injury (Geller et al., 1993); certain glycosaminoglycans, including heparin, have features that allow them to act as a FR sink (Grant et al., 1987). Heparin scavenges FR released by the action of myeloperoxidase (Brestel and McClain, 1983).

Other studies afford additional evidence of the antioxidant actions of heparin activity. It markedly reduced FR release in vivo after reperfusion of ischemic kidneys (Nillson et al., 1993). Dextran sulfate, a heparinoid, and heparin protected porcine arterial EC from FR injury (Hiebert and Liu, 1990, 1993). Xanthine oxidase injures EC by generating FR. Dextran sulfate protected the EC (Hiebert and Liu, 1994). OXLDL increase cytosolic Ca^{2+} in vascular smooth muscle cells (Weisser et al., 1992); this is important in early and late atherogenic events. Diverse risk factors of atherogenesis promote intracellular calcium accumulation (Phair, 1988). Heparin inhibits intracellular calcium release initiated via the inositol triphosphate (IP_3) second-messenger system (Ghosh et al., 1988). Heparin also reduces the rate of Ca^{2+} release after inhibition of Ca^{2+}-ATPase in granulocytes (Favre et al., 1994). The action of heparin on intracellular calcium may have profound effects. This subject requires much additional investigation.

Dextran sulfate completely prevented OXLDL inhibition of porcine artery relaxation (Tanner et al., 1991). Polyanions significantly protected acidic fibroblast growth factor from copper-catalyzed oxidation (Volkin et al., 1993). Neutrophils generate FR via a myeloperoxidase (MPO) system and have large quantities of MPO (Weiss, 1989). Human atherosclerotic lesions contain MPO, which oxidizes proteins and lipids independently of metal ions (Daugherty et al., 1993). There is no MPO in the normal artery intima or media. Heparin and dextran sulfate inhibit MPO (Brestel and Koes, 1989; Hocking et al., 1991).

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Copper ions mediate FR degradation of heparin (Liu and Perlin, 1994); copper binds strongly to heparin (Grant et al., 1992). Heparin binds and sequesters iron (Fe^{2+}) ions and decreases the peroxidation of an unsaturated fatty acid in the presence of Fe^{2+} ions (Ross et al., 1992). Metal chelators have anti-oxidant activity and block activation of NF-kB (Schreck, 1992). The extent to which heparin, via its chelation effects, may reduce NF-kB activation, requires investigation. The chelation of copper and iron by heparin undoubtedly is an important factor in its anti-FR effects. Thus, much evidence indicates that heparin-like activity is part of the organism's anti-oxidant defenses and implies that decreases in heparin activity may enhance the harmful actions of FR in the atherosclerotic process.

VII. Endothelial Injury/Dysfunction

In humans and experimental animals, endothelial injury and/or dysfunction are often initiating factors in atherogenesis (Ross, 1986). Various substances can injure endothelium. Heparin binds to and at least partially inactivates many of them (Engelberg, 1984, 1988, 1990 and references therein). These include cationic proteins, some bacterial toxins and viruses, activated neutrophil products and some other proteases, free oxygen radicals, histamine, activated complement, and thrombin-stimulated platelets. Heparin partially corrected the IL-1-mediated increased permeability of cultured human venous EC (Bannon et al., 1995). Heparin increases endothelial stability. There is much evidence that endogenous heparin, together with growth factor for EC, enhances EC proliferation and repair after injury (reviewed in Engelberg, 1984, 1988, 1990). Heparin and heparan sulfate potentiated the mitogenic activity of vascular endothelial growth factor on vascular EC (Soker et al., 1994). Herpes simplex virus-1 (HSV-1), which has been found in a substantial fraction (70%) of human arteries, markedly enhances the susceptibility of cultured human and porcine EC to injury (Jacob, 1994).

Fibrinogen degradation product Fragment D increases endothelial monolayer permeability (Ge et al., 1991). This would be diminished by the inhibition of thrombin generation and activity by heparin. EC barrier dysfunction is a cardinal feature of inflammation, which produces gaps between EC and increases permeability (Garcia and Schaphorst, 1995). The binding of advanced glycosylation end products (AGE) to their endothelial receptor increases endothelial permeability (Schmidt et al., 1995). In an exhaustive study of human popliteal and coronary arteries (Constantinides and Harkey, 1990), endothelial denudation was not found in any early lesions, although it was seen in some advanced lesions over the disintegrating surface of necrotic caps. However, the endothelium over all lesions was more open and so more permeable to plasma constituents.

Anti-elastase agents protect HSV-1-infected EC against polymorphonuclear leucocyte-mediated damage. By simply residing on HSV-1-infected EC, polymorphonuclear leucocytes are stimulated to secrete large amounts of elastase and other cationic lysosomal proteolytic enzymes. Heparin inhibits elastase (Redini et al., 1988) and cathepsin G (Starkey and Barrett, 1976). HSV-1 strikingly inhibits EC synthesis of surface heparans; thus, their protective actions would be diminished (Jacob, 1994).

It has long been known that hyperhomocysteinemia is a risk factor for atherosclerotic disease. Many studies have shown this and will not be detailed here except to note that elevated blood levels of homocysteine (HCT) are present in 20 to 30% of patients with coronary, carotid or peripheral arterial atherosclerotic disease. HCT inhibits thrombomodulin surface expression and protein C activation in HUVEC (Lentz and Sadler, 1991). It also induced the activation of tissue factor in HUVEC (Fryer et al., 1993). Thus, HCT is thrombogenic. HCT caused cytotoxic damage to cultured HUVEC (Bloom, 1992), and high concentrations of HCT facilitated human arterial EC detachment in vitro (Dudman et al., 1991). Small amounts of copper catalyzed HCT oxidation and the release of oxidant hydrogen peroxide that caused (*a*) lysis of bovine aortic EC and HUVEC (Starkebaum and Harlan, 1986) and (*b*) arterial endothelial dysfunction (Berman and Martin, 1993). Very low HCT concentrations decreased DNA synthesis by HUVEC, increased DNA synthesis in rat aortic smooth muscle cells (SMC) and thymidine incorporation in human aortic SMC (Tsai et al., 1994). Small amounts of HCT suppressed heparan sulfate expression in cultured porcine aortic EC (Nishinaga et al., 1993). Exposure of bovine aortic EC to HCT for 3 hours impaired their endothelium-derived relaxing factor responses (Stamler et al., 1993), which were improved by NO. The beneficial effects on EC, the stimulation of NO production and the inhibition of vascular SMC synthesis by heparin would mitigate the harmful effects of HCT. I am not aware of any published studies of heparin binding to or direct inhibition of HCT.

Several common viruses infect and replicate in human EC in culture producing varying degrees of injury (Friedman, 1981). Of them, the best studied is HSV-1. Its many harmful pro-inflammatory and procoagulant effects on human endothelium have been reviewed (Vercellotti, 1990), as has its possible role in the pathogenesis of atherosclerosis (Hajjar, 1991). HSV-1 inhibits the synthesis of PG by EC in vitro up to 85% (Kaner et al., 1990). Receptors promoting the deposition of immune complexes were induced in human EC by HSV-1 infection. Cytomegalovirus (CMV), another herpes virus family member, caused EC damage and early atherosclerotic lesions in normocholesterolemic rats (Span et al., 1992), and may contribute to human coronary artery restenosis after angioplasty (Speir et al., 1994). The injection of fragments of HSV-1 and HSV-2 genomes into isolated nonhyperlipidemic rabbit arterial segments in-

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duced intimal lesions (Robertson et al., 1995), proving that viruses can initiate atherosclerotic changes. There is much evidence that strongly suggests that CMV is involved in atherogenesis (Melnick et al., 1993 and references therein).

It has long been known that heparin inhibits many of the herpes viruses, including HSV-1 and CMV (reviewed in Engelberg, 1984, 1990). Heparin and heparan sulfate markedly decreased the adsorption of HSV-1 and HSV-2 to erythrocytes, and HSV-1-induced hemagglutination (Trybala et al., 1993). Heparin inhibited the binding of CMV virions to the host cell surface (Neyta et al., 1992). Heparin inhibited varicella-zoster virus growth in vitro (Cohen and Seidel, 1994) and inhibited entry of varicella zoster virus into human embryonic lung fibroblasts (Zhu et al., 1995). Dextran sulfate and heparin blocked synctial formation induced by human T-cell lymphotropic virus type 1 (Ida et al., 1994). The in vitro inhibition of many myxoviruses and retroviruses by heparin has been reviewed (Hosoya et al., 1991). There is a further novel observation that has relevance to the antiviral actions of heparin (Lortat-Jacobs and Grimaud, 1991). Interferon gamma (IFN-G) is an important immunomodulatory lymphokine with antiviral activity. IFN-G binds to the sulfate groups of heparan sulfate and heparin in a specific manner with great affinity. The complex is fully active. The authors suggest that once bound to heparin, IFN-G is protected from proteolytic cleavage and has increased stability. This heparin action thus enhances the antiviral effect of IFN-G. These many antiviral actions of heparin afford protection against these important vectors of EC infection and injury.

VIII. Endothelin and Nitric Oxide

These two factors and their relation to atherogenesis will be discussed together, as many of their actions are related. Endothelin (ET) is a recently isolated potent vasoconstrictor and vascular smooth muscle cell (VSMC) mitogen. Its physiologic functions and pathophysiology have been reviewed (Simonson, 1993 and references therein). Thrombin, inflammatory cytokines, mild hypoxia and oxidized LDL increase ET production by EC. Over 80% of ET is secreted toward the underlying VSMC to which it binds. Low concentrations of ET are comitogenic for VSMC with submaximal amounts of PDGF. There is dense binding of ET to the VSMC of human coronary arteries. The content of ET is increased in atherosclerotic vessel walls. ET plasma levels are elevated in patients with advanced atherosclerotic disease. Circulating and tissue endothelin is increased in hypercholesterolemic swine.

There are more recent pertinent findings. ET immunoreactivity was associated with atherosclerotic plaque macrophages (Zieher et al., 1995b). This was particularly so in the active coronary lesions of patients with unstable angina. The author noted that, besides EC, macrophages and neutrophils can produce ET. In cholesterol-fed hamsters, blockade of ET receptors decreased early atherosclerosis (Kowala et al., 1995), indicating that ET and ET receptors promoted the early inflammatory phase of atherogenesis. ET played a role in neo-intimal formation in vivo in rat carotid arteries after balloon angioplasty (Douglas et al., 1994). ET is probably involved in the development of arteriosclerosis in both acute and chronically rejected rat cardiac allografts (Watschinger et al., 1995). Thus, many observations indicate that ET participates in the atherosclerotic process.

NO is an important modulator of vascular function about which an enormous literature has accumulated in a few years (reviewed in Nathan, 1992; Wennhalm, 1994). NO, synthesized in EC by the interaction of L-arginine and oxygen in the presence of NO synthase, diffuses abluminally to VSMC, where it activates guanylate cyclase and so promotes formation of the vasodilator, cyclic guanosine monophosphate. Luminally diffused NO decreases platelet aggregation and adhesion via the same cyclic guanosine monophosphate mechanism. Thus, NO has antithrombotic activity. NO regulates basal systemic and pulmonary vascular resistance in healthy humans (Stamler et al., 1994). NO suppresses neutrophil and monocyte adherence to the endothelial surface (Caterina et al., 1995). The inhibition of NO increased leukocyte adherence 10-fold and emigration four-fold in rat mesenteric venules in vivo (Arndt et al., 1993). Inhibition of basal NO production up-regulated messenger ribonucleic acid expression and secretion of monocyte chemotactic protein-1 (MCP-1), a key EC adhesion molecule for monocytes (Zieher et al., 1995b). A decrease in NO formation yields a moderate vasoconstriction. NO decreased the thrombin-induced increase in endothelial permeability (Draejer et al., 1995). Thrombin inhibits NO synthase production (Schini et al., 1993). NO inhibition increased the baseline levels of ET production by human EC three- to four-fold (Kourembanas et al., 1993).

NO has antiproliferative properties on VSMC. It suppresses PDGF-B-chain genes and inhibits total protein and collagen synthesis in rabbit aortic SMC (Kolpakov et al., 1995). NO inhibited angiotensin-induced migration of rat aortic SMC. NO is reduced in hypercholesterolemia, and restoration of its activity inhibits atherogenesis (Cooke and Tsao, 1992). There is much additional evidence that NO function is defective in human atherosclerotic disease. Flow-mediated dilation of the coronary arteries is lost when atherosclerosis is present (Nabel et al., 1990) and shows a marked reduction in children and adults at risk of atherosclerosis (Celermaier et al., 1992). Coronary artery responses to acetylcholine infusion suggested that the development of vasoconstriction is an abnormality of endothelial function that precedes or is an early marker of atherosclerosis not detectable by coronary angiography (Vita et al., 1990). Impaired endothelium-dependent coronary microvascular dilation

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was found in patients with early coronary atherosclerosis (Zieher et al., 1991). Even in the absence of angiographic evidence of coronary atherosclerosis, exposure to coronary risk factors is associated with reduced resting and stimulated bioavailability of NO in the human coronary circulation (Quyyami et al., 1995). Studies of coronary arterioles, which predominantly determine myocardial perfusion, showed evidence of NO dysfunction (Egashira et al., 1993). There is good evidence to suggest that endothelial dysfunction in atherosclerotic patients is a systemic process and a ubiquitous and characteristic problem of all phases of atherogenesis (Anderson et al., 1995). It was recently noted that the vasoconstricting properties of ET are greatly increased in atherosclerotic vessels, while the opposing biologic actions of NO are lost.

Heparin suppressed the production and action of ET in spontaneously hypertensive rats (Yokokawa et al., 1992), inhibited ET release stimulated by thrombin, angiotensin II (ANG-II) and arginine vasopressin, and had an inhibitory effect on basal ET synthesis and release by bovine arterial EC (Imai et al., 1993). Heparin inhibited ET-1 production stimulated by arginine vasopressin and PDGF in cultured rat mesangial cells (Kohno et al., 1994). It also weakly but significantly decreased basal ET secretion. Specific heparin fractions suppressed ET-1 production in cultured human EC (Ranucci et al., 1994). It strongly suppressed both basal and thrombin-stimulated ET release by HUVEC and concomitantly increased NO formation (Yokokawa et al., 1993b). The results indicated that the suppression of ET production by heparin was NO-mediated. The authors suggested that heparin regulates vascular tone via a combination of increased NO and decreased ET production. Both of these effects of heparin are at least partly caused by its inhibition of thrombin. When NO production was inhibited, heparin did not suppress ET synthesis by EC (Yokokawa et al., 1993b). Incubation of porcine coronary arteries with dextran sulfate, a heparinoid, prevented the inhibition of endothelium-dependent relaxation of OXLDL (Tanner et al., 1993). Heparin enhanced the recovery of NO generation after aortic injury in rabbits (Light et al., 1993). Heparin increased the production of NO by rat mesangial cells (Mattana and Singhol, 1995).

These apposite actions of exogenous heparin on ET and NO indicate that heparin may retard the atherosclerotic process. Thus, any decrease in endogenous heparin activity would enhance the production and atherogenic actions of ET and lower the beneficial effect of NO.

IX. Inflammatory Factors in Atherogenesis: Heparin Actions

Many inflammatory factors play a role in atherogenesis. Monocytes/macrophages, a major component of host defense, are involved in inflammatory responses at all stages of the atherosclerotic process. The inflammatory process in the atherosclerotic plaque intima is a chronic one (Schwartz et al., 1995a). Increased monocyte infiltration into the arterial wall is the earliest visible cellular reaction after atherogenic lipoprotein insudation (Stary et al., 1994). The macrophage is the principal inflammatory mediator in the atheromatous plaque environment (Ross, 1993). However, its potent destructive forces are difficult to control (Adams and Hamilton, 1992).

The mechanisms involved in monocyte recruitment to and accumulation in the artery wall recently were reviewed (Farqui and Dicorleto, 1993; Beekhuizen and von Furth, 1993). Inflammatory cytokines, the terminal complement complex, histamine, thrombin, OXLDL, minimally modified LDL, and lysophosphatidylcholine are involved. Human PDGF and platelet factor 4 are chemotactic for monocytes. Monocyte chemoattractants are present very early in lesion-prone areas of pigeon atherosclerosis. Elastin-derived peptides from elastin, damaged in early atherosclerotic lesions by neutrophil elastase, are extremely chemotactic for monocytes (Stary et al., 1994). RANTES, a member of the chemokine family that is expressed by a variety of cells within an inflammatory site, is a potent chemoattractant for monocytes and T lymphocytes (Wiederman et al., 1993). P-selectin binds to monocytes and increases their secretion of MCP-1 (Weyrick et al., 1995). Exposure to thrombin increases macrophage expression of MCP-1 (Colotta et al., 1994). It is clear that there are many stimulators of monocyte adhesion to the vascular endothelium.

Monocytes and other neutrophils initially adhere to adhesive molecules expressed on the plasma surface of activated EC. This is an active dynamic process regulated by a cascade of sequential molecular steps (Adams and Shaw, 1994; Springer, 1994). Tethering, the initial response, is mediated by three selectins. Selectins bind to monocyte carbohydrate ligands that contain the Sialyl-Lewis structure (Foxall et al., 1992). Sulfated polysaccharides such as heparin inhibit this binding (Handa et al., 1991; Nelson et al., 1993a; Norgard-Sunnicht et al., 1993) and inhibit the consequent leukocyte rolling in postcapillary venules, which is the earliest visible leucocyte-endothelial interaction in vivo (Tangelder and Arfors, 1987; Ley et al., 1993). This retardation of circulating leukocytes via selectins is a necessary initial step that allows subsequent firmer integrin-mediated binding to take place at physiologic blood flow rates in vivo over a wide range of shear stresses (Lindbom et al., 1992). Blockade of L-selectin inhibits monocyte recruitment to chronic inflammatory sites in vivo (Pizcueta and Luscinskas, 1994). Selectins and the VCAM-1 have been found in the endothelium over atherosclerotic plaques (Johnson-Tidey et al., 1994). Initial leukocyte rolling and tethering are reversible.

Triggering, the second step in leukocyte migration, is mediated by integrins (Adams and Shaw, 1994), which require activation to promote firm adhesion. The regulatory functions of integrins on the luminal and ablumi-

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nal surfaces of EC recently were reviewed (Luscinder and Lawler, 1994). Monocyte B_1 and B_2 integrins have distinct functions in monocyte adhesive interactions with the vascular endothelium. B_1 integrins stabilize the initial monocyte attachment to EC; B_2 integrins are required for spreading and motility of monocytes already adherent to the EC luminal surface. Integrin activation is via IL-8 and PAF, which is rapidly produced by EC after stimulation by MCP-1, thrombin, histamine, leukotrienes, bacterial wall components and activated complement products. Heparin inhibits many of these integrin activators. Heparin activity inhibits the interaction of EC with the core protein of basement membrane perlecan through B_1 and B_3 integrins (Hayashi et al., 1992).

The third (strong adhesion) and fourth (migration) steps of this leukocyte infiltration process into inflammatory sites involve integrins and a diverse set of small molecules called chemokines. It is probable that activation by chemokines is required for high affinity leukocyte-endothelial adhesion (Lasky, 1993). Another chemokine family was recently described (Schwartz, 1994). These small cytokines are heparin-binding and are related to platelet factor 4. Heparin displaced these molecules from the endothelial surface, and decreased monocyte adhesion to rabbit EC monolayers. All chemokines tested thus far have positively charged domains and bind to and are inhibited by heparin (Miller and Krangel, 1992). IL-8, platelet factor 4, macrophage inflammatory proteins A and B, MCP-1 and RANTES are all chemokine family members. Inflammatory cytokines IL-1 and TNF activate human EC to synthesize and secrete MCP-1 (Rollins et al., 1990). Human cytokine-activated microvascular EC express chemokine genes and chemokines (Brown et al., 1994). In summary, the available evidence indicates that heparin activity negatively affects monocyte entry from the blood into the artery wall. Any reduction of vascular EC glycocalyx heparin moieties would facilitate infiltration of this important inflammatory cell mediator of the atherosclerotic process.

Another pro-inflammatory cytokine family was reviewed recently (Oppenheim et al., 1991). All of these homologous cytokines are basic heparin-binding polypeptides that are produced by macrophages and other cell types. One of these, IL-8, is rapidly induced by IL-1 and TNF, and causes the release of neutrophil lysosomal enzymes, increases neutrophil adherence to unstimulated EC and subendothelial matrix proteins, and stimulates the production and release of the inflammatory factors leukotriene B_4 and 5-HETE. Another family member, IL-10, participates in delayed type hypersensitivity reactions. It has long been known that the latter are inhibited by heparin (Engelberg, 1988, 1990).

PAF is an extremely potent mediator of inflammation. Inflammatory cytokines stimulate PAF production by EC. It is highly positively charged and binds to heparin. The first step in PAF synthesis involves the action of phospholipase A_2 (Kuber et al., 1990). The activation of cytosolic phospholipase A_2 is central in the pro-inflammatory actions of TNF (Heller and Kronke, 1994). Heparin inhibits both phospholipase A_2 and PAF activity (Hocking et al., 1992; Diccianni et al., 1990; Sasaki et al., 1993b; Seeds et al., 1993). Only 10 nmols of heparin gave half maximal inhibition of human secretory class II phospholipase A_2 (Dua and Cho, 1994). Functionally similar phospholipase A_2 from widely divergent sources have a remarkable homology and are strongly basic (Forst et al., 1986).

Heparin inhibited the heparanase activity of leukocytes, EC, and platelets and so protected against degradation of vascular basement membranes (Bartlett et al., 1995). Another anti-inflammatory heparin activity is its modulation of T lymphocyte-mediated inflammatory reactions in some autoimmune diseases. This was attributed to the neutralization of heparanase secreted by the T cells, thus modulating their migration (Ekre et al., 1992). Neutrophils release lactoferrin after inflammatory stimulation and in autoimmune diseases (Wu et al., 1995). Lactoferrin binds to heparin with resultant mutual neutralization. A lactoferrin-like substance and advanced glycosylation end-products in diabetic patients are involved in monocyte chemotaxis and other pro-atherogenic actions (Schmidt et al., 1994).

Macrophages from human coronary atherosclerotic plaques have an augmented production and release of the inflammatory cytokines IL-1 and TNF, thus activating EC (Tipping and Hancock, 1993). Pro-IL-1B has to be cleaved to generate biologically active IL-1B, the major form of IL-1 (Hasuda et al., 1990). Elastase, cathepsin G, serine proteases, plasmin, collagenase, and chymptrypsin have been implicated in this proteolytic processing of IL-1 activation. Exogenous heparin inhibits many of these proteases (Engelberg, 1988, 1990, and references therein). The myristolation of the inactive precursors of IL-1A, IL-1B and TNF on specific lysines activates these potent inflammatory mediators (Stevenson et al., 1992, 1993). Heparin binds to lysines (Jackson et al., 1991). This may be an additional activity of heparin in preventing the development of the mature cytokines.

Matrix metalloproteases (MMP) are implicated in the processing of active TNF (Gearing et al., 1994; McGeehan et al., 1994). As previously noted, there is considerable evidence that indicates that heparin may inhibit MMP activity. The chelation of zinc effectively inhibits TNF processing (Mohler et al., 1994), and as already mentioned heparin chelates with zinc. Phosphatidic acid has an important role in a common lipid intracellular signaling pathway stimulated by IL-1 and TNF (Bursten et al., 1991; Agwar et al., 1991; Rice et al., 1994). It also has growth factor-like activity (Moolenaar et al., 1986; Knauss et al., 1990; Fukami and Takenawa, 1992) and may play a role in LDL modification (Aviram and Maor, 1993). Phospholipase A_2 is involved in the formation of

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phosphatidic acid (Abraham et al., 1995), as is thrombin (Wright et al., 1992). Heparin inhibits thrombin and phospholipase A_2. These facts suggest that endogenous heparin activity and the various EC and neutrophil activators act in an opposed fashion in the inflammatory process. It is relevant that there is a decrease in HSPG in atherosclerotic areas of human coronary arteries and of the aorta (Yla-Hertualla et al., 1986; Holliman et al., 1989) and that an increase in dermatan sulfate PG (DSPG) has been consistently reported during atherosclerotic progression. IL-1 up-regulates the production of decorin, a DSPG, by cultured monkey aortic SMC (Edwards et al., 1994).

The numerous anti-inflammatory actions of endogenous and exogenous heparin just described raise the question of the possible hindrance by heparin of the organism's inflammatory defenses against infection. However, I am aware of no mention in the medical literature about such a harmful effect of heparin therapy. It is likely that the stimulus of an acute infection is much stronger than the inflammatory inhibition by heparin. This would probably not be applicable to the lower grade and more chronic inflammatory stimuli in the atherosclerotic process.

X. Heparin Actions on Immune Factors in Atherogenesis

Although inflammatory and immune factors in atherogenesis are closely linked, they are under separate headings in this report. Immune vascular injury enhances and affects the vascular pattern of atherosclerosis in experimental animals and in humans. In various species, the pathogenic effects of immune complexes generally follow their deposition in vascular walls. Soluble and tissue-bound immunoglobulins, the terminal component of activated complement and an abundance of activated T cells have been identified in human atherosclerotic plaques. Plasma autoantibodies were present in 46% of patients with peripheral atherosclerotic disease (Cerilli et al., 1985). It is apparent that the protective immune system might also play a pathophysiologic role in vascular disease (reviewed in Hansson, 1993).

A recent article has reviewed much evidence of immune and autoimmune mechanisms in the atherosclerotic process (Kiener et al., 1995). Heparin effects on immune factors in atherogenesis are difficult to evaluate, as it has both stimulatory and inhibiting actions. Furthermore, both actions may retard or enhance immune damage depending upon the total milieu. Because immune complex deposition might be the major damaging event, let us consider how heparin could affect it. Immune tissue damage is increased by inflammatory cells in vivo (Camussi et al., 1982). Immune complexes increase vascular permeability, induce histamine release from mast cells, activate the complement cascade and induce PAF. An injected polycation markedly enhanced the deposition of immune complexes in glomeruli (Barnes and Venkatochalam, 1984). More highly cationic immunogens increased immune deposits in and damage to kidney glomeruli (Gallo et al., 1983). A decrease of anionic groups precedes immune complex deposition in glomerular capillary walls (Melnick et al., 1981). Because of its high negative charge, heparin binds to cations and decreases their harmful effects. The neutrophil MPO system is involved in vascular immunoglobulin deposition in systemic necrotizing vasculitis, cresceutic glomerulonephritis and in consequent EC injury (Johnson et al., 1988; Falk et al., 1990; Savage et al., 1992). Neutrophil MPO transforms lupus-inducing drugs into cytotoxic products (Jiang et al., 1994). MPO is cationic, binds to and is neutralized by heparin, as is histamine, which is an early and integral component of immune and inflammatory reactions (Jeannin et al., 1994). Heparin attenuated the effect of mitogenic vasoconstrictors on the disposition of immunoglobulin G complexes (Mattana and Singhol, 1995). Heparin antagonized the induction of antigen-presenting class II major histocompatibility complex molecules by interferon-gamma, which binds to heparin with high affinity (Kolipara, 1994). The immunogenicity of an allograft may be increased by cytokines such as gamma interferon. Heparin prolonged the survival of skin allografts (Gorski and Lagodzinski, 1991). An immunoglobulin E-dependent, histamine-releasing factor was recently identified (MacDonald et al., 1995). PAF has an important role in immune complex-mediated dermal vascular injury (Warren et al., 1989). Monocytes and lymphocytes are found together in vivo at sites of antigen-induced inflammation. MCP-1 is present on the endothelial surface in many T-cell-mediated conditions (Carr et al., 1994). Heparin inhibits histamine, PAF and MCP-1. Transforming growth factor-beta (TGF-B) may play a role in autoimmunity (Sporn and Roberts, 1992), and heparin affects TGF-B activity (Kirschenhofer et al., 1995). However, the effects of TGF-B in atherosclerotic plaque progression are complicated (Schwartz et al., 1995b), and so the actions of heparin in this area are hard to evaluate and will not be discussed any further.

Complement activation contributes to tissue damage after immune complex deposition (Yamamoto and Wilson, 1987; Johnson et al., 1986; Ward, 1991; Sacks et al., 1993). Fc receptors, which bind to the Fc portion of antibodies, initiate the inflammatory response to immune complexes; the response is then amplified by complement activation (Sylvestre and Ravitch, 1994). Heparin inhibits immune complex binding to cultured rat mesangial cells (Drakely and Furness, 1994) and causes partial removal of glomerular antigen deposits in rats by a mechanism independent of its anticoagulant properties (Furness and Drakeley, 1992).

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XI. Complement

The complement system is a major physiologic defense mechanism that has a large potential for damage. Its role in atherogenesis has been reviewed (Engelberg, 1990; Seifert and Katzatchkine, 1988). Activated complement binds to vascular endothelium, causing injury in vivo. Atheroma lipids activate complement in situ. Of 30 human atherosclerotic lesions examined, all exhibited antigen staining for the terminal complement complex C5b-9. Normal arteries do not activate complement. The net effect of activated complement is injurious to the artery wall (Seifert and Katzatchkine, 1988).

Human complement factor C5a markedly enhances the release of IL-8, an important inflammatory mediator, from monocytes (Ember et al., 1994). C5a induces P-selectin expression in HUVEC (Foreman et al., 1994). Complement activation directly attenuates endothelium-dependent relaxation of porcine coronary artery rings (Stahl et al., 1995). Complement perturbs the integrity of cultured porcine EC (Saadi and Platt, 1995). Complement activation induces changes in fibrin networks that make it resistant to fibrinolysis (Shats-Tsetylina et al., 1994). Complement factor C3 is a major mediator of monocyte adhesion to surfaces (McNally and Anderson, 1994). Complement affects many aspects of acute and chronic rejection (Baldwin et al., 1995). Xenotransplantation cannot be successful without complement inhibition (Ryan, 1995). Complement becomes locally activated early in the formation of fatty streaks (Kiener et al., 1995). After tissue deposition of antibody, the activation of complement component C7 occurs, with subsequent tissue injury in which plasmin participates (Reinartz et al., 1995). C3 convertase, a key factor in activation of both the classical and alternate complement pathways, was found in human atherosclerotic lesions of coronary, carotid and peripheral arteries (Seifert et al., 1991). Serum amyloid P component, which can activate complement, is present in human aortic atherosclerotic areas (Li et al., 1995a). Complement opsonized immune complexes have a different fate in tissues (Schifferli et al., 1986) than in the blood, where they are transported to the kidneys and eliminated (Fujigaki et al., 1995). In a 4-year follow-up of 860 normal men and women, serum complement component C3 levels were independently associated with subsequent cardiac ischemic events (Muscari et al., 1995). C3 was a very powerful predictor of acute myocardial infarction in men.

It long has been known that heparin inhibits both the classical and alternate pathways of complement activation. Thirteen of 22 human complement proteins bind to heparin (Sabu and Pangborn, 1993). Heparin and native HSPG inhibited complement activation in vivo (Weiler et al., 1992), and this was independent of any affinity for antithrombin. Complement released HSPG from the surface of porcine aortic EC (Platt et al., 1990), thus decreasing this restraint of complement-induced arterial wall injury. Heparin and dextran sulfate-5000 inhibit activated properdine, which stabilizes C3 convertase (Holt et al., 1990). The activation of serum complement by zymosan and cobra venom factor is inhibited by heparin (Edens et al., 1994). Complement C1 inhibitor plus heparin prevent discordant rejection of cardiac transplants (DiStefano et al., 1994) and EC activation in a xenograft hyperacute rejection model (Dalmasso and Platt, 1994). Heparin coating of tubing decreased complement and granulocyte activation during coronary bypass surgery (Fosse et al., 1994). It is unfortunate that, in a recent presentation about the complement system and its regulators (Asghar, 1995), there was no mention of the important inhibitory role of heparin activity.

XII. Medial Vascular Smooth Muscle Cells: Proliferation and Migration

The proliferation and migration of arterial medial SMC are fundamental processes in atherogenesis. SMC are the predominant cell type, even in slightly raised early fatty streaks (Katsuda et al., 1992). SMC proliferation occurs after these cells have changed from their contractile phenotype to a synthetic one (Campbell and Campbell, 1986, 1991). A critical factor maintaining SMC in the contractile phenotype is a species of HSPG produced by EC and contractile SMC. Pretreatment of the HSPG by heparinase prevented this HSPG effect on SMC. Also, a factor stored in macrophage lysozymes degraded SMC-HSPG, thus facilitating a change to the SMC synthetic phenotype.

Factors affecting SMC responses have been reviewed (Campbell and Campbell, 1986; Engelberg, 1988, 1990; Thyberg et al., 1990; Tina-Au et al., 1993). SMC proliferate in response to epidermal and fibroblast growth factors, ANG-II oxygen free radicals, thrombin, and PDGF. Heparin binding epidermal growth factor (HB-EGF) is an important mitogen for SMC (Temizer et al., 1992; Miyagawa et al., 1995). Homocysteine, a substantial factor causing arterial disease, stimulates SMC proliferation (Malinow et al., 1993; Tsai et al., 1994). Proliferating cell nuclear antigen is necessary for the first wave of medial SMC proliferation (Simons et al., 1994). Heparan and dermatan sulfate inhibit DNA synthesis in cultured human arterial SMC. Chondroitin sulfate does not (Fager et al., 1995). Antisense oligonucleotides to c-*myc* inhibit proliferation of SMC from rat carotid arteries and human saphenous veins in vitro and in vivo (Shi et al., 1993; Bennett et al., 1994) and decrease neointimal injury in porcine coronary artery balloon injury (Shi et al., 1994).

Atrial natriuretic peptide decreases ANG-II and PDGF stimulated SMC proliferation (Morishita et al., 1994). ANG-II, PDGF, and thrombin all increase SMC intracellular calcium via the IP_3 second-messenger pathway

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(Marks, 1992 and references therein). The calcium increase is the critical signal for SMC contraction. The rise and fall of intracellular calcium are principal mechanisms that initiate the responsivity, contractility and relaxation of SMC (Somlyo and Somlyo, 1994). IP_3 increased calcium activated calmodulin kinase II, which is required for vascular SMC migration (Pauly et al., 1995). Osteopontin messenger ribonucleic acid is greatly increased in proliferating SMC in culture (Doherty and Detrano, 1994). This probably is related to calcium deposition. Histamine receptor-1 messenger ribonucleic acid, which is expressed in cultured SMC, is pronounced in atherosclerotic foci in human atherosclerotic aorta and coronary artery walls (Takagishi et al., 1995), and it is increased by PDGF. These findings suggest that histamine plays a role in the progression of atherosclerosis. Na-H exchange in vascular SMC is important in SMC-growth activated by ANG-II, thrombin and ET (Lucchesi and Berk, 1995). Inhibition of Na-H exchange blocks SMC growth. Proliferating and quiescent human arterial SMC synthesize PG, of which over 90% are chondroitin sulfate PG (Camejo et al., 1993). These bind LDL, and the PG synthesized by proliferating SMC have considerably more LDL affinity. Catecholamines have long-term trophic effects on vascular SMC (Okazaki et al., 1994) and alpha-adrenergic agonists stimulate PDGF-A chain gene expression in rat aorta SMC (Majesky et al., 1990). Native LDL and OXLDL enhance the production of PDGF and its receptors, but OXLDL are more potent (Stiko-Rahn et al., 1992).

Thrombin induced PDGF gene expression and SMC proliferation in vitro in rat aorta SMC and also in vivo in injured baboon brachial arteries (Okazaki et al., 1992). PDGF gene expression is elevated in SMC and adjacent macrophages at all stages in atherosclerotic lesions in humans and nonhuman primates (Ross, 1993). There is active PDGF gene expression and production by human artery organ cultures (Holt et al., 1994). PDGF mediates ANG-II-induced proliferation of rat aortic SMC (Mangiarna et al., 1994). The action of MMP is important in cell migration (Kenagy and Clowes, 1994), and PDGF up-regulates their transcription (Stetler-Stevenson et al., 1993). PDGF induces SMC migration, perhaps its most significant effect, by a different pathway than that used for its mitogenic signal (Bornfeldt et al., 1994).

The inhibition of SMC proliferation by heparin was first described years ago (Clowes and Karnovsky, 1977). The many subsequent investigations of this important subject have been reviewed (Engelberg, 1988, 1990; Thyberg et al., 1990) and can be summarized as follows:

- exogenous heparin binds to vascular SMC with high affinity via specific receptors and then is rapidly internalized, eventually localizing at the perinuclear region, where it inhibits DNA synthesis;
- it prevents SMC progression through the G1 phase of the cell cycle, preventing entry into the S phase;
- the binding of extracellular matrix (ECM) thrombospodin to the SMC surface is essential for vascular SMC proliferation;
- heparin blocks the incorporation of thrombospodin into the ECM and its facilitation of the mitogenic action of epidermal growth factor (EGF) on SMC;
- TGF-B is essential in the SMC growth inhibition by heparin;
- if this TGF-B activity is blocked by a neutralizing antibody, heparin does not inhibit SMC growth;
- endogenous heparin-like molecules secreted by EC act on SMC much as exogenous heparin does;
- these maintain SMC in a contractile phenotype unresponsive to mitogens, and they inhibit proliferation of serum-stimulated synthetic state SMC;
- heparinase pretreatment abolishes this EC effect;
- the only mitogen capable of reversing these numerous SMC antiproliferative actions of heparin is EGF, and heparin decreases SMC receptors for EGF.

Since the publication of the reviews named in the previous paragraph, additional findings about heparin actions on vascular SMC were published. Immediate changes in ion transport occurs upon cell stimulation. Heparin inhibited Na^+-H^+ exchange in rat aortic SMC but not in EC, indicating a specific SMC effect (Zaragoza et al., 1990). Human atherosclerotic plaques contain large amounts of MMP with matrix-degrading activity (Galis et al., 1994; Sasaguri et al., 1994). Heparin inhibited the expression by primate arterial SMC of MMP (Kenagy et al., 1994). Bovine calf aorta and human iliac artery SMC release a scatter factor that contributes to their mobility. This factor is inhibited by heparin. Scatter factors are basic and bind tightly to heparin (Rosen et al., 1991). Heparin inhibited the transcription of tissue plasminogen activator and interstitial collagenase, both of which are matrix-degrading proteases, in baboon vascular SMC.

The role of TGF-B has been reviewed (Sporn and Roberts, 1992). It is a multifunctional ubiquitous cytokine that acts to lessen the extent of injury to tissues and cells and to facilitate repair. It plays an important role in SMC proliferation and growth (Majack, 1987). Heparin binds to TGF-B, releases TGF-B-like activity from serum by dissociating it from its inactive complex with alpha-2-macroglobulin, and so potentiates TGF-B activity (McCaffrey et al., 1989, 1992; Grainger et al., 1993). Heparin suppressed the proteolytic intracellular degradation of TGF-B (McCaffrey et al., 1993). There has been little investigation of the possibility that heparin may aid other functions of TGF-B. However, it is difficult to evaluate how the relation between heparin and TGF-B affects atherogenesis, as the relation is variable (Orlandi et al., 1994) and the effects of TGF-B are complex (Schwartz et al., 1995b).

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It is well known that PDGF, whether released by platelets or synthesized by vascular wall cells, has an important role in SMC migration and proliferation. The PDGF A-chain contains an amino acid sequence that specifically binds to heparin, causing inactivation of the growth factor (Fager et al., 1990). There is also strong evidence that suggests that heparin prevents PDGF binding to its cell surface receptor (Fager et al., 1992). PDGF does not reverse the inhibition of SMC proliferation by heparin. In the mitogenic signal transduction pathway from the PDGF receptor, there is strong recruitment of mitogen-activated protein kinases (Pelech and Sanghera, 1992). Heparin selectively inhibits an mitogen-activated protein kinases in rat vascular SMC, which is a key intermediate in cell signalling (Ottlinger et al., 1993).

Heparin inhibits pericyte proliferation (Orlidge and D'Amore, 1986). These arterial cells are believed to perform like SMC at the microvascular level. Porcine aortic SMC secrete a protease that removes a binding protein from insulin-like growth factor-1 (Gockerman and Clemmons, 1995), thus releasing insulin-like growth factor-1 SMC proliferating activity. This protease is inhibited by heparin, and totally so by heparin plus antithrombin III. The effect of heparin on plasminogen activators in baboon vascular SMC vary with the mitogen (Kenagy et al., 1995). The release of intracellular calcium in SMC via IP_3 stimulates SMC contraction. Heparin potently inhibits these calcium fluxes and their effect (Mayrleitner et al., 1991).

Heparin also binds to and sequesters basic fibroblast growth factor (b-FGF) (Ross, 1993). b-FGF is an important SMC mitogen, perhaps the key mitogen initiating SMC replication (Reidy and Bowyer, 1993). Heparin facilitates removal of b-FGF from the injured artery wall but has no effect on the uninjured artery b-FGF. HSPG bind and release b-FGF; the subject is complex and not fully understood. The outgrowth of both normal and atherosclerotic human coronary artery explants was markedly reduced by heparin (Caplice et al., 1994). HB-EGF is an important chemoattractant and mitogen for SMC. It has a much greater mitogenic and migratory stimulating effect on bovine aortic SMC than does EGF itself. HB-EGF must bind to the EGF receptor on target cells to accomplish its biologic activity. These receptors are at very low levels in the normal human aorta but are expressed strongly in intimal SMC of atherosclerotic aortas (Miyagawa et al., 1995). Heparin reduces the number of EGF receptors on SMC. HS-EGF receptor interactions are regulated tightly by the available local concentration of heparin-like molecules (Aviezer and Yayon, 1994). It is pertinent that heparin increases the anionic properties of vascular SMC (Williams and Mason, 1991). Vascular SMC have a high binding capacity for phospholipase A_2, which stimulates their synthesis of DNA and their migration. Heparin inhibits the action of phospholipase A_2.

Recently, the evidence was summarized that the oncogene c-*myb* is at the apex of a common mitogenic pathway required by nearly all SMC growth and migration factors (Rosenberg, 1993). Thus, c-*myb* is the critical intracellular mediator of SMC proliferation. Suppression of c-*myb* by antisense oligonucleotides led to a reversible inhibition of rat and mouse aortic SMC growth (Simons and Rosenberg, 1992). Pre-incubation with heparin almost totally blocked the increase in c-*myb* gene expression in serum-stimulated bovine aortic SMC.

There are recent studies indicating the role of endogenous heparin activity in suppressing SMC proliferation. Protamine, which neutralizes heparin, stimulated the proliferation of rat carotid artery SMC after endothelial denudation and interfered with the growth inhibitory actions of heparin in vitro and in vivo (Edelman et al., 1993). The authors stated that the results confirmed the importance of endogenous heparin-like compounds in arterial homeostasis. ECM with a higher content of HSPG, as compared with ECM that is richer in collagen or fibronectin, selectively inhibited the growth of SMC populations (Herman, 1990). The increased proliferation of older rat aortic SMC is related to enhanced PDGF activity and a concomitant decrease in cell growth inhibitors with heparin activity (McCaffrey et al., 1988). Arterial SMC from pigeons susceptible to atherosclerosis had a greater proliferative capacity than SMC from atherosclerosis-resistant pigeons. The SMC outer membranes of the resistant birds contained 50% more HSPG with a higher negative charge density, indicating more heparin regions, than the SMC membranes of the atherosclerosis-susceptible pigeons (Edwards and Wagner, 1992). The authors (Edwards and Wagner, 1992) concluded that "the results are consistent with a growth-regulatory function for this molecule."

These many investigations demonstrate, both in vitro and in vivo, the multiple inhibitory actions of exogenous heparin and of endogenous heparin-like HSPG on SMC proliferation. By blocking the effect of almost all SMC mitogens, they reduce the proliferation and migration of medial arterial SMC of humans and other species and so limit atherosclerotic plaque formation.

XIII. Renin-Angiotensin System: Angiotensin-Converting Enzyme

The renin-angiotensin system has recently been reviewed (Greenwald and Becker, 1994). It plays a central role in the regulation of blood pressure, electrolyte and fluid balance, and blood volume. It might play a harmful role in aging (Inserra et al., 1995). Its physiologic activities are mediated primarily through an effector peptide, ANG-II, which is formed when renin transforms angiotensinogen into ANG-I, which in turn is converted by EC ACE into biologically active ANG-II. The latter is one of the most potent vasoconstrictors known and is of major importance in arterial SMC proliferation (Schilling et al., 1991). There is much recent evidence that the renin-

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angiotensin system is not only systemic but that most, if not all, of its components can be produced locally in vascular walls where they are active. There is biochemical evidence of renin-like activity, ACE, ANG-II in EC and SMC of small, medium and large arteries. Circulating renin can enter vascular walls.

ANG-II decreases thromboresistance (Greenwald and Becker, 1994). It increases plasminogen activator inhibitor (PAI-1) levels in EC. Elevated levels of PAI-1 increase the incidence of thromboembolic episodes via a decrease in fibrinolysis. ANG-II facilitates the platelet-aggregating and vasoconstrictor effects of epinephrine. It rapidly induces the expression of procoagulant tissue factor by vascular SMC. Ang-II is not only a mitogen for SMC but also increased their synthesis of chondroitin and dermatan PG (Bailey et al., 1994). It stimulates the MAPK cascade in renal mesangial cells (Huwiler et al., 1995). Inhibition of ANG-II reduced the extent of atherosclerotic lesions in WHHL rabbits, in minipigs and in monkeys, without lowering the blood pressure (Lonn et al., 1994). This was also true in the early atherosclerosis of hyperlipidemic hamsters (Kowala et al., 1994). In humans, ACE inhibitors are of value in early atherosclerosis (Celermaier, 1995). They protect endothelium against damage (Wiemer et al., 1994).

ANG-II stimulates ET release from human EC (Ciafra et al., 1993). It mobilizes intracellular Ca^{2+} and activates Na^{+}-H^{+} exchange in vascular SMC (Temizer et al., 1992); it also stimulates reduced nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate oxidase activity in cultured rat aortic SMC (Grindling et al., 1994). The latter action is inhibited by NO (Clancy et al., 1992). ANG-II effects on SMC involve activation of 12-lipoxygenase, which is inhibited by NO (Gu et al., 1995), as is ANG-II-induced SMC migration (Dubey et al., 1995). NO plays a major role in the effect of ACE inhibitors (Farhy et al., 1993). ACE opposes the action of bradykinin, which decreases vascular tone and SMC proliferation (Cambien et al., 1992). ANG-II stimulates the synthesis of osteopontin in rat SMC (O'Brien et al., 1994). Osteopontin probably plays a role in arterial calcification. ANG-II can be generated independently of the action of ACE via chymase (Holt et al., 1995) or cathepsin G (Noda et al., 1993). Thus, there is much evidence that the renin-angiotensin system might contribute to the development of coronary atherosclerosis and coronary artery disease.

It is apparent that actions of heparin already mentioned (inhibition of ET, intracellular Ca^{2+} release, Na^{+}-H^{+} activation in SMC, cathepsin G and stimulation of NO) would counteract effects of ANG-II. The lowering of blood pressure in spontaneously hypertensive rats by heparin was thought to be at least partly mediated by suppression of renin-angiotensin activity (Suzie et al., 1988). The authors believed that heparin had an inhibitory effect on ACE. Granulocyte cathepsin G has ACE activity and acts at multiple sites of the renin-angiotensin pathway (Dzau, 1986). Heparin inhibits cathepsin G (Starkey and Barrett, 1976). ANG-II induces PDGF-A chain in rat aorta SMC in culture and in rat aorta in vivo (Greenwald and Becker, 1994). ET stimulates the conversion of ANG-I to ANG-II (Kawaguchi et al., 1990). Heparin inhibits PDGF and ET and most SMC mitogens. Diminution of endogenous heparin activity would limit its many restraints of the potential pathologic effects of an overactive renin-angiotensin system.

XIV. Mural Microthrombi: Role in Atherogenesis

The role of thrombosis in atherogenesis was recognized more than a century ago. The subject has been thoroughly reviewed (Stemerman, 1979; Schwartz, 1988; Nachman, 1992; Loscalzo, 1992; Fuster, 1994; Hamsten et al., 1994; Harker et al., 1995). In summary:

- many pathologic observations in humans indicate that, to a significant extent, plaque development is dependent upon organization and incorporation of mural thrombi;
- thrombin has many actions that promote atherogenesis;
- elements of thrombi can induce an inflammatory response in vascular walls;
- endothelial injury decreases its thromboresistance;
- elevated serum triglycerides accelerate coagulation and impair fibrinolysis;
- fibrin/fibrinogen contributes to atherogenesis through multiple mechanisms;
- the role of elevated serum fibrinogen levels is supported by epidemiologic studies;
- lipoprotein a reduces plasminogen activations and so hampers fibrinolysis;
- episodes of mural thrombosis contribute significantly to the later stages of plaque growth;
- experimental thrombi can become transformed into arterial fatty-fibro plaques resembling human atherosclerotic lesions;
- inflammatory cytokines and activated complement stimulate EC production of tissue factor (TF), which potently enhances coagulation and thrombus formation;
- atherosclerotic plaques contain many TF-synthesizing cells, and TF is present in the necrotic core.

Since those reviews, other important observations were made. In a recent consensus report (Stary et al., 1994), it was agreed that microthrombi contribute to the atherosclerotic process subsequent to the earlier effect of atherogenic lipoproteins. Triglyceride-rich lipoproteins increase the risk of focal thrombosis (Bradley et al., 1994). Thrombotic determinants are critical for plaque development (Rabbani and Loscalzo, 1994). A carotid and popliteal artery ultrasound study of matched pairs supported the antagonistic roles of thrombosis and fibrinolysis at an early stage of plaque development (Salomaa et al., 1995). Leucocyte elastase inactivates TF

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pathway inhibitor (TFPI) (Peterson et al., 1992). ANG-II induces the expression of PAI in EC and SMC (Vaughn et al., 1995; Feener et al., 1995). Neutrophil cathepsin G induces the release of PAI-1 from EC and is a potent agonist of platelet aggregation, suggesting a thrombogenic role for cathepsin G (Marmur et al., 1992). The activation of platelets by cathepsin G and its inhibition by heparin has been confirmed (Cerletti et al., 1994). Patients with elevated levels of lipoprotein-a have decreased fibrinolysis and very rapid progression of coronary artery atherosclerosis on angiography (Terres et al., 1995). P-selectin induces TF expression in monocytes (Celi et al., 1994) and has a role in thrombogenesis (Furie and Furie, 1995). PAF is also a mediator of thrombosis (Lesnik, 1995). The action of FR might contribute to thrombogenesis, as copper induces TF in monocytes (Crutchley and Que, 1995) and TFPI associated with LDL is inactivated by cell and copper-mediated oxidation (Lesnik, 1995). Although both platelet reactions and the coagulation system are involved in thrombus formation, studies of whole blood without the use of anticoagulants clearly indicate that inhibition of thrombin generation is the common denominator of antithrombotic therapy (Kusels et al., 1994). Here, heparin was far more effective than aspirin. Heparin inhibits physiologically relevant platelet reactivity in native blood (Gorog et al., 1991).

Heparin has other antithrombotic actions. It decreases TF production by monocytes and releases and enhances the anticoagulant and antithrombotic effects of TFPI (Nelson et al., 1993b). The release of TFPI by heparin is an important antithrombogenic action, as TFPI can amplify the effect of heparin independent of antithrombin-III (Jeske et al., 1995). Small amounts of locally delivered heparin inhibited platelet-dependent thrombosis (Numer et al., 1995). In a rat model of FR-induced thrombosis in mesenteric arterioles, only heparin and vitamin E, not aspirin, were inhibitory (Jourdan et al., 1995). Heparin lowers elevated plasma fibrinogen levels (Engelberg, 1991), and so decreases blood viscosity. It has been known for many years that heparin enhances fibrinolysis. A decrease of endogenous heparin activity at the endothelial surface would impair these effects and facilitate the formation of mural microthrombi.

XV. Advanced Glycosylation End Products

AGE is a relatively newly recognized factor in atherogenesis. Although it has not been investigated, heparin may play a role in mitigating harmful AGE effects. The latter were recently reviewed (Vlassara, 1994; Brownlee, 1995; and references within). AGE form nonenzymatically via the gradual attachment of simple sugars (glucose, ribose) to proteins. AGE formation occurs on proteins, lipids, and nucleic acids. Long-lived proteins such as collagen are more liable to AGE modification. AGE modifications are irreversible, except perhaps in the early stages, as they resist proteolysis. They increase with normal aging and at an accelerated rate in diabetic patients because of their frequently higher blood glucose levels. This may be a decisive factor in the well-known earlier development of atherosclerosis in diabetics.

AGE are found in plasma and accumulate in vascular walls (Yan et al., 1994). In relation to atherogenesis, they have the following actions (Vlassara, 1994): they contribute to lipid oxidation via the release of free radicals, increase endothelial permeability, induce monocyte/macrophage transendothelial migration, stimulate cytokine release by macrophages, lead to immune complex formation and complement activation in situ, are procoagulant via increasing TF and suppressing thrombomodulin in EC, inhibit the activity of NO, enhance SMC and fibroblast proliferation, and increase DNA mutation rates. AGE bind to and inhibit the antibacterial activity of lysozyme and lactoferrin (Li et al., 1995b) and so enhance susceptibility to infection. Thus, the evidence supports a role for AGE in atherogenesis in vivo.

There are other pertinent observations. The receptor for AGE, called RAGE, is present in the normal vasculature, and the binding of AGE to its receptor induces VCAM-1 expression by EC (Schmidt et al., 1995). VCAM-1 is associated with the early stages of atherosclerosis in humans. The induction of free radicals by AGE in the vessel wall occurs even in the presence of intact anti-oxidant mechanisms (Yan et al., 1994). The modification of LDL by AGE can be fairly rapid, and this blocks LDL uptake by its receptor (Bucala et al., 1995). Diabetic patients have considerably more ($p < 0.01$) glycated LDL than matched controls (Klein et al., 1992). Macrophages avidly took up glycated LDL, which then stimulated their synthesis of cholesterol-ester. Glycated LDL are also more susceptible to oxidation. The formation of AGE in diabetes precedes and correlates with early manifestations of renal and retinal disease. The association of AGE with the lens of the eye increases with age, in both diabetic and nondiabetic individuals (Horiuchi and Araki, 1994). Studies using a more specific monoclonal antibody demonstrated that AGE produced extracellularly are ingested by macrophage and SMC foam cells in human atherosclerotic lesions (Kume et al., 1995).

The initial formation of AGE involves the condensation of glucose with the E-amino groups of lysine (Bailey et al., 1995). Heparin is anionic, binds to positively charged lysine (Jackson et al., 1991), and so may inhibit the production of AGE. The AGE receptor (RAGE) contains a lactoferrin-like peptide highly homologous or identical with lactoferrin (Yan et al., 1994). Heparin binds to lactoferrin with mutual inhibition (Wu et al., 1995). Although it has not been directly investigated, the existing data suggest that heparin might impair AGE formation and its receptor binding. Other actions of heparin in atherogenesis, mentioned earlier, would tend to inhibit AGE effects.

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XVI. Heparin Sulfate Proteoglycans

PG encompasses a diverse group of core proteins with attached sulfated carbohydrate components, the glycosaminoglycans (GAG). The remarkable complexity and diversity of the oligosaccharides of PG and their biologic role has been reviewed (Varki, 1993). Heparin and heparan sulfates comprise one of the four main types of GAG. HSPG are ubiquitously present at cell plasma surfaces and basement membranes and in the ECM. They are probably the most complex of all mammalian carbohydrates, with wide variations in size, structure and pattern of sulfation (Gallagher et al., 1986; Ruoslahti, 1988; Hardingham and Fosang, 1992).

Three major families of PG have been identified in blood vessels and are synthesized by vascular wall cells (Wight, 1989 and references therein). These are chondroitin sulfates (CS), dermatan sulfates and heparan sulfates, and they are distributed differently in the artery wall. Although they are only a minor component of the vascular tissue (2 to 5% by dry weight), HSPG are very important in influencing such arterial properties as viscoelasticity, permeability, lipid metabolism, hemostasis, SMC and thrombosis. EC synthesize and secrete HSPG predominately. SMC synthesize and secrete CSPG and DSPG predominantly, and considerably less HSPG. Arterial CSPG have a marked affinity for LDL. DSPG form insoluble complexes with LDL. The PG that accumulate in the intimal lesions of early and late atherosclerosis involve mainly the CSPG and DSPG families, with little change or a decrease in HSPG.

Specific proteoglycans within the larger chondroitin-dermatan-heparan sulfate families recently have been identified. These include perlecan, syndecan, versican, biglycan, decorin, among others. Their functions may differ, at least in relation to b-FGF (Vlodavsky et al., 1995). Syndecans carry chondroitin and heparan sulfate chains on the same core protein (Ledholt, 1995), as does perlecan (Kokenyesi and Silbert, 1995).

Perlecan is ubiquitous in basement membranes and the extracellular matrix. It is an important charge barrier and is undersulfated in diabetic patients (Iozzo et al., 1994). I am not aware of any data directly relating heparin activity to these specific proteoglycans, and so will only discuss heparin and the larger proteoglycan families.

The role of proteoglycans in biology and pathobiology has been extensively reviewed (Wight, 1989; Kjellen and Lindahl, 1991; Esko et al., 1991; Jackson et al., 1991; Bernfield et al., 1992). PG structure is open to extensive modulation during biosynthesis and cellular expression. The major area of variation and cellular expression is in the GAG chains, resulting in many different chain types with altered properties to suit different biological needs. The number of GAG chains on a protein core may vary from 1 to 100 (Kjellen and Lindahl, 1991). These chains can undergo a series of modifications, giving rise to enormous structural and functional variation that determine many biologic activities (Esko et al., 1991).

A minimum of five different enzymes are involved in the sulfation of heparin and heparan sulfate (Keller et al., 1990). Thus, there is ample opportunity for defective HSPG or heparin biosynthesis. Experimentally produced and spontaneous mutants of Chinese hamster ovary cells occurred at different stages of GAG synthesis. Some mutants showed a marked reduction of sulfate relative to protein (Esko et al., 1985). Cell variants with altered heparan sulfate, especially decreased sulfation, have been found in mice (Keller et al., 1988). In humans, there is a low frequency of naturally occurring genetic mutations affecting PG synthesis, indicating that PGs are essential and so most mutations would be lethal in utero (Esko et al., 1991).

EC surface GAG are vulnerable to and decreased by various factors. Inflammatory cytokines suppress heparin-like compounds of aortic EC. TNF and IL-1 increase the release of HSPG from human EC and decrease HSPG synthesis to less than 60%. This results in an almost complete loss of the endothelial negative surface charge (Klein et al., 1992). TNF decreases the sulfation of mouse aortic EC surface HSPG (Matic et al., 1994). Homocysteine, a known important factor in atherogenesis (Malinow et al., 1993), suppresses anticoagulantly active HSPG in cultured EC (Nishinaga, 1994). Neoplastically transformed cells have decreased amounts and undersulfation of cell surface HSPG (Bernfield et al., 1992). HSV-1 infection inhibited up to 85% of heparan sulfate synthesis in EC (Kaner et al., 1990). HSV-1 is widely distributed in humans. Many viruses bind initially to cell surface HSPG and might have an effect similar to that of HSV-1 on heparan sulfate synthesis, although this has not been fully investigated. EC-HSPG are susceptible to cleavage by human neutrophils. This occurs in the absence of cell lysis and is decreased by inhibition of neutrophil elastase (Key et al., 1992). Heparin inhibits this elastase (Redini et al., 1988).

Activated human T lymphocytes release intact at least 50% of porcine aortic EC-HSPG (Geller et al., 1994). PAF decreases sulfated glycans of the EC glycocalyx (Silvestro et al., 1994). The inhibiting activity of heparan sulfate on endothelial turnover in rats is modified by serotonin (Hladovec and Kornalik, 1994). Atherogenic levels of human LDL increase the permeability of cultured porcine EC. This is mediated, at least in part, by a decrease in EC-HSPG (Guretzki et al., 1994). Multiple heparanase activities may be responsible for the release of heparan sulfate from Chinese hamster ovary cell PG (Bame, 1993). Human neutrophil elastase and the myeloperoxidase-H_2O_2-chloride system additively degrade calf aorta EC matrix HSPG (Klebanoff et al., 1993). Thrombin decreases the GAG content of cultured bovine aortic EC. Exogenous heparin would diminish the effects on HSPG of many of these harmful agents. Also, heparin and low molecular weight heparin stimulated HSPG

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synthesis two- to three-fold by rabbit aortic EC (Pinhal et al., 1994).

Injured EC can be identified by their uptake of the anionic dye Evans blue. Such areas have an increased susceptibility to endothelial injury, increased permeability, and an enhanced infiltration of cholesterol (Gerrity et al., 1977; Hansson et al., 1979). The endothelial glycocalyx is three-fold thicker, and the EC Golgi apparatus, which is involved in mucopolysaccharide synthesis, is more well developed in normal area as compared with areas of Evans blue uptake. Microthrombi were present only in the areas of dye staining. The evidence that lesion-prone or prelesional areas of atherosclerosis are delineated by Evans blue was reviewed recently (Schwartz, 1991). These facts indicate that a decrease in or injury of heparin-like anionic molecules predisposes to the development of atherosclerosis.

Aortic PG have different interacting potentials with lipoproteins. CSPG and DSPG extracted from pig aorta formed insoluble complexes with human LDL in the presence of calcium; HSPG did not (Wegrowski, 1986). In very early atherosclerotic lesions of hypercholesterolemic swine (before there are any grossly visible lesions) there was a statistically significant positive correlation between CSPG expressed as the percentage of the total GAG and the apolipoprotein B of LDL concentration (Hoff and Wagner, 1986). There was a 45 to 50% increase of CSPG and a small increase of DSPG in rat aortic SMC incubated with LDL, which was caused by both overproduction of PG and a decrease in its degradation and release (Vijayagopol, 1993). The binding of CSPG isolated from pigeon aortas was specific for LDL, not for HDL (Steele et al., 1987). There is a reduction in cell surface heparan sulfate octasaccharide sequences in cultured SMC of pigeons with spontaneous atherosclerosis (Flory, 1993). Atherosclerosis-susceptible pigeons' aortic SMC had approximately 50% of cell surface HSPG as compared with the atherosclerosis-resistant pigeons (Edwards et al., 1995). The study indicated that this resulted from increased turnover of HSPG rather than from decreased synthesis. Monkey aortic SMC stimulated by PDGF increase their production of CSPG (Wight, 1989). In diet-induced atherosclerosis of monkeys, heparan sulfate decreased with increasing severity of the lesions and increased as lesions regressed (Radhakrishnamurthy et al., 1982).

The PG findings in humans are similar to those in experimental animals. Heparan sulfate in human atherosclerotic lesions decreased as lesion severity increased (Stary et al., 1994). The loss of heparan sulfate was greater in plaques than in grossly normal areas (Volker et al., 1990). In human aortas, the proportion of heparan sulfate relative to the total GAG is 41% in normal and 20% in atherosclerotic areas (Holliman et al., 1989). CSPG aggregates have been isolated from human atherosclerotic lesions, and they form specific complexes with apolipoprotein B-lipoprotein at physiologic pH and calcium concentrations (Camejo et al., 1988 and references therein). In human coronary arteries, a large decrease of heparin and heparan sulfate content, and a proportional increase of chondroitin-6-sulfate and dermatan sulfate, was associated with the increasing severity of atherosclerosis (Murata and Yokoyama, 1982). The content of HSPG and its proportion to the total PG was also markedly less in atherosclerotic cerebral arteries (Murata and Yokoyama, 1989). The divergent biologic properties of HSPG and chondroitin PG play a crucial role in atherogenesis (Radhakrishnamurthy et al., 1990). The evidence indicates that the decrease in HSPG and the increase in the other PG are antagonistic events in atherogenesis. Although these various endogenous findings do not prove causation, they are suggestive; even if secondary, decreased heparin activity would probably allow acceleration of the disease process. After a thorough review, it was concluded that "HSPG may be considered as an antagonist to lesion development" (Berenson et al., 1984).

It has been noted that agents that contribute to atherosclerosis cause disease only when guardian genes are defective and that a genetic accomplice must be implicated (Brown and Goldstein, 1992). The authors mentioned apolipoprotein E-defective mutants. The inactive mutants of LPL that do not bind to heparin also are applicable to this area. The many factors in atherogenesis already discussed where endogenous heparin activity has a restraining effect suggest that genetically determined heparin levels, or its dysfunction, are important. This applies to heparin per se and to the heparin activity of HSPG. The inverse relation between plasma heparin and triglyceride-bearing lipoproteins, EC glycocalyx defects and their relation to LDL and fibrinogen uptake and to a predisposition to atherosclerosis, the lower HSPG and elevated CSPG in human atherosclerotic plaques, and the lower quantities and sulfation of arterial HSPG in atherosclerosis-susceptible pigeons are all pertinent. Defective HSPG mutants have been demonstrated in hamsters and mice. The subject of proteoglycan mutations has been reviewed (Stanley, 1984). All these indicate that, to a considerable extent, atherosclerosis might be a genetically determined, endogenous, heparin activity deficiency disease.

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