injured and remodeled before the pulmonary arterial pressure rises. Moreover, time may pass during which the disease progresses untreated while the patient sees physicians who do not recognize the illness. An extremely high index of suspicion for PPH must be maintained in the patient who has taken anorexigen. Echocardiography and cardiac catheterization will help in diagnosis.

5. Perhaps the only positive aspect of this second epidemic of anorexigen-related PPH is that it will further drive research efforts into understanding PPH. The issue of genetic predisposition is paramount, and investigators are nearing identification of a gene for familial PPH. The importance of serotonin must be further explored. Given species differences, studies on human cells are essential. Platelet-endothelial-smooth muscle interactions must be examined. With the results of these studies, we may find a method of identifying individuals who may safely take anorexigen, and benefit most from them, and we will certainly gain further insight into the pathogenesis of PPH.

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Familial Primary Pulmonary Hypertension Locus Mapped to Chromosome 2q31-q32*

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The pathogenesis of primary pulmonary hypertension (PPH) is unknown, although families with several affected members suggest a genetic etiology for the familial form. We used microsatellite markers and linkage analyses to map the chromosomal locus linked to PPH in two families with three or more affected members. Previously reported, family 1 (of European ancestry) was known to have nine affected members over five generations. Family 2 (Hispanic) had an unafflicted father with three unaffected children and three affected children by different wives. Two autosomal dominant (AD) models of inheritance were used in the analyses. AD1 considered only affected members in the families, whereas AD2 used disease penetrances assigned according to age- and gender-related incidence data (literature). The genomic screen of family 1 analyzed data from the use of 260 evenly distributed autosomal markers on 22 living, initially available members (3 affected and 19 unaffected; later, autopsies from 2 affected members became available). Only autosome were screened because of male-to-male transmission in both families. Multipoint analysis eliminated 40% of the genome (AD1). The use of additional markers eliminated all but one region. The final analyses included both families, with additional genotypes obtained from autopsies of two affected members of family 1, and analyzed only the markers in the region of interest (D2S1776, D2S324, D2S350, D2S364, D2S1391, D2S152, D2S318, D2S311, and D2S1384). Saturating the candidate region with closely spaced markers mapped the disease locus, PPH1 (GBD/HUGO designation), to a 27 cM region on chromosome 2q31-q32 flanked by recombination events at D2S1776 and D2S1384. Analysis under the AD2 led to a maximal pairwise lod score of 3.21 at D2S1391 and multipoint lod score of 3.87 at D2S350 and D2S364. The lod scores for family 2, although not significant in themselves, indicated cosegregation of PPH with markers for this region and added to the evidence for linkage. Since submission of these findings, the addition of a third large PPH family and of an affected sibling in family 2, previously thought to be asymptomatic, increased the multipoint lod score to >4.5.

The PPH1 region on 2q31-q32 contains a number of potential candidate genes, in particular, a tissue factor pathway inhibitor of coagulation and a cluster of immunoglobulin super family genes that encode integrin subunits αv, αε, and B6. These subunits combine to form heterodimeric signaling molecules involved in a variety of physiological processes, including angiogenesis, immune regulation, and hemostasis. Abnormalities in the function or regulation of integrin subunits or of a coagulation inhibitor may play a role in the vascular remodeling seen in PPH. In addition to familial PPH, identification of the genetic defect at the PPH1 locus may also provide insight into the pathogenesis of sporadic PPH and secondary pulmonary hypertension.

**Mechanisms of Shear Stress Transmission and Transduction in Endothelial Cells***

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Complex vascular geometry, blood flow pulsatility, and variations in blood delivery requirements lead to a three-dimensional and highly dynamic mechanical stress environment within the circulatory system in vivo.1-3 The resulting flow-derived mechanical stresses are transmitted to the vascular wall as a combination of compressive pressure forces, tensile stretch forces, and tangential frictional (or shear) stresses. The endothelium, by virtue of its anatomic location at the interface between the bloodstream and the arterial wall, holds the key to the sensing of these hemodynamic stresses and their subsequent transmission and transduction within the vascular wall. Mechanical forces in general, and fluid shear stress in particular, elicit a large number of humoral, metabolic, and structural responses in endothelial cells. Although many of the mechanisms involved in mechanosensing and transduction remain to be elucidated, much has been learned about the initial signaling events at the endothelial surface and subsequent gene regulatory adaptive processes. These areas have recently been reviewed in depth.4,5

Endothelial responsiveness to shear stress plays a central role in normal vascular physiology through regulation of vascular tone and is involved in the etiology of particular abnormalities, most notably atherosclerosis. Early atherosclerotic lesions localize preferentially in regions of arterial branching and curvature where the fluid mechanical shear stress distribution is largely multidirectional and “disturbed.”7 In contrast, regions of unidirectional shear stress remain largely spared of early lesions. This may be related to the ability of endothelial cells not only to sense fluid mechanical stimuli but also to distinguish among different forms of stimuli. For instance, one of the earliest observations of endothelial responses to steady laminar flow was cellular elongation and alignment in the direction of flow. This, however, does not occur in cells exposed to either turbulent steady flow or to purely oscillatory pulsatile flow (zero net flow rate).8,9 Sensitivity to the precise flow wave form has also been reported for flow-induced oscillations in intracellular calcium concentration.10

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