in EC proliferation and DNA synthesis compared to the stationary control. In contrast, the growth curve for the SMC showed a slower rate of proliferation and DNA synthesis during the same strain regimen. Further studies also indicate that the enhanced proliferation of ECs and the inhibitory effect on SMC proliferation of cyclic deformation could also be noted when the cells were stretched at frequencies of 60 and 100 cycle/min. Studies are under way exploring the effect of various deformation regimens on cell proliferation. However, the initial experiments indicate that different cells from the same tissue can react differently to the same stress regimen and may imply control at the level of cell division. In addition, our recent data suggest that the conditioned media from stretched SMCs will inhibit proliferation of target quiescent SMCs, whereas conditioned media from stretched ECs will stimulate proliferation of quiescent target ECs. We are currently investigating this phenomenon and the production of growth factors and inhibitory substances by vascular cells during cyclic stretching.

What is the transducing signal by which external mechanical forces affect the cell phenotype? Numerous potential pathways exist, but it seems likely that control is at the level of the cell membrane or cytoskeleton or both. At the cell membrane level, cell surface receptors, chemical second messengers such as cyclic adenosine monophosphate or the phosphoinositide metabolites, or the actual deformation of the membrane activating distinct ion channels may be important. The cellular microfilament system might be involved as the extension of the cells, and the generation of tension within them may depend on the microfilament system.

Other important issues need to be addressed in the future. Is the increase in EC growth a result of entry of quiescent cells into the cell cycle or a general speeding up of the cell cycle? Does mechanical deformation alter the composition of the extracellular matrix, and does this in turn modulate cell function? Are autocrine and paracrine substances released by physical stress forces? What is the mechanism for cell alignment with shear and pulsatile stress, and what is the significance of this alignment in terms of cell function? What is the effect of these forces on cell-to-cell interaction?

In summary, it is now evident that the stationary tissue culture condition may be suboptimal and inappropriate for the study of the biology of cells that reside in a dynamic environment in vivo. Further studies detailing the precise contribution of external forces to cell function and adaptation are needed to extrapolate studies done in vitro models with the living dynamic state.

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IS INTIMAL HYPERPLASIA AN ADAPTIVE RESPONSE OR A PATHOLOGIC PROCESS?—OBSERVATIONS ON THE NATURE OF NONATHEROSCLEROTIC INTIMAL THICKENING

The artery wall is a living tissue subserving a mechanical function. Adjustments to imposed deviations from normal or "ideal" conditions should, within fairly well defined limits, be expected to be self-limiting and to terminate when the ideal baseline conditions are reestablished. For the blood-endothelial interface, this condition is related to an apparent ideal wall shear stress level of about 15 dyne/cm².³ The media consist of bundles of commonly oriented smooth muscle cells in close association with an encompassing, similarly oriented array of branched elastic fibers.³ These musculoelastic fascicles, the putative units of structure of the media, are aligned with the direction of the mural tensile forces at any given location, and their size is closely related to vessel curvature. Ideal tensile stress levels are likely to depend on distance from the heart, artery diameter, and pressure. Thus homologous arteries in mammals normally tend to have similar wall structure and similar levels of tensile stress. For the aorta, this level is apparently 2000 dyne/cm for each structural layer. For the pulmonary artery and major muscular arteries the level is about half that value. In general, a tensile stress of about
6 × 10⁶ dyne/cm² prevails in the vessels about the carotid bifurcation.⁶

Widening of the intima by smooth muscle cells can be modulated by changing fluid flow velocity and wall shear stress.⁶ Reduction in wall shear stress is considered to be a stimulus for intimal enlargement and narrowing of the lumen, which then results in an increase of blood flow velocity and wall shear stress. This reaction normally ceases when wall shear stress is restored to baseline values. Conversely, imposition of increased flow velocity causes arteries to enlarge until the increased luminal radius results in the restitution of normal baseline wall shear stress.¹² Since wall shear stress is inversely proportional to the third power of the radius, a small change in diameter is usually sufficient to reestablish baseline values of shear stress. The increase in diameter under these circumstances may stimulate a compensatory increase in mural thickness in the form of intimal widening.¹³ Thus in adjusting to increases in tensile stress or to reduction in flow or both, the corresponding morphologic changes may appear as intimal thickening.

Two principal morphologic forms of intimal thickening may be distinguished: (1) intimal fibromuscular hyper trophy (IFH), an orderly, layered widening including both smooth muscle cells and matrix fibers, echoing but not identical with the architecture of the media, and (2) intimal hyperplasia (IH), a fairly uniform accumulation of cells with smooth muscle and/or myofibroblast features often in a myxoid stroma with some formed fibers but usually without a well-defined layered architectural organization. Both of these changes are different from atherosclerotic plaques (APs), which include smooth muscle cells and matrix fibers but also contain macrophages, foam cells, and regions of necrosis, lipid accumulation, and debris, all arranged in a more or less characteristic topography and associated with vessel deformation. Intimal fibromuscular hypertrophy and AP have been considered to be closely related, because these changes tend to occur in similar locations, and lipids may be identified within IFH thickenings. Regardless of possible relationships to subsequent development of AP, neither IFH or IH contains regions of necrosis, pools of lipid accumulation, or debris and neither deforms or disrupts the artery wall. Very marked IFH may be present without evidence of plaque development, and relatively small plaques and fatty streaks may occur with little or no evidence of IFH.

**Intimal fibromuscular hypertrophy**

In straight artery segments the orderly, stratified layer of intimal cells and formed fibers characteristic of this change may be thicker than the underlying media and may occupy the entire circumference of the vessel. Although the process may be quite extensive, it is not necessarily of uniform width throughout. At bends, these thickenings tend to form on the inner or concave side. At branch sites and bifurcations IFH forms at the proximal inflow edge or opposite the flow divider. These are regions of reduced wall shear stress and increased tangential tension. Although the media tend to be thicker in regions of IFH, and fibrous thickening of the inner media may be present, the internal elastic lamina is usually discernible. Measurements in human arteries reveal that the intimal layers of IFH are quite uniform in width.⁷ The absence of disruption, deformity, or necrosis, and the close relationship to geometric configuration and to associated local modifications of flow and mural tension suggest that IFH is likely to be an adaptive or self-limiting compensatory change. Furthermore, experimental and clinical⁶ findings suggest that the IFH reaction may eventually slow or terminate. In regions of IFH, computations of mural tensile stress, which take into account only the width of the media, yield values that are abnormally elevated compared to regions without IFH. However, if the media and intima are taken as total wall thickness, mural tensile stress approaches normal values. Thus on both microarchitectural and functional grounds it is reasonable to presume that IFH is an adaptive reaction to mechanical stresses related to local features of flow or wall tension or both. The mechanisms that regulate these responses and define their limits remain to be illuminated.

**Intimal hyperplasia**

At anastomotic sites, often between arteries and prosthetic or autogenous vessel replacements, this accumulation of cells and matrix material differs from both IFH and AP. In typical examples neither the uniform fibromuscular layered structure of IFH nor the characteristic topography, composition, and deformation of AP are present. Instead, the cells, although numerous, are distributed within an abundant, relatively amorphous matrix. Similar configurations may also be noted focally in relation to APs, particularly where there is evidence of deformity. Localization of IH at anastomotic sites where vessel walls and prostheses differ in compliance, composition, and dimensions, and where scar tissue replaces vascular tissue, suggests that normal self-limiting adaptive reactions may be inhibited. Abnormal configurations and persistence of reduced flow velocities in such regions are nonetheless likely to continue to stimulate an intimal proliferative response. Thus the adaptive reaction cannot reach completion, because changes in effective lumen configuration or wall thickness or both in response to low flow velocity (or increased tensile stress) continue to be inadequate to restore normal levels of wall shear or tensile stress. In effect, the reaction would seem to be a "runaway" proliferative response. The stimulus persists, but physical constraints prevent the establishment of a stable outcome. Low distal runoff and complex flow fields that engender persistent focal low shear regions would accentuate this situation. Therefore IH may be considered to be a dysplastic-hyperplastic response. Like other dysplasias it appears to reflect the lack of formation of a structure consistent with the establishment of an equilibrium state.

Transitions from one of these intimal reactions to the other and in relation to AP would be expected to occur with local modifications of flow and wall tension and with the imposition or modulation of clinical atherogenic risk factors.⁹¹⁰ Superimpositions of these reactions would also
be likely with changes in geometry and hemodynamics during growth and in relation to changes in peripheral resistance. Progression to stenosis or complication of AP or both would also modify local conditions and influence both proximal and distal rates of flow and degrees of wall tension and wall motion. Examples of superimpositions of IFH, IH, and AP are readily found as are isolated “pure” forms of each reaction. The IFH reaction may persist in the presence of atherogenesis, at least in early stages. Conversely, a region of stabilized intimal thickening, which was initially a response to local diminution of wall shear stress or to increased mural tension, can be the site of subsequent atherogenesis.

Intimal fibromuscular hypertrophy, IH, and AP may, during protracted periods, particularly early in their formation, be inapparent on angiographic examination. Intimal fibromuscular hypertrophy and AP may stabilize, and changes in flow conditions may even result in eventual arrest of IH with superimposition of or transformation to the more structured IFH. This development may be less likely in view of the usual persistence of the underlying abnormal state at sites predisposed to IH. Thus both IFH and IH may reflect potentially self-adjusting attempts at vessel reconstruction to meet altered local conditions. Whether the responses lead to stabilization or to progression to significant interference with flow is probably determined largely by the local physical and metabolic environment.

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INHIBITION OF ADHESIVE RECEPTORS

The interaction of platelets with the vessel wall and with each other to form a thrombus can be partially inhibited by a limited number of drugs such as aspirin and other nonsteroidal, antiinflammatory agents. They block cyclooxygenase pathway of platelet stimulation, but they cannot completely inhibit platelet thrombus (aggregate) formation when the potency of the agonist, for example, thrombin or collagen, is sufficiently high.

Structural and functional studies of fibrinogen, the most abundant adhesive protein in plasma, led to the development of synthetic peptide analogs of platelet receptor recognition domains.1 We have pinpointed platelet receptor recognition domains on the carboxy-terminal segment of the gamma chain encompassing residues 400-411 and on the alpha chain of human fibrinogen containing the sequence RGD (residues 95-97 and 572-574).2 This gave rise to a series of synthetic peptide analogs that do not interfere with the metabolic pathways of platelets, but they block binding of iodine 125 (125I)–fibrinogen to its receptor (glycoprotein [GP] IIb-IIIa) on stimulated platelets, inhibit their aggregation in vitro, and inhibit the formation of a platelet thrombus in vivo.3,4 They constitute a new class of inhibitors of platelet aggregation acting at the final step of platelet stimulation through several pathways. Their utility requires further testing, but currently available data indicate that the concept of therapeutic blockade of platelet receptors for adhesive proteins (fibrinogen, von Willebrand's factor, fibronectin, and vitronectin) is gaining in significance.

In vivo the peptide gamma 400-411 reversibly inhibited the formation of a hemostatic plug in a rabbit mesenteric artery.5 In related ex vivo experiments with whole human blood pumped through a Baumgartner chamber at controlled flow conditions, the synthetic peptide gamma 400-411 and peptide RGDS inhibited platelet thrombus formation.6 A control peptide was inactive in vitro and ex vivo. Thus identification of the carboxy-terminal segment of the gamma chain of human fibrinogen as a domain responsible for its interaction with receptors on activated platelets resulted in development of analogs of the native sequence encompassing residues gamma 400-411 and in application of an antipeptide antibody against gamma 385-411. This antibody is also effective in blocking the interaction of human platelets with fibrinogen adsorbed to a